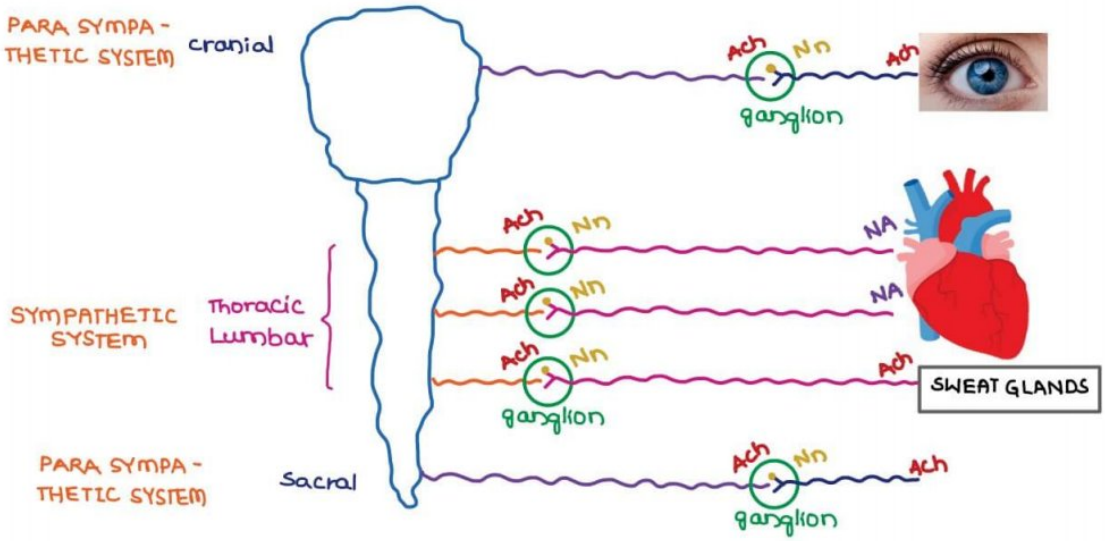


→ Preganglionic fibres are shorter in sympathetic system
Preganglionic fibres are longer in parasympathetic system

→ 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 post ganglionic 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

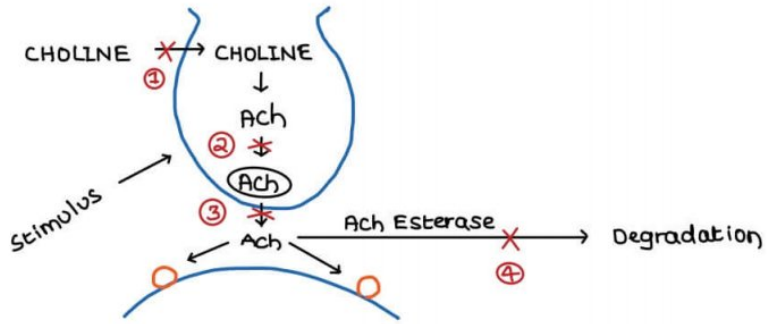
PARASYMPATHETIC SYSTEM			SYMPATHETIC SYSTEM
HEART		↓ ↓	+ + +
OTHERS		↑	↓
Bronchus	→	Broncho constrictⁿ	→ Bronchodilatⁿ
GIT	→	Diarrhoea	→ Constipation
Bladder	→	↑ urine outflow	→ ↓ urine outflow
Glands	→	↑ secretions	→ ↓ secretions
Pupil	→	miosis	→ mydriasis

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 HEMICHOLINIUM
2 VESAMICOL
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 stimulatⁿ in both hyper & hypo stimulatⁿ 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 #

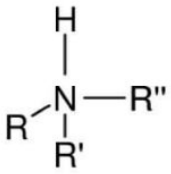
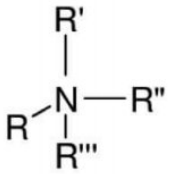
DRUG	ACTS ON	ACTION	INDICATION
PILOCARPINE	Pupil [M_3®]	meiosis	Angle closure glaucoma
BETHANECHOL	Bladder [M_3®]	↑ outflow	Atonic bladder
METHACHOLINE	Myocardium [M_2®]	cardiac suppression	Tachycardia Arrythmias
CARBACHOL	Common Action Nicotinic ® Muscarinic ®		

Drug ε max. nicotinic action → CARBACHOL

Cevimeline

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

ACH ESTERASE

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
   - → TREATMENT

Basal Nucleus of Meynert
↓
Acquiring & retaining memory

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)*

↑ Ach

⊕ N_M Receptors ⊕ M Receptors [M_1, M_2, M_3]

↓ Muscle weakness Side effects

→ R_f → NEOSTIGMINE + ATROPINE

2 COBRA BITE

→ N_m #
→ Neostigmine + Atropine → R_f

3. POST OP PARALYTIC ILEUS → R_f by Neostigmine

4. POST OP URINARY RETENTION → R_f 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

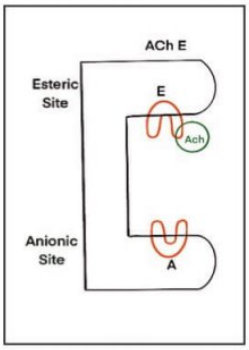
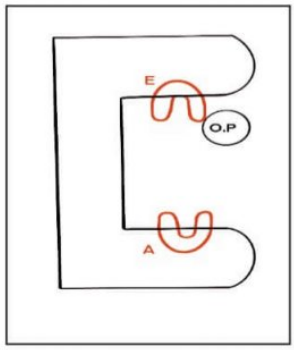
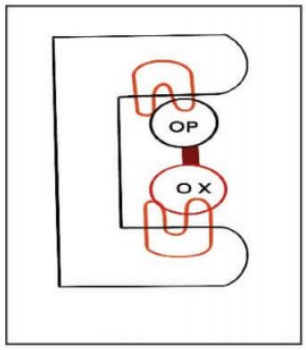
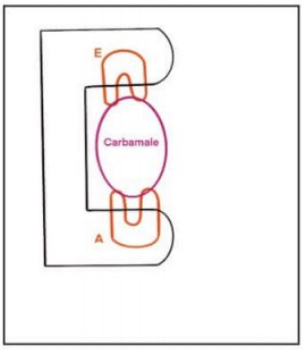
→ IF Pinpoint pupil ⊕, ↑ Secretions ⊕ } AchE # Poisoning

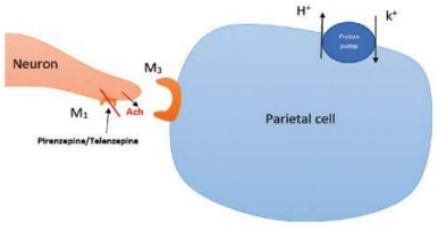
→ ↑ HR, ↑ BP can be seen rarely [dlt N_N® stimulation]
Muscle weakness occurs usually [dlt N_m® overstimulation]

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_2 – 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

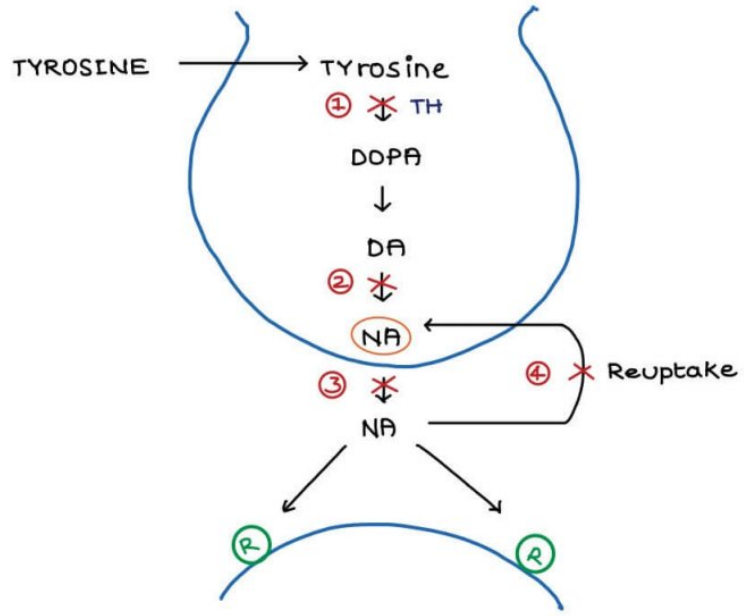
GLANDS	M_3	→ Atropine → Glycopyrrolate	Pre anesthetic Medication	• Dryness [C/I in children] • ↓ Sweating ↓ Fever ↓ Hyperthermia
EYE	M_3	→ Atropine → Homatropine → Cyclopentolate → Tropicamide	• Fundoscopy • Refraction testing • **DOC in** Children – atropine [max. cycloplegic action > 7 days] Adults – 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 ME|TYROSINE 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

$\beta_2 \oplus$ → LIVER
- $\oplus$ Gluconeogenesis
- $\oplus$ Glycogenolysis
- $\ominus$ 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

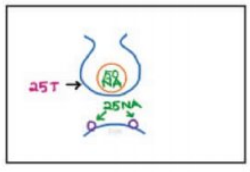
→ TCA Tricyclics anti depression

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)

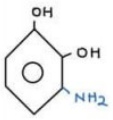
→Use of ephedrine and pseudo ephedrine – Nasal decongestant

→Amphetamines can cross blood brain barrier and,

- Reduces sleep — Used for Narcolepsy (DOC is modafinil)
- Increases attention span — Used for ADHD (DOC is methylphenidate)

Attention deficit hyperkinetic disorder

CATECHOLAMINES



catechol → Di Hydroxy Benzene

COMT → catechol ortho methyl 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

→ stimulati 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 Basic life saving Or CPR
↓ 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

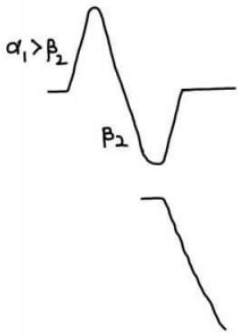
at First BP increases [dlt ($\alpha_1 > \beta_2$) Stimulation]

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_β 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

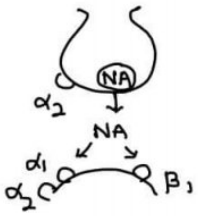
SYMPATHOLYTIC DRUGS

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 ī 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

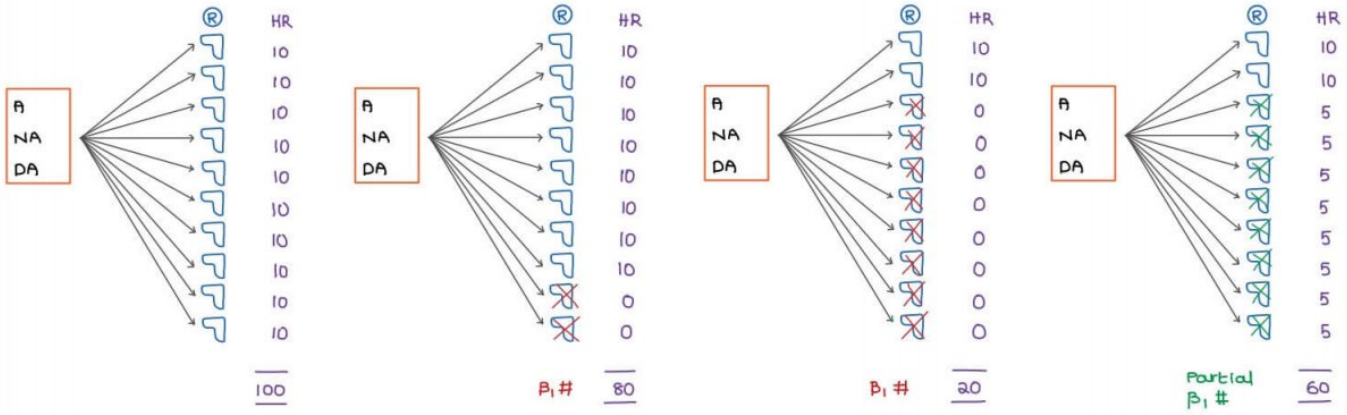
β_2 acts on	RESULT	β_2 #	C/I
Bronchus	Bronchodilatⁿ	Bronchoconstrictⁿ	Asthma
Blood vessels	vasodilatⁿ	vasoconstrictⁿ	Peripheral vas. Dz
Liver	hypoglycemia reversal	stop reversal	DM

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

PrepLadder

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 ĩ 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
↓
stimulatⁿ of sensory n. of Trigeminal nerve
↓
Facial n. stimulated
↓
contraction of Orbicularis Oculi
↓
Eye closure
[CORNEAL REFLX]

→ corneal reflex is masked ĩ 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

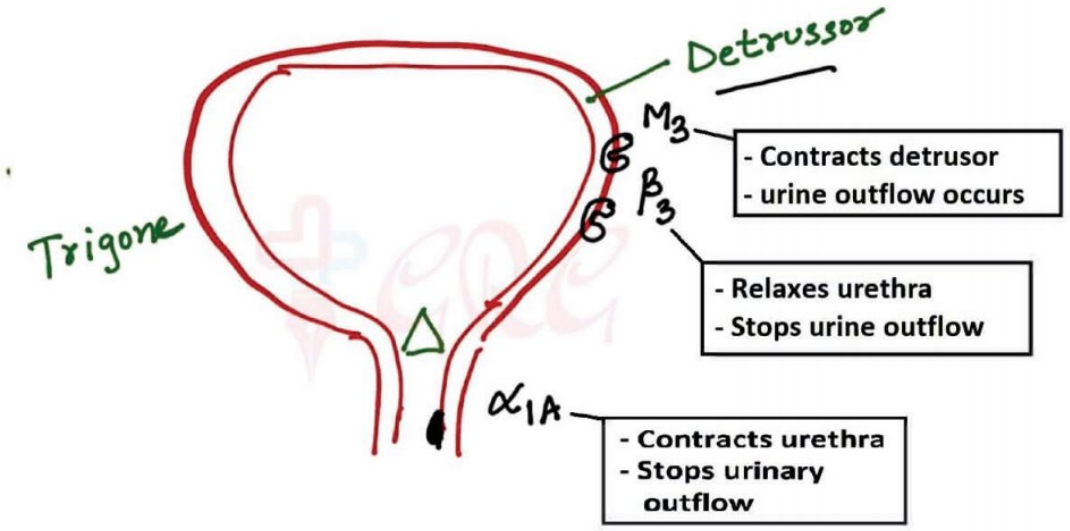
→ **$PGF_{2\alpha}$ analogues (LATANOPROST)**
- Pigmentation of Iris (Heterochromia Iridis)
- Growth of eyelashes (Hypertrichosis)
- Fluid in macula (Macular edema)

→ **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

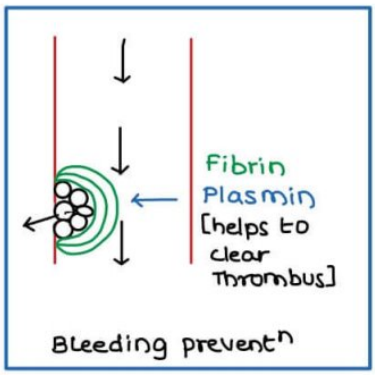


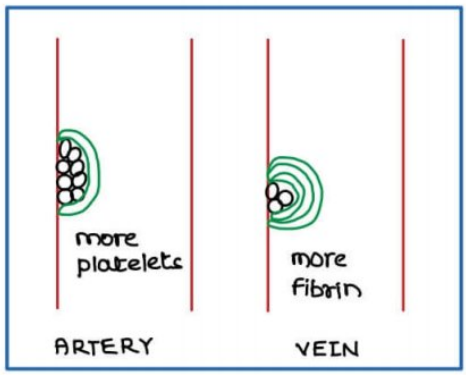
URINARY INCONTINENCE:

It may be of 3 types:
- Urge incontinence
- Stress incontinence
- Overflow incontinence

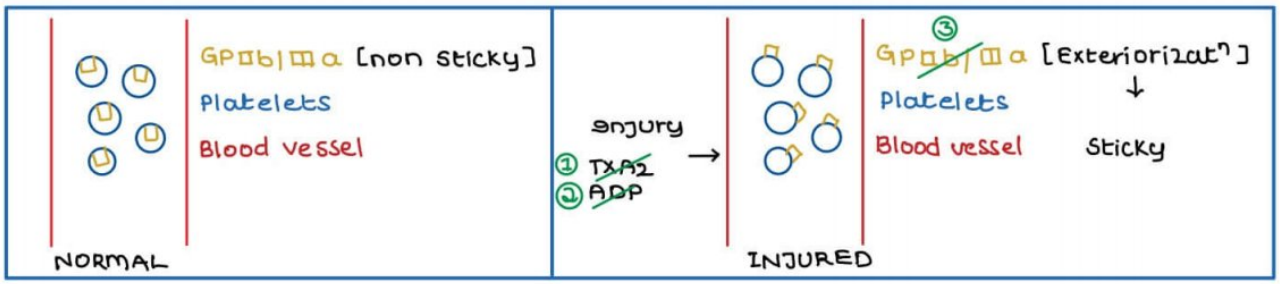
Urge Incontinence	Stress Incontinence	Overflow Incontinence
Also called overactive bladder due to detrusor instability - Urge to urinate comes at lesser urine volume in the bladder - Patient not able to control urine outflow **Rx** Makes – Mirabegron (B_3 +) BladDAR – Darifenacin S – Solefenacin O – Oxybutynin M3# F – Flavoxate – Fesoterodine T – Tolterodine – Trospium	- 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

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

Phospholipids
↓
Arachidonic Acid
↓
Prostaglandins — Leukotrienes
PGG_2/H_2
↓
TXA_2 — PGI_2 — $PGD_2/E_2/F_2$
Platelets — Endothelium — Other

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 ɪ 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

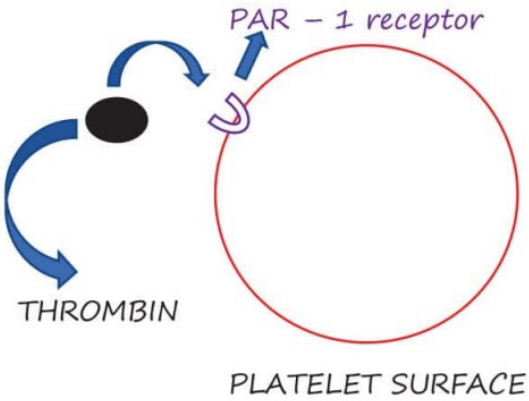
3. DRUGS ACT ON GP IIb/IIIa → strongest antiplatelet drugs

- 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

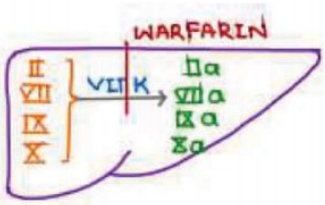
ANTI PLATELEI DRUGS ARE PREFERRED IN ARTERIAL THROMBOSIS

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

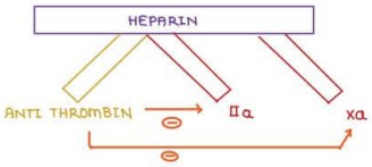
- Andexanet Alpha is the antidote for factor Xa inhibitor overdose,

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

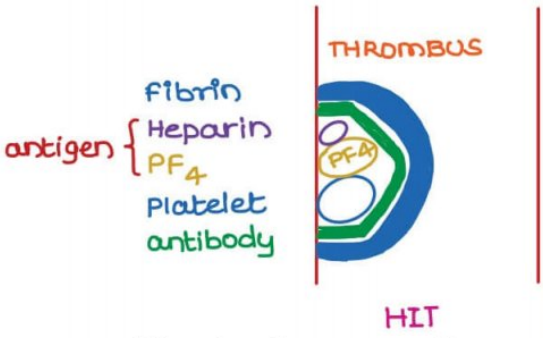
HEPARIN

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. S/E → 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



HIT

2. DIRECT THROMBIN INHIBITORS

→ DRUGS

- HIRUDIN
- LEPIRUDIN
- BIVALIRUDIN
- ARGATROBAN
- MELAGATRAN

} Injectables

- DABIGATRAN → given orally

Direct acting group 3 oral factor X inhibitors are Rivaroxaban and also apixaban edoxaban

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

tPA [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 - R_XOC

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 d/t Chronic Kidney disease
    Anaemia d/t BM suppression

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

G - CSF & GM - CSF

→ INDICATION → Leucopenia d/t anticancer drugs
→ DRUGS
  G - CSF → FILGRASTIM
  PEGFILGRASTIM

Polyethylene glycol is added to make them long functional

  GM - CSF → SARGRAMOSTIM
  MOLGRAMOSTIM

IL - 11 → used for thrombocytopenia d/t anticancer drugs

→ OPRELVEKIN

THROMBOPOIETIN RECEPTOR AGONISTS → used in ITP

→ ROMIPLOSTIM — Idiopathic thrombocytopenic purpura
ELTROMBOPAG Orally Pag mens oral

Newly discovered drugs

Lusutrombopag
Avatrombopag — In liver disease and also given orally

All the growth factors are given by injection in subcutaneous route except eltrombopag lusutrombopag and avatrombopag there names end with pag at the end

ANTICANCER DRUGS

CYTOTOXIC ANTICANCER DRUGS

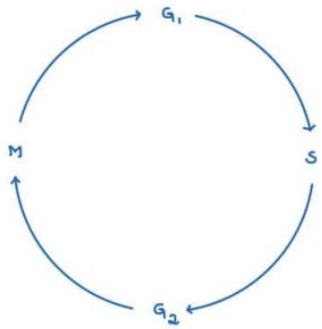
Can kill almost every cell and don't have the ability to differentiate between normal and cancerous cells

ADVERSE EFFECTS

1. BM supression
2. Alopecia Hair
3. Mucositis → Diarrhea
4. Hyperuricemia

CELL CYCLE

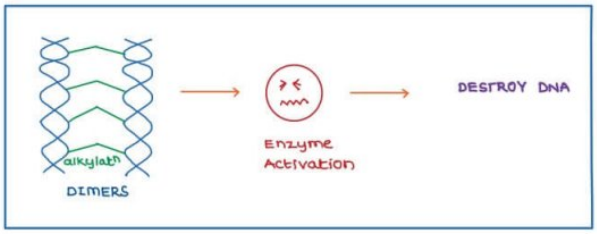
→ SYNTHETIC PHASE [S] → DNA Doubled
MITOTIC PHASE [M] → DNA reduced to half
GAP PHASES [G_1 & G_2]



→ 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 alkylatn → 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 i.e. Carmustin(BCNU), Lomustin(CCNU),Semistin(methyl CCNU)

Text

Take – Temozolomide

My – Melphalan, Mechlorethamine

Cycle – Cyclophosphamide

Ifosfamide and Cyclophosphamide:

(Ifosfamide At any dose can cause heammorhages cystitis and cyclophosphamide at high dose only)

Ifosfamide and cyclophosphamide

↓ Metabolized to

Acrolein Filter through kidney and comes to urinary bladder

↓ 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:

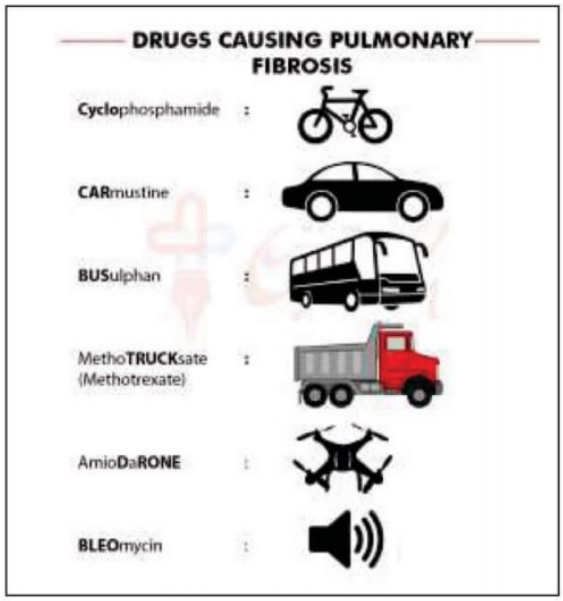
→ Cyclophosphamide

→ 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 is used in Non-small cell lung cancer

- 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
↓ xanthine Oxidase	↓
Degradation	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

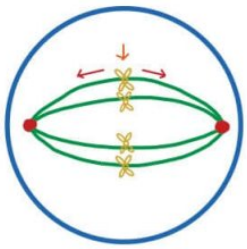
DRUGS

- 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

→ MC 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
SIE → Peripheral neuropathy SIADH	SIE → 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

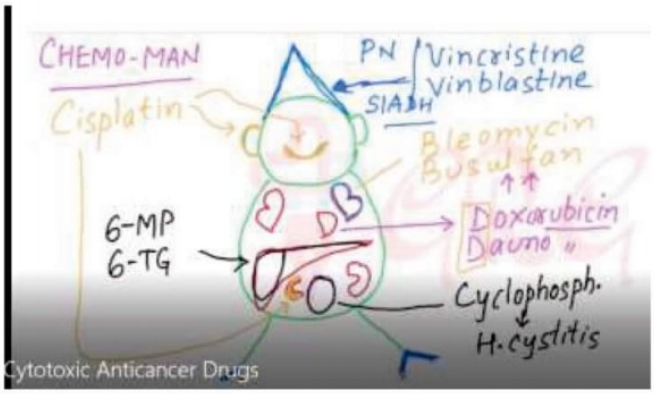
→ used for multiple myeloma

→ 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

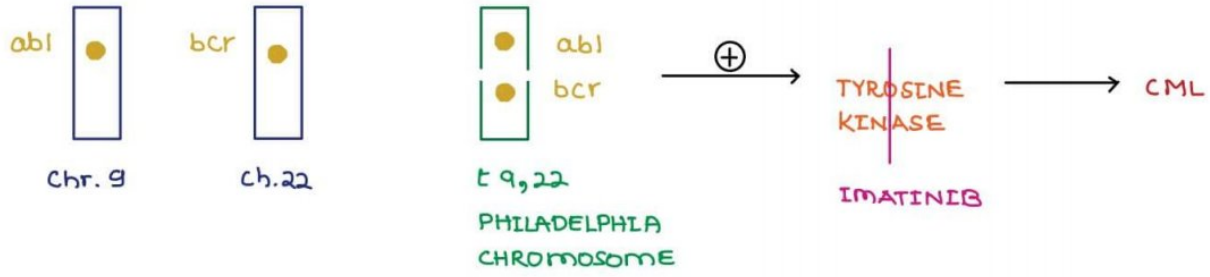
TARGETED ANTICANCER DRUGS

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 → AXITI NIB
   - S → SORAFENIB
   - S → SUNITINIB

4 HEPATO CELLULAR CARCINOMA → SORA FENIB

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

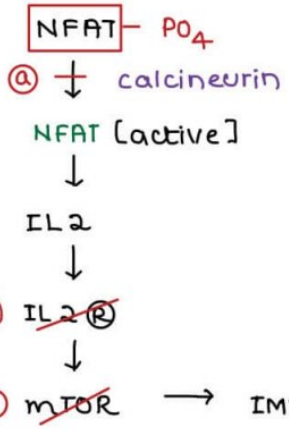
→ end t "MAB"
→ injectables

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 - Nuclear Factor of Activated T cells

a. CYCLOSPORINE
TACROLIMUS

b. DACLIZUMAB
BASILIXIMAB

c. SIROLIMUS
EVEROLIMUS

b. 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 } chimeric [high risk of allergy]
BASILIXIMAB }
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