CONTENTS

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PHARMACO KINETICS → Effect of body on Drug

PHARMACO DYNAMICS → Effect of Drug on Body

Drug:

- Drug is substance which is intended to be used to modify or explore the physiological function or pathological state for the benefit of the recipient.

Risk benefit ratio –

Eg. Streptokinase: –

- Thrombolytic drugs like streptokinase are used in myocardial infarction in which coronary artery is blocked but sometimes also breaks normal physiological thrombus particularly in brain causing cerebral hemorrhage.
- Streptokinase cannot be used in peripheral vascular disease where risk is more than benefit

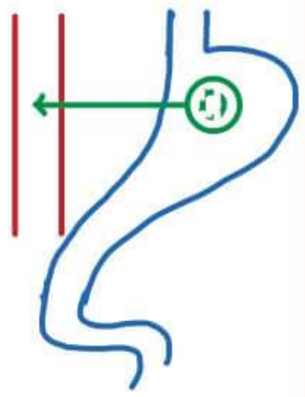
Routes of Drug Administration

- Local
- Systemic
  - Enteral (Through Intestine)
    - Oral
    - Rectal
  - Parenteral (Not through Intestine)
    - **Injectable**
      - i) IV
      - ii) Subcutaneous
      - iii) Intravascular
    - **Non – injectable**
      - i) Sublingual
      - ii) Transdermal
      - iii) Nasal
      - iv) Inhalational

PHARMACOKINETICS

→ aka ADME STUDY
- Absorption
- Distribution
- Metabolism
- Excretion

ORAL ROUTE



ABSORPTION

→ MOVEMENT OF DRUG FROM SITE OF ADMINISTRATION TO BLOOD

→ LIPID SOLUBILITY - Single most important factor in absorpt^{n}
- LIPID SOLUBLE DRUGS ARE ABSORBED

→ FORM OF DRUG

$$H_2O \rightleftharpoons H^+ + OH^-$$

$$HX \rightleftharpoons H^+ + X^-$$

- Ionized form of Drug is water Soluble
- Non Ionized form of Drug is Lipid soluble

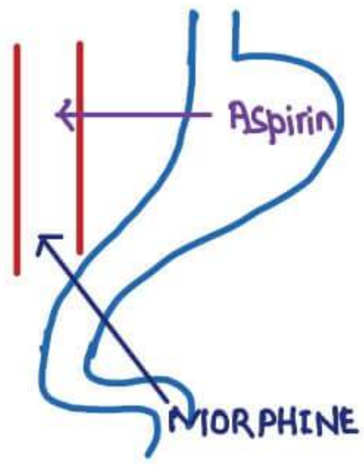
- DRUG IS ABSORBED IN NON-IONIZABLE FORM

→ MEDIUM

- WHEN THE MEDIUM IS SAME, THEN THE DRUG WILL CROSS

DRUG	MEDIUM	FORM	SOLUBILITY	CROSS
Acidic	Acidic	Non ionized	Lipid Soluble	✓
Basic	Basic	Non ionized	Lipid Soluble	✓
Acidic	Basic	ionized	Water Soluble	×
Basic	Acidic	ionized	Water Soluble	×

- Acidic Drug [ASPIRIN] , mainly absorbed from stomach
- Basic Drug [MORPHINE] mainly absorbed from intestine



But practically all drugs (even acidic drugs like aspirin) are absorbed more from intestine as compared to stomach because:

- Large surface are of intestine
- Longer time drug stays in intestine

How much a drug will cross in different media?

Eg. Nature – Acidic

Pka = 6.0

PH	Lipid soluble	Water soluble
3.0	99.9%	0.1%
4.0	99%	1%
5.0	90%	10%
6.0	50%	50%
7.0	10%	90%
8.0	1%	99%
9.0	0.1%	99.9%
10.0	0.01%	99.99%

Henderson Hasselbach Equation

$$pH = pka + \log \frac{[Non - Ionised]}{[Ionised]}$$

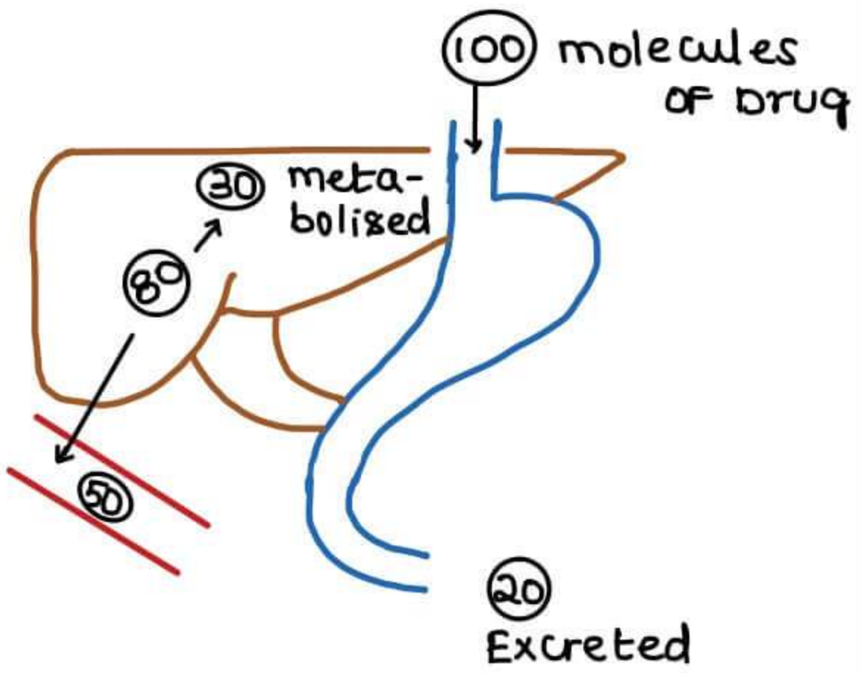
BIO AVAILABILITY

→ FRACTION OF GIVEN DOSE WHICH REACH SYSTEMIC CIRCULATION → Bio Availability

→ determines the DOSE

High bioavailability → Low dose

Low bioavailability → High close



Factors

① Absorption

↑ absorptⁿ → ↑ Bio availability

↓ absorptⁿ → ↓ Bio availability

Bio availability of drugs given by IV route is 100%.

② First Pass metabolism / Pre systemic metabolism

↑ First Pass metabolism → ↓ Bio availability

↓ First Pass metabolism → ↑ Bio availability

NTG [Nitro Glycerine]

- has high first pass metabolism
- SUB LINGUAL ROUTE is preferred

Advantages of sublingual route

- Fast acting → can be used in emergencies
- No first pass metabolism
- Self administratⁿ is possible
- After desirable action, we can spit/ingest the extra dose

How to calculate bioavailability?

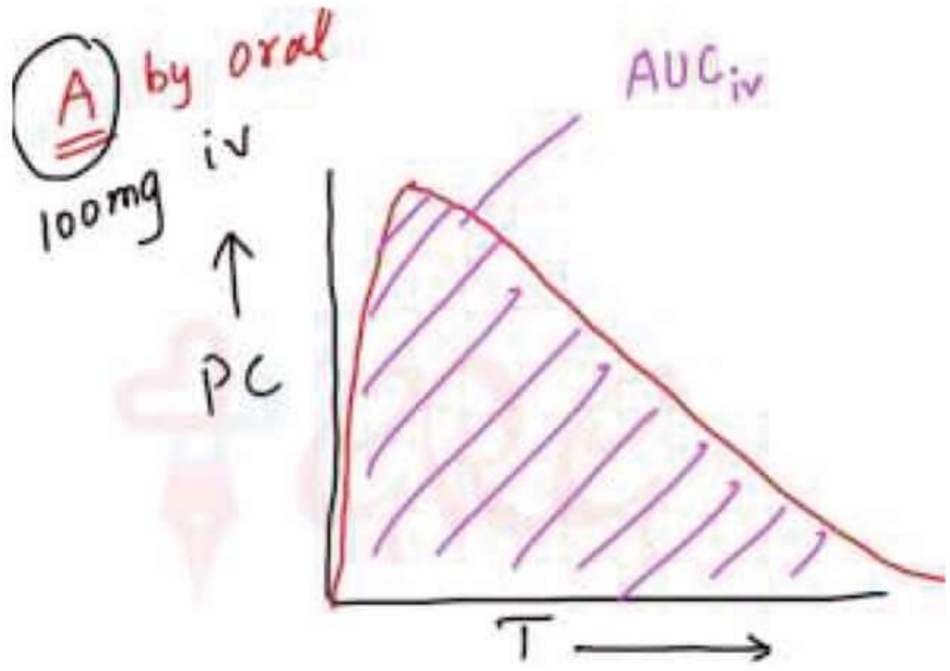
To know the bioavailability of Drug A by oral route

↓

Give drug A 100 mg by IV route

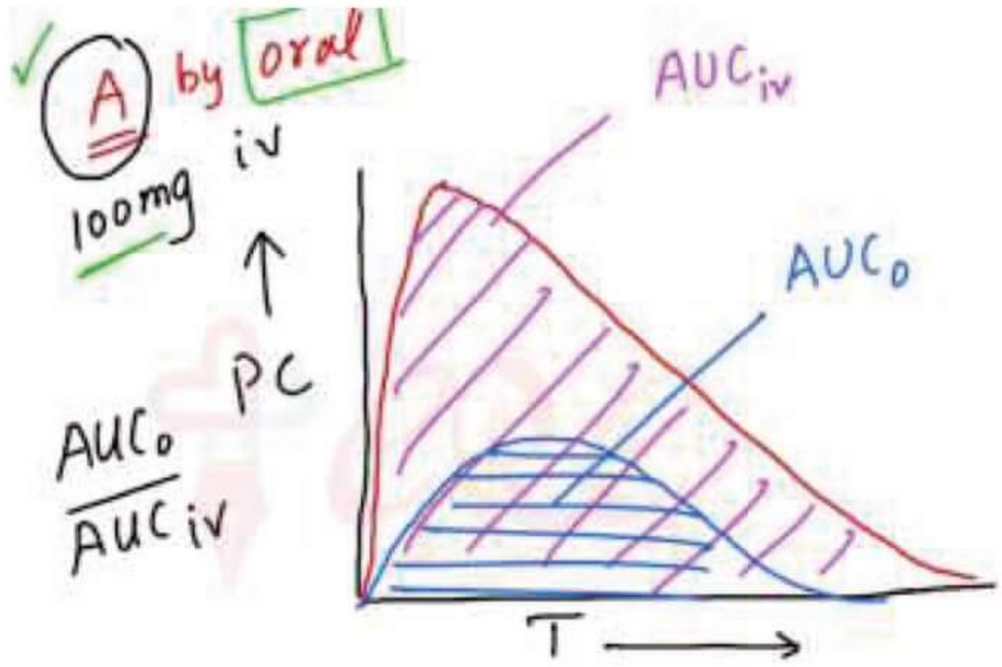
↓

Then plot a graph



- *Measure plasma concentration every 30 min & plot it*
- *Now same dose (100 mg) given orally*

  Plot the same graph



$$\text{Bioavailability} = \frac{\text{AUCo}}{AUCiv}$$

BIOEQUIVALENCE (biologically equivalent)

- 2 brands of same drug are compared

Eg. Aspirin 150 mg

Ecosprin (Brands) Losprin

↓ ↓

100 µg/dl 90µg/dl or 95 or 99.999 µg/dl

- If two brands of same drug have almost similar bioavailability (± 20%), these are called bioequivalent
- Most of the drugs are bioequivalent except phenytoin

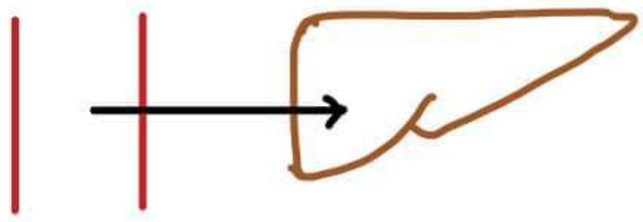
DISTRIBUTION

FACTORS

① LIPID SOLUBILITY → most important factor

Lipid soluble Drugs → Higher Distribution

Water soluble Drugs → Lower Distribution



② PLASMA PROTEIN BINDING

↑ PPB → Low Distribution

→ Acidic drugs bind to → Albumin

→ Basic drugs bind to → α_1 ACID Glycoprotein

→ Different drugs have different percentage of binding

1. **Distribution:**
   - ➔ If PPB is ↑, its volume of distribution (Vd) → ↓↓
2. **Duration:**
   - ➔ If drug has ↑ P.P.B, Duration of action of drug ↑, bcoz plasma protein to which it is bound serves as storage site.
3. **Displacement interactions:**
   - ➔ PPB sites on albumin & α_1 – Acid glycoprotein are non – specific.
   - ➔ Suppose if we give 100 molecules of warfarin to a person & it has 99 % (↑) plasma protein binding, then 99 molecules are already bound to proteins & only 1 mol is free which is producing the action.
   - ➔ Now if this person develops infection (unrelated to warfarin) & to treat that infection; we start sulfonamides.
   - ➔ Sulfonamides also have high PPB & have tendency to bind at the same place where warfarin binds. So, there would be competition b/w warfarin & sulfonamides for binding to same place.
   - ➔ This may ↑ free molecules of warfarin → resulting in warfarin toxicity
   - ➔ This type of interaction is called as displacement interaction.
4. **Dialysis:**
   - ➔ If a drug has ↑ P.P.B; dialysis of that drug cannot be done.
   - ➔ Bcoz proteins are not filtered during dialysis; thus the drug with ↑ P.P.B. is retained along with plasma proteins.
5. If, drug has ↑ P.P.B. its filtration would be lesser.

Dialysis & drug poisoning:

- First A.B.C should be done (i.e maintenance of Airway patency, Breathing & Circulation)
- In poisons, D → Decontamination can also be done. (by giving activated charcoal etc.)
- For some drugs antidote can be given.
- Many drugs don't have antidote, so dialysis is the option in those poisoning.
- Dialysis is effective only if the drug is staying in the plasma (bcoz plasma is filtered in dialysis)
- So, for the dialysis to be effective, the drug should have
  → ↓ volume of distribution (Vd)
  → ↓ plasma protein binding (PDB)
  (↓ P.P.B doesn't always cause ↑ Vd; sometimes there can be ↓Vd due to other factors like ↓ tissue affinity of that drug etc)

*** Drugs in which dialysis is done:**

M → Methanol

L → Lithium

A → Aspirin

*** Drugs in which dialysis is not effective**

A → Amphetamines

V → Verapamil

O → Opioids & organophosphates

I → Imipramine

D → Digoxin

Dialysis → Diazepam (Most of benzodiazepines)

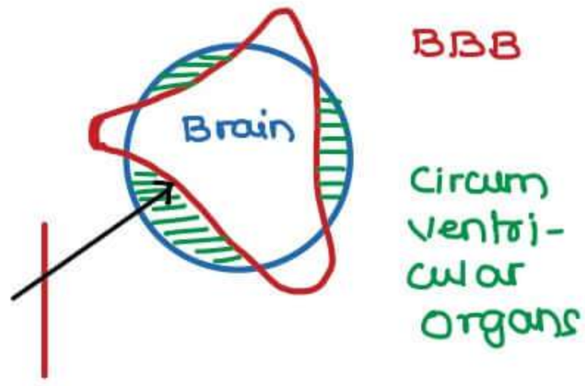
☺ BARRIERS

CIRCUMVENTRICULAR ORGANS [No Blood Brain Barrie]

CTZ [chemoreceptor Trigger zone]

vomiting not caused by → Anti emetics

Anti Psychotics also has anti emetic property

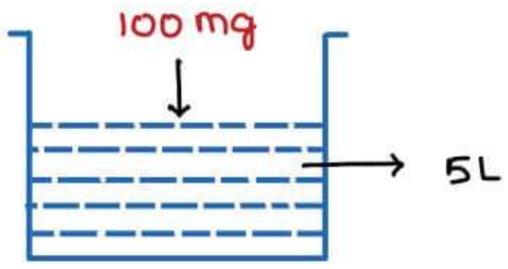


VOLUME OF DISTRIBUTION V_d

→

$$V_d = \frac{\text{Amount given by IV}}{\text{Plasma Concentration}}$$

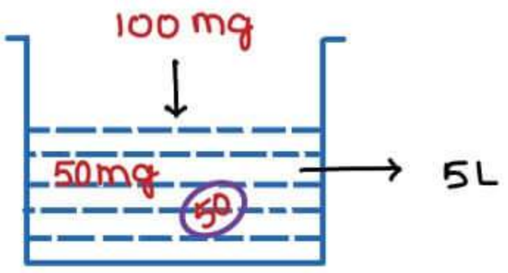
→ CASE 1



$$PC = \frac{100}{5} = 20\ mg/L$$

$$V_d = \frac{100}{20} = 5\ L$$

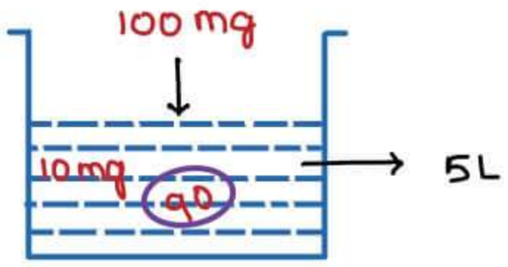
→ CASE 2



$$PC = \frac{50}{5} = 10\ mg/L$$

$$V_d = \frac{100}{10} = 10\ L$$

→ CASE 3



$$PC = \frac{10}{5} = 2\ mg/L$$

$$V_d = \frac{100}{2} = 50\ L$$

→ VOLUME OF DISTRIBUTION V_d ∝ AMOUNT OF DRUG IN TISSUES

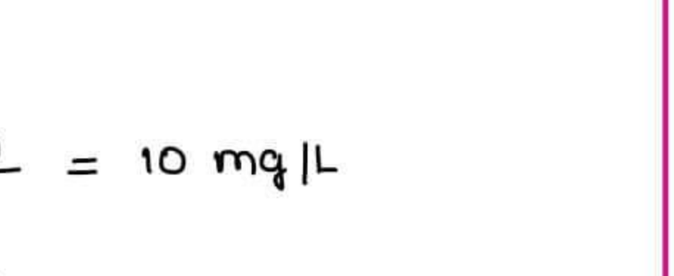
more V_d → more distribution

CHLOROQUINE

Drug i maximum V_d [>13001]

mostly distributed in Liver

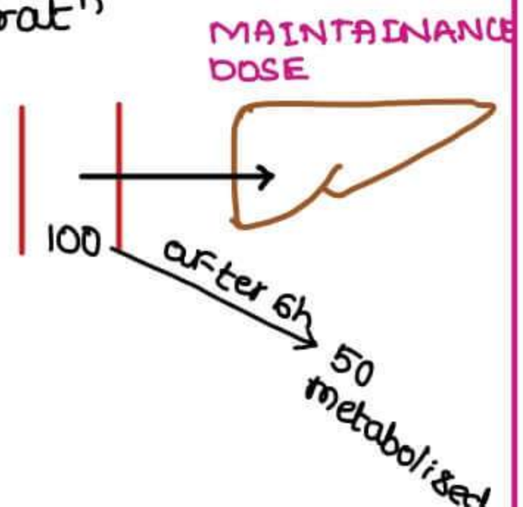
But site of preferred action is RBC



LOADING DOSE [LD]

- initial high dose given to start the preferred action
- LD = V_d x Target Plasma concentration
- LD depends on V_d x Target Plasma Concentrat^n

MAINTAINANCE DOSE



- MD = clearance x Target Plasma conc
- MD depends on clearance & Target plasma conc.

ELIMINATION

→ Termination of action of Drug → ELIMINATION

→ includes Metabolism & Excretion

Metabolism

FATE OF METABOLISM

① Active ⟶ Inactive

② Active ⟶ Active

DIAZEPAM ⟶ OXAZEPAM

③ Inactive [PRODRUG] ⟶ Active

LEVODOPA ⟶ DA [↓ of Parkinsonism]

Prodrugs:

All – ACE inhibitors (PRIL) except Captopril and Lisinopril

Prefer – PPI's (prazole)

Doing – Dipivefrine

M – Methyldopa, Minoxidil, 6-MP

D – levoDopa

In – Irinotecan

Clinical – Clopidogrel, Carbimazole

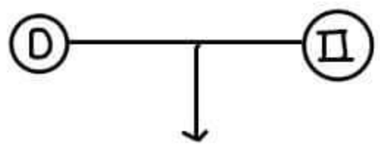
Subjects – Sulfasalazine

AIM of METABOLISM → TO MAKE A DRUG WATER SOLUBLE

PHASE I REACTIONS	PHASE II REACTIONS
→ mostly catabolic Reactions	→ mostly anabolic reactions
→ includes	→ includes
– oxidation	– Glucuronide [mc Phase Reactⁿ]
– Reduction	– Glutathione conjugation
– Hydrolysis	– Acetylation
– Cyclization	– Methylation
– Deamination	– Sulfate

→ Purpose of PHASE II → makes the drug water soluble

→ Purpose of PHASE I → Expose functional Group on the drug



ENZYMES

→ Divided into

Microsomal Enzymes → inside the microsomes

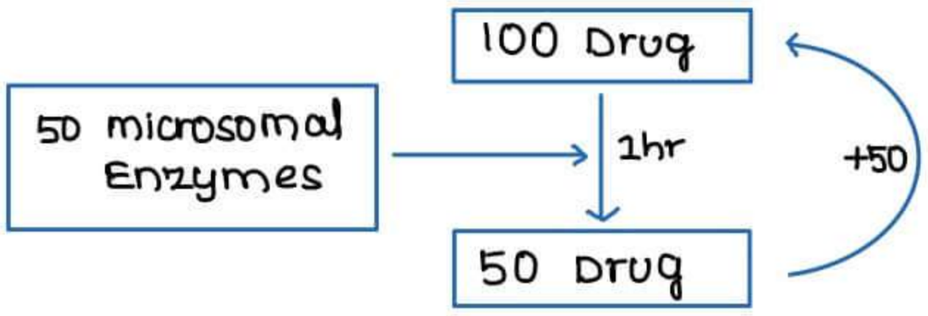
Non Microsomal → out side the microsomes

→ Microsome (Endoplasmic reticulum)

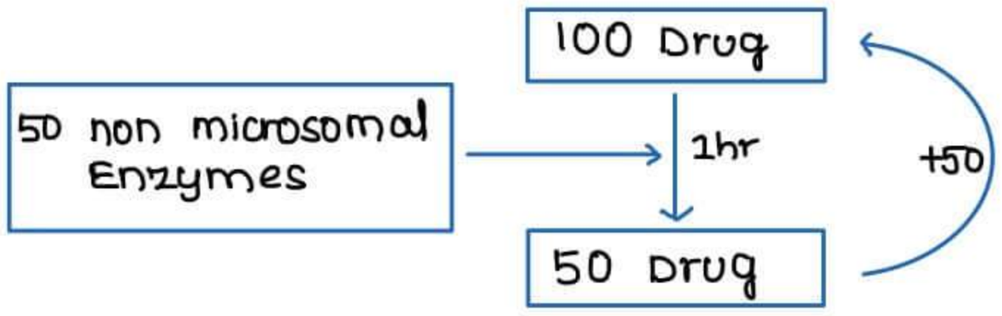
→ only Microsomal enzymes can be induced or inhibited

CASE 1

WARFARIN

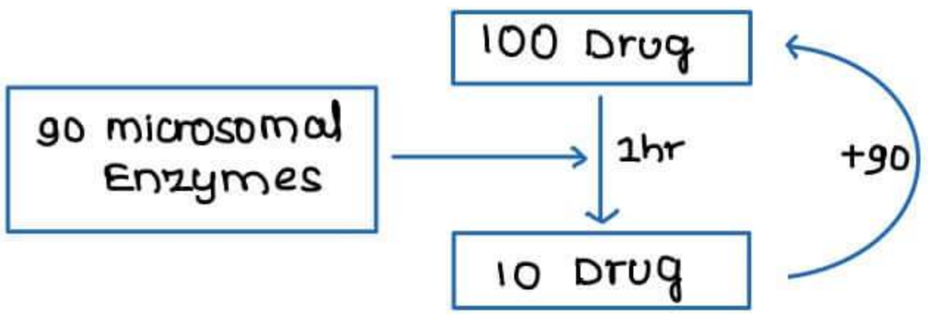


HEPARIN



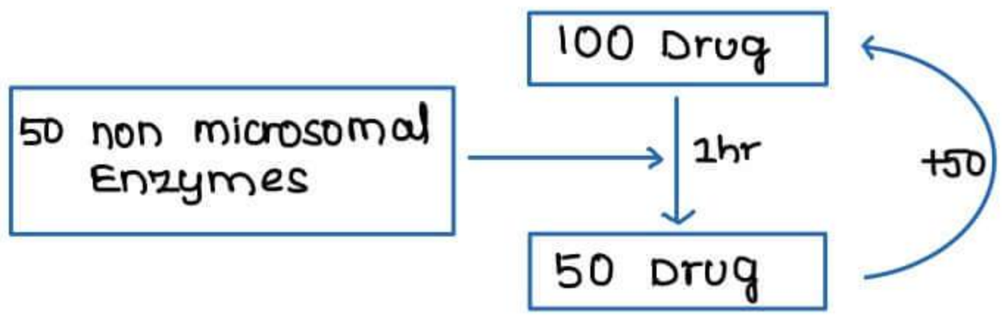
CASE 2 → Along ī RIFAMPICIN [enzyme inducer]

- 50 ME ⟶ 90 ME



- Drug dose to be increased

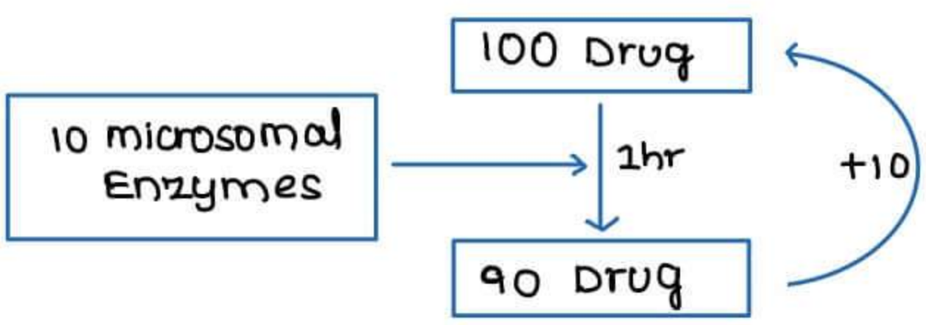
- 50 NmE ⟶ 50 NME



- No change required

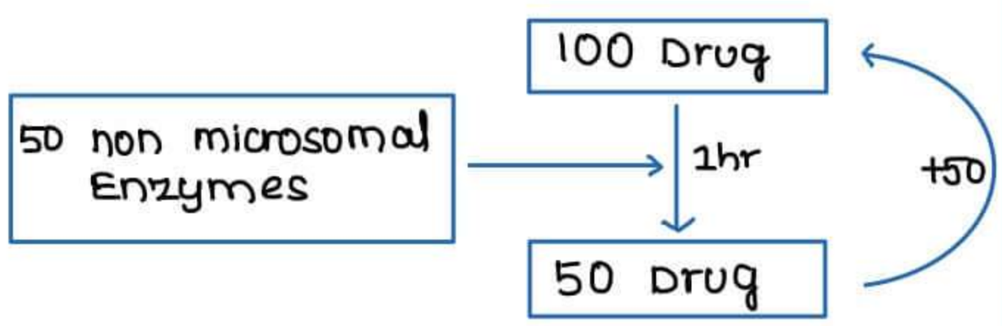
CASE 3 → Along ī CIMETIDINE [enzyme inhibitor]

- 50 ME ⟶ 10 ME



- Drug dose to be decreased

- 50 NmE ⟶ 50 NME



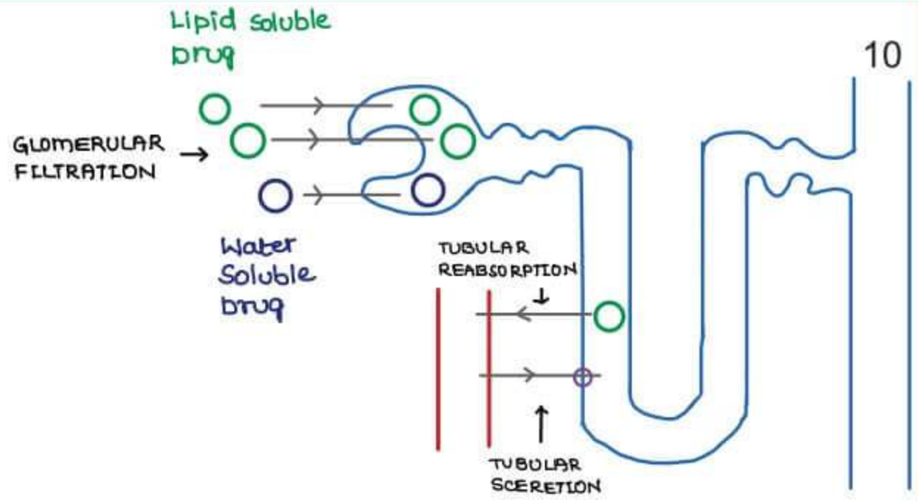
- No change required

ENZYME INDUCERS		ENZYME INHIBITORS	
G	GRISEOFULVIN	Vit	VALPROATE
P	PHENYTOIN	K	KETOCONAZOLE
R	RIFAMPICIN	Can't	CIMETIDINE
S	SMOKING	Cause	CIPROFLOXACIN
Cell	CARBAMAZAPINE	Enzyme	ERYTHROMYCIN
Phone	PHENO BARBITONE	Inhibitⁿ	ISONIAZIDE

most of anti epileptics → ENZYME INDUCERS

most of anti biotics → ENZYME INHIBITORS

EXCRETION



GLOMERULAR FILTRATION

→ Lipid soluble drugs filtered easily
Water soluble drugs also filtered

→ Filtration $\frac{1}{\alpha}$ Plasma Protein binding

→ Ⓝ GFR = 125 ml/min
= 7.5 ltr/hr
= ~180 Ltr/Day

→ Ⓝ Output of urine → 2L/Day

TUBULAR REABSORPION

→ 99% of GFR is reabsorbed
- Lipid soluble drugs reabsorbed
- Water soluble drugs excreted

→ If drug & media are same → drug absorbed
drug & media are different → drug not absorbed

→ Acidic drug poisoning [Aspirin], R_t by $NaHCO_3$ [Forced Alkaline Diuresis]
Alkaline drug poisoning [Amphetamine, R_t by NH_4Cl [Forced acid Diuresis]

TUBULAR SECRETION

→ dlt pumps / transporters in proximal tubules

→ These transporters are SATURABLE
- Penicillin is short acting
- Penicillin + Probenecid → Long acting
  - Probenecid has higher affinity for transporters & prevents Penicillin secretion

→Drugs enter urine via
- Glomerular filtration
- Tubular secretion

→Some of the drug can be reabsorbed by tubular reabsorption.

→Remaining part of drug is expelled in clearance.

Scenario 1:

→If 100 molecules of a drug is filtered through glomerular filtration and 150 molecules are expelled out in clearance

→If clearance is more than glomerular filtration which is due to,
- Tubular secretion

→Tubular reabsorption may or may not be present.

Scenario 2:

→If 100 molecules of a drug are filtered through glomerular filtration and only 50 molecules are expelled out in clearance.

→If the clearance is less than the glomerular filtration which is due to,

- Tubular reabsorption

→Tubular secretion may or may not be present.

SOME MORE FORMULAS

RATE OF ELIMINATION [R]

→ incomplete parameter

$$R \rightarrow \frac{\text{Amount of Drug Eliminated}}{\text{Time}}$$

CLEARANCE [CL]

→ complete parameter

$$CL \rightarrow \frac{R}{PC}$$

PC = Plasma concentration

Extraction Ratio

Hepatic extraction ratio in relation to clearance

Suppose

100 molecules of drug enter the liver through the arteries, 80 molecules of drug go out to other organs from liver through veins which means 20 molecules have been extracted by liver.

Formula

$$\text{Extraction ratio} = \frac{\text{Concentration of drug in arteries} - \text{Concentration of drug in veins}}{\text{Concentration of drug in the arteries}}$$

i.e. $\frac{\text{Amount of drug extracted by the organ}}{\text{Amount of drug entering the organ}}$

If a drug has high hepatic extraction ratio, on oral administration, liver can extract large amount of drug before it reaches the systemic circulation, leading to poor oral bio-availability which is known as First Pass Metabolism.

The drugs with high First pass metabolism/ High hepatic extraction ratio

L- Lignocaine

P- Propranolol

G- GTN (Glyceryl tri nitrate/ Nitroglycerine)

Hepatic Clearance = Hepatic Extraction Ratio × Blood flow to liver.

Renal Clearance = Renal Extraction ratio × blood flow to kidney

Total body clearance= Sum of all the clearances of individual organs.

HALF LIFE [$t_{1/2}$]

100

↓ $t_{1/2}$

50

↓ $t_{1/2}$

25

↓ $t_{1/2}$

12.5

↓ $t_{1/2}$

6.25

→ $t_{1/2}$ for most drugs is constant

Q $t_{1/2}$ = 6 hrs , after 1 day
- → How much drug remains in body → 6.25%
- → How much drug eliminated from body → 93.75%

→ Dose can't be calculated
DOSING INTERVAL / FREQUENCY can be known

→ $t_{1/2}$ $\propto$ volume of distribution [V_d]
$t_{1/2}$ $\frac{1}{\propto}$ clearance

$$t_{1/2} \quad 0.693 \times \frac{Vd}{CL}$$

ORDER of KINETICS

Rate of elimination $\propto = (Plasma\ concentration)^{order}$

First order kinetics- Rate of elimination $\propto$ plasma concentration

Zero order kinetics- Rate of elimination is constant.

Likewise,

Second order kinetics- Rate of elimination $\propto$ $(\text{plasma concentration})^2$

Third order kinetics- Rate of elimination $\propto$ $(\text{plasma concentration})^3$

FIRST ORDER KINETICS	ZERO ORDER KINETIS
→ Fraction is constant	→ Amount is constant
R ∝ PC CL = constant $t_{1/2}$ = constant	R = constant CL $\frac{1}{\alpha}$ PC $t_{1/2}$ α PC

FIRST ORDER

	R	CL	t1/2
100 ↓ 1hr 50 ↓ 1hr 25 ↓ 1hr 12.5 ↓ 1 hr 6.25	50/hr ↓ 25/hr ↓ 12.5/hr ↓ 6.25/hr	½ ↓ ½ ↓ ½ ↓ ½	1hr ↓ 1hr ↓ 1hr ↓ 1hr

ZERO ORDER

	R	CL	t1/2
100 ↓ 1hr 80 ↓ 1hr 60 ↓ 1 hr 40 ↓ 1 hr 20	20/hr ↓ 20/hr ↓ 20/hr ↓ 20/hr	0.20 ↓ 0.25 ↓ 0.33 ↓ 0.50	2.5 hr ↓ 2hr ↓ 1.5 hr ↓ 1 hr

→ Majority drugs follow first order kinetics

DRUGS FOLLOWING ZERO ORDER KINETICS are

ZERO → ZERO ORDER KINETICS
W → WARFARIN
A → ALCOHOL | ASPIRIN
T → THEOPHYLLINE
T → TOLBUTAMIDE
Power → PHENYTOIN

Dose dependent actions of Aspirin

1. Antiplatelet action (Low dose is required)
2. Fever
3. Pain
4. Inflammation (Highest dose is required)

If aspirin is used for Anti-inflammatory action- it follows zero order kinetics and when concentration decreases, it will follow First order kinetics.

So, zero order kinetics are also known as Pseudo- Zero order kinetics/ Non- Linear kinetics.

REASON

→ Order of kinetics depends on Enzyme Saturation
  → if enzymes are abundant → follow 1st order kinetics
  → if enzymes are limiting factor → follow ZERO ORDER KINETICS [SATURATION KINETICS]

PHARMACODYNAMICS

→ 

AFFINITY → ability of a drug to bind to a receptor

INTRINSIC ACTIVITY → ability to produce action after binding to receptor

→ CLASSIFICATION OF DRUGS BASED ON INTRINSIC ACTIVITY

AGONIST → Maximum intrinsic activity [+1]

PARTIAL AGONIST → Submaximum intrinsic activity [0 to +1]

INVERSE AGONIST → Opposite action to agonist [-ve]

ANTAGONIST → NO action [0] but interferes action of other drugs

→ 

↑

Signal tranduction Mechanism

CLASSIFICATION OF DRUGS BASED ON SIGNAL TRANSDUCTⁿ MECHANISM

① INOTROPIC RECEPTORS

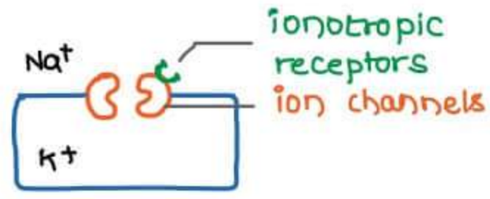
→ Fastest acting receptors

→ Examples

→ $GABA_A$ receptors → N_N receptors

→ NMDA receptors → N_M receptors

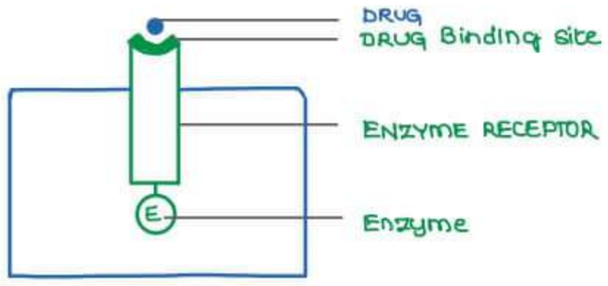
→ AMPA receptors → $5HT_3$ receptors



② ENZYMATIC RECEPTORS

→ aka TYROSINE KINASE RECEPTORS

[mostly associated enzyme is Tyrosine kinase]



→ Examples

cytokines

P Prolactin

I Insulin

G Growth hormone

3 Types

1. **Intrinsic tyrosine kinase activity**

- Whenever drug bind outside
  - Tyrosine kinase enzyme gets activated inside
- E.g. Insulin receptor

2. **No Intrinsic activity**

- Some proteins present on Enzyme, which recruit tyrosine kinase from the cytoplasm
- Enzyme itself does not possess enzyme activity

Eg:

1. JAK – STAT (JAK recruits STAT that will result in enzymatic activity)
2. Prolactin, Growth hormone
3. Cytokines

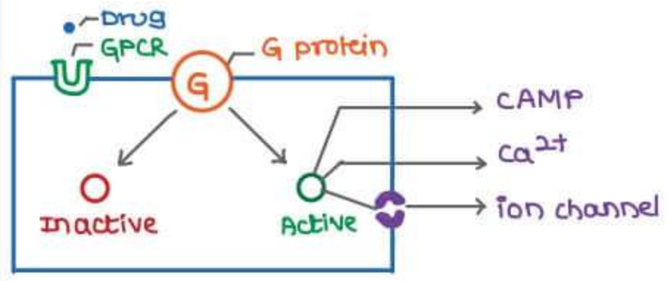
3. **Guanylate Cyclase**

- Whenever drug binds outside, guanylate cyclase gets activated inside and generates cGMP.
- Substances which act through Gyanylate cyclase are ANP, BNP, CNP

③ G - PROTEIN COUPLED RECEPTORS [GPCR]

Adrenaline
↓
acts on β receptor
↓
Stimulates G protein
↓
Active component
↑ cAMP
– ↑ HR
– Bronchodilat^{n}

Adrenaline
↓
acts on α receptor
↓
Stimulates G protein
↓
Active component
↑ Ca^{2+}
– vasoconstrict^{n}



G PROTEIN

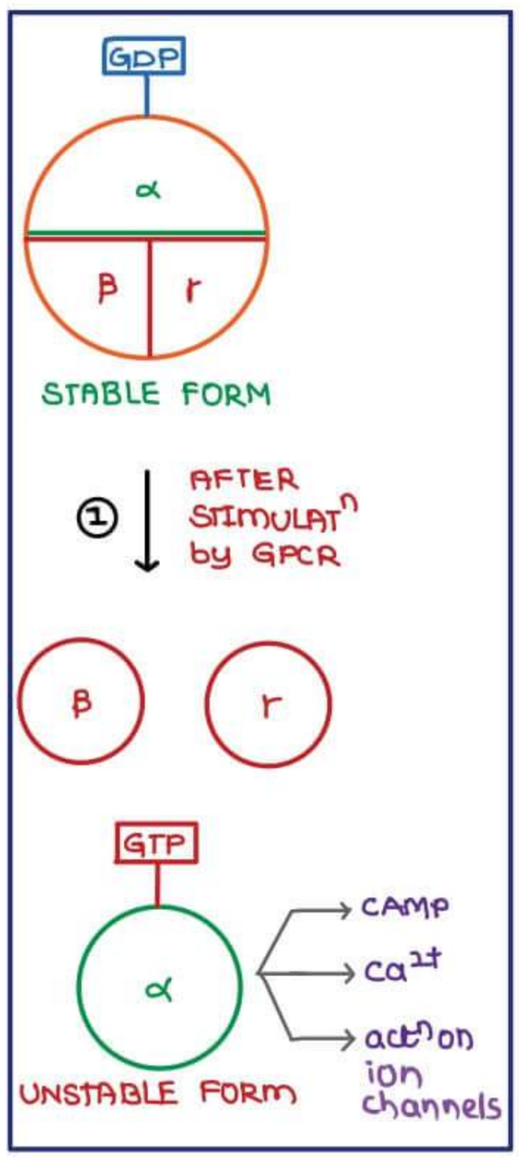
G stands for GDP/GTP binding protein

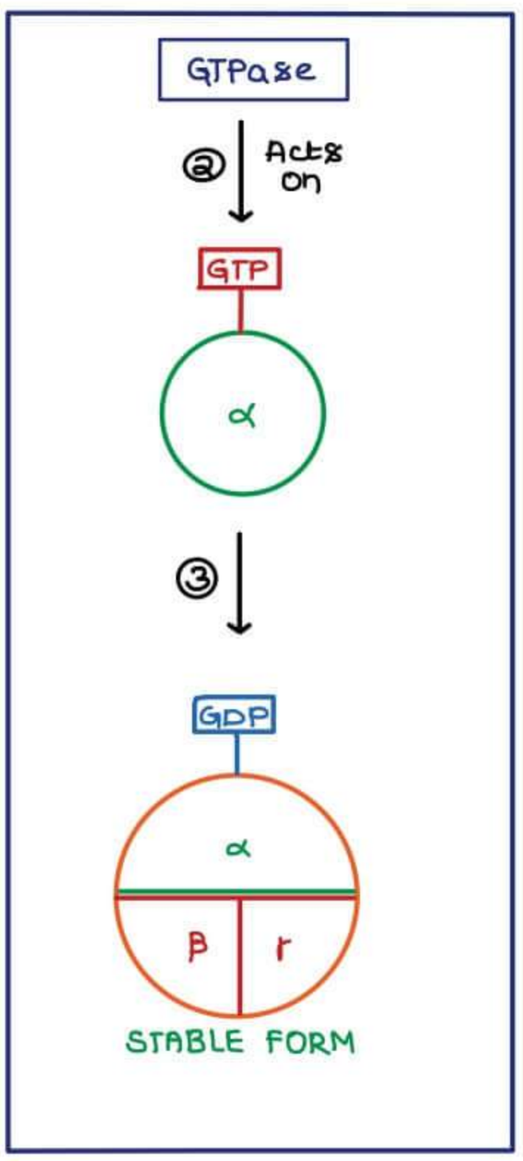
Components

α → GDP binds here in resting State
β
γ

When G protein stimulated, phosphorylat^{n} occurs, GDP converted to GTP
↓
components seperates
β & γ components are inactive
α ∴ GTP is active
produce one of following act^{n} on
→ cAMP
→ Ca^{2+}
→ act^{n} on ion channels

α component also has GTPase activity
→ converts GTP to GDP
→ G protein Stabilizat^{n} occurs
→ Recyling of G protein





Types of G proteins

Gs → Adenyl cyclase (+) → ↑ CAMP

Gi → Adenyl cyclase (-) → ↓ CAMP

Gq → ↑ Ca^{2+} via PIP2 pathway

[Phosphatidyl inositol bisphosphate (PIP_2)

↓

IP_3 + DAG

↓

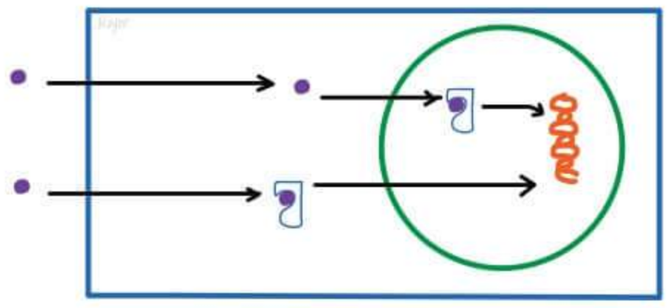
↑ Ca^{2+} [IP_3, DAG, Ca^{2+} are second messenger]

In some books Ca^{2+} → 3rd messenger

④ INTRACELLULAR RECEPTORS

a. CYTOPLASMIC RECEPTORS

b. NUCLEAR RECEPTOR



→ only lipid soluble drugs acts through these receptors

→ slowest acting receptors

→ commony named as NUCLEAR RECEPTOR SUPERFAMILY

Cytoplasmic Receptors	Nuclear Receptors
C → Corticosteroids	P → PPAR
Gluco	S → Sex Hormones → E, P, T
Mineralo	V → Vit A
D → Vit D	T → T_3, T_4

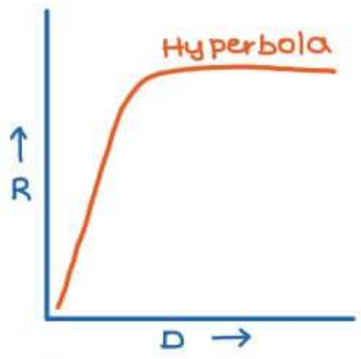
DOSE RESPONSE CURVE [DRC]

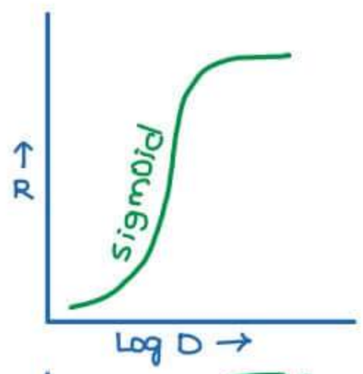
→ HYPERBOLA SHAPE

Log DOSE RESPONSE CURVE [log DRC]

→ S shaped curve [SIGMOID CURVE]

→ Clinically more useful than DRC



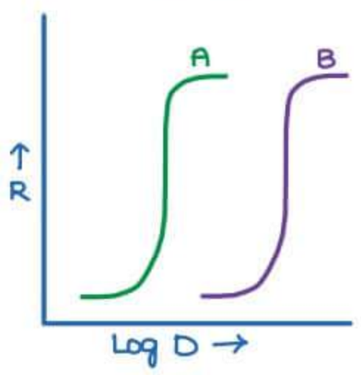


POTENCY

→ relates to POWER

→ left sided curve is more potent (A)

→ Right sided curve is less potent (B)

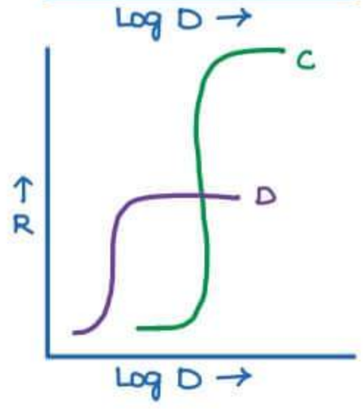


EFFICACY

→ relates to effect regardless of dose

→ C is more efficaceous

D is less efficaceous



Q

BP

160

↓ -40

120

DOSE	A	B
5mg	10	0
10 mg	20	10
20 mg	25	20
40 mg	25	30
80 mg	25	40
	more potent	more efficacious

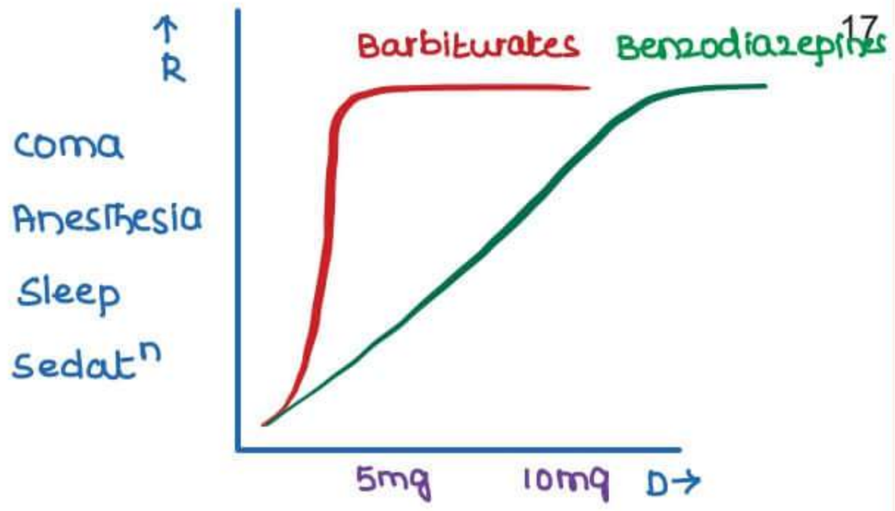
→ EFFICACY is more important than potency ∵ respect to R↓

SLOPE

→ slope related to SAFETY

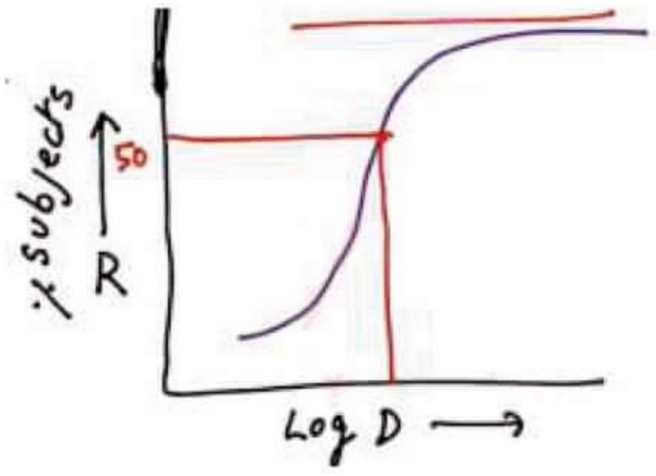
→ Drug ↑ less slope is more safer

Drug ↑ deep slope is less safer



QUANTAL DRC

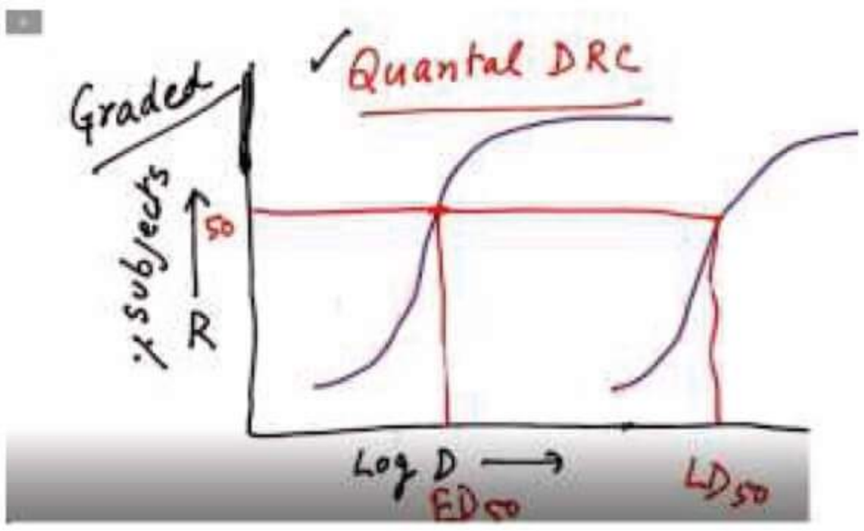
- For All or none phenomenon → On Y axis grade of response cannot be plotted.
- Percentage of subjects responding are kept on Y-axis.



If 50% respond to a particular dose → Then it is called ED_{50} (Median Effective dose)

ii)

If 50% of animals die after receiving a particular dose → it is called LD50 (Median Lethal dose)



- If
- If

- LD_{50}/ED_{50} = Therapeutic Index
- Therapeutic Index tells about the Safety of drug.

↑ Therapeutic Index – drug is safe

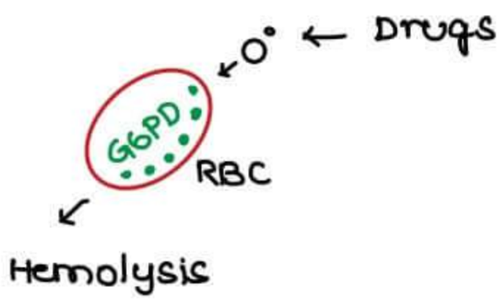
↓ Therapeutic Index – drug is unsafe

PHARMACO GENETICS

① G-6 PD DEFICIENCY

→ G-6 PD protects RBC from free radical injury

- PRIMAQUINE
- SULFONAMIDES
- NITROFURANTOIN
- FURAZOLIDONE



② ACETYLATION

→ enzyme → NAT [N Acetyl Transferase]

→ FAST acetylator of INH → no response

SLOW acetylator of INH → Peripheral neuropathy

→ S → SULFONAMIDE [DAPSONE]

H → HYDRALAZINE

I → INH

P → PROCAINAMIDE

→ SHIP Drugs can cause SLE also

③ Sch INDUCED APNEA

Sch [SUCCINYL CHOLINE]

→ Muscle relaxant

→ Shortest acting [< 5 min]

- d/t Pseudocholinesterase

→ used for Endotracheal intubation

ATYPICAL PSEUDOCHOLINESTERASE

→ metabolizes Sch in 30 minutes or longer

→ causes prolonged Apnea

THERAPEUTIC DRUG MONITORING [TDM]

CASE 1 → AIM → reduce BP from 160 → 120 mm Hg,
Prescribed drug Ⓐ @ 10 mg for 1 week,
check BP after 1 week, change the dose accordingly

CASE 2 → Epilepsy Patient,
Prescribed DRUG Ⓑ @ 100 mg, then

→ required plasma concentrat^{n} → 10-20 µg/L
check plasma concentrat^{n} & change the dose accordingly

→ not used commonly

→ CRITERIA TO USE TDM

1. RESPONSE CAN'T MEASURABLE
2. LOW THERAPEUTIC INDEX DRUGS
3. INCONSISTENT PHARMACOKINETICS OF DRUGS

IMPORTANT POINTS ABOUT TDM

→ *The dose and plasma concentration graph need not be linear because if the plasma concentration is increasing, the dose can be reduced and therapeutic Drug monitoring is not essential.*

→ *The graph between Response and Plasma concentration should be Linear, because response does not increase in correspondence to increasing plasma concentration then there is no effect in measuring plasma concentration.*

→ *In therapeutic drug monitoring (TDM), the drug response should be directly proportional/ linear to plasma concentration.*

→ *TDM is not indicated for drugs which are activated in the body like pro-drugs.*

→ *TDM is used for measuring the compliance in case of long-term medications like epileptic drugs.*

→ TDM done for

A → Antibiotics
Drug → DIGOXIN
Possessing → PHENYTOIN [most antiepileptic drugs]
Low → LITHIUM
Therapeutic → TRICYCLIC ANTI DIPRESSANTS [TCA]
Index → IMMUNO SUPPRESANT DRUGS
→ CYCLOSPORINE
→ TACROLIMUS

PHARMACOLOGICAL ANTAGONISTS

→ acts on same receptors to produce opposite effects

→ ADRENALINE	Propronolol
↓	↓
β_2 R ⊕	β_2 R ⊖
↓	↓
Broncho dilation	Broncho constriction

→ Propronolol is pharmacological antagonist of adrenaline

CLINICAL TRAILS → Testing of drug in humans

PHASE I

→ done in HEALTHY PEOPLE

→ We can't do EFFICACY TESTING

→ MTD [maximum tolerable dose] can be found

→ Phase I can also be done in Patients for Toxic drugs

PHASE II

→ done in patients [20-200 number]

→ Indicator of Efficacy [1st time efficacy is known]

PHASE III

→ done in patients [upto 5000]

→ Multicentric trails done [covers different genetic make up]

→ EFFICACY CONFIRMATION can be known

PHASE IV

→ Post marketing study done [max. no. of patients tested]

→ RARE SIDE EFFECTS can be studied

→ CHRONIC SIDE EFFECTS can be studied

FDA APPLICATIONS

INDA	→	Investigational New Drug Application
	→	Applied before starting clinical trails
NDA	→	New Drug Application
	→	Applied before marketing the drug

DETAILED INFORMATION ABOUT CLINICAL TRIALS

Licensing authority

→ Authority to give approval for a new drug in USA = **US – FDA**

→ Authority to give approval for a new drug in India = **CDSCO (Central Drug Standard Control Organization)**, headed by **DCGI (Drug controller General of India)**

FDA Applications

→ **INDA (Investigational New Drug Application)** – Applied to start Clinical trials for a given drug

→ **NDA (New Drug Application)** – Applied to get permission for Marketing the drug

Ethical guidelines

→ Controlling authority for Animal studies / Pre-clinical studies – **CPCSEA (Committee for the Purpose of Control & Supervision of Experiments on Animals)**

→ Guidelines for Clinical trials on Humans – **GCP (Good Clinical Practice) Guidelines**

Phases of Clinical trials

→ **Phase I** – Maximum tolerable dose can be found

→ **Phase II**

- II_A = Proof of Concept study
- II_B = Dose – Ranging study

→ **Phase III** – Pivotal clinical trials

→ **Phase IV** – Post Marketing studies

→ **Phase O**

- Micro-dosing study
- Maximum amount of drug given is **100µg or (1/100)th of Human Equivalent Dose**
- Radiolabeled substances are added with this sub-therapeutic dose to know the Pharmacokinetics of the drug
- It is not mandatory

Control & Blinding

→ **Drug group** – Newly developed drug will be given

→ **Control group**

- Placebo given
- For Life-threatening diseases – Standard drug given
- Placebo effect is mostly due to release of endorphins

→ **Blinding** - To keep drug or control group or both, unaware of the treatment

- **Single blind study**
  - Only the subject (Patient) is unaware of the treatment
  - Done in Phase II
- **Double blind study**
  - Both the Investigator & the subject are unaware of the treatment
  - Eliminate Investigator bias (considered as the best study)
  - Done in Phase III

PHARMACOVIGILANCE

→ It is the study of Detection, Assessment, Understanding & Prevention of Adverse effects of drugs

→ Adverse event (AE) – Includes anything adverse happening to the person while on drug therapy

→ Adverse drug reaction (ADR) – Out of Adverse events, adverse reactions caused by drugs are included

Detection

→ Detect all the adverse events happened

Assessment

→ Assess adverse reactions caused by drugs out of all adverse events

→ All ADR are AE but all AE are not ADRs

→ Dechallenge & Rechallenge method can be used

→ Severity of ADR is also assessed

Understanding

→ Postulate a mechanism for the cause of Adverse reaction by the given drug

Prevention

→ Proper advice to avoid the Adverse event from happening

NATIONAL PHARMACOVIGILANCE PROGRAM OF INDIA (NPVPI)

ADR monitoring centers (AMC)

→ Uses a software known as Vigiflow

→ It collects all the Adverse drug reactions reported and send them to National Coordinating center

National Coordinating center (NCC)

→ It is Indian Pharmacopoeia Commission (IPC)

→ Located in Ghaziabad (UP)

→ From here the data is sent to Uppsala Monitoring Center

Uppsala Monitoring Center (UMC)

→ Located in Uppsala, Sweden

→ Collects data from all over the world & analyses it - Report it to FDA

Food & Drug Administration (FDA)

→ May issue Black box warning or even withdrawal of drug from market

Note

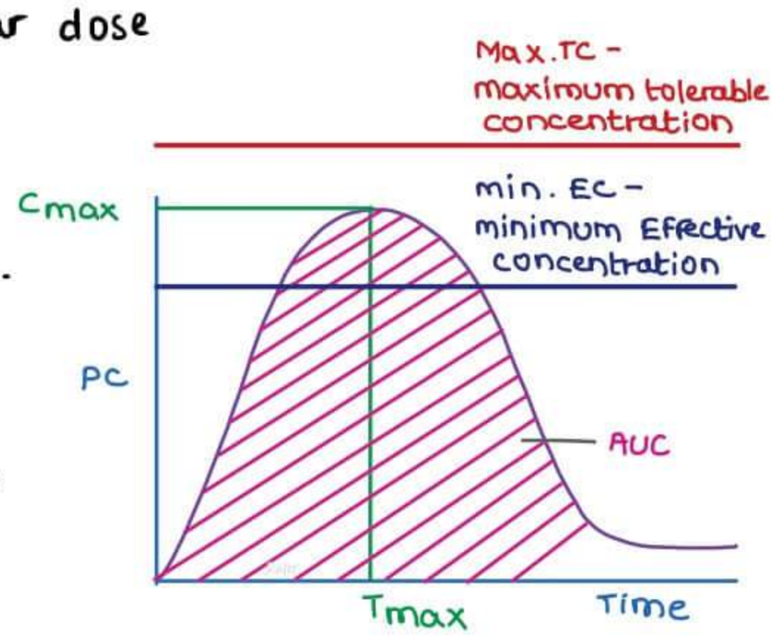
→ Materiovigilance – Program for Medical devices

PLASMA CONCENTRATION & TIME GRAPH

C_{max} → max plasma conc. obtained by a particular dose
depends on dosage
→ should lie b/w Min EC & Max TC

T_{max} → time in which concentrat^{n} becomes max
tells the RATE OF ABSORPTION

AUC → Area under the curve
→ tells the EXTENT OF ABSORPTION



TYPES OF DRUG ANTAGONISM

PHYSICAL → physical presence of drug stops the act^{n} of other [charcoal]

CHEMICAL → chemical react^{n} stops the action [ANTACIDS]

PHYSIOLOGICAL

PHARMACOLOGICAL

PHYSIOLOGICAL ANTAGONISTS

→ acts on different receptors produces opposite effects

→

Histamine	Adrenaline
↓	↓
H_1 ®	β_2 ®
↓	↓
Broncho constriction	Bronchodilation

→ Histamine is physiological antagonist of Adrenaline

ENZYME INHIBITION

COMPETITIVE → Drug can not bind to enzyme substrate complex

NON COMPETITIVE → Drug can bind to enzyme / enzyme substrate complex

UN COMPETITIVE → Drug mainly binds to enzyme substrate complex

	K_m	V_{max}
COMPETITIVE	↑	—
NON COMPETITIVE	—	↓
UN COMPETITIVE	↓	↓

CYP [CYP → Cytochrome P_{450}]

SUBSTRATES FOR

CYP3A4

C → CYCLOSPORINE , CALCIUM CHANNEL BLOCKER

T → TACROLIMUS

S → STATINS

C → CAT DRUGS

A → AMIADARONE

N → NAVIRS [Protease inhibitors]

C → CISAPRIDE

A → ASTEMIZOLE

T → TERFENADINE

Withdrawn d/t QT Prolongat^{n}

CYP 2D6

2 → B → β BLOCKERS

D → Depress^{n} → ANTI DEPRESSANTT DRUGS

TCA

SSRI

SNRI

6 → ↑ HR → ANTI ARRYTHMICS Except AMIODARONE [by CYP3A4]

CYP 2C19

→ CLOPIDOGREL $\xrightarrow{CYP2C19}$ ACTIVE

→ PPI

- PPI acts as competitive inhibitor
- clopidogrel should not be given ī PPIs

CYP 2C9

C → Clotting → WARFARIN

9 → P → PHENYTOIN

COMBINED EFFECT OF DRUGS

1. ADDITION / SUMMATION → 2 + 2 = 4
2. SYNERGISM → 2 + 2 ≅ 10
3. POTENTIATION → 2 + 0 ≅ 5
4. ANTAGONISM → 2 + 2 < 4

ADDITION / SUMMATION → Individual effects of 2 drugs, simply added

SYNERGISM

→ COTRIMAXOZOLE → SULPHAMETHOXAZOLE + TRIMETHOPRIM
[Bacteriocidal] [Bacteriostatic] [Bacteriostatic]

POTENTIATION

→ LEVODOPA + CARBIDOPA [Inactive] → Efficacy of Levodopa ↑ses

ANTAGONISM → Combined effect of two drugs will be lesser

DIFFERENT TYPE OF DRUGS

Orphan drugs –

- These are drugs for which the expenditure done for the development of the drug is unlikely to be recovered from sale of the drug
- Includes drugs which are used for rare diseases
- Also includes drugs for relatively common diseases in third world countries with less paying capacity

Essential drugs

→ These are drugs that cater to Priority health care needs of a population
→ These drugs should be
  - Always available
  - In Adequate quantity
  - With Assured quality

→ Mostly available as single compound

Me-too drugs

→ Includes drugs that has similar Mechanism of action (similar Pharmacodynamics) & minor Pharmacokinetics differences
→ Examples
  - Enalapril
  - Ramipril
  - Captopril
  - Lisinopril

Spurious drugs –

Include drugs that are manufactured, concealing the true identity of the product and made to resemble another drug (especially some popular brand)

Misbranded drugs –

Includes drugs that have false or misleading information on the drug label

Contaminated drugs –

Includes drugs that contain unhygienic or filthy mater

Spare Receptors

➢ At particular number of receptors stimulation, the response become maximum and those receptors which are present in body beyond these, are known as spare receptors

RECEPTOR REGULATION

Continuous stimulation of receptor can decrease the action. Following mechanisms are involved:

→ **Masking of receptors**
- Receptors present on surface of cell membrane mask themselves by going inside of cell membrane immediately.

→ **Down-regulation of receptors**
- Decrease in number of receptors either by stopping of receptor synthesis or by degradation of already present receptors.

→ **Uncoupling of signal transduction pathway**
- For example, constant agonistic action on G- protein coupled receptor results in decreased activation of G proteins. This Uncoupling happens due to presence of enzyme G- protein coupled Receptor kinase (GRK).
- Constant agonistic action will cause GRK to phosphorylate the receptor. The phosphorylated receptors is not able to interact with G protein
- In cases of Beta-adrenergic receptors, GRK is known as BARK (Beta adreno receptor kinase). This phosphorylated receptor binds to protein called arrestin to block interaction with G-proteins.

Constant antagonistic activity on receptors causes the activity of receptor to increase by the following methods:

→ **Unmasking of receptors**
- Receptors present near/ down /sideways of membrane moves up to increase activity.

→ **Up-regulation of receptors**
- Increase in synthesis and decrease in degradation of receptors

→ **Increase in signal transduction**

PRACTICALS IN GENERAL PHARMACOLOGY

→ **Drug label**

→ **Drug advertisement**

1. DRUG LABEL

Name

→ Generic name (Aspirin) – Must be present on drug label

→ Brand name (Ecosprin)

→ Chemical name (Acetylsalicylic acid)

Abbreviations

→ IP – Indian Pharmacopoeia

→ BP – British Pharmacopoeia

→ USP – United States Pharmacopoeia

→ BNF – British National Formulary

OTC (Over the Counter) drugs- Do not require prescription.

→ Schedule H drugs require prescription from a registered medical practitioner to be given to patients. Red line is seen on the drug label which indicates that it should be given on prescription only.

Expiry date (EXD) – MAY 2020

→ Expiry date indicates that the drug can be used until last day of the month.

→ Expiry date does not mean that the drug will become ineffective or toxic. It is the time till which the drug is expected to behave similar to, as written in Pharmacopoeia

→ Shelf life – The time between manufacturing date and expiry date.

Storage temperature

→ Keep frozen (freezer) at -20°c

→ Keep cold (Refrigerator) at 2 to 8°c

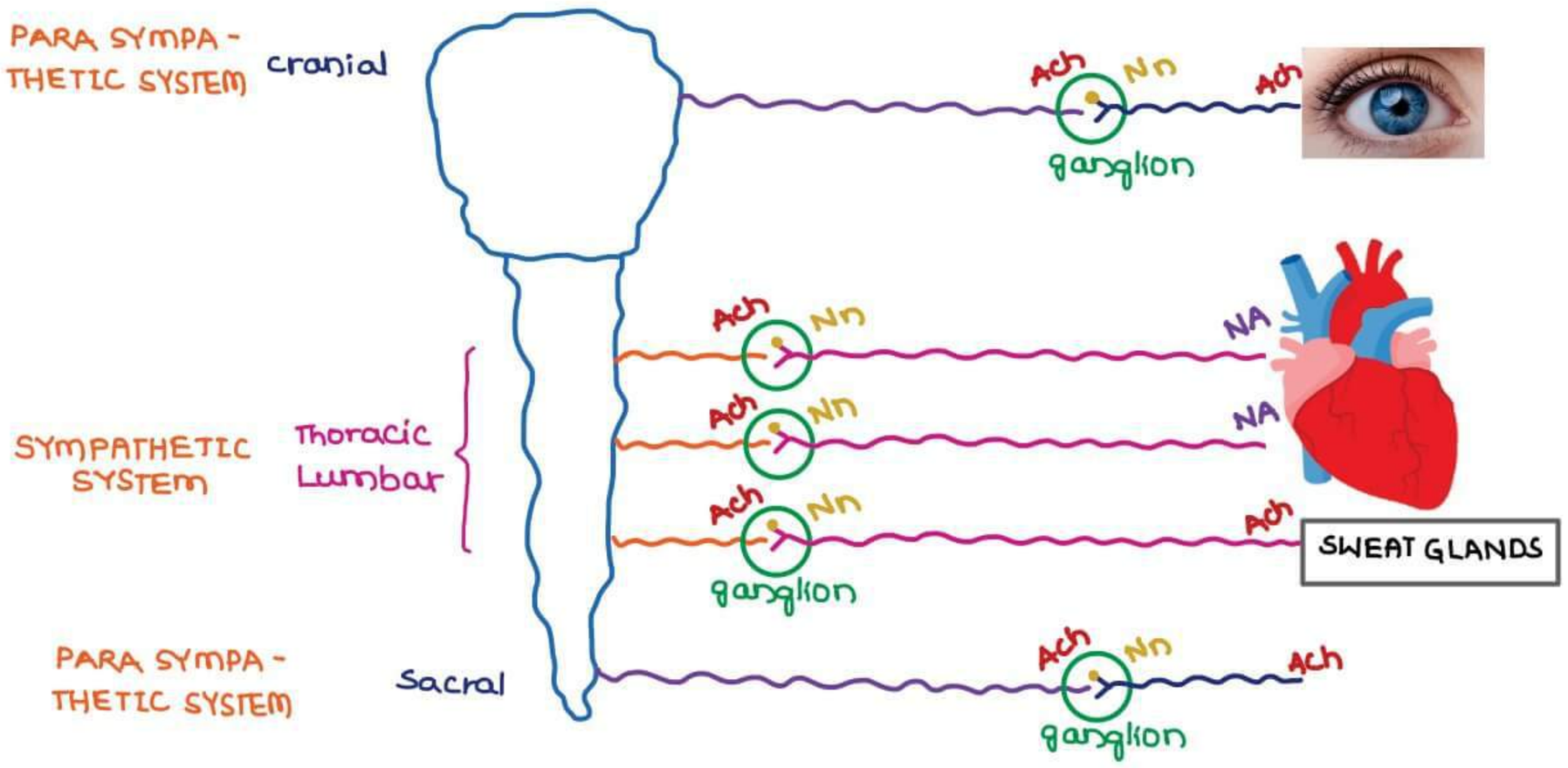
→ Keep cool (Room temperature) at 8 to 15°c in US (8 to 25°c in India)

2. PROMOTIONAL DRUG LITERATURE

1. Name
   - Brand name
   - Generic name (must be written compulsory)
   - Chemical name

   The ratio of brand name to generic name should be within a ratio of 3:1 and should not exceed it
2. Details
   - Indications of drug
   - Route of administration
   - Frequency of dosing
   - Duration of treatment
3. Cost of therapy
4. Adverse effects of the drug
   - Serious effects
   - Common effects

   Both should be mentioned in the drug advertisement leaflet
5. If some claims are made, these should be supported by appropriate reference
6. Address of manufacturing company
7. Expiry date is not required in the advertisement leaflet



→ Preganglionic fibres are shorter in sympathetic system
Preganglionic fibres are longer in parasympathetic system

→ Postganglionic fibres are longer in sympathetic system
Postganglionic fibres are shorter in parasympathetic system

→ Neurotransmitter secreted by all preganglionic fibres → Ach
→ receptor present on postganglionic fibre → N_n
→ NT secreted by the postganglionic fibres of parasym. system → Ach
→ NT secreted by Parasympathetic system is Ach → CHOLINERGIC SYSTEM
→ NT secreted by postganglionic fibres of sympathetic system → NA
  – aka, ADRENERGIC SYSTEM
  – EXCEPTION, postganglionic fibres of sweat glands secrete → Ach

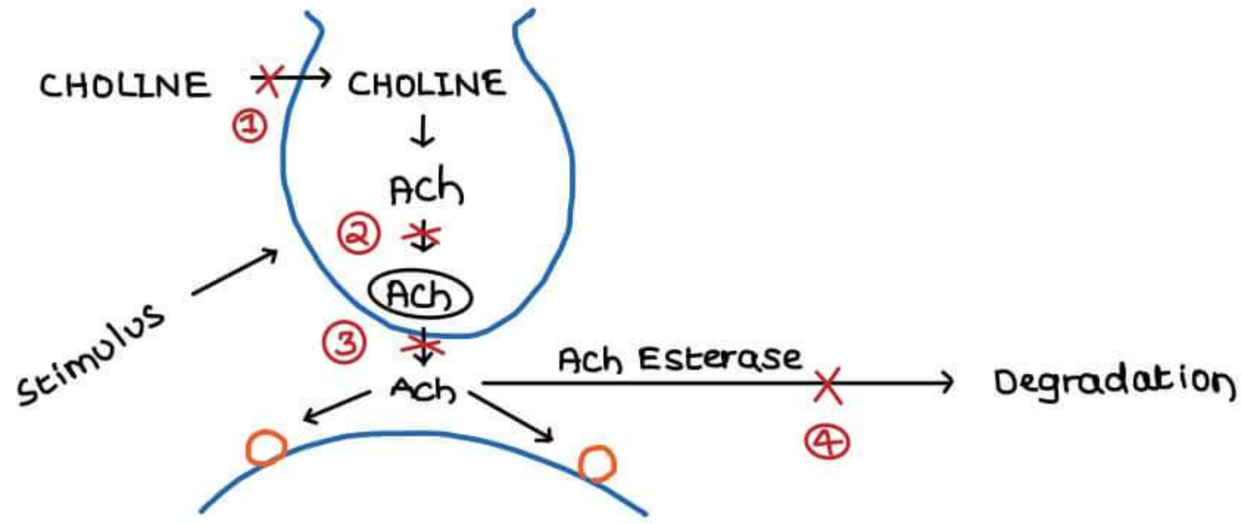
	PARASYMPATHETIC SYSTEM	SYMPATHETIC SYSTEM
HEART	↓ ↓	+ + +
OTHERS	↑	↓
Bronchus	→ Bronchoconstrictn	→ Bronchodilatn
GIT	→ Diarrhoea	→ constipation
Bladder	→ ↑ urine outflow	→ ↓ urine outflow
Glands	→ ↑ secretions	→ ↓ secretions
Pupil	→ miosis	→ mydriasis

PARASYMPATHETIC SYSTEM

ORIGIN

Cranial nerves → 3, 7, 9, 10
Sacral nerves → 2, 3, 4

ACETYL CHOLINE [Ach]



→ slowest step → uptake of choline

↓ Para sympathetic activity

1. HEMI|CHOLI|NIUM
2. VESA|MI|COL
3. BOTULINUM TOXIN

Ach Esterase Inhibitor → ↑ Para sympathetic activity

4. PHYSOSTIGMINE

RECEPTORS OF Ach

NICOTINIC ® LOCATION	MUSCARINIC ® LOCATION
N_N → Ganglia N_M → NMJ require Optimal stimulat^n in both hyper & hypo stimulat^n muscle weakness occurs	M_1 → stomach M_2 → Heart M_3 → Bronchus GIT Bladder Glands Pupil

PARASYMPATHOMIMETICS

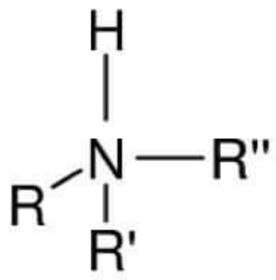
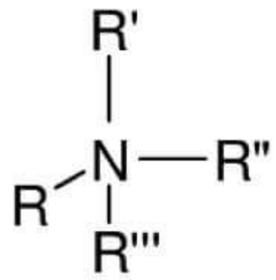
DIRECTLY ACTING DRUGS	INDIRECTLY ACTING DRUGS
→ directly acts on receptors	→ acts by ↑ing Ach AchEsterase #

DRUG	ACTS ON	ACTION	INDICATION
PILOCARPINE	Pupil [M_3®]	meiosis	Angle closure glaucoma
BETHANECHOL	Bladder [M_3®]	↑ outflow	Atonic bladder
METHACHOLINE	Myocardium [M_2®]	cardiac suppression	Tachycardia Arrythmias
CARBACHOL	Common Action Nicotinic ® Muscarinic ®		

Drug ∈ max. nicotinic action → CARBACHOL

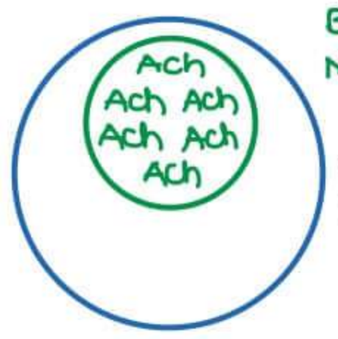
Cevimeline

- *Stimulate M3 receptor especially in glands [↑ secretion]*
- *Used for Xerostomia [Dry mouth] in Sjogren syndrome*

Lipid soluble drugs	Water soluble drugs
Physostigmine	**Neostigmine**
→ Natural product	→ Synthetic product
→ **Tertiary Amine** • 3 Atoms are attached to Nitrogen  • Non-Polar & Non-ionized • Lipid soluble, so cross the BBB	→ **Quaternary Amine** • 4 Atoms are attached to Nitrogen  • Polar & Ionized • Water soluble, so cannot cross the BBB
GIT → √ → Orally given	GIT → X → Injectable
BBB → √ → Central effects +nt	BBB → X → No central effects
Pupil → √ → Used in glaucoma	Pupil → X → No effect on pupil

LIPID SOLUBLE DRUGS — USES

1. ANGLE CLOSURE GLAUCOMA → by Physostigmine
2. ATROPINE POISONING
   - → ATROPINE
     - → Muscarinic receptor blocker [m_1, m_2, m_3]
     - → cross BBB
   - → DOC for atropine poisoning → Physostigmine
3. SENILE DEMENTIA / ALZHIEMER'S DEMENTIA
   - → dlt degeneration of Cholinergic neurons in Basal Nucleus of Meynert



Basal Nucleus of Meynert
↓
Acquiring & retaining memory

   - → TREATMENT

PHYSOSTIGMINE → not used
→ Peripheral action leads to side effects

TACRINE → has only central action
→ Was the DOC
→ Disadvantages
→ very short acting
→ hepatotoxic in some

D → DONEPEZIL
R → RIVASTIGMINE
Gobind → GALANTAMINE
} Long acting, non hepatotoxic, DOC for Alzhieme's disease

MEMANTINE

- → acts by blocking NMDA receptor of glutamate.
- → Used for Alzheimer's' disease

WATER SOLUBLE DRUGS

1. NEOSTIGMINE
2. PYRIDOSTIGMINE
3. EDROPHONIUM

1 MYSTHENIA GRAVIS

↓

Ab against N_M Receptor

↓

N_M Receptors understimulated

↓

MUSCLE WEAKNESS

↑

N_m Receptors overstimulated

↑

CHOLINERGIC CRISIS

EDROPHONIUM TEST

→ IV Edrophonium given

→ very short acting [<10min]

→ If the condition improves for 10 min → Mysthenia gravis

If the condition worsens for 10 min → Cholinergic crisis

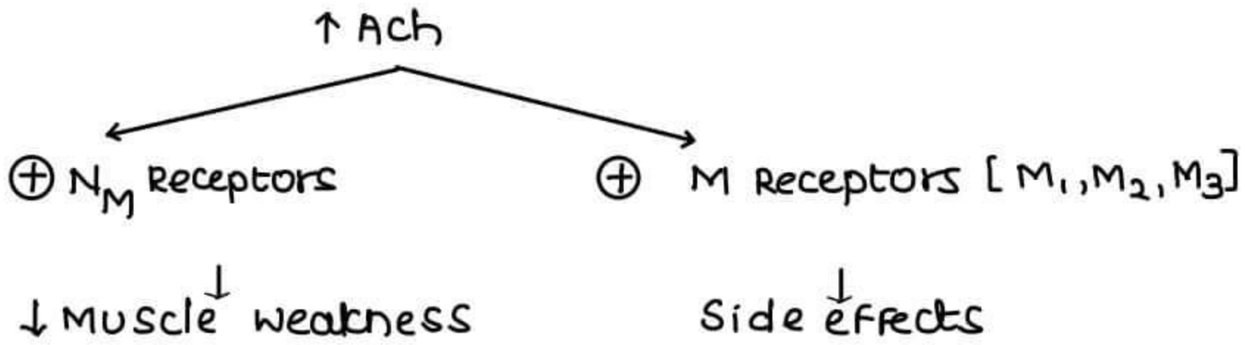
TREATMENT

→ NEOSTIGMINE or

PYRIDOSTIGMINE

→ *Pyridostigmine longer acting than neostigmine*

→ *Pyridostigmine & Neostigmine (both) have additional direct Nm receptor stimulating action (Agonist of Nm receptors)*



→ R_I → NEOSTIGMINE + ATROPINE

2 COBRA BITE

→ N_m #

→ Neostigmine + Atropine → R_I

3. POST OP PARALYTIC ILEUS → R_I by Neostigmine

4. POST OP URINARY RETENTION → R_I by Neostigmine

5. REVERSAL OF ACTION OF NON-DEPOLARIZING MUSCLE RELAXANTS

- **Atracurium and Pancuronium like drugs** act by blocking NM receptor and they are used commonly during surgery
- Reversal of muscle relaxation is done by increasing Acetylcholine and this is done by drugs like Neostigmine and Pyridostigmine
- Atropine should be given with neostigmine and pyridostigmine to stop the muscarinic side of acetylcholine

IRREVERSIBLE ACH ESTERASE

Include

Organophosphates – Malathion, Parathion, DFP, Tabun, sarin.

Carbamates – Carbaryl, Propoxur

[**Note:** Endrin – is organochlorine]

→ Highly Lipid Soluble → can cross intact skin

→ ↑ Ach

coma { M_1 R ⊕ → ↑ HCl
M_2 R ⊕ → ↓ HR, ↓ BP
M_3 R ⊕ → Pinpoint pupil, ↑ secretions, Diarrhoea, Urinary incontinence, Bronchoconstriction

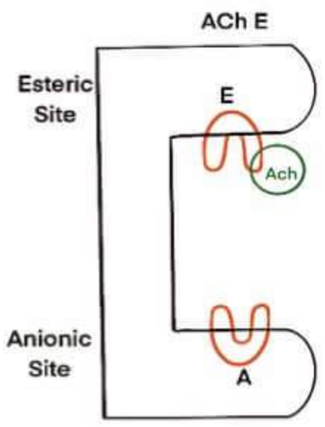
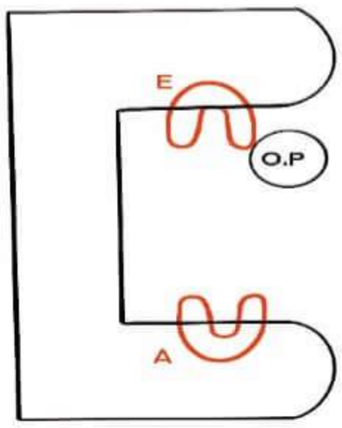
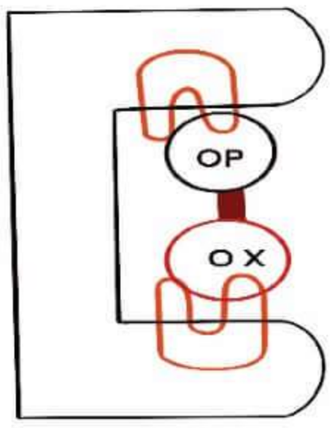
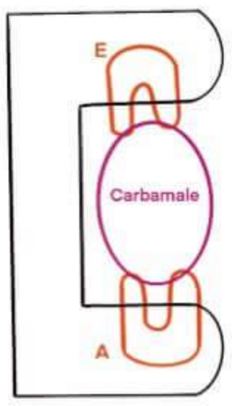
→ IF { Pinpoint pupil ⊕, ↑ Secretions ⊕ } AchE # Poisoning

→ ↑ HR, ↑ BP can be seen rarely [dlt N_N® stimulation]
Muscle weakness occurs usually [dlt N_m® overstimulation]

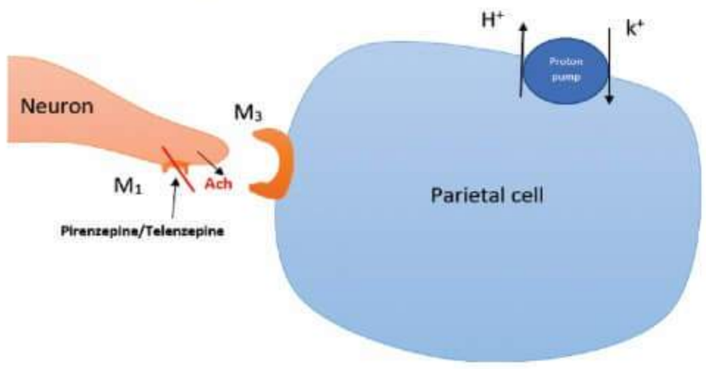
Causes of Pinpoint pupil
("O P" poisoning)
O → *Organophosphate and carbamate poisoning*
→ *Opioid poisoning*
P → *Pontine hemorrhage*
→ *Phenol (Carbolic acid) poisoning*

TREATMENT

1. ATROPINE
   → DOC for OP & carbamate poisoning
   → by iv route, in every 5 min till signs of Atropinization occurs
      → ↓ Secretions → most reliable / specific sign
      → Mydriasis → most common sign
      → HR > 100
   → can't reverse muscle weakness
2. AchE REACTIVATORS
   OXIMES
   PRALIDOXIME [PAM]
   DI ACETYL MONOXIME [DAM
      → not DOC
      → only effective in OP Poisoning
      → PAM acts only peripherally, DAM has both actions

Normal	Action of OP	Reversal by oximes	Carbamates
			
→ Ach binds to esteratic site & is broken → Reaction is so rapid that we can assume this site to be never occupied	→ Instead of Ach, OP binds to esteratic site → ACh cannot bind so cannot be broken → Thus AChE has been inhibited	→ Oximes bind to anionic site and forms bond with OP → Bond between OP and Oximes is very strong → OP is removed from esteratic site → AChE is reactivated	→ Carbamates bind to both esteratic and anionic sites → Oximes cannot bind → Carbamate poisoning cannot be reversed with oximes

Parasympatholytics

Organ	Receptor blocked	Drugs	Uses	S/E
Stomach	M_1	→ Pirenzepine → Telenzepine 	• Peptic ulcer	
Note → **Atropine** – Contraindicated in Peptic ulcer because Not only acts on M_1 but also on M_3 causing delay in Gastric emptying – leads to delay in healing of peptic ulcer (M_3 receptors are also present on smooth muscles of GIT)				
Heart	M_2	→ Atropine (DOC) • Blocks Presynaptic M_1 – Initial Bradycardia • Blocks Presynaptic M_2 – Tachycardia (Later)	• Bradycardia • AV block	
Bronchus	M_3	→ Ipratropium • Fast acting • Non selective (Blocks M_1, M_2, M_3) → Tiotropium • Long acting • Selectively blocks M_1 & M_3	• Bronchial asthma • COPD	
Bladder	M_3	→ **S** – Solefenacin → **O** – Oxybutynin → **F** – Flavoxate → **T** – Tolterodine → **T** – Trospium → **BladDAR** – Darifenacin → **Solefenacin & Darifenacin** – Vesicoselective → **Trospium** • Has less CNS side effects (do not cross BBB) • Primarily excreted by Kidney (C/I in Renal failure)	• Overactive bladder (or) • Detrusor instability (or) • Urinary retention	• Urinary retention – Hence, C/I in BHP • Dry mouth • CNS adverse effects

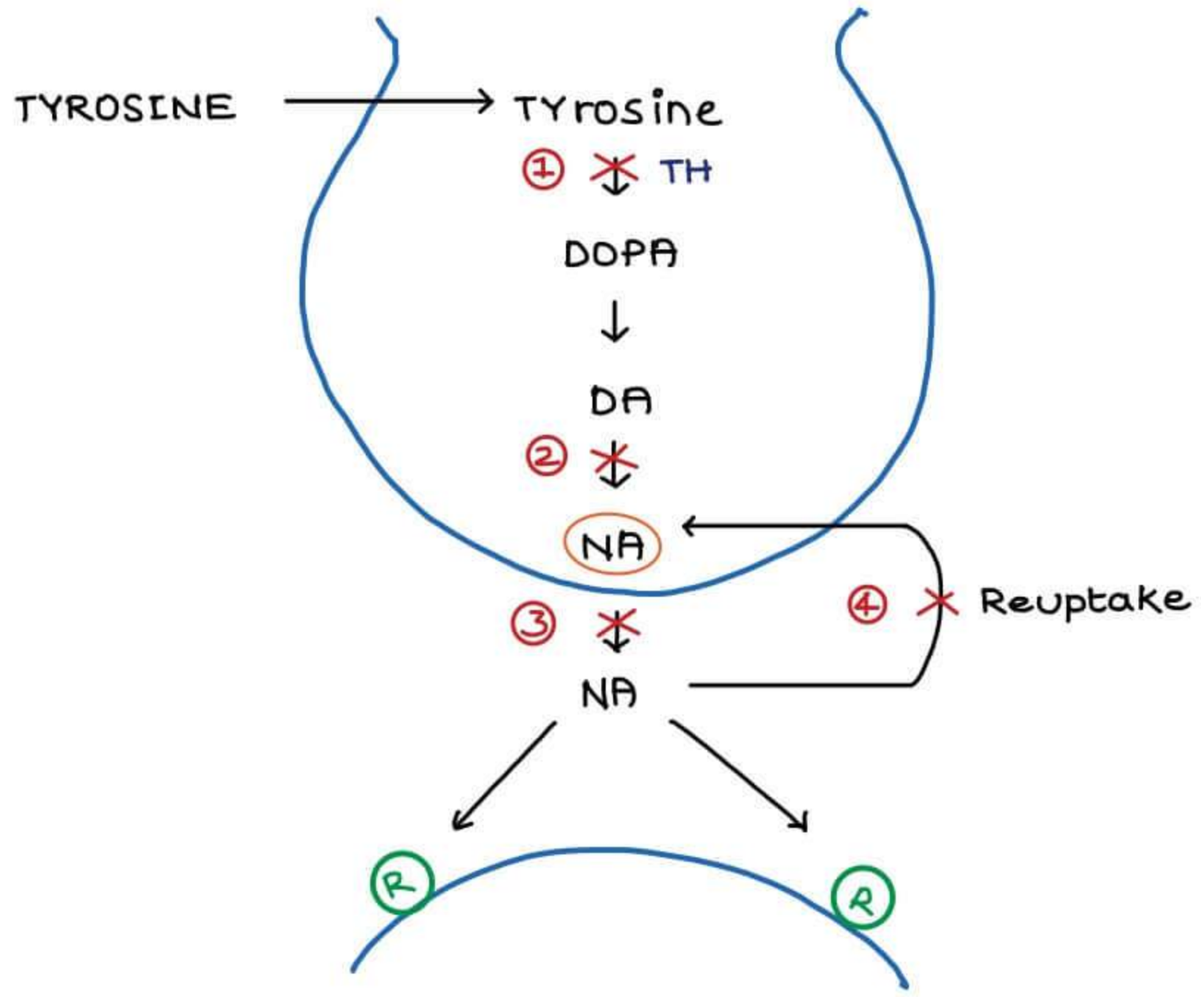
GLANDS	M_3	→ Atropine → Glycopyrrolate	Pre anesthetic Medication	• Dryness [C/I in children] • ↓ Sweating ↓ Fever ↓ Hyperthermia
EYE	M_3	→ Atropine → Homatropine → Cyclopentolate → Tropicamide	• Fundoscopy • Refraction testing • **DOC in** Children – atropine [max. cycloplegic action > 7 days] Adults – Tropicamide [Shortest acting]	• C/I in ACG • Blurred vision d/t cycloplegia – Loss of accommodation d/t M_3 #
CNS		→ Hyoscine [SCOPOLAMINE]	• Motion sickness Prophylaxis	
		→ Benzhexol [Trihexyphenidyl] → Benztropine → Biperiden	• Parkinsonism [DOC for drug induced parkinsonism → Ach #]	

Motion → Vestibular System ⊕ → CTZ ⊕ → Vomiting → Motion sickness
Very high altitudes (Leh ladakh) → ↓ PO_2 → Hypoxia → Mountain Sickness
DOC for motion sickness → Hyoscine [CNS depressant] DOC for mountain sickness → Acetazolamide
In parkinsonism → Balance b/w Ach & DA system disturbed → Anticholinergics are DOC – For Drug induced Parkinsonism → Drugs used are • Benzhexol (Trihexyphenidyl) • Benztropine • Biperiden

Poisoning	DOC
→ Organophosphates & Carbamate	• Atropine
→ Atropa Belladonna / Datura	• Physostigmine
→ Early Mushroom poisoning	• Atropine

Mushroom poisoning	
Early Mushroom poisoning	**Late Mushroom poisoning**
→ **Caused by** – Inocybe / Clitocybe species	→ **Caused by** – Amanita group of species
→ Shows symptoms similar to **Organophosphate poisoning** ↓ DOC – Atropine	→ It is also known as Hallucinogenic Mushroom poisoning → Shows symptoms **similar to Atropine poisoning** ↓ Atropine is C/I → Management is purely Symptomatic

NORADRENALINE



↓ NA in synapse ↓ Sympathetic activity
① METYROSINE ② RESERPINE ③ GUANETHIDINE
Reuptake Inhibitor ↑ Sympathetic activity
④ COCAINE

NA RECEPTORS

α_1		α_2
Location	Action	presynaptic α_2 receptor → acts like brake to sympathetic system [Main function of α_2]
Blood vessels	vasoconstrict^n	
Eye	Mydriasis	
Prostatic urethra	↓ Outflow	post Synaptic α_2 receptor → indistinguishable from α_1 ®
– Prazosine (α_1#) used for BHP		

β_3 → Acts on Adipose tissues → causes Lipolysis

β_1		β_2	
Location	Action	Location	Action
Heart	↑HR, ↑BP	Lungs	Bronchodilation
JG cells	Renin secretion	GIT	constipat^n
		Bladder	↓ outflow
		Glands	↓ secretions
		Uterus	Tocolytic
		Blood vessels	vasodilation
		Skeletal muscle spindles	Tremors
		Liver	↑ Blood sugar

→ α_1 → vasoconstriction & β_2 → vasodilation
→ Effect depends on predominance of type of receptor
→ Heart & Muscles → $\beta_2 > \alpha_1$ → vasodilation
→ Skin, Internal organs → $\alpha_1 > \beta_2$ → vasoconstriction

on hypoglycemia

WARNING SYMPTOMS → dlt sympathetic system stimulation

β_1	β_2	Ach
↓	↓	↓
Tachycardia	Tremors	Sweating
Palpitations		

→ Have to take sugar

→ IF sugar is not taken, even then

β_2 ⊕ → LIVER
- ⊕ Gluconeogenesis
- ⊕ Glycogenolysis
- ⊖ Glycogenesis

↓

↑ Sugar

↓

Reversal of hypoglycemia

→ β Blockers causes (in diabetic patients)

1. masking of warning symptoms
2. no reversal of hypoglycemia

β blockers are contraindicated in diabetic patients

Sweating is only reliable symptom of hypoglyemia in diabetics on β Blocker medication

SYMPATHOMIMETIC DRUGS

→ DIRECTLY ACTING DRUGS

→ INDIRECTLY ACTING DRUGS

INDIRECTLY ACTING DRUGS

A. Reuptake Inhibitors

→ COCAINE

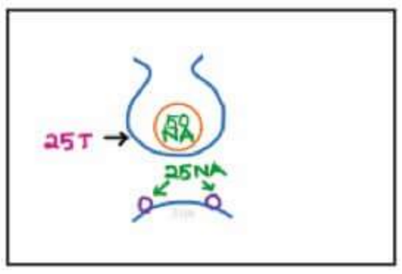
→ TCA

B. Drugs acting by displacement

→Tyramine – acts by displacement of nor adrenaline (indirect effect only).

Major source of tyramine is Cheese.

→Ephedrine
→Pseudo ephedrine
→Amphetamine
} Mixed effect (both direct and indirect effects)



→All these drugs show tachyphylaxis (Rapid development of tolerance)

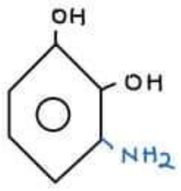
→Use of ephedrine and pseudo ephedrine – Nasal decongestant

→Amphetamines can cross blood brain barrier and ,

- Reduces sleep
- Increases attention span

} Used for Narcolepsy (DOC is modafinil)
Used for ADHD (DOC is methylphenidate)

CATECHOLAMINES



catechol → Di Hydroxy Benzene

COMT → catechol ortho methy transferase recognise catecholamine
→ abundant in GIT → not effective Orally

ENDOGENOUS CATECHOLAMINES	EXOGENOUS CATECHOLAMINES
ADRENALINE	DOBUTAMINE
NA	ISOPRENALINE
DOPAMINE	FENOLDOPAM

DOPAMINE

Acts on

D_1 R	@	<2 µg/kg/min	→	max in Renal BV Blood vessels	→ vasodilation
β_1 R	@	2-10 µg/kg/min	→	Heart	
α_1 R	@	> 10 µg/kg/min	→	vasoconstriction	

Uses

1. CHF
2. SHOCK + OLIGURIA [DOC]

DRUG ☐ DOPA in their name acts on D_1 ®, others do not

DOBUTAMINE

→ do not act on D_1 receptors
→ mainly acts on β_1 receptors
→ used for CHF

FENOLDOPAM

→ Stimulate only D_1 Receptors
→ used in Hypertensive emergencies

	SBP	DBP	HR		
	β_1	α_1 β_2	DIRECT EFFECT ON ♡ (β_1)	INDIRECT EFFECT ON ♡	FINAL
ADRENALINE EPINEPHRINE α_1 α_2 β_1 β_2	↑	↔	↑	↔	↑
NORADRENALINE NOREPINEPHRINE α_1, α_2, β_1	↑	↑↑	↑	↓↓	↓
ISOPRENALINE β_1, β_2	↑	↓	↑	↑↑	↑↑↑

→ Blood vessels contains Baroreceptors
mainly sense MBP [DBP]

$$MBP = DBP + \frac{1}{3} PP$$

↑ DBP → + BR → PSS → ↓ HR
↓ DBP → + BR → SS → ↑ HR

NA EFFECT ON HR

1. In Ⓝ person → ↓
2. In a person ī transplanted heart → ↑ [no indirect action]

USES

ISOPRENALINE → β_1 → CHF
→ β_2 → Asthma

NA → α_1 → Shock
→ β_1 → CHF

ADRENALINE

→ α_1 & β_2 → 1. ANAPHYLACTIC SHOCK
→ DOC
→ Route → im > SC
→ Conc. → 1 : 1000
1gm in 1000 ml Solution
Dose → 0.5 ml of 1:1000 concentration

→ IF donot improve, repeat the dose ī in 10 min
→ IF still not responded,
IV Adrenaline [1 : 10,000]

2 CARDIAC ARREST

BLS
↓ no response
iv Adrenaline
- 1:1000
- central veins [Jugular veins] are preferred
next preferred route → Intraosseous
still next preferred route → Endotracheal

VASOMOTOR REVERSAL OF DALE

ADRENALINE

Strong — Sensitive

$\boxed{\alpha_1}$ α_2 β_1 $\boxed{\beta_2}$

↓ ↓

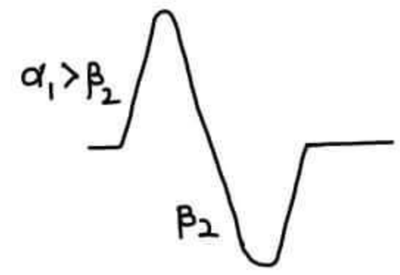
VC VD

BIPHASIC RESPONSE

When Adrenaline given iv at high doses

at First BP increases [dlt ($\alpha_1 > \beta_2$) stimulation]

then BP will decreases [dlt β_2 stimulation]



When Adrenaline given iv at high dose ī α_1 βlocker

Exaggerated Fall of BP occurs

→ VASOMOTOR REVERSAL OF DALE

In Pheochromocytoma

↓

↑↑ adrenaline

↓

↑ BP

If R_1 by α blocker, then vasomotor reversal of Dale occurs & death can occur.

α blockers are C/I in patients of Adrenaline producing Pheochromocytoma

STATUS OF DRUGS IN PHEOCHROMOCYTOMA

Tumor producing	α # alone	β # alone	α + β #
Adrenaline	C/I	C/I	✓
Nor adrenaline	✓	C/I	✓

NON CATECHOLAMINES

Stimulates	Drugs	Action
α_1	a) PHENYLEPHRINE eye drops	→ Mydriasis without cycloplegia
	b) METHOXAMINE MEPHENTERMINE MIDODRINE	→ Vasoconstriction → Used in shock
	c) XYLOMETAZOLINE nasal drops OXYMETAZOLINE nasal drops NAPHAZOLINE nasal drops	→ Nasal decongestants
α_2	a) CLONIDINE b) METHYLDOPA	→ Break for sympathetic system → Used for HTN
β_2	a) SALBUTAMOL b) TERBUTALINE c) SALMETEROL d) FORMOTEROL	→ Bronchodilation → Used for asthma by inhalational route
	a) RITODRINE b) ISOXSUPRINE	→ Tocolytic → Used for preterm labor
β_3	a) MIRABEGRON	→ Overactive bladder

ANTI ADRENERGIC DRUGS

SYMPATHOLYTIC DRUGS

α BLOCKERS

$\alpha_1 + \alpha_2$ BLOCKERS

α_1 BLOCKERS

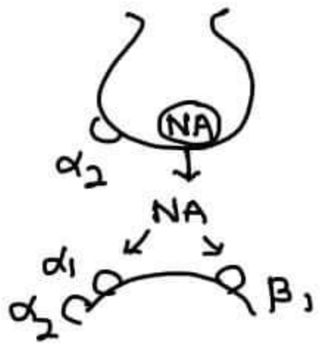
α_2 BLOCKERS → YOHIMBINE [no clinical use]

→ Selective & non selective # used for HTN

→ Non selective α # can cause severe tachycardia

Non selective α # used for severe HTN

Selective α # used for mild to moderate HTN



NON SELECTIVE

IRREVERSIBLE	REVERSIBLE
PHENOXY BENZAMINE	PHENTOLAMINE TOLAZOLINE
USES	USES
Pheochromocytoma	Cheese Reaction Clonidine withdrawal

CHEESE REACTION

Tyramine → MAO → Break down

MAO | GIT

Tyramine → MAO | MAO INHIBITORS → Sudden severe HTN [CHEESE REACTION]

→ DOC → Phentolamine, Tolazoline

CLONIDINE WITHDRAWAL

→ Clonidine

→ α_2 agonist

→ reduces BP

→ sudden stoppage after prolonged use → REBOUND HTN

– dlt upgradation of receptors

→ DOC → Phentolamine, Tolazoline

α_1 BLOCKERS

PRAZOSIN

TERAZOSIN

DOXAZOSIN

ALFUZOSIN

USES

- BPH (due to α_{1A} blockade)
- can be used in other conditions (due to α_{1B} blocking property) like
    - Hypertension
    - Peripheral vascular disease (PVD) like Raynaud's disease
    - Scorpion sting – D.O.C – Prazosin
    - Have beneficial effect on lipid profile

FIRST DOSE / POSTURAL HYPOTENSION

→ α_1 # always started at bed time

TYPES

α_{1A}	α_{1B}
acts on Prostatic urethra	acts on Blood vessels
TAMSULOSIN SILODOSIN → no postural hypotension → DOC for Normotensives ± BHP	

Benign Prostatic Hyperplasia: (BHP)

→ In BHP prostate grows both outside and inside. This causes obstruction of urethral lumen leading to urinary retention. This is complicated by α1A receptors which gets stimulated due to irritation results in contraction of urethra.

α1 A blockers:

- Tamsulosin – stops the DYNAMIC COMPONENT and do not affect the size of urethra i.e., they only improve the symptoms of BHP but do not stop the growth of prostate.

5 α reductase inhibitors:

- Finasteride – stops the conversion of Testosterone to DHT which controls/stops the growth of Prostate in BHP (STATIC COMPONENT).

β BLOCKERS

$\beta_1 + \beta_2$ # [Non selective] — 1st Generation β #

β_1 # — 2nd Generation β #

β_2 # → BUTOXAMINE [no clinical significance]

→ Both used for cardiac indications

→ Non selective β # have both cardiac & non cardiac indications
Selective β # have only cardiac indications

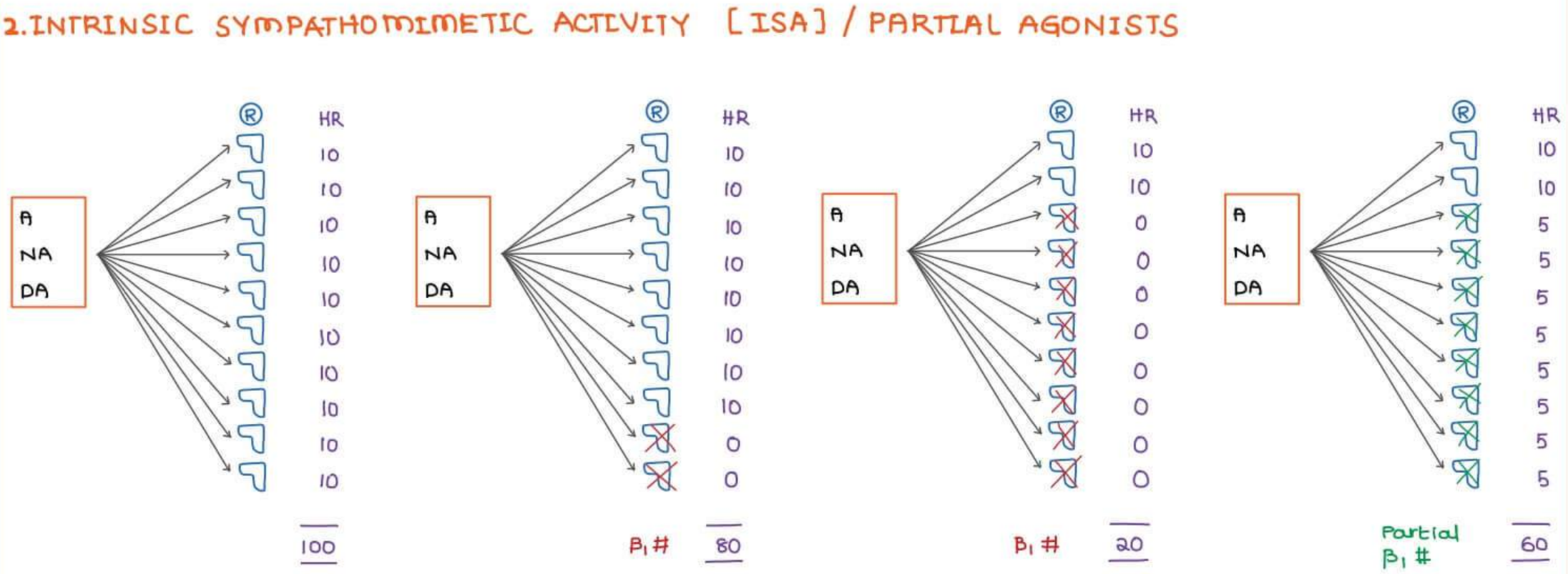
β_2 acts on	RESULT	β_2 #	C/I
Bronchus	Bronchodilatⁿ	Bronchoconstrictⁿ	Asthma
Blood vessels	vasodilatⁿ	vasoconstrictⁿ	Peripheral vas. Dz
Liver	hypoglycamia reversal	stop reversal	DM

1. β_1 # or CARDIOSELECTIVE or 2nd GENERATION β

New → NEBIVOLOL
Beta → BETAXOLOL
Blockers → BISOPROLOL
Act → ACEBUTOLOL
Exclusively → ESMOLOL [shortest acting β #, degraded by pseudocholineE.]
At → ATENOLOL
Myo → METOPROLOL
Cardium → CELIPROLOL

→ These are relatively safe in Asthma, PVD & DM

2. INTRINSIC SYMPATHOMIMETIC ACTIVITY [ISA] / PARTIAL AGONISTS



A. Normal phenomenon

1 ® stimulation → HR = 10

10 ® stimulation → HR = 10 × 10 = 100

B. β blocker usage in normal person

β blocker blocks 20% of ® → HR = 10 × 8 = 80

c. β blocker usage in β blocker in a β blocker sensitive person
   → β blocker blocks 80% of R → HR = 10 x 2 = 20
   → Severe bradycardia manifests
   → So, sensitivity should be checked ī HR monitoring in β blocker prescribed patients
   → In these patients, partial agonists are useful
      → less chances of causing severe bradycardia [Safer drug]
      → But less efficaceous

Contain → CELIPROLOL
Partial → PINDOLOL
Agonist → ALPRENOLOL
Activity → ACEBUTOLOL

3 MEMBRANE STABILIZING / Na^+ channel # / LOCAL ANESTHETIC PROPERTY
   → indicated in Arrhythmias
   → not indicated in Glaucoma
      → cornea is protected by corneal reflex [Protective Reflex]

Injury / Insult
↓
Stimulat^n of sensory n. of Trigeminal nerve
↓
Facial n. stimulated
↓
contraction of orbicularis oculi
↓
Eye closure
[CORNEAL REFLX]

→ corneal reflex is masked ī these drugs
→ DRUGS

Possess	→	PROPANALOL [maximum]
Membrane stabilising or	→	METOPROLOL
Local	→	LABETALOL
Anaesthetic	→	ACEBUTALOL
Property	→	PINDOLOL

4. WATER SOLUBILITY:
   →Water soluble beta blockers cannot cross blood brain barrier.
   →No CNS side effects like delirium, nightmares
   →But these beta blockers are contraindicated in Renal failure.

Water soluble beta blockers:
   A - Atenolol
   N - Nadolol (Longest acting beta blocker)
   S - Sotalol

Note:

Esmolol is lipid soluble beta blocker. It is Extremely Short acting Beta blocker (< 5 mins) because it is metabolized by Pseudocholinesterase like Succinylcholine.

5. 3RD GENERATION BETA- BLOCKERS

- Any β # which possess additional vasodilatory property

Additional Property	Drugs	Special points
α blockade	LABETALOL CARVEDILOL	Carvedilol possess additional anti-oxidant properties
NO release	NEBIVOLOL NIPRADILOL	
Ca channel blockade	CARVEDILOL	
K channel opening	TILISOLOL	
B_2 agonism	CELIPROLOL	It increases HDL (Beta blockers usually decrease HDL)

USES OF β BLOCKERS

β_1 # USES

1. HTN
2. classical Angina [C/I in variant angina]
3. MI
4. Chronic CHF [CI in acute CHF]
5. Arrhythmia

β_2 # USES

1. Glaucoma
2. Anxiety
3. Migraine
4. Essential tremors
5. Thyrotoxicosis

ADVERSE EFFECTS / C/I

β_1 #

1 ↓ Rate → Bradycardia
Sick sinus syndrome

2 ↓ conduction → AV Block

3 ↓ Contractility → Acute CHF

β_2 #

1. Asthma
2. Peripheral vascular Disease
3. DM

β # contraindicated in

A → Asthma
B → Block [AV]
C → CHF [Acute]
D → DM

ACTIVE & PASSIVE MYDRIASIS

EFFECT OF DRUGS ON EYE

→ Contraction of Sphicter pupillae → Active miosis
contraction of Dilator pupillae → Active mydriasis
Relative overactivity of Dilator pupillae → Passive mydriasis

→ Active miosis → caused by cholinergic drugs
→ Active mydriasis → caused by α_1 agonists
→ Passive mydriasis → caused by Anticholinergic drugs

GLAUCOMA

→ ↑ IOP
↑ Aqueous humor production
↓ Aqueous humor drainage

→ Aqueous Humor produced by ciliary blood vessels
→ α_1 → vasoconstriction ⊕
→ ADRENALINE, DIPIVEFRINE } stimulate α_1 receptors

→ APRACLONIDINE, BRIMONIDINE } stimulate post synaptic α_2 receptors

→ β_2 → vaso dilation → β_2 # can be used

↑ Aqueous outflow

↑ Trabecular outflow	↑ Uveoscleral outflow
→ major pathway → DRUGS → MIOTICS PILOCARPINE	→ $PGF_{2\alpha}$ / LATANOPROST – DOC for POAG

ADVERSE EFFECTS

→ **MIOTICS**

- Cataract
- Stenosis of NLD
- Spasm of Accommodation

→ **$PGF_{2\alpha}$ analogues (LATANOPROST)**

- Pigmentation of Iris (Heterochromia Iridis)
- Growth of eyelashes (Hypertrichosis)
- Fluid in macula (Macular edema)

→ **APRACLONIDINE**

- Lid retraction

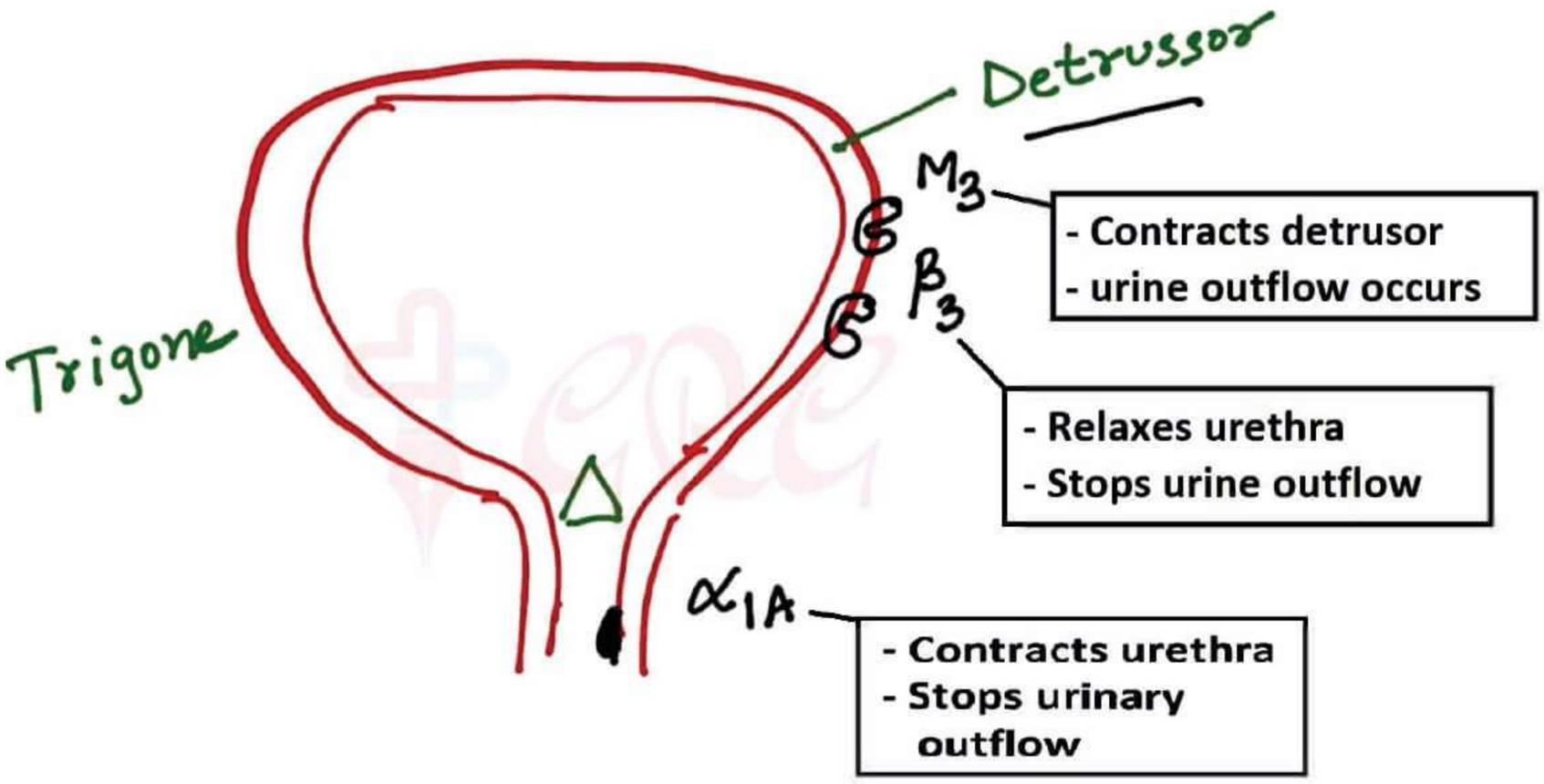
→ **BRIMONIDINE**

- Causes Brain suppression (Leads to Apnea)
- C/I in children < 2yrs

→ **EPINEPHRINE (ADRENALINE)**

- It is metabolized to form **Adrenochrome** – Causes Black pigmentation of Conjunctiva

BLADDER PHARMACOLOGY



URINARY INCONTINENCE:

It may be of 3 types:

- Urge incontinence
- Stress incontinence
- Overflow incontinence

Urge Incontinence	Stress Incontinence	Overflow Incontinence
Also called overactive bladder due to detrusor instability - Urge to urinate comes at lesser urine volume in the bladder - Patient not able to control urine outflow **Rx** Makes – Mirabegron (B_3 +) BladDAR – Darifenacin S – Solefenacin O – Oxybutynin F – Flavoxate – Fesoterodine T – Tolterodine – Trospium M3#	- Patient not able to control urine in situations where intra-abdominal pressure is increased eg. Jumping, exercise, coughing, laughing - d/t weakness of pelvic muscles **Rx** - Pelvic floor exercises - Surgery - DULOXETINE	- Patient gets no urge to urinate - Urine overflow occurs when the bladder is full Seen in : - Atonic bladder - BPH **Rx** **Atonic bladder** - M_3 agonists like BETHANELOL **BPH** - α_{1A} blockers like - TAMSULOSIN

CONGESTIVE HEART FAILURE

AIM

1. ↓ FLUID → DIURETICS
2. ↑ PUMPING → INOTROPICS

DIURETICS

LOOP DIURETICS	THIAZIDES
→ Strong	→ Weak
→ Short acting	→ Long acting
→ Used in CHF	→ Used in HTN
COMMON SIE	
→ ↓ Na^+	→ ↑ Sugar
→ ↓ K^+	→ ↑ Lipids
→ ↓ H^+	→ ↑ uric acid
→ ↓ Mg^{2+}	
Difference	
→ Loop looses Ca^{2+} → ↓ Ca^{2+}	→ ↑ Ca^{2+}

INOTROPICS

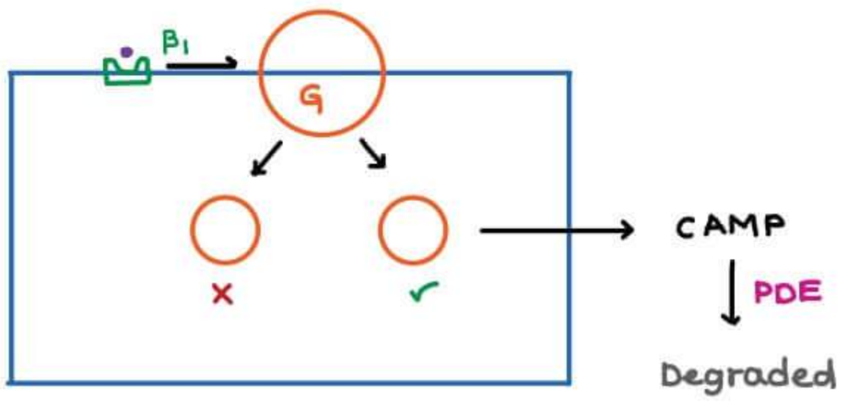
1. β_1 AGONISTS

DA → D_1, β_1, α_1

DOBUTAMINE → β_1

NA → $\alpha_1, \alpha_2, \beta_1$

ISOPRENALINE → β_1, β_2



2. PHOSPHODIESTERASE INHIBITORS [PDEI]

AMRINONE

MILRINONE

→ also acts on Blood vessels → VASODILATION

– aka → INODILATORS

– *Inotropic DOC for right heart failure are inodilators*

3 DIGITALIS / CARDIAC GLYCOSIDES

→ Digitalis inhibits $Na^+ K^+$ ATPase

↓

NCX Inhibition

↓

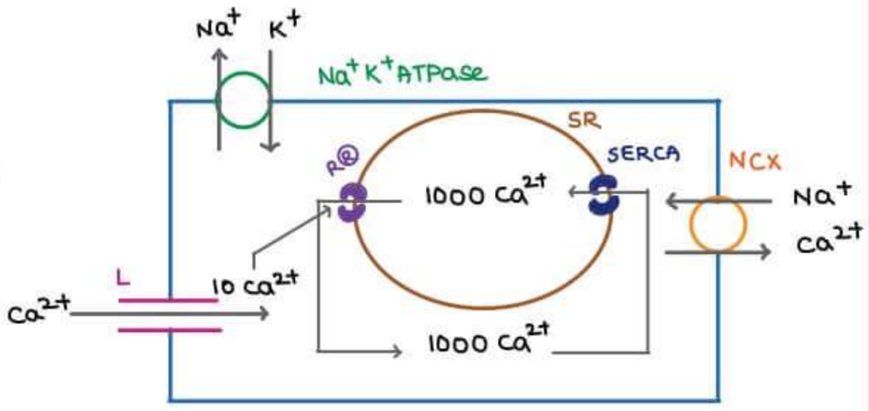
↑ Ca^{2+} in cytoplasm

↓

↑ Ca^{2+} in ER

↓

↑ Contractility



→ digitalis depot ↑ HR → DD ↑ in workload on heart

→ VAGOMIMETIC EFFECT

↓

↓ HR

↓ Conduction

→ Useful in ATRIAL FIBRILLATION

→ HR → 400 – 500 bpm

→ ineffective contractions → Fibrillations

→ aim of mx → ↓ ventricular rate

Digitalis ↓ses conduction from atrium to ventricles

DIGOXIN	DIGITOXIN [Withdrawn]
→ mainly excreted by kidney C/I Renal failure	→ mainly metabolised by liver C/I in liver failure

DIGOXIN

→ only inotropic drug that can be given ORALLY

→ AIE

1. Nausea, vomiting [mc]
2. Arrhythmias

mc arrhythmia	→	Ventricular bigeminy
most specific / characteristic	→	NPAT ī AV Block [Non paroxysmal Atrial Tachycardia ī AV Block]
not seen	→	Atrial flutter Mobitz Type II heart block

3 Gynaecomastia

4. XANTHOPSIA / YELLOW VISION

DRUGS CAUSING GYNAECOMASTIA		
D I	}	DIGOXIN
S	→	SPIRONOLACTONE
C	→	CIMETIDINE
O	→	OESTROGENS

DIGITALIS TOXICITY

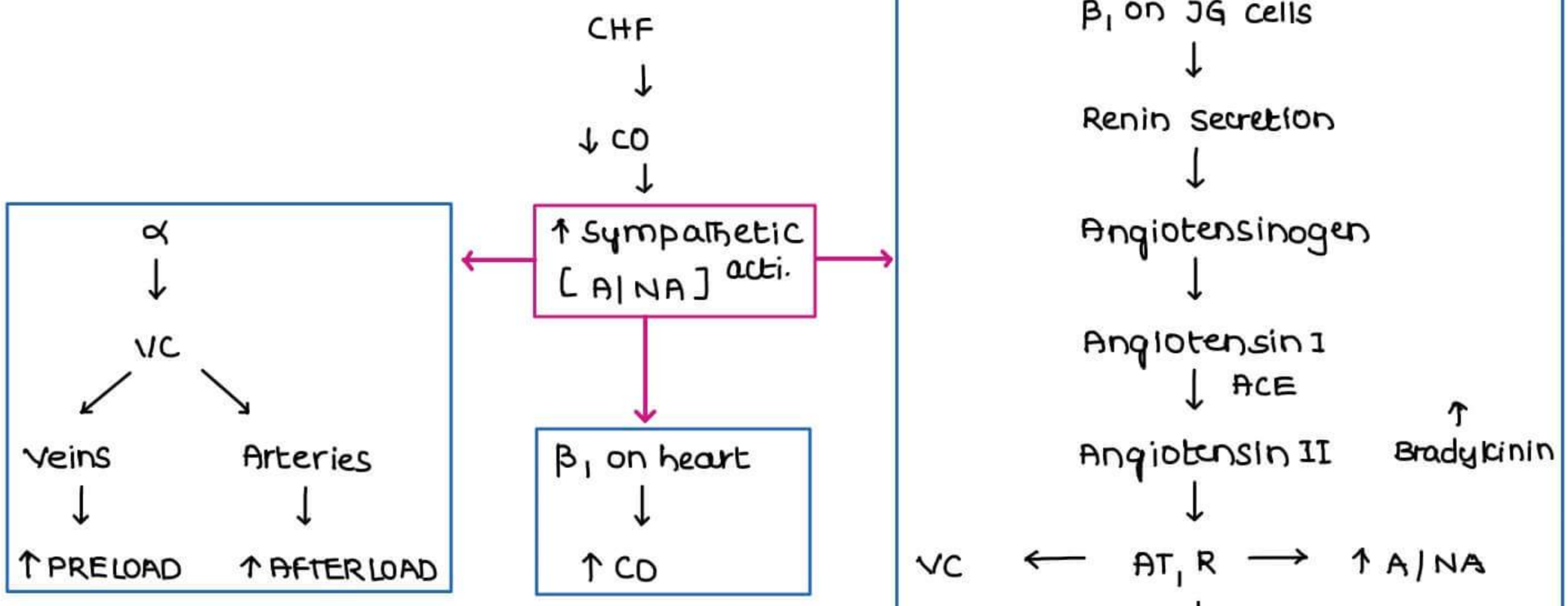
FACTORS ↑ing DIGITALIS TOXICITY

METABOLIC	DRUGS	PATHOLOGICAL
↑ Ca^{2+} ↓ K^+ ↓ $Mg2^+$	QUINIDINE (PK interaction; ↑ Plasma level) VERAPAMIL (PK interaction; ↑ Plasma level) AMIODARONE (PK interaction; ↑ Plasma level) THIAZIDES (PD interaction; Cause ↑ Ca^{2+}, ↓ K^+, ↓ Mg^{2+}	RENAL FAILURE: Digoxin LIVER FAILURE: Digitoxin

Mx OF DIGITALIS TOXICITY

1. correct the cause
2. DOC for Digitalis induced arrhythmias → LIGNOCAINE / PHENYTOIN
3. DIGIBIND for Severe poisoning

CHRONIC CHF



AIM OF TREATMENT

1. ↓ Work
2. ↓ Fluid
3. ↓ LVH [cardiac Remodelling]

1. ↓ WORK → VASODILATORS

VENODILATORS	ARTERIODILATORS	VENO + ARTERIO DILATORS
NITRATES	HYDRALAZINE	Na NITROPRUSSIDE ACEI ANGIOTENSIN RECEPTOR BLOCKERS

2. ↓ FLUID → LOOP DIURETICS
3. ↓ LVH [cardiac Remodelling]
   → These drugs ↓ MORTALITY
   1. β BLOCKER
   2. ACEI
   3. ANGIOTENSIN RECEPTOR BLOCKERS
   4. ALDOSTERONE ANTAGONISTS

β BLOCKERS

CARVEDILOL

METOPROLOL

BISOPROLOL

→ *Beta blockers are contra-indicated in acute CHF.*

→ *Beta blockers are used in chronic CHF and these can decrease mortality by reversing LVH*

→ *Dose of beta blocker should be gradually increased in CHF because high dose beta blocker may cause decompensation which leads to Acute Heart Failure. So, beta blockers should be started with 1/10th of final dose which is gradually increased every 2 to 3 weeks to reach the final dose in around 2 to 3 months.*

→ *Most commonly used beta blocker in CHF is carvedilol.*

ALDOSTERONE ANTAGONISTS / POTASSIUM SPARING DIURETICS

SPIRONOLACTONE → cause gynaecomastia

EPLERONONE → -

ACEI [ACE INHIBITORS]

→ also inhibit Bradykinin metabolism [↑ Bradykinin]

→ SIE → Dry Cough

Angioedema

→ DRUGS

→ CAPTOPRIL		
→ LISINOPRIL		
→ ENALAPRIL	→	Enalaprilat
→ RAMIPRIL	→	Ramiprilat
→ PERINDOPRIL	→	Perindoprilat
→ MOEXIPRIL	→	Moexiprilat

} Active forms

A	→	Active
C	→	Captopril
L	→	Lisinopril

→ ADVERSE EFFCTS

C	→	Cough
A	→	Angioedema
P	→	Prodrugs except captopril & Lisinopril
T	→	Taste alteration [Dysgusea]
O	→	Orthostatic / Postural hypotensⁿ [max ↕ captopril]
P	→	C/I in pregnancy
R	→	C/I in B/L Renal Artery stenosis
I	→	C/I in Increased K^+
L	→	Lower the risk of Diabetic Nephropathy

ARBs

T	→	Taste alteration [Dysgusea]
O	→	Orthostatic / Postural hypotensⁿ
P	→	C/I in pregnancy
R	→	C/I in B/L Renal Artery stenosis
I	→	C/I in Increased K^+
L	→	Lower the risk of Diabetic Nephropathy

ARBs [ANGIOTENSIN [AT_1] RECEPTOR BLOCKERS]

LOSARTAN	S	→ Selective
VALSARTAN	A	→ AT_1
TELMISARTAN	R	} Receptor
IRBESARTAN	T	
EPROSARTAN	A	} Antagonists
CANDESARTAN	N	

→ TELMISARTAN

→ also stimulates PPAR - γ

→ used to Reverse Insulin Resistance

LOSARTAN

→ cause ↓ in uric acid

BNP [Brain Natriuretic Peptide]

→ cause Natriuresis [↓ Na^+]

→ cause vasodilation

BNP

↓ NEP [Neprilysin]

Degradatⁿ

1. NESIRITIDE

→ Recombinant BNP

→ not given orally, given iv

→ Short acting

→ Used for acute cases

2. NEP INHIBITORS

SACUBI TRIL → Effective orally

ECADO TRIL

3 VASOPEPTIDASE INHIBITORS

→ Inhibit both ACE & NEP

→ OMAPATRILAT

SAM PATRILAT

→ S/E → cough

Angioedema

4. ARNI (ANGIOTENSIN – RECEPTOR BLOCKER + NEP INHIBITOR)

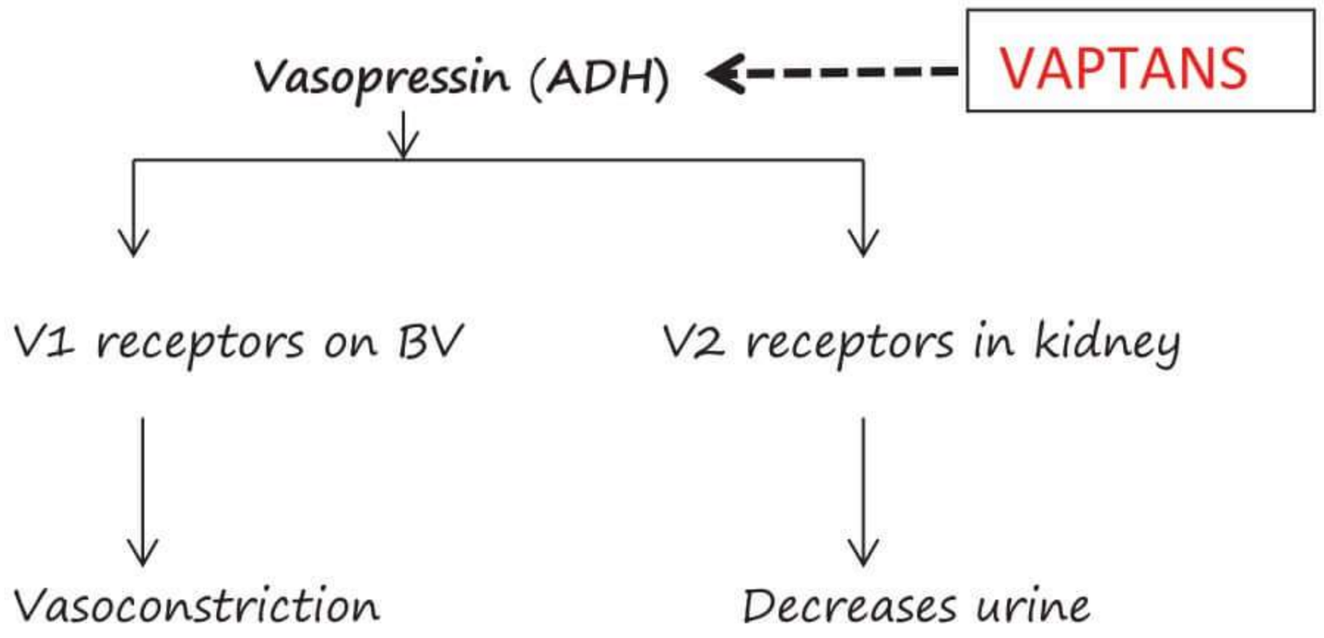
Valsartan (ARB) + Sacubitril (NEP inhibitor)

5. FUNNY CURRENT BLOCKER

IVABRADINE:

- Acts by causing BRADYcardia
- Acts by blocking funny current (I_f) in S.A node by blocking Na channels
- S/E – ↓ in Visual Acuity

6. VASOPRESSIN ANTAGONISTS:



- In C.H.F, we need to reverse actions of vasopressin (i.e. vasodilation & ↑ urine output is required), so these receptors should be blocked → Done by Vaptans

VAPTAN – VAsoPressin ANtagonist

CONIVAPTAN

- Given by I.V route

TOLVAPTAN

- Given orally
- Approved in APKD (autosomal dominant adult polycystic kidney disease)

ANGINA PECTORIS

I CLASSICAL / EXERTIONAL

II VARIANT
PRINZMETAL
VASOSPASTIC

CLASSICAL ANGINA PATHOLOGY

→ dlt atherosclerosis of small branches of coronary artery, Ischemia occurs

ISCHEMIA
↓
↑ Effective Diameter OF artery
↓
NO pain at Ⓝ activity

→ During Exercise / Exertion, ↑ effective diameter of artery not suffice for compensation → PAIN occurs

AIM OF TREATMENT → ↓ Work on heart

VARIANT ANGINA PATHOLOGY

→ dlt SPASM OF MAIN CARONARY ARTERY

→ Pain @ rest occurs

→ AIm of TREATMENT → Dilation of coronary artery

DRUGS

I NITRATES

II CALCIUM CHANNEL BLOCKERS

III β BLOCKERS

IV POTASSIUM CHANNEL OPENERS

I NITRATES

Mechanism of action:

Nitrates

↓ Metabolized to

Nitric oxide

↓ stimulates

Guanylate cyclase enzyme

↓ which helps in formation of

↑ CGMP

↓ which activates

Protein kinase G

↓ inhibits action of

Myosin light chain kinase

↓

VASODILATION

→ Nitrates

↓ Aldehyde dehydrogenase (ALD) – more in veins > Arteries

NO

→ ALD either present in cytoplasm or in mitochondria

→ **Glyceryl Tri nitrate** is activated by mitochondrial aldehyde dehydrogenase while all other nitrates activated by cytoplasmic aldehyde dehydrogenase.

→ MOA of NO in classical angina – ↓ Preload

→ MOA of NO in variant angina – Dilation of coronary arteries

→ DRUGS

GLYCERYL TRINITRATE / NITROTRIGLYCERATE [GTN/NTG]
ISOSORBIDE DINITRATE [IDN]
ISOSORBIDE MONONITRATE [IMN]
PENTA ERYTHRYTAL TETRA NITRATE [PETN]
AMYLNITRITE [AN]

→ GTN/NTG & IDN
  → has high 1st pass metabolism
  → Sub lingual route preferred
  → Doc for acute attack of angina

→ IMN has minimum 1st pass metabolism
→ Longest acting → PETN
→ Shortest acting → AN
→ NITRATE FREE PERIOD
  → tolerance occur if nitrates continuously present
  → to avoid tolerance, 6-8 hrs of Nitrate free period should be maintained

→ NITRATES
↓
NO
↓
CGMP

SILDENAFIL
↓⊖
Phosphodiesterase → Degraded

↓
Vasodilation

NITRATES should not be given ī SILDENAFIL [Risk of Severe hypotension]

Uses of Nitrates:

A – Angina

B – Biliary colic

C – Cyanide poisoning (Drug of choice – Hydroxocobalamin)

D – Dil Ka Daura (MI)

E – Esophageal spasm

F – Failure (CHF)

Cyanide poisoning:

Mechanism:

→ Cytochrome oxidase enzyme is involved in electron transport chain to produce ATP. When it binds to cyanide during cyanide poisoning, the energy production (ATP) decreases.

→ **Hemoglobin + Amyl nitrite (Inhalational route)**

↓ forms

Methemoglobin

↓ in cyanide poisoning it forms

Cyanmethemoglobin (TOXIC METABOLITE)

↓ Sodium thiosulphate given

Sodium thiocyanate, is formed and excreted by kidney

→ Hydroxocobalamin (vit b12) if given in cyanide poisoning, it binds with cyanide to form cyanocobalamin (vit b12).

→ so one form of vitamin B 12 is converted into another form.

→ Hydroxocobalamin is the drug of choice / Antidote of choice for Cyanide poisoning which is administered in IV route.

II. CALCIUM CHANNEL BLOCKERS

→ CALCIUM CHANNELS
  → L TYPE → present in CVS
  → T TYPE → present in CNS

→ L - CALCIUM CHANNEL BLOCKERS

	BLOOD VESSELS	HEART RATE		
		DIRECT	INDIRECT	NET
VERAPAMIL	vasodilation ↓ DBP	↓↓↓	↑	↓↓
DILTIAZEM	vasodilation ↓ DBP	↓↓	↑	↓
DHP [DIHYDROPYRIDINES] NIFEDIPINE AMLODIPINE NICARDIPINE CLEVIDIPINE	vasodilation ↓ DBP	↔	↑	↑

DIHYDROPYRIDINES should be avoided in angina [↑HR]

Fast acting calcium channel blocker

→ Nifedipine
→ Clevidipine
} Can cause severe ↑↑ HR → Precipitate Angina

Therefore, these drugs are not used in Angina

Long acting drugs

→ Amlodipine and Nicardipine gradually cause vasodilation. Therefore, Tachycardia causing potential is very less. These drugs are used in Angina.

→ DOC for variant angina – CCB

→ Nimodipine – Cerebro-selective CCB

↓

Used in subarachnoid hemorrhage

→ Clinidipine – Blocks both L– Ca^{2+} # and N- Ca^{2+} channels

ADVERSE EFFECTS OF CALCIUM CHANNEL BLOCKERS

→ Headache
→ Constipation
→ Gum hypertrophy

III POTASSIUM CHANNEL OPENER

NICORANDIL

→ NO Releaser + K^+ channel opener

IV β BLOCKERS

β #
↓
↓ HR
↓
↓ WORK
↓
useful in classical angina

→ β Blockers are C|I in variant angina

NEW DRUGS

I BRADYCARDIAC AGENT → IVABRADINE

Na^+ channels in SA Node
↓
Funny current [I_f]

I VA BRADI NE
I_f blocker
S|E → visual acuity
Bradicardiac agent

→ Ivabradine inhibit Na^+ channel [funny current]
→ S|E → ↓ visual acuity
→ recently approved for CHF

2. Rho KINASE INHIBITOR → FASUDIL

→ Rho kinase → causes vasoconstriction

→ Rho kinase ⊖ → causes vasodilation

→ FASUDIL – Used for Angina

→ NETARSUDIL – New Rho kinase inhibitor

– Approved for glaucoma treatment

3 METABOLIC MODULATORS

→ GLUCOSE + 100 O_2 → 100 ATP [Other parts of Body]

Fatty acids + 200 O_2 → 100 ATP [Heart]

→ FA require more O_2 for same energy production

→ METABOLIC MODULATION → Making heart to utilise glucose instead of fatty acids

DRUGS

1 TRIMETAZIDINE

2 RANOLAZINE

→ also acts by blocking Na^+ channels along ↓ FA metabolism inhibition

MI

→ ANGINA → Myocardial Ischemia [Reversible]

MI → Myocardial Infarction [Irreversible]

→ NON – STEMI

Management

M → MORPHINE

O → OXYGEN

N → NITRATES

A → ASPIRIN

→ STEMI

MANAGEMENT

S → STREPTOKINASE

O → OXYGEN

N → NITRATES

A → ASPIRIN

M → MORPHINE

BLOOD PRESSURE → Lateral pressure exerted by moving column of **BLOOD** on **WALL OF BLOOD VESSEL**

ANTI HYPERTENSIVE DRUGS

1. DIURETICS
   - → ↓ BLOOD VOLUME
   - → ↓ HARDNESS OF BLOOD VESSEL [↓ S. Sodium]

2. VASODILATORS
3. SYMPATHETIC SYSTEM BLOCKERS
4. RAAS BLOCKERS

I DIURETICS

LOOP DIURETICS	THIAZIDES
→ Strong	→ Weak
→ Short acting	→ Long acting
	→ used as 1st line drugs for HTN

II VASODILATORS

1. NO RELEASERS
   - → Na NITROPRUSSIDE
   - → HYDRALAZINE

   - → Both are Fast acting → used in HTN Emergencies
   - → Na Nitroprusside
     - → MICRODRIP SET used
       - – 64 drops → 1 ml
     - → long term use → Leads to CYANIDE POISONING
       - → Antidote → HYDROXOCOBALAMINE
   - → HYDRALAZINE
     - → metabolised by → Acetylation
     - → S|E → SLE

2. L – CALCIUM CHANNEL BLOCKERS
   - → VERAPAMIL
     DILTIAZEM
     DHP

3. K^+ CHANNEL OPENERS
   - M → MINOXIDIL
   - D → DIAZOXIDE
   - H → HYDRALAZINE

DRUGS CAUSING HIRSUITSM		
P	→	PHENYTOIN
C	→	CYCLO SPORINE
M	→	MINOXIDIL

→ MINOXIDIL causes hair growth
  → used for Alopecia
  → avoided in young females

→ *MINOXIDIL is a prodrug [itself is inactive]*
  - *It must be metabolized to form minoxidil sulphate [active metabolite]*
  - *Activation of minoxidil is a phase II reaction.*

→ DIAZOXIDE
  → Decreases the release of Insulin
    → CII in DM
    → used in INSULINOMA

III SYMPATHETIC SYSTEM BLOCKERS

1. GANGLION BLOCKERS

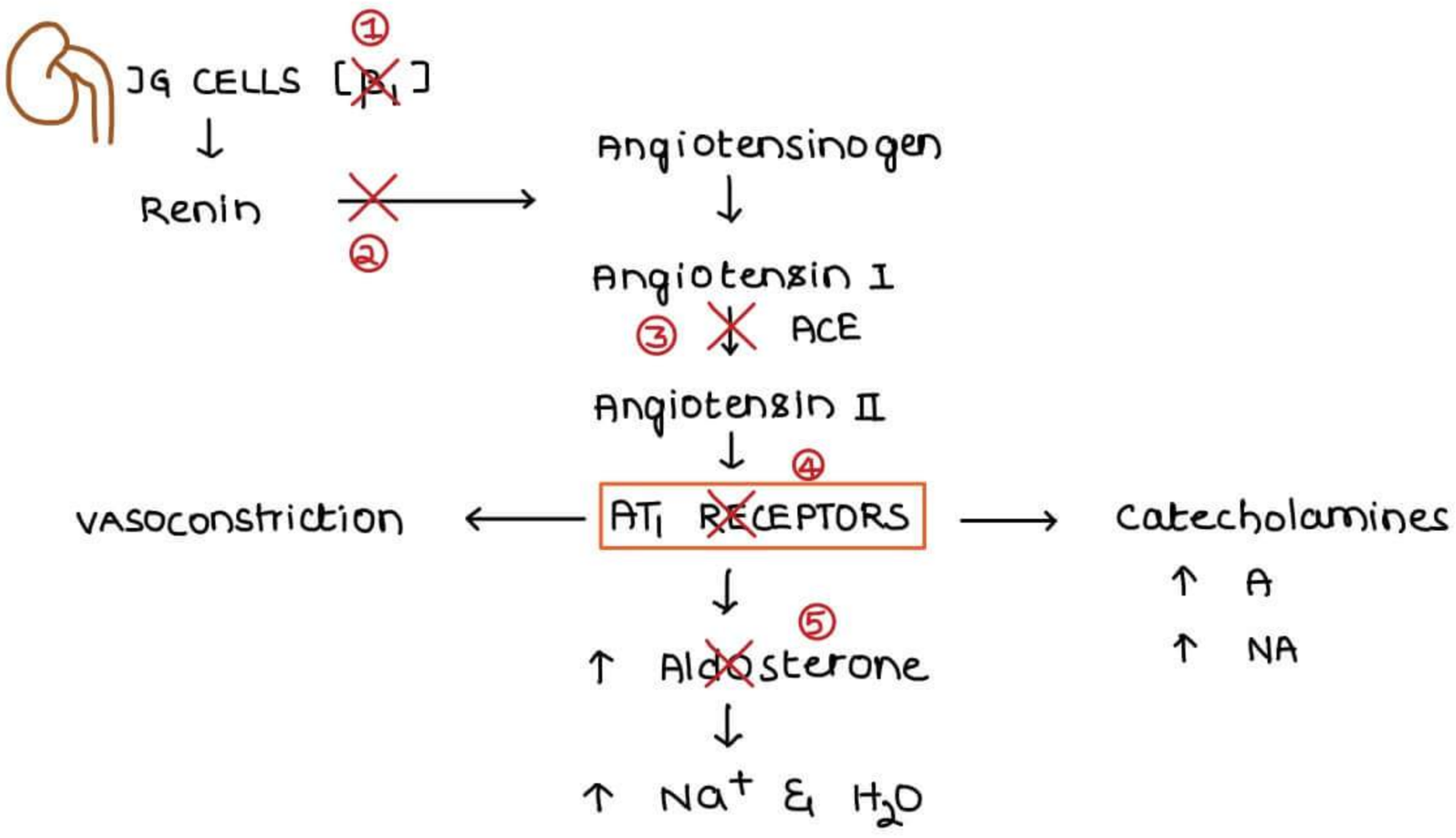
→ N_N Receptor antagonists
→ TRIMETHAPHAN
  HEXAMETHONIUM
→ mainly used as Antidote for NICOTINIC POISONING

2. α_2 AGONISTS

→ CLONIDINE, METHYLDOPA } Both are safe in pregnancy; Both can cause dry mouth & sedation
→ CLONIDINE sudden stoppage causes REBOUND HTN
→ METHYLDOPA can cause Hemolytic Anaemia

3. α & β BLOCKERS

IV RAAS BLOCKERS [RAAS → Renin Angiotensin Aldosterone System]



RENIN INHIBITORS

→ ALISKIREN
REMIKIREN
ENALKIREN
} ORAL DRUGS

RENIN INHIBITORS → ALISKIREN, REMIKIREN, ENALKIREN

RENIN RELEASE INHIBITORS → β BLOCKERS

TREATMENT OF HTN

JNC – 8 GUIDELINES

Category	Systolic Blood Pressure	Diastolic Blood Pressure
Normal	< 120	< 80
Pre hypertension	120 – 139	80 – 89
Hypertension (HTN)	≥ 140	≥ 90
Grade 1 HTN	140 – 159	90 – 99
Grade 2 HTN	≥ 160	≥ 100

1. BP ≥ 140/90 [any one (SBP/DBP) can be considered]
2. START Rx → BP ≥ 140/90 not controlled inspite OF LIFESTYLE MODIFICATION [Low Na^+ diet & regular exercise]
3. FIRST LINE DRUGS [IF there are no other compelling indications]
   - A → ACEI / ARB
   - C → CCB
   - D → DIURETICS [Thiazides]
4. GOAL
   - → < 140/90 in all patients
   - → < 150/90 in > 60 yrs patients tout DM or CKD
   - → Both SBP & DBP should be corrected
5. DOC

	JNC – 8	HARRISON
HTN in Pregnancy	→ METHYLDOPA	→ Oral LABETALOL
HTN Emergency in Pregnancy	→ HYDRALAZINE	→ IV LABETALOL
HTN	→ THIAZIDES	→ THIAZIDES
HTN Emergency	→ NITROPRUSSIDE	→ NICARDIPINE

AMERICAN SOCIETY OF HYPERTENSION GUIDELINES:

Category	Systolic blood pressure	Diastolic blood pressure
Normal	<120	< 80
Elevated BP	120 – 129	< 80
HYPERTENSION (HTN)	≥130	≥ 80
HTN GRADE 1	130 – 139	80 – 89
HTN GRADE 2	≥140	≥ 90

→ Grade 1 hypertension does not require any medical treatment whereas Grade 2 hypertension requires medical treatment.

ANTI HTN DRUGS SAFE IN PREGNANCY

BETter → β # [LABETALOL]

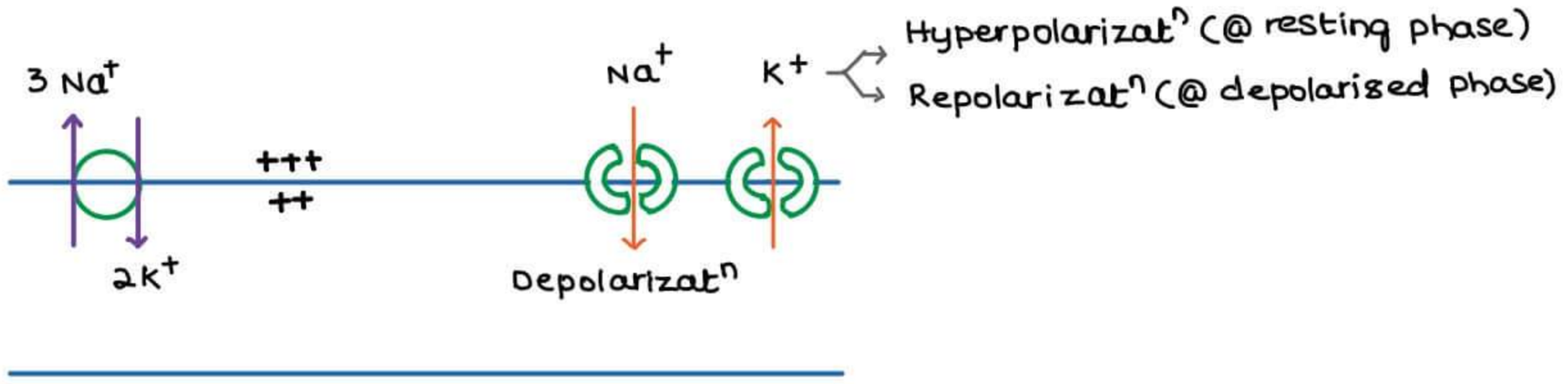
Mother → METHYLDOPA

care → CLONIDINE

During → DHPs

HYpertensive → HYDRALAZINE

PRegnancy → PRAZOSIN [α #]



RESTING MEMBRANE POTENTIAL [−90 mV]

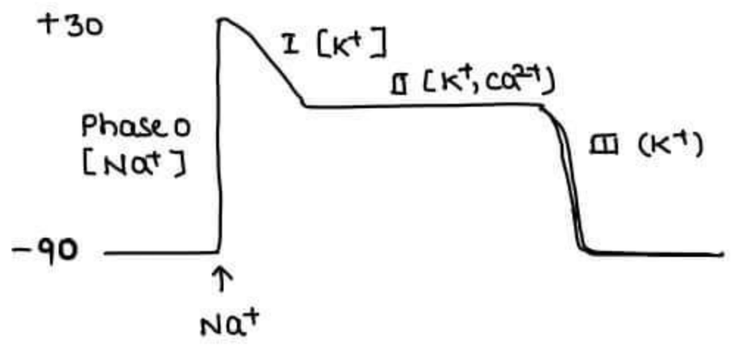
→ Relative negative charge inside the membrane dlt $Na^+ K^+$ ATPase

DEPOLARIZATION → dlt Na^+ entry through Na^+ channel

HYPERPOLARIZATION → dlt K^+ exit through K^+ channel at resting state

REPOLARIZATION → dlt K^+ exit through K^+ channel at depolarizatn state

ACTION POTENTIAL



1. Na^+ CHANNEL BLOCKERS

→ acts by ↓ SLOPE [$^{dV}/_{dt}$] OF Phase 0

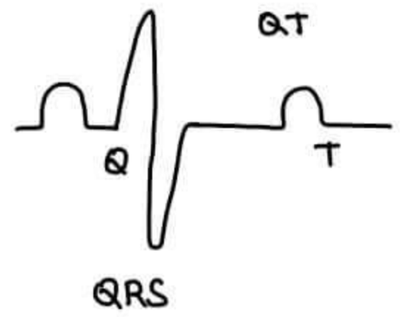
2 K^+ CHANNEL BLOCKERS

→ ↑ Action Potential duration [APD]

→ QT INTERVAL → Depolarisatn + repolarasation

→ manifests as ↑ QT interval on ECG

→ TORSADES' DE POINTES [TDP] → ↑ QT Interval



3 K^+ CHANNEL OPENERS

→ ↓ Action Potential Duration [APD]

ANTI ARRHYTHMIC DRUGS

VAUGHAN WILLIAMS CLASSIFICATION

→ Based on predominant mechanism of action

CLASS I → Na^+ CHANNEL BLOCKERS

CLASS II → β BLOCKERS

CLASS III → K^+ CHANNEL BLOCKERS

CLASS IV → Ca^{2+} CHANNEL BLOCKERS

CLASS V → OTHERS

CLASS I → Na^+ CHANNEL BLOCKERS

→ ↓ Slope of phase 0

→ I_a → block K^+ channels → Precipitates TDP

I_b → Open K^+ channels

I_c → no effect on K^+ channels

Class Ia drugs	Class IIb drugs	Class IIIC drugs
→ Quinidine → Procainamide	→ Lignocaine → Phenytoin → Tocainide	→ Encainide → Flecainide → Propafenone
→ Causes **QT prolongation**	→ Used only for **Ventricular arrhythmia** → **Lignocaine** is the DOC for most of the arrhythmias	Used for **WPW syndrome** (Treatment of choice for WPW syndrome is radiofrequency ablation of aberrant pathway

CLASS II → β BLOCKERS

→ used in Tachy arrhythmias

CLASS III → K^+ CHANNEL BLOCKERS

B → BRETYLIUM

I → IBUTILIDE

N

D → DOFETILIDE

A → AMIODARONE

S → SOTALOL

→ SOTALOL has both CLASS III [major] & class II Actions

AMIODARONE

→ Longest acting [$t_{1/2}$ → > 3 WKS] anti arrhythmic drug

→ MOA

1. Na^+ channel Blocker
2. β blocker
3. K^+ channel Blocker [main action]
4. Ca^{2+} channel Blocker

→ Indicated in all arrhythmias except TDP

→ Adverse effect of amiodarone:

- The: Thyroid(hypo/hyper) (40% iodine is present in amiodarone)
- Periphery of: peripheral neuropathy
- My: Myocardial depression
- Lung: Lung fibrosis
- Liver: Liver toxicity
- Cornea is: corneal deposits
- Photosensitive: Photosensitivity: Rash on exposure to sun (bluish: blue man syndrome)

→ DRONEDARONE: Amiodarone without iodine but less effective and less antiadrenergic property.

→ BRETYLIUM:

- Was used for ventricular fibrillation
- Pharmacological defibrillator

→ IBUTILIDE AND DOFETILIDE:

- Used for atrial fibrillation
- Drugs like CCB, beta blockers and digoxin are also use for treatment of atrial fibrillation but these mainly control ventricular rate.
- Ibutilide and Dofetilide converts Atrial Fibrillation to normal sinus rhythm therefore it controls atrial rate also.

DRUGS CAUSING PULMONARY FIBROSIS:

- Cyclophosphamide
- Busulfan
- Methotrexate
- Amiodarone
- Bleomycin

CLASS IV → L - Ca^{2+} CHANNEL BLOCKERS

VERAPAMIL

DILTIAZEM

DHPs [not used]

→ used in Tachyarrhythmias

Should not combine ī β blocker [Risk of severe cardiac depression]

CLASS V → OTHERS

- DIGOXIN – used for AF
- ATROPINE – DOC for Bradycardia & AV block
- ADENOSINE
  - Shortest acting antiarrhythmic drug ($t_{1/2}$ < 10s)
  - DOC for PSVT
  - It is given as **Rapid IV push** in the Central veins
- MAGNESIUM – DOC for Long QT Syndrome / Torsades' De Pointes

DYSLIPIDEMIA

ANTI - DYSLIPIDEMICS

STATINS

MOA

1. Inhibit HMG - COA Reductase
2. compensatory ↑ of LDL - ®
3. Cholesterol is taken from blood
4. ↓ Serum cholesterol

Includes

ATORVASTATIN

ROSUVASTATIN [Longest Acting]

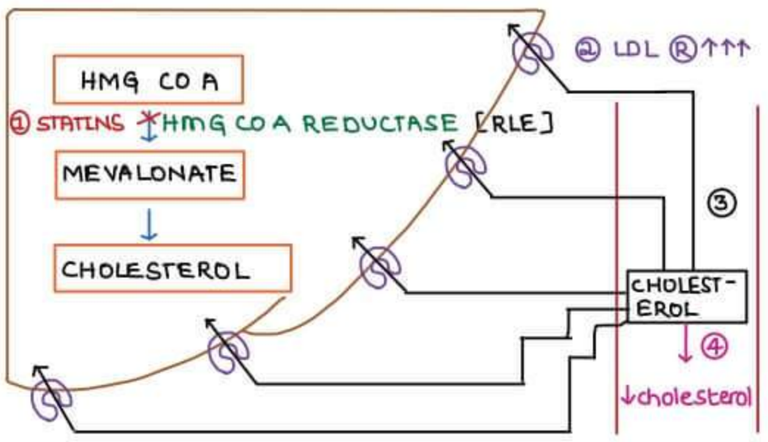
PRAVASTATIN

SIMVASTATIN

FLUVASTATIN

CERIVASTATIN

PITAVASTATIN



NON ANTI DYSLIPIDEMICS
ENDS ī STATIN
CILASTATIN
PENTOSTATIN
SOMATOSTATIN

1. Statins have maximum LDL-cholesterol lowering potential
2. Given @ Late evening / night

→ Atorvastatin & Rosuvastatin are long acting, can be given at anytime of the day

3. ADVERSE EFFECTS
   Myopathy → Risk further ↑'d ĩ FIBRATES
   Hepatotoxicity
4. ↑ DM
5. PLEIOTROPIC EFFECTS [Beneficial]
   PL → plaque stabilizatⁿ
   E → ↓ Endothelial dysfunction
   I → ↓ Inflammation
   O → ↓ Oxidative stress
   TR → ↓ Thrombosis
   Opic

SPECIAL POINTS ABOUT INDIVIDUAL STATINS

Simvastatin and Lovastatin:

- Prodrugs
- Maximum CNS Penetration

Rosuvastatin

- Longest acting

Pravastatin

- Negligible metabolism by CYP3A4
- Risk of myopathy is very less
- Very less interaction with meals

INTESTINAL CHOLESTEROL ABSORPTION INHIBITOR [EZETIMIBE]

- Inhibit NPLICI in the intestine (so cholesterol can't be absorbed)
- There is upregulation of HMG-COA reductase on the liver, so liver will start synthesizing more cholesterol
- So ezetimide is combined with statins to Prevent tolerance

FIBRATES

→ includes

CLOFIBRATE

FENOFIBRATE

BEZAFIBRATE

GEMFIBROZIL

→ act by PPAR α stimulation

↓

↑ LPL [Lipo protein Lipase]

↓

↓ Triglycerides

→ Fibrates have max. TG lowering potential

BILE ACID BINDING AGENTS [BABA]

→ includes

CHOLESTYRAMINE

COLESTIPOL

CHOLESEVALAM

→ MOA

ENTERO HEPATIC CYCLE → Bile Acid carry Substance From Gut & releases in blood & reabsorbed

BABA interupts enterohepatic cycle & BA excreted
Liver Synth s'zes BA r ch l sl l > l ch l sterol

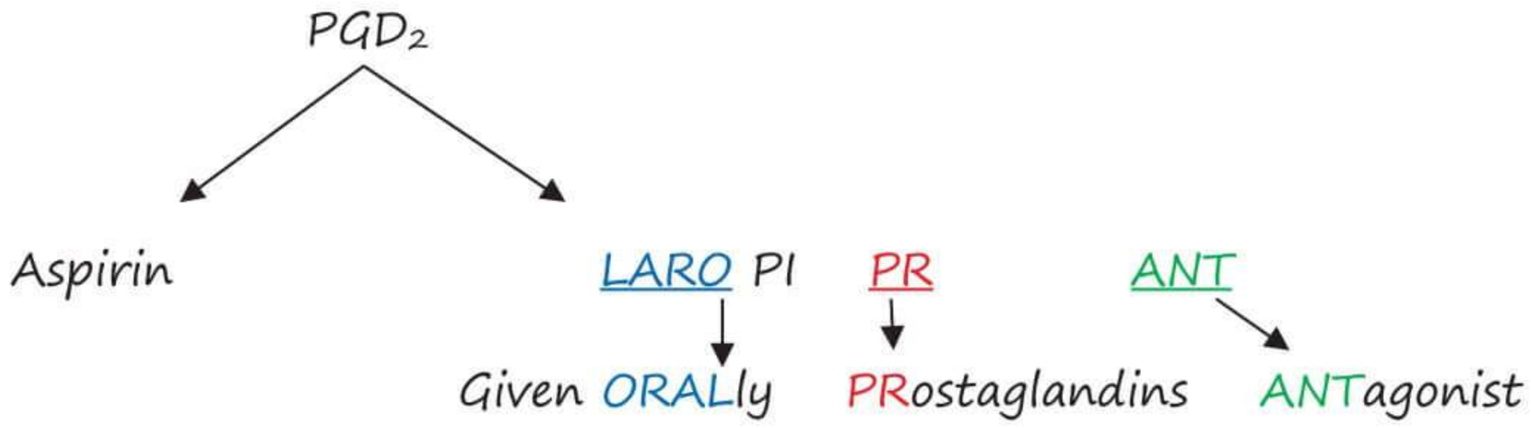
→ DOC in children & pregnancy [safe drugs]

→ cholestyramine & colestipol not easily palatable

(Cholesevalam can be taken orally)

NIACIN [VITAMIN B_3]

- *Has MAXIMUM HDL-CHOLESTEROL INCREASING potential*
- *Only drug that DECREASES LIPOPROTEIN A*
- *Least expensive*
- *Compliance limiting adverse effects are flushing and itching (due to release of PGD_2)*
- *This can be prevented by aspirin or Laropiprant.*



- *Specifically indicated for niacin induced flushing / itching*
- *Because it will block the action of PGD_2*

- **Other side effects of niacin**
    - Hyperuricemia
    - Hepatotoxicity
    - Insulin resistance

NEW DRUGS

1. PCSK – 9 (PRE-PROTEIN CONVERTING SUBTILISIN KEXIN – TYPE 9) INHIBITORS

- PCSK-9 binds to LDL– receptors and take it to lysosomes that result in breakdown of LDL receptors.
- Thus PCSK 9 inhibitors prevent breakdown of LDL receptors. When more LDL receptors are present, they can take up more LDL-cholesterol from blood.
- So, we can use these drugs as hypolipidemic drugs.

Inhibition of PCSK – 9 formation	**Monoclonal antibody against PCSK-9**
INCLISIRAN	**ALIROCUMAB**
-Small molecule inhibitor of RNA	**EVULOCOMAB**

2. MTP (MICROSOMAL TRIGLYCERIDE TRANSPORT PROTEIN) INHIBITORS

- Triglycerides are packed in VLDL by MTP

- Drug inhibiting MTP is **LOMITAPIDE**

3. MIPOMERSEN

- Antisense oligonucleotide against Apo B_{100}
- Decrease all Apo B_{100} containing lipids

4. CETP (CHOLESTEROL ESTER TRIGLYCERIDE TRANSPORT PROTEIN) INHIBITORS

- Normally LDL cholesterol deposit in the tissues
- HDL will take up the cholesterol and bring back into the liver (reverse cholesterol transport).
- VLDL and LDL try to exchange cholesterol ester of HDL with triglyceride present in that
- This exchange is done by CETP
- Thus CETP inhibitors will increase HDL-cholesterol
- Drugs inhibiting CETP – **ANACETRAPIB**

PULMONARY HYPERTENSION

CCB [Ca^{2+} CHANNEL BLOCKER]

IV VASODILATOR TESTING

→ IF positive, DOC → CCB

→ IF negative, DOC → ENDOTHELIN ANTAGONIST

BOSENTAN

AMBRISENTAN

MACITENTAN

PDEI [PHOSPHODIESTERASE INHIBITORS] → SILDENAFIL

PGI_2 ILOPROST

PGE_2 TREPROSTINIL

→ most effective drugs for pulmonary HTN

→ can't be given orally

SELEXIPAG

→ Prostacyclin agonist

→ can be given orally

SELE	→	Selective
XI	→	non injectable [oral]
P	→	PGI_2
AG	→	Agonist

RIOCIGUAT

→ Stimulate Guanylate cyclase → ↑ cGMP → vasodilation

-ypoa ren o — -ero

CORONARY STEAL PHENOMENON

→ Caused by Drugs which dilate small vessels only

→ d/t which blood supply to ischemic area is taken towards area receiving adequate blood

→ Coronary steal phenomenon is also known as **reverse Robinhood phenomenon**

→ **Shown by**

H → HYDRALAZINE

I → ISOFLURANE

D → DIPYRIDAMOLE

E → ENFLURANE

→ **Beta blockers** are found to cause **Robinhood phenomenon** as these increase the blood flow to the ischemic area as compared to non-ischemic area

SHOCK MANAGEMENT

→ Shock → ↓ Tissue perfusion

→ COLD EXTREMITIES

- Cardiogenic shock
- Hypovolumic shock

WARM EXTREMITIES

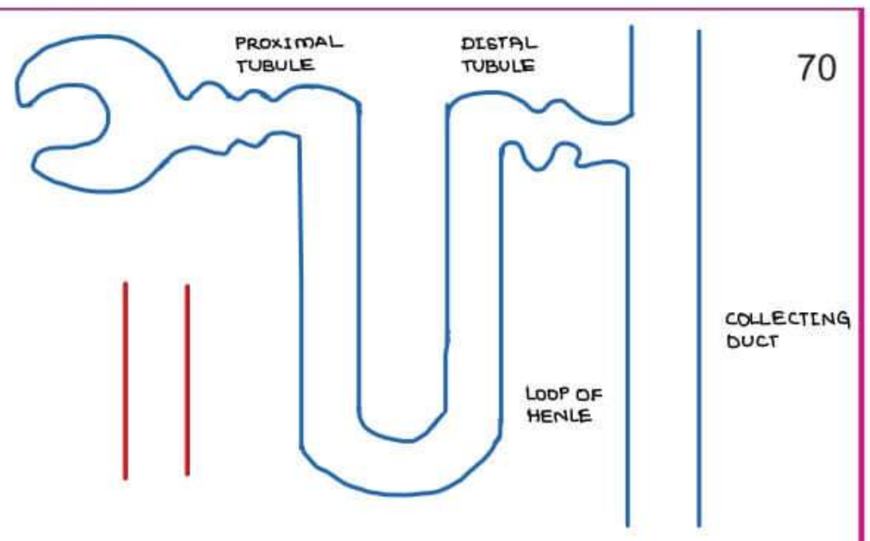
- Vasodilatory / distributive shock

→ DISTRIBUTIVE SHOCK

1. Septic shock
2. Anaphylactic shock
3. Neurogenic shock
4. Hypoadrenal shock

→ TREATMENT

1. CAB
2. FLUID REPLACEMENT
   - → CVP should be maintained b/w 8-12 mm of Hg
   - → NS or RL preferred
   - → blood given if required
3. VASOPRESSORS
   - → Septic Shock
     1. NA [DOC]
     2. PHENYLEPHRINE [in case of ↑ risk of arrhythmias]
     3. NA + VASOPRESSIN also used
   - → cardiogenic shock → DOC → NA > DA
   - → Anaphylactic Shock
     - → DOC → im ADRENALINE > SC ADRENALINE
       - → 1:1000 → 1g : 1000ml [1mg/ml]
       - → Dose → 5ml of 1:1000 concentratn
     - → 1:10,000 iv Adrenaline given in non responsive cases
4. SPECIFIC TREATMENT
   1. Septic shock → Broad spectrum Antibiotics
   2. " d ad sh ck > Sl 'ds



DIURETICS

→ cause loss of Na^+ & H_2O in urine

AQUARETIC → cause loss of H_2O only

CLASSIFICATION based on Site of ACTION

1. OSMOTIC DIURETICS

→ includes MANNITOL

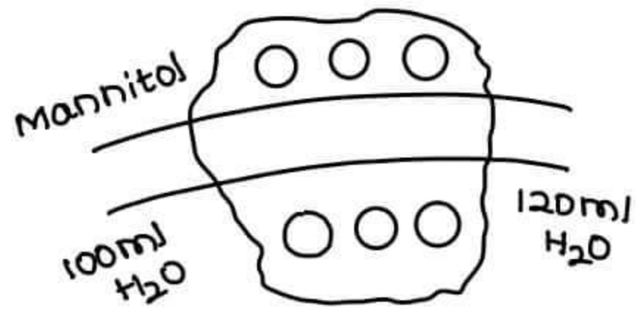
→ PROPERTIES

→ should be freely filterable

→ should not be reabsorbed

→ should not react chemically

→ should exert osmotic effect



USES:

- Glaucoma
- Cerebral edema
- Incipient renal failure

CONTRA-INDICATIONS:

- Cerebral hemorrhage
- Acute renal failure
- Pulmonary edema

2. CARBONIC ANHYDRASE INHIBITORS

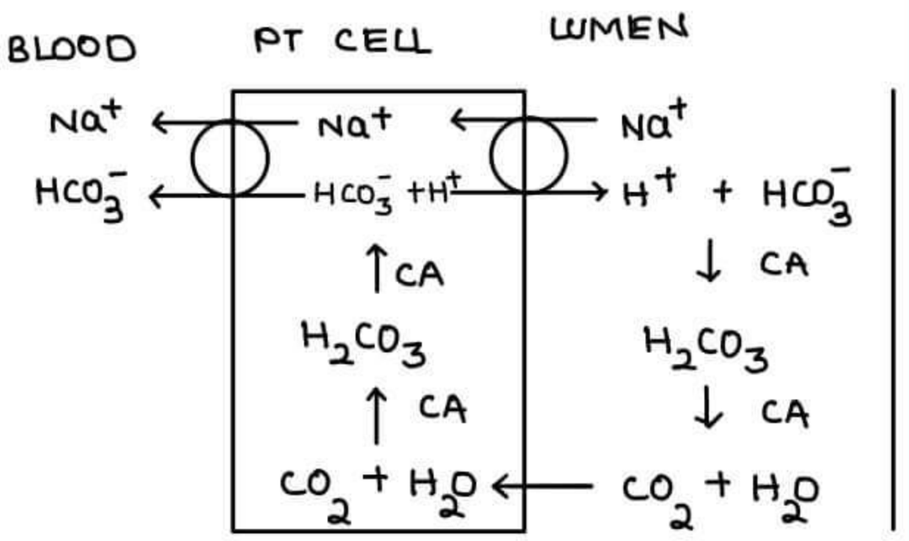
→ Acts on Proximal tubule

→ Inhibits carbonic anhydrase

→ causes loss of Na^+ & HCO_3^- in urine

↓ $Na^+ + H_2O$ → DIURESIS

↓ HCO_3^- → URINARY ALKALOSIS
METABOLIC ACIDOSIS



→ have self limiting action

→ includes

ACETAZOLAMIDE
BRINZOLAMIDE
DORZOLAMIDE
} given as eye drops

→ ACETAZOLAMIDE

→ can be given orally / Injectable form

INDICATIONS:

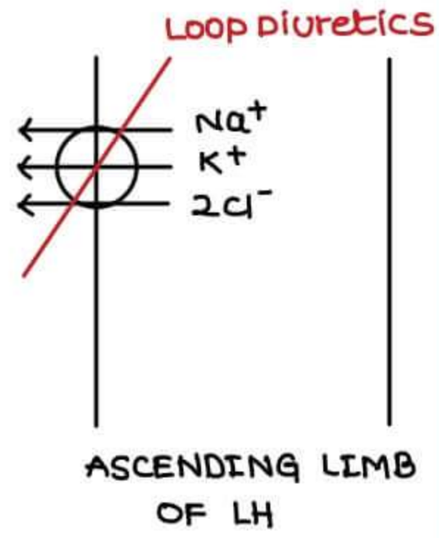
- Glaucoma (Angle closure glaucoma)
- Alkalinization of urine
- Mountain Sickness [DOC]
- Epilepsy

ADVERSE EFFECTS:

- Metabolic Acidosis
- Hypokalaemia [Max. Hypokalaemia among diuretics]
- Paraesthesia
- Renal Stones

CONTRA-INDICATION:

- Liver disease



3 LOOP DIURETICS

→ acts on ascending limb of loop of Henle

→ inhibits $Na^+ K^+ 2Cl^-$ symporter

→ includes

FUROSEMIDE

TORSEMIDE

BUMETANIDE

→ High ceiling diuretics [High efficacy Diuretics]

→ 20-25% of Na^+ is reabsorbed from ascending Limb of LH

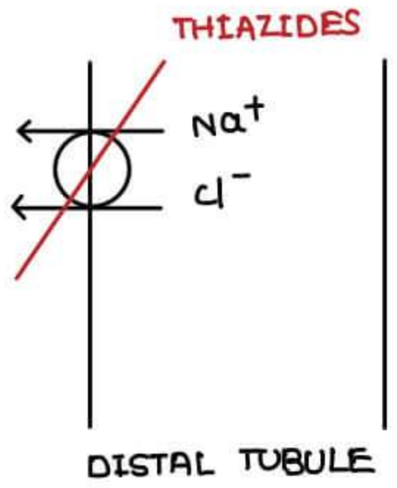
USES OF LOOP DIURETICS

— Edema (CHF etc.)

— Hypertensive emergency

— Bromide and Iodide poisoning

— Hypercalcemia



4 THIAZIDES

→ acts on distal tubule

→ inhibits $Na^+ Cl^-$ symporter

→ includes

METHIAZIDE

POLY THIAZIDE

CHLORTHIAZIDE

INDAPAMIDE } Thiazide like Diuretics

XIPAMIDE }

↓ Na^+ ↑ Glucose

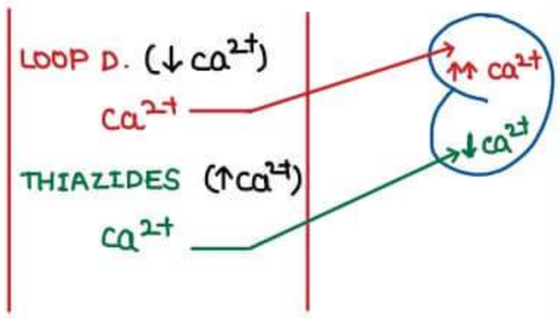
↓ K^+ ↑ Uric Acid

↓ Mg^{2+} ↑ Lipids

↓ H^+

Loop looses ca^{2+} → ↓ ca^{2+} used in Hypercalcemia

Thiazides ↑ ca^{2+} used in osteoporosis



Q Diuretic preferred in Recurrent Renal stones ?

A Thiazides

B Loop Diuretics

Even though Thiazides ↑ S. ca^{2+}, Less ca^{2+} reaches Kidney

∴ Loop diuretics, more ca^{2+} reaches Kidney

USES OF THIAZIDES

— Hypertension (DOC)

— Edema

— Recurrent renal calcium stones

— Bromide and Iodide poisoning

— Osteoporosis

— Diabetes insipidus

DIABETES INSIPIDUS

→ ADH retains only water

TYPES	ETIOLOGY	TREATMENT
CENTRAL DI	↓ ADH	DESMOPRESSIN [DOC]
NEPHROGENIC DI	Renal cause	THIAZIDES

→ THIAZIDES → MOA in DI

→ DI → ↑ urine [~ 100 L - 200 L]

→ ↑ plasma osmolarity

compensatory mechanisms

1. ↑ ADH
2. Thirst centre stimulation

→ Thiazides cause excret^{n} of concentrated urine

↓ osmolarity

↓

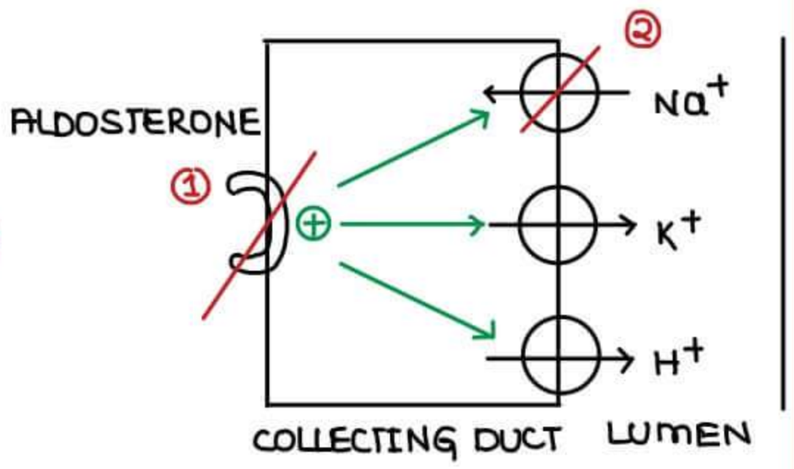
↓ Thirst

↓

↓ urine formation

5. K^+ SPARING DIURETICS

→ acts on collecting duct



1. ALDOSTERONE Ⓡ #	2. epithelial Na^+ channel #
SPIRONOLACTONE	AMILORIDE
EPLERONONE	TRIAMTERENE

→ These drugs cause

↓ Na^+ & H_2O → Diuresis

↑ K^+ → Hyperkalemia

↑ H^+ → Metabolic Acidosis

→ P → Potassium sparing DIURETICS

A → AMILORIDE

S → SPIRONOLACTONE → cause gynaecomastia

T → TRIAMTERENE

E → EPLERONONE → do not cause gynaecomastia

→ ALL DIURETICS WORK FROM LUMINAL SIDE EXCEPT ALDOSTERONE ANTAGONISTS

ALDOSTERONE ANTAGONISTS WORK FROM BASOLATERAL SIDE

USES:

- Conn's syndrome (DOC are aldosterone antagonists)
- Edema in Cirrhosis (DOC are aldosterone antagonists)
- Prevent hypokalemia cause by other diuretic
- CHF
- Resistant hypertension (DOC are aldosterone antagonists)

COUGH

DRY COUGH	PRODUCTIVE COUGH
Rx by ANTITUSSIVES CODEINE PHOLCODEINE DEXTROMETHORPHAN NOSCAPINE	Rx by MUCOKINETICS • Expectorants • Mucolytics

Mucokinetics (Aid in removal of secretions from lungs)

Expectorants (Increase secretions)

- Guafenesin
- Potassium iodide

Mucolytics (Lyse mucus)

- Ambroxol
- Bromhexine
- Acetylcysteine
- Dornase alfa

BRONCHIAL ASTHMA

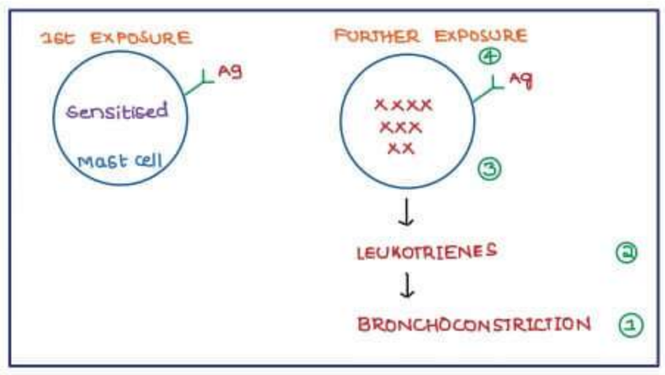
1. BRONCHODILATORS

a. SYMPATHOMIMETICS

β_2 AGONISTS

given by inhalation

- SALBUTAMOL, TERBUTALINE — Short Acting — used in acute attacks
- SALMETEROL, FORMETEROL — Long acting — used for prophylaxis



→ SALMETEROL → Slow acting → only used for Prophylaxis
FORMETEROL → Fast acting → can also be used for Acute Attacks

→ SIE of β_2 AGONISTS

T – Tachycardia
T – Tremors (Most common side effect)
T – Tolerance (Mainly with long acting beta 2 agonists)
T – T wave changes (Because of hypokalaemia)

These drugs also cause hyperglycaemia

b. PARASYMPATHOLYTICS

M_3 BLOCKERS

IPRATROPIUM
TIOTROPIUM

→ given by inhalational route
→ DOC for acute attack in patients on β blocker therapy

C. PDEI [PHOSPHODIESTERASE INHIBITORS]

- Include Theophylline and aminophylline
- Given orally or by intravenous route (not available by inhalational route)

Mechanism

→ Inhibits PDE (thereby ↑ cAMP)
→ Adenosine A_1 receptor antagonist
→ Can restore the activity of histone deacetylase (anti-inflammatory action)

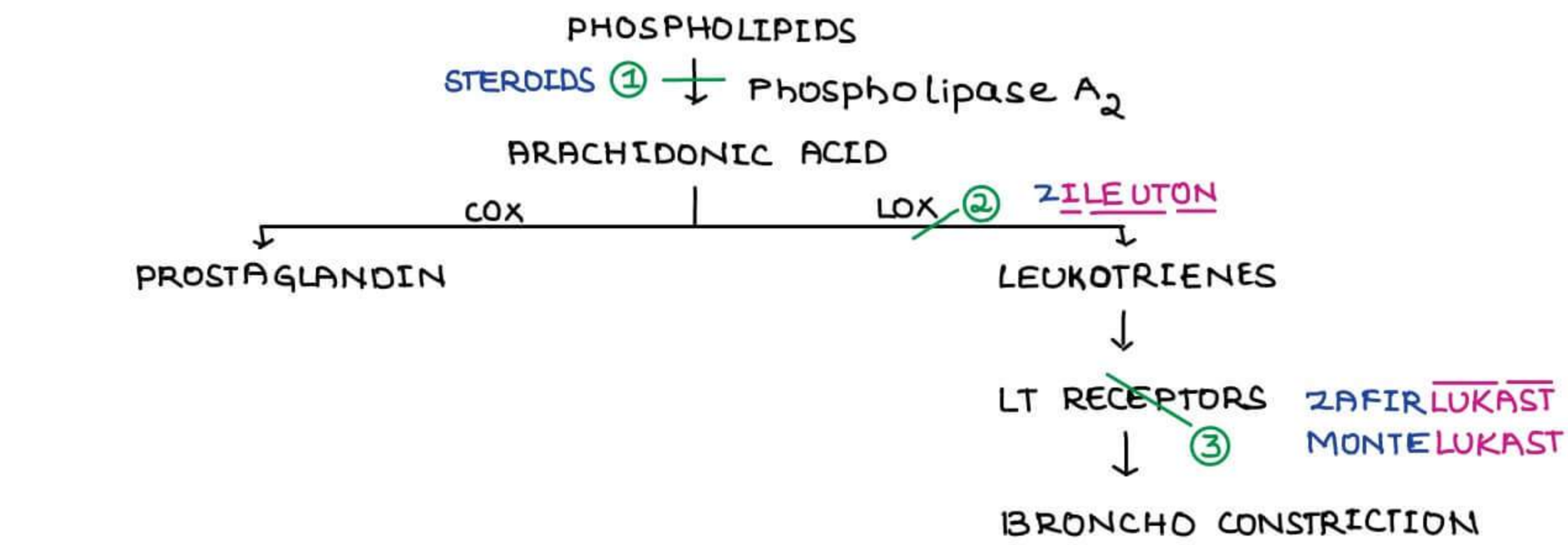
Adverse effects

Due to PDE inhibition	Due to adenosine A1 antagonism
GIT: Nausea, Vomiting, Diarhhea	Diuresis
Headache	Seizures
Arrhythmias	Arrhythmias

Special points

→ Theophylline follows zero order kinetics
→ Theophylline is metabolized by microsomal enzymes, so prone to drug interactions
  - Enzyme inducers (like smoking) decrease the effect, therefore smokers require higher doses
  - Enzyme inhibitors (like ciprofloxacin and erythromycin) can result in toxicity (seizures, arrhythmias etc.)

2.



STEROIDS

→ DOC for prophylaxis
→ also used in acute attack along ī bronchodilators

→ **Inhalational corticosteroids:**

- Beclomethasone
- Budesonide
- Fluticasone
- Flunisolide
- Triamcinolone
- Mometasone
- Ciclesonide

→ Only 5% of inhalational corticosteroid reaches the bronchus, 95% sticks on epithelium of respiratory pathway leading to immunosuppression.

- MC side effect is oropharyngeal candidiasis
- Topical Nystatin is used to treat candidiasis
- Gargling after every dose will prevent this adverse effect

→ Ciclesonide is a prodrug which is activated only in bronchus, therefore, it doesn't cause candidiasis.

3. MAST CELL STABILIZERS

→ include

SODIUM CROMOGLYCATE

NEDOCROMIL

→ only used for prophylaxis

4. OMALIZUMAB

→ monoclonal antibody against IgE

→ only used for prophylaxis

→ given subcutaneously

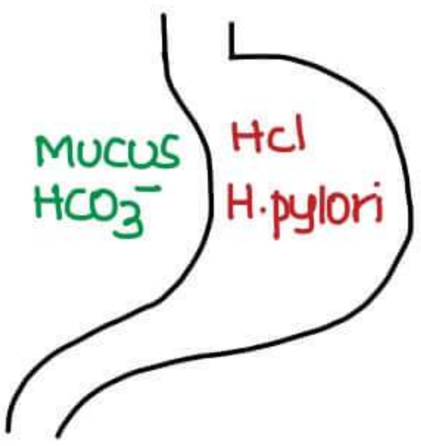
GASTROINTESTINAL TRACT

PEPTIC ULCER DISEASE

→ dlt imbalance between Aggressive & protective factors

Aggressive factors → HCl , H. pylori

Protective factors → mucus & HCO_3^-



TREATMENT

1. ↓ ACID

HCl

→ produced by Parietal cell of Stomach

→ PROTON PUMP [H^+K^+ PUMP]

→ helps in Secretⁿ of Acid

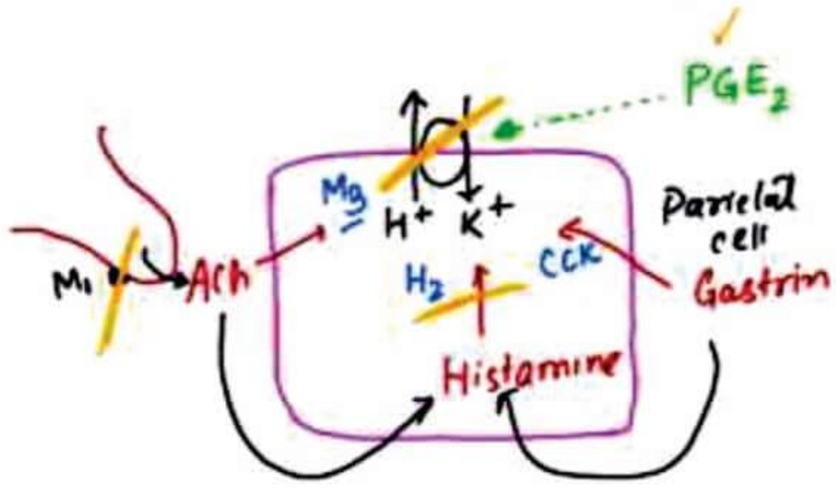
→ stimulated by

Ach [M_1]

Histamine [H_2]

Gastrin [CCK]

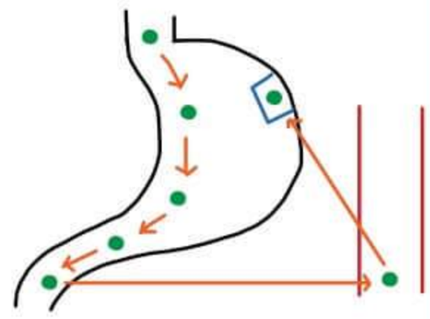
→ inhibited by PGE_2



M_1 BLOCKERS	H_2 BLOCKERS	PGE_2	PPI
PIRENZEPINE	CIMETIDINE	MISOPROSTOL	OMEPRAZOLE
TELENZEPINE	RANITIDINE		ESOMEPRAZOLE
	FAMOTIDINE		PANTOPRAZOLE
	LOXATIDINE		LANSOPRAZOLE
			RABEPRAZOLE

→ most specific drug for NSAID induced Peptic ulcer → Misoprostol
→ DOC for NSAID induced peptic ulcer → PPI

PPIs [PROTON PUMP INHIBITORS]

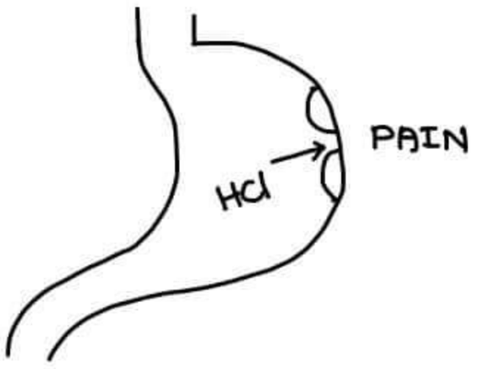


→ Irreversible inhibitors
→ Example of HIT AND RUN DRUGS
→ exerts systemic effect [not work locally]
  - normally acid labile
  - given ī acid resistant coating → Enteric coating

→ DOC for PUD dlt any reason
DOC for GERD
DOC for Zollinger Ellison syndrome

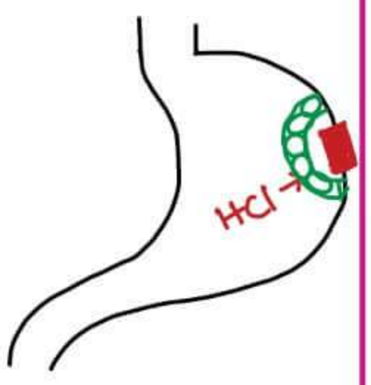
→ S|E [chronic use]
  - ↓ Ca^{2+} [osteoporosis]
  - ↓ vit B_{12} [Megaloblastic anaemia]
  - ↑ Infections
  - Carcinoid syndrome [not noted in humans]

2 ANTACIDS



→ fastest pain relievers OF PUD
→ includes
  $Al[OH]_3$ → cause constipatⁿ
  $Mg[OH]_2$ → cause Diarrhoea

3. ULCER PROTECTIVES



→ SUCRALFATE
COLLOIDAL BISMUTH SUB CITRATE

→ Sucralfate acts by Polymerizatⁿ, requires acidic pH [<4]
  - Should not combined ī antacids
→ CBS can cause BISMUTH POISONING
  - Bone → osteodystrophy
  - Brain → Encephalopathy

4. H. PYLORI DRUGS

→ AMOXYCILLIN
METRONIDAZOLE
CLARITHROMYCIN

→ TRIPLE DRUG THERAPY → PPI + 2 AMA
C → CLARITHROMYCIN
A → AMOXYCILLIN
P → PPI
} Preferred

ANTI EMETIC DRUGS

1. ANTI CHOLINERGIC DRUGS → HYOSCINE
2. H_1 BLOCKERS → DOXYLAMINE [DOC for morning sickness]
3. $5HT_3$ BLOCKERS
   ONDANSETRON
   GRANISETRON
   TROPISETRON
   PALONOSETRON [most potent]
   } DOC for
   chemotherapy induced vomiting
   Radiotherapy induced vomiting
   Post Op. vomiting
4. NEUROKININ ANTAGONISTS [SUBSTANCE P ANTAGONISTS]
   APREPITANT
   NETUPITANT
   ROLAPITANT
   } DOC for
   Delayed vomiting by CISPLATIN
5. D_2 ANTAGONISTS

METOCLOPRAMIDE	DOMPERIDONE
Cross BBB can cause dystonia	Do not cross BBB Do not cause dystonia DOC for Levodopa induced vomiting
$5HT_3$ # $5HT_4$ ⊕	NO other action

ANTI DIARRHEAL DRUGS

1. ORS
   → contains
   NaCl
   KCl
   } Replenishes electrolytes
   Tri Sodium Citrate → prevent acidosis
   Glucose → to aid Na^+ absorption

2. ANTI MICROBIALS FOR INFECTIONS
   METRONIDAZOLE for ameobic infect^n
   CIPROFLOXACIN for bacterial infect^n
   } combined usage is irrational

3. NON INFECTIVE DIARRHEA

→ LOPERAMIDE
DIPHENOXYLATE
} ↓ Intestinal motility

4 SECRETORY DIARRHEA

→ OCTREOTIDE → somatostatin analogue

5 RACECADOTRIL

→ ENKEPHALINS [endogenous opioid] —Enkiphalinase→ Degradatⁿ

→ Enkephalinase inhibitor

INFLAMMATORY BOWEL DISEASE

ULCERATIVE COLITIS

1. 5 ASA DERIVATIVES → DOC
   1. SULFASALAZINE → 5 ASA – SULFAPYRIDINE
   2. OLSALAZINE → 5 ASA – 5 ASA
   3. MESALAMINE

2. STEROIDS → IF not responding ī 5 ASA derivatives

CROHN'S DISEASE

1 STEROIDS → DOC

2. TNF α BLOCKERS → IF not responding ī sterolds
   - ADALIMUMAB
   - CERTOLIZUMAB
   - ETANERCEPT
   - INFLIXIMAB
   - CETROLIZUMAB

LAXATIVE PURGATIVES

→ Laxative → causes Semi solid stools
Purgative → causes watery stools

→ USES

1. Functional constipation [not for obstructive constipation]
   → constipation preferrably Rɣ by High fibre diet & regular exercise
2. TO PREVENT STRAINING
   → Hernia
   → Piles
   → Anal fissure
3. x – RAYS of KUB
4. Along ī ANTI HELMINTHIC DRUGS [NICLOSAMIDE]

→ Includes

1. BULK FORMING [should be given ↑ plenty of water]
   - → DIETARY FIBRE
     PSYLLIUM
     METHYL CELLULOSE
   - → CI in mega colon

2. OSMOTIC PURGATIVES
   - → SALINE PURGATIVES
     - → $MgSO_4$, $Mg(OH)_2$
     - → CI in chronic renal failure
   - → LACTULOSE
   - → POLY ETHYLENE GLYCOL

3. STOOL SOFTNERS
   - → ↓ surface tension of fluids in GIT
   - → DOCUSSATE – Di octyl sodium sulfosuccinate

4. STIMULANT PURGATIVES
   - → ORGANIC → BISACODYL
     Na PICOSULPHATE
     - → SIE – colonic atony [on longterm usage]
   - → ANTHRAQUINONES → SENNA
     CASCARA
     - → SIE – Melanosis coli
   - → CASTOR OIL
   - → Stimulant purgatives are CI in Obstructive Constipation

5. NEW DRUGS

1. *Chloride channel activators – act by releasing chloride ions (Cl^-) in lumen of intestine. To maintain the electroneutrality, Sodium (Na^+) is also released in the lumen which carries water with it. This makes the stool soft to treat the constipation.*

   → Two mechanisms of Chloride channel activators,

   - *Direct Cl channel 2 activator*

     → Lubipristone

- Guanylyl Cyclase activator

↓

↑CGMP

↓

CFTR is activated

↓

Opens Cl^- channels

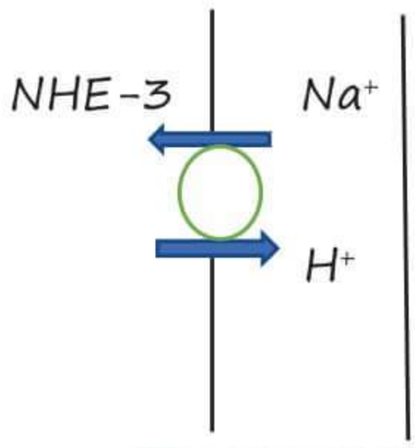
→ Drugs of Guanylyl Cyclase activators:

- Plecanatide
- Linaclotide

→ Common side effect of both direct chlorine channel 2 activator and Guanylyl cyclase activator is DEHYDRATION.

→ So, these drugs are indicated only after 18 years of age and avoided in children.

2. NHE3 inhibitor:



→ Tenapanor (Sodium hydrogen exchange antagonist) is the drug that inhibits the exchange of sodium and hydrogen. It is administered via Oral route and prevents the reabsorption of sodium in GIT. Water follows sodium which makes the stool soft.

→ Tenapanor increases the tight junctions in intestine and by that mechanism it inhibits the phosphate reasbsorption also.

3. Peripheral Opioid antagonists:

- Alvimopan
- Methylnaltrexone
- Naloxegol
- Naldemedine

These are indicated for opioid induced constipation.

ANTERIOR PITUITARY

PITUITARY GLAND HORMONES	HYPOTHALAMUS CONTROL
Growth Hormone [GH]	GHRH [GH Releasing Hormone]
	GHIH [GH Inhibiting Hormone]
Thyroid Stimulating Hormone [TSH]	TRH [Thyrotropin Releasing Hormone]
Adreno CorticoTropic Hormone [ACTH]	CRH [corticotropin Releasing Hormone]
Gonadotropins	GnRH [Gn Releasing Hormone]
Prolactin	PIH [Prolactin Inhibiting Hormone]

→ All hormones of anterior pituitary are under the control of hypothalamus so hypothalamus will increase or decrease the level of anterior pituitary hormones

→ If there is loss of connection/ lesion between pituitary and hypothalamus

→ the level of all the anterior pituitary hormones will decrease and only prolactin level will increase

→ Growth hormone and prolactin are under inhibitory control (GHIH and PIH respectively)

→ Prolactin is under only inhibitory control because there is no releasing hormone for prolactin

GROWTH HORMONE INHIBITING HORMONES [GHIH] / SOMATOSTATIN

ORGAN	ACTION	USES
• PITUITARY	→ ↓ GH	→ Acromegaly
• PANCREAS		
α cells [Glucagon]	→ ↑ Blood sugar	
β cells [Insulin]	→ ↓ Blood sugar	
δ cells [Somatostatin]	→ ↓ Glucagon	→ Isletcell tumors
	↓ Insulin	
• GIT	→ ↓ Secretions	→ Secretory diarrhoea
• BLOOD VESSELS	→ vasoconstriction	→ Oesophageal varices

→ SOMA to statin

S → Secretory diarrhea

O → Oesophageal varices

M → Malignancy [Islet cell tumors]

A → Acromegaly

→ Somatostatin → Short acting

OCTREOTIDE → long acting somatostatin derivative

→ ANY PHYSIOLOGICAL SUBSTANCE ENDING i 'IN' IS PEPTIDE

→ They will be degraded when given by oral route

→ OCTREOTIDE → given by SC route

GONADOTROPIN RELEASING HORMONE [GnRH]

PULSATILE FASHION ↑ Gonadotropins	CONTINUOUS FASHION ↓ Gonadotropins
↑ Estrogen, ↑ Progesterone ↑ Testosterone	↓ Estrogen, ↓ Progesterone ↓ Testosterone

INDICATIONS of GnRH

In Pulsatile manner

① Hypogonadotropic hypogonadism
② Delayed Puberty
③ Anovulatory infertility

In continuous fashion

① cancers
→ Prostate cancer → Breast cancer
② Endometriosis
③ Precocious puberty

GnRH AGONISTS

① LEUPROLIDE
② NAFARELIN
③ GOSERELIN
④ BUSURELIN
⑤ HISTARELIN

→ FLARE UP REACTION
→ When these drugs given in continuous manner, initial 2-3 days there is aggrevation of disease

GnRH ANTAGONISTS

① CETRORELIX
② GANIRELIX
③ ABARELIX
④ DEGARELIX

→ No flare up reaction
→ but they do not ↑se sex hormones

ELAGOLIX

→ Recently approved GnRH antagonist
→ Can be used orally (No other GnRH agonist or antagonist is effective orally)
→ Approved for pain due to Endometriosis

PROLACTIN INHIBITING HORMONE [PIH] ≅ DOPAMINE [DA]

→ DA acts through D_2 Receptors
→ Drugs stimulating D_2 Receptors act like PIH
→ D_2 RECEPTOR AGONISTS
→ BROMOCRIPTINE
→ CABERGOLINE [Long acting]
→ INDICATIONS
① HYPERPROLACTINEMIA
→ CABERGOLINE → DOC, can be given orally

② PARKINSONISM

③ ACROMEGALY

→ CABERGOLINE is the preferred drug

→ ↓ GH

→ can be given orally

PEG VISOMANT [GH RECEPTOR ANTAGONIST]			
→ PEGVI SOM ANT	→	Somatotropin Antagonist	
→ PEG VI SOMANT	→	causes VIsual field defect	
→ PEG VISOMANT	→	PolyEthyleneGlycol	→ Long acting

④ TYPE 2 DM

→ BROMOCRIPTINE → ↓ Insulin resistance

⑤ *SUPPRESSION OF LACTATION*

- *Prolactin is a milk secreting hormone. Decreasing the level of prolactin can stop lactation.*
- *Dopamine acts as Prolactin inhibiting hormone. So, D2 receptor agonists are used for suppression of lactation.*

USES OF DOPAMINE AGONISTS

Dopamine - Diabetes mellitus
Agonists - Acromegaly (DOC- Cabergoline: as it is oral and long acting)
Suppress - Suppression of lactation
Plasma - Parkinsonism
Prolactin - Hyperprolactinemia

POSTERIOR PITUITARY

Secretes 2 main hormones

1. Oxytocin
2. Vasopressin (Antidiuretic hormone)

OXYTOCIN

Main function: To stimulate the uterine contractions.

- DOC for augmentation of labor
- DOC for treatment and prophylaxis of postpartum hemorrhage.

Other function- Ejection of Milk

- DOC for Breast engorgement.

VASOPRESSIN (ANTIDIURETIC HORMONE)

Main functions- Vasoconstriction and Water retention

Act on V1 receptor and V2 receptor

- V1 receptors are present in blood vessels and cause vasoconstriction
- V2 receptors are present in kidney and cause decrease in urine.
- V2 receptors are also present in endothelium of blood vessels where VWF and Factor VIII are released.

VASOPRESSIN RECEPTOR AGONISTS

V1 agonist: Terlipressin: DOC for Esophageal Varices

V2 agonist: Desmopressin:

- DOC for neurogenic (central) diabetes insipidus (given by nasal route)
- DOC for nocturnal enuresis
- Can be used for von Willebrand disease and hemophilia

Diabetes insipidus

→ It is of two types
→ Central Diabetes insipidus/ Neurogenic Diabetes insipidus- due to deficiency of ADH
→ Nephrogenic Diabetes Insipidus- due to ADH being secreted normally in Pituitary but not able to work on kidney.
→ DOC for Central / Neurogenic Diabetes Insipidus- Desmopressin by nasal route (Selective V2 receptor Agonist)
→ DOC for Nephrogenic Diabetes insipidus- Thiazides.

VASOPRESSIN RECEPTOR ANTAGONISTS

Vaptans- Vasopressin Antagonists

Conivaptan – given via Intravenous route

Tolvaptan – given via Oral route

Uses of vaptans:

- Congestive heart failure (due to property of diuresis and Vasodilation).
- SIADH
- Recently Tolvaptan is approved for treatment of Autosomal dominant Adult polycystic kidney disease.

Excessive ADH causes increased water retention leading to Dilutional Hyponatremia.

Stepwise management in cases of SIADH

1. Fluid restriction
2. 3% Nacl
3. If symptoms persist, then drugs are given - DOC- Vaptans (Conivaptan / Tolvaptan)
4. Demeclocycline (inhibits the release of ADH from posterior pituitary) can also be used.

THYROID

→ SECRETES

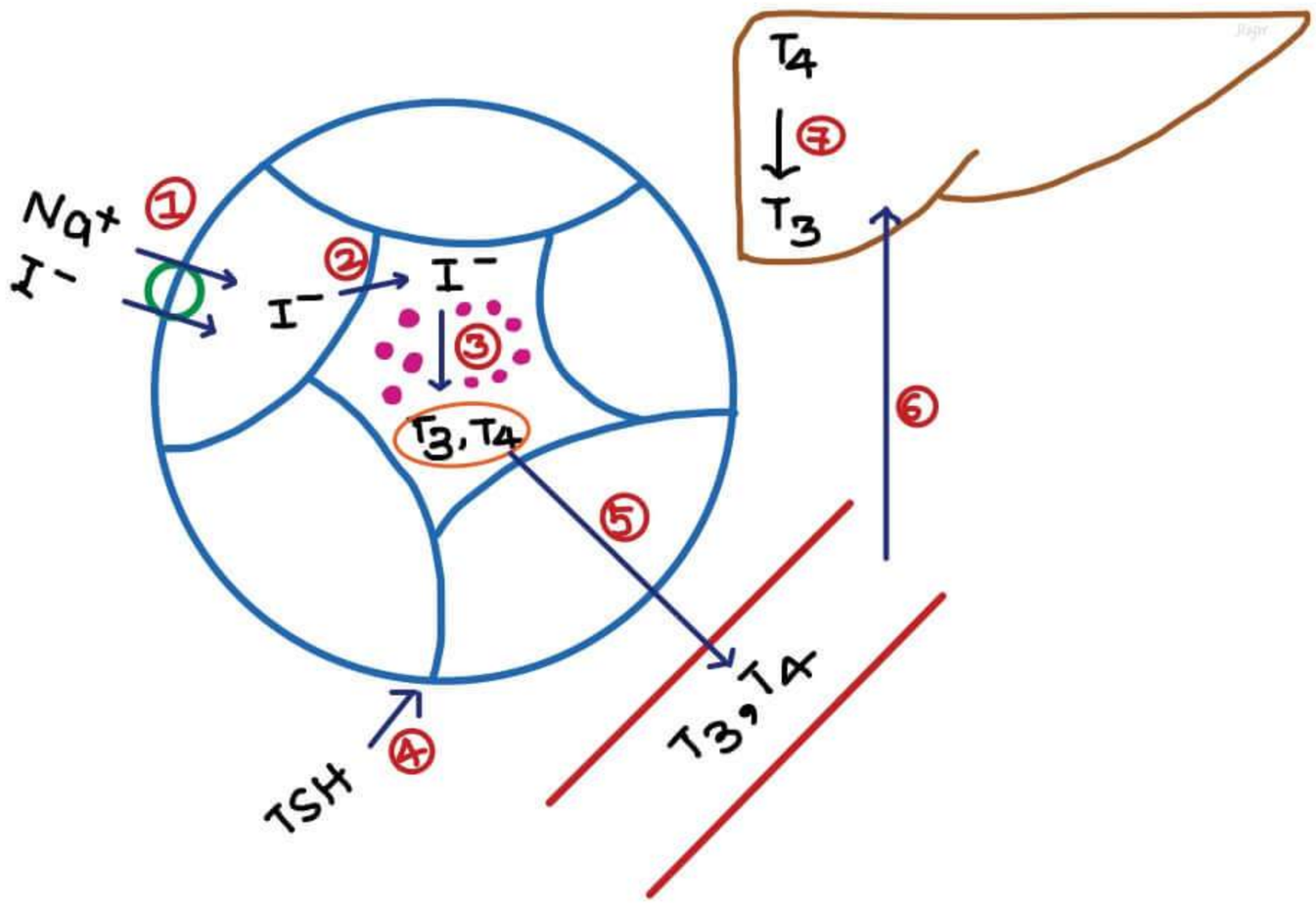
T_3

T_4

CALCITONIN

T_3	T_4
→ Short acting → more active	→ longer acting → Less active
→ LIOTHYRONINE – only indicat^n → Myxedema coma [Emergency]	→ L-THYROXINE – DOC for hypothyroidism – DOC for myxedema coma

PHYSIOLOGY OF THYROID HORMONE PRODUCTION



① Iodide [I^-] enters into thyroid follicle by $Na^+ I^-$ symporter

② From follicles Iodide enters into colloid

③ In COLLOID

I^-
↓ oxidation
I°
↓ organificatⁿ ⁱ tyrosine
MIT
DIT
↓ coupling
T_3
T_4

→ all the 3 reactions catalysed by Thyroid Peroxidase

→ T_3, T_4 stored in colloid

④ TSH stimulates thyroid

⑤ T_3, T_4 released into circulation

⑥ Hormone reaches peripheral tissues/organs [Liver]

→ In the blood, T_3 is active but less in quantity
T_4 is abundant but not much active

⑦ Peripheral conversion takes place in peripheral tissues/organs [Liver]

T_4 ——metabolised——→ T_3

→ Subscript 3, 4 in T_3 & T_4 represents → Number of Iodine atoms.

T_3 → 3,5,3' – Tri-Iodothyronine

T_4 → 3,5,3',5' – Tetra-Iodothyronine

→ These are the positions where Iodine is attached on the chemical structure

→ When iodine attaches to atoms without prime, it ↑ thyroid hormone activity

→ When Iodine attaches to atoms with prime, it ↓ thyroid hormone activity

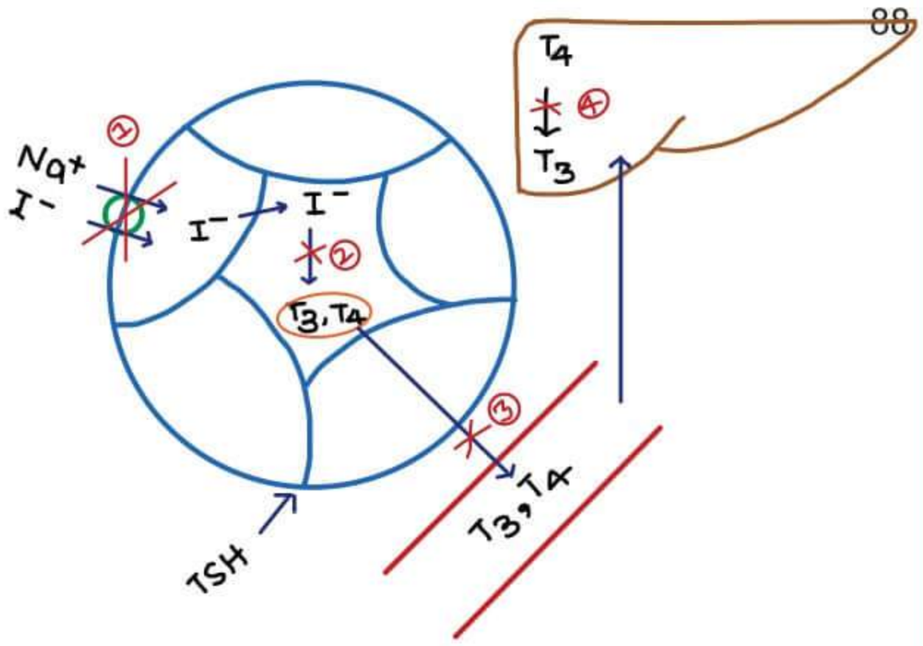
- In T_3 →2 atoms are without prime & 1 atom is with prime → **T_3 is quite active**
- In T_4 → **2 atoms ↑ & 2 atoms ↓ activity → T_4 is less active**
- **Reverse T_3 → 3,3',5', – Tri-Iodothyronine → Totally inactive**

→ When we want to convert T_4 to T_3 (Peripheral conversion)

T_4 (3,5, 3',5' – Tetra-Iodothyronine)
↓ 5' – De-Iodinase → help in peripheral conversion of T_4 → T_3
T_3 (3,5,3' – Tri Iodothyronine)

HYPERTHYROIDISM — DRUGS

① NIS INHIBITORS
② THYROID PEROXIDASE INHIBITORS
③ SECRETION INHIBITORS
④ PERIPHERAL CONVERSION INHIBITORS
⑤ THYROID DESTROYING DRUGS



NIS INHIBITORS

① PERCHLORATE
② PERTECHNETATE
③ THIOCYANATE

→ not used clinically [Toxic]
→ cabbage is a rich source of Thiocyanate → GOITROGEN

THYROID PEROXIDASE INHIBITORS

① CARBIMAZOLE [inactive] ↓ ② METHIMAZOLE [active]	③ PROPYLTHIOURACIL [PTU]
→ more potent	→ less potent
→ more plasma $t_{1/2}$	→ less plasma $t_{1/2}$
→ crosses placenta easily	→ less crossing of Placenta → DOC in 1st trimester pregnancy
→ no action on peripheral convers^{n}	→ decreases peripheral conversion

→ Slow acting drugs
→ on Ⓝ person, stored T_3, T_4 suffice for 1-2 wks
on hyperthyroidism, they suffice for 3-4 wks
Dose increase of these drugs should be done after 4 wks.

SECRETION INHIBITORS

① NaI
② KI
③ LUGOL'S IODINE

→ Fastest acting anti-thyroid drugs
→ Given preoperatively to:
- Make the gland small, firm and less vascular reducing the blood loss during surgery.

PERIPHERAL CONVERSION INHIBITORS

① PROPRANOLOL
② PTU
③ PREDNISOLONE

THYROID DESTROYING DRUGS [I^{131}]

→ I^{131} used because

① Na^+I^- symporter is specific for Iodine intake
→ restricts I^{131} to thyroid gland
② I^{131} stored in colloid, emission of radioactive rays confined
③ I^{131} emits β rays, have less penetrating power

→ C/I in pregnancy
→ can be given orally

→ Radioactive drugs cause Irreversible hypothyroidism, requires life long thyroid hormone thearapy → C/I in < 35 yrs aged patients
→ All other antithyroid drugs cause Reversible hypothyroidism, discontinuatn of drug suffice

→ I^{131} $t_{1/2}$ → 8 days

DRUGS USED FOR CONTROLLING SYMPTOMS

→ Mostly symptoms are sympathetic (like tachycardia, palpitations, tremor, hypertension etc).

So, β – blockers can be used

- Most imp β # → Propranolol

[along with treating the symptoms, it also ↓ peripheral conversion of T_4 → T_3)

→ It is the life-saving drug in Thyroid storm

THYROID STORM:

- D.O.C. for thyroid storm → propranolol
- Antithyroid DOC: Propylthiouracil

TREATMENT OF HYPERTHYROIDISM IN PREGNANCY:

Trimester	DOC for Hyperthyroidism
First Trimester	Propylthiouracil
Second Trimester	Carbimazole/Methimazole
Third Trimester	Carbimazole/Methimazole
Trimester not mentioned	Prophylthiouracil

	SECRETES	ACTION	USES
α cells	Glucagon	↑ Blood Sugar	hypoglycemia
β Cells	Insulin Amylin	↓ Blood Sugar	
δ cells	Somatostatin		

GLUCAGON

Uses

1. HYPOGLYCIMIA

→ MOA → acts by GLYCOGENOLYSIS

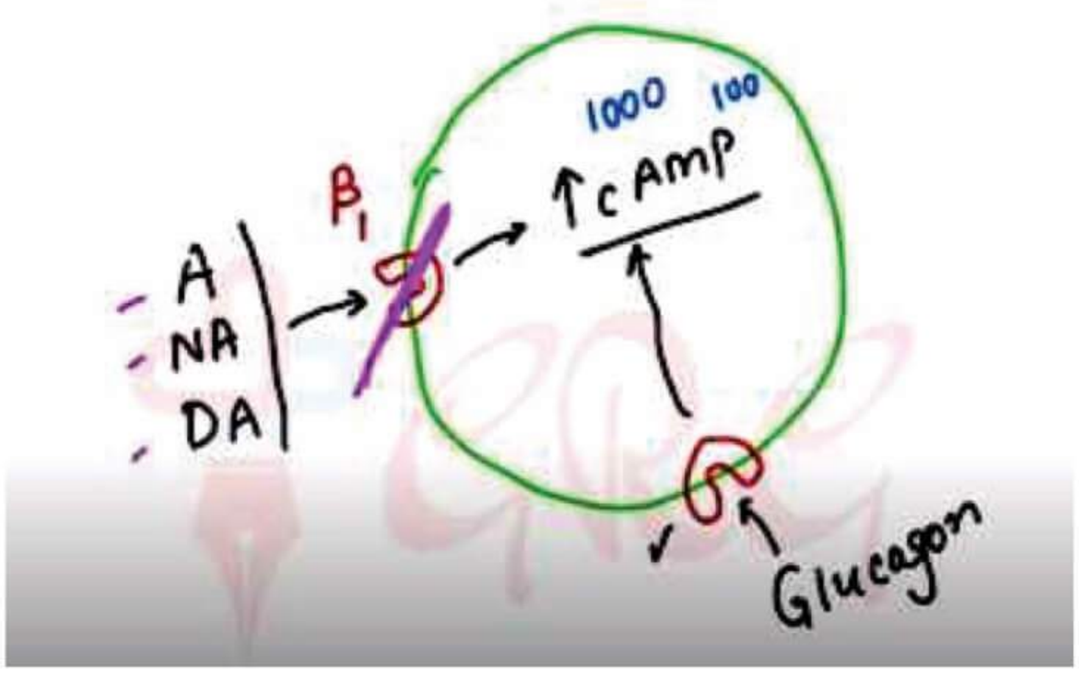
– Not useful in hypoglycemia caused by

- Starvation
- Alcohol induced hypoglycemia

2. β BLOCKER POISONING [DOC]

- In β – blocker poisoning, these receptors are not working, resulting in depression of heart → Bradycardia and ↓ in contractility
- As β receptors are not working, we should ↑ cAMP by other methods like
  - ➢ On heart, there are glucagon receptors

Glucagon
↓ stimulates
Glucagon receptors on heart (GPCR)
↓
↑cAMP
↓
Heart is stimulated



- Glucagon is antidote for β–blocker poisoning.

INSULIN

INDICATIONS

1. TYPE 1 DM [IDDM] → All patients require insulin
2. TYPE 2 DM [NIDDM] → Uncontrolled patients
3. GESTATIONAL DM → DOC
4. DIABETIC KETOACIDOSIS → DOC
5. TIDE STRESS
6. ACUTE HYPERKALEMIA → non diabetic use

ROUTES OF ADMINISTRATION:

→ **Sub – cutaneous route:**

- MC route
- All insulin preparations can be given by subcutaneous route.
- Site of administration
  - Entire abdomen except area around umbilicus (thickness of skin is not uniform) so insulin absorption is affected
  - Anterior thigh
  - Lateral thigh
  - Arm

→ **Intravenous route**:

- Only regular insulin can be given
- So, insulin of choice in diabetic ketoacidosis → Regular insulin.

→ **Inhalational route:**

→ Exubera → withdrawn from the market bcoz of pulmonary complications.

→ Afreeza → Short acting insulin → so, should be given before every meal

→ It is not a stand-alone insulin (given with injectable insulin).

PREPARATIONS

RAPID ACTING	→	LISPRO ASPART GLULISINE
SHORT ACTING	→	REGULAR SEMI - LENTE
INTERMEDIATE ACTING	→	NPH LENTE
LONG ACTING	→	ULTRA - LENTE
ULTRA LONG ACTING	→	GLARGINE

→ Other long acting insulins include
- Insulin detemir
- Insulin Degludec → longest acting

→ These are also known as peak less insulin [bcoz they are slowly released & never attain peak in the plasma]

→ Long acting insulins have low risk of causing hypoglycemia.

→ All insulin preparations are at → Neutral PH

Glargine is at acidic PH [<4] [No insulin should be mixed ī it]

S/E

HYPOGLYCEMIA

→ mc & most dangerous

→ Advise to patients for preventⁿ

1. donot skip meals
2. Keep Glucose

ORAL ANTI DIABETICS

Acts by ↑ Insulin	acts by other mechanisms
→ S/E → hypoglycemia → >30% functional β cells should be present	→ no hypoglycemia → no such requirement

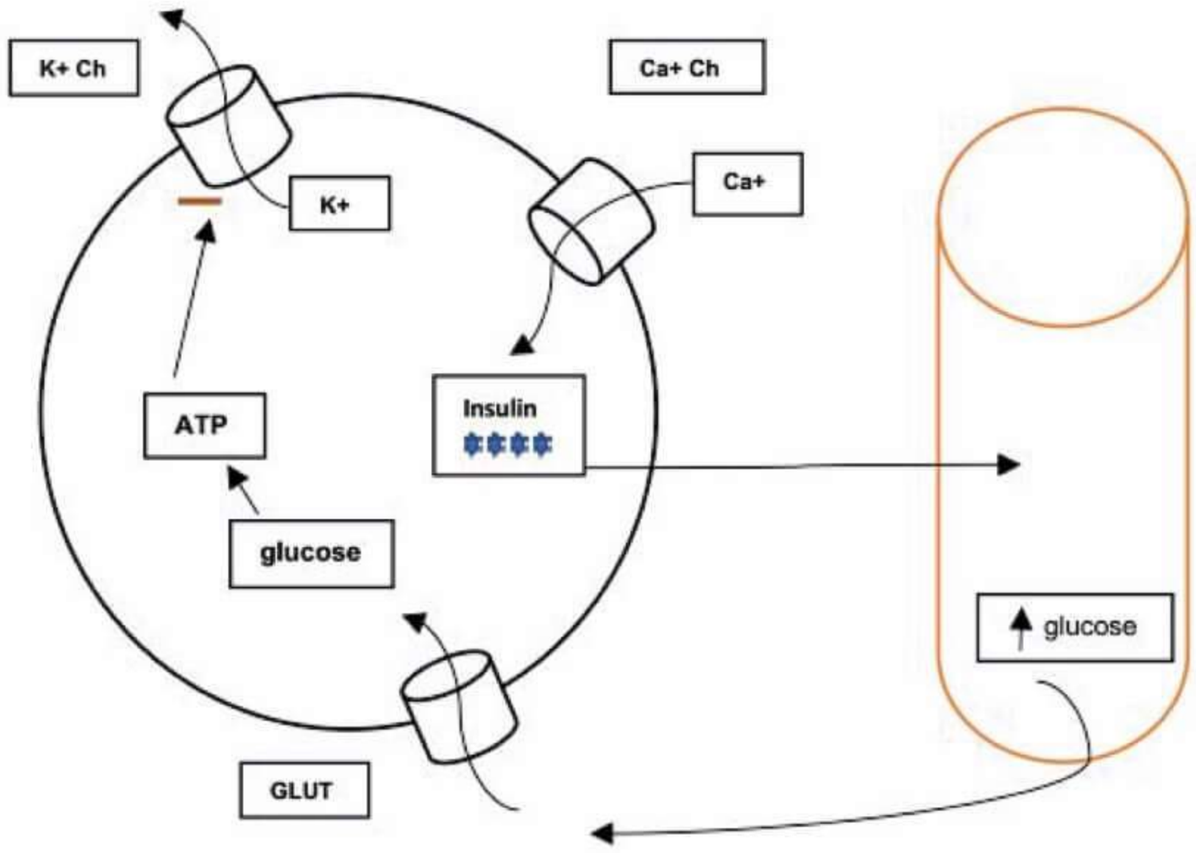
DRUGS ACTS BY ↑ INSULIN

SULFONYLUREAS	MEGLITINIDES
1st GENERATION	NATE GLINIDE REPA GLINIDE
CHLORPROPAMIDE TOLBUTAMIDE	
2nd GENERATION	
GLIPIZIDE GLICLAZIDE GLIBENCLAMIDE	

Other than Insulin, drugs ending ĩ 'IDE' can cause → hypoglycemia

How beta cell secrete insulin:

1. Increase blood glucose
2. Opening of GLUT and entry of glucose in beta cells
3. Glucose under anaerobic metabolism forms ATP
4. ATP blocks K_{ATP} (ATP sensitive K+ channel
5. Increase K+ inside cell leads to slight depolarization
6. Slight depolarization leads to opening of calcium channel.
7. Influx of calcium leads to depolarization and release of insulin.



SULFONYLUREAS

- → cause hypoglycemia
- → cause weight gain
- → CHLOPROPAMIDE S/E
  - – Jaundice
  - – Disulfiram like reaction
  - – ↑ ADH [retains H_2O] → Dilutional hyponatremia
    - → also indicated for Diabetes insipidus

MEGLITINIDES

- → Short acting [~1hr]
- → indicated in Postprandial hyperglycemia

DRUGS ACT BY OTHER MECHANISMS

1. METFORMIN
   PHENFORMIN

→ *These drugs act by activating an enzyme* **AMP kinase**

↓ *Phosphorylates*

Rate limiting enzymes of many metabolic pathways

↓ *resulting in*

Some pathways → Activated

↓ Blood sugar ⟸

Some pathways → Inactivated

AMP kinase effects:

- *Gluconeogenesis (–)*
- *Glycogenolysis (–)*
- *Glycogenesis (+)*
- *Glycolysis (+)*

→ *These drugs do not release insulin → so do not cause hypoglycemia*

→ S/E

1. Megaloblastic Anaemia → more a/w Metformin
2. Lactic acidosis → more a/w Phenformin [not used now]

→ *How these two drugs cause lactic acidosis?*
- *These drugs stimulate glycolysis generating lactic acid.*
- *Normally, the lactic acid is diverted to gluconeogenesis to form glucose*
- *But, these drugs also inhibit gluconeogenesis*
  So, lactic acid accumulates resulting in lactic acidosis.
- *Risk of this further ↑, if there is*
  → *Liver disease (Gluconeogenesis cannot occur totally)*
  → *Renal disease (Lactic acid cannot be excreted)*

→ PHENFORMIN → has more a/w Lactic Acidosis [not used now]

→ METFORMIN
- → has more a/w Megaloblastic anaemia
- → It can also cause lactic acidosis
  - contraindicated in
    Liver diseases
    Renal diseases
    Lung diseases
- → DOC for TYPE 2 DM
  - no risk of hypoglycemia
  - max. reduction in HbA_{1c}
  - can cause weight loss

MOST
- M → Metformin preferred in
- O → Obese patients
- S → Sulphonylureas preferred in
- T → Thin patients

→ Metformin also indicated for PCOD [reverses Insulin Resistance]

2. TROGLITAZONE
   ROSIGLITAZONE
   PIOGLITAZONE

→ acts by stimulating PPAR-γ → Reversal of Insulin Resistance

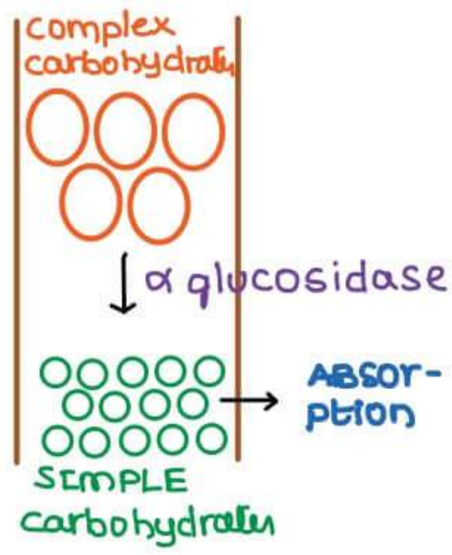
→ S/E
1. Hepatotoxic
   → max. hepatotoxicity → Troglitazone [withdrawn]
   → Rosiglitazone & Pioglitazone requires LFT monitoring

2. Na^+ & water Retention → avoid in CHF & HTN
3. ↑ risk of MI by ROsiglitazone
4. ↑ risk of urinary bladder carcinoma by Pioglitazone

3. α GLUCOSIDASE INHIBITORS [α GI]

→ Acts by inhibiting the absorpt^n of carbohydrates

→ ACARBOSE
MIGLITOL
VOGLIBOSE



→ Flatulence → mc side effect

→ C/I in Inflammatory bowel disease
Ulcerative colitis
Crohn's disease

→ hypoglycemic prophylaxis in αGI → only by Glucose

NEW ANTIDIABETIC DRUGS:

1. INCRETINS

→ Normal physiological substances which are released in GIT after food intake and stimulates release of insulin which controls blood sugar.

→Most important endogenous incretin is GLP (Glucagon like peptide). Its major function is increased insulin secretion and decrease in appetite.

→Decrease in appetite is due to 2 reasons

- decreased Gastric emptying.
- stimulates satiety centre of brain.

→Other functions of GLP includes prevention of apoptosis of beta cells of pancreas.

→GLP is metabolized by DPP-4 and becomes inactive.

→Incretin-mimetic drugs are of two types

- GLP analogues
- DPP-4 inhibitors

(a) GLP analogues:

→ Exenatide

- Given subcutaneously (cannot be given orally)
- Causes weight loss
- Risk of hypoglycemia is very less

Side effect:

- Acute pancreatitis (major side effect)
- Nausea (most common)
- Increased risk of Medullary carcinoma of Thyroid.

Other drugs in GLP analogues:

- Liraglutide (also approved for obesity treatment)
- Albiglutide
- Dulaglutide
- Semaglutide
- Teduglutide (GLP-2 analogue)

GLP – 1:

- Major function – insulin secretion
- Minor function – decrease in gastric emptying

GLP – 2: (Teduglutide)

- Major function – decrease in gastric emptying
- Minor function – insulin secretion
- Teduglutide is indicated in Short Bowel Syndrome as it decreases gastric emptying.

Semaglutide:

- Only GLP analogue given Orally.

(b) DPP – 4 inhibitors :

- Sitagliptin
- Vildagliptin
- Alogliptin
- Linagliptin
- Dapagliptin
- Saxagliptin

→Gliptins are oral anti diabetic drugs. These can cause weight loss but do not cause hypoglycemia

Side effects:

- Nasopharyngitis (most common)
- Pancreatitis

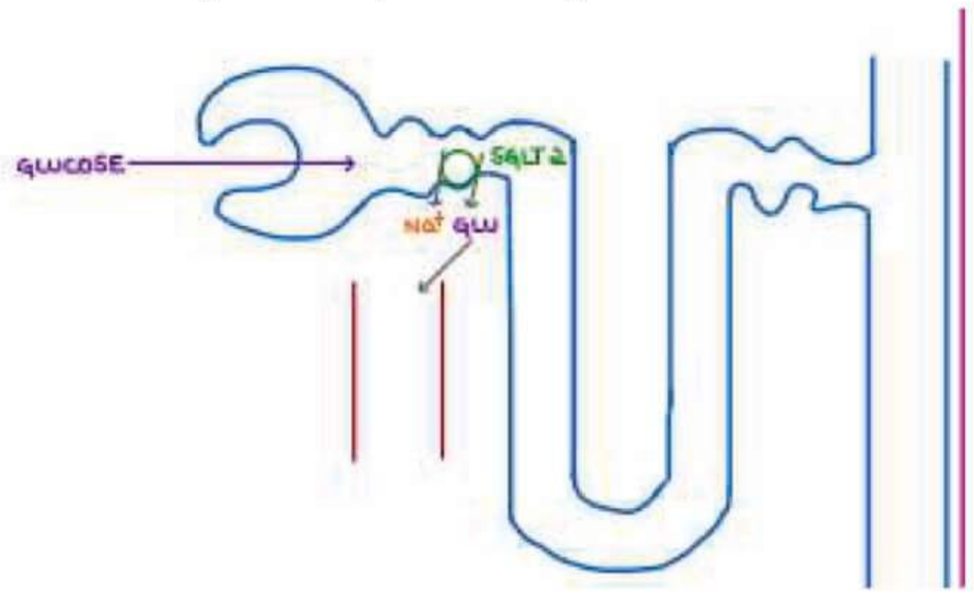
Contraindications:

- Gliptins are contraindicated in renal failure except Linagliptin which is safe in renal failure.

2. SGLT -2 INHIBITORS:

→Glucose is freely filtered in glomerulus but the clearance of glucose in urine is negligible.

→Because the reabsorption takes place in proximal tubule by sodium glucose transporter (SGLT-2).



→SGLT -2 inhibitors inhibits the sodium glucose transporter and hence glucose is not reabsorbed in proximal tubule and expelled in urine, which is also known as GLUCOSURIA.

→**Drugs are,**

- Canagliflozin
- Dapagliflozin
- Empagliflozin
- Ertugliflozin

→Most common side effect of SGLT -2 Inhibitors is Urinary Tract Infections and genital tract infections.

→if gliflozins are taken by type 1 diabetes patients , it controls blood sugar level and makes it normal and then if the patient stops taking insulin, it will result in Diabetic ketoacidosis (as type 1 diabetes is characterized by complete deficiency of insulin).

3. AMYLIN ANALOGS:

→Pramlintide is an amylin analogue which is given by subcutaneous route and it causes hypoglycemia as side effect.

→It is approved for both type 1 and 2 diabetes.

→Only 2 drugs are given in type 1 diabetes which are Insulin and Pramlintide, rest all other drugs are indicated only in type 2 diabetes.

4. BROMOCRIPTINE

→ Decreases insulin resistance and it has been recently approved for type 2 diabetes treatment.

→ Given in small dose and taken at early morning on awakening.

→ Increases early morning dopaminergic acitivty and decreases sympathetic activity. This restores insulin sensitivity.

ADRENAL

MEDULLA	CORTEX
→ Secretes A NA DA	→ Secretes Gluco corticoids Mineralo corticoids

ALDOSTERONE → Major endogenous Mineralocorticoid

ACTIONS

1. ↑ Na^+ , ↑ H_2O
2. ↓ K^+ , ↓ H^+

HYDROCORTISONE → Major endogenous GlucoCorticoid

ACTIONS

1. CATABOLIC ACTION
   - Carbohydrates [CHO] breakdown to glucose → avoided in DM
   - Proteins breakdown → myopathies can occur
   - Fats breakdown [mainly from periphery] → CUSHING SYNDROME
   - Ca^{2+} metabolism → causes Osteoporosis

2. ANTI - INFLAMMATORY ACTION
   - → mainly by inhibition of chemotaxis
   - → used in inflammatory conditions ['itis']
   - → cause delayed wound healing

3. IMMUNO SUPPRESSANT ACTION
   - → Indicated in Transplantat^n & Autoimmunity
   - → but predispose to infections

4. ANTI CANCER ACTION
   - → Indicated in
     - → HL [Hodgkin lymphoma]
     - → NHL [Non Hodgkin lymphoma]
     - → LL [Lymphocytic leukemia]
   - → C/I in Kaposi sarcoma

5. EFFECT ON BLOOD:

→ All the blood cells are produced in bone marrow and then send to the blood.

→ Glucocorticoids increase movement of neutrophils from bone marrow to blood which results in Neutrophilia, but glucocorticoids inhibit the movement of lymphocytes from bone marrow to blood.

→ Hence the net effect of glucocorticoids in blood is,

- Neutrophilia.
- Lymphopenia.

GLUCOCORTICOIDS [Anti Inflammatory]	MINERALD CORTICOIDS [↑ Na^+, ↑ H_2O]
SHORT ACTING	ALDOSTERONE
CORTISONE	FLUDROCORTISONE
HYDRO CORTISONE	DOCA
INTERMEDIATE ACTING	
PREDNISONE	
PREDNISOLONE	
TRIAMCINOLONE	
LONG ACTING [1½ Days]	
DEXAMETHASONE	
BETAMETHASONE	
PARAMETHASONE	

max. glucocorticoid activity	→	DEXAMETHASONE
max. glucocorticoid potency	→	BETAMETHASONE
glucocorticoid ī max. mineralocorticoid activity	→	HYDRO CORTISONE
max. mineralocorticoid activity	→	ALDOSTERONE
mineralocorticoid ī max glucocorticoid activity	→	FLUDROCORTISONE
Glucocorticoid ī zero mineralocorticoid activity O → zero M → mineralocorticoid activity	→	TRIAMCINOLONE DEXAMETHASONE BETAMETHASONE PARAMETHASONE
mineralocorticoid ī zero glucocorticoid activity O → ZERO C → cortisone like activity	→	DOCA

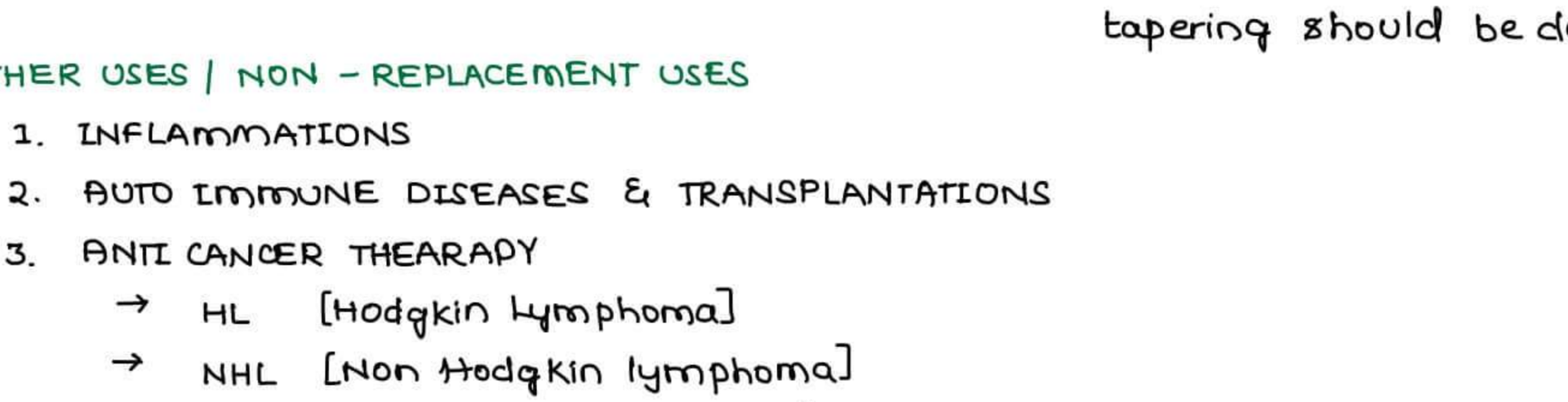
USES OF CORTICOSTEROIDS

ANTENATAL USES	REPLACEMENT USES	OTHER USES
Dexa / Betamethasone For fetal lung maturity	Acute Adrenal insufficiency / Addisonian crisis [by iv] Chronic Adrenal Insufficiency / Addison's disease [by oral]	INFLAMMATIONS AUTO IMMUNE DISEASES TRANSPLANTATIONS ANTI CANCER THEARAPY ASTHMA

ANTE NATAL STEROIDS

						Total DOSE	TOTAL Durat^{n}
BETAMETHASONE	→	im	12 mg per 24 hrs	×	2 Doses	→	24 mg	48 hr
DEXAMETHASONE	→	im	6 mg per 12 hrs	×	4 Doses	→	24 mg	48 hr

HYPOTHALAMO - PITUITARY - ADRENAL AXIS [HPA AXIS]



HPA AXIS SUPPRESSION

→ occurs when corticosteroids are given continuously for > 2wks.

→ PREVENTIVE MEASURES

1. STOP UNNECESSARY USE OF Steroids
2. If indicated, prescribe them for < 2WKS
3. If indicated for long periods, prescribe them on ALTERNATE DAY
   - Long acting steroids are avoided
4. if indicated daily & longer periods → DON'T STOP ABRUPTLY
   tapering should be done

OTHER USES / NON - REPLACEMENT USES

1. INFLAMMATIONS
2. AUTO IMMUNE DISEASES & TRANSPLANTATIONS
3. ANTI CANCER THEARAPY
   - → HL [Hodgkin Lymphoma]
   - → NHL [Non Hodgkin lymphoma]
   - → LL [Lymphocytic leukemia]
   - → MM [Multiple myeloma]
4. ASTHMA

5. DEXAMETHASONE SUPPRESSION TEST

- *Excessive glucocorticoids in the blood may be a normal physiological process or due to Cushing syndrome*
- *Dexamethasone suppression test is used to confirm whether excessive steroids are due to Cushing syndrome or normal physiological process*

1 mg dexamethasone at night 11 pm

↓

Measure the cortisol level at 8 am

↓↓ *Normal physiological Process*

↑ *Cushing syndrome*

G → Glaucoma [open angle glaucoma] [by long term e|d usage]
L → Limb muscle atrophy
U → Ulcer [peptic ulcer]
C → Cataract [mostly posterior subcapsular] [long term oral usage]
O → Osteoporosis
C → Cushing syndrome
O → Osteonecrosis [Avascular necrosis]
R → Renal failure
T → TB [Ileo caecal] → C|I
I → Infections
C → CHF } C|I
O → oedema }
I → Impair healing
D → DM → C|I
S → Suppression OF HPA axis [most dangerous complication]

OSTEOPOROSIS

	serum Ca^{2+}	serum PO_4^{3-}
VITAMIN D	↑	↑
CALCITONIN	↓	↓
PTH [Parathyroid Hormone]	↑	↓

VITAMIN D, ↑ serum calcium by
↑ absorption
↓ Excretion
} ↑ Bone Ca^{2+} → used in osteoporosis

PTH, ↑ serum calcium by
Resorption of Bone → ↓ Bone Ca^{2+} → causes osteoporosis

calcitonin, ↓ serum calcium by
moving Ca^{2+} to bone → ↑ Bone Ca^{2+} → used in osteoporosis

OSTEOPOROSIS
DRUGS USED
1. VITAMIN D
2. CALCITONIN
3. THIAZIDES
4. BISPHOSPHONATES
→ ALENDRONATE
RISEDRONATE
ZOLENDRONATE

BISPHOSPHONATES

→ Inhibit Osteoclasts [Bone eaters]

→ DOC for Osteoporosis [for any reason]

→ Highly toxic to oesophagus

Preventive measures

1. Given on empty stomach
2. Given ↑ full glass of water
3. Should not lie down for a min. of 30 min after taking

→ Alendronate, Risendronate } given orally

Zolendronate → Given IV once yearly

* *USES OF BISPHOSPHONATES:*

i. D.O.C for osteoporosis (due to any reason)

ii. D.O.C for hypercalcemia of malignancy

Cancer → metastasis to Bone → Stimulates osteoclasts → resorption of bone → Hypercalcemia

iii. D.O.C. for Paget's disease

* *SIDE EFFECTS OF BISPHOSPHONATES*

- Esophagitis

- Osteonecrosis of mandible

- Zolendronate → Causes renal failure

POST MENOPAUSAL OSTEOPOROSIS

ESTROGEN → responsible for Post menopausal osteoporosis

→ ACTIONS

BONE	→ ↑	formation
BLOOD	→ ↑	HDL / LDL Ratio
BREAST	→ ↑	Carcinoma
ENDOMETRIUM	→ ↑	carcinoma
LIVER	→ ↑	clotting factors → Thrombo Embolism

→ Not preferred for Rx of PM osteoporosis

→ Earlier HRT [Estrogen + Progesteron] given, but not now

SERM [SELECTIVE ESTROGEN RECEPTOR MODULATORS]

1. RALOXIFENE

→ Used in PM osteoporosis

→ Additional Benefits

→ ↑ HDL

→ ↓ Breast & Endometrial carcinoma risk

→ SIE → Thromboembolism

1. PTH ANALOGUES

→ Each parathyroid molecule contains 84 amino acids (i.e. PTH 1 – 84).

Full molecule stimulates osteoclast and induces osteoporosis by resorption of bone.

A fraction of parathyroid (PTH 1 – 34) stimulates Osteoblast and it is isolated and used for osteoporosis treatment.

→Drugs (PTH1-34) are,

- Teriparatide and
- Abaloparatide (new drug)

Mechanism of action – stimulation of osteoblasts.

→Route of administration – Not effective orally; given Subcutaneously.

→Side effect – increases the risk of Osteosarcoma.

2. STRONTIUM RANELATE

→Has dual activity of stimulating osteoblast and inhibiting osteoclast

- Side effect
  - Thromboembolism

3. ROMOSOZUMAB

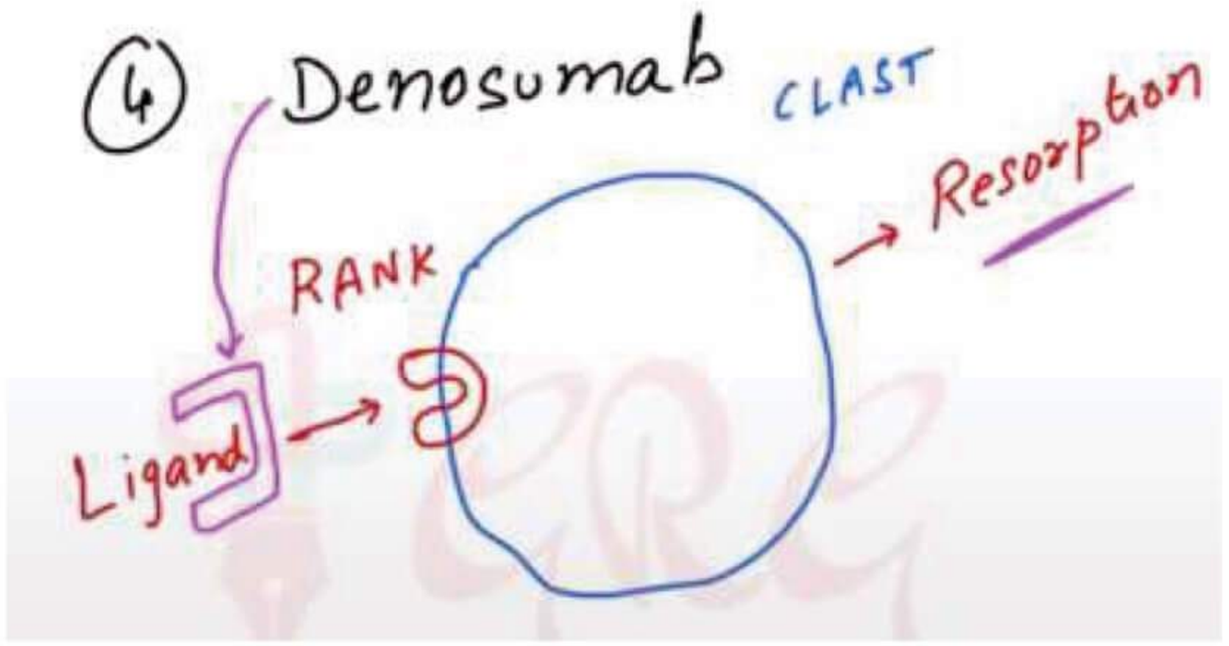
→**Sclerostin** is a protein which has the function of inhibiting osteoblast and stimulating osteoclast.

- Romosozumab is the drug which inhibits sclerostin activity.
- Thus romosozumab also has dual mechanism.

4. DENOSUMAB

→On the surface of osteoclast cells, RANK receptors are present. when ligand binds, it stimulates the resorption of bone.

- So, when the drug Denosumab binds to RANK ligand it inhibits the osteoclastic activity or resorption of bone.



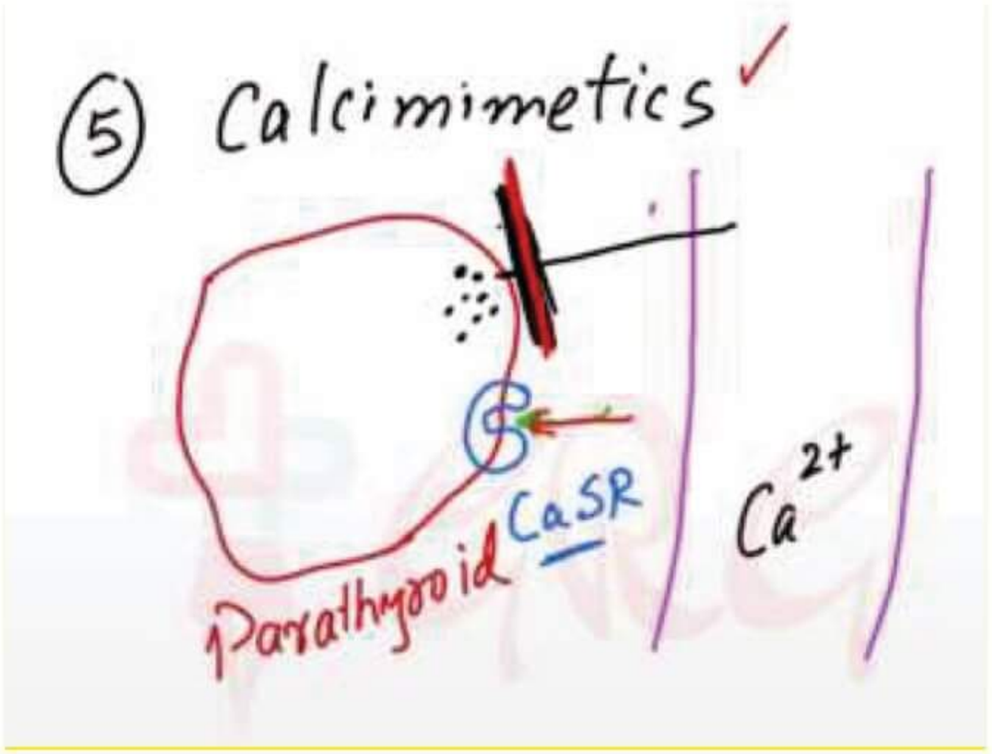
5. CALCIMIMETICS

Parathyroid gland has Calcium sensing receptor (CaSR). Whenever it senses and binds to calcium, it inhibits PTH release from Parathyroid gland.

- Hypocalcemia stimulates PTH release from Parathyroid gland.
- In Hyperparathyroidism patients, inspite of Hypercalcemia still PTH is more in the blood because the calcium is not able to stimulate CaSR.

- CALCIMIMETICS are agonist of CaSR and when these stimulate CaSR, PTH is not released and bone resorption does not occur.

  Drugs are,
  - Cinacalcet
  - Etelcalcetide



SEX HORMONES

- Ovary in females secrete Estrogen and Progesterone.
- Testes in males secrete Testosterone.

ESTROGENS

NATURAL ESTROGENS

There are three types

→ E1 – ESTRONE – PREDOMINANT IN POST MENOPAUSAL PERIOD

→ E2 – ESTRADIOL – PREDOMINANT IN REPRODUCTIVE AGE GROUP

→ E3 – ESTRIOL – PREDOMINANT IN PREGNANCY

DRUGS WORKING THROUGH ESTROGEN RECEPTORS:

1. SERM (Selective estrogen receptor modulators)

2. SERD (Selective estrogen receptor downregulators)
3. STEAR (Selective tissue estrogen activity regulators)
4. Aromatase inhibitors

→ Estrogen works at:

- Bone: inhibit osteoclast, so it increases bone formation
- Blood: increase HDL/LDL ratio
- Breast: increase the risk of cancer
- Endometrium: increase risk of cancer
- Liver: increase clotting factors and can lead to thromboembolism

→ In condition where there is absence of estrogen as in postmenopausal, there is vasomotor symptoms like hot flushes and vaginal atrophy.

1. SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERM):

These act as agonist to estrogen receptor in some tissues and antagonist in some tissues.

Ideal SERM:

- Increase bone formation
- Increase HDL/LDL ratio
- Decrease breast cancer risk
- Decrease endometrial cancer risk
- Decrease thromboembolism
- Closest to ideal SERM is RALOXIFENE, however it is agonist at liver, therefore the major side- effect is thromboembolism.

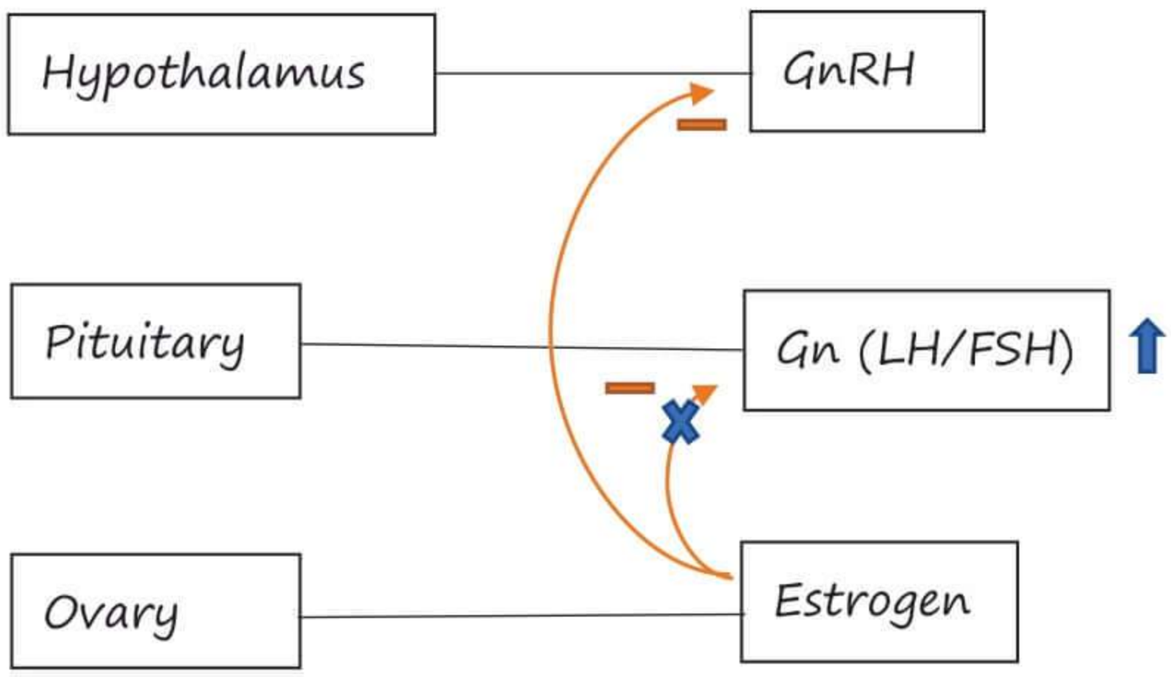
- Newer SERM like:
  - Tamoxifen
  - Doloxifen
  - Toremifen

  →
  - Decrease breast cancer risk
  - Increase bone formation
  - Increase HDL/LDL ratio
  - Increase risk of endometrial cancer
  - Increase risk of thromboembolism

- These new SERM are beneficial on three B'S:
  - Bone
  - Blood
  - Breast

→ Clomiphene:

- SERM which are estrogen receptor antagonist in pituitary.
- By inhibiting negative feedback of estrogen, it can increase LH/FSH and it can be used for treatment of anovulatory infertility.
- Main side effect:
  - Multiple pregnancy



→ Ospemifene:

- Estrogen receptor agonist mainly in vagina.
- Used for treatment of dyspareunia in post- menopausal women.

→ Ormeloxifene (Centchroman):

- Estrogen antagonist in endometrium
- It is used for contraception
- Brand name: SAHELI (synthesize by Central Drug Research Institute in India Lucknow)

2. SELECTIVE ESTROGEN RECEPTOR DOWNREGULATOR (SERD):

→ Fulvestrant:

- Used for Tamoxifen resistant breast cancer
  - More effective
  - Safer
  - Long acting

3. SELECTIVE TISSUE ESTROGEN ACTIVITY REGULATORS (STEAR):

→ Tibolone: (Designer HRT)

- metabolized to different metabolites in difference tissue. In some tissue, it forms agonist and in some it forms antagonist.
- Forms agonist metabolite in:
  - Vagina (prevent vaginal atrophy)
  - Blood vessel (prevent vasomotor symptoms)
  - Bone (prevent osteoporosis)

4. Aromatase inhibitors:

→ These drugs are only indicated in post-menopausal breast cancer, which is due to estrogen production outside ovary like adrenal gland.

→ Drugs:

- Letrozole
- Anastrozole
- Exemestane

→ Androgen ⟶ estrogen

✚

Aro~~m~~tase

PROGESTERONES

	ALSO CALLED	POTENCY	ANDROGENIC ACTIVITY
1ST GENERATION	ESTRANGES	+	+++
2ND GENERATION	GONANES	++	++

3RD GENERATION		+++	+
4TH GENERATION		++++	Anti-androgenic

1ST GENERATION	2ND GENERATION
NOR- ETHINDRONE NOR – ETHINODREL	NORGESTREL LEVONORGESTREL (LNG)
3RD GENERATION	**4TH GENERATION**
DESOGESTREL NOR GESTIMATE GESTIDONE	NOMEGESTREL DROSPIRENONE

DROSPIRENONE → also has anti-mineralocorticoid activity

SELECTIVE PROGESTERONE RECEPTOR MODULATORS (SPRM)

→Mifepristone

→Onapristone

→Ulipristal

MIFEPRISTONE:

→Acts as antagonist of

- Progesterone receptors in uterine endometrium
- Glucocorticoid receptors
- Androgen receptors

Major uses of mifepristone:

M – Morning after pills (emergency contraception)

I – Induction of abortion

F – Fibroid

E – Endometriosis

PR – Progesterone Receptor positive cancers like Breast cancer and Meningioma

I – Increased
S – Steroids
} Cushing syndrome

tone

ONAPRISTONE:

→Only Progesterone antagonist (Does not block Glucocorticoid receptors).

→ Indicated for abortion

ULIPRISTAL:

→Emergency contraceptive which can be given even after 120 hours of unprotected sexual intercourse as a single dose of 30mg .

ANDROGENS

TESTOSTERONE

→5 α reductase converts testosterone into Dihydrotestosterone (DHT) which works on androgen receptors. Testosterone also can directly work on androgen receptors.

Functions of Testosterone:

F – Feedback inhibition

I – Internal genitalia development

S – Spermatogenesis

H – Hematopoiesis

Functions of Dihydrotestosterone:

S – Secondary sexual characters

E
X
} - External genitalia development

U – Urine (Prostate)

A – Alopecia (male pattern baldness)

L – Loss of hair

5 ALPHA REDUCTASE INHIBITORS:

- Finasteride
- Dutasteride

ANDROGEN RECEPTOR BLOCKERS:

- Flutamide
- Nilutamide
- Bicalutamide
- Enzalutamide
- Apalutamide

→Androgen receptor blockers are more potent than 5 α reductase inhibitors as it directly blocks androgen receptors.

→In treatment of prostatic cancers androgen receptor blockers are commonly used.

→In treatment of BPH and Androgenital alopecia (Male pattern baldness) 5 α reductase inhibitors like Finasteride are used.

Side effects of both the class of drugs:

- Impotence

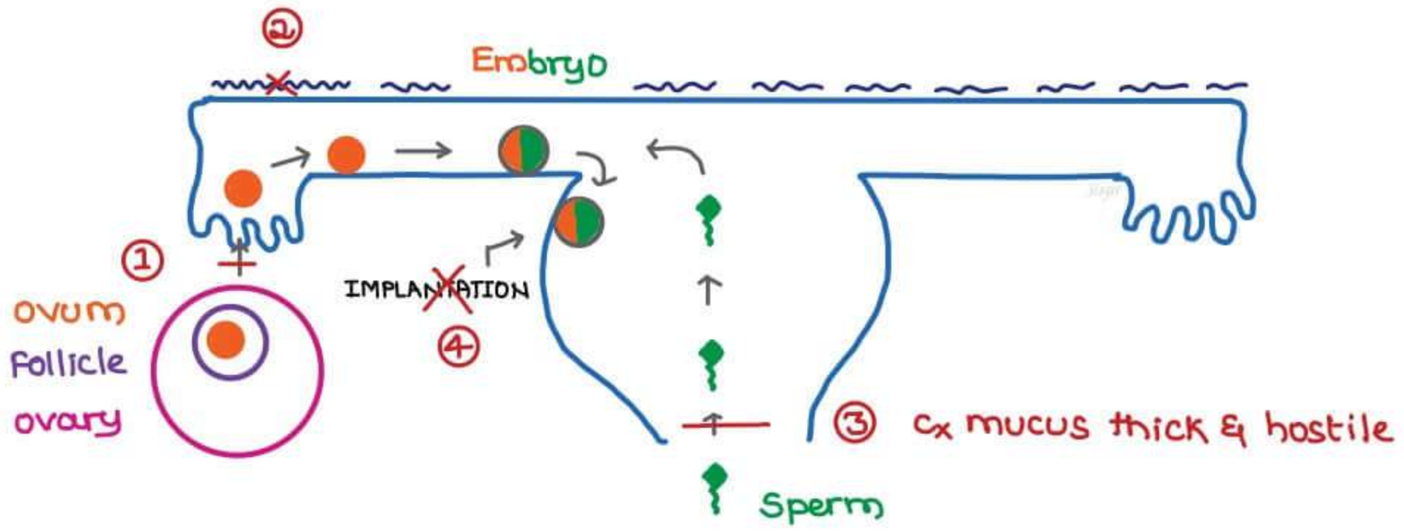
ANABOLIC STEROIDS:

- Two main actions of testosterone
  - Androgenic
  - Anabolic
- After intake of anabolic steroids the proportion of androgenic action to anabolic action is increased to 1:3 from its normal ratio of 1:1
- Examples of anabolic steroids are
  - Nandrolone
  - Stanozolol

Side effects of anabolic steroids:

- Hepatotoxicity
- Impotence
- In Dope test, which is done in competitive sports like Olympics, athletes are tested for intake of anabolic steroids.

ORAL CONTRACEPTIVES



	MAIN MECHANISM
COMBINED OCP [E+P]	Inhibition of ovulation
PROGESTERONE ONLY PILLS / MINIPILLS	C_x mucus thick & hostile
EMERGENCY / POST COITAL / MORNING AFTER PILLS	Disloging of implantation

COMBINED ORAL CONTRACEPIVE PILLS

→ Estrogen → ETHINYL ESTRADIOL
Progesterone → LEVONORGESTREL

→ DOSAGE
→ 1 tablet daily for 21 days from 1st day of menstrual cycle
→ no tablet for next 7 days

→ TO ↑ compilatⁿ,
28 Tablets Strip i
1st 21 tablets contains drug
next 7 tablets contains fe

→ 1. IF 1 tablet is missed → Take 2 tablets on next day
2. IF 2 tablets missed → Discard remaining tablets & practice other method of contraceptⁿ t it. start afresh from next cycle

→ BREAKTHROUGH BLEEDING
→ bleeding @ 1 - 21 days
→ prevented by PHASIC PILLS
– gradual ↑ OF Progesterone from 1 to 21 days

POP / MINIPILLS

→ contains LNG

→ INDICATIONS

1. Thromoembolism risk
2. Lactation [contraceptive of choice]

EMERGENCY CONTRACEPTIVES

1. COC → 2 tablets at start + 2 tablets after 12 hrs
2. POP [LNG] → 1 tablet at start + 1 tablet after 12 hrs or
   → 2 tablets at start
3. MIFEPRISTONE
   → SPRM – Selective Progesterone Receptor Modulator
   → USES
      1. Emergency contraception
      2. Induction of abortion

→ Above 3 drugs should be used ĩ in <72 hrs of unprotected sex.

4. ULIPRISTAL
   → can be used ĩ in 120 hrs

ADVERSE EFFECTS OF OCP

MILD	MODERATE	SEVERE
N → Nausea	Acne	CVS [Thrombo Embolism]
O → Oedema	weight gain	CNS [Depression]
R → Recurrent headache	chloasma	Cholestasis
M → Mastalgia		Cancers
A → Abnormal bleeding		↑/↔ Breast CA
L → Loss of Withdrawal bleeding		↑ cervical CA

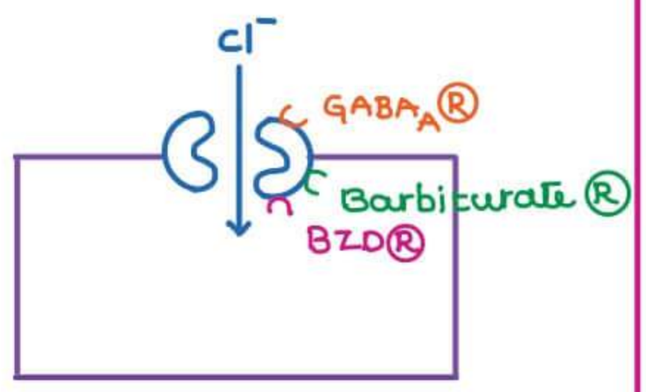
NON CONTRACEPTIVE BENEFITS

Other → ↓ Ovarian cyst [DOC for PCOD]
B → ↓ Benign Breast Disease
E → ↓ Endometriosis
N → ↓ Neoplasia [Endometrial & ovarian cancers]
E → ↓ Ectopic pregnancy
F → ↓ Fibroid
I → ↓ Iron deficiency Anemia
T → ↓ Premenstrual Tension syndrome
S → ↓ Skeletal Disease [osteoporosis]

SEDATIVES - HYPNOTICS

GABA [Inhibitory neurotransmiter of Brain]

	BARBITURATES	BENZODIAZEPINES
GABA	mimetics	GABA facilitatory
K^- channel	↑ duration	↑ Frequency
DRC	Steep	Flat
Inducers	+++	xx
Addiction	++++	+
Amnesia	+++	+
Antidote	xx	FLUMAZENIL



BENZODIAZEPINE

↓

FLU MAZE|NIL

[Antidote]

BENZODIAZEPINES

→ includes

- DIAZEPAM → OXAZEPAM [active metabolite]
- FLURAZEPAM
- NITRAZEPAM
- FLUNITRAZEPAM

→ BZD are LONG ACTING dit active metabolites

→ cause Hangover

→ C/I in elderly

→ C/I in Liver failure

→ BZD NOT FORMING ACTIVE METABOLITES

- S → SHORT ACTING BZD
- T → TEMAZEPAM
- O → OXAZEPAM
- L → LORAZEPAM
- E → ESTAZOLAM

GOOD QUALITY SLEEP	→	Sleep architechture [phases OF REM & Non-REM] maintained
Barbiturates & BZD	→	Distort the normal sleep architecture [Quality]
	→	also ↓ Latency of sleep onset
	→	↑ Quantity of Sleep

Z DRUGS

- *ZOLPIDEM*
- *ZOPICLONE*
- *ZALEPLON*
- *ESZOPICLONE*

↓

Stimulate α_1 / ω_1 subunit of Benzodiazepine receptor

↓

- Only ↓ Latency
- Does not ↓ the duration of sleep
- Lack antianxiety, Muscle relaxant, Anticonvulsant property.
- Only hypnotic property (+)
- Antidote is Flumazenil

↓

Drug of choice for Insomnia

MELATONIN RECEPTOR AGONISTS

- Melatonin is secreted at night and produce sedative effect
- Maintain day-night cycle

Ramelteon

- Melatonin receptor agonist
- Indicated for jet lag, shift workers and Insomnia
- <2% oral bioavailability
- Psychiatric adverse effects in overdose
- Metabolized by microsomal enzymes, so prone to drug interactions

OREXIN RECEPTOR ANTAGONIST

- Orexin receptor stimulation promote wakefulness
- Suvorexant is orexin antagonist to induce sleep

SUV OREX ANT

Sedation (use) OREXin ANTagonist

PARKINSONISM

→ Normally, Balance b/w Dopaminergic (DA) & cholinergic (Ach) neurons

→ In Parkinsonism, this balance is lost [Relative cholinergic excess

DA ⇌ Ach	DA ⇌ Ach
100 100	50 100
Normal	Parkinsonism

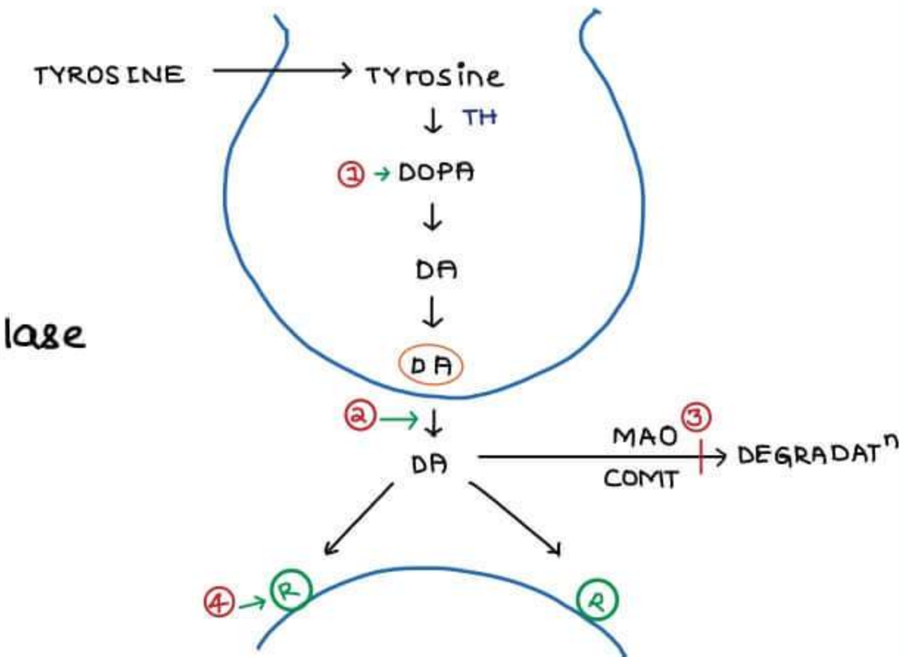
DOPAMINERGIC DRUGS

1. LEVODOPA

→ LEVODOPA alone

→ is LESS efficacious

→ as peripheral DOPA decarboxylase convert it to Dopamine



→ DA causes PERIPHERAL SIDE EFFECTS

→ D_1 + → Hypotension

β_1 + → Arrhythmias

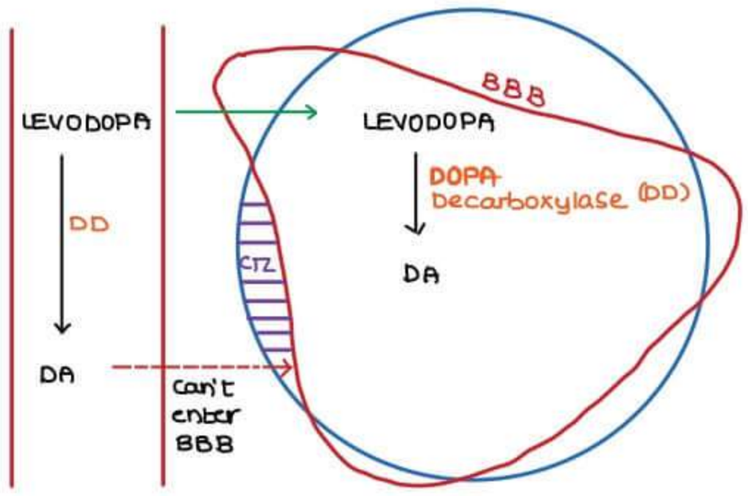
α_1 + → Hypertension

CTZ + → Vomiting

→ CARBIDOPA, BENSERAZIDE } Peripheral DOPA Decarboxylase inhibitors

→ ↑ Efficacy of Levodopa

→ ↓ Peripheral SIE of DA



→ Pyridoxine is a cofactor for dopa-decarboxylase

→ If Vitamin B complex (containing pyridoxine) is given with levo-dopa, it will decrease its efficacy by increasing peripheral formation of dopamine

→ PSYCHOSIS [dlt excessive DA in brain]

→ all antiParkinsonism drugs can cause Psychosis

→ all antipsychotic drugs can cause Parkinsonism

→ central SIE can't be prevented by carbidopa

→ Psychosis

→ Dyskinesia

On-Off phenomenon:

- In late Parkinsonism, When we give levodopa, it controls symptoms for 20-22 hours, after that wearing off occurs, leading to appearance of symptoms. This is called wearing off phenomenon.
- In extreme cases, On Off phenomenon occurs. During on period, excess dopamine leads to psychosis
- During off period, lack of dopamine leads to appearance of Parkinsonism symptoms.

2 AMANTADINE

→ acts by releasing DA from vesicle

→ also used as antiviral drug for Influenza virus

Side effects

- Ankle edema (reversible)
- Livedo reticularis (Pinkish pigmentation of skin in form of meshwork)

→Recently approved for treating Levo-dopa induced Dyskinesia as Amantadine acts as a NMDA ANTAGONIST

MAO INHIBITORS

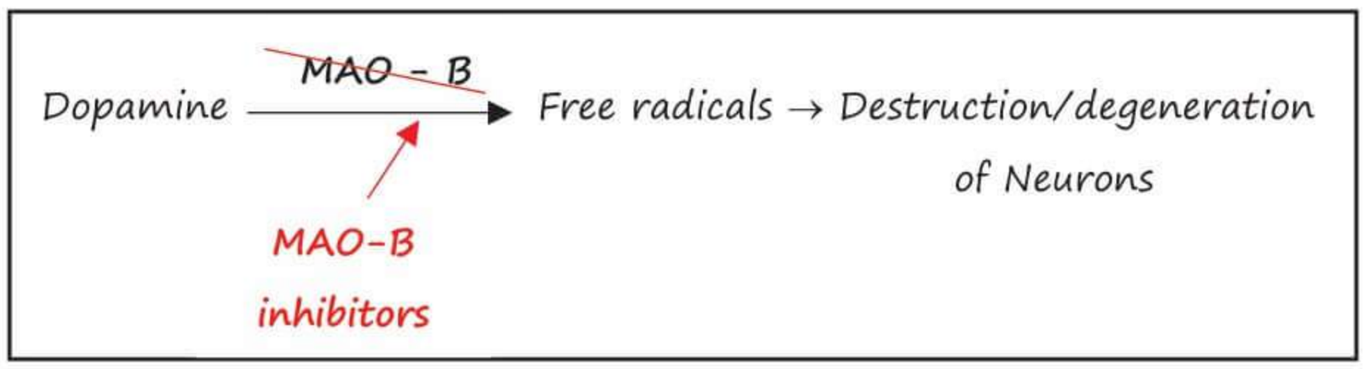
MAO A	MAO B
present at all places metabolises all substances	present mainly in Brain metabolises DA

SELECTIVE MAO-B INHIBITORS

→ Drugs
- Selegiline
- Rasagiline
- Safinamide – approved for On-Off phenomenon of Levodopa

→ May act as disease modifying agents for Parkinsonism (decrease neuronal degeneration)

→ **Mechanism of action**



COMT INHIBITORS

→ Includes

ENTACAPONE → preferred

TOLCAPONE → Toxic to Liver

4. DOPAMINE AGONIST

	ERGOT	NON ERGOT
	BROMOCRIPTINE PERGOLIDE	PRAMIPEXOLE ROPINIROLE
		safest Long Acting
VC → Gangrene	✓	x
Fibrosis	✓	x

- Pramipexole and ropinirole are **DOC for Parkinsonism**
- Pramipexole and ropinirole are **DOC for Restless leg syndrome** also
- These associated with excessive day-time sleepiness and impulse control disorders

ANTI CHOLINERGIC DRUGS [central Ach #]

→ DOC for Drug Induced Parkinsonism

→ includes

- BENZHEXOL [TRIHEXIPHENYDIL]
- BENZTROPINE
- BIPERIDINE
- PROCYCLIDINE

1st Generation Anti-histaminic drugs

→ Can cross Blood Brain Barrier

→ Has anticholinergic activity

→ **Promethazine** – used as an alternative to Benzhexol in treating Drug induced Parkinsonism

DOC FOR PARKINSONISM	→	PRAMIPEXOLE / ROPINIROLE
MOST EFFECTIVE DRUG FOR PARKINSONISM	→	LEVODOPA + CARBIDOPA
DOC FOR DRUG INDUCED PARKINSONISM	→	BENZHEXOL

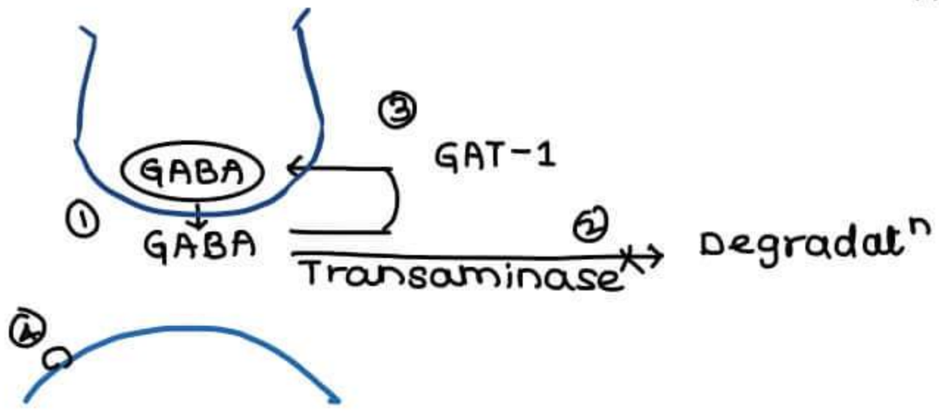
1 GABA↑

2. GLUTAMATE ↓

3 Ca^{2+} #

4 Na^{+} #

5 K^{+} CHANNEL OPENERS



1 DRUGS ↑ GABA

1. PREGABALIN

GABAPENTIN

→ Drugs act by releasing GABA

→ DOC for Neuropathic pain dlt

Diabetic neuropathy

Post Herpetic neuralgia

→ Recent update → MOA → mainly by Ca^{2+} channel inhibition

2 VIGABATRIN

VIsual field contractn [S/E]

↑

VI GABA TR IN — INfantile Spasm [USE]

↓

GABA TRansaminase INhibitor [MOA]

→ DOC for infantile spasm – ACTH

→ DOC for infantile spasm in a patient with Tuberous Sclerosis – vigabatrin

3 TIAGABINE

→ Transport Inhibitor [GAT1] [Reuptake Inhibitor] of GABA

4 BARBITURATES → PHENOBARBITONE

BZD → DIAZEPAM

LORAZEPAM

CLONAZEPAM

CLOBAZAM

Phenobarbitone can cause Hyperkinesia in children

DOC for febrile seizures → Diazepam

DOC for status epilepticus → Lorazepam

used for absence seizures → clonazepam

used in Lennox Gastaut Syndrome → clobazam

2 ↓ GLUTAMATE ACTIVITY

NMDA #	AMPA #
FELBAMATE	PERAMPANEL
S/E → Bone Marrow Suppression	Used in focal seizures

3. T - Ca^{2+} CHANNEL BLOCKERS

ETHOSUXIMIDE

→ used only for Absence seizure

4 Na^{+} CHANNEL BLOCKERS

PHENYTOIN, CARBAMAZEPINE, OXCARBAZEPINE } C/I in absence & myoclonic seizures; Useful in GTCS & focal seizures

TOPIRAMATE, ZONISAMIDE } cause Renal Stones

LACOSAMIDE, RUFINAMIDE } used in focal seizures

TOPIRAMATE OTHER USES

→ ↓ Craving of Alcohol
→ Obesity
→ Migraine prophylaxis
→ Bipolar disorder

CARBAMAZEPINE

→ DOC for Focal seizures
→ DOC for Trigeminal neuralgia
→ can be used for
  Diabetes insipidus [DOC for DI → DESMOPRESSIN]
  Bipolar Disorder [DOC for BD → LITHIUM]

→ **Adverse effects (Remembered as 4 A)**

Auto induction: *Increase metabolism of other drugs & itself. Initially started with lower dose and gradually has to be increased due to tolerance.*

Aplastic Anemia: *CBZ causes bone marrow suppression.*

ADH release from post pituitary: *Result in SIADH as S/E*

↑ ADH = ↑ water = Dilution of ions
= ↓ Na^{+}
= Dilutional hyponatremia

Therefore CBZ is avoided in Elderly patient.

DOC for focal seizures in Elderly = Lamotrigine

Ataxia – *Nystagmus, vertigo [mainly seen with overdose]*

PHENYTOIN

→ Follows Zero order Kinetics
→ Enzyme inducer
→ Used for Arrhythmias too
→ Used for GTCS & focal seizures
→ c/I in Absence & Myoclonic Seizures

ADVERSE EFFECTS

H → Hirsutism, Hypertrophy of gums
O → Osteomalacia
T → Teratogenecity [Fetal Hydantoin Syndrome]
M → Megaloblastic anaemia [↓folate]
A → Arrhythmia [only in overdose]
L → Lymph node enlargement
I → ↓ Insulin
K → ↓ vitamin K
A → Ataxia, Nystagmus, vertigo [cerebellar symptoms] [only at ↑dose]

→*Phenytoin in pregnancy results in*

- *Congenital malformations*
- *High risk of hemorrhagic disease of newborn (Vit K deficiency)*

→*So, after the delivery, new born should be given Vitamin K supplementation.*

5. K^+ CHANNEL OPENER

RETIGABINE [EZOGABINE]

→ used for focal seizures
→ does not act on GABA

SODIUM VALPROATE

MOA

Na channel Blocker
Ca^{2+} channel Blocker
↑ GABA
↓ Glutamate

DOC for → GTCS
→ Absence seizures
→ Myoclonic seizures
→ Atonic seizures
→ Lennox Gastaut syndrome

→ also used for Bipolar disorder

ADVERSE EFFECTS

V – Vomiting

A – Alopecia/ Curling of hair

L – Liver disease (hepatotoxicity in young children has high incidence)

P – Pancreatitis, ↑ risk of PCOD (gender Specific S/E)

R – Rash, allergy

O – Obesity

A – Ataxia (in overdose)

TE – TEratogenicity (most teratogenic Antiepileptic drug)

↓

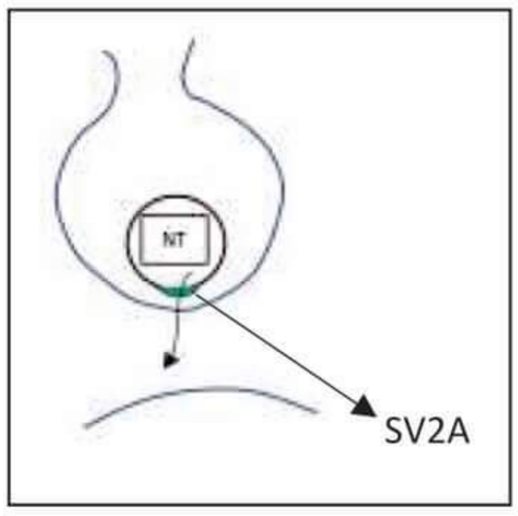
Therefore if administered in pregnancy, a high dose of folic acid (4000 µg/ day) should be supplemented to prevent neural tube defects

LAMOTRIGINE

- DOC for focal seizures in elderly
- Acts by Blocking Na channels, Increasing GABA and Decreasing glutamate activity
- Side effects:
  - Steven Johnson Syndrome (skin surface < 30%)
  - Toxic Epidermal Necrolysis (skin surface > 30%)

NEW ANTIEPILEPTIC DRUGS

1. Bind to SV2A: LEVETIRACETAM
   BRIVARACETAM



2. CANNABIDIOL:

   - Stimulate CB1.
   - Approved for Dravet syndrome

3. STIRIPENTOL:

   - Increases the action of GABA
   - Inhibits the enzyme LDH

EPILEPSY IN PREGNANCY:

- Most teratogenic: Valproate
- Least teratogenic: Lamotrigine, Levetiracetam
- If patient controlled on antiepileptic medication: Don't change the medication even if it's valproate, add high dose folic acid i.e 4000 microgram per day to prevent teratogenic effects.
- For first time treatment of epilepsy in pregnancy: Levetiracetam or Lamotrigine are preferred.
- For Eclampsia: MgSO4 IV is DOC. It has neuroprotective properties.

Epilepsy in pregnancy	Seizures in Eclampsia
➢ Seizures not occurring now, but want to prevent seizure ➢ Therefore drug given throughout pregnancy to prevent seizures. ➢ Drug given has least teratogenicity → Most – Valproate → Least – Lamotrigine/ Levetiracetam	➢ Acute episode of seizures in pregnancy, occurring now d/t high B.P ➢ DOC – $mgSO_4$ IV [cause neuronal protection in baby also]

PSYCHIATRIC ILLNESS

PSYCHOSIS [no insight]	NEUROSIS [insight present]
1. SCHIZOPHRENIA	1. GENERALISED ANXIETY DISORDER
2. MOOD DISORDERS	2. PHOBIAS
a. MANIA	3. OCD
b. DEPRESSION	4. BULIMIA
c. MANIC DEPRESSIVE PSYCHOSIS/ BIPOLAR DISORDER	5. POSTTRAUMATIC STRESS DISORDER

SCHIZOPHRENIA

ANTI PSYCHOTIC DRUGS

TYPICAL ANTI PSYCHOTICS [D_2 #]

ATYPICAL ANTI PSYCHOTICS [$5HT_2$ #]

→ Most drugs possess both properties

→ $\frac{D_2\ \#}{5HT_2\ \#} > 1$ → Typical Antipsychotics

→ $\frac{D_2\ \#}{5HT_2\ \#} < 1$ → Atypical Antipsychotics

TYPICAL ANTIPSYCHOTICS

1 STRONG D_2 #

→ HALOPERIDOL [Highest risk OF EPS]

DROPERIDOL

FLUPHENAZINE

2 WEAK D_2 #

→ CHLORPROMAZINE

THIORIDAZINE [Least risk of EPS]

3 INTERMEDIATE D_2 #

→ THIOTHIXENE

CHLORPROTHIXENE

SIDE EFFECTS

1. EXTRA PYRAMIDAL SYMPTOMS [EPS]
   1. Dystonias [earliest]
   2. Akathesia [mc]
   3. Parkinsonism
   4. Tardive dyskinesia [Latest]
   5. Malignant neuroleptic Syndrome

→

TREATMENT

BENZHEXOL → Dystonias [DOC]
Parkinsonism [DOC]
Akathisia
Malignant neuroleptic syndrome

→ C/I in Tardive dyskinesia

PROPRANOLOL → Akathisia [DOC]

DANTROLENE → Malignant neuroleptic syndrome [DOC]

VALBENAZINE → Tardive dyskinesia

Pathogenesis of Tardive dyskinesia

→ *Different from all other EPS*

→ *Occurs with withdrawal of Anti-psychotic drugs*

→ *Chronic blockade of D_2 receptors leads to Supersensitivity*

→ *Therefore dopamine depleters like valbenazine (VMAT-2 inhibitor) are used for treatment*

VMAT 2 INHIBITORS

→ *Vesicular monoamine transporter-2 (VMAT-2) transports the monoamine like dopamine and serotonin into the vesicle.*

→ *Inhibiting the transporter can decrease the entry of dopamine in vesicle leading to decreased release of dopamine and NA in the synapse.*

→ *But these also inhibit serotonin, causing decrease in serotonin.*

DRUGS

RESERPINE

TETRABENAZINE

DEUTETRABENAZINE

VALBENAZINE

→ *Reserpine was the first VMAT inhibitor developed for Antihypertensive action (due to decrease in NA leading to reduction in Blood pressure).*

→ *But it also decreased Serotonin resulting in Depression and people ended up in suicides and so withdrawn now.*

→ *Tetrabenazine and Deutetrabenazine are used for Huntington's Chorea (increased dopamine)*

→ *Valbenazine is approved for Tardive dyskinesia*

2. HYPERPROLACTINEMIA

→ D_2 → ↓ Prolactin

D_2 # → ↑ Prolactin

→ m/c a/w strong D_2 #

3. Ach # → dryness, blurring of vision etc
4. α # → ↓BP
5. H_1 # → sedation
6. Seizures

} more common ī weak D_2 #

DISADVANTAGES OF TYPICAL DRUGS

1. S|E
2. not effective against -ive symptoms

ATYPICAL ANTI PSYCHOTICS

ADVANTAGES

1. Lesser S|E
2. Effective against both positive & negative symptoms

DRUGS

- → CLOZAPINE
- → OLANZAPINE
- → QUEITAPINE
- → ASENAPINE
- → ZOTEPINE
- → ARIPIPRAZOLE
- → RISPERIDONE
- → PALIPERIDONE
- → ILOPERIDONE
- → ZIPRASIDONE
- → LURASIDONE
- → PIMAVANSERIN

SIDE EFFCTS

- → ↑ Glucose
- → ↑ Lipids
- → Weight gain
- → Insulin Resistance

} LIPODYSTROPHY SYNDROME [highest risk ī clozapine & olanzapine]

CLOZAPINE

- DOC for Resistant Schizophrenia
- Adverse effects are:
  - → Agranulocytosis [Dose dependent]
  - → Seizures [Dose dependent]
  - → Myocarditis
  - → Sedation
  - → Sialorrhea (due to blockade of α_2 & stimulation of M_4 receptors)

QUETIAPINE

→ Causes Cataract

ZIPRASIDONE

→ Causes Torsades de Pointes [↑ QT interval]

RISPERIDONE

→ Has maximum D2 blocking property among the atypical drugs

→ Maximum risk for extrapyramidal symptoms and hyper-prolactinemia among atypical drugs

PIMAVANSERIN

→ Atypical antipsychotic drug acts by blocking 5HT2 receptor and specifically approved for treatment for Parkinsonism Induced Mental Anomalies (Psychosis).

USES OF ANTIPSYCHOTIC DRUGS:

- Anti: Antiemetic property
  Antimanic
- Psy: Psychosis
- Cho: Huntingtons chorea (Tetrabenazine: DOC)
- Tics: Tic Disorder (Gille de la Tourette syndrome):
  Tetrabenazine is DOC
  Haloperidol, Clonidine and Guanafacine are also used

MOOD DISORDERS

ACUTE MANIA

→ Rx of Acute Episode → SEDATIVES [Anti psychotics / BZD] + LITHIUM
→ Prophylaxis → LITHIUM [DOC]
→ LITHIUM

L → Leucocytes } Leucocytosis
I → Increase }
T → Tremors [mc]
H → Hypothyroidism
I → Increase } Polyuria
U → Urine }
M → avoided in Mothers [Lithium in pregnancy → Ebstein anomaly]

→ Plasma concentration Norms

Acute mania → 0.8 – 1.2 mEq/L
Prophylaxis → 0.5 – 0.8 mEq/L
TOXIC → > 2 mEq/L

MECHANISM OF ACTION

Lithium controls,

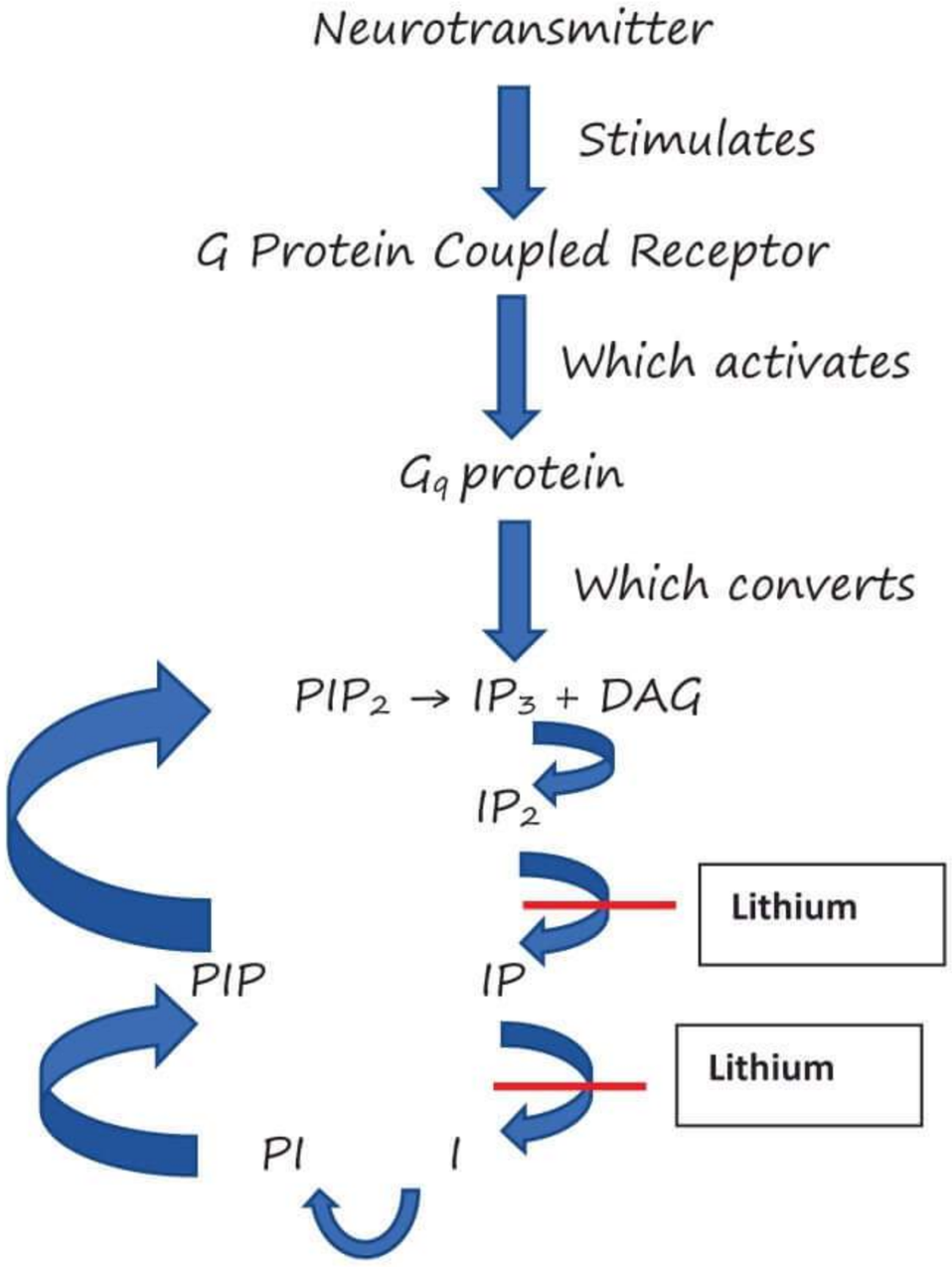
- Mania
- Depression

→ Mania occurs due to Overactivity of Neurotransmitters in brain particularly which acts through Calcium and the brain gets stimulated.

→ In Depression, there is deficiency of BDNF (Brain Derived Neurotrophic Factor) which is required for Neuronal Plasticity (connections between neurons).

Neuronal plasticity is lost in depression.

MANIA:



→ IP_3 (Inositol triphosphate) is required for increasing Calcium, when calcium increases it causes overactivity of brain.

→ After activation of calcium it is metabolized to IP_2 with help of phosphatase enzyme

→ Further it is metabolized to form IP.

→ IP is further metabolized to form Inositol by removing one more phosphate group.

→ Inositol will attach with phosphatidyl group which results in formation of Phosphatidyl Inositol (PI).

→ PI is then phosphorylated to PIP.

→ PIP will then be converted and regenerated again to PIP2 (Phosphatidyl Inositol Phosphate) and this recycling process continues to produce more Calcium leading to increased neuronal activity.

→ In Mania, Lithium acts by inhibiting phosphatase enzymes which then decreases Calcium production and Mania is controlled.

→ In Depression, BDNF is usually metabolized by Glycogen Synthase Kinase 3 Beta (GSK-3-β) enzyme which is inhibited by Lithium leading to decrease in BDNF breakdown which leads to increase in Neuronal Plasticity, hence it reverses Depression.

USES OF LITHIUM:

- Acute Mania
- Bipolar disorder (Drug of Choice)
- Depression
- Neutropenia

BIPOLAR DISORDER:

BIPOLAR

Prevention of Mania

- Lithium (DOC for Mania prophylaxis)
- Anti – epileptic drugs
  - Carbamazepine
  - Valproate (DOC for Rapid cyclers)
  - Topiramate
- Anti – Psychotics
  - DOC for Bipolar in Pregnancy, as Lithium is contraindicated In pregnancy.

Prevention of Depression

1. Lithium (DOC for prevention of depression)
   - It is the only drug that decreases suicidal risk in bipolar patients.
2. Lamotrigine.

→ Overall Drug of Choice for Bipolar patients is Lithium.

DEPRESSION:

→ Earlier it was believed, decrease in Monoamines (MA) (5HT > NA >> DA) causes depression.

→ Later it was linked with decrease in BDNF i.e., when

↑ MA → ↑ BDNF → ↑ Neuro Plasticity → ↓ Depression

ANTI DEPRESSANTS

Deficiency of monoamines (5HT > NA > DA) cause Depression

→ Typical Anti Depressants → acts by ↑ 5HT

Atypical Anti Depressants → acts by other mechanisms

TYPICAL ANTIDEPRESSANTS

1 MAO-A INHIBITORS

→ MOCLEBEMIDE

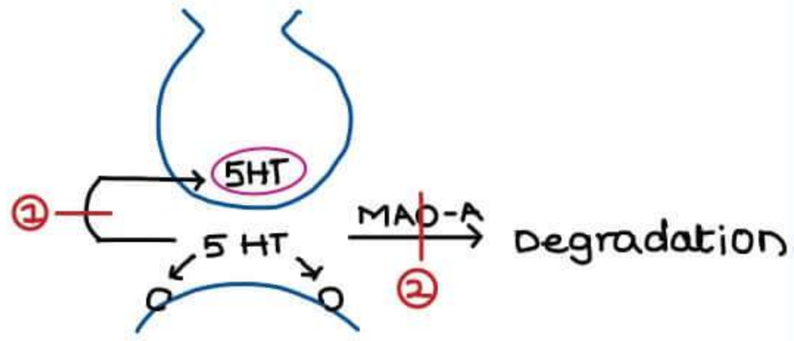
→ aka RIMA

R → Reversible

I → Inhibitor of

M → MAO

A → A



2 REUPTAKE INHIBITORS

NON SELECTIVE	SELECTIVE
→ inhibit reuptake of 5HT & NA	→ inhibit reuptake of 5HT
→ Avoided in cardiac patients	→ can be used in cardiac patients
→ indicated for severe depression	→ indicated for mild to moderate depression

NON SELECTIVE

TCA [Tricyclic antidepressants]

→ includes

IMIPRAMINE

DESIPRAMINE

CLOMIPRAMINE

AMITRIPTYLINE

NORTRIPTYLINE

→ SIE → Ach #

→ α #

→ H_1 #

→ Seizures

→ Arrhythmias

→ Metabolic acidosis

SNRI [SEROTONIN NORADRENALINE REUPTAKE INHIBITORS]

→ ↑ 5HT & ↑ NA

→ Less SIE

→ DOC for severe depression

→ DRUGS

VENLAFAXINE

DULOXETINE

MILNACIPRAN

DES VENLAFAXINE

LEVO MILNACIPRAN

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

→ DRUGS

- FLUOXETINE
- PAROXETINE
- FLUOXAMINE
- SERTRALINE
- CITALOPRAM
- ES-CITALOPRAM
- DAPOXETINE → for premature ejaculation

→ DOC for mild - moderate depression / depression

→ DOC for all neurotic disorders

→ *Adverse Effects of SSRI*

- *Nausea (most common)*
- *Anxiety (due to up-regulation of 5HT2 receptors)*
- *CNS: Headache, bad dreams*
- *Sexual: Anorgasmia*
- *Delayed ejaculation (Dapoxetine used for Pre Mature Ejaculation)*
- *Discontinuation syndrome (Least with Fluoxetine)*
- *Delayed action*

ATYPICAL ANTI DEPRESSANTS

→ DRUGS

- BUPROPION → Anti-smoking drug
- AMINEPTIN, TIANEPTIN } ↑ reuptake of 5 HT
- MIRTAZAPINE
- AMOXAPINE → D_2 # also
- ATOMOXETINE → used in ADHD
- MIANSERIN

MIRTAZAPINE

→ *It is a **Noradrenergic & Specific Serotonergic Antidepressant (NSSA)***

→ *Acts by **blocking α_2 & 5-$HT_{2,3,4}$** receptors*

→ *It **increases both Noradrenaline & Serotonin in synapse** –*

Noradrenaline can act on any receptor but Serotonin can act on 5-HT_1 only (as 5-HT_2 / 5-HT3 / 5-HT_4 are blocked by Mirtazapine)

→ **Advantages**

- *Has less sexual side effects compared to other Anti-depressants*

ESKETAMINE

→ *Acts by **blocking NMDA receptor** of Glutamate*

→ *Used a Nasal spray for depression*

BREXANOLONE / ALLOPREGNANOLONE

→ *Approved for Post-partum depression*

OPIOIDS

→ Obtained from Opium [crude extract of Poppy plants]

→ OPIATES → drugs derived from opium

→ major opiate → MORPHINE

→ OPIOIDS → Opiate like substances

MORPHINE

→ acts on μ, K, δ Receptors

→ Stimulatn of μ, K, δ Receptors cause → Analgesia

μ RECEPTOR FUNCTIONS

S	→	Sedation	→	can cause coma
A	→	Analgesia	→	used in severe pain
C	→	Constipation	→	used in diarrhea
R	→	Respiratory depression	→	avoid in asthma & COPD
U	→	eUphoria	→	Addictive drugs
m	→	Miosis		

→ In Morphine poisoning, the patient usually present in Comatose state as μ receptor causes depression of brain.

→ Morphine is used to treat any pain like cancer pain, pain of Myocardial Infarction but it should not be used to treat Biliary colic.

→ Because in Biliary colic, stone in bile duct irritates it, when morphine is given in biliary colic it causes spasm of Sphincter of Oddi leading to increased contraction and the bile cannot be drained which increases the intra biliary pressure leading to rupture of bile duct.

→ Morphine can cause decreased GI motility which causes Constipation.

→ Morphine is avoided in conditions like Asthma, COPD because it worsens the conditions as it may cause severe Respiratory depression.

→ Morphine causes euphoria and it is highly addictive. Addictive drugs have 2 important properties,

i. Tolerance	ii. Dependence
→ Same doses of morphine which was able to cause euphoria previously, is unable to cause now → Due to tolerance, the person keeps on increasing the dose. → Q. Tolerance can occur to all the actions of morphine except?	→ **Psychological:** Characterized by craving. → **Physical:** Characterized by withdrawal symptoms - **Withdrawal symptoms of any addictive drug**:

3Cs C – Constipation C – Constriction of Pupil C – Convulsions	→ 2 types * **Sympathetic symptoms:** - Tachycardia, palpitations, tremors, Hypertension - Common to every addictive drug. * **Opposite to normal action of the drug:** Eg. Morphine → Causes sedation Opposite action → Stimulation of brain

→ Morphine causes constriction of pupil – miosis

If overdose occurs → Results in **pinpoint pupils.**

→ **Absolute C/I of morphine: Head injury**

1. **causes miosis**
   - Head injury patients →Mostly they will be comatose state
   - Progress of patient after giving drugs is assessed by pupillary reaction
   - Morphine → Pupil remains in miosis → assessment of progress cannot be done

↓

Treatment is interrupted

2. **It causes respiratory depression**

Head injury → R.R is already depressed

↓

Morphine aggravates it

3. **Morphine ↑ intracranial pressure**

Respiratory depression → Co_2 accumulates → vasodilation →↑ Intracranial pressure

CLASSIFICATION

OPIOID AGONISTS → Stimulate all 3 Receptors [μ, κ, δ]
OPIOID PARTIAL AGONISTS → partial agonist at μ receptors
OPIOID AGONIST - ANTAGONISTS → agonist on one [κ], antagonist on other [μ]
OPIOID ANTAGONISTS → blocks all 3 Receptors

AGONISTS

→ DRUGS

MORPHINE
HEROIN → 100 times more addictive than morphine
METHADONE → very long acting, used in deaddictⁿ of opioid
PETHIDINE
CODEINE / PHOLCODEINE / DEXTROMETHORPHAN / NOSCAPINE
LOPERAMIDE / DIPHENOXYLATE
TRAMADOL / TAPENTADOL
FENTANYL
ALFENTANYL
SUFENTANYL
REMIFENTANYL

CODEINE / PHOLCODEINE / DEXTROMETHORPHAN / NOSCAPINE

→ cough suppresants / Anti tussives

→ indicated for dry cough

PETHIDINE
- MAO-A, 99% → Degradatⁿ
- 1% → NOR PETHIDINE [very long acting]
  - → SIE → Seizures [on chronic usage]
  - → C/I along ɪ MAO - Inhibitors

LOPERAMIDE / DIPHENOXYLATE

→ Indicated for non-infective diarrhea

→ C/I in infections

→ To prevent the drug abuse, the market preparation of loperamide and diphenoxylate → are always given in combination with Atropine (Sub therapeutic dose)

TRAMADOL / TAPENTADOL

→ MOA
  - → M, K, δ +
  - → ↑ 5HT & NA in Spinal cord

  } causes analgesia

— use For anesthesia

FENTANYL, ALFENTANYL, SUFENTANYL & REMIFENTANYL

→ highly lipid soluble drugs

> d

→ causes Post op. muscle rigidity [post op. muscle pain c/b succinyl choline]

→ SUFENTANYL → most potent opioid

→ REMIFENTANYL → Shortest acting opioid [d/t metabolism by Pseudo ChE]

2. PARTIAL AGONISTS

→ BUPRENORPHINE → has CEILING EFFECT on respiratory depression

3. AGONIST ANTAGONIST

→ DRUGS
  - P → PENTAZOCINE
  - N → NALBUPHINE
  - B → BUTORPHANOL

→ agonist @ κ & antagonist @ μ

→ SIE → hallucinations

4. ANTAGONISTS

→ DRUGS
  - NALOXONE → Short acting, given IV
  - NALTREXONE → Long acting, given Orally

→ DOC for acute opioid poisoning → Naloxone

→ DOC for maintainance in opioid poisoning → Naltrexone

OPIOID DEADDICTION

SHORT TERM ADDICTION	LONG TERM ADDICTION
Stop opioids ↓ WITHDRAWAL SYMPTOMS Sym. System ⊕ OPPOSITE TO OPIOIDS ↓ by — β # — CLONIDINE ↓ by — BZD	REPLACE ĩ METHADONE [less addictive & Long acting cause less euphoria] ↓ ↓ dose gradually & STOP RELAPSE PREVENTION NALTREXONE

ALCOHOLS

ALCOHOL	ETHYL ALCOHOL	METHYL ALCOHOL
↓ Alc. dehydrogenase	↓	↓
ALDEHYDE	Acetaldehyde	Formaldehyde
↓ Ald. dehydrogenase	↓	↓
ACID	Acetic Acid	Formic Acid

ETHYL ALCOHOL

DISULFIRAM

→ inhibits Acetaldehyde dehydrogenase

→ used as ALCOHOL AVERSION THERAPY

→ instead of euphoria, unpleasant symptoms occur on consuming alcohol dit ↑ acetaldehyde

DISULFIRAM LIKE REACTION

→ DRUGS

C → CEPHALOSPORINS [some]
CHLORPROPAMIDE

G → GRISEOFULVIN

M → METRONIDAZOLE

P → PROCARBAZINE

METHYL ALCOHOL

→ Both formaldehyde and formic acid can cause retinal damage and blindness

→ For inhibiting alcohol dehydrogenase → Ethanol has been used.

→ Ethanol (Ethyl alcohol] act as a competitive inhibitor of methanol

→ **Ethanol:**

- Cannot be given Intravenously
- Given by intra – gastric route (through Ryle's tube)
  - Dependent on GIT absorption
  - ↓
  - Not reliable
  - ↓
  - So, we cannot exactly titrate the effect with the dose
- It is alcohol → So produce inebriant effect

→ To avoid the above side effects, new drug has been developed called

Four Methyl Pyrazol / FOMePizole

- Competitive inhibitor of alcohol dehydrogenase itself
- Can be given by I.V route
- It is not an inebriant
- D.O.C for methanol poisoning

→ Folic acid → ↑ the metabolism of formaldehyde /formic acid

ETHYLENE GLYCOL

- Used as Anti – freeze / lubricant in the industry
- Act like alcohol → i.e. metabolized to form aldehyde

Ethylene glycol

↓ Alcohol dehydrogenase

Glycol aldehyde

↓ converted to

Glycolic acid

↓ metabolized to form

Oxalic acid

→ Q. A person has consumed some industrial solvent, & the person comes with metabolic acidosis & has oxalate crystals in the urine. What is the diagnosis?

Ans. Ethylene glycol poisoning

→ **Treatment**: Fomepizole (Inhibit alcohol dehydrogenase)

ALCOHOL DE – ADDICTION

→ There are 3 methods:

i. Replacement method

ii. By giving drugs which ↓ craving of alcohol

iii. Aversion therapy

(i) **Replacement method**:

→ Replace the addictive drug with similar type of drugs which are long acting.

*Alcohol → CNS depressant

→ So, replaced by long acting C.N.S depressant

i.e Benzodiazepines → Chlordiazepoxide / Diazepam

↓

Gradually ↓ dose

↓

Stop

(ii) **Drugs ↓ alcohol craving**:

None – Naltrexone → can't ↓ opioid craving; it ↓se risk of relapse in opioids

Of – Ondansetron

The – Topiramate

Above – Acamprosate

(iii) **Alcohol Aversion Therapy**:

Ethanol

↓ Alcohol dehydrogenase

Acetaldehyde

↓ Aldehyde dehydrogenase

Acid

➔ Major euphoric effect of alcohol is caused by ethanol

➔ After sometime, metabolism occurs and produce → acid → inactive → no effects

➔ If acetaldehyde accumulates, it causes adverse effects

- Vomiting
- Headache
- Labile B.P
- Blurring of vision

➔ If aldehyde dehydrogenase doesn't work, aldehyde accumulates

➔ Drug inhibiting aldehyde dehydrogenase → Disulfiram → used for alcohol de-addiction

→ It doesn't ↓ craving

→ The person would be afraid of taking alcohol bcoz of the adverse effects he had experienced due to disulfiram. → Alcohol aversion therapy.

* **Psychological dependence**

→ **Person has craving** & person is psychologically dependent that he cannot live without alcohol

→ But if person doesn't get alcohol, there may not be any physical symptoms.

***Physical dependence**

→ **Person is physically dependent**

→ If the person doesn't get the alcohol, the person develops physical symptoms

↓ called

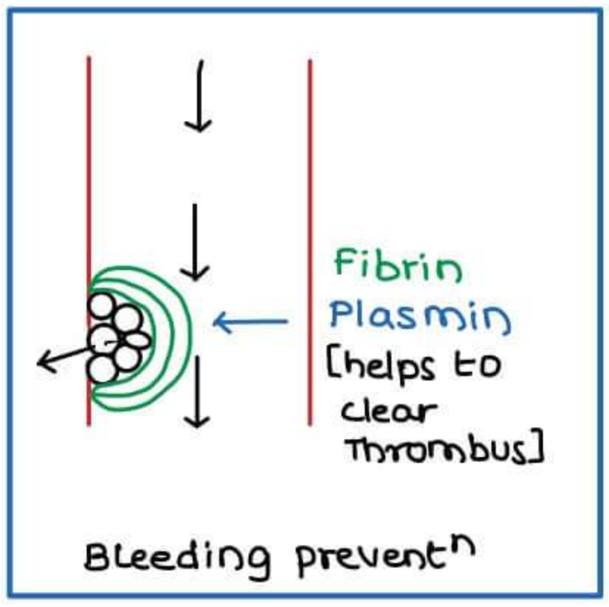
Withdrawal symptoms

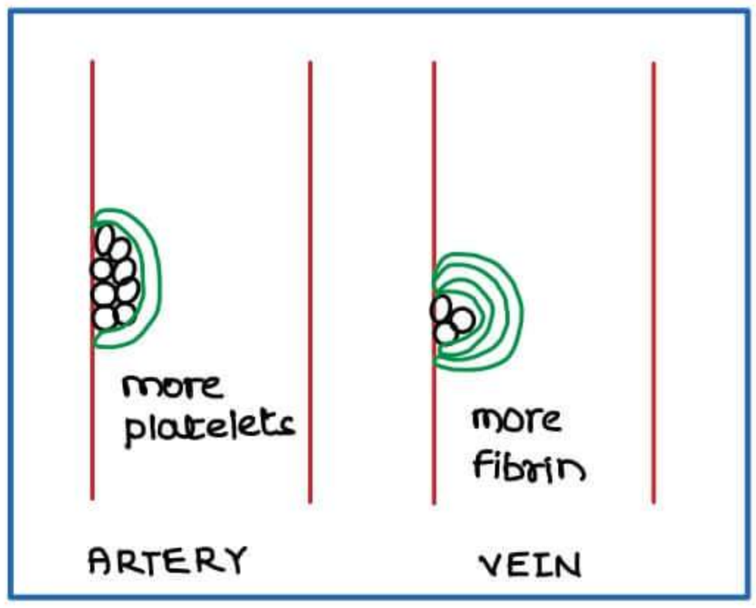
Disulfiram

→ Only indicated in psychological dependent patients.

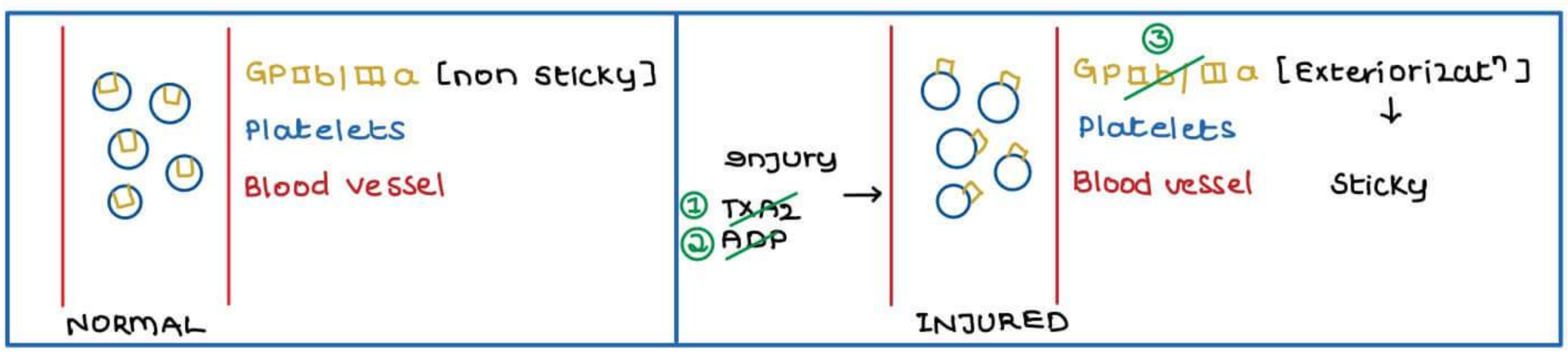
→C/I in physically dependent person

DRUGS AFFECTING FLOW





ANTI PLATELET DRUGS

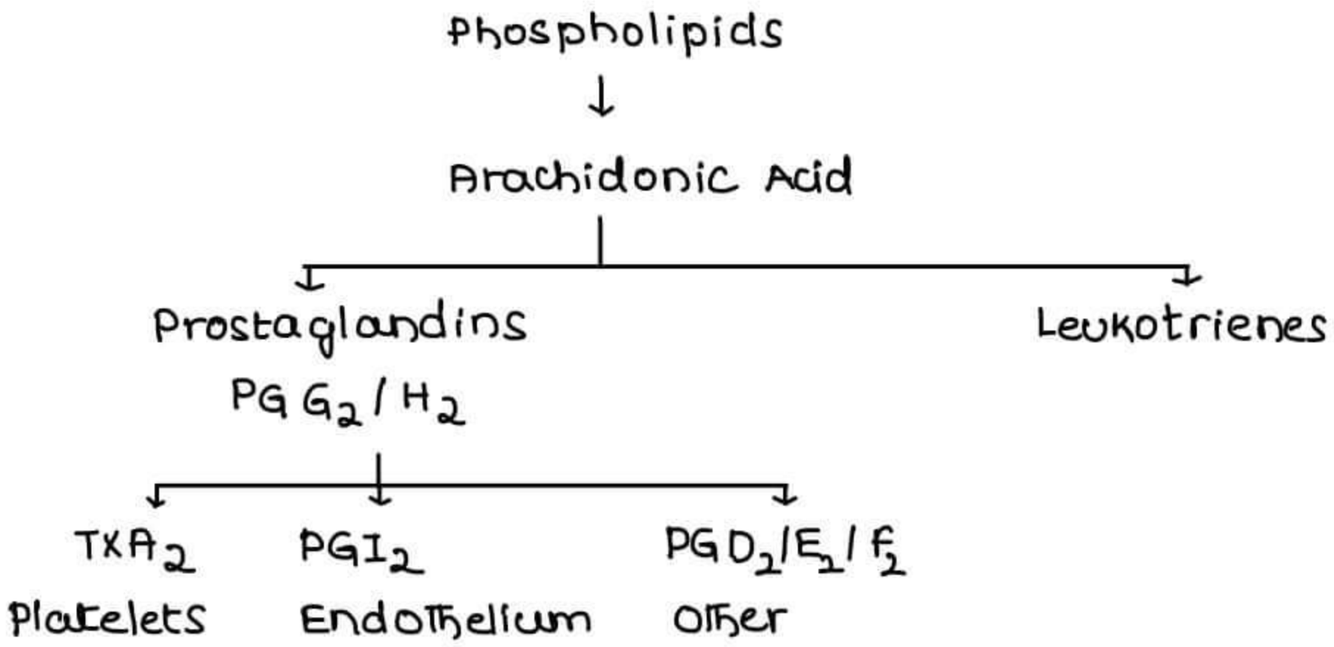


1 ASPIRIN → act on TXA_2

2. CLOPIDOGREL, TICLOPIDINE } act on ADP

3. ABCIXIMAB, TIROFIBAN, EPTIFIBATIDE } act on GP IIb/IIIa

1. DRUGS ACT ON TXA_2



TXA_2 → cause Aggregation

PGI_2 → Inhibit aggregation

ASPIRIN → Irreversible inhibitor of COX

2. DRUGS ACT ON ADP

→ ADP Receptor → P_2Y_{12}

→ DRUGS

CLOPIDOGREL

TICLOPIDINE

→ These drugs irreversibly inhibit P_2Y_{12}

→ Both are Prodrugs [inactive]

→ Activated by CYP2C19

→ OMEPRAZOLE inhibit CYP2C19

→ should not combine ī these drugs

PRASUGREL

- Like clopidogrel, it is also an irreversible inhibitor of ADP
- Faster acting than clopidogrel
- But prasugrel is high risk of causing cerebral stroke (therefore C/I in stroke)

→ REVERSIBLE P_2Y_{12} INHIBITORS

CANGRELOR

TICAGRELOR

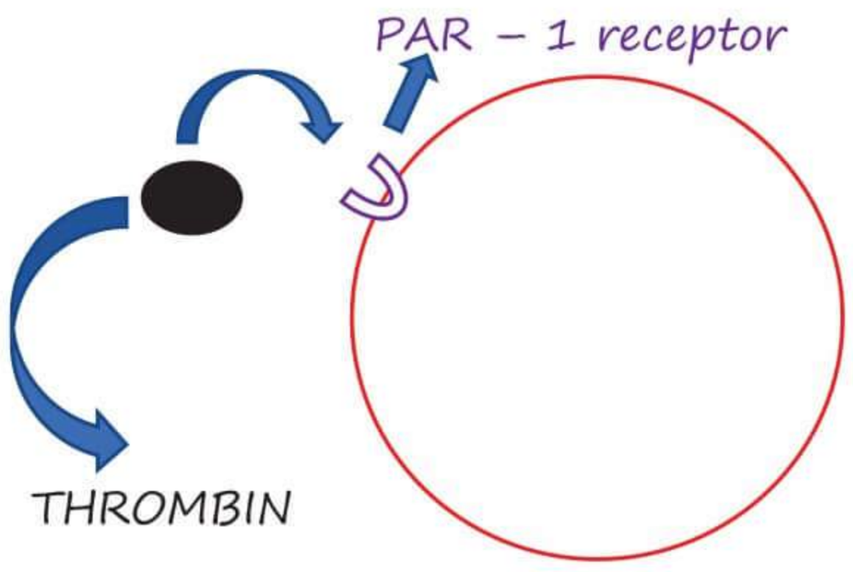
3. DRUGS ACT ON GP IIb/IIIa → strongest antiplatelet drugs

- ABCIXIMAB
- TIROFIBAN
- EPTIFIBATIDE

4. DRUGS ACTING ON THROMBIN RECEPTORS

→ Like Thromboxin A2 and ADP, Thrombin can also activate Platelets.

→ However, Main function of thrombin is to generate Fibrin.



→ On the surface of platelets, PAR – 1 receptors are present, thrombin binds to this receptor and results in activation of platelets, drugs are developed which inhibit PAR – 1 receptors leading to anti- platelet action.

PAR – 1 Antagonist:

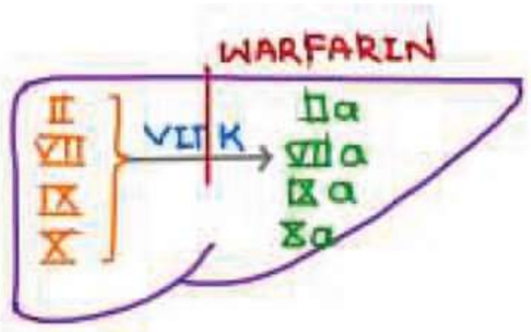
- ATOPAXAR
- VORAPAXAR

ANTI FIBRIN DRUGS / ANTI COAGULANTS

ORAL ANTI-COAGULANTS

1. Vitamin K antagonist
2. Direct thrombin inhibitor
3. Factor Xa inhibitor

1. WARFARIN



→ Liver can produce all clotting factors but 4 factors (II, VII, IX, X) require vitamin K to become active

→ Vitamin K result in γ-carboxylation of glutamate residues of II, VII, IX, and X to make them active.

→ Vitamin K can also activate certain anti-clotting factors like protein C and protein S.

→ Warfarin acts by inhibiting vitamin K

→When we start warfarin for initial 1 or 2 days there is increased in risk of clotting known as Hypercoagulation or Dermal vascular necrosis. It also known as Purple toe syndrome (mainly seen in genetic deficiency of protein C)

Properties of Warfarin:

1. Oral anticoagulant
2. Inhibit vitamin – K
3. 4-5 days to produce action
4. Mainly used for maintenance purpose
5. Anticoagulant effect
   - In vivo (inside the body)- Effective
   - In vitro (outside the body) – Not effective
6. Contraindicated in pregnancy: Fetal Warfarin Syndrome

   Warfarin prevents activation of osteocalcin
   ↓
   Leads to skeletal deformity
   ↓
   Microcephaly, Nasal hypoplasia
7. Effect of warfarin is monitored by PT / INR

→ MONITORING

→ mainly affects extrinsic pathway

→ monitored by Pro Thrombin Time or INR

→ CLOTTING PATHWAY

Extrinsic pathway monitored by Prothrombin Time [PT]

Intrinsic pathway monitored by activated Partial Thromboplastin Time

NORMAL VALUES

PT → 12-16 sec [~ 15S]

aPTT → 26-32 sec [~ 30sec]

On WARFARIN therapy, PT → 2-3 times the control value

HEPARIN mainly affects Intrinsic pathway, monitored by aPTT

W → Warfarin
E → Extrinsic pathway
PT → Prothrombin Time

H → Heparin
INT → Intrinsic pathway

PROTHROMBIN TIME MEASUREMENT

	LAB 1	LAB 2	LAB 3
BEFORE WARFARIN THERAPY	10 sec	15 sec	20 sec
AFTER WARFARIN THERAPY	20 sec	30 sec	40 sec

→ DIFFerent labs gives different control values for the same sample
→ SOLUTION → Measure both samples in SAME LAB

INR [International Normalised Ratio]

$$INR \rightarrow \left[\frac{PT\ test}{PT\ control}\right]^{ISI}$$

ISI → International Sensitivity Index

→ value of INR will be same in all labs

WARFARIN OVERDOSE:

→ Overdose of Warfarin causes bleeding
→ Active factors like IIa, VIIa, IXa, Xa (which are known as Four Factor Complex (or) Prothrombin Factor complex) is the Treatment of choice.
→ If Four Factor Complex is not availabale, then fresh frozen plasma can be used.
→ if the fresh frozen plasma is also not available, Whole blood should be given.
→ But the Treatment of choice for bleeding tendency due to warfarin is Vitamin K.
→ Vitamin K is also antidote for Warfarin overdose.

INR values and Treatment of warfarin overdose:

- <5 – Warfarin should be stopped.
- 5 to 20 – Warfarin should be stopped and Vitamin K is administered
- >20 – Warfarin should be stopped and Four factor complex is given.

2. DIRECT THROMBIN INHIBITORS:

- Dabigatran- can be given Orally and does not require monitoring.
- Dabigatran overdose / toxicity is treated with a monoclonal antibody called Idarucizumab.

3. DIRECT FACTOR Xa INHIBITORS:

- Rivaroxaban – reversible oral Xa blocker / antagonist, and this drug do not require monitoring.
- Other drugs are,
  - Apixaban
  - Edoxaban
  - Betrixaban

Rivar	→	Reversible
O	→	Oral
XA	→	XA
B	→	Blocker (or)
AN	→	Antagonist

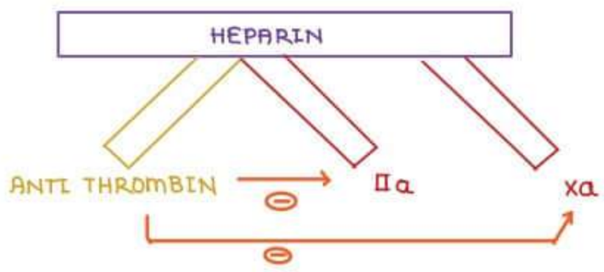
- Andexanet Alpha is the antidote for factor Xa inhibitor overdose,

INJECTABLE ANTICOAGULANTS / THROMBIN [IIa] INHIBITORS

1. INDIRECT IIa INHIBITORS
2. DIRECT IIa INHIBITORS

1. INDIRECT IIa INHIBITORS [HEPARIN]

Heparin + Anti Thrombin
↓
Antithrombin Activated
↓
AT inhibit Thrombin in COMPLEX
[Heparin + AT + IIa]



Heparin + Anti Thrombin
↓
Antithrombin Activated
↓
AT inhibit Xa

UFH – activate antithrombin – Inhibit factor IIa = Xa

LMWH – activate antithrombin – inhibit factor Xa > IIa

Fondaparinux – activate antithrombin – only inhibits factor Xa

HEPARIN

1. Route → S/C or IV
2. Inhibit Xa & IIa
3. Immediate Action → useful in acute conditions
4. Anticoagulant of choice in pregnancy
5. monitoring done by aPTT
6. Antidote → PROTAMINE SULPHATE
7. SIE → Bleeding
   Heparin Induced Thrombocytopenia

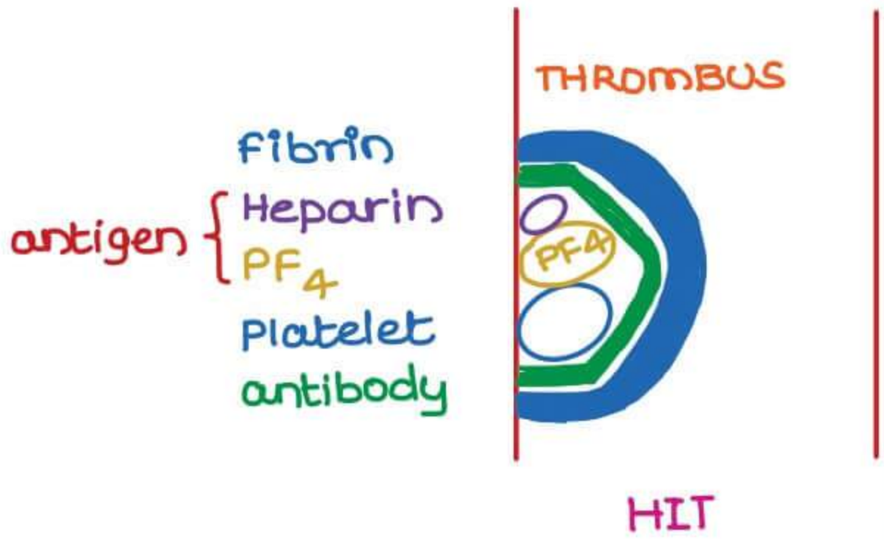
- LMWH usually does not require monitoring
- But in a patient with renal failure we need to monitor the LMWH by doing **anti factor Xa Assay**

HEPARIN INDUCED THROMBOCYTOPENIA [HIT]

→ Thrombocytopenia occurs

→ THROMBOSIS present

→ DOC → DIRECT THROMBIN INHIBITORS



2. DIRECT THROMBIN INHIBITORS

→ DRUGS

- HIRUDIN
- LEPIRUDIN
- BIVALIRUDIN
- ARGATROBAN
- MELAGATRAN

} Injectables

- DABIGATRAN → given orally

ANTICOAGULANTS ARE MORE EFFECTIVE IN VENOUS THROMBOSIS

– indicated in DVT & Pulmonary Embolism

THROMBOLYTIC DRUGS / TISSUE PLASMINOGEN ACTIVATORS / FIBRINOLYTIC DRUGS

→ PLASMIN removes thrombus

$$\text{Plasminogen} \xrightarrow{t\text{PA}} \text{Plasmin}$$

→ DRUGS

- STREPTOKINASE
- UROKINASE
- ALTEPLASE

} Short acting, given iv

- RETEPLASE
- TENECTEPLASE

} Long acting, given as bolus
Tenecteplase → Longest acting

STREPTOKINASE

→ derived from Streptococcus

→ can cause ALLERGY

→ ANTIBODIES against Streptokinase produced

rtPA [RECOMBINANT TISSUE PLASMINOGEN ACTIVATORS]

→ ALTEPASE
RETEPLASE
TENECTEPLASE

→ No allergy, no antibody formatⁿ occurs

Overdose of thrombolytics leads to bleeding

Antidote: EPLISON AMINO CAPROIC ACID (EACA)

TRANEXAMIC ACID

DRUGS AFFECTING CELLS

- **Hematinics**
- **Growth factors**

HEMATINICS

These are nutritional substances which help in formation of blood

E.g.

1. Iron (Fe) – deficiency leads to microcytic anemia
2. Folic acid (FA)] deficiency leads to megaloblastic anemia
3. Vitamin B12]

Iron Deficiency Anemia

I.e. Microcytic hypochromic anemia

Cause of iron deficiency –

1. Nutritional deficiency
2. Blood loss (e.g. menstruation)
3. Hookworm infestation

Rx – Oral Iron – RxOC

For children iron drops are available. These should be given deep in mouth or else they cause skin pigmentation.

After giving treatment

- Earliest response – Reticulocytosis
- If Hb is improving by 0.5 g/dl/week, that means adequate response.
- Oral iron treatment is continued for 2-3 months even after the Hb levels come to normal to replenish the iron stores in body.

INJECTABLE IRON

Iron dextran – iv and im

Iron sorbital citrate (im only)

Intramuscular iron is given by z-track technique to avoid pigmentation

- **Indication of injectable iron:-**

1. Oral iron cannot be given

   e.g. – malabsorption

   - Not tolerated (due to GI symptoms)

2. Given with erythropoietin

   Erythropoietin will stimulate RBC formation and will unmask any iron deficiency

- Dose = 4.3 x Hb deficit (g/dl) x body weight (kg)

Megaloblastic anemia

Causes

1. Folic acid deficiency

   Rx – folic acid orally

2. Vitamin B12 deficiency

- If It is due to intrinsic factor (IF) deficiency: Injectable vitamin B12

Note - In undiagnosed megaloblastic anemia, never give FA alone

Reason –

FA → stimulates RBC production

Vitamin B12 → stimulates RBC production
- Myelin sheath formation

So if a person has megaloblastic anemia due to B12 deficiency and we do not know the cause (ie. B12 or FA deficiency) and we start treating on FA alone.

His blood picture will improve (RBC, Hb) and his symptoms will improve initially. But due to B12 deficiency, myelin formation won't take place so his neurological symptoms will get worse. Also the B12 stores will get used up in forming RBC. This will further worsen the symptoms. It can result in Sub-Acute Combined Degeneration of spinal cord.

HEMATOPOIETIC GROWTH FACTORS

Cells	Growth factor	Indications
RBC	Erythropoietin	Anemia d/t chronic renal failure Anticancer drugs induced bone marrow suppression
WBC	G-CSF GM – CSF	a. Leukopenia due to bone marrow ↓ b. Mobilize PBSC peripheral blood stem cells
Platelets	IL-II Thrombopoietin	Thrombocytopenia d/t BM ↓

ERYTHROPOIETIN

→ INDICATIONS
  → Anaemia dlt Chronic Kidney disease
  Anaemia dlt BM suppression

→ Overdose causes → Polycythemia
→ DRUG → DARBOPOIETIN [Recombinant Erythropoietin]

G - CSF & GM - CSF

→ INDICATION → Leucopenia dlt anticancer drugs
→ DRUGS
  G - CSF → FILGRASTIM
  PEGFILGRASTIM

  GM - CSF → SARGRAMOSTIM
  MOLGRAMOSTIM

IL - 11 → used for thrombocytopenia dlt anticancer drugs

→ OPRELVEKIN

THROMBOPOIETIN RECEPTOR AGONISTS → used in ITP

→ ROMIPLOSTIM
  ELTROMBOPAG

ANTIMICROBIAL DRUGS

CELL WALL SYNTHESIS INHIBITORS

CLASSIFICATION OF AMA BASED ON

1 CIDAL DRUGS [kills]

STATIC DRUGS [inhibits growth]

→ Static and cidal drugs both can be used in normal immunocompetent persons.

→ In Immune-suppressed persons only cidal drugs are used, static drugs should not be used.

→ Major cidal drugs are, (BEVAFA)

- BE – BEta lactams
- VA – VAncomycin
- F – Fluoroquinolones
- A – Aminoglycosides

2 TYPE OF ORGANISMS

3 CHEMICAL STRUCTURE

4. SOURCE → ANTIBIOTICS & NON-ANTIBIOTICS

5. MECHANISM OF ACTION

a. Cell wall synthesis Inhibitors

b Protein synthesis Inhibitors

c. Metabolism

d. DNA

c. Membranes

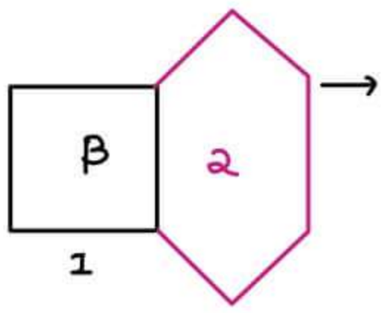
CELL WALL SYNTHESIS INHIBITORS

→ DRUGS

Firmly	→	FOSFOMYCIN	→ used for UTI
Bind to	→	BETA LACTAMS	
Bacterial	→	BACITRACIN	→ Local use only
Cell	→	CYCLOSERINE	→ used in TB
Wall	→	VANCOMYCIN	

BETA LACTAMS

1. PENICILLINS
2 CEPHALOSPORINS
3 CARBAPENEMS
4 MONOBACTAMS



→ 2nd ring is different in different β lactams & absent in monobactams

PENICILLINS

PENICILLIN G / BENZYL PENICILLIN

LIMITATIONS

1 not effective orally [Acid labile]
2 Short acting [dlt rapid tubular secretion]
3 Narrow Spectrum
4 Resistance
5. Allergy

1. ACID RESISTANT / ORAL PENICILLINS

V → PENICILLIN V
O → OXACILLIN
D → DICLOXACILLIN
C → CLOXACILLIN
A → AMPICILLIN
AMOXYCILLIN

2. ↑ DURATION OF ACTION OF PENICILLIN G

→ PROBENECID compete ī Penicillin at tubular pumps → ↑ duration of action of Penecillin

→ DEPOT PREPARATIONS
- → BENZATHINE PENICILLIN G → Longest acting Penicillin
- → PROCAINE PENICILLIN G

→ Depot preparations are given by im only

3. SPECTRUM OF PENICILLIN G

GRAM +ive
- cocci → Strepto, Staphylo
- Bacillus → Bacillus, clostridium, Diphtheria, Listeria

Gram −ive
- cocci → Neisseria
- Bacilli → not effective

EXTENDED / WIDE SPECTRUM PENICILLINS

A → AMPICILLIN, AMOXYCILLIN
Ci → CARBENICILLIN
Ty → TICARCILLIN
M → MEZLOCILLIN
A → AZLOCILLIN
P → PIPERACILLIN

} ANTI PSEUDOMONAL DRUGS

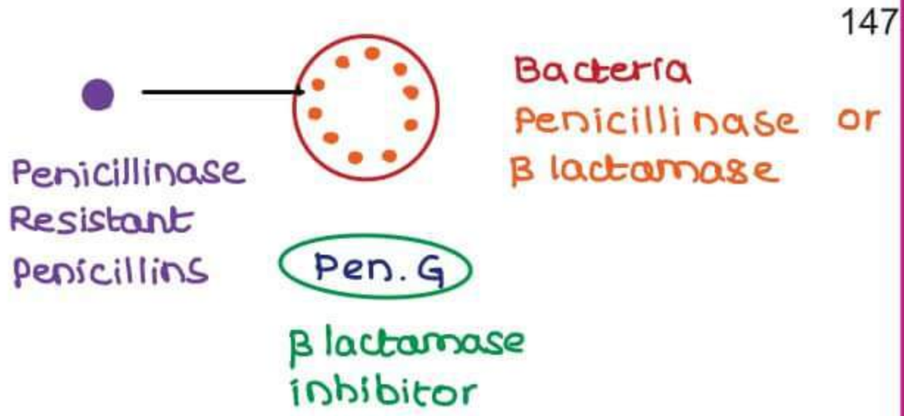
VANCOMYCIN IS NOT EFFECTIVE AGAINST PSEUDOMONAS

4. β LACTAMASE INHIBITORS

CLAVULINIC ACID + AMOXYCILLIN

SULBACTAM + AMPICILLIN

TAZOBACTAM + PIPERACILLIN



PENICILLLINASE RESISTANT PENICILLINS

C → CLOXACILLIN

O → OXACILLIN

N → NAFCILLIN

D → DICLOXACILLIN

O

M → METHICILLIN [most resistant]

→ MRSA [Methicillin Resistant Staph. aureus]

→ resistance is d/t alterat^{n} in Penicillin Binding Protein

→ β lactams are ineffective except 5th gen. Cephalosporins

5. ALLERGY

→ SKIN TESTING done by Intradermal injectn of drug

→ CROSS ALLERGY → allergic to one penicillins, all β lactams are allergic except MONOBACTAMS

PENICILLIN G INDICATIONS

FIRST LINE DRUGS IN

L → LISTERIA

A → ACTINOMYCOSIS

S → SYPHILIS

T → TETANUS

M → MENINGOCOCCUS

A, N } ANTHRAX

LISTERIA:

→ Drug of choice for listeria is Ampicillin.

SYPHILIS:

SYPHILIS TYPES		TREATMENT
Primary syphilis		single injection of Benzathine Penicillin G
Secondary syphilis	Early	IM route, Dose of 2.4 MU
Latent		
	Late	3 injections (1 injection a week) of
Tertiary syphilis (except neuro)		Benzathine Penicillin G, IM with 2.4 MU

Neurosyphilis – Penicillin G (Aqueous/Crystalline) is the Drug of Choice of Neurosyphilis, Procaine Penicillin G Can also be used for the treatment.

TETANUS:

→ Drug of choice and First line drug for Tetanus is Penicillin G ≫ Metronidazole.

MENINGOCOCCI:

Meningococci

- **Treatment**
  - Empirical → Ceftriaxone
  - Definitive → Penicillin G
- **Prevention**
  - 1. Ciprofloxacin
    - → Less effective
    - → C/I in Pregnancy and children
    - → Can be given Orally.
    - → DOC for Prophylaxis of Meningococcal Meningitis.
  - 2. Ceftriaxone
    - More effective than ciprofloxacin
    - DOC in pregnancy and lactation
    - Injectable only

ANTHRAX:

→ Drug of choice and first line treatment is Penicillin G ≫ Ciprofloxacin.

GONOCOCCI:

→ Drug of choice for Gonococcal Urethritis is Ceftriaxone.
→ Drug of choice for Non-Gonococcal Urethritis is Azithromycin.
→ Drug of choice for Mixed (Gonococcal and Non gonococcal) urethritis is Azithromycin.

CEPHALOSPORINS

1st GEN.	2nd GEN.	3rd GEN.	4th GEN	5th GEN
EFFECTIVE AGAINST				
Gm +ive	Gm +ive Gm -ive Anaerobic	Gram +ve Gram -ive Widest spectrum	Gram -ive	MRSA

1st GEN.	2nd GEN.	3rd GEN.	4th GEN	5th GEN
CEFAZOLIN	CEFUROXIME	CEFOPERAZONE	CEFEPIME	CEFTIBIPROLE
CEFALEXIN	CEFOXITIN	CEFTRIAXONE	CEFPIROME	CEFTAROLINE
CEFALOTHIN	CEFMETAZOLE	CEFOTAXIME		
CEFALORIDINE	CEFOMANDOLE	CEFTIZOXIME		
CEFADROXIL	CEFACLOR	CEFPODOXIME		
		CEFTAZIDIME		
		CEFTIBUTEN		
		MOXALACTAM		
		CEFIXIME		

1 BILE SECRETED CEPHALOSPORINES

→ safe in renal failure

→ includes

CEFOPERAZONE

CEFTRIAXONE

BILE SECRETED ANTIMICROBIAL AGENTS		
Cef in	→	CEFOPERAZONE, CEFTRIAXONE
R	→	RIFAMPICIN
E	→	ERYTHROMYCIN
N	→	NAFCILLIN
A	→	AMPICILLIN
L	→	LINCOSAMIDES [CLINDAMYCIN]
Disease	→	DOXYCYCLINE

2 ANTI PSEUDOMONAL CEPHALOSPORINS

→ includes

CEFEPIME

CEFPIROME

CEFOPERAZONE

CEFTAZIDIME [most effective antipseudomonal cephalosporin]

3 DISULFIRAM LIKE REACTION

→ not to be given ± alcohol

→ includes

CEFOPERAZONE

MOXALACTAM

CEFOTETAN

CEFOMANDOLE

4 ↓ PROTHROMBIN

→ includes

CEFOPERAZONE

MOXALACTAM

CEFOTETAN

CEFOMANDOLE

CARBAPENEMS

Imipenem:

- Effective against Gram (+), Gram (-) and Anaerobes
- Always given with Cilastatin because if given alone it is broken down by Dehydropeptidase enzyme in the kidney
- Imipenem is a broad spectrum antibiotic, it is also effective against Pseudomonas.

Side effect of imipenem: Seizures

Contraindication: Epileptic patients

Other Carbapenems:

- Meropenem
- Ertapenem
- Doripenem
- Faropenem

} cilastatin not required, lesser risk of seizures

→ All carbapenem's are injectable except Faropenem which can be given Orally.

→ Any bacteria (mostly Klebsiella) which has Extended Spectrum Beta Lactamase (ESBL) enzyme is resistant to most of the antibiotics (except carbapenems)

Limitations of ESBL:

→ Cannot break carbapenems and hence carbapenems are the drug of choice for ESBL producing bacteria.

→ Can be inhibited by Beta lactamase inhibitors like Piperacilllin + Tazobactam combination.

New Delhi metallo-beta lactamase (NDM):

→ NDM can break most of the antibiotics (just like ESBL) and it

- Can break even Carbapenems
- It cannot be inhibited by Beta lactamase inhibitors

→ This infection is also known as **Superbug.**

→ **Colistin** can kill the bacteria that produces NDM beta lactamase

→ Colistin is the drug of choice for **NDM producing bacterial infections**

MONOBACTAM

AZTREONAM

→ do not show cross allergy

→ effective only against Gm -ive bacteria including Pseudomonas

VANCOMYCIN

→ Not effective orally [NOT ABSORBED]

→ given by iv → releases HISTAMINE → RED MAN SYNDROME

→ SIE

→ nephrotoxic

→ ototoxic

→ not effective against Pseudomonas

→ USE

→ MRSA [DOC]

→ PSEUDO MEMBRANOUS COLITIS

→ commensal bacteria protect the GIT from infection

→ by competing ℃ nutrition & producing BACTERIOCIN

→ Broad spectrum antibiotics Kills commensals, which Predisposed to SUPER INFECTION

→ WBC forms a membrane → PSEUDO MEMBRANE

PSEUDOMEMBRANE COLITIS

1 mc organism responsible → Clostridium difficile

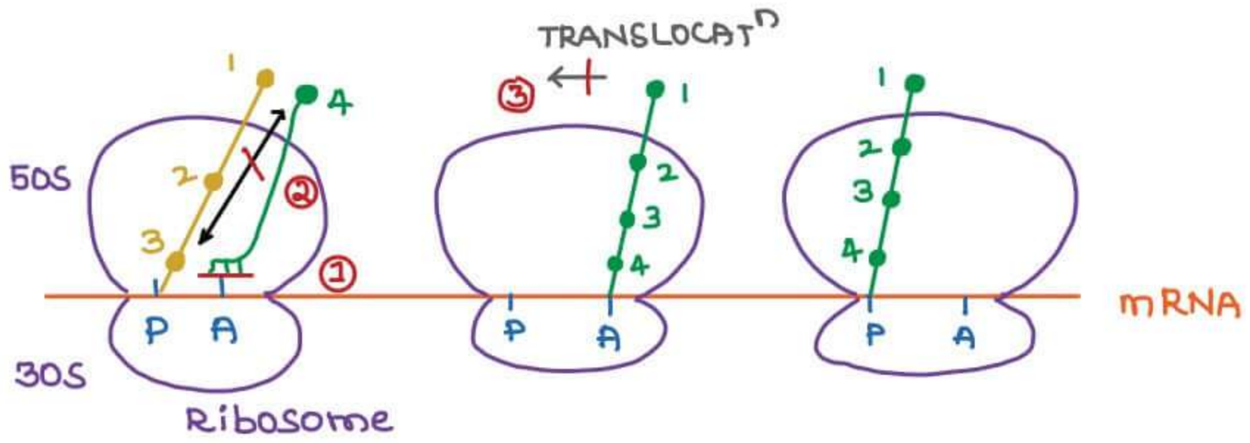
2. mc cause → 3rd gen. cephalosporins > Clindamycin

3. DOC → ORAL VANCOMYCIN
[only oral indicatⁿ of vancomycin]

GLYCOPEPTIDES	
VANCOMYCIN TEICOPLANIN ORITAVANCIN DALBAVANCIN TELAVANCIN	DO not cause RED MAN SYNDROME

PROTEIN SYNTHESIS INHIBITORS

PROTEIN SYNTHESIS INHIBITORS



1. TETRACYCLINES → inhibit the attachment of tRNA to A site
2. CHLORAMPHENICOL → inhibit the joining of 2 AA [peptide bond formatⁿ]
3. M → MACROLIDS
   C → CLINDAMYCIN
   Q → QUINPRISTIN
   } Inhibit Translocation
4. AMINOGLYCOSIDES → acts by causing Misreading of mRNA codon
   → only cidal protein synthesis inhibitor

BINDING

Binding	
A	AMINOGLYCOSIDES
T	TETRACYCLINES
30S	bind @ 30S Ribosome

Rest all bind at 50S ribosome

1. TETRACYCLINES

DRUGS

TETRACYCLINE

OXYTETRACYCLINE

CHLORTETRACYCLINE

DEMECLOCYCLINE → most phototoxic, highest risk of DI

DOXYCYCLINE

MINOCYCLINE → highest vestibular dysfunction

ADVERSE EFFECTS

K → Kidney failure → C/I except Doxycycline

A → Anti anabolic

P → Phototoxic

I → Insipidus diabetes

L → Liver failure C/I

D → Dentition & Bone (C/I in pregnancy & children)

E → not be given after Expiry [risk of Fanconi syndrome]

V → Vestibular dysfunctⁿ

USES

S → SIADH [Demeclocycline]

R → Rickettsia [DOC]

I → Granuloma Inguinale [DOC]

L → LGV

A, N → Atypical pNeumonia [DOC → MACROLIDES]

K → Cholera [DOC]

A → Luminal Amoebiasis [DOC for amoebiasis → METRONIDAZOLE]

RESISTANCE:

→ Resistance to tetracyclines → Due to development of efflux pumps in bacteria.

TIGECYCLINE

→ Resistant to efflux pump

→ Mechanism of action is similar to tetracycline but chemical structure belongs to Glycylcycline.

→ Tigecycline is a broad-spectrum antibiotic but it is not effective against pseudomonas

→ It is secreted in bile and so it is safe in case of renal disease.

2. CHLORAMPHENICOL

→ It is a protein synthesis inhibitor

→ It binds to 50 s ribosomes and inhibits the joining of amino acids.

→ Bacteriostatic drug (like most of the protein synthesis inhibitors).

→ Rarely used now a days → bcoz, Not effective and toxic.

→ Initially, chloramphenicol was the DOC for enteric fever.

→ But now most of salmonella has become resistant to Chloramphenicol by developing inactivating enzymes.

→ It has high risk of causing **BONE MARROW SUPPRESSION**

→ It is contraindicated in newborn babies due to risk of development of cyanosis in babies → **Grey Baby Syndrome.**

→ Now-a-days, it is mainly used in Meningitis (for bacteria resistant to ceftriaxone).

→ It is effective against anaerobic bacteria.

→ Rarely if chloramphenicol is sensitive to Salmonella, it is used in typhoid fever/ enteric fever

3 MACROLIDES

DRUGS

- ERYTHROMYCIN
- CLARITHROMYCIN
- ROXITHROMYCIN
- AZITHROMYCIN

} 2nd Line drugs to Penicillins

DOC for
- C → Chancroid
- L → Legionella
- A → Atypical pneumonia
- P → Pertussis

FIDAXOMICIN → used in mild to moderate Pseudo Membrane colitis

→ causes stimulation of Motilin ® in GIT
- → Diarrhea is SIE
- → used in Diabetic gastroparesis

AZITHROMYCIN	OTHER 'THROMYCINS'
→ very long acting	→ Relatively short acting
→ non microsomal enzyme ⊖	→ microsomal enzyme inhibitors
→ Fewer drug interactions	→ more drug interactions

→ Major adverse effects of Macrolides: (MACRO)
- M: Stimulate Motilin receptor (used in diabetic gastroparesis and paralytic ileus)
- A: Allergy
- C: Cholestasis: Erythromycin estolate (higher risk in pregnancy therefore CI in pregnancy but it is not teratogenic)
- R: Reversible
- O: Ototoxicity

→ Drugs which are safe in pregnancy: PCM
- Penicillin
- Cephalosporin
- Macrolide

→ Irreversible ototoxicity is seen in:
- Cisplatin
- Vancomycin
- Aminoglycoside

→ Macrolides: have both antimicrobial and immunosuppressant activity.

→ Macrolide with stronger immunosuppressant activity: Tacrolimus

→ Spiramycin is used to treat Toxoplasmosis in pregnancy.

CLINDAMYCIN

→ Secreted in Bile

→ causes Pseudo membranous colitis

→ used in anaerobic bacterial Infections

MAJOR USES OF CLINDAMYCIN:

→ C – Cocci

→ A – Anaerobes

→ P – Parasites

- Pneumocystis
- Malaria
- Toxoplasma

QUINPRISTIN + DALFOPRISTIN

→ Both are Streptogramins

→ indicated in VRSA [DOC → DAPTOMYCIN]

4. AMINOGLYCOSIDES

DRUGS

STREPTOMYCIN
GENTAMICIN
TOBRAMYCIN
NETILMYCIN
NEOMYCIN
CAPREOMYCIN
KANAMYCIN
AMIKACIN

- Not effective orally [not absorbed]
- active mainly on Gm –ive [incl. Pseudomonas]
- not effective on anaerobic bacteria
- cidal drugs
- nephrotoxic [max. by Neomycin]
- ototoxic
  - Auditory [max. by Amikacin]
  - vestibular [max. by Streptomycin]
- cause neuromuscular blockade [max by Neomycin]

→ CAPREOMYCIN is chemically not aminoglycoside

STREPTOMYCIN – TB, PLAGUE

CAPREOMYCIN
KANAMYCIN
AMIKACIN
} 2ND LINE DRUGS FOR T.B

NEOMYCIN – HEPATIC COMA [GIVEN ORALLY]

Hepatic coma:

→In our GIT, urea is present which is converted into ammonia (NH3) by the enzyme urease.

→Ammonia is absorbed and goes to brain causing hepatic coma.

Neomycin:

→ It is effective against gram negative organisms and kills urease producing organisms in GIT.

→ It is given orally for Hepatic coma and this use of neomycin is known as Gut sterilization.

PTERIDINE + PABA + GLUTAMATE

SULFONAMIDES ⊣ FOLIC ACID SYNTHASE

Dfet ⟶ FOLIC ACID

TRIMETHOPRIM
PYRIMETHAMINE ⊣ DIHYDRO FA REDUCTASE

TETRA HYDROFOLIC ACID [FOLINIC ACID]

↓

DNA

SULFONAMIDES / SULFA DRUGS

DRUGS		ADVERSE EFFECTS
SULFADOXINE	A →	Aplastic anemia
SULFACYTINE	B →	Bilirubin displacement → cause Kernicterus in newborns
SULFASOXAZOLE	C →	Crystalluria
SULFAMETHOXAZOLE	R →	Rash
SULFASALAZINE	A →	Acetylation
SULFADIAZINE	S →	SLE
DAPSONE	H →	Hemolysis in G6PD deficiency

- *Sulfonamides are structural analogs of PABA, which is essential for synthesis of folic acid. Therefore, sulfonamides are competitive inhibitor of FA synthase enzyme.*
- *In any infection, where pus is present, which usually contains PABA, Sulfonamides are unlikely to be effective.*

→ Sulfonamide ↓ minimum risk of crystalluria → Sulfasoxazole

→ Sulfadoxine → longest acting

→ Sulfacytine → shortest acting

→ Sulfasalazine

→ prodrug

→ uses → Ulcerative colitis [DOC]

→ Rheumatoid Arthritis

→ Ag Sulfadiazine → used for Burn dressing

→ Dapsone → used for Leprosy

Dermatitis Herpetiformis [DOC]

COMBINATIONS

1 COTRIMOXAZOLE

TRIMETHOPRIM + SULFAMETHOXAZOLE

→ ratio for best bactericidal activity → 1 : 20

ratio in tablet to attain this ratio → 1 : 5

→ DOC for

P → Pneumocystis jiroveci

N → Nocardia

B → Burkholderia cepacia

2. SULFADOXINE + PYRIMETHAMINE

→ Indicated in Parasitic infections → Malaria
→ Toxoplasmosis

DNA GYRASE INHIBITORS

→ DNA GYRASE → introduces negative coils & helps in replication

→ DNA gyrase Inhibitors

→ Inhibit replication

→ Chemically these are QUINOLONES

QUINOLONES

1 NALIDIXIC ACID → Used in UTI

2 FLUORD QUINOLONES

FLUORDQUINOLONES

DRUGS

NORFLOXACIN → Used in UTI

CIPROFLOXACIN → Oral drug for Typhoid & DOC for Anthrax

OFLOXACIN

PEFLOXACIN

SPARFLOXACIN

LEVOFLOXACIN

MOXIFLOXACIN → Long acting, also active against anaerobes

GATIFLOXACIN → Withdrawn [causes dysglycemia]

TROVAFLOXACIN

→ Oral cidal drugs

→ Wide spectrum [Gm +ive & Gm -ive]

→ CI in pregnancy & children [<18yrs] [cause cartilage & tendon damage]

→ Induce seizures [avoided in Epilepsy]

→ CI in Renal Failure

EXCEPTION

P → PEFLOXACIN

M → MOXIFLOXACIN

T → TROVAFLOXACIN

→ Phototoxicity [max. ↑ Sparfloxacin]

→ RESPIRATORY FQ

O → OFLOXACIN

M → MOXIFLOXACIN

G → GATIFLOXACIN

LEVOFLOXACIN [isomer of ofloxacin, Long acting]

→ active against respiratory infections caused by

Gm +ive bacteria

Gm -ive bacteria

Atypical bacteria

Mycobacterium TB

→ Recently FDA issued a black box warning which says that they cause neurological side effects.

→ Neurological side effects are of two types,

- CNS
- Peripheral Neuropathy (PN)

Norfloxacin:

→ Mainly excreted by kidney and it is used for Urinary tract infection

→ Among all the fluoroquinolones

- Minimum oral bioavailability - Norfloxacin.
- Maximum oral bioavailability – Levofloxacin.

Ciprofloxacin:

→ Drug of choice for prophylaxis of Meningococcal meningitis

→ Contraindicated in pregnancy and children.

→ Ciprofloxacin is co – drug of choice in Anthrax. (Penicillin G is DOC)

→ Used in enteric fever.

Sparfloxacin :

→ Most phototoxic and longest acting fluoroquinolone.

→ Second longest acting fluoroquinolone is Moxifloxacin.

Gatifloxacin :

→ Gatifloxacin can affect blood glucose level causing Dysglycemia leading to hyperglycemia or hypoglycemia.

→ Due to these side effects it has been withdrawn from india.

Moxifloxacin :

→ Second longest acting fluoroquinolone.

→ Safe in renal failure like (Pefloxacin and Trovafloxacin).

→ Respiratory fluoroquinolones with widest spectrum used for treating many infections.

→ Effective against anaerobes.

DRUGS AFFECTING CELL MEMBRANES

→ DAPTOMYCIN (Drug of choice for VRSA but not in case of VRSA causing Pneumonia; as it is inactivated by pulmonary surfactant)

→ POLYMYXIN B

→ POLYMYXIN E also called as Colistin

→ Drug of choice for VRSA causing Pneumonia – Linezolid.

→ Major side effect of Daptomycin - Myopathy.

→ Polymyxins are effect against Gram negative organisms including Pseudomonas.

→ Colistin is effective against Metallo B lactamase and not effective against serratia and proteus.

ANTIMICROBIAL AGENTS PHARMACOKINETICS

BACTERICIDAL drugs may follow

- Concentration dependent killing (CDK)
- Time dependent killing (TDK)
- Area under curve (AUC) dependent killing (AUC-DK)

CIDAL Drugs

BE – **BE**ta lactams

VA – **VA**ncomycin

F – **F**luroquinolones (FQ)

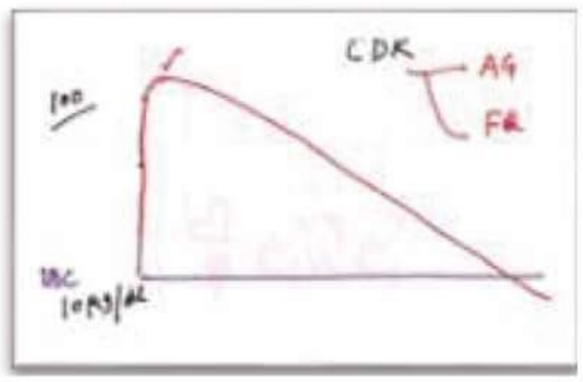
A – **A**minoglycosides (AG)

CDK

→ More the conc. of drug more is the killing ie. At higher concentration more killing activity

→ Given as a single high dose

→ Followed by AG and FQ



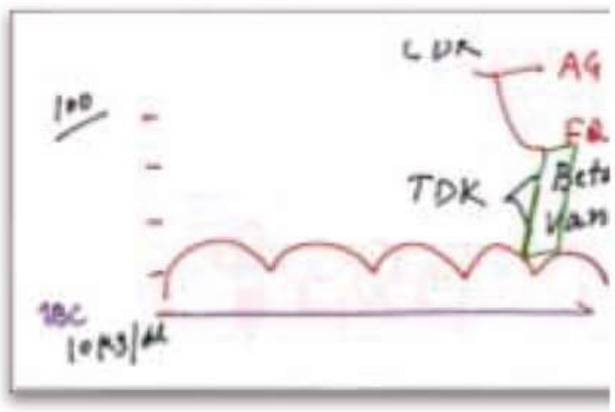
TDK

→ Killing activity depends on time for which concentration of drugs remains above MBC

→ Killing activity does not depend on concentration

→ Given as multiple dose but small doses

→ Followed by Beta lactams and vancomycin

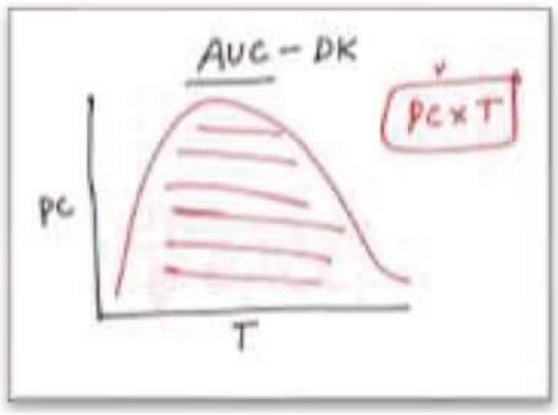


Mnemonic **BV** ko **Time** nahi doge to **kill** kar degi

AUC-DK

→ Killing activity depends on the area of PC-time curve

→ Followed by daptomycin and newer FQ like moxifloxacin



POST ANTIBIOTIC AFFECT (PAE)

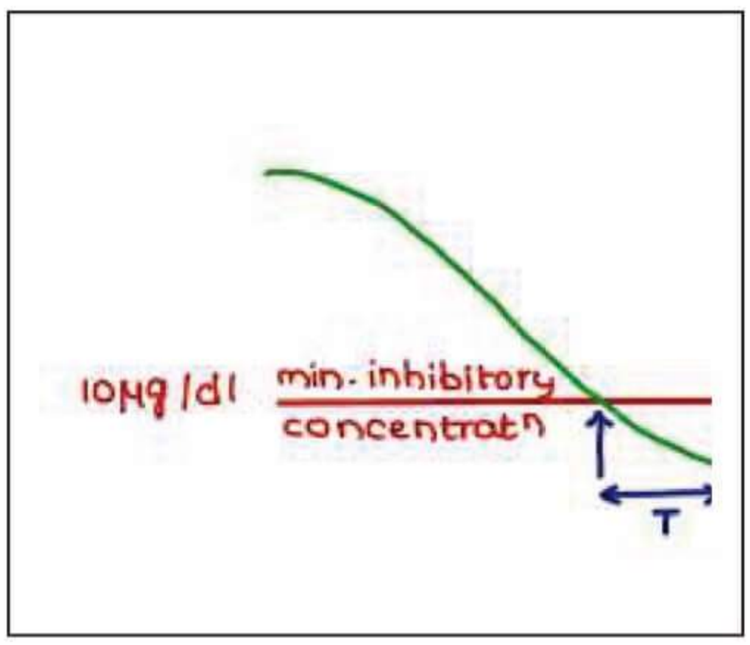
- Applies to both CIDAL and STATIC drugs

  - Time for which antibiotic bacteria is not able to show bacterial growth even when its concentration is below MIC
  - Bacteria prepare for growing
  - Almost all drugs have long PAE for gram +ve bacteria
  - Drugs with short PAE (<90 min) against gram negative bacteria are:

    i) β - lactams except carbapenems

    ii) Vancomycin

  - Drugs with long PAE (>90 min) are:
    - DNA inhibitors – eg FQ
    - Proteins synthesis inhibitors e.g.
      - Tetracyclines
      - Macrolides
      - Clindamycin
      - AG
    - Carbapenems



DRUGS NOT AFFECTIVE AGAINST PARTICULAR BACTERIA

Bacteria	Resistant to	DOC
1. Mycoplasma	Cell wall inhibitors	Macrolides
2. MRSA	Beta lactams	Vancomycin (for treatment) For Nasal Carriers – Mupirocin, Bactracin
3. Pseudomonas	Vancomycin	Aminoglycoside + Ceftazidime
4. Enteric fever	Aminoglycosides	Ceftriaxone
5. Anaerobes	Aminoglycosides	Metronidazole

MYCOBACTERIAL DISEASES

TUBERCULOSIS

ANTI TUBERCULAR DRUGS

FIRST LINE DRUGS

- H → ISONIAZID
- R → RIFAMPICIN [RCIN]
- Z → PYRAZINAMIDE
- E → ETHAMBUTOL
- S → STREPTOMYCIN

	ACTIVITY	BACTERIA	HEPATOTOXIC	PREGNANCY
H	cidal	Both	✓	safe
R	cidal	Both	✓	safe
Z	cidal	i/c	✓✓✓	avoided
E	static	Both	×	safe
S	cidal	e/c	×	CI

MYCOBACTERIA	LOCATION	MOST EFFECTIVE DRUG
FAST GROWING	Wall	H
INTERMEDIATE GROWING	Spurters [casseous necrosis]	R
SLOW GROWING	i/c	Z

ISONIAZID (INH)

- Causes pyridoxine (vitamin B6) deficiency resulting in peripheral neuropathy. So, pyridoxine is used for treatment as well as prevention.
- Hepatotoxic (INH: Isoniazid causes Neuropathy and Hepatotoxicity)
- Metabolized by acetylation and cause SLE as an adverse effect (SHIP).

  →Isoniazid is metabolized by N – Acetyltransferase to form acetyl isoniazid and it is further metabolized to form acetyl hydrazine

  →Isoniazid accumulation can cause

  - Peripheral neuropathy

  →Acetyl hydrazine can cause

  -Hepatotoxicity

  →In slow acetylators, there is less amount of N – Acetyltransferase leading to slow metabolism leading to isoniazid accumulation causing peripheral neuropathy

  →In fast acetylators, there is more amount of N – Acetyltransferase leading to acetyl hydrazine accumulation causing Hepatotoxicity.

SHIP drugs:
S – Sulfonamides
H – Hydralazine
I – Isoniazid
P – Procainamide

RCIN

1. Should given on empty stomach
2. Secreted in Bile → safe in RF
3. Enzyme Inducer

INTERACTIONS

Warfarin —Replace t→ Heparin

OCP —Replace t→ Other contraceptive method

Anti HIV drugs ——→ RCIN replaced t RIFABUTIN

	RIFABUTIN	RIFAMPICIN
Enzyme inducer	+	+ + + +
Durat^{n} of act^{n}	Longer acting	Long acting
Effective on	Atypical mycobacteria	M.TB
S/E	no hepatotoxic Pseudojaundice Uveitis	Hepatotoxic

4. Causes discoloration of secretions:

→ Orange colored urine

→ Staining of contact lens due to discoloration of tears

5. OTHER USES:

→ Leprosy

→ DOC for Brucella (doxycycline + rifampicin)

→ Effective against Gram positive bacteria (including MRSA)

→ Effective against Gram negative bacteria (including Pseudomonas)

→ It was used for prophylaxis of meningococcus meningitis

Meningococcal meningitis prophylaxis
Ciprofloxacin (DOC)
Ceftriaxone (most effective drug; Injectable: DOC in pregnancy and children)
Rcin (Not preferred now)

PYRAZINAMIDE (Z)

→ Effective only against intracellular bacteria

→ Most hepatotoxic

→ Causes hyperuricemia

→ Possess the best sterilizing activity (can kill the slow growing bacteria) and makes the medium sterile.

ETHAMBUTOL (E)

→ Affect eye

- Red green colour blindness (optic neuritis)
- Initially reversible, later irreversible
- Avoid in <64 year age children

STREPTOMYCIN (S)

→ Not effective orally (given i.m.)

→ Nephrotoxic

→ Ototoxic

→ Cause neuro-muscular blockade

→ Streptomycin was initially in first line anti tubercular drugs, it was shifted to supplementary category as it needs to be given as injection. Now-a-days it is not even considered as first line drug.

2ND LINE DRUGS

1. FQ

→ OFLOXACIN

→ MOXIFLOXACIN

→ GATIFLOXACIN

→ LEVOFLOXACIN

2. INJECTABLE

→ CAPREOMYCIN

→ KANAMYCIN

→ AMIKACIN

3. **LINEZOLIDE** – Also used for VRSA
   CLOFAZIMINE – Also used for multibacillary leprosy

4. **CYCLOSERINE** – Causes neuropsychiatric S/E
   ETHIONAMIDE – Hepatotoxic, causes hypothyroidism
   PAS – Causes hypothyroidism

5. OTHER DRUGS

- **Thioacetazone:**
  - Never given in HIV patients

- **Antitubercular with uncertain efficacy:**
  - Amoxycillin + clavulanic acid
  - Imipenem

- **New drugs approved for MDR/XDR TB:**
  - **BEDAQUILINE** act by inhibiting ATP synthase enzyme, can result in QT prolongation

- **DELAMANID** act by inhibiting mycolic acid in mycobacteria, can result in QT prolongation
- **PRETOMANID** act by inhibiting mycolic acid in mycobacteria, is hepatotoxic

- **NEW REGIME FOR MDR / XDR TB: BPaL REGIME:**
  - Bedaquiline (B)
  - Pretomanid (Pa)
  - Linezolid (L)

TREATMENT OF TUBERCULOSIS (RNTCP 2018):

- **DRUG SENSITIVE TB:**

Drug sensitive	IP	CP
Category 1	2 HRZE	4 HRE
Category 2	2 HRZE	4 HRE

- **DRUG RESISTANT TB:**

Mono drug	Resistant to any one of HZE
Poly drug	Resistant to more than one of HZE
Multi drug (MDR)	Resistant to H+R
Rifampicin resistance	Resistant to R but sensitive to H
Extensive (XDR)	Resistant to H + R + one of FQ + one of injectable
Total (TDR)	Resistant to all available drugs for TB

- **Treatment**
  - Drug sensitivity testing is done before we start antitubercular drugs for MDR, RR and XDR.

Resistant TB	IP in months	CP in months
Mono	3 (FLD + Lf + Inj)	6 (FLD + Lf)
Poly	3 (FLD + Lf + Inj + Ethio)	6 (FLD + Lf + Inj + Ethio)
MDR	6 (minimum 6 drugs)	18 (minimum 4 drugs)
RR	6 (Tx of MDR + H)	18 (Tx of MDR + H)
XDR	6 (minimum 7 drugs)	18 (minimum 6 drugs)

FLD: First line oral drugs to which bacteria is sensitive

Lf: levofloxacin

Inj: injectable drug

Ethio: Ethionamide

LEPROSY

MULTIBACILLARY LEPROSY

RCIN	600 mg	Once monthly	Supervised	X 12 MONTHS
CLOFAZIMINE	300 mg	Once monthly	Supervised	
CLOFAZIMINE	50 mg	Once daily for 28 days	Unsupervised	
DAPSONE	100 mg	Once daily for 28 days	Unsupervised	

PAUCIBACILLARY LEPROSY

RCIN	600 mg	Once monthly	Supervised	X 6 MONTHS
CLOFAZIMINE	300 mg	Once monthly	Supervised	
CLOFAZIMINE	50 mg	Once daily for 28 days	Unsupervised	
DAPSONE	100 mg	Once daily for 28 days	Unsupervised	

→ **In case of resistance, the drugs used are**

- Ofloxacin
- Minocycline
- Clarithromycin

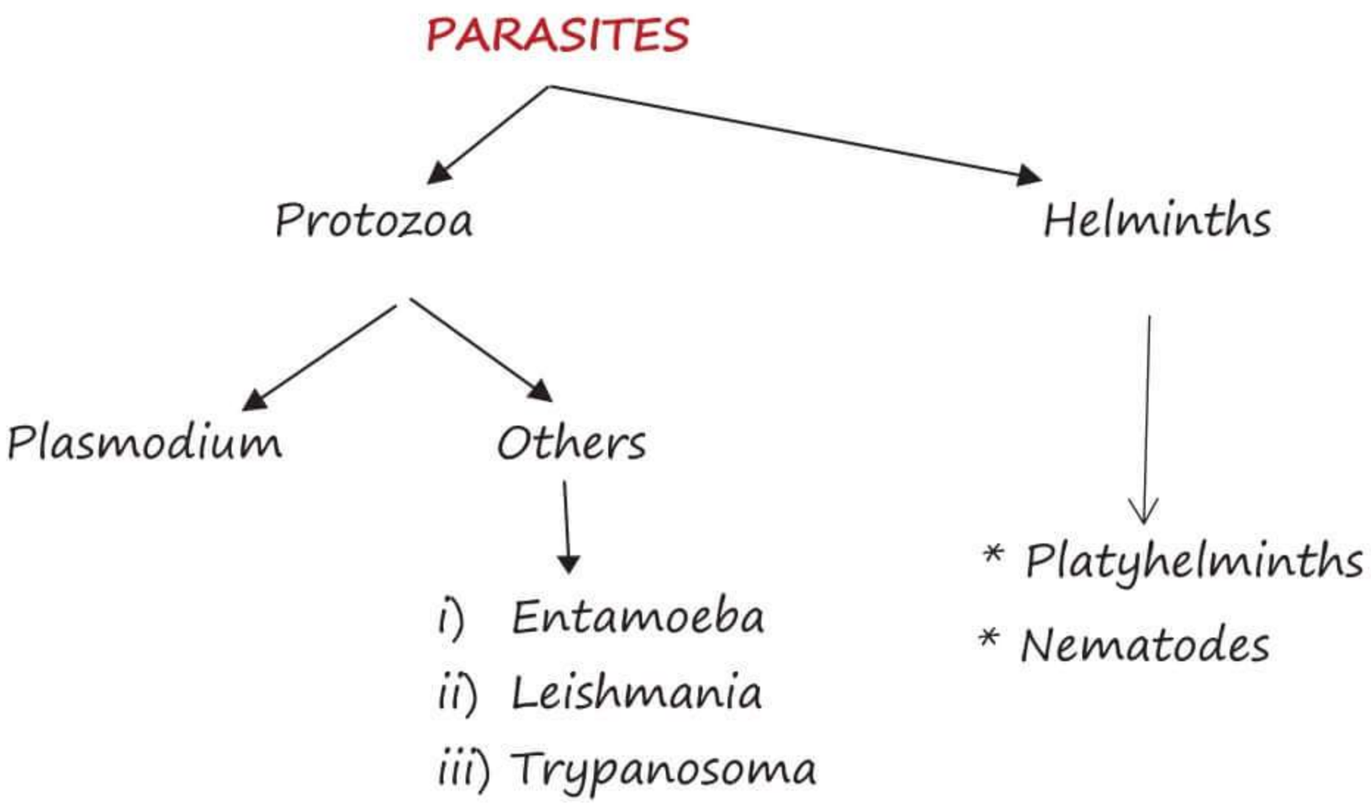
MAC (MYCOBACTERIUM AVIUM COMPLEX)

→ **Associated with immunocompromised patient (HIV)**

→ **Treatment**: Rifabutin + Ethambutol + Clarithromycin

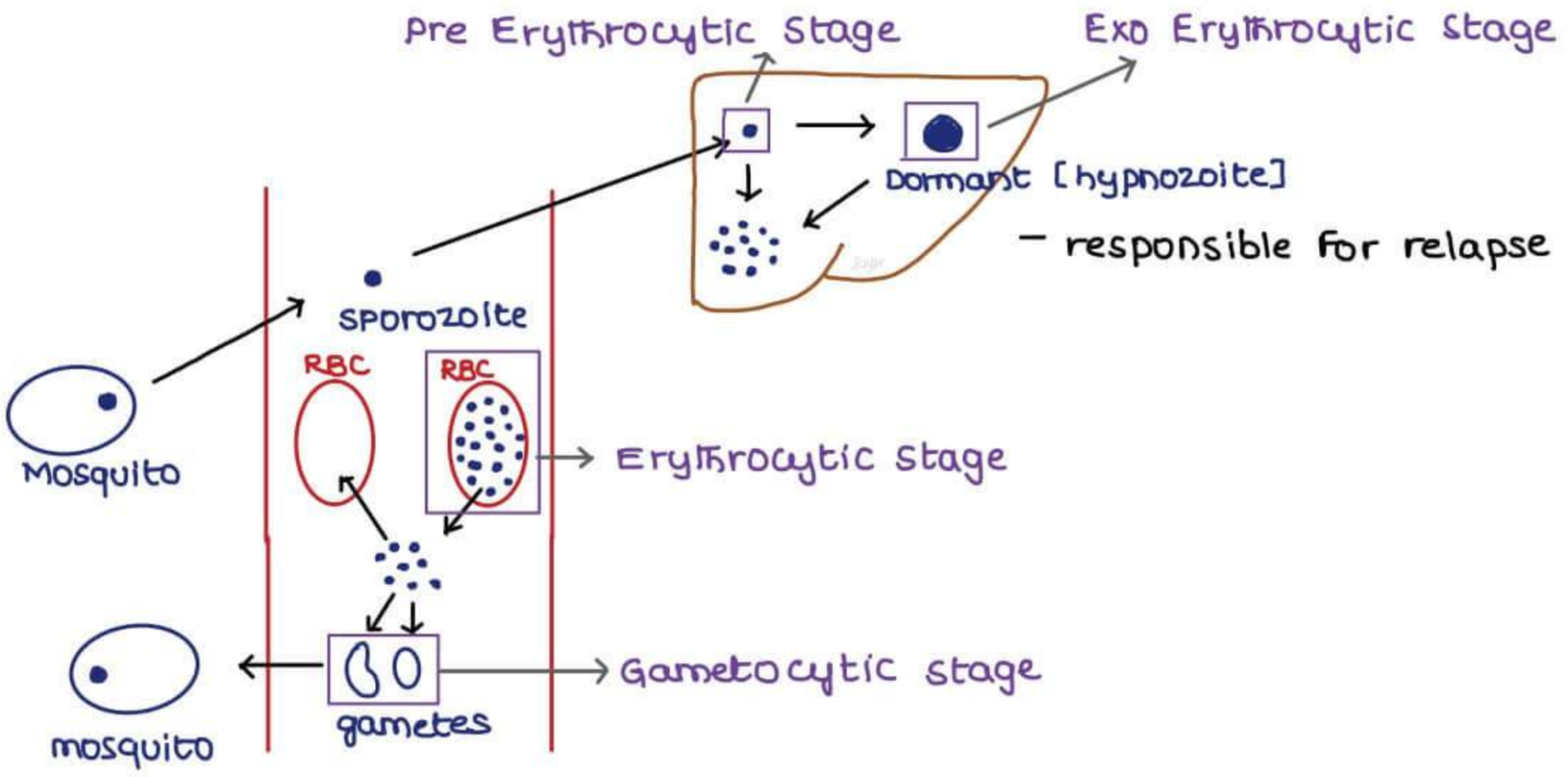
→ **Prophylaxis**: Azithromycin (weekly) OR Clarithromycin (daily)

ANTIPARASITIC DRUGS



ANTI MALARIAL DRUGS

→ Plasmodium Knowlesi can also cause malaria



TREATMENT MODALITIES

- CURE
  - CLINICAL → R_f Erythrocytic Stage
  - RADICAL → R_f Exo-Erythrocytic Stage
- PROPHYLAXIS
  - SUPPRESSIVE → R_f Erythrocytic Stage
  - CAUSAL → R_f Pre Erythocytic Stage

PRIMAQUINE

→ ACTS ON

- PRE ERYTHROCYTIC STAGE → used for causal Prophylaxis
- EXO ERYTHROCYTIC STAGE → used for Radical cure
- GAMETOGENIC STAGE → used to prevent transmission

→ can't act on ERYTHROCYTIC STAGE → not useful to R_f or prevent malaria

→ can cause HEMOLYSIS in G6PD Deficiency

→ CI in Pregnancy & infants

→ Can kill the gametes of all species of plasmodium (vivax, falciparum, ovale, malariae) in a single dose whereas chlorquine and quinine can kill gametes of plasmodium vivax only.

→ Can kill the exoerythrocytic stage (hypnozooites) when given for 14 days.

→ In plasmodium falciparum there is no exoerythrocytic stage and hence there is no relapse in plasmodium falciparum.

→So in ,

- Plasmodium falciparum, single dose of primaquine is given (to kill gametes).
- Plasmodium vivax, it is given for 14 days to kill the hypnozoites.

CONTRAINDICATIONS OF PRIMAQUINE :

→ G6PD deficiency patients

→ Pregnancy

→ In infants (< 1 year of age)

TAFENOQUINE

→ Can kill the hypnozoites in single dose

→ Like Primaquine, it can also cause hemolysis and hence it is also contraindicated in G6PD deficient patients, pregnancy and infants.

DRUGS ACTING ON ERYTHROCYTIC STAGE

FAST ACTING

M → MEFLOQUINE
A → ATOVAQUONE
C → CHLOROQUINE
H → HALOFANTRINE
A → ARTEMISININS
R → RES - Q [QUININE]

SLOW ACTING

PROGUANIL
PYRIMETHAMINE
SULFADOXINE
DOXYCYCLINE
CLINDAMYCIN

CHLOROQUINE

→ causes BULL'S EYE MACULOPATHY [on prolonged usage for 2-3 yrs]

USES

R → Rheumatoid Arthritis
E → Extra intestinal Ameobiasis
D → DLE
L → Lepra reaction
I → Infectious mononucleosis
P → Photogenic Reactions
Mahatma → Malaria
Gandhi → Giardiasis

MEFLOQUINE:

- Long acting drug
- Neuropsychiatric side effects

QUININE:

- Safe in 1st trimester of pregnancy
- Derivatives of cinchona plant: excess will lead to development of Cinchonism (headache, blurred vision, tinnitus, deafness)
- If only quinine has to be given, it is given for 7 days for treatment for malaria.
- Therefore, we add doxycycline or clindamycin to quinine, so that we decrease duration of treatment to 3 days.

ARTEMISININS

DRUGS

ARTESUNATE
ARTETHER
ARTEMETHER
DIHYDRO ARTEMISININ

→ Fastest acting antimalarials
→ effective against MDR parasites
→ short acting
→ CI in 1st trimester

ARTEMISININ COMBINATION THERAPY [ACT]

→ Artimisinin + Long acting drug
→ DOC for Chloroquine resistance
→ COMBINATIONS

LUMEFANTRENE + ARTEMETHER → DOC in North Eastern States
ARTESUNATE + SULFADOXINE – PYRIMETHAMINE → DOC for rest of India

TREATMENT OF MALARIA UNDER NVBDCP

		1st Trimester
P. vivax malaria	Chloroquine	Chloroquine
P. falciparam malaria	ACT	Quinine
mixed infection	ACT	Quinine
complicated or severe or cerebral Malaria	iv Artesunate + ACT	iv Artesunate

MALARIA PROPHYLAXIS

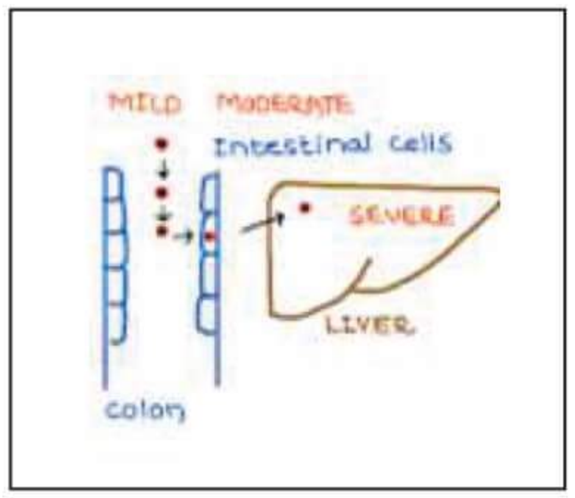
- Given to traveler going from non-endemic area to endemic area.
- Drugs are given before the journey.
- Prophylaxis depends on duration of stay:

Short term (<6 weeks)	Long term (>6 weeks)
• Doxycycline • Given daily • Start 2 days before journey to • 4 weeks after journey	• Mefloquine • Given weekly • Start 2 weeks before journey to • 4 weeks after journey

OTHER PROTOZOAL DISEASES

1. AMOEBIASIS

- Entamoeba histolytica comes through feco-oral route
- Through mouth it can penetrate cells of intestine → reach liver



1. Luminal amoebiasis – Enters mouth to lumen
2. Intestinal amoebiasis – when it penetrates intestinal cells
3. Extra intestinal amoebiasis – when it penetrates tissue

DRUG OF CHOICE

- Luminal amoebiasis & carrier state – Diloxanide Furoate (or) Paromomycin
- Intestinal & Hepatic amoebiasis – Nitroimidazole (Nidazole)

  Eg. Metronidazole, Tinidazole, Secnidazole, Ornidazole, Satranidazole

  ↓

  Cause disulfiram like reaction

  C/I in alcoholics (except satranidazole)

→ Other uses of Metronidazole

G – Giardiasis, Gardnerella vaginalis

U – Ulcer (Peptic ulcer)

P – Pseudomembranous colitis

T – Trichomoniasis

A – Amoebiasis, Anaerobic bacterial infection

2. LEISHMANIASIS

Leishmania

Visceral	Mucocutaneous	Dermal
(KALA AZAR)		(PKDL)
DOC – Liposomal AMB	Liposomal AMB	Miltefosine
(IV Single dose)		(Only oral drug)
Other drug – Antimony (Stibogluconate)		

3. TRYPANOSOMIASIS

AFRICAN TRYPANOSOMIASIS / SLEEPING SICKNESS	SOUTH AMERICAN TRYPANOSOMIASIS/ CHAGA'S DISEASE
EARLY STAGES – SURAMIN (DOC) LATE STAGES – MELARSOPROL (DOC)	BENZNIDAZOLE (DOC)

ANTI HELMINTHIC DRUGS

PLATYHELMINTHS

Tapeworms

→ DOC → PRAZIQUANTAL
except Echinococcus granulosus [DOG Tapeworm]

→ DOC for Echinococcus granulosus
→ ALBENDAZOLE

Flukes

→ DOC → PRAZIQUANTAL
except for Liver fluke [Fasciola hepatica]

→ DOC for Liver fluke → TRICLABENDAZOLE

NEMATODES

→ DOC for all nematode incl. larvae → ALBENDAZOLE
→ Except
Filaria → DEC [Di Ethyl Carbamazine]
Strongyloides, Onchocerca } IVERMECTIN

→ Ivermectin is the only oral drug approved for scabies
→ DOC for Scabies – Permethrin
→ Treatment of **Neurocysticercosis** : ALBENDAZOLE (DOC)
PRAZIQUANTAL

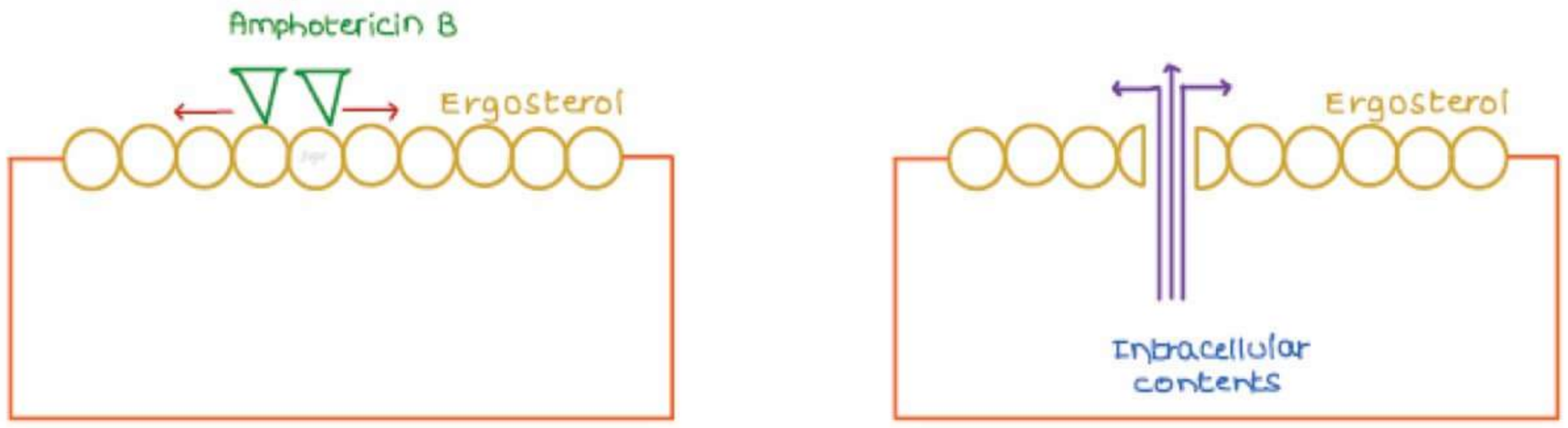
ANTIFUNGAL DRUGS

1. POLYENES:

→ Amphotericin B
→ Nystatin
→ Hamycin

Mechanism of action

Bind to Ergosterol, creates pores leading to death of fungus, which makes them fungicidal.



AMPHOTERICIN B

→ Used for serious fungal infections (DOC for cryptococcal meningitis, mucormycosis)

→ Given IV

→ Very toxic (side effect):

- Infusion related reaction (MC side effect): chills, fever
- Nephrotoxic (RTA with hypokalemia): MC dose dependent side effect.
- BM suppression

→ Liposomal amphotericin B:

- Less nephrotoxic as compared to conventional amphotericin B
- But cost is higher
- DOC for KALA AZAR

NYSTATIN: Used topically for oropharyngeal candidiasis

HAMYCIN: Used topically

2. ALLYL-AMINES

→ Allyl-amines inhibit Sq epoxidase and lead to accumulation of squalene which is toxic to fungal cell (fungicidal drugs). Azoles inhibit 14 alpha demethylase and are fungistatic.

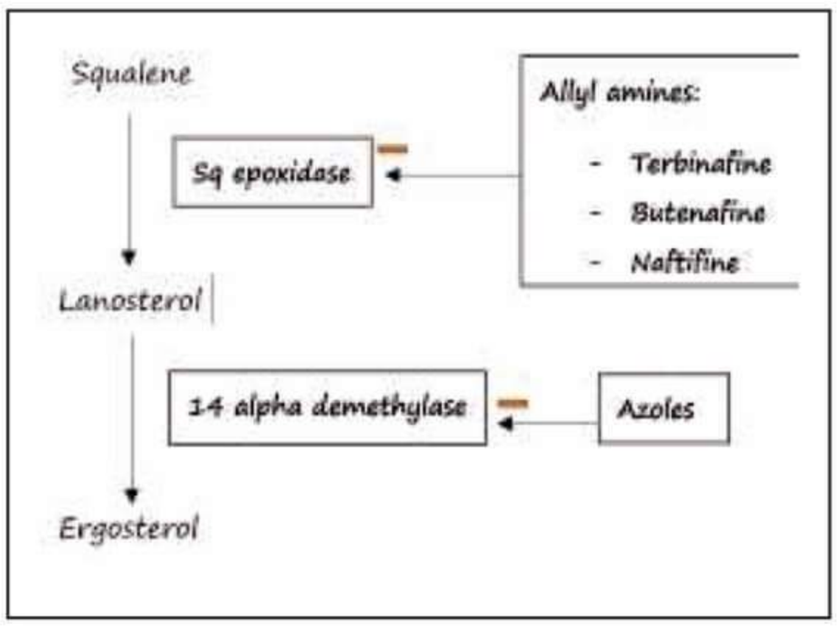
→ Allyl-amine: are fungicidal and available in oral form as well as topical preparations.

A. TERBINAFINE

B. BUTENAFINE

C. NAFTIFINE

- After absorption, these drugs accumulate in Keratin rich areas like skin, hair and nails.
- Therefore, these drugs are used in fungal infection of skin, nail and hair, i.e. dermatophytosis (tinea infection).



3. AZOLES

→ Azoles are fungistatic drugs:

A. KETOCONAZOLE
B. FLUCONAZOLE
C. ITRACONAZOLE
D. VORICONAZOLE
E. POSACONAZOLE

- Ketoconazole: not much in use these days due to:
  - Microsomal enzyme inhibition
  - Cause Gynaecomastia
  - Cause Adrenal suppression
  - Hepatotoxic
- Fluconazole:
  - max oral bioavailability
  - max CNS penetration
  - DOC for candida and Cryptococcus (maintenance phase)
  - DOC for cryptococcal meningitis is Ampho B (Acute phase)
- Itraconazole: DOC
  - Histoplasma
  - Sporothrix
  - Blastomyces
- Voriconazole: DOC
  - Aspergillosis
- Posaconazole: can be use in
  - Mucormycosis (DOC is Ampho B)

Drugs causing gynaecomastia

DI: **D**igitalis

S: **S**pironolactone

C: **C**isplatin

K: **K**etoconazole

O: **O**estrogen

4. HETEROCYCLIC BENZOFURAN: GRISEOFULVIN

- Act on mitotic spindle
- Oral, static drug
- High affinity for keratin
- Used for dermatophytosis
- Avoided in patient taking Disulfiram.

5. 5-FLUCYTOSINE:

- Inhibit DNA polymerase

6. ECHINOCANDINS:

- CASPOFUNGIN (use for Candida and aspergillosis)
- Act on beta 1,3 – glycan of cell wall

- New drugs are:
    - Micafungin
    - Anidulafungin

7. TAVABOROLE

- Topical antifungal drug for dermatophytosis
- Acts by inhibiting fungal tRNA synthase (protein synthesis)

ANTIVIRAL DRUGS

Virus multiplication:

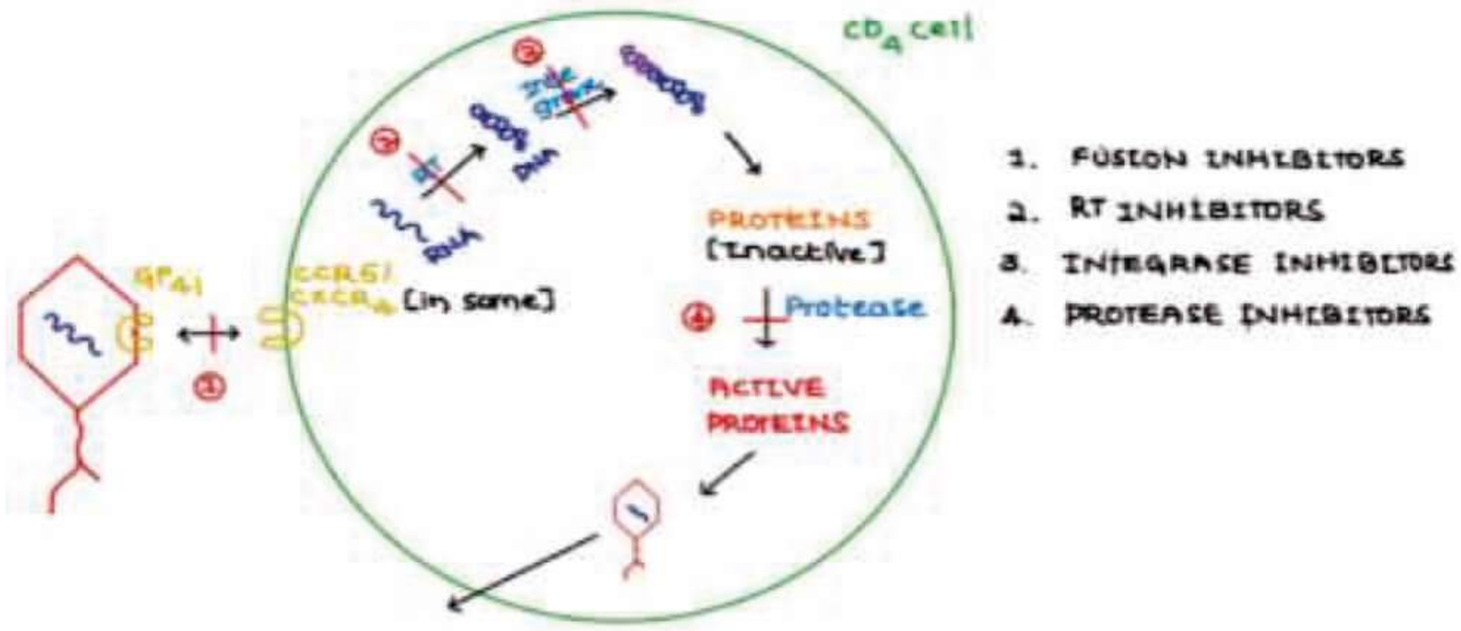
→Virus fuse with human cell and sends the genetic material inside human cell; uncoating occurs genetic material is set free and then it multiplies, replication occurs and forms inactive proteins.

→Inactive proteins are activated and then assembly and maturation occurs, virus matures and is released outside the cell.

DRUGS:

1. **Fusion inhibitors**
    - Enfuvirtide (inhibits the fusion of virus and human cell)
2. **Uncoating inhibitors**
    - Amantadine
3. **Virus nucleic acid inhibitors** - Acyclovir
4. **Protease inhibitors** – inhibits activation of proteins
5. **Virus maturation inhibitors** - Tecovirimat
6. **Virus release inhibitors**
    - Oseltamivir

ANTI-HIV DRUGS



1. FUSION INHIBITOR

ENFUVIRTIDE	MARAVIROC	IBALIZUMAB
• Binds with GP 41 of Envelope & Fusion of VIRus with T cell is Inhibited • Given subcutaneously	• Binds with CCR-5 • Given orally • Can't bind with CD4 cells with CxCR4	• Monoclonal antibody against CD4 receptors • Given intravenously

2. REVERSE TRANSCRIPTASE INHIBITORS

→ Inhibit reverse transcriptase (RNA dependent DNA polymerase)

→ May be competitive (NRTI) or non-competitive (NNRTI)

COMPETITIVE		NON COMPETITIVE	
NRTI (nucleotide or side RT inhibitors)		NNRTI (Non NRTI)	
Nucleoside RTI	Nucleotide RTI	1st Gen	2nd Gen
Zidovudine Lamivudine Stavudine Didanosine Zalcitabine Emtricitabine Abacavir	Tenofovir	Efavirenz Nevirapine Delavirdine	Etravirine Rilpivirine Doravirine

NUCLEOSIDE OR NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)

Most cause peripheral neuropathy & pancreatitis

→ Max risk of peripheral neuropathy – Stavudine

→ Max. risk of pancreatitis – Didanosine

→ Min. risk of peripheral neuropathy – Lamivudine (safest NRTI)

→ Min. risk of pancreatitis - Lamivudine

Bone marrow suppression by – Zidovudine

MI predisposition by – Abacavir

NRTIs used for hepatitis B.

L – Lamivudine

E – Emtricitabine

T – Tenofovir

NON- NUCLEOSIDE/TIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)

→ Prone to develop Resistance (hence not given alone)

→ Effective against HIV -1 only

→ Metabolized by CYP (microsomal) enzymes and are prone to drug interactions.

Nevirapine:

→ Prevents vertical transmission from HIV infected mothers

→ Hepatotoxic (should not be given with other hepatotoxic drugs)

→ Examples of hepatotoxic drugs include TB drugs like Isoniazid, Rifampicin.

3. INTEGRASE INHIBITORS

→ Can be given orally and according to latest 2018 guidelines they are one of the first line drugs of HIV

→ First line HAART therapy – 2 NRTI'S AND 1 NNRTI (or) Integrase inhibitor

→Elvitegravir is combined with cobicistat which is a CYP3A4 inhibitor to boost the effect of elvitegravir.

4. PROTEASE INHIBITORS

RITONAVIR

LOPINAVIR

AMPRENAVIR

FOSAMPRENAVIR

ATAZANAVIR

SAQUINAVIR

NELFINAVIR

INDINAVIR

→ Metabolized by CYP3A4

→ CYP3A4 inhibitors themselves

- Strongest – Ritonavir
- Ritonavir boosting – boost the other inhibitors

→ Cause lipodystrophy syndrome (also caused by atypical antipsychotics)

- ↑ Glucose
- ↑ Lipids
  - Insulin resistance

•Wt. gain

RITONAVIR

→Strongest microsomal enzyme inhibitor

→It is not used as a protease inhibitor

→ In low doses, it is used to inhibit microsomal enzymes and to boost the effect of other protease inhibitors except nelfinavir.

NELFINAVIR: Effect not boosted by ritonavir

INDINAVIR

→Causes Renal stones, hyperbilirubinemia, Kidney stones

ATAZANAVIR

→Among all the protease inhibitors it has the minimum risk of causing LIPODYSTROPHY SYNDROME, but it can result in hyperbilirubinemia.

HAART – HIGHLY ACTIVE ANTI RETRO VIRAL THERAPY

1. When to start Rx – All patients irrespective of CD4 count
2. How long – Life long
3. WHAT – minimum 3 drugs from minimum 2 groups

- 2 NRTI + 1 NNRTI /Integrase Inhibitor
- T +L+E (preferred)

POST EXPOSURE PROPHYLAXIS:

→ To prevent development of HIV after exposure

→ Used commonly in health care workers

→ Should be started as early as possible after exposure (within maximum limit of 72 hours)

→ Should be given for 28days (4 weeks)

→ All the drugs are given orally

→ Drugs: TENOFOVIR + LAMIVUDINE + PROTEASE INHIBITOR

- If protease inhibitor is contraindicated, prefer EFAVIRENZ

PREVENTION OF VERTICAL TRANSMISSION:

- Transfer of HIV from mother to baby through vertical transmission
- Prevented by giving
  - → Mother should be given full HAART therapy (TLE)
  - → After delivery, Baby is given Nevirapine for 6 weeks
- If mother is already exposed to Nevirapine alone, then zidovudine is given

ANTI-INFLUENZA DRUGS

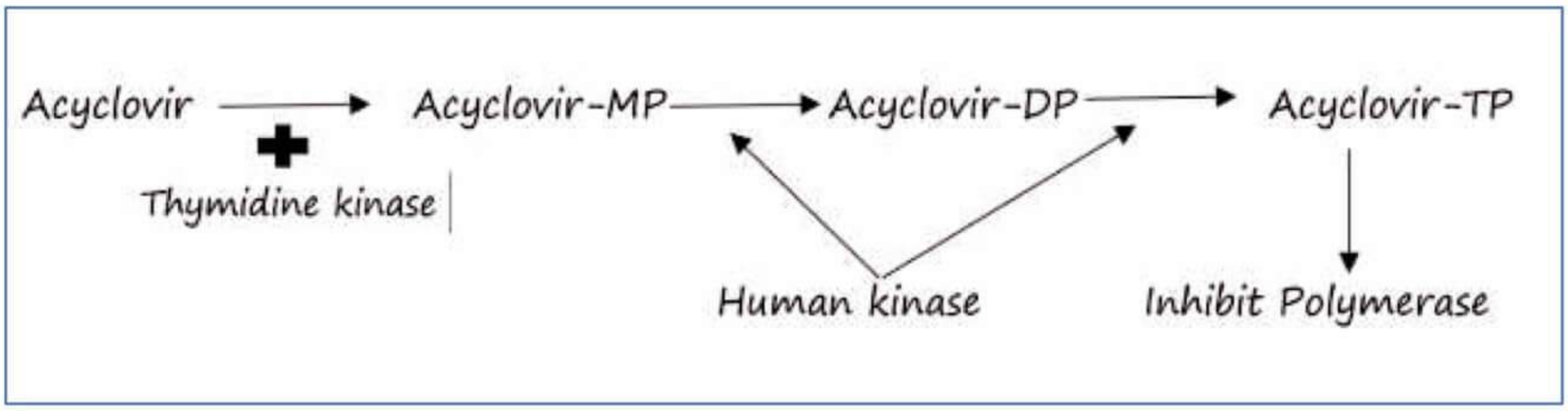
- 3 types of drugs

Uncoating inhibitors	Neuraminidase inhibitors	Polymerase inhibitors
Genetic material cannot become free	– Virus after maturation ↓	Baloxavir ↓ inhibit

as uncoating is inhibited **Drugs:** **AMANTADINE** *Anti-Parkinson drug * used only for influenza -A **RIMANTADINE**	Has to leave that cell & infect other cells - Its connection with that cell should be removed to infect other cells ↓ Done by Neuraminidase - If this enzyme is inhibited, the virus remains clumped to that human cell only & its infection is limited - Drugs: ○ Oseltamivir – oral ○ Zanamivir – inhalational ○ Peramivir – Parenteral These are D.O.C for ○ Bird flu – H5N1 ○ Swine flu – H1N1	multiplication of influenza virus -It is single dose treatment for influenza

ANTI-HERPES VIRUS DRUGS

- HSV-1: Mucocutaneous Herpes and Herpes Encephalitis
- HSV-2: Genital Herpes
- VZV: Chicken pox
- DOC for all of them is **ACYCLOVIR**



- Acyclovir will be activated in only those cells which are being infected by virus, As this drug require viral thymidine kinase for activation

↓

If mutation occurs in this enzyme

↓

Virus becomes resistant to this drug

- Acyclovir – short acting
  - Nephrotoxic
- Other drugs which belongs to acyclovir group are:
  - Valacyclovir
  - Penciclovir
  - Famciclovir
- Ganciclovir is a DOC for CMV. Ganciclovir also cause BM suppression therefore it shouldn't be combined with Zidovudine.

ANTI-HEPATITIS VIRUS DRUGS

- HEPATITIS A & E → self-limiting → no anti-viral drug is recommended.
  - Only symptomatic treatment is enough
- HEPATITIS D – causes infection only with hepatitis -B .So if we treat hepatitis -B; hepatitis – D will not occur
- HEPATITIS B – D.O.C – Tenofovir (1st priority) / Entecavir
  - Alternate to this, drugs which can be given orally that are effective against H.I.V also are
    - L- Lamivudine
    - E – Emtricitabine
    - T- Tenofovir
  - If oral drugs are not effective, injection should be given – interferon(IFN) – non-specific & very toxic
- HEPATITIS C
  - Previously treated with Interferons and ribavirin
  - Treatment was very toxic
  - Now all oral treatment is used

NEW ORAL DRUGS FOR HEPATITIS C

PROTEASE INHIBITORS	NS5A INHIBITORS	NS5B INHIBITORS
PREVIRS	ASVIRS	BUVIRS
Telaprevir	Elbasvir	Sofosbuvir
Simprevir	Ledipasvir	Dasabuvir
Boceprevir	Daclatasvir	Beclabuvir
Grazoprevir	Ombitasvir	
Paritaprevir	Pimbrentasvir	

ANTICANCER DRUGS

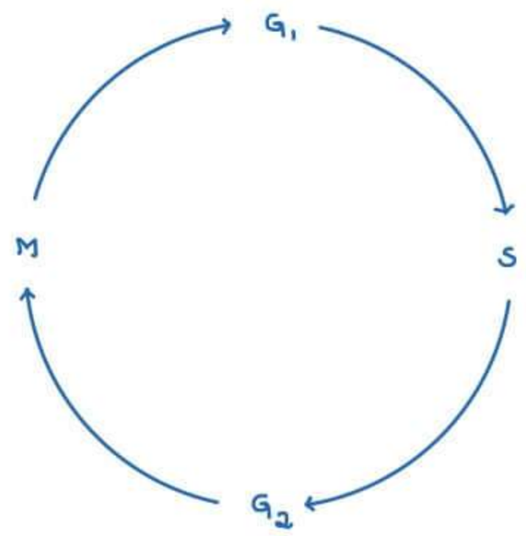
CYTOTOXIC ANTICANCER DRUGS

ADVERSE EFFECTS

1. BM supression
2. Alopecia
3. Mucositis → Diarrhea
4. Hyperuricemia

CELL CYCLE

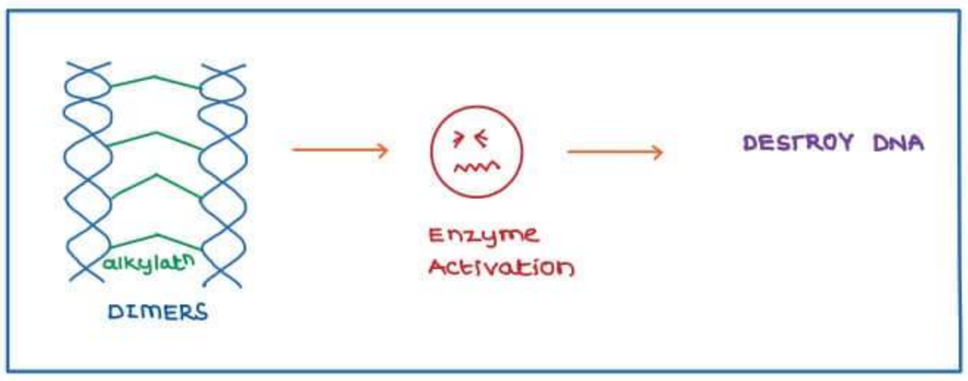
→ SYNTHETIC PHASE [S] → DNA Doubled
MITOTIC PHASE [M] → DNA reduced to half
GAP PHASES [G_1 & G_2]



→ Non selective Drugs → bind to DNA
S phase specific Drugs → inhibit DNA synthesis
M Phase Specific Drugs → inhibit mitosis

1 ALKYLATING AGENTS

MOA



mc site of alkylath
→ N_7 of Guanine

ADVERSE EFFECTS

1. BM supression
2. Alopecia
3. Mucositis → Diarrhea
4. Hyperuricemia
5. 2° Leukemia
6. Sterility

DRUGS:

If – Ifosfamide

Bus – Busulfan

Not – Nitrosoureas

Present – Procarbazine

Take – Temozolomide

My – Melphalan, Mechlorethamine

Cycle – Cyclophosphamide

Ifosfamide and Cyclophosphamide:

Ifosfamide and cyclophosphamide

↓ Metabolized to

Acrolein

↓ causes

Hemorrhagic cystitis (Ifosfamide ≫ Cyclophosphamide)

Prevention of Hemorrhagic cystitis:

- MESNA – MercaptoEthaneSulfoNicAcid

Treatment of Hemorrhagic cystitis:

- Steroids

→ Every dose of Ifosfamide should be given with MESNA whereas only High dose of Cyclophosphamide should be given with MESNA.

Drugs causing Pulmonary Fibrosis:

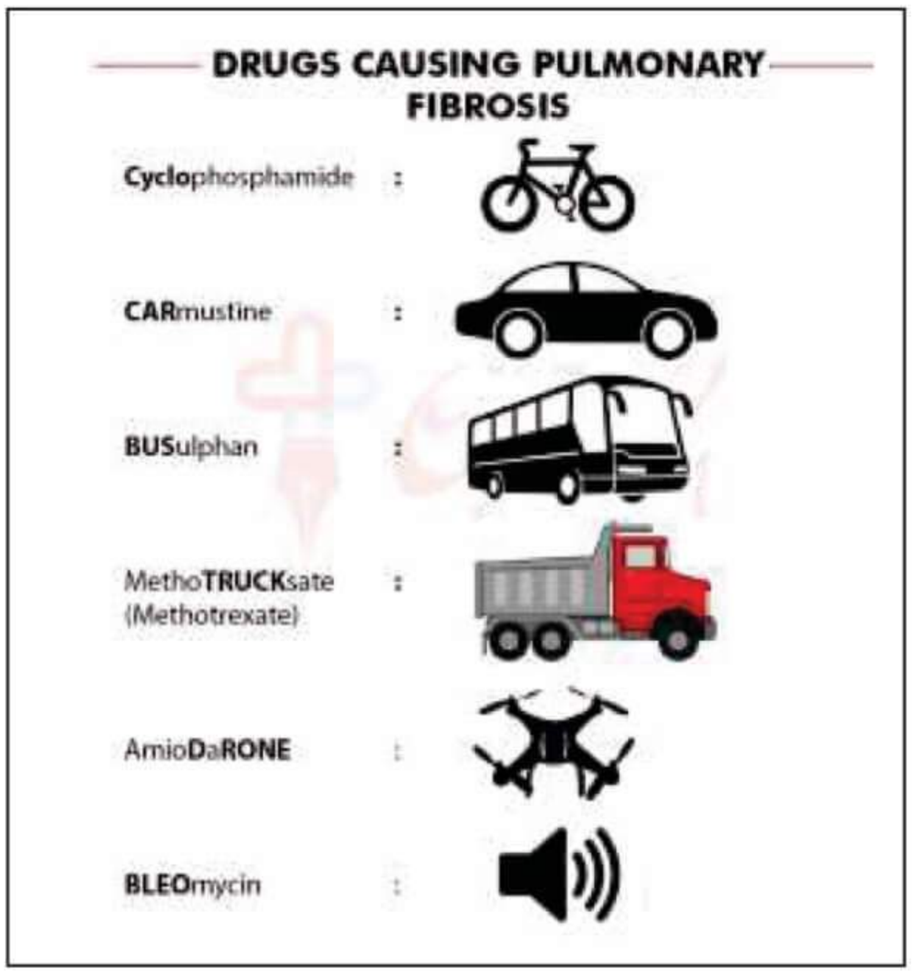
→ Cyclophosphamide

→ Busulfan

→ Methotrexate

→ Amiodarone

→ Bleomycin



Nitrosoureas :

→ Carmustine (BCNU)

→ Lomustine (CCNU)

→ Semustine (Methyl CCNU)

Use of Nitrosourea drugs:

→ As they can cross Blood Brain Barrier, they are used in Brain tumors.

Side effects:

→ Causes Delayed bone marrow suppression and Neutropenia.

Procarbazine:

→ causes Disulfiram like reaction i.e., intolerance to alcohol

Temozolomide:

→ Drug of choice for GLIOMA.

Melphalan:

→ Used in Multiple Myeloma.

2. PLATINUM COMPOUNDS

DRUGS

CISPLATIN

CARBOPLATIN

OXALIPLATIN → used for COLORECTAL CARCINOMA

MOA ≅ Same as Alkylating Agents

AIE ≅ Same as Alkylating Agents

CISPLATIN

→ most emitogenic anticancer drug [DOC → $5HT_3$ # (ondansetron)]

→ nephrotoxic

→ ototoxic

Vomiting:

→ Early vomiting (<24 hours)

- Drug of choice – $5HT_3$ antagonists (Setron's) like

  Ondansetron, Granisetron.

→ Delayed vomiting (>24 hours)

- Drug of choice – Neurokinin / substance P antagonist like

  Aprepitant.

Nephrotoxicity:

→ Reversible

→ Prevention of nephrotoxicity

- Slow intravenous infusion of cisplatin
- Saline loading can be done
- Amifostine

Ototoxicity:

→ Irreversible.

OXALIPLATIN:

→ Used in Colorectal carcinoma.

COLORECTAL CARCINOMA REGIMEN

FOLFOX REGIME	FOLFIRI REGIME
FOLINIC ACID +	FOLINIC ACID +
5-FU +	5-FU +
OXALIPLATIN	IRINOTECAN

3. ANTIMETABOLITES

→ S Phase Specific

a. Drugs affecting FOLIC ACID METABOLISM
b. Drugs affecting PURINE METABOLISM
c. Drugs affecting PYRIMIDINE METABOLISM

a. DRUGS AFFECTING FA METABOLISM

FOLIC ACID SYNTHESIS

PTERIDINE + PABA + GLUTAMATE

↓

Diet → DIHYDRO FOLIC ACID [FH_2] [Folic Acid]

METHOTREXATE ⊣ DHFRase

TETRA HYDRO FOLIC ACID [FH_4] [Folinic Acid]

↓

DNA

METHOTREXATE

→ Methotrexate Poisoning Rx by FOLINIC ACID / LEUCOVORIN / CITROVORUM
→ can cause megaloblastic anemia
→ hepatotoxic
→ DOC for Choriocarcinoma
→ mc used DMARD

USES OF METHOTREXATE:

C - Choriocarcinoma – D.O.C
A – Acute leukemias (ALL, AML)
N – Non-Hodgkin's lymphoma
C – Crohn's disease
E – Ectopic pregnancy
R- Rheumatoid arthritis – D.O.C

ADVERSE EFFECTS OF METHOTREXATE:

- Bone marrow suppression, alopecia, diarrhea, hyperuricemia
- It inhibit folic acid metabolism – causes megaloblastic anemia
- It is hepatotoxic

NEW DHFRase INHIBITORS

- Pemetrexate – used in mesothelioma
- Pralatrexate – peripheral T- cell lymphoma

] – both causes megaloblastic Anemia

PURINES	PYRIMIDINE
Adenine	cytosine
Guanine	Thymine

b. DRUGS AFFECTING PURINE METABOLISM

DRUGS

6 - MERCAPTO PURINE } hepatotoxic
6 - THIOGUANINE }
CLADRIBINE → DOC for Hairy cell Leukemia
FLUDARABINE → DOC for CLL

6 - MERCAPTOPURINE

6 - MERCAPTOPURINE → (xanthine oxidase) → Degradation
xanthine → uric Acid

↓ ALLOPURINOL combination, 6 MP dose should be reduced
↓ ALLOPURINOL combination, AZATHIOPRINE dose should be reduced
→ 6MP is the active metabolite of Azathioprine

C DRUGS AFFECTING PYRIMIDINE METABOLISM

DRUGS

5 – FLUORO URACIL [5-FU] → cause Hand & foot syndrome

CAPECITABINE → given orally, metabolised to 5-FU

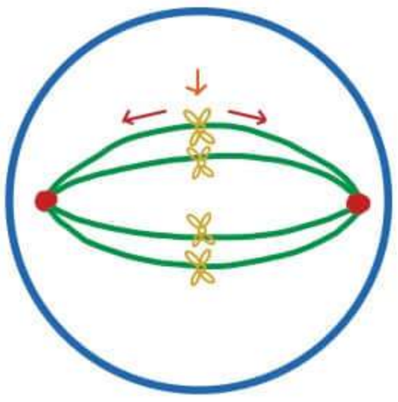
GEMCITABINE → DOC for Pancreatic carcinoma

CYTARABINE → causes cerebellar side effects

→ MIC SIE OF 5-FU → Diarrhea

4. DRUGS ACTING ON MITOTIC SPINDLE

SPINDLE FORMATION



Polymerization of TUBULIN → Spindle formation

→ Specific for M-Phase of cell cycle

SPINDLE FORMATⁿ INHIBITORS	SPINDLE BREAKDOWN INHIBITORS
VINCRISTINE VINBLASTINE	PACLITAXEL
S/E → Peripheral neuropathy SIADH	S/E → Allergy

VINCRISTINE → Marrow sparing anticancer drug

NEW DRUGS WHICH ACT ON MITOTIC SPINDLE:

- Eribulin
- Ixabepilone
- Estramustine

→ M – phase specific

- ERIBULIN – Inhibit tuBULes
- Eribulin
  Ixabepilone
  – used in breast carcinoma

Estramustine – used for prostate cancer

5. TOPOISOMERASE INHIBITORS

→ Topoisomerase introduces negative coilings & aid in replication

TOPOISOMERASE I INHIBITORS	TOPOISOMERASE II INHIBITORS
IRINOTECAN → used for colorectal carcinoma	ETOPOSIDE ANTHRACYCLINES → cardiotoxic DOXORUBICIN DONORUBICIN

ETOPOSIDE → can cause 2° Leukemia [Early in onset]

ANTHRACYCLINES → cause cardiotoxicity

→ prevented by DEXRAZOXANE

→ RADIATION RECALL SYNDROME:

If a person had head/neck cancer and treated with radiotherapy & after 6months we plan for chemotherapy with anthracyclines, adverse effects (like redness, swelling etc) can be seen in those areas where radiation was given

6. MISC DRUGS

BLEOMYCIN

→ Marrow sparing

→ cause pulmonary fibrosis

- Bleomycin Metabolized by **bleomycin hydrolase**

Deficient at

Lungs → Pulmonary fibrosis

Skin → Flagellated pigmentation

L - ASPARAGINASE

→ marrow sparing

→ used For ALL

→ cause Allergy

→ cause Acute Pancreatitis

AS_2O_3

RETINOIC ACID

→ used in Acute Promyelocytic leukemia [M_3 - AML]

→ acts as maturation agents

THALIDOMIDE

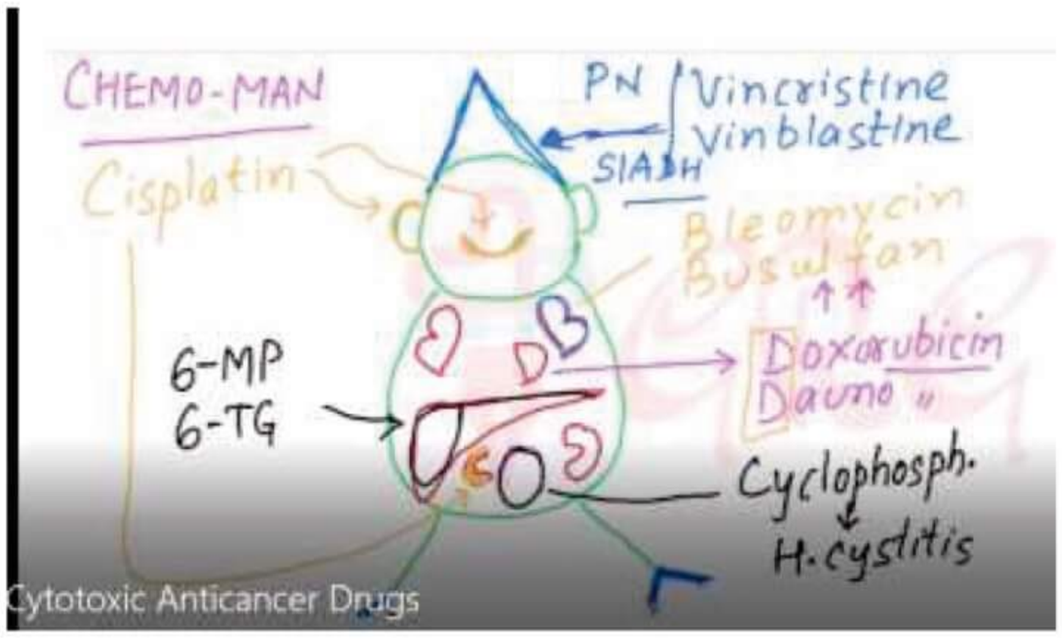
→ Used for multiple myeloma

→ CI in pregnancy

→ cause Peripheral neuropathy

→ cause constipation

ADVERSE EFFECTS OF IMPORTANT ANTI-CANCER DRUGS:



- Vincristine, Vinblastine] – peripheral neuropathy, SIADH
- Cisplatin – ototoxicity, Nephrotoxicity, Max vomiting
- Bleomycin, Busulfan] – pulmonary fibrosis
- Doxorubicin, Daunorubicin] – (DIL) – cardio-toxicity
- 6-MP, 6-TG] – hepatotoxicity
- Cyclophosphamide – hemorrhagic cystitis

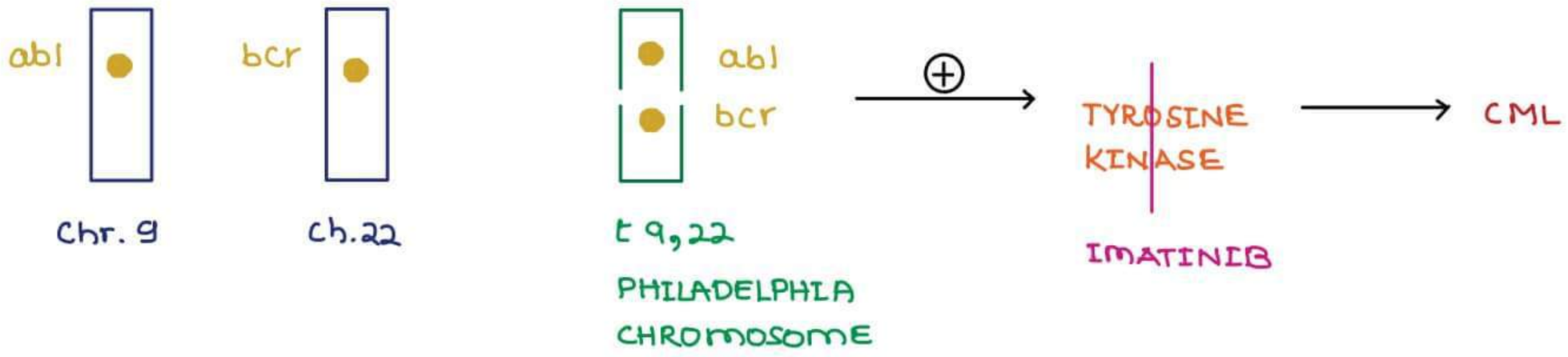
TARGETED ANTICANCER DRUGS

SMALL MOLECULES
Can be given Orally

MONOCLONAL ANTIBODIES
Injectables

SMALL MOLECULES

1. TYROSINE KINASE INHIBITORS



→ DOC for Chronic Myeloid Leukemia → IMATINIB

GENERAL PROPERTIES

1. All end i 'nib'
2. orally effective
3. metabolised by microsomal enzymes

USES

1. CML
   - I → IMATINIB [DOC]
   - N → NILOTINIB
   - D → DASATINIB

2. LUNG CARCINOMA
   - After → AFATINIB
   - E → ERLOTINIB
   - C → CERITINIB
   - G → GEFTINIB

3 RENAL CELL CARCINOMA
   - P → PAZOPANIB
   - A → AXITINIB
   - S → SORAFENIB
   - S → SUNITINIB

4 HEPATO CELLULAR CARCINOMA → SORAFENIB

5 GIST [Gastro Intestinal Stromal Tumors]
   - S → SUNITINIB
   - I → IMATINIB [DOC]
   - R → REGORAFENIB → also used for colorectal carcinoma

6 MALIGNANT MELANOMA
   - D → DABREFENIB
   - V → VEMURAFENIB
   - T → TRAMELTENIB

7 MEDULLARY CA OF THYROID → VANDETANIB

2 PROTEASOME INHIBITORS
   - BORTEZOMIB
   - CARFILZOMIB
   - IXAZOMIB

ZOMBI DRUGS

→ used for Multiple Myeloma

3 PARP INHIBITORS [Poly ADP Ribose Polymerase Inhibitor]

OLAPARIB → used in ovarian carcinoma

- O → ovarian carcinoma [use]
- L
- A
- P → Poly
- A → ADP
- RIB → Ribose Polymerase

4 CYCLIN DEPENDENT KINASE INHIBITOR [CDKI]

PALBOCICLIB → oral drug for Breast carcinoma
→ acts on CDK-4, CDK 6

- PAL
- B → Breast cancer [use]
- O → oral
- CICLIB/N → cyclin dependent kinase inhibitor

MONOCLONAL ANTIBODIES

→ end ɛ "MAB"
→ injectables

DRUGS

- CETUXIMAB → used for colorectal CA
- PANITUMUMAB → used for colorectal CA
- RITUXIMAB → used for NHL
- TRASTUZUMAB → used for Breast CA ; SIE - cardiotoxicity
- PERTUZUMAB → used for Breast CA
- DARATUMUMAB → used for multiple myeloma
- OLARATUMAB → used for SOFT tissue sarcoma

IMMUNOSUPPRESSANTS

1. STEROIDS
2. DRUGS TARGETING THE CALCINEURIN PATHWAY

NFAT – PO_4
ⓐ ⊣ calcineurin
NFAT [active]
↓
IL2
↓
ⓑ IL2Ⓡ
↓
ⓒ mTOR → IMMUNITY

NFAT - Nuclear Factor of Activated T cells

a. CYCLOSPORINE
TACROLIMUS

b. DACLIZUMAB
BASILIXIMAB

c. SIROLIMUS
EVEROLIMUS

a. CYCLOSPORINE & TACROLIMUS

→ nephrotoxic
hepatotoxic
neurotoxic

→ ↑ BP
↑ sugar
↑ K^+
↑ Lipids

→ Hirsutism → caused by cyclosporine

c SIROLIMUS & EVEROLIMUS → cause BM suppression

3 ANTI METABOLITES

METHOTREXATE
AZATHIOPRINE
MYCOPHENOLATE MOFETIL
LEFLUNOMIDE

4 MONOCLONAL ANTIBODIES

→ monoclonal Ab end ī 'MAB'
MAB + fusion proteins end ī 'CEPT'

→ __ MAB
↑
SOURCE
→ Animal [high risk of allergy]
→ Mixture
– Chimeric → end ī 'XI mab'
– Humanized → end ī 'ZU mab'
→ Human → end ī 'U mab'

INFLIXIMAB
BASILIXIMAB
} chimeric [high risk of allergy]
TRASTUZUMAB → Humanized
PANITUMUMAB → Human [least risk of allergy]

→ __ __ __ mab
↑
TARGET → TU → TUMOR

CETUXIMAB
RITUXIMAB
TRASTUZUMAB
PERTUZUMAB

→ _ _ _ _ _ _ mab

↑

TARGET

TU	→	Tumor	→ TRASTUZUMAB	→ Breast cancer
VI	→	Virus	→ PALIVIZUMAB	→ RSV
CI	→	Circulation	→ ABCIXIMAB	→ Antiplatelet Drug
			→ BEVACIZUMAB	→ Inhibit angiogenesis
BAC	→	Bacteria	→ RAXIBACUMAB	→ Anthrax
TOX	→	Toxin	BEZLOTOXUMAB	→ Pseudomembranous colitis
			OBILTOXAXIMAB	→ Anthrax
OS	→	Bone	→ DENOSUMAB	→ Osteoporosis
OC	→	Over cholesterol	→ ALIROCUMAB	→ Hypercholesterolemia
			→ EVOLOCUMAB	
LI	→	↓ Immunity	→ ADALIMUMAB	→ All are MAb against TNF α
			→ CERTOLIZUMAB	→ All are used for RA, Crohn's
			→ ETANERCEPT	Disease and Psoriasis
			→ INFLIXIMAB	
			→ GOLIMUMAB	
			→ DACLIZUMAB	→ MAb against IL-2 R (CD25)
			→ BASILIXIMAB	→ For transplantation
			→ EFALIZUMAB	→ Used for Psoriasis
			→ NATALIZUMAB	→ Used for multiple sclerosis
			→ ECULIZUMAB	→ Mab against C5 used for PNH
			→ OMALIZUMAB	→ Mab against IgE
				→ For Bronchial Asthma

5. TNF - α #
6. IL-1 # → ANAKINRA
7. IL-6 # → TOCILIZUMAB
   SARILUMAB → used for RA

8 CO- STIMULATION INHIBITORS → ABATACEPT → used for RA
9 THALIDOMIDE → used for ENL

AUTACOIDS

→ have autocrine effects [LOCAL EFFECTS]

→ Based on Chemical Structure

a. PEPTIDE AUTACOIDS → ANGIOTENSIN
→ BRADYKININ

b. AMINE AUTACOIDS → HISTAMINE
→ 5 - HT

c. LIPID AUTACOIDS → PROSTAGLANDINS
→ LEUKOTRIENES
→ THROMBOXANE

HISTAMINE

RECEPTORS

	LOCATION	ACTION	BLOCKERS
H_1		1. Allergy Inflammation 2. Stimulates RAS Promote wakefulness	
H_2	Stomach		
H_3	Pre synaptic	BRAKE	H_3 # or INVERSE AGONIST TIPROLISANT [PITOLISANT] used for NARCOLEPSY
H_4	WBC		

H_1 BLOCKERS

1st GENERATION	2nd GENERATION
cross BBB, cause sedatⁿ	do not cross BBB, no sedatⁿ
Ach # → Anticholinergic SIE occur	no Ach #
useful For motion sickness Drug induced Parkinsonism muscular dystonias allergy	useful only for allergy
PROMETHAZINE [max. actⁿ] DIPHENHYDRAMINE DIMENHYDRINATE PHENIRAMINE CHLORPHENIRAMINE CYCLIZINE CINNARIZINE	TERFENADINE → not used [TDP] FEXOFENADINE → Terfinadine metabolite ASTEMIZOLE → not used [TDP] LORATIDINE DES - LORATIDINE CETIRIZINE, LEVOCETIRIZINE AZELASTINE, OLOPATADINE → Topical

WITHDRAWN DRUGS

Cisapride
Astemizole
Terfenadine

'CAT drugs' (cat is cute 'QT' prolongation)
withdrawn because of QT prolongation.

- These drugs were metabolized by CYP 3A4
- Enzyme inhibitors
    - Ciprofloxacin
    - Ketoconazole
    - Erythromycin
- If any of these drugs are combined with (cisapride, astemizole, Terfenadine) result in QT prolongation

5 - HT

SEROTONIN RECEPTORS

→ 7 Receptors , $5\text{-}HT_1$ - $5\,HT_7$
→ $5\text{-}HT_{5,6,7}$ → Present in Brain

	LOCATION	ACTION	AGONIST/ANTAG.	DRUG	USES	S/E
$5HT_1$						
IA			Agonist	BUSPIRONE	Anxiety	
IB/ID	BV of Brain	VC	Agonist	SUMATRIPTAN NARATRIPTAN ELETRIPTAN RIZATRIPTAN	Acute Severe migraine [DOC]	
$5HT_{2A/2C}$			Blockers	CLOZAPINE OLANZAPINE	Atypical antipsychotics	LDS
			$5HT_{2C}$ Agonist	LORCASERIN	Obesity	
$5HT_3$	CTZ	Emesis	Blockers	ONDANSETRON GRANISETRON TROPISETRON PALONOSETRON	DOC for chemotherapy / Radiotherapy induced vomiting Post op vomiting	
$5HT_4$	GIT	↑Peristalsis	Agonists / prokinetics	CISAPRIDE MOSAPRIDE	GERD [DOC - PPIs]	

LDS → LIPOdystrophy Syndrome

MIGRAINE :

→It is unilateral and pulsatile headache and the major reason of migraine is assumed to be inflammation and dilation of blood vessels in the brain.

→Latest theory states that migraine occurs due to release of Calcitonin Gene Related Peptide (CGRP) and its major functions are inflammation and vasodilation.

Treatment of acute attack:

→ Drug of choice – NSAIDs (paracetamol , diclofenac)

→ Drug of choice for **acute severe attack** – **Triptans** (sumatriptan, naratriptan, rizatriptan, eletriptan, frovatriptan)

Mechanism of action of drugs:

→ Triptans act by stimulating 5HT 1B/1D receptor which
- Acts on Blood vessels causing vasoconstriction
- Inhibit CGRP release that inhibits vasodilation and inflammation.

→ Ergotamine also stimulates 5HT 1B/1D receptor and can also be used in acute severe attack of migraine but because of side effects (ncreased vomiting and gangrene); Triptans are preferred over ergotamine.

→ Both triptans and ergotamine together should never be given because they can cause vasoconstriction which causes coronary artery spasm and so they are also avoided in patients with coronary artery disease.

Prophylaxis of migraine :

A	B	C	of Migraine
ANTIDEPRESSANTS • Imipramine ANTIEPILEPTICS • Valproate • topiramate	BETA BLOCKERS • Propranolol (DOC) BOTULINUM TOXIN	CCBs • Flunarizine CGRP # • Erenumab • Fremanezumab • Galcanezumab	METHYSERGIDE • Ergot derivative • Risk of pulmonary fibrosis (so, not preferred)

NEW DRUGS FOR MIGRAINE:

1. **LASMIDITAN**

→stimulates **5HT1F receptor** which stimulates F receptor and decrease CGRP and prevents vasodilation and inflammation.

→It is recently approved for **Acute attacks of migraine.**

2. MONOCLONAL ANTIBODIES AGAINST CGRP

→Approved for **prophylaxis of migraine.**

a. Erenumab

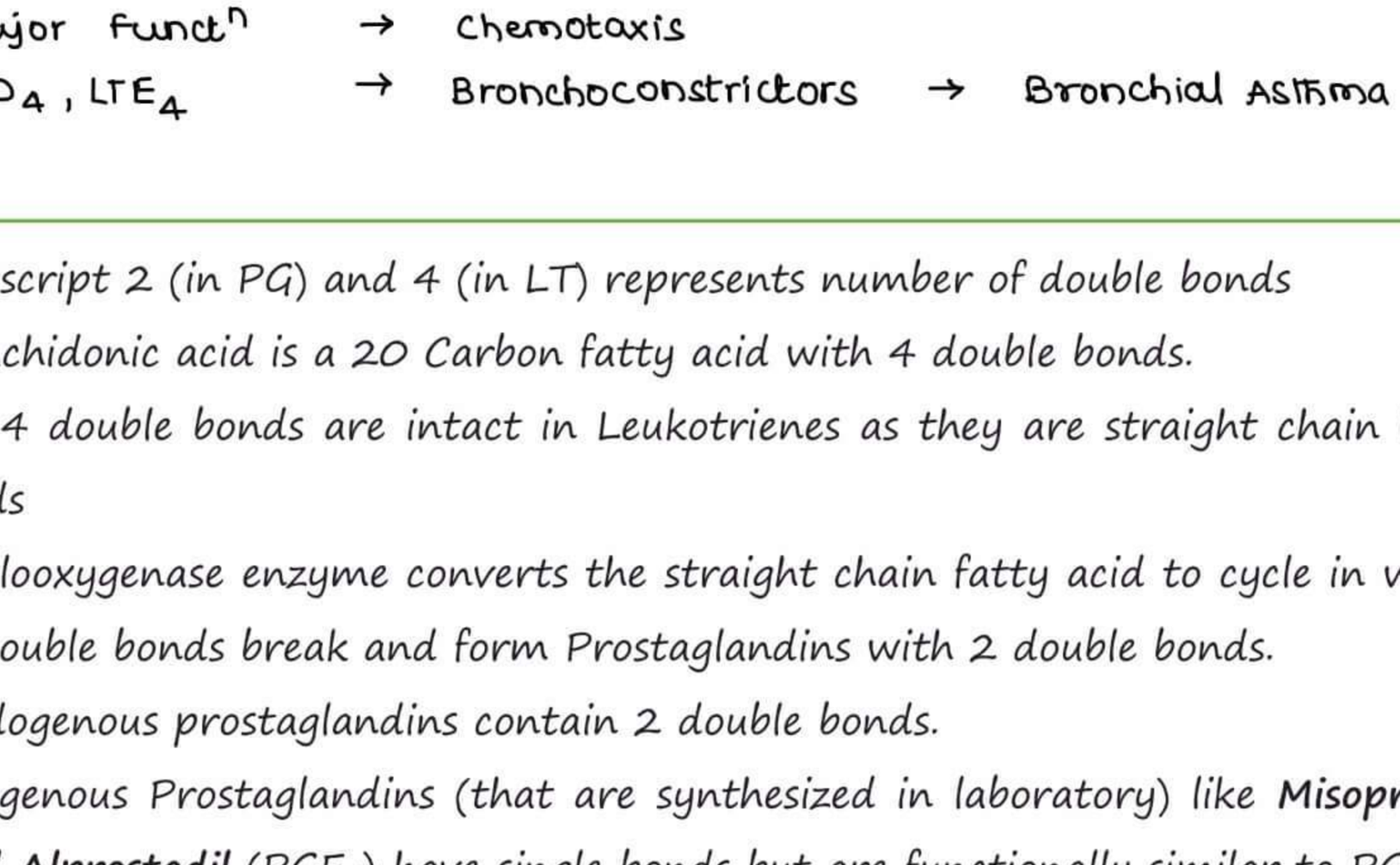
b. Framanezumab

c. Galcanezumab

3. CGRP ANTAGONIST:

→ OLCEGEPANT

LIPID AUTACOIDS



LTB_4 major funct^n → Chemotaxis

LTC_4, LTD_4, LTE_4 → Bronchoconstrictors → Bronchial Asthma

→ Subscript 2 (in PG) and 4 (in LT) represents number of double bonds

→ Arachidonic acid is a 20 Carbon fatty acid with 4 double bonds.

→ All 4 double bonds are intact in Leukotrienes as they are straight chain fatty acids

→ Cyclooxygenase enzyme converts the straight chain fatty acid to cycle in which 2 double bonds break and form Prostaglandins with 2 double bonds.

→ Endogenous prostaglandins contain 2 double bonds.

→ Exogenous Prostaglandins (that are synthesized in laboratory) like **Misoprostol and Alprostadil** (PGE_1) have single bonds but are functionally similar to PGE_2

PROSTAGLANDINS

EFFECTS

1 Fever

Pain

Inflammation

2 PLATELETS

TxA_2 → Aggregation

PGI_2 → Inhibition of aggregation

3 HEART

DUCTUS ARTERIOSUS

→ connects pulmonary trunk to aorta

→ Present in IUL

→ it is kept open by PGE_2

PDA [patent ductus Arteriosus]

TREATMENT

ASPIRIN

INDOMETHACIN

IBUPROFEN

TRANSPOSITⁿ OF GREAT VESSELS

ALPROSTADIL [PGE_1 analogue] indicated to keep open the DA

4 BLOOD VESSELS

→ PGE_2, PGI_2 } cause vasodilation

→ ILOPROST [PGI_2] → used for Pulmonary HTN

5 UTERUS

→ PGE_2, $PGF_{2\alpha}$ } Contracts upper segment of uterus

→ PGE_2 → Relaxes Lower segment of uterus

→ MISOPROSTOL [PGE_1 analogue]

USES

→ Abortion

→ cervical ripening in induction of labour

→ CARBOPROST used for PPH [DOC – OXYTOCIN]

6 STOMACH

PGE_2

→ inhibit Proton Pump
→ ↑ mucous & bicarbonate
→ vasodilation

} Protects for PUD

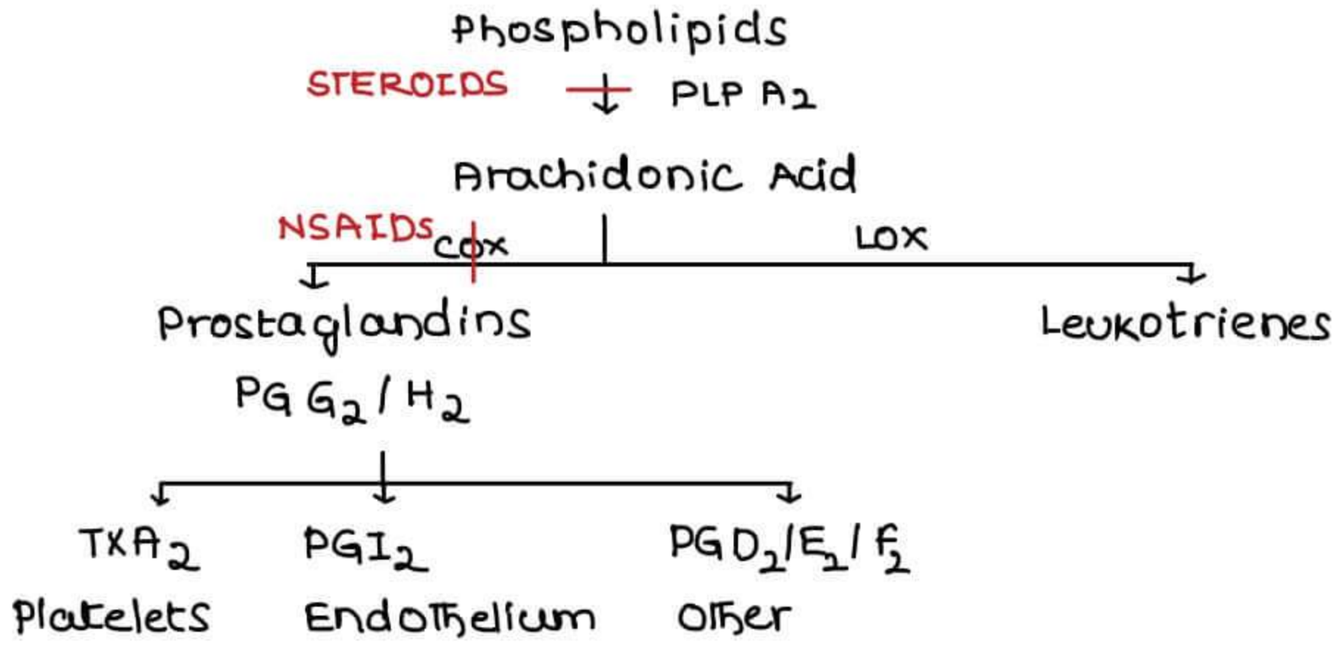
→ COX Inhibitors [NSAIDs] cause PUD → NSAID INDUCED PEPTIC ULCER
Rx by MISOPROSTOL [DOC → PPIs]

7 EYE

$PGF_{2\alpha}$ → ↑ Uveo Scleral outflow
→ LATANOPROST → DOC for Primary Open Angle Glaucoma
→ S/E

P — Pigmentation of Iris [Heterochromia iridis]
G — Growth of eyelashes [Hypertrichosis]
$F_{2\alpha}$ — Fluid in macula [macular edema]

NSAIDS



COX 1	COX - 2
Constitutive Enzyme Inducible at site of inflammatn	Inducible enzyme Ⓝ sites → Kidney Endothelium CNS

NSAIDs

NON SELECTIVE COX INHIBITORS
↑ risk of PUD

SELECTIVE COX-2 INHIBITORS
less risk of PUD

NON SELECTIVE COX INHIBITORS

DRUGS

ASPIRIN
PARACETAMOL [ACETAMINOPHEN]
IBUPROFEN → NSAID of choice in children

DICLOFENAC
INDOMETHACIN → Sedative
MEFENAMIC ACID
PIROXICAM → Long acting
PHENYL BUTAZONE

USES
- Fever
- Pain
- inflammatn

SIE
- PUD

PARACETAMOL / ACETAMINOPHEN

→ Only NSAID with no anti-inflammatory activity
→ Less risk of PUD

- Peroxide Theory → PCM is inactive in presence of H_2O_2
- COX 3 Inhibition Theory → PCM inhibits COX – 3 in CNS
- Analgesic action may be mediated by a metabolite which acts on vanilloid receptors (TRPV)

→ Approved in children for fever & pain
→ **NAPQI (N-Acetyl) Para – amino benzo quinone Imine**

PCM
↙ ↘
99 % Inactive 1 % NAPQI

→ NAPQI has high affinity for → SH group
→ Glutathione produced by liver binds with NAPQI & neutralizes it

PCM TOXICITY

→ Occurs d/t
1. Overdosage
2. Liver disease
3. Chronic Alcoholism

→ ANTIDOTE → N-ACETYL CYSTEINE (DOC)

ASPIRIN

→ only Irreversible cox inhibitor
→ antiplatlet drug
→ CI in child ↑ viral infect^{n} [Risk of Reye's syndrome]
→ can cause Hyperuricemia at therapeutic doses → avoid in gout

SALICYLISM

Respiratory centre ⊕
↓
Hyperventilation
↓
↓ CO_2
↓
Respiratory Alkalosis → Reversible

↓ HCO_3^-
↑ Lactic acid
Aspirin
↓
Metabolic Acidosis → Irreversible

→ TREATMENT

$NaHCO_3$

→ reverses metabolic acidosis
→ helps in aspirin Excretion

SELECTIVE COX 2 INHIBITORS

DRUGS

CELECOXIB
ROFECOXIB
VALDECOXIB
ETORICOXIB
PARECOXIB
LUMIRACOXIB

↓ GI Toxicity
↑ MI
↑ Stroke
} not 1st line drugs

→ Etoricoxib → Longest acting
→ Rofecoxib & valdecoxib → Withdrawn because of MI and stroke
→ Parecoxib is given by → Parenteral route
→ Lumiracoxib is withdrawn → Due to Liver toxicity.

PREFERENTIAL SELECTIVE COX-2 INHIBITORS

→ Inhibit cox2 > cox 1
→ Intermediate between non-selective and selective cox-2 inhibitors.
→ D- Diclofenac
→ M- Meloxicam
→ E- Etodolac
→ N- Nabumetone

ACUTE GOUT

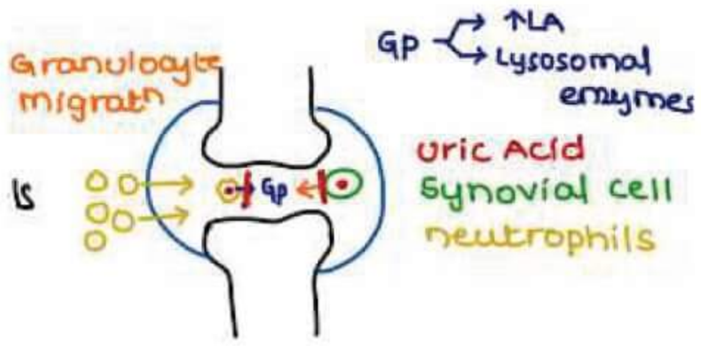
1. NSAIDs [DOC]
2. STEROIDS
3. *COLCHICINE*

Mechanism of Colchicine

→ Inhibit granulocyte migration

→ Inhibit the release of glycoprotein from neutrophils

→ Inhibit mitotic spindle in neutrophils



CHRONIC GOUT

URIC ACID PRODUCTION

Proteins / Purines

↓

xanthine

↓ xanthine oxidase ①

uric Acid → Excretion ②

in birds { ↓ uricase ③

ALLANTOIN

↓ Formatⁿ of uric Acid	↑ Excretⁿ of uric Acid [URICOSURIC DRUGS]
ALLOPURINOL → inhibit xanthine oxidase → DOC for chronic gout FEBUXOSTAT → inhibit xanthine oxidase	PROBENECID SULFINPYRAZONE BENZBROMARONE LESINURAD → Plenty of fluids should be taken
↑ Uric Acid Metabolism	
ⓇASⒷURICASE → Recombinant uricase PEGLOTICASE → Long acting	

RHEUMATOID ARTHRITIS

NSAIDS STEROIDS	DMARDS or SAARDS
↓ Pain & inflammation no effect on disease progression fast acting	Slows down the disease progression Slow acting

DMARDS → Disease Modifying Anti Rheumatoid Drugs

SAARDS → Slow Acting Anti Rheumatoid Drugs

DMARDS CLASSIFICATION	
Conventional DMARDS	**Biological DMARDS**
→ Available since long time	→ Formed by Biological methods like recombinant DNA technology against some particular target.

1. CONVENTIONAL DMARDS:

Cute &	→	Chloroquine	DMARD of choice in pregnancy
P	→	Penicillamine	→ Chelating agent → Used for Cu poisoning / Wilson's disease
A	→	Azathioprine	
G	→	Gold salts	
L	→	Leflunomide	Inhibit formation of pyrimidines by ⊖ Dihydroorotate dehydrogenase
I	→	Inhibitors of JAK	
Malika	→	Methotrexate	M.C. used (D.O.C for R.A]
Sherawat	→	Sulfasalazine	→ Used in R.A. & U.C → Only DMART used as dis modifying agent in ankylosing spondylitis

METHOTREXATE:

Used for

Cancer	R.A
- High dose - ⊖ DHFRase (↓folic acid) - Cause megaloblastic anemia	-Low dose → 7.5 mg weekly - ↑ Extracellular adenosine ↓ Anti – Inflammatory property

→ Can cause Hepatotoxicity (L.F.T monitoring is recommended)

JAK INHIBITORS:

→ Given orally for R.A

→ ↑ risk of Infections

* TOFACITINIB
* BARICITINIB

2. BIOLOGICAL DMARDS:

i. By ⊖ TNF – α

ii. By ⊖ I.L – 1

iii. By ⊖ I.L. – 6

iv. Co stimulation inhibitor

i. DRUGS ⊖ TNF–ALPHA:

- All are injectable

A – Adalimumab –Subcutaneous route [S.C]

C – Certolizumab – S.C

E – Etanercept – S.C

Inhibitor – Infliximab – I.V

GoLI – Golimumab – S.C

→ ↑ risk of infections like T.B. & Hep-B (So C/I in these pts; even if subclinical infection is present)

→ Apart from R.A., these drugs can be used for Crohn's disease as well as psoriasis

ii. I.L – 1 RECEPTOR ANTAGONISTS:

- ANAKINRA

A – 1st letter

KIN – Interleukin

R – Receptor

A – Antagonist

iii. I.L – 6 ANTAGONISTS:

- Tocilizumab → 1st I.L – 6 targeted monoclonal Antibody.

→ Approved for treatment of cytokine release syndrome also

- SARILUMAB → Used for rheumatoid arthritis

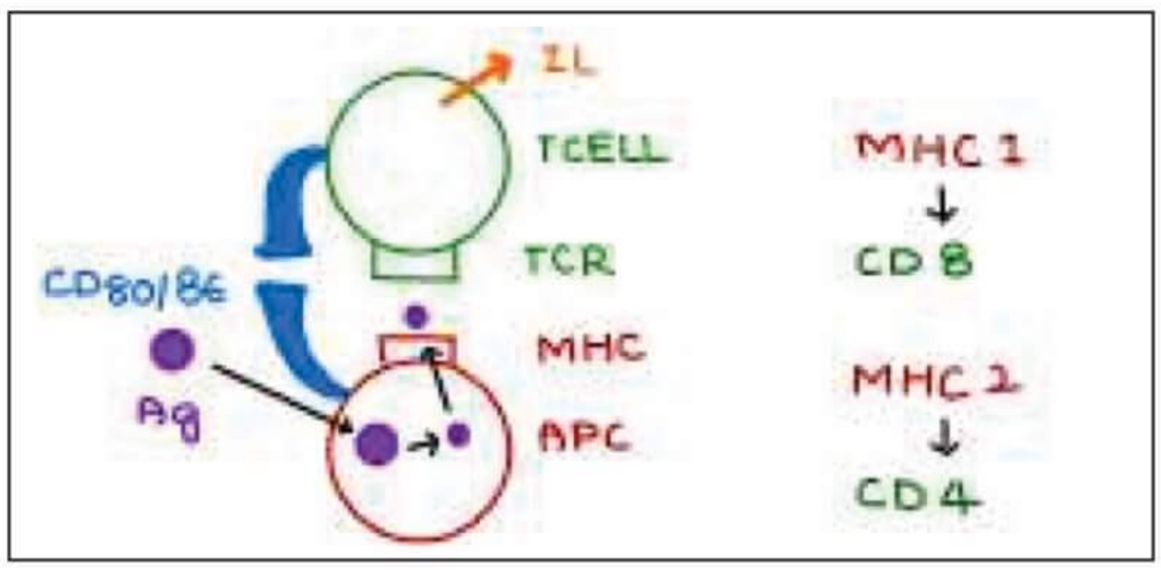
S – Six

AR – R.A.

MAB – Monoclonal antibody

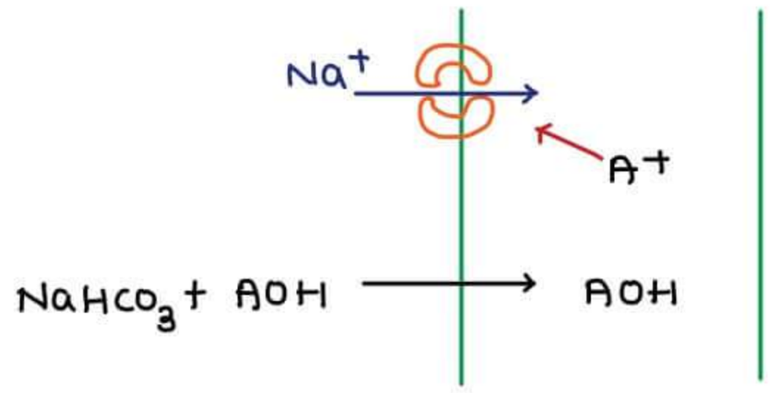
iv. COSTIMULATION INHIBITORS

→ ABATACEPT



LOCAL ANAESTHETIC AGENTS

ESTER	AMIDE
COCAINE	LIGNOCAINE
PROCAINE	BUPIVACAINE
CHLORPROCAINE	PRILOCAINE
TETRACAINE	ETIDOCAINE
BENZOCAINE	ROPIVACAINE
	DIBUCAINE



→ Only LA causing vasoconstrictⁿ → COCAINE
→ mc used LA → LIGNOCAINE
→ Shortest acting LA → Chlorprocaine
→ LA causing methaemoglobinemia → Prilocaine
→ max. cardiotoxic → Bupivacaine

INFILTRATION ANESTHESIA

→ short acting
→ Systemic adverse effect
} dlt entry into blood

→ Adrenaline / Epinephrine added for long action

→ *Adrenaline should not be added to local anesthetic in those area where end arteries are present.*

→ *End artery are present in:*
- *Pinna*
- *Tip of nose*
- *Tip of finger*
- *Penis*

Vasoconstriction at end arteries will cause ischemia of distal portion of constricted part.

SKELETAL MUSCLE RELAXANTS

CENTRAL

→ **DEPRESS CNS**

$GABA_A$ (+)	→	DIAZEPAM
$GABA_B$ (+)	→	BACLOFEN
α_2 (+)	→	TIZANIDINE
Inhibit polysynaptic reflexes	→	MEPHENESIN
		CHLORZOXAZONE
		THIOCHOLCHICOSIDE

PERIPHERAL

DIRECTLY ACTING

DANTROLENE

Rynadine ® #

used for malignant hyperthermia

Neuroleptic malignant syndrome

Hepatotoxic

NEURO MUSCULAR BLOCKER [NMJ #] / INDIRECTLY ACTING

DEPOLARIZING MR

SCh

→ Shortest acting MR [<5 min]

→ CII in nerve & muscle injuries [can cause severe hyperkalemia]

→ Hyperthermia [precipitate malignant hyperthermia]

→ FASCICULATIONS

→ responsible for post operative muscle pain

[post operative muscle rigidity caused by FENTANYL]

NON DEPOLARIZING / COMPETITIVE

D-TUBOCURARINE

→ do not cause post op. muscle pain

→ release Histamine

→ cause bronchoconstriction

↓ BP

CURIUM [release less histamine]	CURONIUM [no histamine released]
ATRACURIUM	PANCURONIUM
CIS - ATRACURIUM	PIPE
MIVACURIUM [shortest acting]	VE
	RO
	RAPA

HOFFMAN'S ELIMINATION

→ Shown by Atracurium & Cis atracurium

→ MR of choice in liver & Renal disease

ATRACURIUM	CIS-ATRACURIUM
• Release Histamine • Metabolism of atracurium by liver can generate – Laudanosine ↓ cause seizures	• Negligible release of Histamine • 100% Hofmann elimination ↓ No risk of seizures

GANTACURIUM

- Shortest and fastest acting (10 mins) non depolarising muscle relaxant

REVERSAL AGENTS

Used to reverse action of NDMR after surgery

- Neostigmine
- Suggamadex

Stimulates

Nm Receptors: Reverse action of NDMR

M1, M2, M3 Receptors:

— Produce cholinergic adverse effects
— Atropine stops these s/e

→ Directly binds to muscle relaxant and remove them from N_m receptor.

→ Also called Selective Relaxant Binding Agent [SRBA)

→ Faster acting than neostigmine

→ Higher risk of allergy

GENERAL ANAESTHETICS

IV / INDUCING AGENTS

INHALATIONAL / MAINTAINANCE AGENTS

IV / INDUCING AGENTS

THIOPENTONE

PROPOFOL

KETAMINE

ETOMIDATE

THIOPENTONE

→ highly lipid soluble
→ very fast acting
→ very short acting dlt REDISTRIBUTION

PROPOFOL

→ DOC for Day care Sx
→ enject^n is painful

DRUGS USED IN DAY CARE Sx

Dr → DESFLURANE
Manmohan → MIDAZOLAM
Singh → SEVOFLURANE
IS → ISOFLURANE
A → ALFENTANIL
Prime → PROPOFOL
Minister → MIVACURIUM

ETOMIDATE → cause Adrenal Suppression

KETAMINE

K → Kids [iv anaesthetic agent of choice in children]
E → Emergence reaction
T → Thalamo - cortical junction [site of action] DISSOCIATIVE ANESTHESIA
A → Analgesic
M → Meals [full stomach]
I → ↑ BP / IOP / ICP [iv anaesthetic agent of choice in shock]
N → NMDA # [avoided in Glaucoma & head injury]
E → Excellent Bronchodilator

INHALATIONAL / MAINTAINANCE AGENTS

infla-mmable:
- ETHER
- CHLOROFORM
- CYCLOPROPANE
- TRILENE

non-infla-mmable:
- NITROUS OXIDE
- HALOTHANE
- ENFLURANE
- SEVOFLURANE
- ISOFLURANE
- DESFLURANE
- METHOXYFLURANE
- XENON

MAC [minimum Alveolar Concentration]

→ min. conc. in alveoli to produce anaesthesia
→ Mac $1/\alpha$ POTENCY
  Highest MAC → N_2O [104%]
  Lowest MAC → METHOXYFLURANE

BLOOD SOLUBILITY

→ inversly proportional to speed of anaesthesia

→ measured by Blood : Gas partition co-efficient

→ highest → methoxyflurane

→ Lowest → xenon > Desflurane

BOYLE'S MACHINE

→ ↓ pressure of anaesthesia drugs

→ SAFETY MEASURES

1. COLOUR CODING

N_2O	→	blue	NEELA
cyclo propane	→	orange	SANTRI
O_2	→	Black & white	
Entonox [$N_2O + O_2$] (50% 50%)	→	Blue & white	

2. PIN INDEX SYSTEM

Air	1, 5
O_2	2, 5
N_2O	3, 5
CO_2 > 7.5%	1, 6
CO_2 < 7.5%	2, 6
cyclopropane	3, 6
Entonox	7

SPECIAL PROPERTIES OF INDIVIDUAL AGENTS

1) **N_2O** – Has highest MAC (MAC = 104%)

2) **Halothane**

- Cause Hepatitis on repeated use
- Sensitizes heart to adrenogenic action of Adrenaline

3) **Enflurane** – Has highest risk of Epilepsy

4) **Isoflurane & Sevoflurane** – Safe in Cardiology & Neurology patients

5) **Desflurane** – Causes Maximum respiratory irritation

6) **Methoxyflurane**

- Most potent & slowest acting
- Not preferred because of its Nephrotoxic effect

7) **Xenon** – Known as Ideal anesthetic agent

XENON

→ closest to IDEAL ANESTHETIC AGENT
- Anesthetic
- Analgesic
- MR
- Fastest acting
- Safe
- smooth induct^{n} & recovery

→ costly

MISCELLANEOUS

CHELATING AGENTS → used for heavy metal poisoning

BAL [British Anti Lewisite] / DIMERCAPROL

USES
- B → Bismuth poisoning
- A → Arsenic poisoning
- L → Lead poisoning

CII
- Cadmium poisoning
- Fe poisoning

$CaNa_2EDTA$

USES
- M → Manganese poisoning
- I → Iron poisoning
- L → Lead poisoning
- K → Cadmium poisoning

d - PENICILLAMINE

USES → Cu poisoning [wilson disease]

Fe chelating agents

DESFERIOXAMINE → injectable, used for acute iron poisoning

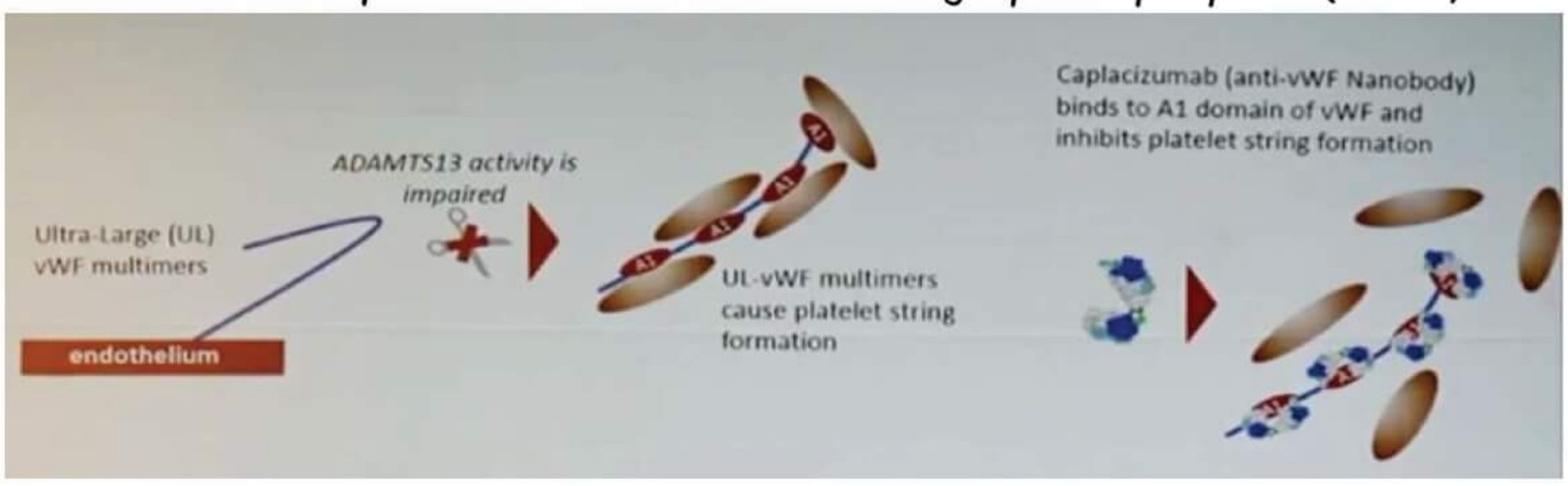
DEFERIPIRONE → oral, used for chronic iron overload

1. PRABOTULINUMTOXIN A

- Acetylcholine release inhibitor
- To improve glabellar lines

2. CAPLACIZUMAB

- von Willebrand factor (vWF)-directed antibody fragment.
- Targets the A1-domain of vWF, and inhibits the interaction between vWF and platelets, thereby reducing both vWF-mediated platelet adhesion and platelet consumption.
- For acquired thrombotic thrombocytopenic purpura (aTTP)



3. ELAPEGADEMASE

- Recombinant adenosine deaminase enzyme replacement therapy.
- For ADA-SCID
- By intramuscular injection
- Decrease in toxic adenosine and deoxyadenosine nucleotides levels
- Increase in lymphocyte number

4. INOTERSEN

- Transthyretin directed antisense oligonucleotide
- Causes degradation of mutant and wild-type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.
- For polyneuropathy of hereditary transthyretin mediated amyloidosis
- Subcutaneous injection
- Can cause thrombocytopenia and glomerulonephritis

5. TALAZOPARIB

- PARP inhibitor like olaparib
- For breast cancer

6. BALOXAVIR MARBOXIL

- Prodrug: converted by hydrolysis to baloxavir
- Inhibits the endonuclease activity of the polymerase acidic (PA) protein, an influenza virus-specific enzyme in the viral RNA polymerase complex required for viral gene transcription, resulting in inhibition of influenza virus replication.
- Oral single dose treatment of acute uncomplicated influenza

7. REVEFENACIN

- Long-acting muscarinic antagonist
- For Maintenance of patients with chronic obstructive pulmonary disease.
- Inhalational route

8. CALASPARGASE PEGOL

- L-asparaginase is an enzyme that catalyzes the conversion of the amino acid L-asparagine into aspartic acid and ammonia.
- It is an asparagine specific enzyme.
- Leukemic cells have a reduced ability to synthesize L-asparagine, and therefore depend on an exogenous source of L-asparagine for survival. The pharmacological effect of calaspargase is thought to be based on selective killing of leukemic cells due to depletion of plasma L-asparagine.
- For acute lymphoblastic leukemia (ALL) by intravenous route

9. BREXANOLONE

- Allopregnanolone; A neuroactive steroid
- GABA-A receptor positive modulator.
- For the treatment of postpartum depression
- Intravenous administration.
- Risk of excessive sedation or sudden loss of consciousness

10. SOLRIAMFETOL

- Dopamine and norepinephrine reuptake inhibitor.
- To improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea.
- Oral administration

11. ESKETAMINE

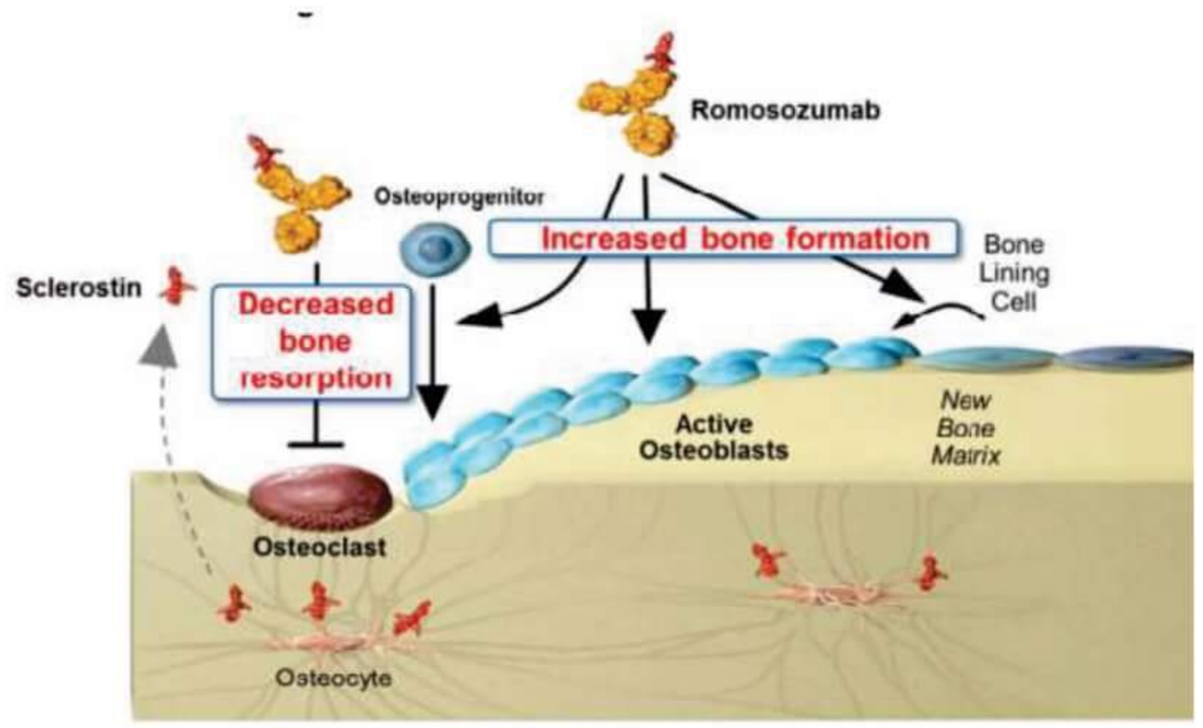
- Non-competitive NMDA receptor antagonist.
- For treatment-resistant depression in adults.
- Supplied as a spray for intranasal administration.
- Black Box Warning:
    i. Risk for sedation and dissociation after administration.
    ii. Potential for abuse and misuse.
    iii. Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants.

12. SIPONIMOD

- For the treatment of relapsing forms of multiple sclerosis (MS)
- Oral administration.
- Sphingosine-1-phosphate (S1P) receptor modulator like fingolimod.
- Siponimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood.

13. ROMOSOZUMAB

- MAb against sclerostin
- Sclerostin stimulates osteoclasts and inhibits osteoblasts
- Romosuzumab provide dual benefit:
    i. Stimulate osteoblast and
    ii. Inhibit osteoclast



14. ERDAFITINIB

- TK inhibitor
- For Bladder cancer

15. RISANKIZUMAB

- Mab against IL-23
- For Plaque psoriasis

16. TAFAMIDIS

- Functions as a chaperone that stabilizes the correctly folded tetrameric form

- In people with Familial Amyloid Polyneuropathy, the individual monomers fall away from the tetramer, misfold, and aggregate; the aggregates harm nerves.
- Used for preventing cardiomyopathy in TTR amyloidoisis

17. ALPELISIB

- PI3 kinase inhibitor
- For breast cancer
- Other PI-3 kinase inhibitors: idelalisib, duvelisib

18. POLATUZUMAB

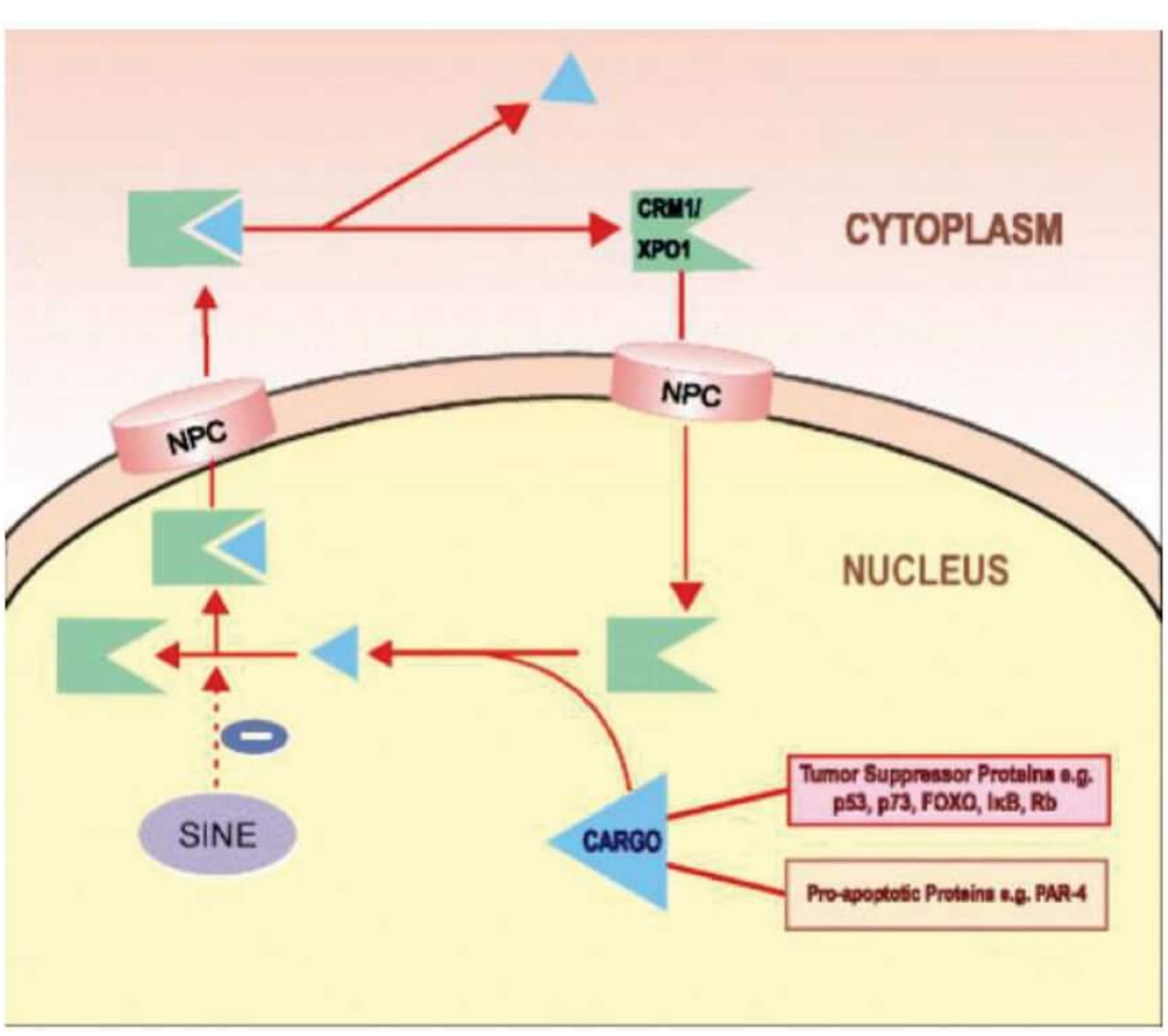
- Antibody targeting the CD79b component of the B-cell receptor
- For Relapsed or refractory diffuse large B-cell lymphoma.

19. BREMELANOTIDE

- For Hypoactive sexual desire disorder in females
- Melanocortin receptor agonist
- Subcutaneous
- Another drug flibanserin (ORAL)

20. SELINEXOR

- Oral SELective Inhibitor of Nuclear Export (SINE) compound.
- Selinexor functions by binding with, and inhibiting, the nuclear export protein, XPO1, leading to the accumulation of tumor suppressor proteins in the cell nucleus. This reinitiates and amplifies their tumor suppressor function and leads to the selective induction of apoptosis in cancer cells, while largely sparing normal cells.
- For multiple myeloma and Diffuse large B-cell lymphoma (DLBCL)



21. **RELEBACTAM**
- Beta lactamase inhibitor
- Like sulbatam, tazobactam, avibactam

22. **DAROLUTAMIDE**
a. Androgen receptor blocker like flutamide
b. For prostate cancer

23. **PEXIDARTINIB**
- Tyrosine kinase inhibitor of CSF-1 receptor
- Used for tenosynovial giant cell tumor

24. **PRETOMANID**
- Inhibit mycolic acid synthesis
- Used with bedaquiline and linezolide (in BPaL regimen)
- For MDR tuberculosis

25. **PITOLISANT**
- H3 inverse agonist
- For narcolepsy

26. **ENTRECTINIB**
- Oral TK inhibitor
- For ROS-1 +ve Non small cell lung cancer and NRTK positive solid tumors

27. **FEDRATINIB**
- Oral JAK 2 inhibitor
- For Myelofibrosis

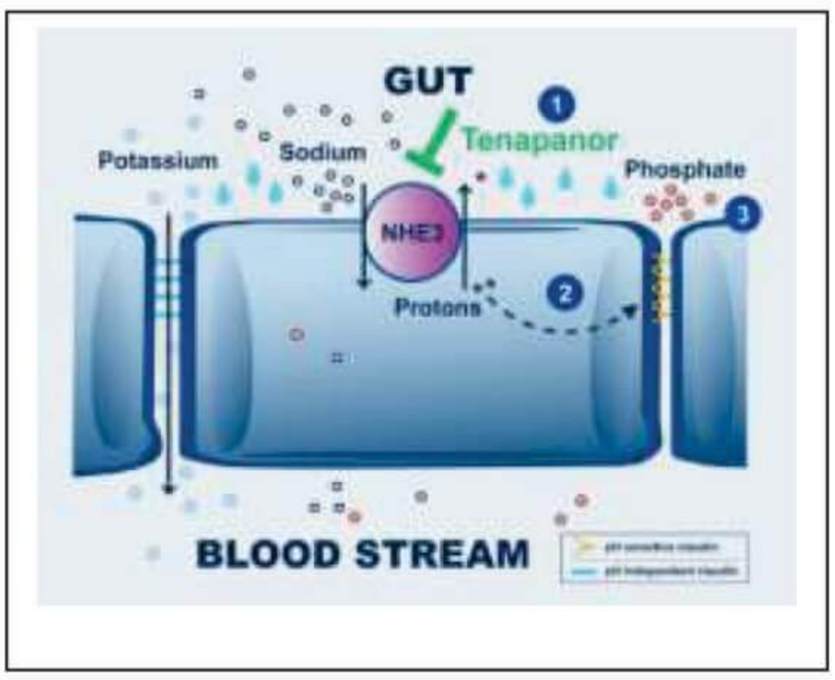
28. **UPADACITINIB**
- Oral JAK inhibitor like tofacitinib
- For Rheumatoid arthritis

29. **LEFAMULIN**
- Protein synthesis inhibitor
- For community acquired pneumonia

30. **ISTRADEFYLLINE**
- Adenosine A2 receptor antagonist
- Oral treatment
- Off episodes of Parkinsonism

31. **TENAPANOR**
- NHE inhibitor
- Oral treatment
- For IBS with constipation

32. **TRIFAROTENE**
- Retinoic acid receptor agonist
- Topical use
- For acne vulgaris



33. BROLUCIZUMAB

- VEGF inhibitor
- Intravitreal injection
- For neovascular age related macular degeneration

34. AFAMELANOTIDE

- Melanocortin-1 receptor agonist
- For treatment of phototoxicity in patients with erythropoietic protoporphyria

35. LASMIDITAN

- 5HT1F agonist
- For acute severe migraine

36. ELEXACAFTOR/IVACAFTOR/TEZACAFTOR

- Elexacaftor and tezacaftor are CFTR correctors
- These fix the defective CFTR protein so that it can move to the proper place on the cell surface.
- Ivacaftor is a potentiator.
- Once CFTR protein reaches the cell surface, potentiators help facilitate the opening of the chloride channel to allow chloride and sodium to move in and out of the cell.
- Indicated for cystic fibrosis

37. LUSPATERCEPT

- Recombinant fusion protein that binds several endogenous TGF-β superfamily ligands
- Diminishes Smad2/3 signaling
- Promotes erythroid maturation
- Indicated for anemia in patients with beta thalassemia

38. ZANUBRUTINIB

- Bruton tyrosine kinase inhibitor like ibrutinib
- For Mantle cell lymphoma

39. CEFIDEROCOL

- Cefiderocol is a synthetic conjugate, with a cephalosporin moiety to inhibit cell wall synthesis and a siderophore moiety to gain entry into bacterial cells
- Its mechanism of entry into bacterial cells is by binding to iron, which is actively transported into the bacterial cells along with the cefiderocol.
- First siderophore antibiotic to be approved by the FDA
- Effective against MDR gram negative bacteria including Pseudomonas
- Used for UTI

40. CRIZANLIZUMAB

- Monoclonal antibody against P-selectin
- To reduce the frequency of veno-occlusive disease in sickle cell anemia

41. GIVOSIRAN

- Small interfering RNA
- Causes degradation of aminolevulinate synthase (ALS-1) mRNA in hepatocytes
- Thus decreases the neurotoxic levels of ALS
- Used for acute hepatic prophyria

42. CENOBAMATE

- Voltage-gated sodium channel (VGSC) blocker.
- Selective blocker of the inactivated state of VGSCs, preferentially inhibiting persistent sodium current.
- Additionally enhances presynaptic release of GABA
- Used for focal seizures

43. VOXELOTOR

- A sickle hemoglobin (HbS) polymerization inhibitor
- Increases the affinity of hemoglobin for oxygen.
- This stabilizes red blood cells in an oxygenated state, preventing hemoglobin polymerization and the resultant sickling and destruction of the red blood cells.
- Used for oral treatment of sickle cell anemia

44. GOLODIRSEN

- Induces exon 53 skipping in dystrophin gene
- For Ducchene's muscular dystrophy

45. ENFORTUMAB VEDOTIN

- Nectin-4-directed antibody and microtubule inhibitor conjugate
- Nectin-4 (Poliovirus Receptor-related 4; PVRL4), is located on the surface of cells and highly expressed in bladder cancer.
- Used for urothelial carcinoma

46. LUMATEPERONE TOSYLATE

- Second generation antipsychotics
- Partial agonist at presynaptic D2 receptors, resulting in reduced presynaptic release of dopamine
- Antagonist at postsynaptic D2 receptors
- D1 activation resulting in NMDA activity
- Inhibit serotonin transporters (SERT)
- 5-HT2A receptor antagonist.

47. LEMBOREXANT

- Orexin receptor antagonist like suvorexant
- For treatment of insomnia

48. FAM-TRASTUZUMAB DERUXTECAN

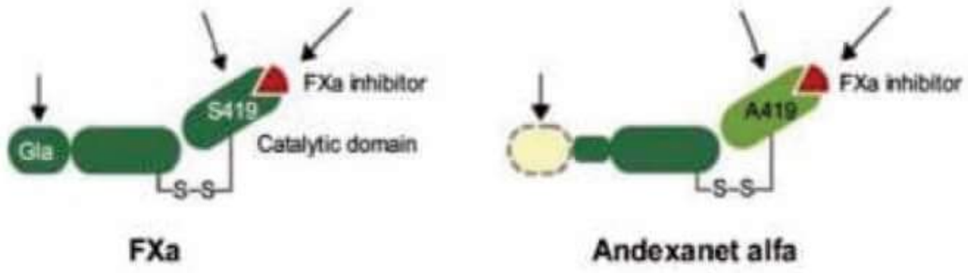
- Conjugation of MAb against HER-2 with topoisomerase inhibitor
- For Breast cancer

49. UBROGEPANT

- Oral CGRP antagonist
- For acute treatment of migraine

NEW DRUGS 2018

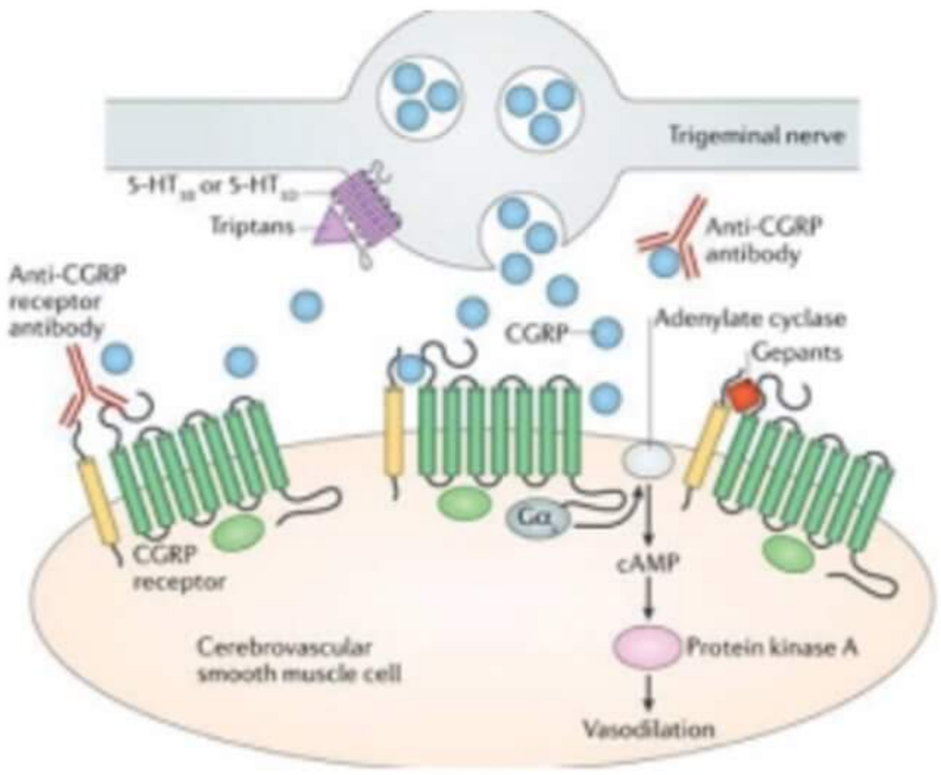
1. ANDEXANET ALFA



→ Factor Xa INHIBITORS
RIVAROXABAN
EDOXABAN

→ Antidote for Factor Xa inhibitors.

2. ERENUMAB – AOEE
GALCANEZUMAB - GNLM
FREMANEZUMAB – VFRM



3. MIGALASTAT

FABRY DISEASE

→ Mutation of α – galactosidase (GalA) on X chromosome
→ Leads to misfolding of α – GalA
→ MIGALASTAT - Pharmacological chaperone
- Improve misfolding

4. PATISIRAN

→ Small interfering RNA – based drug
→ Gene silencing drug, interferes with production of abnormal Transthyretin
→ Approved for polyneuropathy with hereditary Transthyretin – mediated amyloidosis

5. **ELAGOLIX SODIUM**

→ GnRH antagonist

→ Given orally

→ approved for pain a/w endometriosis

→ Short acting

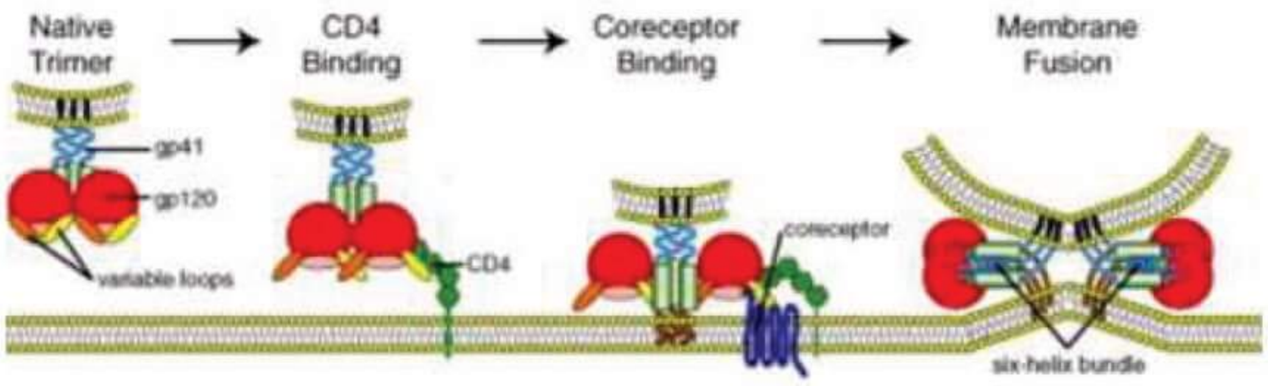
6. **TAFENOQUINE**

→ Used for radical treatment of P. Vivax malaria

→ Cause hemolysis in G6PD deficiency

→ Single dose is enough

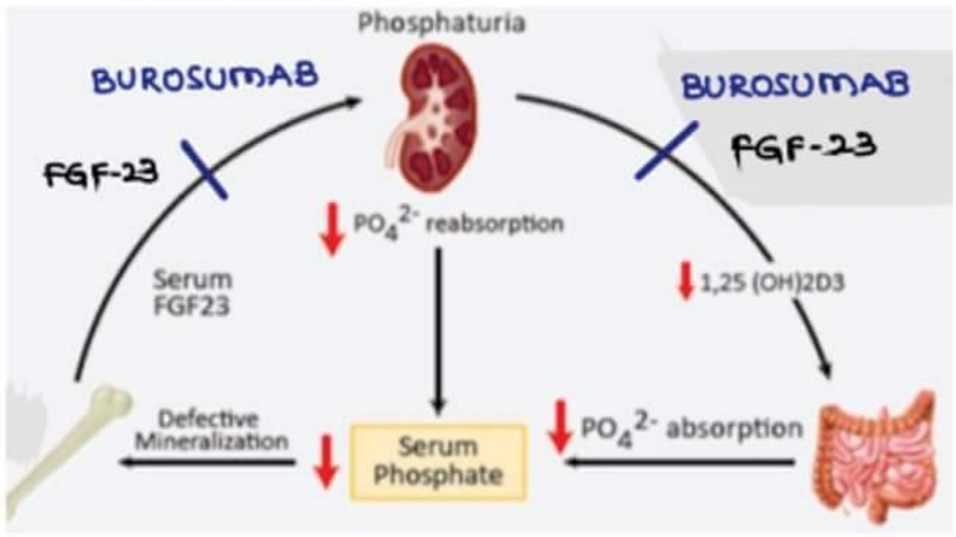
7. **IBALIZUMAB**



→ MAB against CD_4 ®

→ Used in HIV

8. **BUROSUMAB**



X LINKED Hypophosphatemia

→ Overactivity of FGF – 23

9. **ELTROMBOPAG** → Approved for ITP

AVATROMBOPAG → Approved for chronic liver disease patients with thrombocytopenia prior to Sx

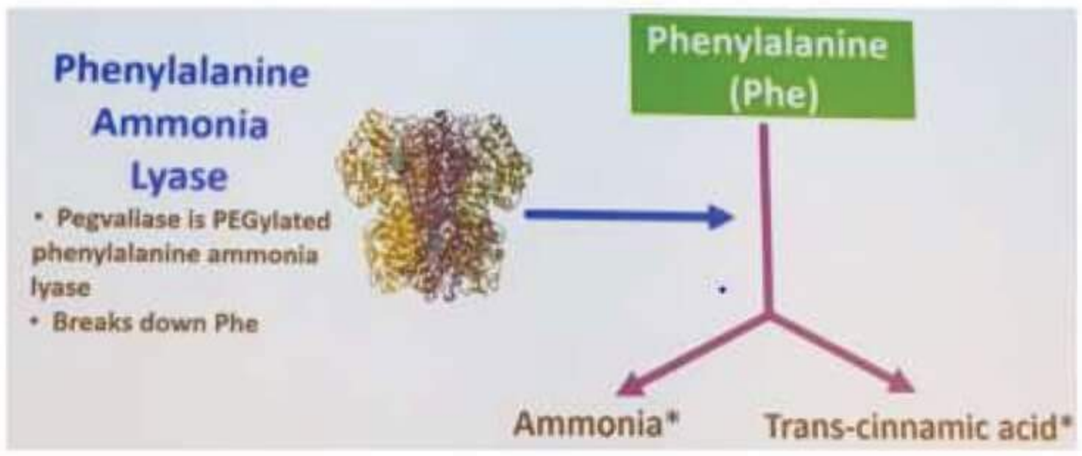
→ Thrombopoietin agonist

LUSU TROMBOPAG → Same as AVATROMBOPAG

10. **TILDRAKILUMAB**

- MAb against IL-23
- Approved for psoriasis

11. **PEG VALIASE**



→ Recombinant form of phenylalanine ammonia lyase

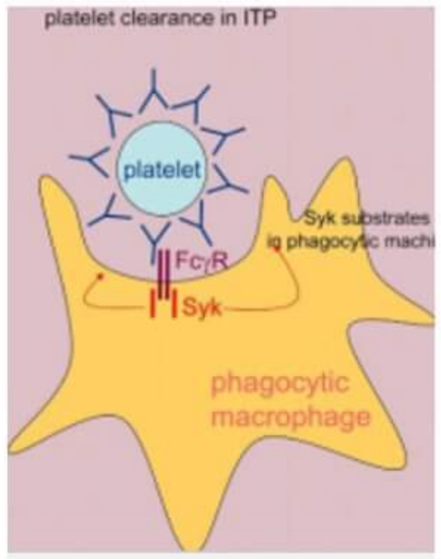
→ Used in phenylketonuria

→ Long acting

12. **FOSTAMATINIB**

→ Spleen tyrosine kinase inhibitor

→ Used in ITP

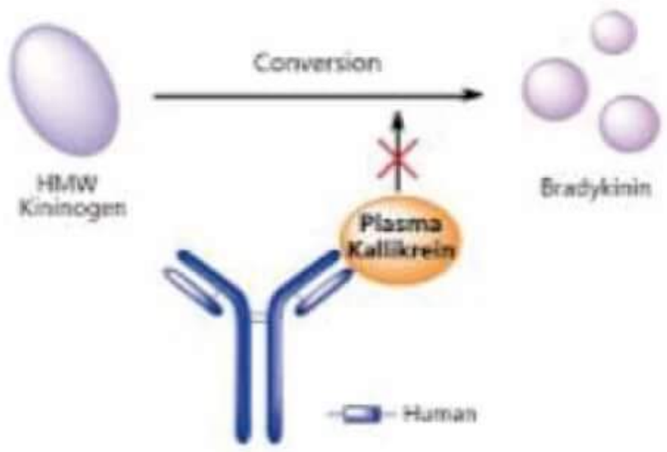


13. **SODIUM ZIRCONIUM CYCLODILICATE**

→ K^+ Binder

→ Used to R_x Hyperkalemia

14. **LANADELUMAB**



→ HERIDITARY ANGIONEUROTIC EDEMA is d/t excessive bradykinin

→ LANADELUMAB

→ Inhibits plasma Kallikrein

→ Used for HAE

→ ICATIBANT

→ Used for HAE

→ Bradykinin antagonist

15. **CENEGERMIN**

→ RECOMBINENT human Nerve growth factor

→ Used for neurotrophic Keratitis

→ Eye drops

16. **STIRIPENTOL**

→ Approved for DRAVET syndrome, along with CLOBAZAM

→ ↑ GABAergic activity

→ Inhibit LDH [required for energy metabolism of neurons]

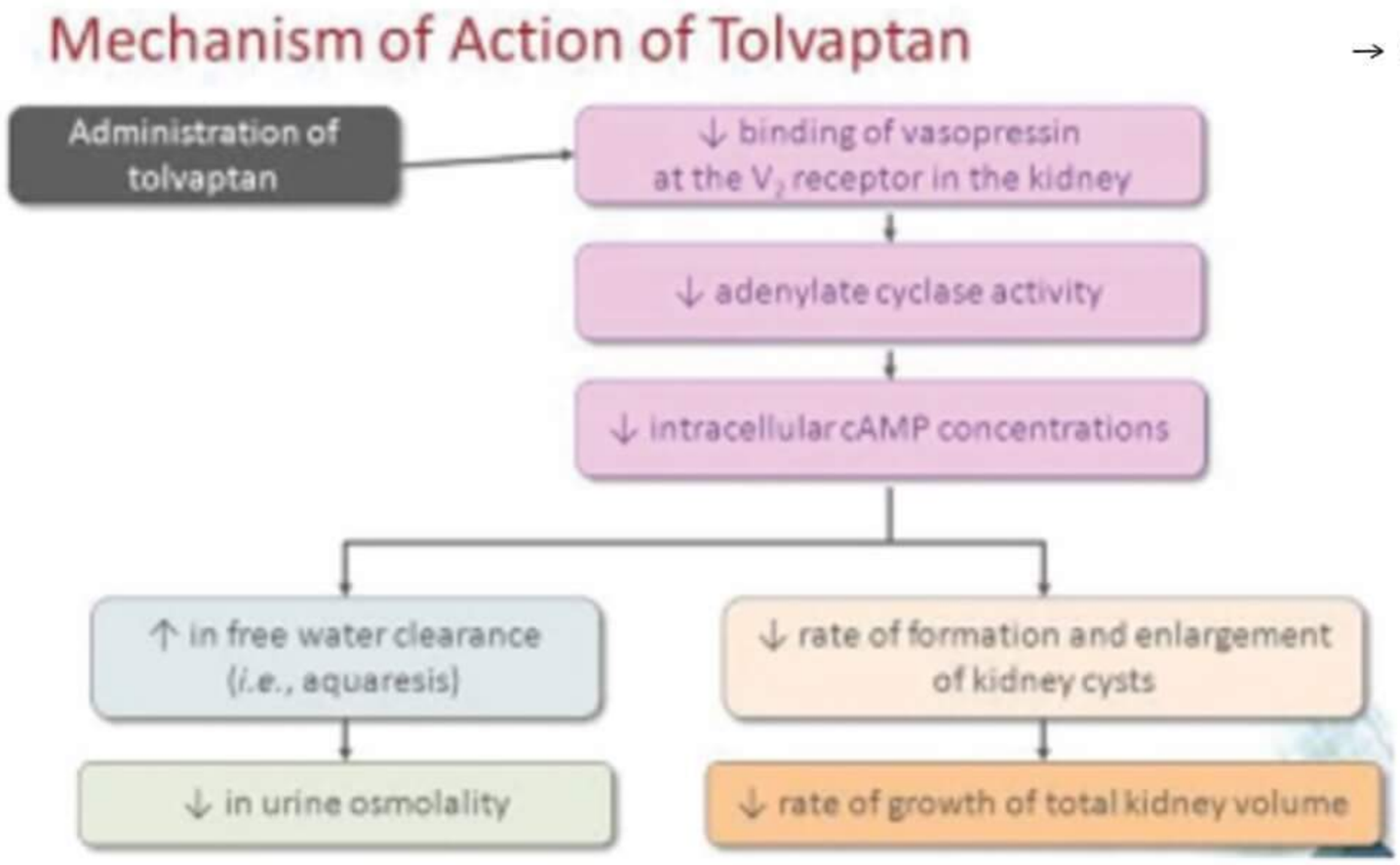
17. **CANNABIDIOL**

→ Derived from marijuana

→ For LGS & Dravet syndrome

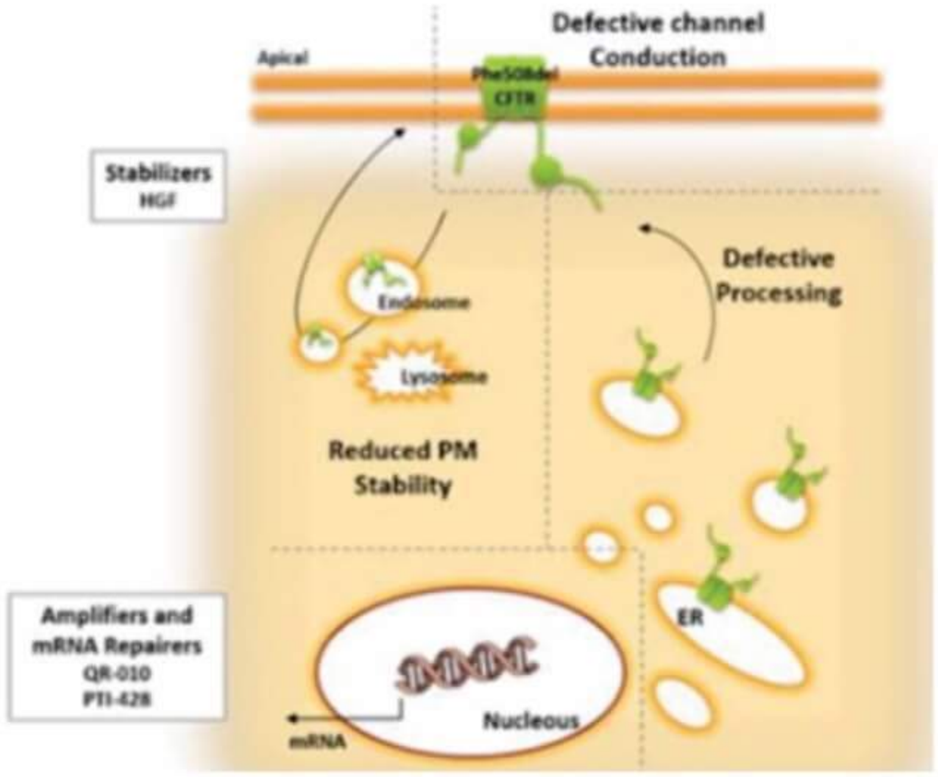
→ First FDA approved drug which is directly obtained from cannabis

18. **TOLVAPTAN**



→ For AD polycystic kidney disease

19. TEZACAFTOR / IVACAFTOR



Cystic fibrosis

→ d/t defective CFTR

TEZACAFTOR → Corrector

IVACAFTOR → Potentiator

20. APALUTAMIDE

FLUTAMIDE

NILUTAMIDE

BICALUTAMIDE

ENZALUTAMIDE

→ Androgen receptor blockers

→ Used for prostate cancer

21. LOFEXIDINE

→ α_2 agonist → Break to sympathetic system

→ Approved for Opioid addiction

22. LUTETIUM LU 177 DOTATATE

→ Approved for Pancreatic neuroendocrine tumor

23. BICETEGRAVIR / EMTRICITABINE / TENOFOVIR ALAFENAMIDE

→ For HIV R_x

24. PLAZOMICIN

→ New aminoglycoside

→ IV route

→ For complicated UTI including pyelonephritis

25. OMADACYCLIN

→ For Community Acquired Pneumonia & acute skin & skin structure infections

→ Tetracycline

→ Has activity against bacterial strains expressing tetracycline resistance by efflux & ribosomal protection

26. SARECYCLINE → Tetracycline approved for acne vulgaris

27. ERAVACYCLINE → For complicated intra-abdominal infections in ≥ 18 yrs

28. DORAVIRINE

→ NNRTI (2^{nd} gen)

→ For HIV

29. **MOXIDECTIN**
   → New antihelmenthic drug for onchocerciasis [River blindness]
   → Binds to GABA & GLUTAMATE channels

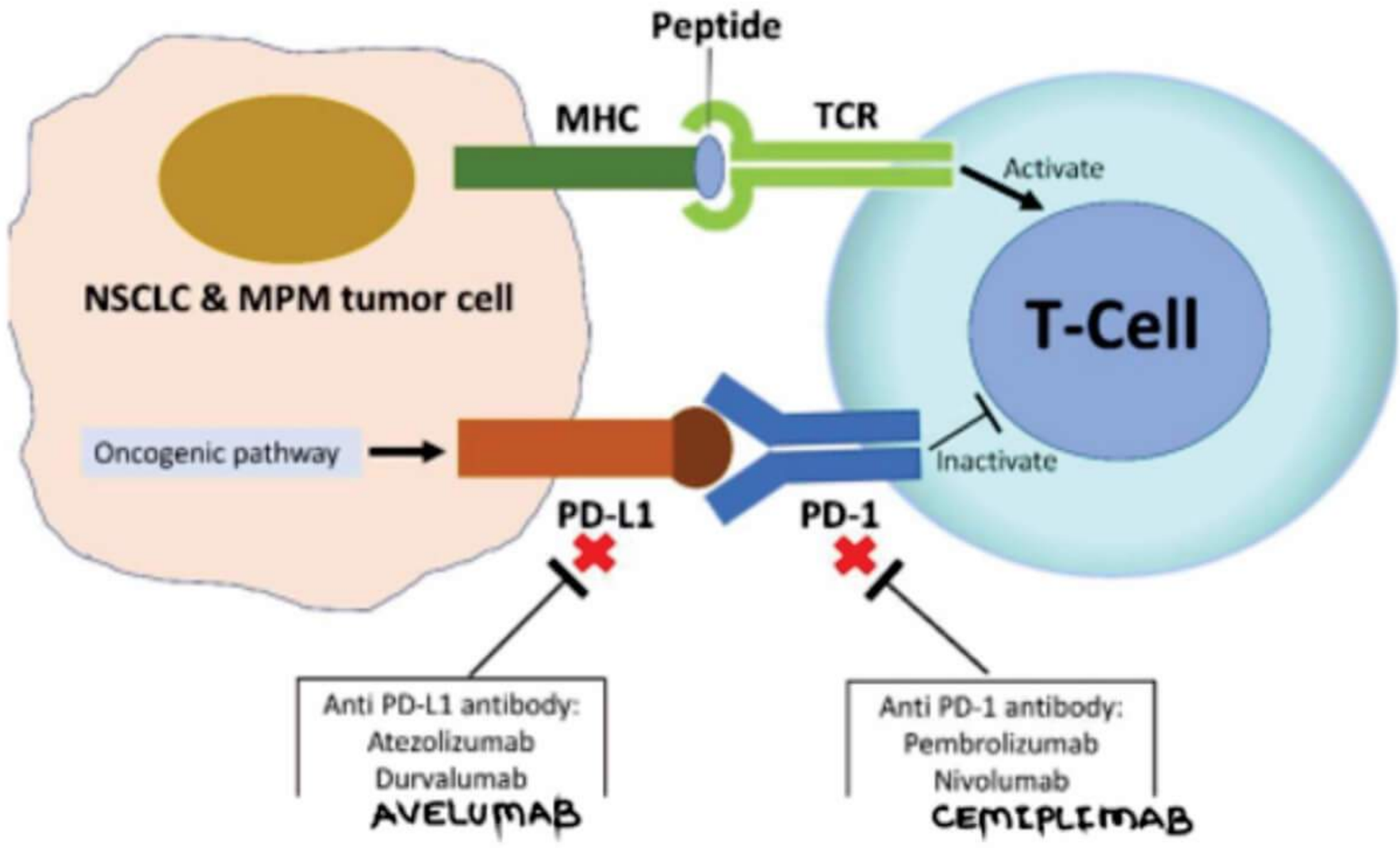
30. **TECOVIRIMAT**
   → For smallpox [For bioterror attacks]
   → Oral
   → Binds to envelop protein P_{37} & inhibit e/c viral forms
   → Inhibits transmission

31. **SEGESTERONE acetate + ETHINYL ESTRADIOL**
   → Vaginal ring of contraception
   → Once yearly

32. **BARICITINIB**
   → JAK inhibitors for RA similar to tofacitinib
   → Oral

33. **MOXETUMOMAB PASUDOTOX**
   → Moxetumomab + Pseudomonas toxin
   → For hairy cell leukemia

34. **CEMIPLIMAB**



→ CEMIPLIMAB → APPROVED FOR CUTANEOUS SQUAMOUS CELL CARCINOMA
→ PEMBROLIZUMAB
  NIVOLUMAB
  AVELUMAB
  } APPROVED FOR NON - SMALL CELL CA OF LUNG
→ ATEZOLIZUMAB
  DURVALUMAB
  } APPROVED FOR UROTHELIAL CARCINOMA

35. **DUVELISIB**

→ Similar to IDELALISIB, COPANLISIB → Phosphoinositide – 3 kinase δ inhibitors

→ Duvelisib → PI-3 δ & γ inhibitor (Dual inhibitor)

→ For CLL, small lymphocytic lymphoma & follicular lymphoma

36. **IVOSIDENIB**

→ Similar to Enasidenib

→ For AML with IDH 1 mutation

37. **ENCORAFENIB**

→ Encorafenib + Binimetinib for malignant melanoma

→ Oral

→ Braf kinase inhibitors

38. **MOGAMULIZUMAB**

→ MAB against CCR4

→ For mycosis fungoides & Sezary disease

→ AFUCOSYLATED → increase ADCC

39. **DACOMITINIB**

→ Inhibits tyrosine kinase activated by EGFR

→ For non-small cell lung carcinoma

NEW DRUGS 2017

1. VORETIGENE NIPARVOVEC

→ For Leber's congenital amaurosis (RPE65)

→ AAV2 vector containing human RP#65 CDNA

→ Subretinal injection

2. NETARSUDIL

→ For glaucoma

→ Rho kinase inhibitor

→ ↑ aqueous outflow

→ Unknown mechanism

3. LATANOPROSTENE BUNOD

→ Metabolized by esterases to Latanoprost and Butanediol mononitrate

Latanoprost → ↑ uveoscleral outflow

Butanediol → ↑ trabecular outflow

→ Approved in glaucoma

4. BETRIXABAN

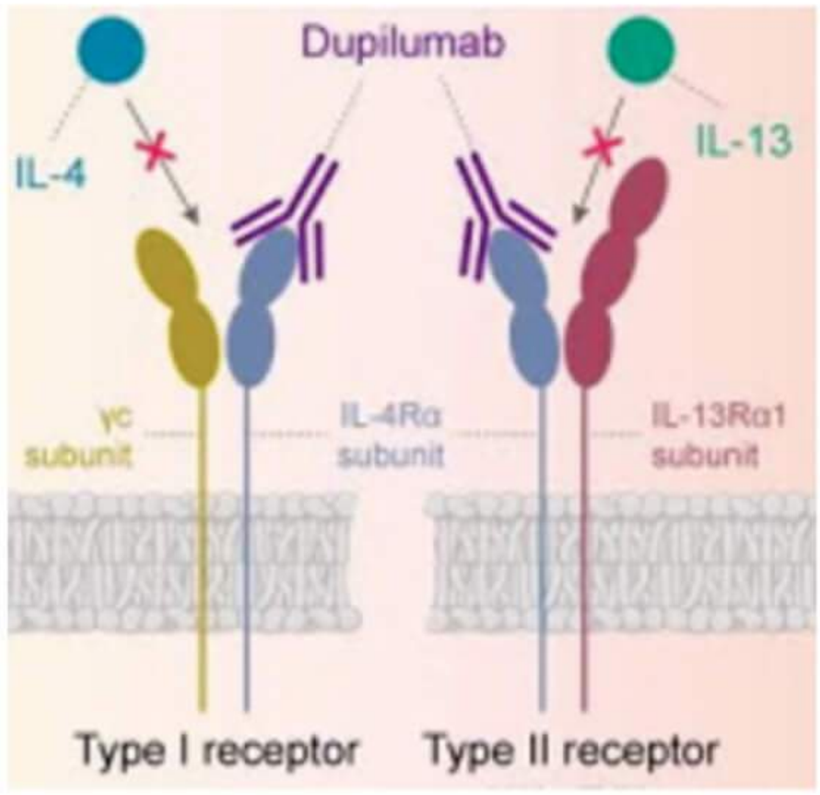
→ Oral Anti-coagulant

→ Others - RIVAROXABAN
APIXABAN
EDOXABAN

5. DUPILUMAB

→ Approved for atopic dermatitis

→ Mab against IL-4R α



6. SEMAGLUTIDE

→ Recombinant GLP – analogues

→ Only oral drug from this group

→ Approved for type 2 DM

7. ETECALCETIDE

→ Calcium sensing Receptor agonist

→ Calcimimetic drug

→ Other drug → CINACALCET

→ For hyperparathyroidism

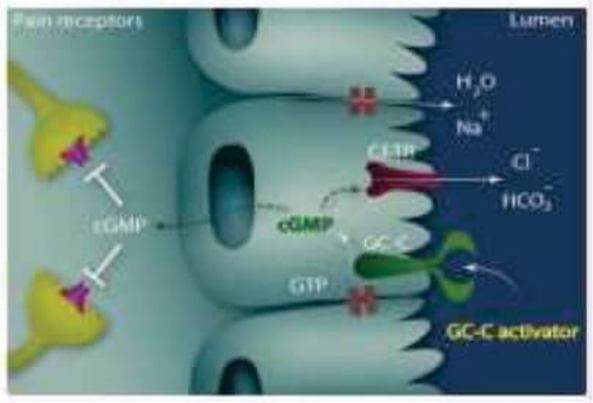
8. DAPAGLIFLOZIN

ERTUGLIFLOZIN

→ SGLT – 2 #

→ For type 2 DM

→ Canagliflozin, Dapagliflozin, Ertugliflozin } Other similar drugs



9. PLECANATIDE

→ Stimulates GC –C

→ Approved for chronic idiopathic constipation

10. NALDMEDINE

→ Opioid μ receptor blocker

→ Not absorbed from GIT

→ Approved for opioid induced constipation

11. TELOTRISTAT ETHYL

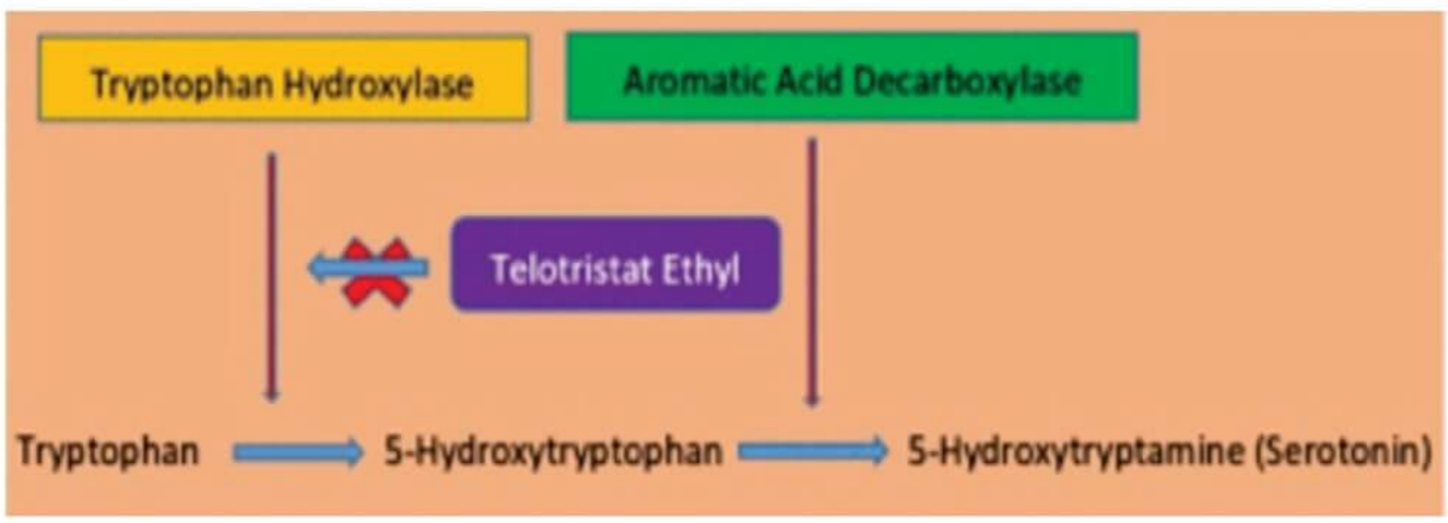
In Carcinoid syndrome

→ ↑ 5-HT → Diarrhea

→ Inhibit tryptophan hydroxylase

→ Thereby decrease 5HT production

→ Approved for diarrhea d/t carcinoid syndrome



12. CERLIPONASE ALPA

→ For infantile neuronal ceroid lipofuscinosis

→ Recombinant Tripeptidyl peptidase 1 (TPP-1)

13. VESTRONIDASE ALFA

→ MPS VII

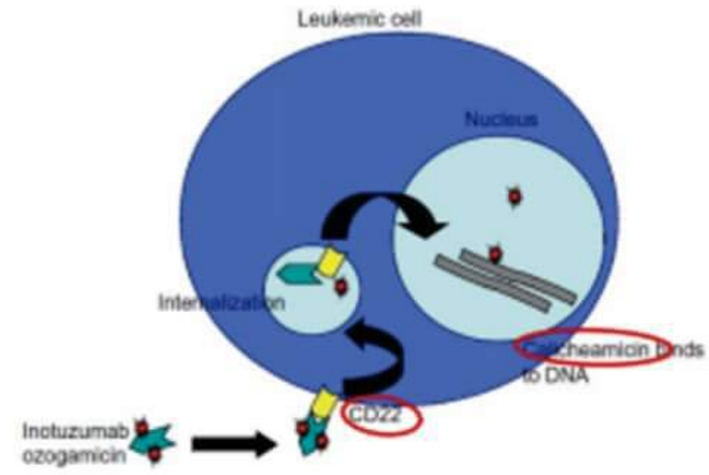
→ d/t deficiency of β glucuronidase

→ Vestronidase – recombinant β glucuronidase

14. INOTUZUMAB OZOGAMICIN

→ MAb against CD 22 linked to calicheamicin

→ Approved for acute lymphoid leukemia



15. EMICIZUMAB

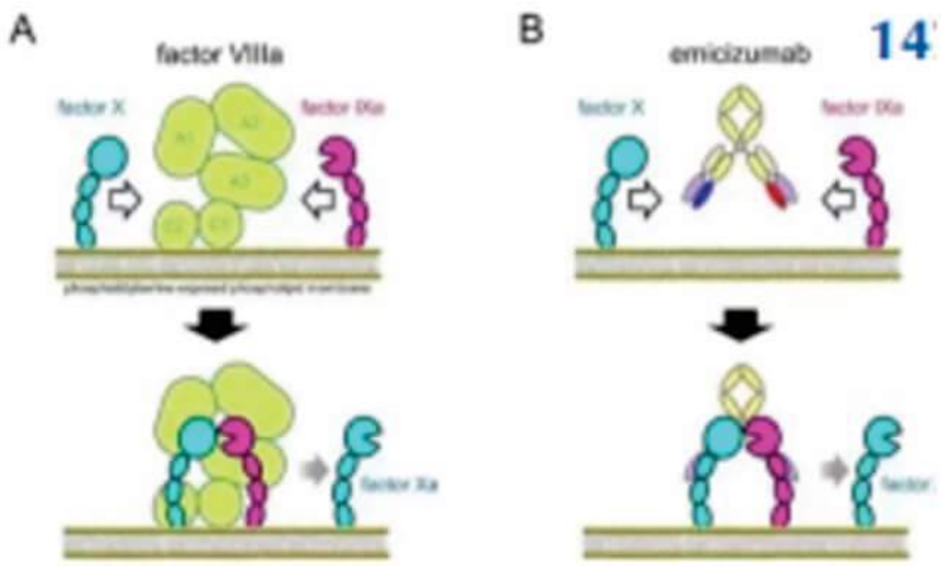
→ Bispecific MAb

→ Bind to both factor IX and X

→ Help in activation of factor X

→ Factor VIII is not required

→ Approved for Hemophilia



16. GLICAPREVIR / PRIBRENTASVIR

→ Approved in Hepatitis C

→ Combination of protease Θ with NS5A Θ

17. SOFOSBUVIR / VELPATASVIR / VOXILAPREVIR

→ Approved for Hepatitis C

→ NS5B Θ with protease Θ with NS5A Θ

18. TOCILIZUMAB

→ MAB against IL6

→ For RA & cytokine release syndrome Rx

19. LETERMOVIR

→ Drug against CMV

→ Inhibit DNA terminase complex

20. LESINURAD

→ Inhibit URAT -1

→ Uricosuric agent

→ Used for chronic gout

21. SARILUMAB

→ MAB against IL6

→ For RA

22. ABALOPARATIDE

→ PTH_{1-34}

→ Used for osteoporosis

→ Injectable

23. AMANTADINE

→ NMDA receptor #

→ Used for levodopa induced dyskinesia

24. EEDRAVONE

→ Free radical scavenger

→ Used for Amyotropic lateral sclerosis

25. SAFINAMIDE

→ MAO – B #

→ Used for Parkinsonism

26. RIBOCICLIB
ABEMCICLIB
PALBOCICLIB

→ CDK 4 & 6 Inhibitors

→ Used for Breast cancers

27. NIRAPARIB

→ Inhibit poly ADP ribose polymerase

→ like OLAPARIB

→ used for Ovarian cancers

28. DURVALUMAB

→ MAB against PD ligand

→ used for bladder carcinoma, urothelial carcinoma