

24/9/24

SOURCES OF DRUGS

Main sources of drugs are classified into (i) Natural
(2) Semisynthetic
(3) Synthetic
(4) Biotechnology based.

1. Natural → plants, animals, microbes, minerals.
2. Semisynthetic → produced in laboratory by modification of materials found in nature
3. Synthetic → molecules created in the laboratory
4. Biotechnology → produced through recombinant DNA technology.

1) Natural sources

a) Plants.

Chemically, active ingredients of plant fall in several categories.

* Alkaloids - eg: morphine, atropine

* Glycosides - eg cardiac glycosides.

* Oils [edipoxin, ouabain]
Fixed (non volatile oils) - eg: groundnut oil.
Essential (volatile oils) - eg: eucalyptus oil

* Other plant products like tannin are astringent, gums are demulcents
Resins and balsams - antiseptic in cough mixtures.

b) Animals.

* Medicines eg: Adrenaline, thyroxine, insulin.

* Few vaccines & antisera are also produced.

c) Medicines

- * Most antibiotics are obtained from fungi, actinomycetes & bacteria eg. penicillin, gentamicin
- * Enzymes like diastase & streptokinase

d) Minerals

- * Eg: Iron salts, calcium salts etc.

II Semisynthetic Drugs Eg. Amikacin.

III Synthetic Drugs Eg: Aspirin, Paracetamol

IV Biotechnology Eg: Human Insulin, Recombinant Erythropoietin

TOLERANCE

* Refers to the requirement of higher dose of a drug to produce a given response

Types: Natural & Acquired, cross tolerance.

A) Natural species/individuals are inherently less sensitive to the drug. Eg: Rabbits are tolerant to atropine
Some individuals are nonresponsive to antiparkinsonian action of levodopa

B) Acquired: Occurs by repeated use of a drug in an individual who was initially responsive
→ An uninterrupted presence of drug in body favours development of tolerance
→ However significant tolerance does not develop to atropine, digoxin, cocaine, sodium nitroprusside etc.
→ Tolerance may not develop equally to all

actions of a drug, however.

Index of a drug may increase/decrease with prolonged use.

Eg: tolerance to sedative action of chlorpromazine, but not to its antipsychotic action.

c) Cross tolerance. development of tolerance to pharmacologically

Eg: related drugs, consequently therapeutic index of a drug may increase/decrease with prolonged use

Eg: tolerance $\left\{ \begin{array}{l} \rightarrow \text{Pharmacokinetic / drug deposition tolerance eg: barbiturates} \\ \rightarrow \text{Pharmacodynamic / cellular tolerance eg: morphine.} \end{array} \right.$

TAUYPHYLAXIS.

Refers to rapid development of tolerance when doses of a drug repeated in quick succession result in marked reduction in response.

Seen in inherently acting drugs like nicotine, tyramine.

THERAPEUTIC INDEX

the gap b/w therapeutic effect DRC (Drug response curve) and the adverse effect DRC defines the safety margin or therapeutic index of drug

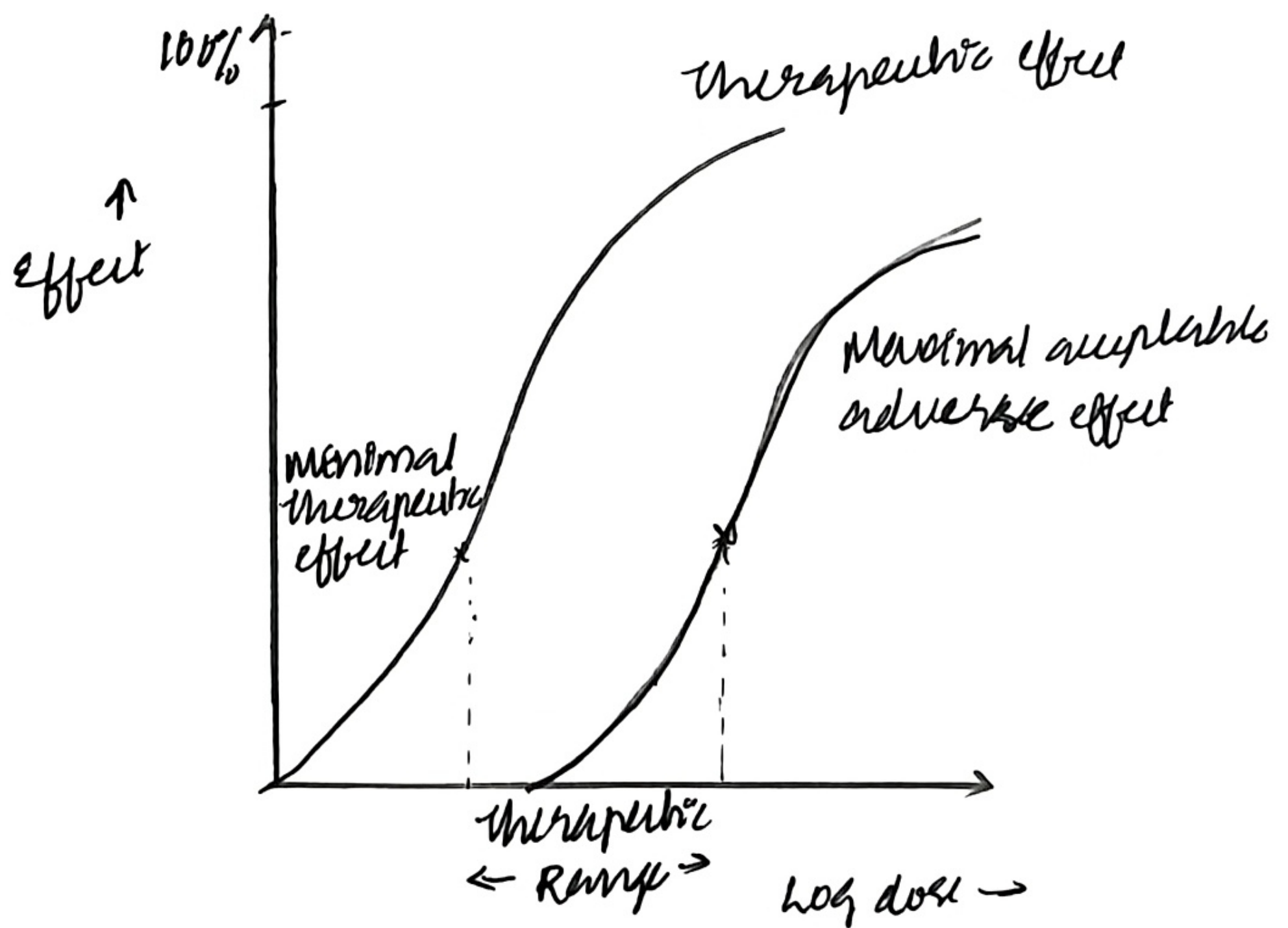
$$\text{Therapeutic Index} = \frac{\text{Median lethal dose or LD}_{50}}{\text{Median effective dose ED}_{50}}$$

Where median lethal dose [LD₅₀] - dose which kills 50% of the recipients.

Median effective dose [ED₅₀] - dose which produces specified effect in 50% individuals

THERAPEUTIC RANGE/WINDOW.

Therapeutic Index is irrelevant in clinical setup, where Therapeutic Range/window is bounded by dose which produces minimal therapeutic effect and dose which produces maximal acceptable adverse effect. However, defining therapeutic range for many drugs is a challenging task because of the individual variability.



Illustrative DRs for therapeutic effect and adverse effect of the same drug.

DRUG POTENCY AND EFFICACY

Drug potency: Amount of drug needed to produce a certain response.

Drug efficacy: Maximal response that can be elicited by the drug. It is a more decisive factor in choice of drug.

Consider the example given below to differentiate b/w potency & ~~efficiency~~ efficacy of different drugs.

- Aspirin is less potent as well as efficacious analgesic than morphine.
- Pethidine is less potent but equally efficacious analgesic as morphine.
- Furosemide is less potent but more efficacious diuretic than metolazone.
- Diazepam is more potent but less efficacious CNS depressant than Pentobarbitone.

RECEPTORS

I G-protein coupled receptors.

- Large family of cell memb receptors which are linked to effector (enzyme/channel/transporter) through 1 or more GTP activated proteins (G proteins) for response effluence.
- The molecule has 7 α helical memb. spanning hydrophobic amino acid segments which run into 3 extracellular & 3 intracellular loops.
eg: Muscarinic receptors [M_1, M_2, M_3], adrenergic receptors ($\alpha_1, \alpha_2, \beta$)

→ there are 3 major effector pathways through which GPCR function: Adenylate cyclase: cAMP pathway, phospholipase C: IP_3 - PKC pathway; channel Regulation.

II ION CHANNEL RECEPTORS/Ligand gated ion channels.

→ Enclosed selective channels (for Na^+/K^+ / Ca^{2+} or Cl^-) within their molecules

→ It is usually a pentameric protein.

→ Agonist binding opens the channels and causes depolarisation/hyperpolarisation or change in cytosolic ion composition, depending on the ion that flows through

eg: Nicotinic cholinergic receptors; glycine (inhibitory AA) etc.

III Transmembrane Enzyme Linked Receptors

→ Utilised primarily by peptide hormones. eg Receptor tyrosine kinases.

→ Made up of large extracellular ligand binding domain, connected through a single transmembrane helical peptide chain to an intracellular subunit having enzymatic property.

→ Their dimerization also promotes receptor internalisation, degradation in lysosomes and downregulation if activation is fast enough.

IV Transmembrane JAK-STAT binding Receptors

- Differs from Receptor tyrosine kinases (RTKs) in not having any intrinsic catalytic domain.
- Agonist-induced dimerisation alters the intracellular domain conformation to increase its affinity for a cytosolic tyrosine protein kinase JAK.
- the bound JAK gets activated and phosphorylates tyrosine residues of receptor, which now bind another free moving protein STAT.
- Pairs of phosphorylated STAT dimerize and translocate to nucleus to regulate gene transcription resulting in biological response. Eg: cytokines (many), growth hormones etc act through this type of Receptor.

II Receptors Regulating Gene Expression.

- there are intracellular soluble proteins that respond to lipid soluble messengers.
- All steroidal hormones, thyroxine, Vit D and Vit A function in this manner.
- this transduction mechanism is slower in its time course of action because adequate quantity of effector proteins will have to be produced before the response occurs.