Pharmacodynamics: what a drug does to the body

→ effect of drugs are only quantitative, but never qualitative

→ drugs can only accelerate / depress the normal physiological / biochemical functions of an organ but cannot confer entirely a new activity on it.

→ drug action always precedes the drug effect.

Site of Drug Action:

extracellular
cellular
intracellular

site of pilocarpine for producing miosis: circular muscle of iris

site of morphine for producing miosis: stimulation of 3rd cranial nerve nucleus.

Extracellular site:

- antacids neutralizing gastric acidity
- chelating agents forming complexes with heavy metals
- magnesium sulfate acting as osmotic purgative by retaining the fluid inside the lumen of intestine & increasing the faecal bulk.

Cellular site:

- action of acetylcholine on nicotinic receptors of motor end plate, leading to skeletal muscle contraction
- inhibition of membrane-bound ATPase by cardiac glycosides
- effect of sympathomimetics on heart muscle & blood vessels

Intracellular site:

- trimethoprim or sulfa drugs act by interfering with the synthesis of folic acid which is an intracellular component
- incorporation of 5-fluorouracil (anticancer drug) into messenger RNA in place of uracil.

Mechanism of Drug Action:

- receptor - mediated
- non-receptor mediated
- targeting specific genetic changes

I] Receptor Mediated Mechanisms:

Receptor: specific macromolecular protein (membrane-bound / intracellular) which is capable of binding with the specific functional groups of the drug or endogenous substance.

→ formation of drug-receptor complex [DR] is responsible for triggering the biological response.

$$D + R \rightleftharpoons [DR] \rightsquigarrow \text{Response}$$

→ The binding of D & R is usually specific & reversible when there is formation of Hydrogen bonds, van der Waals bonds or electrostatic bonds; sometimes it is irreversible due to formation of covalent bond.

→ Binding may be stereoselective to specific d or l isomers of the drug

→ Types of receptors:
- receptor for hormones
- autacoids
- growth factors
- neurotransmitters

Acceptor Site / Non-specific Binding Site: if the binding of the drug to some chemical components of cell does not lead to any pharmacological effect.

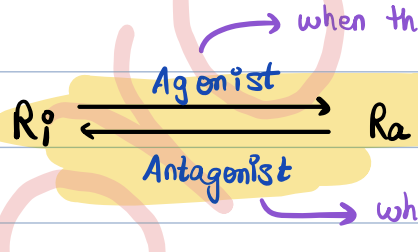
Affinity: (A) capability of a drug to form complex with its receptor [DR]

Intrinsic Activity or Efficacy (E): ability of a drug to trigger pharmacological action after [DR] is formed.

Types of Receptors on the Basis of A & ε:

Agonist	Antagonist	Partial Agonist	Inverse (IA) Agonist (aka negative antagonist)
→ high A → ε = 1 ∴ trigger maximum biological response or mimic the effects of the endogenous substance eg: methacholine is a cholinomimetic drug which mimics the effect of Ach on cholinergic receptors.	→ high A → ε = 0 → drugs bind to the receptor, but don't mimic, rather, block/interfere with binding of endogenous agonist eg: Atropine blocks the effect of Ach on cholinergic - muscarinic receptors	→ high A → 0 ≤ ε ≤ 1 ∴ partly effective as agonists eg: pentazocine (narcotic analgesic) is a partial antagonist at the μ receptor subtype of opioid receptors	→ high A → -1 ≤ ε ≤ 0 ∴ IA inactivate the constitutively active receptors & thus, prevent even its basal activity. → they produce an effect opposite to agonist / drug even its absence.

Two conformations of receptors: R_a (active), R_i (inactive)



Examples of IA:

- β-carbolines act as IA at benzodiazepine receptor & produce effects like anxiety, insomnia, seizures which are the opposite of therapeutic effects of benzodiazepines (antianxiety, sedation, anti-epileptic).

Types of Receptors & Signal Transduction Mechanisms:

① Ion-channel Coupled Receptors / Ionotropic Receptors:

→ localised on cell membrane & are coupled directly to an ion channel.

→ open only when the receptor is occupied by an agonist.

→ response: depolarization or hyperpolarisation of cell membrane

aka Ligand-gated ion channels / Receptor operated Channel (ROC)

eg: – nicotinic cholinergic receptor
– $GABA_A$ receptor
– glutamate receptor
– glycine receptor

eg: – benzodiazepines allosterically enhance chloride transport through $GABA_A$ chloride channel.

② G-Protein Coupled (GPCRs) Receptors / Metabotropic Receptors:

→ membrane-bound receptors which are coupled to the effector system (enzyme/channel) through GDP/GTP binding proteins called G-proteins.

eg: – muscarinic-cholinergic receptors
– adrenoceptors
– dopaminergic receptors
– 5HT receptors
– opiate receptors
– purine receptors

→ GPCRs are composed of 7 transmembrane helices which have an extracellular domain as drug/NT binding site & an intracellular domain that couples to G-protein

→ G-proteins are heterotrimeric molecules – α, β, γ subunits.

→ further classification is based on the identity of their distinct α subunits

→ 3 main varieties of $G\alpha$ - proteins : G_s, G_i, G_q
(although there are 17 known variants)

→ G_s, G_i ⇒ stimulation / inhibition of adenylate cyclase

→ G_q ⇒ stimulates phospholipase - C activity

G - protein	Associated Receptors	Effector Pathway
G_s (stimulates membrane-bound adenylate cyclase)	• β - adrenoceptors • Histamine • Serotonine • Dopamine (D_1) receptor	↑ adenylyl cyclase activity ↓ ↑ cAMP
G_i (inhibits membrane-bound adenylate cyclase)	• α_2 adrenoceptors • Muscarinic (M_2) receptors • opioid receptors • some 5HT receptors • dopamine (D_2) receptors	↓ adenylyl cyclase activity ↓ ↓ cAMP
G_q / $G_{12/13}$ (activates phospholipase - C)	• α_1 adrenoceptors • Muscarinic (M_1) receptors • angiotensin receptor [AT_1]	Activates phospholipase - C ↓ ↑ IP_3, ↑ DAG, ↑ Ca^{2+} entry

(3) **Kinase - Linked Receptors**: receptors are linked directly to:

- tyrosine kinase (receptors for insulin & various growth factors) or
- guanylate cyclase (receptors for atrial natriuretic peptide).

→ these receptors are ligand - activated transmembrane enzymes having catalytic activity

→ Agonist binds to extracellular domain of the receptor

↓

conformational change

↓

dimerisation followed by autophosphorylation of tyrosine residues in the intracellular tyrosine binding domain.

↓

phosphorylated tyrosine residues couple with SH_2 domain of Grb_2 protein

↓

mediation of response

(4) **Intracellular / Cytosolic Receptors**: this nuclear receptor family senses signals from the lipid-soluble substances & other hormonal substances to influence the gene expression.

→ receptors are located in cytoplasm in an inactive state complexed with heat shock protein - 90 (hsp-90)

[glucocorticoids have a very high affinity to this receptor]

↓

Glucocorticoid crosses the cell membrane

↓

Receptor dissociates from hsp-90 & forms homodimer with Glucocorticoids (GR + GR) → *

* → (GR + GR) translocates into the nucleus

↓

these dimers transactivate / transrepress genes by binding to positive or negative glucocorticoid Responsive Elements (GRE).

↓

Alteration in gene transcription

(5) Enzymes as Receptors : both intracellular & extracellular enzymes

→ drugs can either mimic the enzyme's substrate or may bind to allosteric site on enzyme to produce an effect.

eg: - angiotensin converting enzyme (ACE) which converts Angiotensin I to Angiotensin II (vasoconstrictor)

∴ ACE enzyme is a receptor for ACE inhibitg drugs which lower blood pressure.

(6) Voltage-Gated Ion Channels / Voltage Operated Channels (VOC) :

→ ion channels that are gated only by voltage

→ the gating/opening/conductance is controlled by changes in membrane potential.

- voltage-gated Na^+ channels
- voltage-gated Ca^{2+} channels
- voltage-gated K^+ channels

- ROCs ⇒ assume only 2 states - open, closed
- VOCs ⇒ also attain a 3rd state - refractory or inactivated state
  - In this state, the channel is unable to open or reactivate for a certain period of time even when the membrane potential returns to a voltage that normally opens or activates the channel.

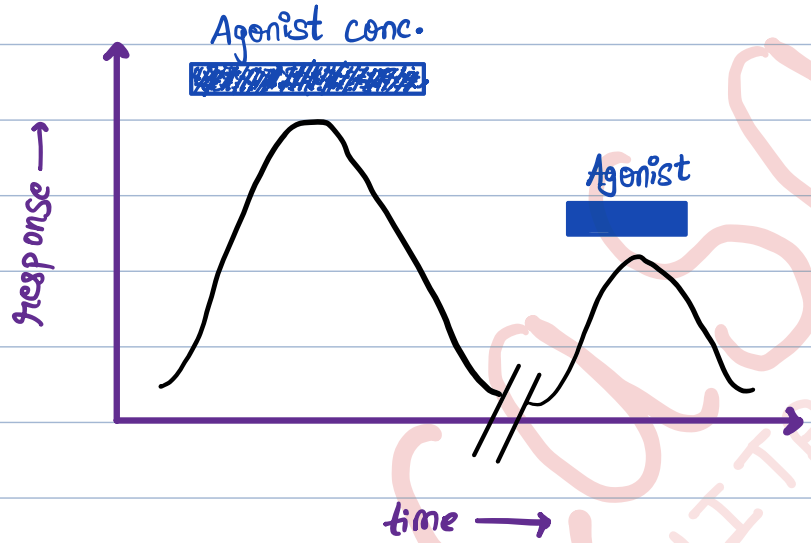
Receptor Desensitization : (desensitization with time & repeated use)

→ after reaching an initial high level, the response gradually diminishes over seconds / minutes even in the continuing presence of the agonist.

→ desensitization is usually reversible which makes it different from "down-regulation" of receptors

→ Desensitization is a self-defense mechanism provided by nature to protect our cells from excessive stimulation.

eg: — neuromuscular junction
— β-adrenoceptors.



Up & Down Regulation of Receptors :

→ prolonged exposure to high conc. of agonist causes a reduction in the number of receptors available for activation ⇒ DOWN REGULATION

⇒ occurs due to endocytosis or internalisation of the receptors from cell surface.

→ prolonged occupation of receptors by a blocker (antagonist) leads to an increase in the number of receptors ⇒ UP REGULATION

⇒ there is also subsequent increase in receptor sensitivity

⇒ due to externalisation of the receptors out again from inside the cell.

eg:- In thyrotoxicosis, thyroid hormones bring about up-regulation of β_1 receptors of cardiac muscle which increases the cardiac sensitivity to catecholamines leading to tachycardia.

- In endogenous depression, there is down regulation of α-adrenoceptors & the prolonged use of tricyclic antidepressants results in down regulation of β-receptors (with relative up-regulation of α-adrenoceptors)

Spare Receptors (Receptor Reserve):

→ **Maximal efficacy**: state at which receptor-mediated signaling is maximal & that, further increase in the drug dose does not produce any additional response.

⇒ Theoretically, it should happen when all the receptors get occupied by the drug

⇒ Normally, drugs can produce the maximal response when even less than 100% of receptors are occupied

∴ the remaining unoccupied receptors are just serving as receptor reserve & are called spare receptors.

Denervation Supersensitivity of Receptors:

→ in denervated muscle, new receptors are synthesized [up-regulation]

→ similar proliferation of receptors is seen in case of prolonged blockade by any antagonist.

→ These receptors show supersensitivity to even small amounts of neurotransmitter.

eg:- Pharmacological basis of tardive dyskinesia (excessive involuntary oro-buccal-lingual motions; a side effect of neuroleptics after prolonged use) is explained by the supersensitivity of dopamine receptors.

Receptor - Related Diseases:

- Myasthenia gravis: Antibodies developed against cholinergic - nicotinic receptors at motor end plate
- some forms of insulin - resistant diabetes: antibodies developed against insulin receptors.
- testicular feminisation (male pseudohermaphroditism): due to androgen receptor insensitivity
- familial hypercholesterolemia: due to decrease in receptors for LDL.

II] Non - Receptor Mediated Mechanisms: not all drugs are mediated by receptors.

① By Chemical Action:

Neutralization: - antacids act by neutralizing gastric hyperacidity

- anticoagulant action of heparin (strongly acidic mucopolysaccharide) is by neutralising basic groups of various clotting factors & thus, prevents the action of thrombin

Chelation: some drugs (chelating agents) trap heavy metals in their ring structure & form water-soluble complexes which are finally excreted.

- EDTA $[Ca^{2+}]$
- Calcium disodium edetate $[Pb^{+2}]$
- dimercaprol $[Hg^{+2}]$
- penicillamine $[Cu^{2+}]$
- desferoxamine [iron]

∴ all these drugs are used to treat heavy metal poisoning.

Ion exchangers: anion exchange resin like cholecystyramine exchanges Cl^- ions from the bile salts ⟹ resulting complex is not absorbed & is excreted out

∴ this drug is used as a cholesterol lowering agent.

② By Physical Action:

Osmosis: magnesium sulfate acts as a purgative by exerting osmotic effect within the lumen of the intestine

- mannitol acts nonspecifically by changing the osmolarity in nephron directly.

Adsorption: Kaolin adsorbs bacterial toxins & acts as an antidiarrhoeal agent.

- methyl polysiloxane & simethicone adsorb gases & are used as antiflatulent.

Protectives: various dusting powders to provide local effects

Demulcents: drugs coat the inflamed mucous membrane & provide a soothing effect

- pectin (in antidiarrhoeal preparations)
- menthol & syrup vasaka (in cough tinctus)

Astringents: they precipitate & denaturate mucosal proteins & ∴ protect the mucosa by firming up the mucosal surface

- tannic acid in gum paint

Saturation in the Biophase: general anaesthetics simply saturate the cellular sites of CNS

③ By Counterfeit / False Incorporation Mechanisms:

- sulfa drugs
- antineoplastic drugs (like methotrexate)

→ bacteria synthesize their own folic acid from PABA, for their growth & development

→ sulfa drugs resemble PABA in chemical configuration & ∴ falsely enter into the process of synthesis in place of PABA.

∴ the folic acid derivative formed has a sulfa drug moiety in place of PABA & is thus, nonfunctional & has no utility in bacterial growth & development.

→ methotrexate resembles folic acid & irreversibly binds to dihydrofolate reductase enzyme which is responsible for folic acid synthesis ∴ production of active form of folic acid (folinic acid) is prevented leading to death of cells.

④ By Virtue of Being Protoplasmic Poisons: — germicides & antiseptics like phenol & formaldehyde

→ act as protoplasmic poisons causing the death of bacteria.

⑤ Through Formation of Antibodies: by inducing the formation of antibodies & thus, stimulate the defense mechanisms of the body

- vaccines against small pox & cholera
- antisera against tetanus & antidiptheria.

⑥ Through Placebo Action: placebo is a pharmacologically inert & harmless substance which is sometimes given to the patient in dosage form which resembles the actual medicament in size, shape, colour, smell, weight.

→ If the physician commands a good confidence of the patient, even the placebo given by him to his patient can bring dramatic relief in subjective symptoms associated with his psychological problems

eg: - starch or lactose

⑦ By Targeting Specific Genetic Changes:

- Inhibitors of ras - modifying - enzyme farnesyl transferase that reverses the malignant transformation in cancer cells containing the ras oncogene
- inhibitors of specific tyrosine kinase that block the activity of oncogenic kinases.

Adverse Drug Reactions (ADRs): Besides producing the desirable/beneficial effects, drugs also cause undesirable adverse effects.

→ aim of pharmacotherapy is to provide maximum benefits with minimal risk

① Expected Undesirable Effect [Type - A ADR] (Augmented Effects):

→ largely predictable, dose-dependent adverse effects

→ incidence rate is high

→ mortality rate is low

→ reduction in dose can minimise these adverse effects.

(i) Side Effects:

→ undesirable effects which are observed even with the therapeutic dose of the drug & are usually mild & manageable

eg: - dicyclomine (anticholinergic drug) relieves pain of intestinal colic due to its antispasmodic action ⇒ DESIRABLE EFFECT ; side-by-side it also causes dryness of mouth ⇒ SIDE EFFECT

- promethazine (antihistaminic drug) has antiallergic action (desirable) but it also produces sedation ⇒ side effect

→ To minimize the symptoms of side effects ⇒ properly adjust the dose or use countermeasures.

(ii) Secondary Effects: indirect consequences of the main pharmacodynamic action of the drug

- Development of superinfection after suppression of bacterial flora by antibiotics & weakening of host defenses after use of corticosteroids

(iii) **Toxicity:** exaggerated form of side effects which occur predictably either due to overdose or after prolonged use of the drug.

eg: – bleeding due to high doses of heparin
- coma due to high doses of barbiturates
- crystaluria or glomerular nephritis due to precipitation of sulfonamides in acidic urine
- nephrotoxicity due to gentamicin in cases having renal insufficiency.
- delirium, hyperpyrexia, hallucinations with overdoses of atropine (atropine poisoning)

(2) Unexpected Undesirable Effects [Type – B ADR] (Bizarre Effects):

→ arise unexpectedly even when the drug is in therapeutic doses
→ occurs by a mechanism unrelated to the main pharmacological effect of the drug.
→ relatively uncommon
→ mortality rates are high
→ reduction in dose does not reduce the risk

(i) **Drug Allergy (Hypersensitivity Rx):** allergic responses to the drug occur when there has been previous exposure to the drug / its metabolites & when this sensitized individual is re-exposed to the same drug.
→ first exposure is uneventful; specific antibodies are formed against this antigen which keep on circulating
→ on re-exposure, there is Ag–ab reaction which results in the release of chemical mediators of allergy (histamine, serotonin, leukotrienes, etc.)
→ effects like urticaria, rhinitis, pruritus, asthma, anaphylactic shock.

- **CROSS ALLERGY**: allergic reactions within the members of the same group of drugs is most common.

(ii) **Genetically Determined Abnormal Responses of A Drug**: variations due to single mutant gene (genetic polymorphism) show quantitative differences in drug response.

(iii) **Idiosyncratic Drug Responses**: harmful (sometimes fatal) reaction due to unexplained causes.

eg:
- condition of malignant hyperpyrexia, a dangerous idiosyncratic reaction to drugs like halothane, succinylcholine & neuroleptic drugs (like chlorpromazine & haloperidol)
- occurrence of aplastic anemia with a single dose or with low dosage of chloramphenicol is in approximately 1: 50,000 patients.
- Aspirin-induced late-onset asthma or chronic renal failure & thiazide diuretics induced erectile impotence.

(3) **Type C [Chronic Effects]**: adverse effects that are associated with prolonged use of drug.
- orofacial dyskinesia after prolonged use of phenothiazine neuroleptics
- Cushing syndrome after chronic use of prednisolone
- analgesic nephropathy with aspirin
- colonic dysfunctions after prolonged use of laxatives.

④ Type D (Delayed Effects) ADR :

→ delayed adverse effects occurring in patients years after the treatment or effects appearing in children who did not receive that treatment.

eg: - secondary cancers in patients treated with alkylating agents for Hodgkin's disease
- clear cell carcinoma of vagina in daughters of women who took diethyl stilbestrol during pregnancy.
- teratogenic effects

⑤ Type E (End of Treatment Effects) ADR :

→ occurs when a drug is suddenly discontinued
- rebound hypertension after abrupt withdrawal of propranolol (β-adrenoceptor blocker)
- withdrawal seizures after suddenly stopping phenytoin (antiepilectic drug)
- adrenocortical insufficiency after sudden stopping of prednisolone (a glucocorticoid)

⑥ Type F (Failure of a drug to produce the desired effect) ADR :

→ sometimes, administration of a drug does not produce therapeutic effect due to genetic variability (polymorphism)

→ ADRs are the most common cause of iatrogenic diseases (diseases induced by drug therapy); iatrogenic disease may persist even after the offending drug has been withdrawn.
- reserpine leads to endogenous depression
- glucocorticoids precipitate diabetes & hypertension
- aspirin causes peptic ulcer
- chlorpromazine produces parkinsonism
- hydralazine causes SLE.

Specific Toxicity of Some Particular Drugs:

→ toxic effects of drugs can be:

- related to their principal pharmacological action (or)

  eg: - hypoglycaemic coma with insulin
  - bleeding with anticoagulant drugs
  - arrhythmias with cardiac glycosides

- unrelated to their principal pharmacological action.

Quantitative Aspects of Drug Effects:

→ degree of effect produced by a drug depends on the quantity of drug administered (dose)

Dose: (aka therapeutic dose) required amount of drug in weight, volume, moles or International Units (IU), that is necessary to provide a desired effect.

① **Single Dose:**

eg: - single oral dose of albendazole (400 mg) is sufficient to eradicate roundworms
- single I.M. dose of 250 mg of ceftriaxone can be given to treat gonorrhoea.

② **Daily Dose:** quantity of drug to be administered in 24 hr, either all at once or in equally divided doses.

eg: - 10 mg daily dose (all at once) of cetrizine : Allergy
- erythromycin (1g/day) to be given in 4 equally doses of 250mg every 6hr as an antibiotic

③ **Total Dose:** maximum quantity of the drug that is needed during the complete course of therapy

- procaine penicillin-G ⇒ 6 million units : Early Syphilis
  [0.6 million units per day for 10 days]

④ **Loading / Priming Dose:**

→ large dose of the drug to be given initially to provide the effective plasma conc. rapidly

⑤ **Maintenance Dose:** loading dose is normally followed by a maintenance dose which is usually half of the loading dose.

→ it is needed to maintain the steady plasma conc. attained after administration of loading dose.

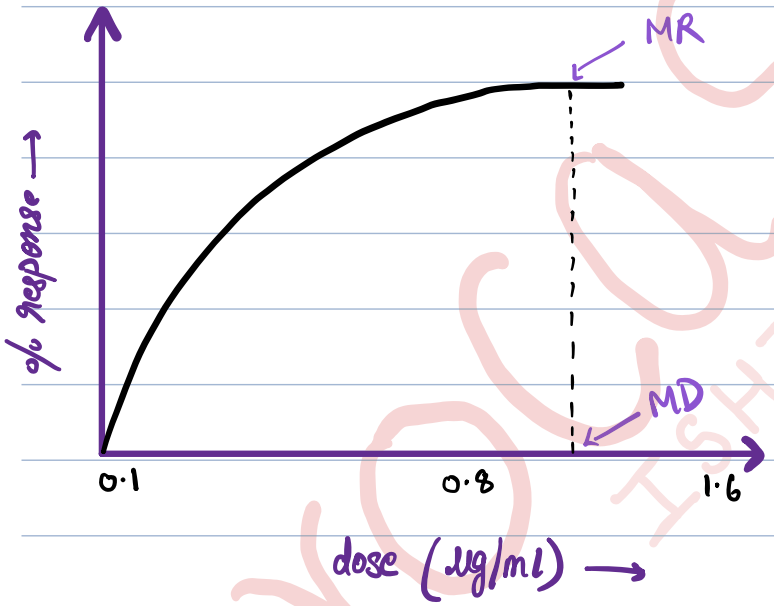
- Dose - plasma conc. curve
- Time - plasma conc. curve
- Graded Dose-Response Curve: relationship b/w different doses & their relative response.
- Quantal Dose-Response Curve: eliminates response either by quantifying it or by prefixing its criteria on "all or none".

Graded Dose-Response Curve:

→ as the dose increases, magnitude of response also increases until a stage where there is no further increase in response on increasing the dose

- This response ⇒ Maximal / Ceiling Response [MR]
- This Dose ⇒ Maximal / Ceiling Dose [MD]

hyperbola



Limitations:

→ initial portion of the curve is so steep that it is impossible to gauge the magnitude of ↑ in response corresponding to small ↑ in dose.

→ closer to MR, large ↑ in dose produces very small changes in response (too small to be evaluated with accuracy.)

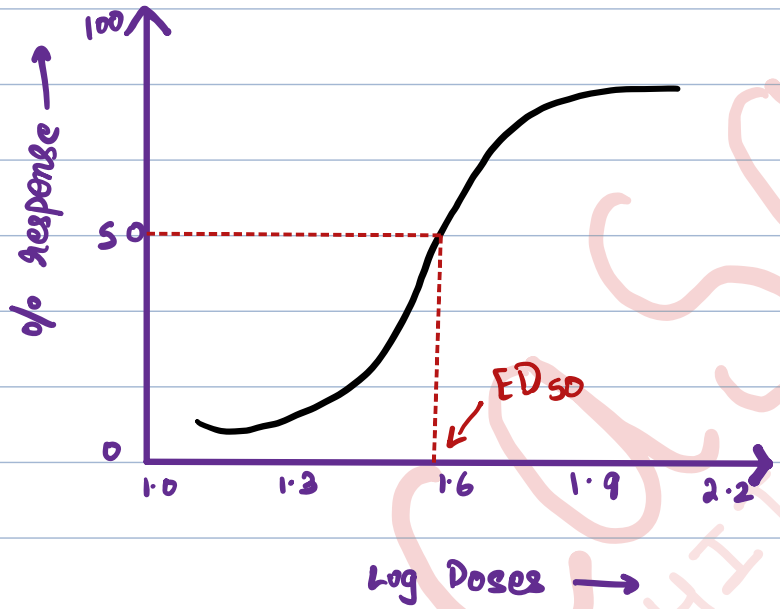
Log Dose - Response Curves: (LDR)

→ each selected dose (0.1, 0.2, 0.4, 0.8, 1.6 µg/ml ....) is double of its preceding dose ⇒ interval on log-scale is constant = 0.3

$$\left\{ \begin{array}{l} \because \log a = b \\ \log(2a) = b + 0.3 . \end{array} \right\}$$

→ sigmoid curve (S-shaped) ; middle portion of the curve is almost linear

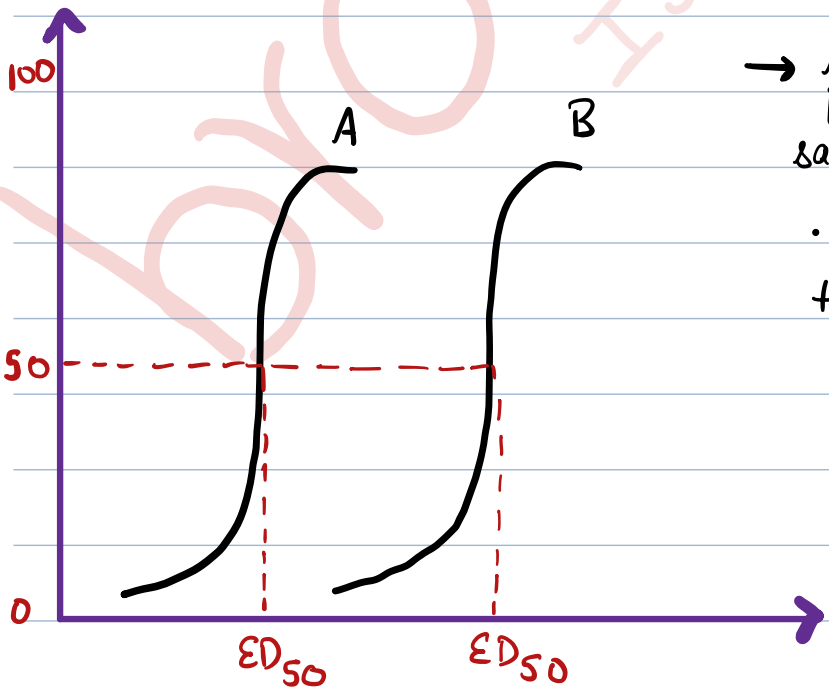
→ Top most portion of curve = MR



→ from the middle portion of the curve (linear segment), ED_{50} can be found out for the given drug

ED_{50} : effective dose which can provide 50% of MR.

Smaller ED_{50} ⇒ more potency of drug.



→ frequently, two drugs produce the same effect by the same mechanism. ∴ curves of both drugs run parallel to each other & among them, the curve of the less potent drug would be located on the right side.

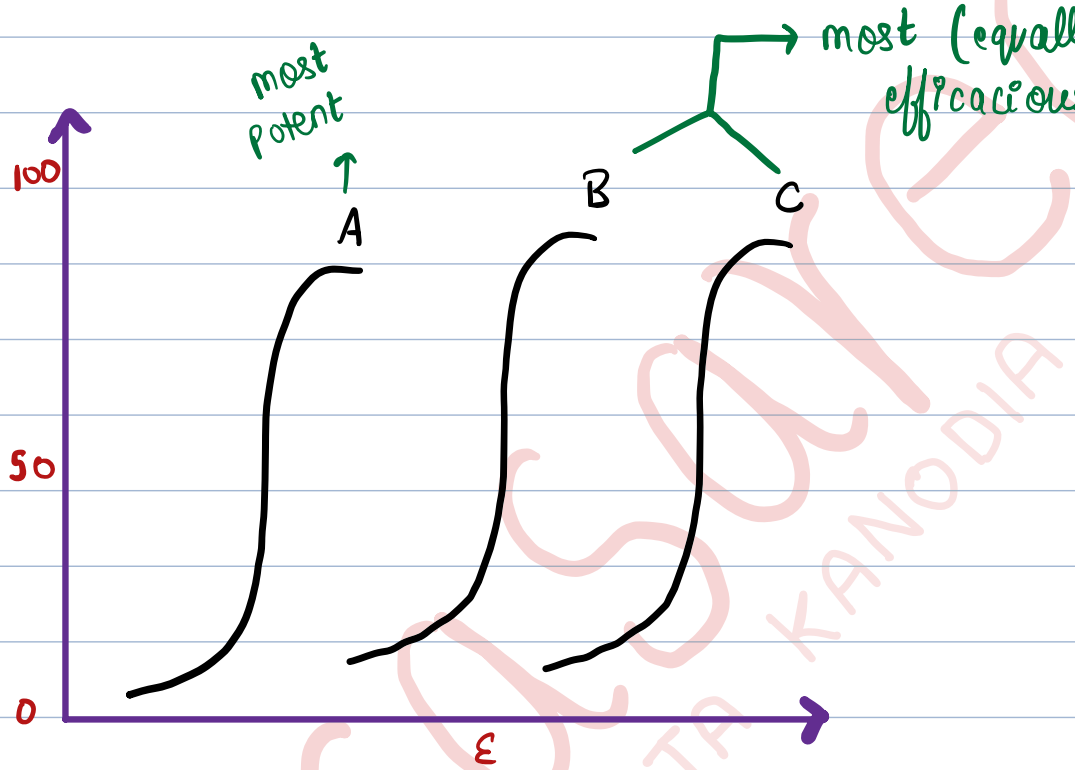
∴ potency of A > B.

→ LDR also helps differentiate between relative potency & relative efficacy.

Potency: dose of drug required to produce a standard effect.

- closer the LDR to ordinate ⇒ smaller dose required ⇒ greater potency

Efficacy: maximal response as reflected by the height of the curve on its ordinate.

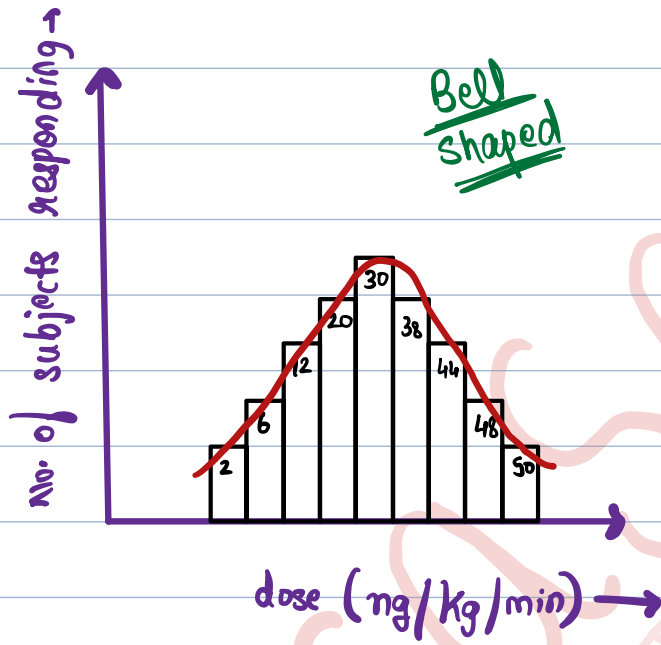


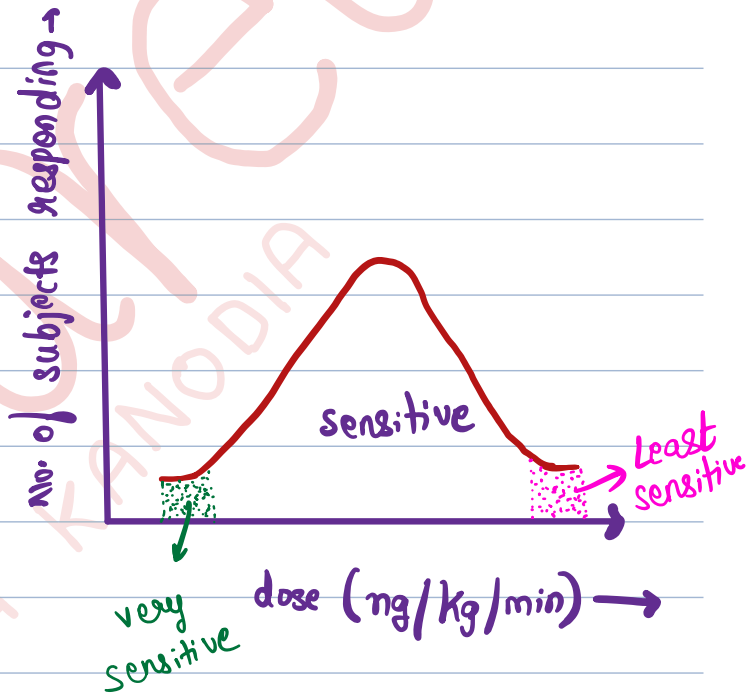
Quantal Dose - Response Curve :

→ eliminates response either by quantifying it or by prefixing its criteria on "all or none".

Frequency: number of subjects exhibiting the 'stated / prefixed response' to a certain dose of the drug

→ an individual can range from very sensitive to sensitive to least sensitive.

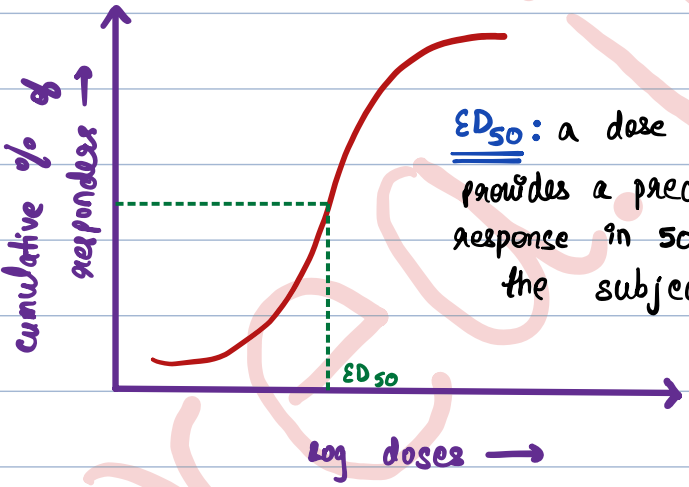




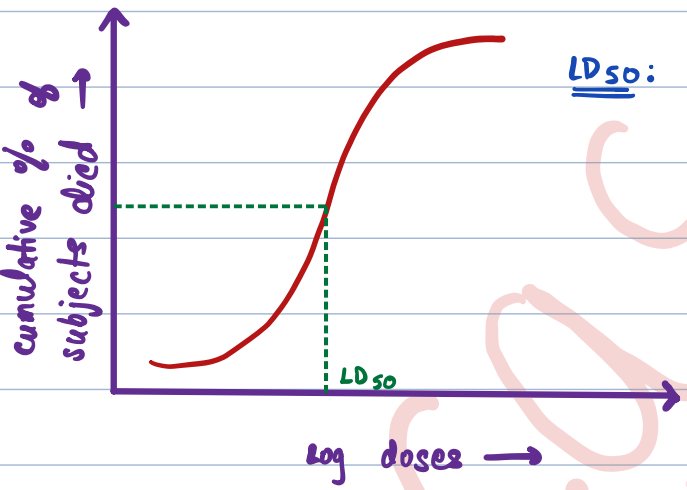
→ maximum no. of responders are found in the middle portion of the dose range

Limitations: one cannot collect data like ED_{50} or LD_{50} from the curve

Summation of Frequency Histogram: graph of log doses vs. cumulative percentage of responders.



ED_{50}: a dose which provides a predetermined response in 50% of the subjects



LD_{50}: a dose which is lethal to 50% of the subjects

Therapeutic Index (Margin of Safety):

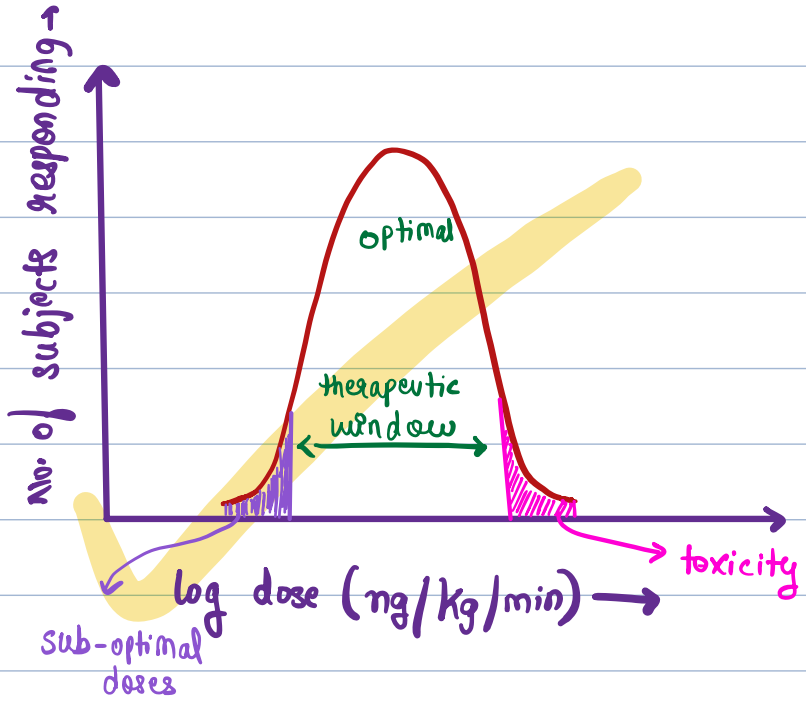
$$\text{Therapeutic Index (TI)} = \frac{LD_{50}}{ED_{50}}$$

[For a safe drug, TI ≥ 1]

Certain Safety Factor (CSF): better parameter to assess drug safety

$$CSF = \frac{LD_1}{ED_{99}}.$$

Therapeutic Window: In between toxicity & sub-optimal doses, there is an optimal therapeutic range of plasma conc. at which most of the patients experience desired effects; this range is called therapeutic window.



Dosage: "method of dosing"

- dosage form & amount of drug to be administered at one time
- route of administration
- interval between doses
- duration for which the drug administration is to be continued.

Factors Affecting Drug Response:

① Age, Body Weight, Body Surface Area:

→ average adult dose is calculated on the basis of quantity of drug that will produce a desired effect in – 50% population

- between 18 to 65 years of age
- weighing about 70 kg (or 150 lb).

Formulae for Calculating Child Doses:

- **Young's Formula:** (for children upto 12 years of age)

$$\text{Child's Dose} = \frac{\text{Age in years}}{\text{Age} + 12} \times \text{adult dose.}$$

- **Dilling's Formula:** (makes an assumption that a 20 y/o must receive an adult dose)

$$\text{Child's Dose} = \frac{\text{Age in years}}{20} \times \text{Adult dose}$$

- **Clark's formula:** (average adult weighs 70 kg or 150 lb)

$$\text{Child's Dose} = \frac{\text{wt. of child (lb)}}{150} \times \text{Adult dose}$$

→ for children, body surface area (BSA) is a more precise index for dose adjustment.

- $\text{Child's Dose} = \frac{\text{BSA } (m^2)}{1.8} \times \text{Adult dose}$ (average adult weighing 70kg has BSA = $1.8\ m^2$)

- $(1.5 \times \text{wt in kg}) + 10 = \%$ of adult dose to be given to the child

→ medicaments for topical use, doses of antisera, etc. are not governed by these rules.

② **Sex:**

- morphine & barbiturates may produce excitation prior to sedation in women.
- ephedrine may produce more excitation & tremors in women than in men.
- Clonidine, α-methyl dopa, β-blockers, diuretics, Ketoconazole ⇒ can cause loss of libido only in men.

③ **Environment & Time of Drug Administration:**

- slightly higher doses of sedative hypnotics are needed to induce sleep in day light than at night.
- glucocorticoids taken as single morning dose, minimise the risk of pituitary – adrenal suppression which is a serious hazard of long-term steroid therapy.

④ **PLACEBO:** response to administration of pharmacologically inert material called PLACEBO

- PLACEBO (I will please) ⇒ relieves symptoms of illness by creating expectations for the good
- NOCEBO (I will harm) ⇒ harms by creating a panic or fear for nothing

(Nocebo reactors ⇒ pessimistic persons whose symptoms of illness do not respond to medication)

⑤ Genetic Factors & Idiosyncrasies

⑥ Metabolic Disturbances & Pathological State:

- low acidity decreases iron (Fe^{2+}) absorption & results in a decreased response to iron therapy ; it also decreases aspirin absorption by favouring its ionization
- bioavailability of drugs having first-pass metabolism is increased in patients with liver diseases
- in patient with impaired renal functions, drugs like streptomycin, gentamycin, Kanamycin may accumulate to toxic levels causing nephrotoxicity & ototoxicity as these are not adequately excreted by kidneys
- patients with hyperthyroidism are very sensitive to sympathomimetics & are relatively resistant to digitalis or morphine.
  patients with hypothyroidism respond to sympathomimetics in the opposite manner
- drugs given orally in diarrhoea & vomiting may prove to be ineffective.

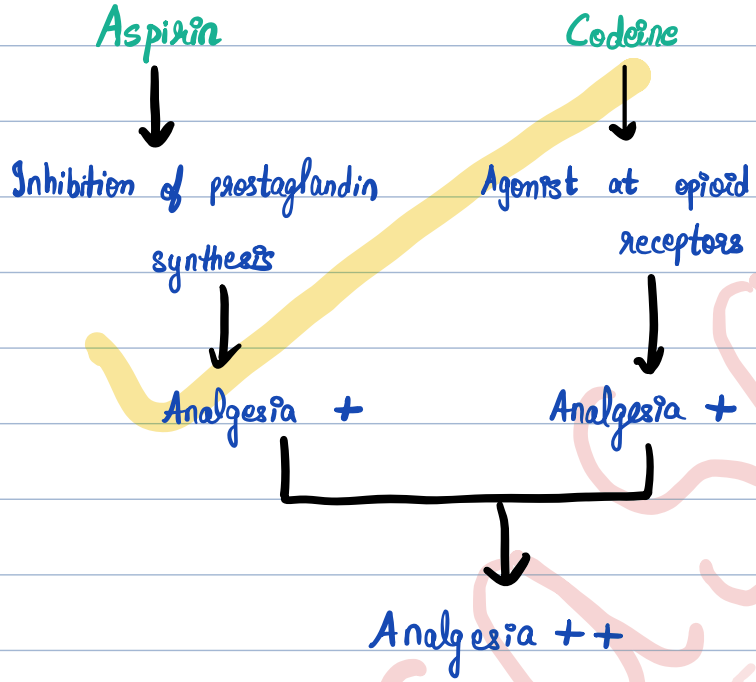
⑦ Route & Frequency of Drug Administration: route of administration governs the speed & intensity of drug response

- Magnesium sulphate
  - causes purgation (orally)
  - reduces swelling (on local application)
  - causes CNS depression & hypotension (i.v.)

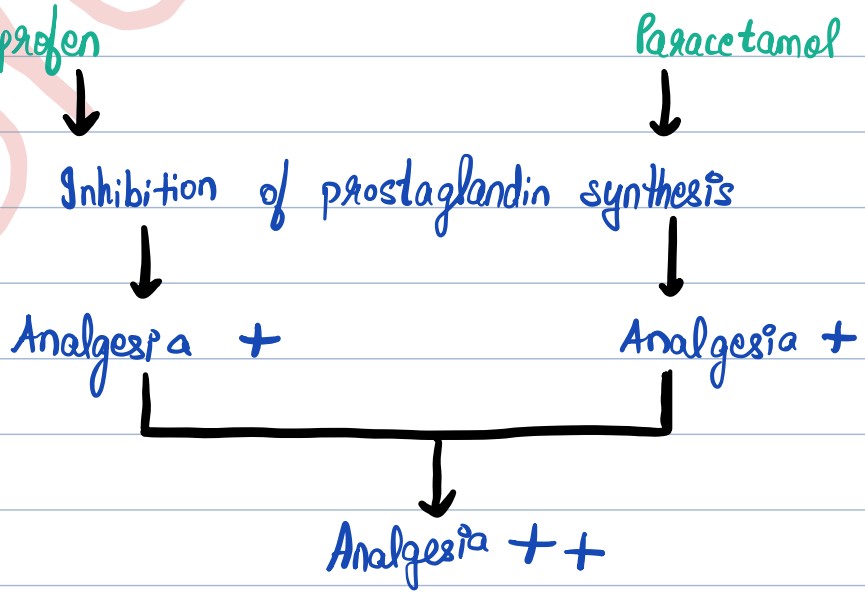
- **Oxytocin**
  - infused slowly i.v. for induction of labour
  - given i.m. to check postpartum haemorrhage
  - intranasal spray for let-down of milk from engorged breasts.

Modified Drug Effects After Concurrent Administration of Two Different Drugs:

① **Summation:** when 2 drugs elicit the same response, but with different mechanism, & their combined effect is equal to the algebraic sum of their individual effects.



② **Additive Effects:** combined effect of 2 drugs acting by the same mechanism is equal to that expected by simple addition.



③ **Synergism:** combined effect of 2 drugs is greater than the algebraic sum of their individual effects

→ net outcome is — potentiation or prolongation of effects.

→ occurs when 2 drugs act at different sites or when one drug alters the pharmacokinetics of the other drug

eg: · sulfamethoxazole → bacteriostatic

· trimethoprim → bacteriostatic

sulfamethoxazole + trimethoprim = cotrimoxazole → bactericidal

↙ inhibits folic acid synthesis in bacteria by competing with PABA for the enzyme dihydropteroic acid synthetase

↘ sequentially blocks folic acid synthesis by inhibiting dihydrofolate reductase.

- synergistic action of: antihypertensive drugs (eg: β-blockers) + diuretics (frusemide)

- Levodopa + carbidopa ⇒ treatment of parkinsonism

↳ prevents peripheral metabolic degradation of levodopa, thus, favouring greater amounts of levodopa to reach the brain.

④ **Drug Antagonism:** when the combined effect of 2 drugs is less than the sum of the effects of the individual drugs

- Chemical Antagonism
- Physiological / Functional Antagonism
- Pharmacological Antagonism
  - Competitive Antagonists
    - Reversibly competitive
    - Irreversibly competitive
    - Pseudo-irreversibly competetive
  - Non-competitive Antagonists
    - Those which interfere with down-stream events after receptor activation by the agonist
    - Those which act on the allosteric site instead of competing with the agonist binding site of the receptor

Chemical Antagonism: when the drug acts merely as chemical antidotes to each other

- anticoagulant (-vely charged) action of heparin is antagonized by protamine (+vely charged protein)
- neutralization of gastric acid by antacids like aluminium hydroxide, magnesium hydroxide or sodium bicarbonate.

- chelating action of drugs (like BAL or calcium sodium edetate) which form inactive soluble complexes with heavy metals like arsenic or lead.

Physiological / Functional Antagonism: when 2 antagonists, acting at different receptors, counterbalance each other by producing opposite effects on the same physiological system.

- CNS stimulants antagonize CNS depressants
- effect of histamine (vasodilator) on BP can be cancelled out by norepinephrine (vasoconstrictor)

Pharmacological Antagonism: antagonist either competes with the agonist for its binding sites on receptor [COMPETITIVE ANTAGONISM] or may antagonise the effects of agonist by acting at a site different from the agonist receptor site [NON-COMPETITIVE ANTAGONISM]

Competetive Antagonism [CA]: antagonists combine & competes with the same receptor sites as does the agonist but has no intrinsic activity.

Reversible / Equilibrium CA: antagonist binds reversibly (by forming weak bonds) to the same receptor sites as that of agonist

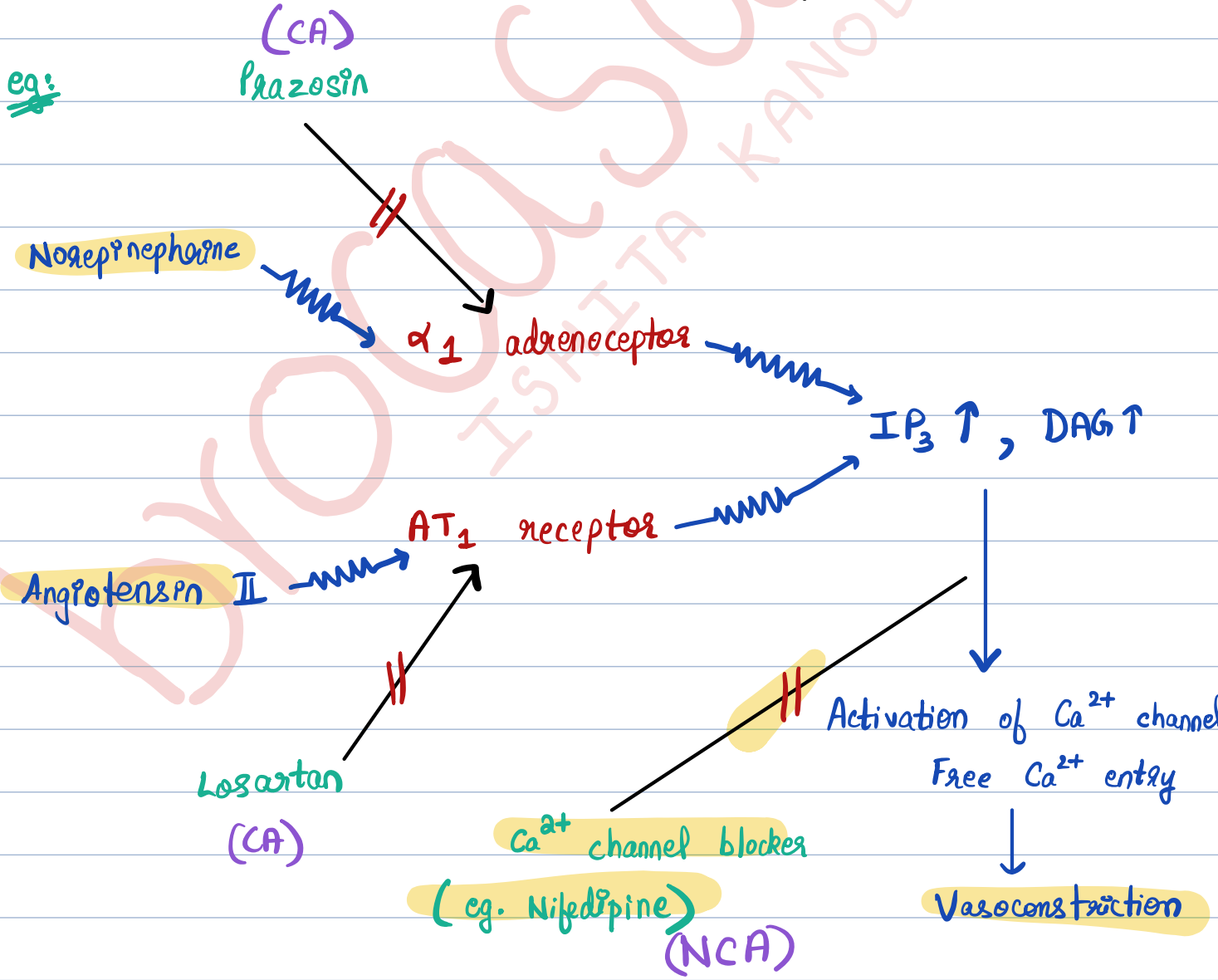
- Atropine (antagonist) inhibits Ach or bethanechol (agonists) at various muscarinic receptors
- Naloxone (antagonist) inhibits morphine (agonist) at different opioid receptors
- Propranolol (antagonist) inhibits norepinephrine (agonist) at β_1 adrenoceptor.

Irreversible / Non-equilibrium CA: antagonist binds irreversibly (by forming a stable covalent bond) to agonist receptor site

- dibenamine (antagonist) inhibits norepinephrine (agonist) at β_1 adrenoceptor.

Pseudo-reversible CA: In few cases, classical irreversible antagonism, may not be that obvious
→ happens due to a lesser degree of receptor occupancy by the antagonist
∴ increasing conc. of agonist (in presence of such a antagonist) will initially shift the LDR curves to the right showing maximal response; but eventually if the conc. of this antagonist is increased, there will be reduction in maximal response

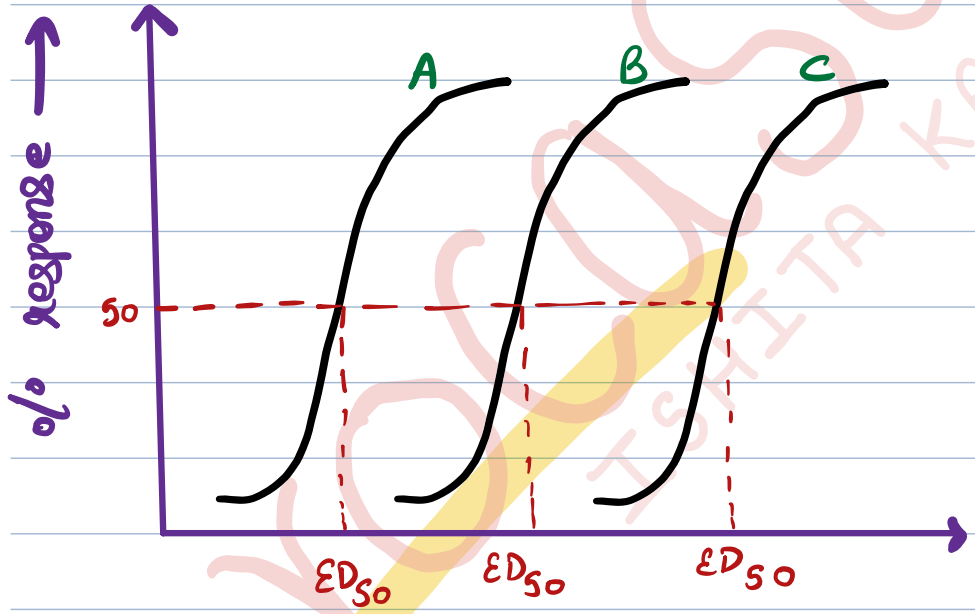
Non-Competitive Antagonism (NCA):
- antagonist may interfere with the down-stream events after receptor activation by agonist
- drug may antagonise the effects of agonist by acting at an allosteric site of the receptor beyond the agonist-receptor site.



Allosteric NCA: allosteric receptor antagonists bind to receptor at a site other than agonist site. (This site is called allosteric site)

→ they prevent activation of receptor by the agonist.

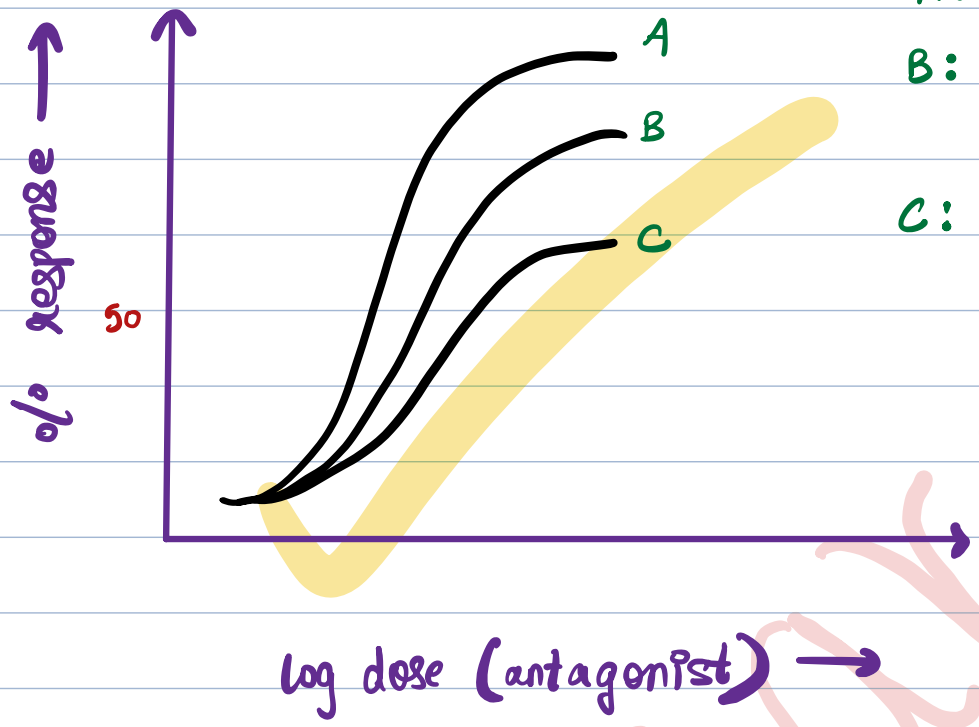
- Flumazenil (by binding to benzodiapene site) antagonises the effect of benzodiazepines by preventing the binding of GABA to $GABA_A$ receptor.
- Bicuculline which is a CA of binding of GABA to its receptor sites, indirectly blocks the effects of benzodiazepines (BZDs) like diazepam non-competitively; because BZDs facilitate GABA-ergic activity by binding at the modulatory site of GABA receptor.



A = LDR curve for agonist alone

B = LDR curve for agonist + CA

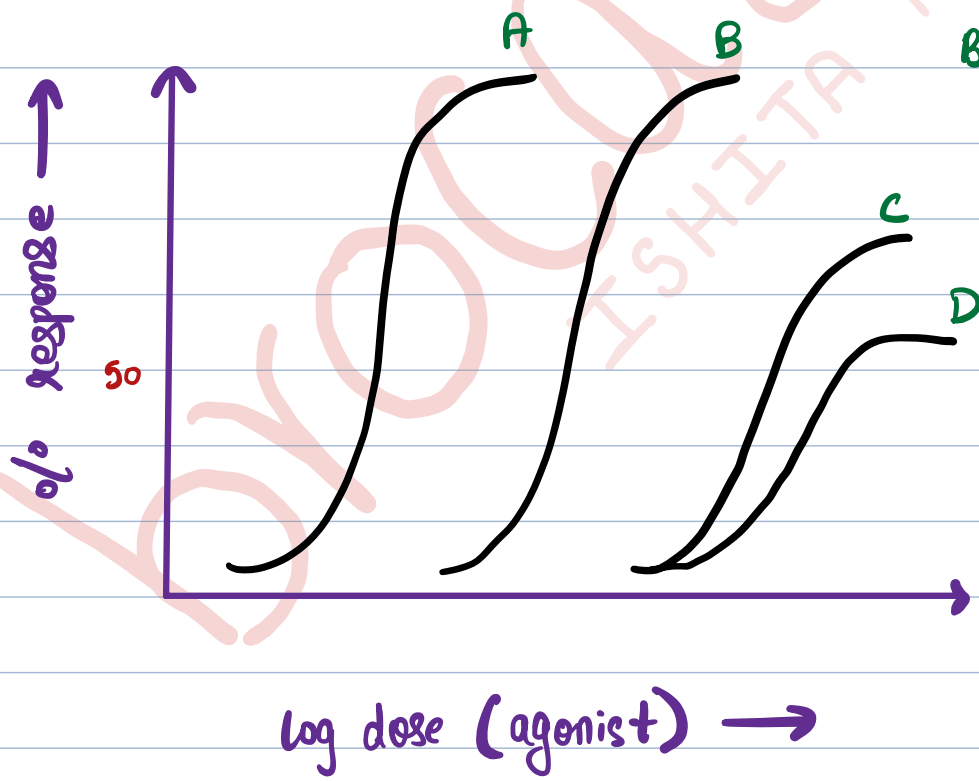
C = LDR curve for agonist + increasing conc. of CA



A: LDR curve of agonist alone

B: LDR curve for agonist + irreversible CA

C: LDR curve for agonist + increasing conc. of irreversible CA.



A: LDR curve for agonist alone

B: LDR curve for agonist + pseudoreversible CA

C & D: LDR curve for agonist + increasing conc. of pseudoreversible CA.

DRUG DISCOVERY	PRECLINICAL PHASE	CLINICAL TRIAL PHASE			REGULATORY PHASE	RESTRICTED MARKETING
• compound centered or target centered approach ↓ Lead finding ↓ Lead optimisation ↓ LEAD COMPOUND	• Pharmacokinetics • Pharmacodynamics • Toxicology • Safety Index	**Phase I** • Non-blind open trials: 25 - 100 subjects	**phase II** Early phase II : upto 200 subjects Late phase II : 200 - 400 subjects	**phase III** • Large scale multi-centered trials • 1000 - 5000 subjects	Submission of new drug application (NDA) for obtaining License to market the drug in the country	• Post-marketing surveilance
2-5 yrs	1.5 - 2 yrs	5 - 7 yrs			1.5 yrs	Upto 4 yrs

FREE MARKETING OF DRUG

Orphan Drugs: Sometimes a drug is not developed into a usable medicine because the cost incurred will not be recovered by the developer.

∴ the free market economy is liable to leave some rare disease as untreated

→ this disease ⇒ Orphan disease

this drug ⇒ Orphan drug

patient suffering ⇒ Orphan patient.

Orphan Drug	Orphan Disease
Acetyl cysteine	for paracetamol overdose toxicity
Miltefosine	Kala azar
Anagrelide	Polycythemia vera
Antithrombin III	Hereditary antithrombin III deficiency
Arginine butyrate	Sickle cell Disease, β-thalassemia
Atovaquone	AIDS associated pneumocystis carinii pneumonia
Betaine	Homocysteinuria
2-chlorodeoxy adenosine	Acute myeloid leukaemia
Fomepizole	Methyl alcohol poisoning
Erythropoietin	Anemia of end-stage renal disease & anemia associated with cancers
Factor XIII	Congenital Factor XIII deficiency
Relaxin	Progressive systemic sclerosis
Denileukin diftitox	Cutaneou T-cell lymphoma refractory to other drugs

Pharmacovigilance: (as defined by WHO) ⇒ science & activities relating to Detection, Assessment, Understanding & Prevention (DAUP) of adverse effects or any other drug-related problems & generally refers to continuous monitoring of unwanted effects & other safety related aspects of marketed drugs.

→ post-marketing surveillance (PMS) or Post-approval surveillance studies (PASS)

→ During the first 4 years of marketing a new drug, the manufacturers has to submit the Periodic Safety Update Reports (PSURs) every six months for the first 2 years & then once annually for the next 2 years.

Pharmacovigilance Programme of India (PvPI):

→ year 2010

→ Ministry of Health & Family Welfare (MoHFW) in collaboration with:

- Central Drugs Standard Control Organisation (CDSCO)
- Indian Pharmacopoeia Commission (IPC)

Objectives of PvPI:

① to monitor ADRs in Indian population

② create awareness amongst health professionals about the importance of ADR reporting

③ monitor benefit-risk profile of medicines approved, marketed & used in the country

④ generate independent evidence-based recommendations on the safety of medicines

⑤ support the CDSCO in formulating safety-related regulatory decisions for medicines.

Essential Medicines:

→ Essential Drugs: those drugs that satisfy healthcare needs of the majority of population & which should thus, be available at all times, in adequate amounts & in appropriate dosage forms.

1975

→ Essential Medicines: (2002) medicines that are supposed to be available for proper functioning of the basic health care system at all times, in adequate amounts, in appropriate dosage forms, with assured quality, with adequate information & at a price the individual & community can afford.

Latest: 20th model of "Essential Medicines List (EML)" in 2017.

→ In India, National List of Essential Drugs ⇒ revised in 2003, 2011, 2015.

Rational Use of Drugs:

- right drug
- right patient
- right dosage
- right cost
- right documentation
- should fulfill SANE criteria - Safety, Affordability, Need, Efficacy of the drug should always be considered before prescribing to the patient.

P-drugs: preferred / personal drug to treat a particular disease

Criteria for Selection of a P-drug:

1. Define the diagnosis ⇒ pathogenesis
2. Specify the therapeutic objective ⇒ immediate requirement
3. Make a list of effective group of drugs
4. Choose the effective group of drugs

Efficacy Safety Suitability Cost

- Group A
- Group B
- Group C

5. Choose a P-drug from this chosen group

Efficacy Safety Suitability Cost

- Drug 1
- Drug 2
- Drug 3

6. Finalise the drug, dosage form, dose schedule & duration of treatment
7. Monitor the treatment through follow-ups.

① Define the Diagnosis :

Ex: "Stable Angina Pectoris" caused by a partial occlusion of the coronary arteries

② Specify Therapeutic Objective : Immediate requirement : provide quick relief from pain

→ this can be achieved by :

- increasing oxygen supply ⇒ difficult due to arteriosclerotic occlusion in coronary artery (✗)
- reducing oxygen demand of cardiac muscle (✓)

  can be achieved by – decreasing preload
  – decreasing contractility
  – decreasing heart rate
  – decreasing the afterload of cardiac muscle

③ Make a List of Effective Group of Drugs :

- nitrates
- β-blockers
- calcium channel blockers

④ Choose the effective group of drugs : (SE = side effects)

	Efficacy	Safety	Suitability	Cost
Nitrates	(sublingual) +	lesser SE	better due to sublingual administration	inexpensive
β-blockers	(inj.) +	–	–	–
Ca channel blockers	(inj.) +	–	–	–

⑤ Choose a P-drug from this chosen group :

	Efficacy	Safety	Suitability	Cost
• Nitroglycerin	✓	✓	✓	cheapest (+++)
• Isosorbide mononitrate	✓	✓	✓	(+)
• Isosorbide dinitrate	✓	✓	✓	(++)

↳ available as sublingual tablets with rapid effect

∴ P-drug : nitroglycerin (glyceryl trinitrate)

Alternative : isosorbide dinitrate.