Pharmacodynamics:
Concern with the mechanism of drug action and the biochemical and physiologic effects of drugs on the body (the response to drug), i.e; ***what drugs do to the body and how they do it.***
e.g., Phentolamine drug act on vascular smooth muscle and block α receptors (***mechanism of action)*** → cause vasodilation and hypotension (***Response*** or drug effect).

How the drugs produce their actions?

In general drugs can produce their effects by;
I- Non – Receptor Interactions (Non Selective)
Drugs with nonspecific mechanisms of action do not interact with receptors
1- Physical interactions;
e.g; mannitol , kaoline (adsorbent),....
2- Chemical interactions
e.g; - Antacids which is an alkaline substance can neutralize gastric acid by chemical reaction.
- Chelating agents (EDTA) can form complex with divalent metals.
II-Drug-targets interactions
Most of drugs exert effects (*both beneficial and harmful*) by interacting (*binding*) to specialized cellular targets as;
• Ion channel.... e.g *lidocaine* block Na channel
• Transporter; .....e.g; fluoxetine inhibit transporters of serotonin
• Enzyme, ...e.g; Allopurinol inhibit *xanthine oxidase*
Aspirin inhibit *cyclooxygenase*
• Receptor,.....e.g; Methacholine. Adrenaline, ...

Receptors: Functional macromolecule present in the membrane or inside the cell and have a specific binding site for a ligand (drug) to produce certain biological effect.
D + R → D-R COMPLEX → RESPONSE

Types of Receptor Families:
1) ligand-gated ion channels
2) G protein–coupled receptors
3) enzyme-linked receptors
4) intracellular receptors.

The degree by which drug bind to the receptor:
✓ **Affinity;** is the ability of drug to bind to the receptor that measure the strength of the formed bonds, or the tightness of drug-receptor interaction.
✓ **Efficacy;** the maximal response produced by drug receptor complex, when the drug bind with *best fit to the receptor and with strongest affinity*.

✓ **Intrinsic activity;** The ability of a drug to activate the receptor and give a response and its usually reflect the efficacy of drug. The higher is the intrinsic activity the higher is the efficacy.

❖ **Drugs classified according to their affinity and efficacy** into

I-Agonist drug:

The drug which has affinity to bind to the receptor and produce a response (intrinsic activity or efficacy).

A. **Full agonist:**
   The drug binds to the receptor and produces a maximal biologic response that mimics the response to the endogenous ligand. For example, ***phenylephrine*** is a full agonist at α-1adrenoceptors.
B. **Partial agonist**: It has affinity to the receptors but gives submaximal response. so, the **efficacy = *greater than zero but less than one***.

II- Antagonist drug:

It has affinity to bind the receptor with no response, has ***zero efficacy or intrinsic activity***.

They produce their effects by preventing receptor activation by endogenous regulatory molecules or agonists.

e.g; Antihistamines, suppress allergy symptoms by binding to receptors for histamine, thereby preventing activation of these receptors by histamine released in response to allergens**.**

DOSE-RESPONSE RELATIONSHIPS

It is the relationship between the **size of administered dose** and the **intensity of the response** produced.

This relationship can be utilized to determine how much of drug is required to produce a therapeutic drug response? and how much to increase or decrease the used dosage to produce the desired increase or decrease in response?

The dose response curve present in two forms:

A. Graded dose–response relationship

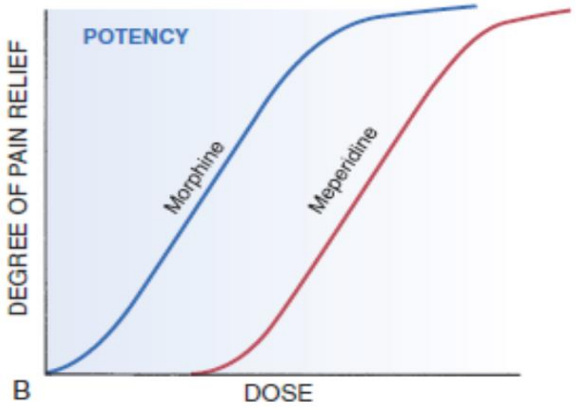
As the concentration of a drug increases, its pharmacologic effect also increased gradually.

Plotting the magnitude of response against increasing doses of a drug produces a graded dose–response curve that has the general sigmoid shape**.**

❖ **Pharmacodynamic Parameters Obtained from the Dose-Response Curve**

- **Potency:** It is the measure of the *amount of drug that must be given to produce an effect***.** Potency is indicated by the *relative position of the dose-response curve along the x (dose) axis.* It's *determined* by;

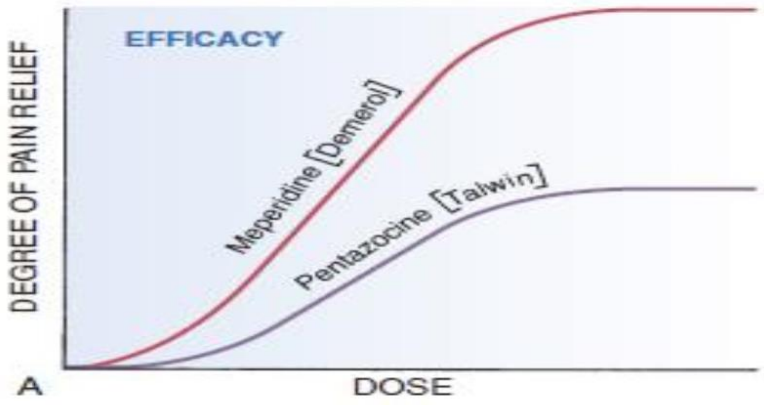
- *(EC50)* concentration**,** which indicate the ***concentration of drug required to produce 50% of maximum response*****.** Used to Compare the potency of different agonists.



e.g; pain relief with meperidine requires higher doses than with morphine. We would say that morphine is more potent than meperidine

Maximal efficacy (Emax); Which refer to the largest effect that a drug can produce. Maximal efficacy is indicated by the height of the dose-response curve. Above which no increase in response is observed with increase of concentrations of drug.

e.g; As shown in the figure below that *the maximum degree of pain relief* we can achieve with ***pentazocine*** is smaller than that of **meperidine.**



B. Quantal Dose–Response Relationships

individuals responding to the used dose of the drug.

These responses are known as quantal responses, because, for any individual, **either the effect occurs or it does not.** It is useful for determining doses to which most of the population responds.

ED50: is the dose of drug that causes a therapeutic response in 50% of the population.

Therapeutic index:

It is a value that give indication for drug's safety and represent the ratio of *Lethal dose in 50% experimental animals (LD50)* over *Effective dose 50 (ED50)*.

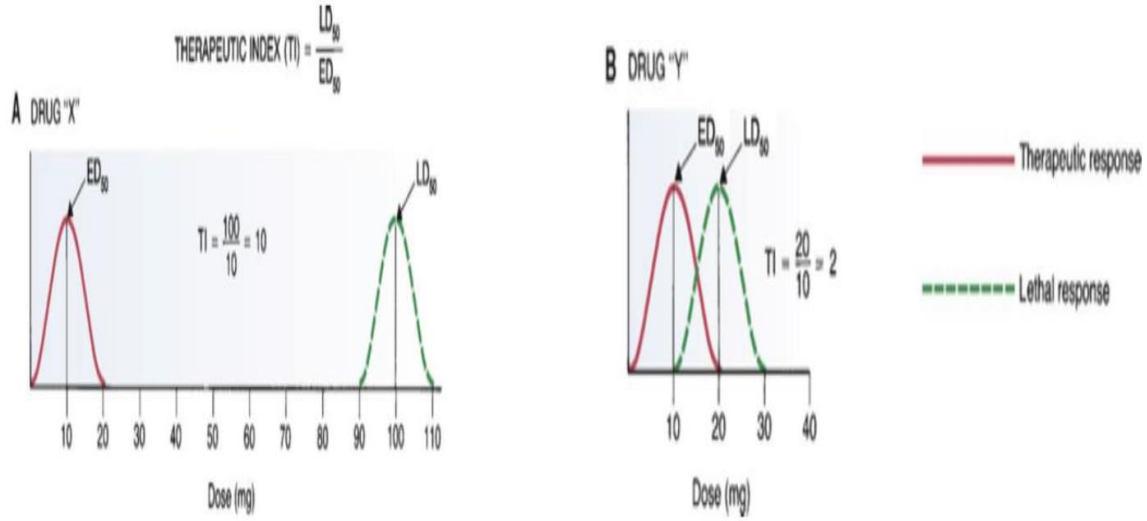
$$\textbf{Therapeutic index} = \frac{\textbf{Lethal Dose } LD_{50}}{\textbf{Effective Dose } ED_{50}}$$

$$\textbf{For humans} = \frac{\textbf{Toxic Dose } ED_{50}}{\textbf{Effective Dose } ED_{50}}$$

TD50 : is the toxic that cause toxicity in 50% of a group of tested individuals.

The lower is the therapeutic index means that the difference between a therapeutically active dose and a toxic dose is small causing an adverse reaction, and therefore its use requires closer monitoring. Examples of such drugs are warfarin theophylline, and digoxin. In contrast, a drug with **a high therapeutic index**, such as amoxicillin, is rarely associated with overdose.

- **The nurse is responsible for monitoring drugs with low therapeutic index.**



Drug Antagonism

The process by which the antagonist can block or Oppose the effect of agonist drug.

Types of Antagonism

1-Pharmacological antagonism

Antagonist drugs compete with the agonist for the same receptor site preventing the binding of agonist and reduce its effect. This can be further divided into:

a. **Competitive antagonists (surmountable)**
   If the antagonist binds to the same site on the receptor as the agonist in a **reversible manner**, it is "competitive." A competitive antagonist interferes with an agonist binding to its receptor. Therefore increasing the concentration of agonist relative to antagonist can overcome this inhibition. Thus, competitive antagonists characteristically shift the agonist dose–response curve to the right and increase the EC50 without affecting maximal respone Emax

b. **Noncompetitive Irreversible antagonists (non surmountable)**
   Irreversible antagonists bind covalently to the active site of the receptor, thereby permanently reducing the number of receptors available to the agonist. An irreversible antagonist decrease the Emax, with no effect on EC50 values. The addition of more agonist does not overcome the effect of irreversible antagonists, so This antagonism is noncompetitive.

2-Functional (physiologic)antagonism

An antagonist may act at **a completely separate receptor**, initiating effects that are functionally opposite those of the agonist.
e.g; histamine-induced bronchoconstriction by binding to H1 histamine receptors on bronchial smooth muscle, as well as causes vasodilatation. While epinephrine bind to adrenergic receptors on bronchial smooth muscle, causes bronchodilation and vasoconstriction.

3- Chemical antagonism

A type of antagonism through which one drug counteract or neutralize the effect of other drug by simple chemical reaction (not bind to receptor). e.g; **protamine sulphate and heparin**.