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Class: B.Pharm. Semester	IV
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Learning Outcome of Module-2

LO	Learning Outcome	Course Outcome Code
LO1	To Understand the principles and mechanism of drug action	BP404.2
LO2	To Understand the receptor theories &receptors classification.	BP404.2
LO3	To Understand the dose response relationship, therapeutic index and factor modifying drug action drug action.	BP404.2
LO4	To understand the Adverse drug reactions and Drug Interactions	BP404.2
LO5	To Understand the Drug discovery and Clinical evaluation of new drug, Pharmacolvigilance	BP404.2

Content Table

Topic
• Pharmacodynamics- principles and mechanisms of drug action. • Receptor theories and classification of receptors, regulation of receptors. • Drug receptors interactions signal transduction mechanisms, • G-protein-coupled receptors, ion channel receptor, transmembrane enzyme linked receptors, • Transmembrane JAK-STAT binding receptor and receptors that regulate transcription factors. • Dose response relationship, therapeutic index. • Combined effects of drugs and factors modifying drug action. • Adverse drug reactions, drug interactions. • Drug discovery and clinical evaluation of new drugs -drug discovery phase, preclinical evaluation phase, clinical trial phase, phases of clinical trials. • Pharmacolvigilance.

PHARMACODYNAMIC

Pharmacodynamic- Pharmacodynamic is a study of drug's effect on body, so we can say it's a study of- what does DRUG do to the BODY.

Pharmaco **D**ynamics- What does **DRUG** [1]do to the **BODY**[2]. Means is Drug is in the first line. (**D** of Dynamic and **D** of Drug is in continues mode)

Pharmacodynamics is concerned with the study of the mechanism of drug and pharmacological effect produced on the body. The drugs administered are not having effectiveness only but they have also adverse effect side effect and toxicity.

The drug used for the treatment should be of maximum effectiveness and with minimum toxicity and side effect.

Action of drug: it is the process by which the drug or chemical substance induce change in pre-existing physiological function of living organisms.

Effect of drug: The series of changes occurs after drug action is called effect of drug,

Ex. In case of fever, the body trmprature is elveted (increased) above normal body temperature. Tablet Acetaminophen (Paracetamol) is antipyretic the drug administered, it disintegrates, absorb then act on heat regulating center. It lowersthe raised body temperature to normal body temperature.

Principles of Drug Action

Drugs (except those gene based) do not impart new functions to any system, organ or cell; they only alter the pace of ongoing activity. However, this alone can have profound medicinal as well as toxicological impact. The basic types of drug action can be broadly classed as:

Irritation- There is few drugs which irritate the site of action and produce there effect. Example- Senna and some other drug used in constipation irritate the intestine and increase defecation. Other balm in case of headache will irritate the forehead tissue and gives relief from pain for short duration.

Stimulation- Stimulation means to increase the function of any specialized organ, which will result in extra work, like in case of fear or fight adrenaline is gets secreted and heart rate increase which give FFF (Fight-Flight-Freeze response).

Depression- The simple meaning of depression is the reduction of specialized activity. For example- Barbiturate and benzodiazepine depress the CNS and give depression action. As same Omeprazole reduce gastric acid secretion.

Replacement- When any hormone or biochemical substance is in inadequate quantity and there recovery is not possible then there is one option of replacement. The replacement is done for

insulin in case of insulin dependent diabetes; here insulin is given by injection to maintain the requirement

Cytotoxic- When there is entry of any parasite, or there is no other option to control the growth of own body cell then Cytotoxic drugs are used. They kill the microorganism of kill the uncontrolled and excessive growing cells.

Mechanism of Drug Action

Only a handful of drugs act by virtue of their simple physical or chemical property; examples are:

• Bulk laxatives (ispaghula)—physical mass

• Dimethicone, petroleum jelly—physical form, opacity

• Para amino benzoic acid—absorption of UV rays

• Activated charcoal—adsorptive property

• Mannitol, mag. sulfate—osmotic activity

• 131I and other radioisotopes—radioactivity

• Antacids—neutralization of gastric HCl

• Pot. Permanganate—oxidizing property

• Chelating agents (EDTA, dimercaprol)—chelation of heavy metals.

• Cholestyramine—sequestration of bile acids and cholesterol in the gut

• Mesna—scavenging of vasicotoxic reactive metabolites of cyclophosphamide

Majority of drugs produce their effects by interacting with a discrete target biomolecule, which usually is a protein. Such mechanism confers selectivity of action to the drug

Functional proteins that are targets of drug action can be grouped into *four* major categories, *viz.*

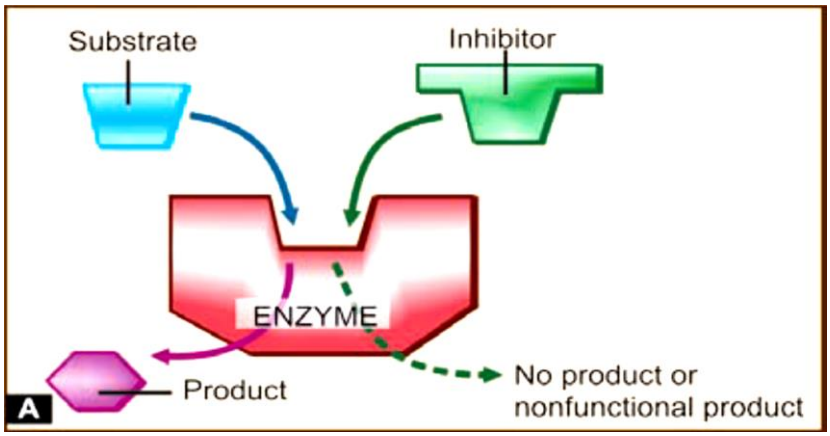
- Enzymes
- Ion channels
- Transporters
- Receptors

ENZYMES

Almost all biological reactions are carried out under catalytic influence of enzymes. Drug can either increase or decrease the rate of enzymatically mediated reactions

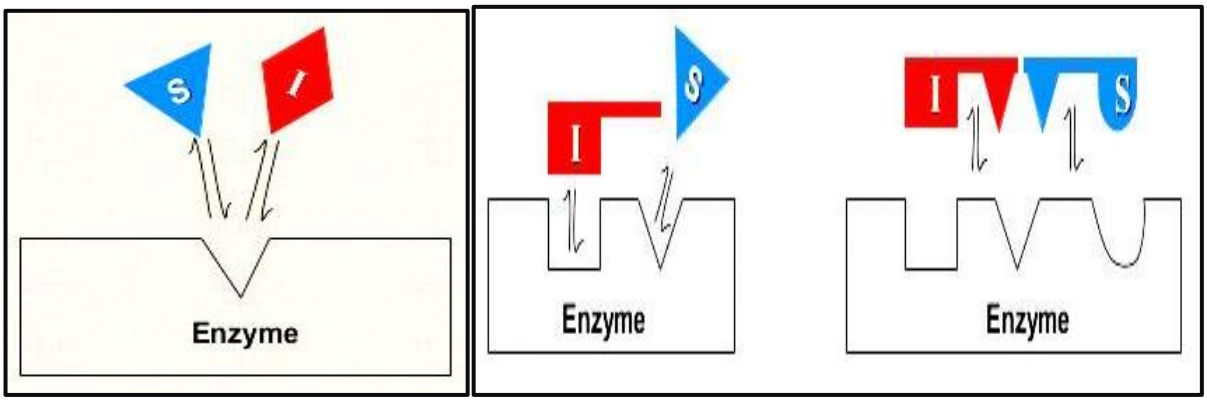
Enzyme Inhibition:

Selective inhibition of particular enzyme is common mode of action. Such inhibit on is either competitive or non-competitive.



Competitive Inhibitions:

When the active site or catalytic site of an enzyme is occupied by the substance other than the substrate of that enzyme. Its activity is inhibited. This type of inhibition is also known competitive inhibition.



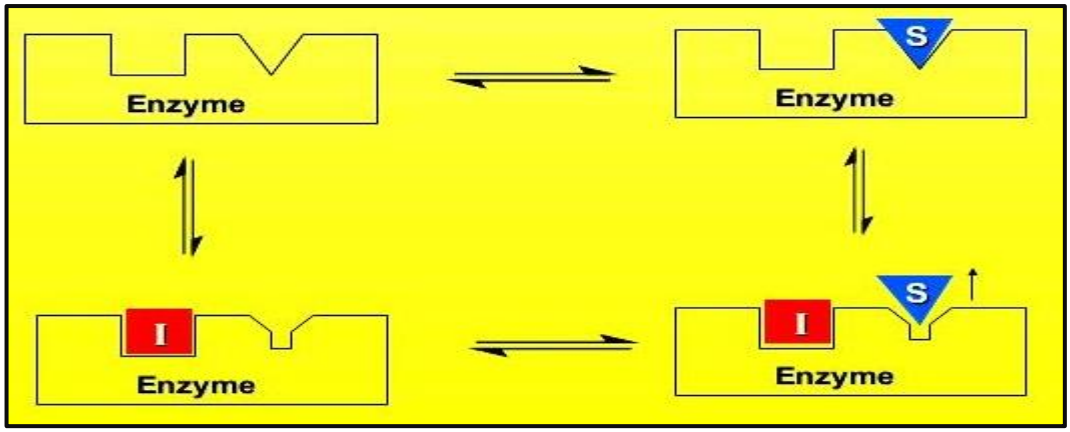
In such inhibition both ES and ET complex are formed during their reaction. With the increase in conc. Of inhibitors, lowers the rate of enzymatic reaction, Such inhibitors increase the kM but the Vmax remains unchanged. However when the concentration of substrate is increased the effect of inhibitor can be reversed forcing it out from EI complex.

Non-Competitive Inhibitions:

These are not influenced by the concentration of the substrate of inhibits by binding irreversibly to the enzyme but not at the active site.

They also bind with same affinity to the free enzyme and form the enzyme substrate complex

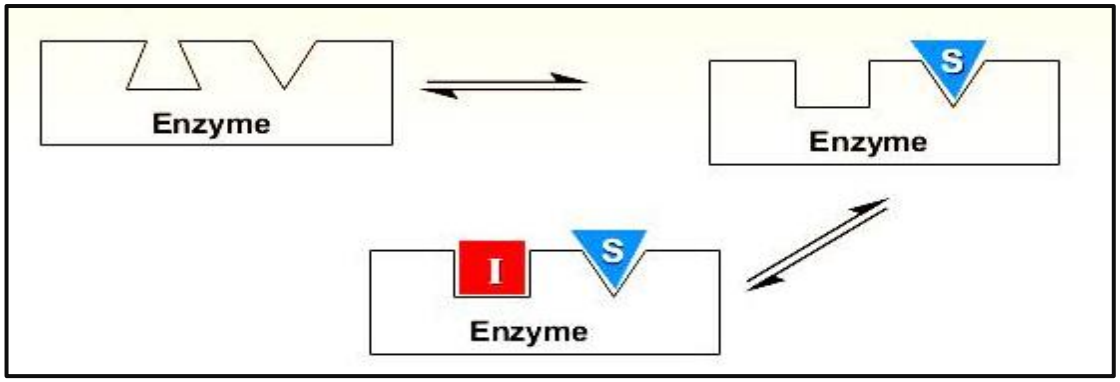
It changes the shape of enzyme and active site



Uncompetitive Inhibitions:

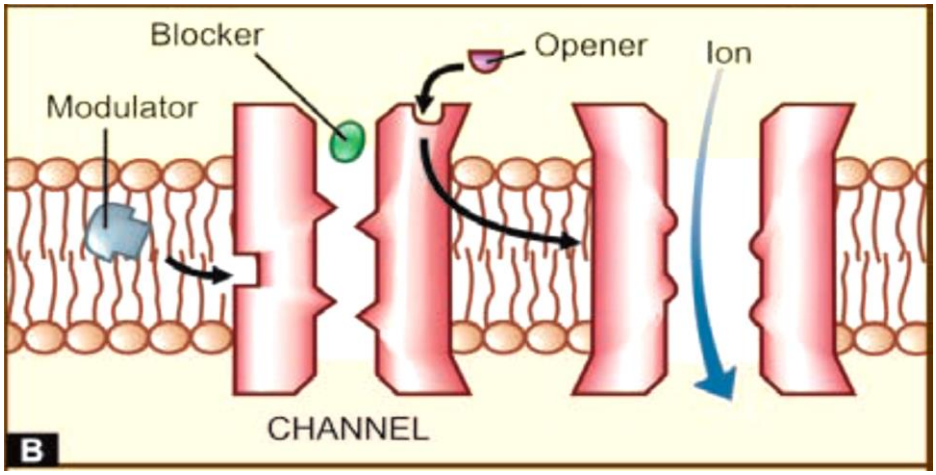
Uncompetitive inhibitors do not bind to the free enzyme. They bind only to the enzyme substrate complex to yield inactive ESI complex.

Uncompetitive inhibitors frequently observed in multimutated reaction. Inhibition can't be reversed by increasing the Since I doesn't compete with s from the same binding site.



ION CHANNELS:

- Ion channels are pore forming membrane proteins that allow ions to pass through the channel pore.
- Their functions include establishing a resting membrane potential shaping action potentials and other electrical signals by gating the flow of ions across the cell membrane.
- The rate of ion transport through the channel is very high.
- Ions pass through channels down their electrochemical gradient which function of ion concentration and membrane potential "Downhill'' without the input of metabolic energy.
- e.g Adenosine Triphosphate, active transport mechanism.



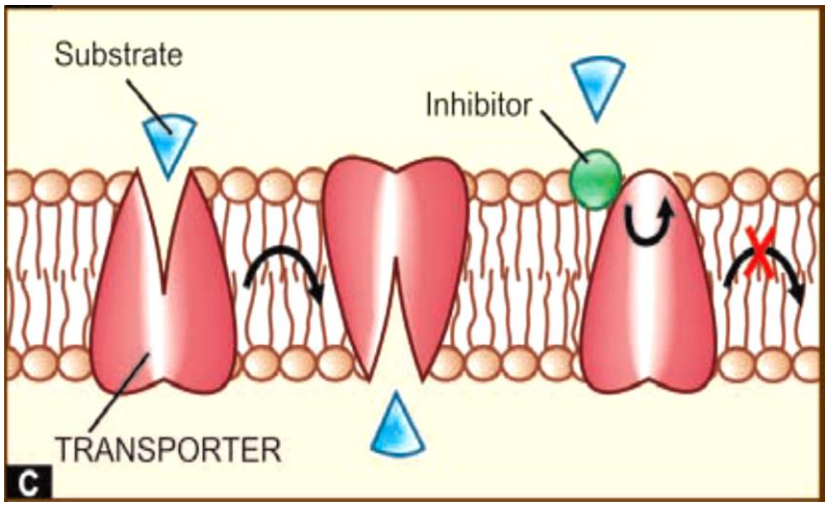
They are operated by specific signal molecules either directly and are called *ligand gated channels* (e.g. nicotinic receptor,) or through G-proteins and are termed *G-protein regulated channels* (e.g. cardiac adrenergic receptor activated Ca^{2+} channel. Drugs can also act on *voltage operated* and *stretch sensitive* channels by directly binding to the channel and affecting ion movement through it, e.g. local anesthetics which obstruct voltage sensitive Na^{+} channels.

- Quinidine blocks myocardial Na^{+} channels.
- Dofetilide and amiodarone block myocardial delayed rectifier K^{+} channel.
- Nifedipine blocks L-type of voltage sensitive Ca^{2+} channel.
- Nicorandil opens ATP-sensitive K^{+} channels.
- Sulfonylurea hypoglycaemics inhibit pancreatic ATP-sensitive K^{+} channels.
- Amiloride inhibits renal epithelial Na^{+} channels.
- Phenytoin modulates (prolongs the inactivated state of) voltage sensitive neuronal Na^{+}channel.
- Ethosuximide inhibits T-type of Ca^{2+} channels in thalamic neurons

TRANSPORTERS:

Several substrates are translocate across membranes by binding to specific transporters (carriers) which either facilitate diffusion in the direction of the concentration gradient or pump the metabolite/ion against the concentration gradient using metabolic energy. Many drugs produce their action by directly interacting with the solute carrier (SLC) class of transporter proteins to inhibit the ongoing physiological transport of the metabolite/ion.

Ex: Desipramine and cocaine block neuronal reuptake of noradrenaline by interacting with norepinephrine transporter . Fluoxetine (and SSRIs) inhibit neuronal reuptake of 5-HT by interacting with serotonin transporter (SERT).



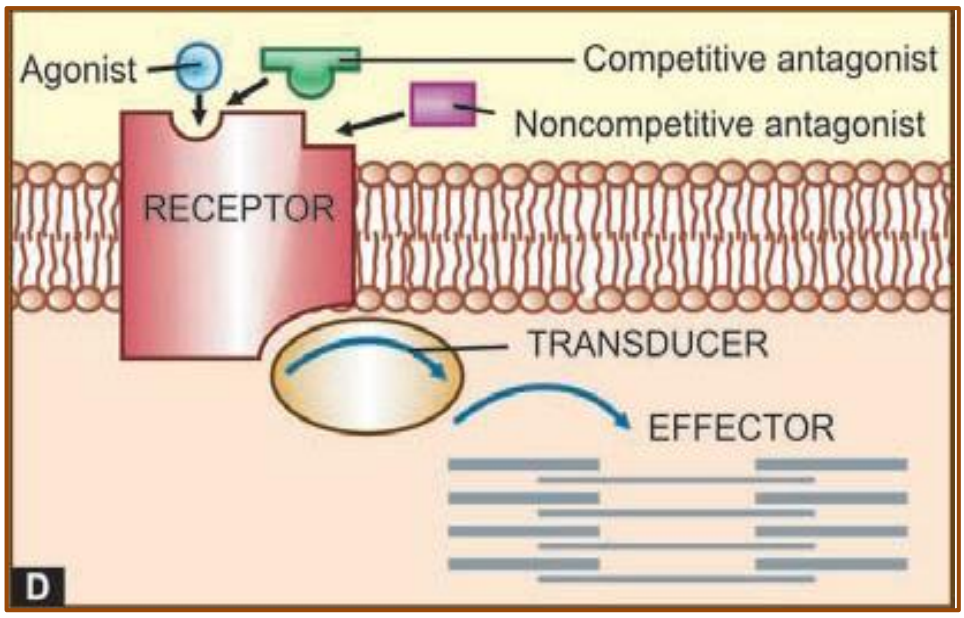
RECEPTORS

It is defined as a macromolecule or binding site located on the surface or inside the effector cell that serves to recognize the signal molecule/drug and initiate the response to it, but itself has no other function.

OR

Receptors are macromolecules involved in chemical signaling between & with in the cells. They may be located on the cell surface membrane or within cytoplasm.

The largest number of drug that do not bind directly to the effectors like Enzyme, Channels, Transport structural protein, template biomolecule. But act through specific regulatory macromolecules or the site which bind and interact with the drug are called "**Receptor**"

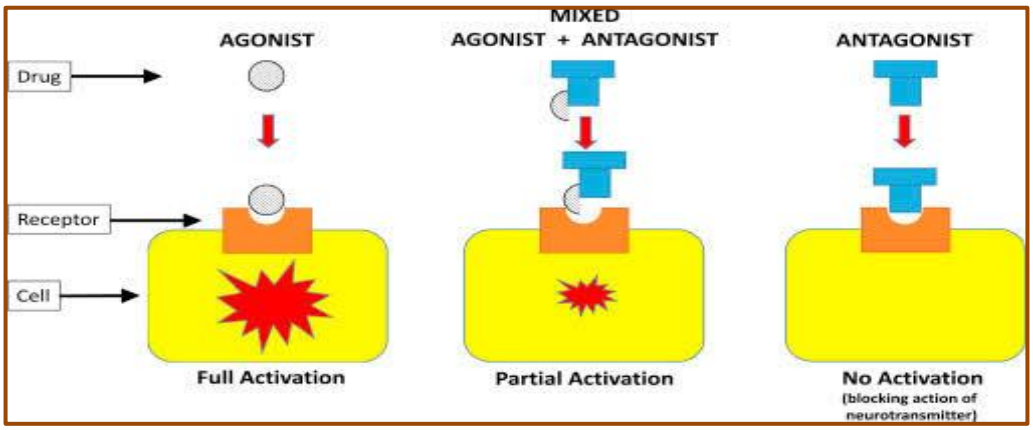


Following terms related to receptor and drug receptor complex

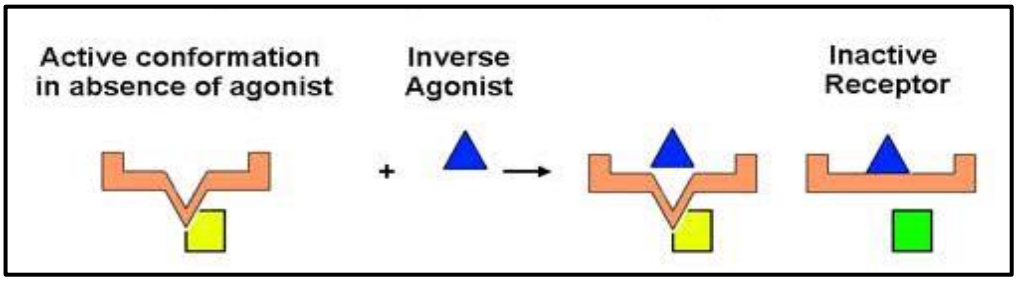
Agonist: An agent which activates a receptor to produce an effect similar to that of the physiological signal molecule.

Antagonist: An agent which prevents the action of an agonist on a receptor or the subsequent response, but does not have any effect of its own.

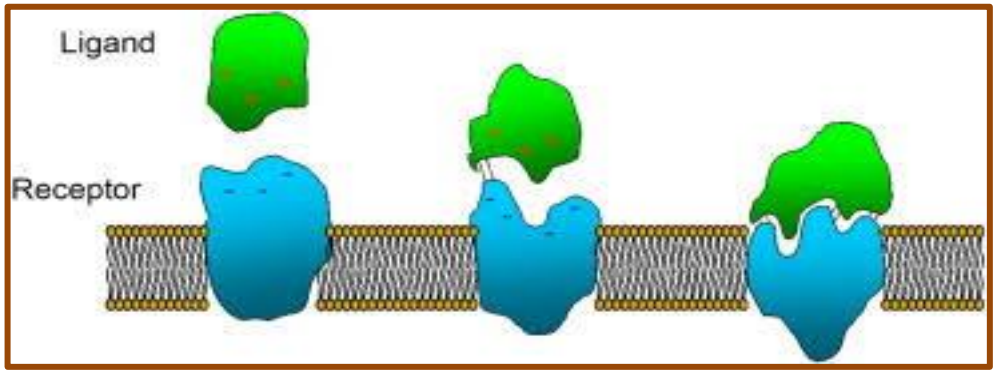
Partial agonist: An agent which activates a receptor to produce submaximal effect but antagonizes the action of a full agonist.



Inverse agonist: An agent which activates a receptor to produce an effect in the opposite direction to that of the agonist.



Ligand: (Latin: *ligare* —to bind) - Any molecule which attaches selectively to particular receptors or sites. The term only indicates affinity or ability to bind without regard to functional change: agonists and competitive antagonists are both ligands of the same receptor.



RECEPTOR THEORIES

RECEPTORS – A receptor is the specific chemical constituent of the cell with which a drug interacts to produce its Pharmacological effects.

Some receptor sites have been identified with specific parts of proteins and nucleic acids.

The term drug receptor or drug target denotes the cellular macromolecule or macromolecular complex with which the drug interacts to elicit a cellular response, i.e., a change in cell function.

D + R → D-R → Drug Response

A Receptor is analogous to a switch that it has two configurations: "ON" and "OFF"

Receptor: Any cellular macromolecule that a drug binds to initiate its effects.

Drug: A chemical substance that interacts with a biological system to produce a physiologic effect. All drugs are chemicals but not all chemicals are drugs.

The ability to bind to a receptor is mediated by the chemical structure of the drug that allows it to interact with complementary surfaces on the receptor.

Once bound to the receptor an agonist activates or enhances cellular activity.

Examples of agonist action are drugs that bind to beta receptors in the heart and increase the force of myocardia contraction or drugs that bind to alpha receptors on blood vessels to increase blood pressure. The binding of the agonist often triggers a series of biochemical events that ultimately leads to the alteration in function.

THEORIES FOR DRUG RECEPTOR INTERACTION

Over the years a number of hypotheses have been proposed to account for the ability of a drug to interact with a receptor and elicit a biological response. Several of the more important proposals are:

OCCUPATION THEORY

The occupancy theory of Gaddum and Clark states that the intensity of the pharmacological effect is directly proportional to the number of receptors occupied by the drug.

Maximal response occurs when all the receptors are occupied.

D + R ↔ DR⇒ RESPONSE

The concept of drug–receptor interactions involve two stages: first, there is a complexation of the drug with the receptor, which termed the affinity; second, there is an initiation of a biological effect, which termed the intrinsic activity and the efficacy.

Affinity is a measure of the capacity of a drug to bind to the receptor.

Intrinsic activity (α) or Efficacy is the property of a compound that produces the maximum response or the ability of the drug– receptor complex to initiate a response.

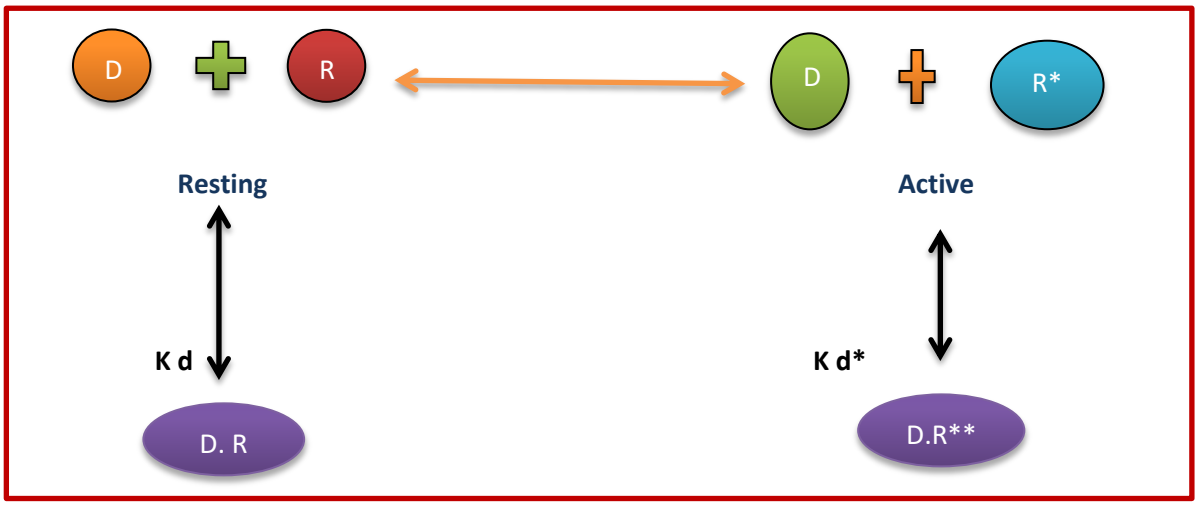
THE TWO-STATE (MULTISTATE) MODEL OF RECEPTOR ACTIVATION

It was developed on the basis of the kinetics of competitive and allosteric inhibition as well as through interpretation of the results of direct binding experiments.

It postulates that a receptor, regardless of the presence or absence of a ligand, exists in two distinct states: the R (relaxed, active or on) and T (Tense, inactive or off) states, which are in equilibrium with each other. In the absence of the natural ligand or agonist, receptors exist in equilibrium (defined by equilibrium constant L; Figure 4) between an active state (R*), which is able to initiate a biological response, and a resting state (R), which cannot.

In the absence of a natural ligand or agonist, the equilibrium between R* and R defines the basal activity of the receptor.

A drug can bind to one or both of these conformational states, according to equilibrium constants Kd and K*d for formation of the drug– receptor complex with the resting (D•R) and active (D•R*) states, respectively.



Full agonists bind only to R*

Partial agonists bind preferentially to R*

Full inverse agonists bind only to R

Partial inverse agonists bind preferentially to R

Antagonists have equal affinities for both R and R* (no effect on basal activity)

RATE THEORY

- The response is proportional to the rate of drug-Receptor complex formation.
- Effect is produced by the drug molecules based on the rates of association and dissociation of drugs to and from the receptors.
- As an alternative to the occupancy theory, Paton proposed that the activation of receptors is

proportional to the total number of encounters of the drug with its receptor per unit time.

- Therefore, the rate theory suggests that the pharmacological activity is a function of the rate of association and dissociation of the drug with the receptor and not the number of occupied receptors. Each association would produce a quantum of stimulus.
- In the case of agonists, the rates of both association and dissociation would be fast.
- The rate of association of an antagonist with a receptor would be fast, but the dissociation would be slow.
- Partial agonists would have intermediate drug–receptor complex dissociation rates.

INDUCED-FIT THEORY

- The induced-fit theory of Koshland was originally proposed for the action of substrates with enzymes, but it could apply to drug–receptor interactions as well.
- According to this theory, the receptor need not necessarily exist in the appropriate conformation required to bind the drug.
- As the drug approaches the receptor, a conformational change is induced, which orients the essential binding sites.
- The conformational change in the receptor could be responsible for the initiation of the biological response (movement of residues to interact with the substrate).
- The receptor (enzyme) was suggested to be elastic, and could return to its original conformation after the drug (product) was released.
- The conformational change need not occur only in the receptor (enzyme), the drug (substrate) also could undergo deformation, even if this resulted in strain in the drug (substrate).
- According to this theory, an agonist would induce a conformational change and elicit a response, an antagonist would bind without a conformational change, and a partial agonist would cause a partial conformational change.
- The induced- fit theory can be adapted to the rate theory. An agonist would induce a conformational change in the receptor, resulting in a conformation to which the agonist binds less tightly and from which it can dissociate more easily.
- If drug–receptor complexation does not cause a conformational change in the receptor, then the drug–receptor complex will be stable, and an antagonist will result.

MACROMOLECULAR PERTURBATION THEORY

- Having considered the conformational flexibility of receptors, Belleau suggested that in the interaction of a drug with a receptor two general types of macromolecular perturbations

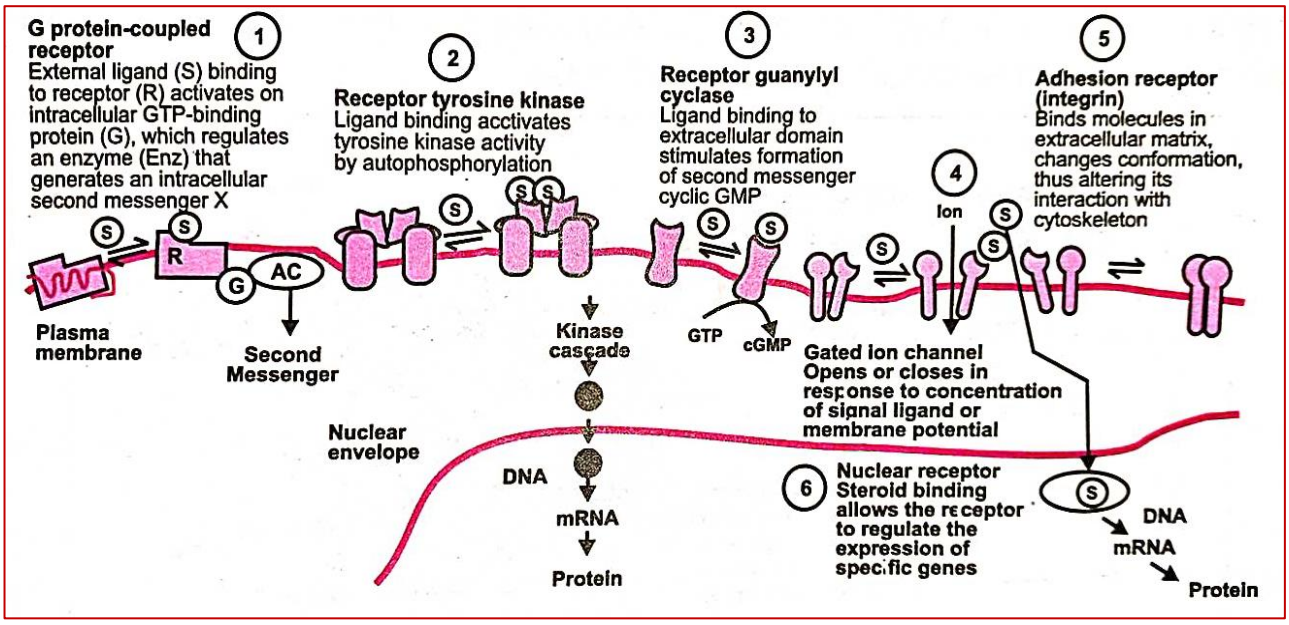
could result:

- A specific conformational perturbation makes possible the binding of certain molecules that produce a biological response (an agonist).
- A non- specific conformational perturbation accommodates other types of molecules that do not elicit a response (e.g., an antagonist).
- If the drug contributes to both macromolecular perturbations, a mixture of two complexes will result.
- This theory offers a physicochemical basis for the rationalization of molecular phenomena that involve receptors, but does not address the concept of inverse agonism

CLASIFICATION OF RECEPTORS

Receptor is a membrane bound or soluble proteins or proteins complex which exerts a physiological effect after binding its natural ligand. The drugs can acts though various types of receptors with their signal Transduction Mechanism,

The receptors are classified on the basis of nature of receptor and regulate path



TRANSDUCTION MECHANISM

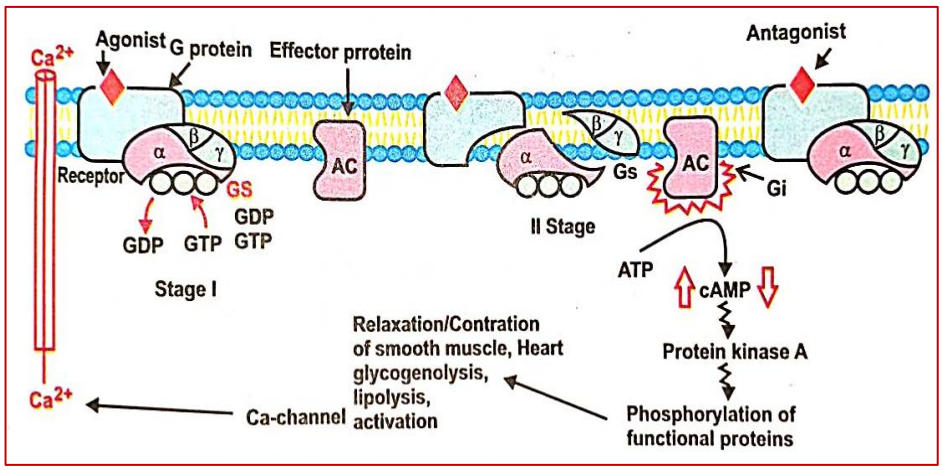
- ✓ G protein- coupled receptors
- ✓ Enzyme linked receptor
- ✓ Voltage dependent ion channels
- ✓ Other member receptors
- ✓ Nuclear receptors

G - Protein- Coupled Receptors (GPCRs)

- GPCRS are the largest family of membrane proteins and mediate most cellular responses to hormones and neurotransmitters, as well as responsible for vision, olfaction and taste.
- GPCRS are characterized by the presence of seven membrane spanning alpha helical segments separated by alternating intra and extracellular loop regions.
- If agonist and antagonist bind to Gpcr iI cause the receptor and g-protein change conformation.
- The alpha subunits exchange the guanosine triphosphate (GTP) for guanosine diiphosphate (GDP) and dissociates from the other subunits, where it interacts with an effectors proteins (adenylate cyclase and phospholipase c)
- This effector protein can stimulate or inhibit second massager molecules to produce a physiological effect.
- The alpha subunit then hydrolysis the bound GTP to GDP and reassociates with the other subunits.
  - G_s protein activate cAMP
  - G_i proteins inhibit cAMP
  - G_q protein activate phospholipase C, which increase DAG and IP_3
- When G protein is activated, GTP replaced GDP on the alpha subunit. Following activation of Protein, GTP is rapidly degraded to inactive GDP by Activte of the alpha subunit GTPase

G. protein couple receptor regulates through Adenylyl cyclase: cAMP pathway

Agonist or ligand bind to GPCR that activate Gs stimulate Adenylate cyclase to convert ATP to the cAMP Cyclic adenosine monophosphate.

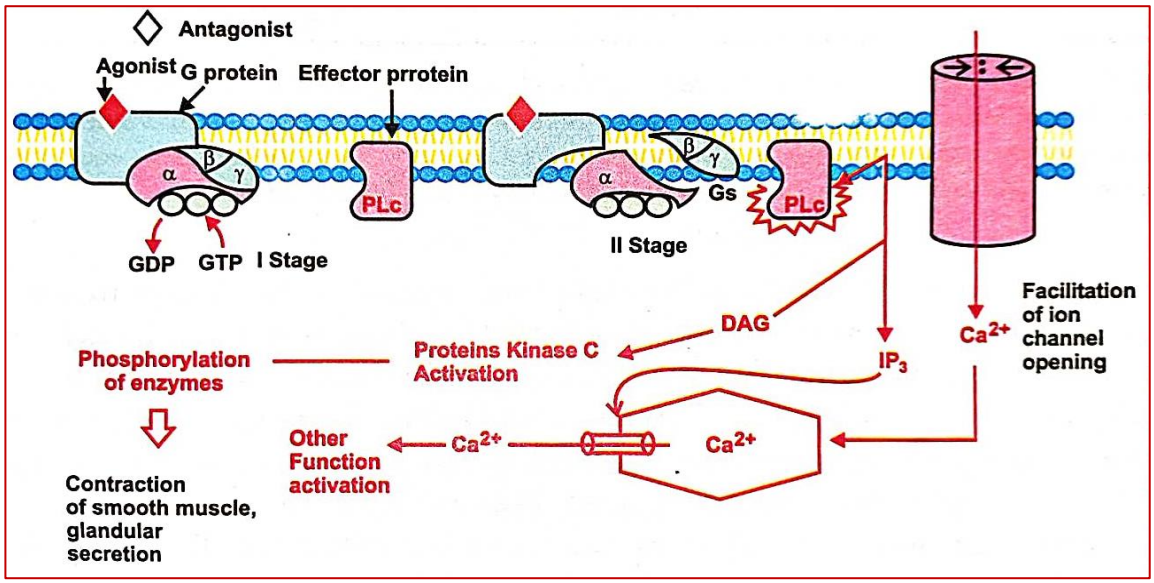


G PCR, action through Adenylate cyclase system. Stimulation/Inhibition depend upon nature of agonist and antagonist

Then cAMP Activate Second massager of Protein kinase A which phosphorylated the protein, resulting in alter the function of many enzymes, ion channel, carrier and structural proteins to results as increased contraction, relaxation on smooth muscle, glycogenolysis, lipolysis etc. When the ligand bind to GPCR than Activates G_i inhibit adenylate cyclase (↓CAMP) Therefore protein kinase A is not activated and proteins are note phosphorylated. It is opposite process activation.

G. protein couple receptor regulates through Phospholipase C- IPS-DAG Pathway

- Activation of phospholipase C by the activated GTP carrying ά subunits of Gq hydrolyses the membrane phospholipids inositol 4,5 bisphosphate to generate the second messenger inositol 1,4,5 triphosphate (IP_3)and diacylglycerol (DAG)
- The IP_3 being water soluble diffuse to the cytosol and mobilize Ca^{2+} from endoplasmic reticulum depot.
- The lipophilic DAG remains within the membrane but recruits protein kinase and activate it with the help of Ca^{2+}
- The activated protein kinase phosphorylates many intra cellular proteins and mediates various physiologicalresponses. That's why it serve in signaling function.
- The cytosolic concentration of Ca^{2+} is kept very low (About l00nM) by specific pumps located at plasma membrane and at the endoplasmic reticulum.
- Triggering by IP_3 the released Ca^{2+} (3rd Messenger) act as highly versatile regulator acting throughcalmodulin.



GPCR regulate through IP3DAG pathway.

Agonist shows stimulation action and antagonist shows inhibition action

Ligand Gated Ion Channels

- It is made up of five multi subunit proteins (2ά,β,γ and δ)
- It is a large group of intrinsic transmembrane proteins that allow the passage of ion upon activation by specific chemical.
- Most endogenous ligand bond to distinct from the ion conduction pore and binding directly causes opening or closing of the chemical.
- Ligand can bind extracellular eg Glutamate, ACH and GABA or intracellular Ca^{2+} on Ca^{2+} activated K^{+} channels.
- It is important to note that the ligand itself is not transported across cell membrane.

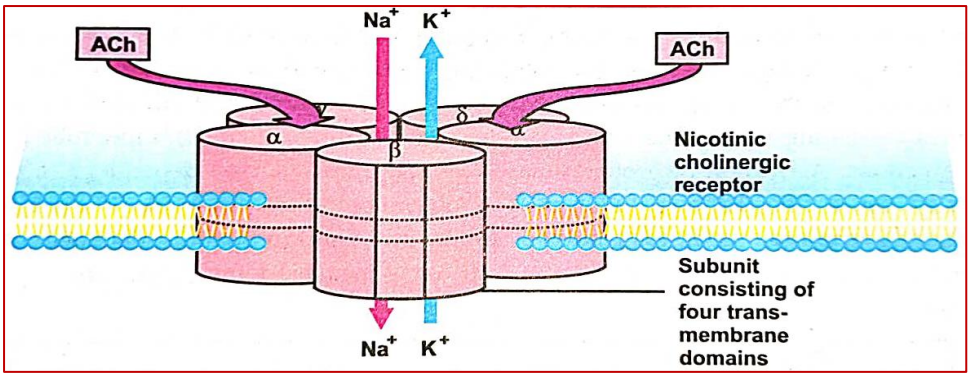


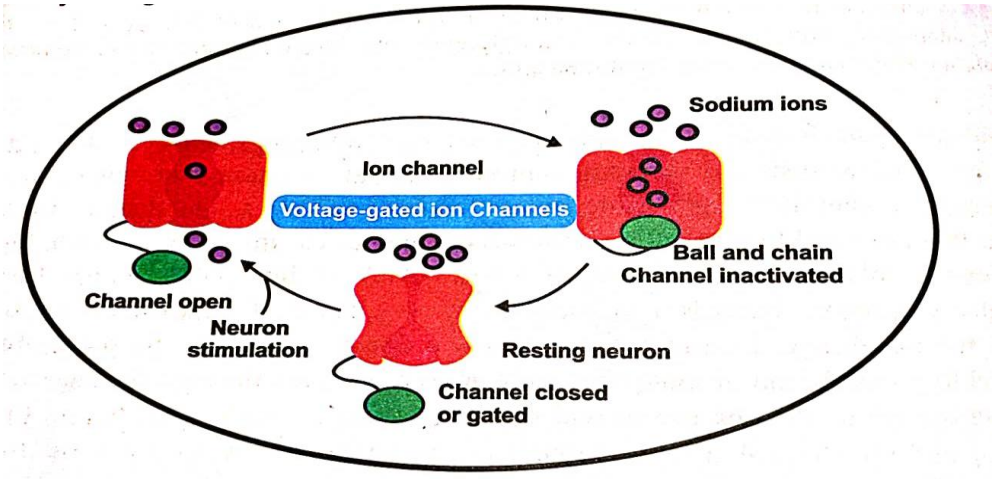
Diagram represented the ligand gated ion channel

- Ligand binding causes a drastic change in the permeability of the channels to a specific ion or ions; effectively no ions can pass through the channel when it is inactive but to 10^{7} ions per second can allow trough upon ligand binding.
- This ligand gated ion channel, a type of ion tropic receptor, allows specific ions (like Na^{+} K^{+} Ca^{2+} and Cl^{-}) to flow in and out of the membrane.
- Examples of ligand gated ion channels include ach receptors , serotonin, $GABA_A$ and Glutamate receptor.

Voltage Dependent Ion Channels

- Voltage dependent ion channels are a class of transmembrane proteins that form ion channel that are activated by change in the electrical membrane potential near the channel.
- The membrane potential alters the confirmation of the channel positive proteins, regulating their opening and closing.
- It is normally open or close in response to changes in the membrane potential, but they can also function receptors for drugs.

- Example: The Calcium channel blockers bind to voltage-dependent Ca^{2+}/Na^{2+} channels and block Ca^{2+},Na^{2+} entry into the cells when stimulated . This cause decreased contractility in target tissues, such as cardiac and smooth muscle.



A systematic diagram of movement of ions and their effects

Transmembrane Enzyme-linked receptor

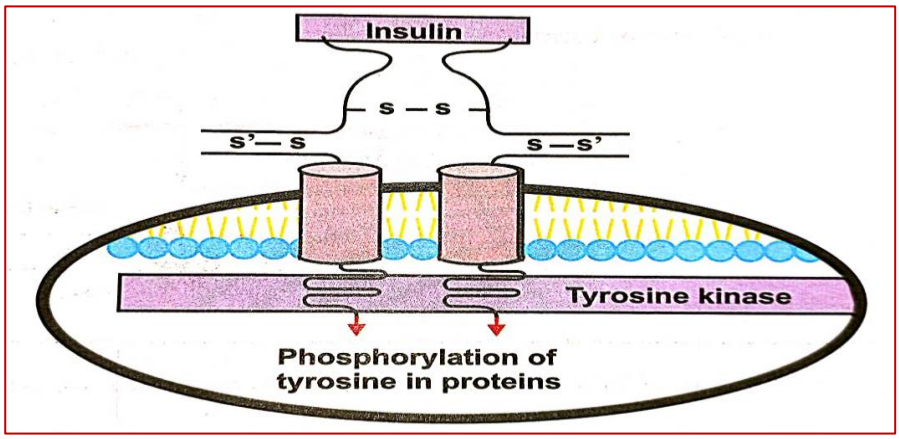
It is the class of receptor themselves is enzymatic proteins. When a drug binds to this type receptor, it causes an enzyme to become "switched on" intercelluarly.

This enzyme then catalyzes the formation of other signal proteins that ultimately lead to the cellular response. Some peptide hormones and cytokines act through this class of receptors.

The enzyme in most cases is a tyrosine proteins kinase.

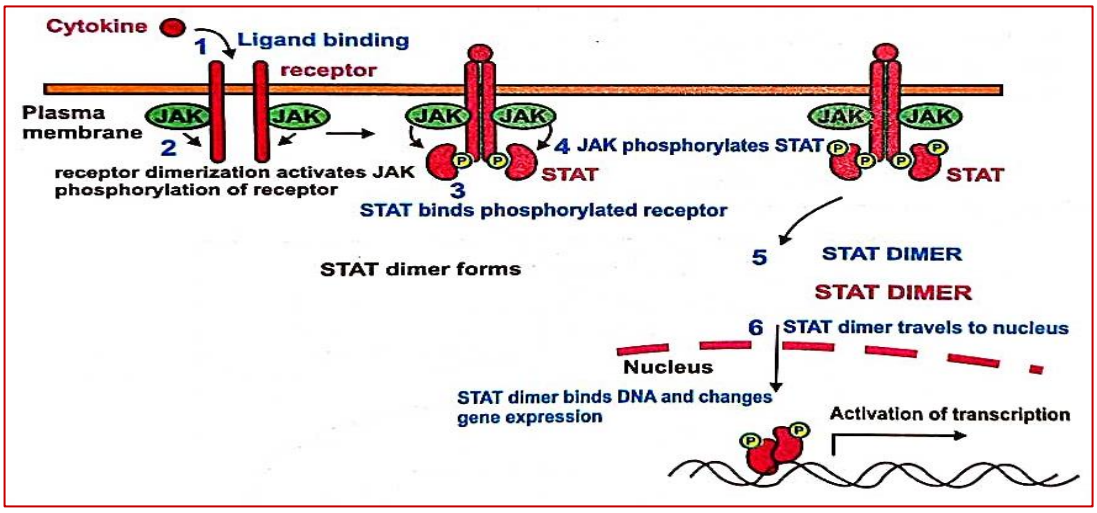
Enzyme Linked insulin receptors

Eg. Insulin bind to the tyrosine kinase receptor cause the enzyme to phosphorylate tyrosine residues in proteins. The proteins can then signal other proteins to be formed resulting in glucose uptake.



Transmembrane JAK-STAT binding

- The Tyrosine kinase activity of JAK is activated when the regulatory molecule binds and brings two receptor molecules together to form a dimer.
- Receptor dimerization brings the two JAKs into close proximity where they can phosphorylate each other.
- Phosphorylation further activates JAK allowing it to phosphorylate the receptor.
- The phosphotyrosine residues on the receptor proteins are binding sites for STAT proteins.
- STAT stands for Signal Transducer and Activator of Transcription.
- The STAT proteins are considered latent transcription factor. Latent means that they are always present in the cytoplasm and waiting to be activated by JAK.
- When STAT bind to receptor, that brings it into position where it can phosphorylated by JAK.
- Once phosphorylated, Two STATs can then form STAT dimer. The STAT dimer is in active transcription factor.



Systematic diagram of transmembrane receptor tyrosine kinase activity of JK

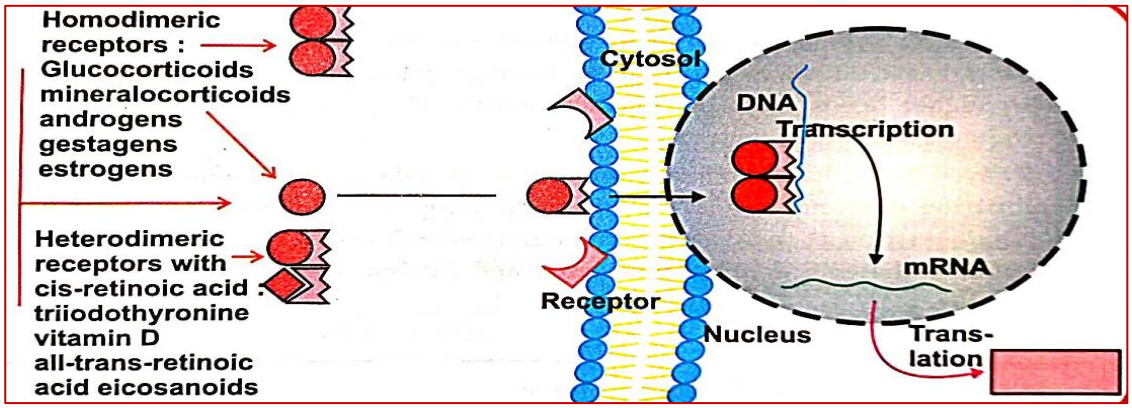
- It travels nucleus where it binds to specific sequences in the DNA. Inactivation occurs when phosphatases remove phosphate groups from various proteins in the signaling pathway.

Other member receptor

- Integrin is obligate heterodimers, means they have two subunits; alpha and beta.
- Integrin's in mammals have twenty four alpha and nine beta subunits.
- Integrin's are transmembrane receptors that facilitate cell-extracellular matrix (ECM) adhesion. Upon ligand binding, integrin's activate signal transduction pathways that mediate cellular signals such as regulation of cell cycle, an organization of the intracellular cytoskeleton, and movement of new receptors to the cell membrane.
- The presence of integrin allows rapid and flexible responses to events at the cell membrane.
- The presences of integrin allow rapid and flexible responses to events at the cell surface.

Nuclear Receptor

- The lipid-soluble drugs diffuse through cell membrane and bind either in the cellular cytosol or in the nucleus.
- Gene expression is altered, and protein synthesis is either increased or decreased, which causes the cellular response.
- This mechanism is the slowest and effects can usually be measured in term of hours rather than minutes or seconds.



Nuclear Receptor

- Various drug acts through nuclear receptor. Lipophilic substances, such as steroid hormones and thyroid hormones, can diffuse through the cell membrane and interact with receptors in the cytoplasm or nucleus.
- The hormone receptors complex than alters gene transcription, causing the synthesis of effector proteins mRNA. The hormone complex interacts with DNA in pairs; these may be identical (homodimeric) or non-identical (heterodimeric) pairs

FUNCTION OF RECEPTORS

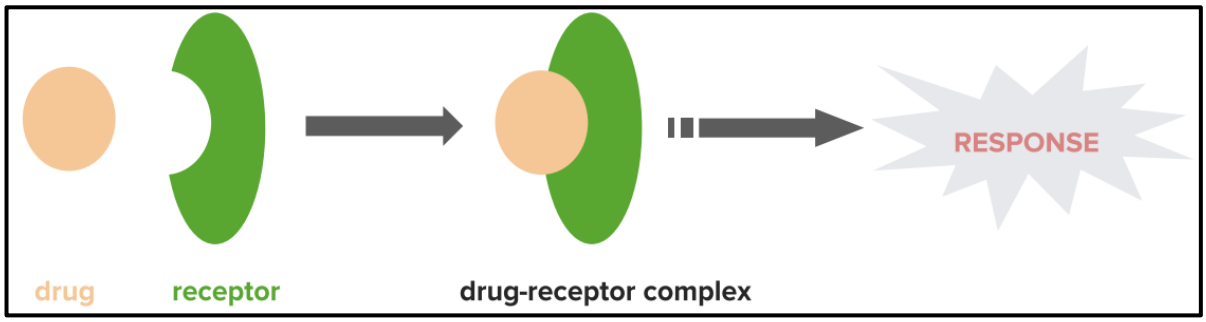
- To propagate regulatory signals from outside to inside the effector cell when the molecular speciescarrying the signal can't itself penetrate the cell membrane
- To amplify the signals
- To integrate various extracellular and intracellular regulatory signals.
- To adapt to short term and long term changes in the regulatory melieu and maintain homeostasis.

DOSE RESPONSE RELATIONSHIP

DOSE – Amount of drug administered in the patient. e.g If 500 mg of paracetamol is taken dose is 500mg.

RESPONSE - Effect shown by the body to a particular drug e.g Paracetamol is antipyretic drug so response is it should bring body temperature to normal.

Drug +Receptor ⟶ Drug-Receptor Complex ⟹ Response



Dose Response Relationship

A relationship used to analyze a kind of response obtained after administering specific dose of drug e.g If 10mg of ILLAPRAZOLE is administered response is it should inhibit formation of proton pumps at 10mg specifically

Dose response relationship has two components

Dose plasma concentration relationship

Plasma concentration response relationship

Dose Response Curve

Relationship of dose to response can be illustrated by a graph which is called as dose response curve. Dose response curve is required:-

Deciding dose of drug

Comparing dosage to percentage of people showing different effects

Intensity of response increases with increase in dose and dose response curve is rectangular hyperbola

Dose response and log dose-response curves

Dose response curve is rectangular hyperbola

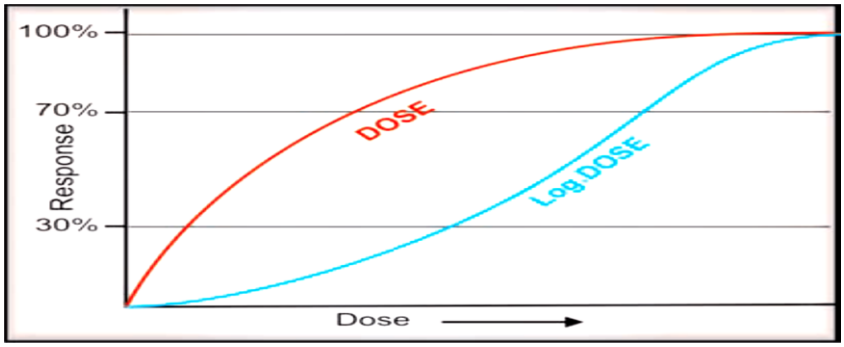
This is because drug-receptor interaction obeys law of mass action, accordingly

$$E = Emax \times [D] / Kd \times [D]$$

Where E = Observed effect of dose of drug

Emax = maximal response

Kd = dissociation constant of drug receptor complex

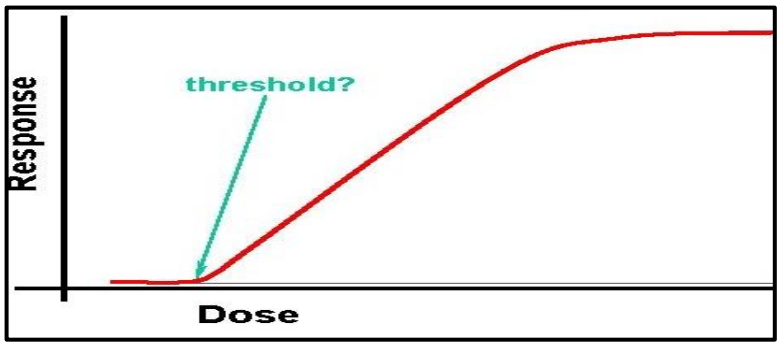


Advantages of Plotting Log Dose Response Curves

- Wide range of drug doses can be displayed on graph.
- Comparison between agonist and antagonist becomes easy.

THRESHOLD

A dose below which there are no adverse effects from exposure to chemicals



TYPES OF DOSE RESPONSE CURVES

1. GRADED DOSE RESPONSE CURVES

- Graded dose response curves are constructed for response that are measured on continuous scale e.g heart rate
- Graded dose response curves relates the intensity of response to size of dose hence used in characterizing actions of drug Graded dose response means slight increase of drug brings small increase in response. e.g increased dose of Histamine causes gradual contraction of guinea pig ileum
- Very low dose of histamine has no effect and response is obtained only beyond the threshold dose of 20 mg
- Very high dose of more than 50 mg has no additional effect and response remains constant at this maximal levels
- Graded dose response means the pharmacological effect of drug expressed in quality or number such as heart rate by beat and blood pressure by mmHg

2. QUANTAL DOSE RESPONSE CURVES

- Quantal dose response curves are constructed for those drugs that elicit all or none response. e.g presence or absence of epileptic seizures.
- Indicates that given dose of drug has or has not evoked a certain effect in various subject under investigation that is pharmacological effects are expressed in passive or negative.
- Quantal dose response curves.
- An experiment performed on 100 subjects and the effective dose to produce a quantal response was determined for each individual.

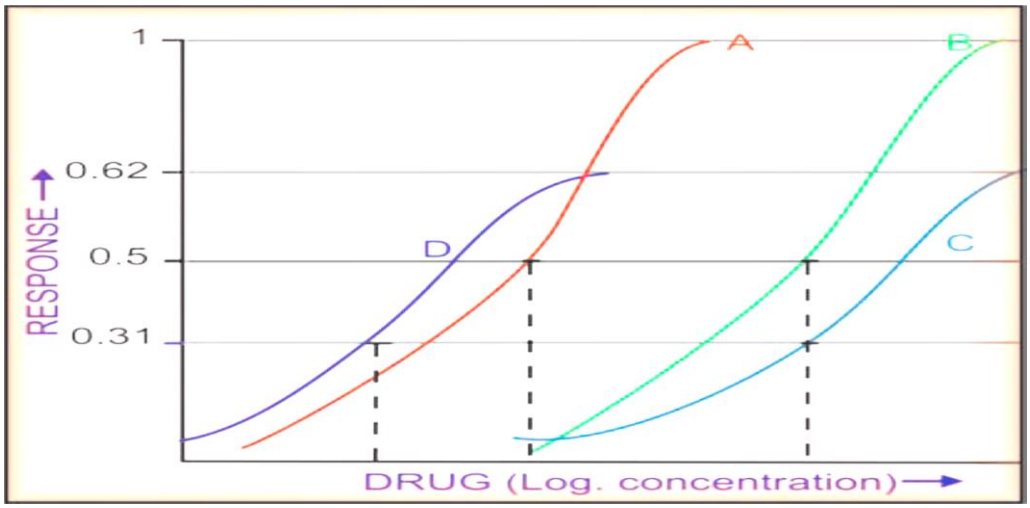
DOSE RESPONSE CURVE INFORMATION

Drug potency and efficacy

Drug Potency refers to amount of drug needed to produce a response. Relative potency is more meaningful than absolute potency. e.g If 10 mg of morphine=100 mg of pethidine, morphine is 10 times more potent than pethidine.

Drug Efficacy refers to ability of drug to elicit a response when it binds to a receptor

e.g Morphine produces a degree of analgesia not obtainable with any dose of aspirin hence Morphine is more efficacious than aspirin



Drug potency and efficacy curves

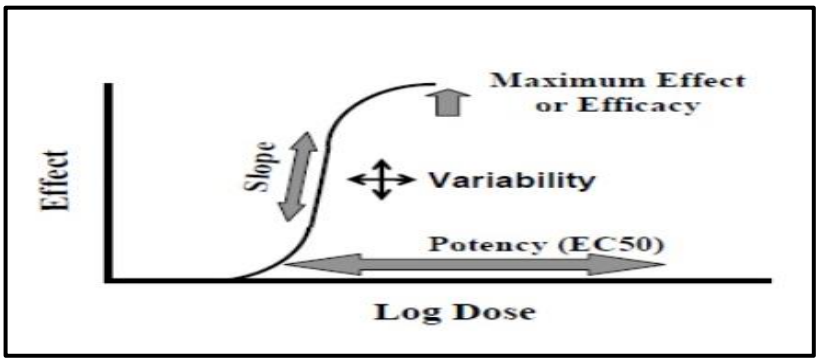
Drug potency and efficacy curves

- Drug B is less potent but equally efficacious as drug A
- Drug C is less potent and less efficacious than drug A ,But equally potent and less efficacious than drug B
- Drug D is more potent than drug A, B,& C but less efficacious than drugs A&B and equally efficacious as drug C.

SLOPE AND VARIABLITY

Effect of incremental increase in dose

Variability is reproductively of data different for different people



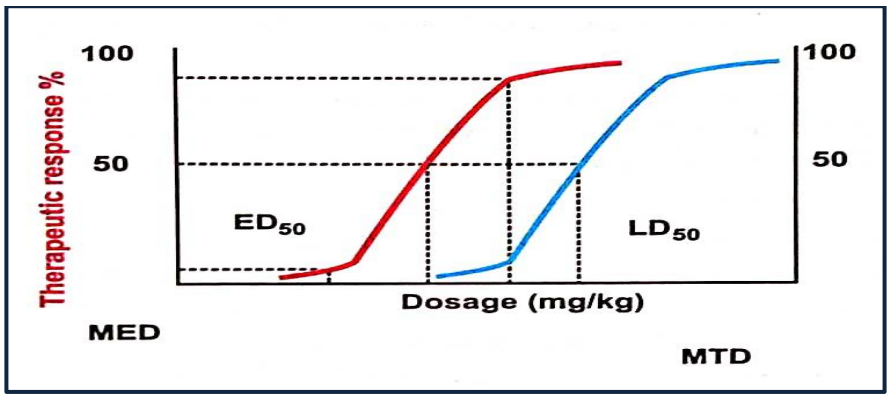
THERAPEUTIC INDEX

It is the ratio of LD_{50} to ED_{50}. The ratio of LD1 and ED99 will give batter index safety of the drug. The therapeutic index is a means of comparing the amount of a drug required to attain the therapeutic level in 50% of patients to the amount that is lethal 50% of patients. It is expressed as the ratio LD_{50}/ED_{50}.

A high therapeutic index is preferable, as the margin of safety between the dose that would be sufficient to achieve therapeutic levels and that which would produce toxic effects is high.

Therapeutic Index = Median lethal dose/ Median effective dose

Or LD_{50}/ED_{50}



Quantal DRC showing LD_{50} and ED_{50}.

ED_{50}-Dose which will be therapeutically effective in 50% of animal

LD_{50}- Dose which will on average kills 50% of animals in population.

MED- Minimum effective dose (the least dose that is likely to be effective). Also called toxic dose low (TDL).

MTD- Maximum tolerated dose (minimum toxic dose) (more than this will produces signs of toxicity). Also called highest nontoxic dose (HNTD).

COMBINE EFFECT OF DRUG

Synergism: When the action of one drug is facilitated or increased by the other, they are said to be synergistic. They are further of two types:

Additive: The effects of the two drugs are in the same direction and simply add up:

Effect of Drugs A + B = Effect of Drug A + Effect of Drug B

For example: combination of paracetamol and aspirin will provide the effect of both i.e. antipyretic + analgesic.

Supra-additive: The effect of combination is greater than the individual effects of the components:

Effect OF Drug A + B > Effect of Drug A +Effect of Drug B

For example: combination of levodopa and carbidopa increase the effect of drug, because carbidopa inhibit the peripheral metabolism of levodopa.

Antagonism: When one drug decreases or abolishes the action of another, they are said to be antagonistic.

Effect of Drugs A + B < Effect of Drug A + Effect of Drug B

For example: Glucagon and insulin on blood sugar level. Glucagon increase the blood sugar level where insulin reduce the blood sugar level. Hence, if they are given in combination they will act opposite to each other and the net effect will be nil.

FACTORS AFFECTING DRUG ACTION

Variation in response to the same dose of a drug between different patients and even in the same patient on different occasions is a rule rather than exception.

Body size: It influences the concentration of the drug attained at the site of action. The average adult dose refers to individuals of medium built. For exceptionally obese or lean individuals and for children dose may be calculated on body weight (BW) basis:

Individual dose = BW (kg)/70 × average adult dose

It has been argued that body surface area (BSA) provides a more accurate basis for dose calculation, because total body water, extracellular fluid volume and metabolic activity are better paralleled by BSA.

Individual dose = BSA (m2)/1.7× average adult dose

The BSA of an individual can be calculated from Dubois formula:

BSA (m2) = BW (kg) 0.425 × Height (cm)0.725 × 0.007184

Age The dose of a drug for children is often calculated from the adult dose

Child dose= age/ (age+12) (young's formula)

Child dose= Age/ 20 X Adult dose (Dilling's formula)

It can also be calculated (more accurately) on BW or BSA basis (see above), and for many drugs, manufacturers give dosage recommendations on mg/kg basis. Average figures for children are given below. However, infants and children are not small adults. They have important physiological differences from adults. The newborn has low g.f.r. and tubular transport is immature.

Similarly, hepatic drug metabolizing system is inadequate in newborns — chloramphenicol can produce gray baby syndrome. Chloramphenicol can produce gray baby syndrome. Blood-brain barrier is more permeable—drugs attain higher concentration in the CNS (accumulation of unconjugated bilirubin causes kernicterus). Drug absorption may also be altered in infants because of lower gastric acidity and slower intestinal transit.

Age	Ideal BW (Kg)	BSA (m2)	% of Adult dose
Newborn	3.2	0.23	12.5
1 month	4.0	0.26	15
3 months	5.5	0.32	18
6 months	7.5	0.4	22
1 year	10	0.47	25
3 years	14	0.62	33
5 years	18	0.73	40
7 years	23	0.88	50
12 years	37	1.25	75

After the first year of life, drug metabolism is often faster than in adults. theophylline, phenytoin, carbamazepine t½ is shorter in children. Also, higher per kg dose is needed for drugs which are primarily excreted unchanged by kidney, e.g. daily dose of digoxin is about 8–12 µg/kg compared to adult dose of 3–5 µg/kg. In the elderly, renal function progressively declines compared to young adults. Drug doses have to be reduced. There is also a reduction in the hepatic microsomal drug metabolizing activity and liver blood flow: oral bioavailability of drugs with high hepatic extraction is generally increased, but the overall effects on drug metabolism are not uniform.

Sex: Females have smaller body size and require doses that are on the lower side of the range. Subjective effects of drugs may differ in females because of their mental makeup. Maintenance

treatment of heart failure with digoxin is reported to be associated with higher mortality among women than among men. A number of anti-hypertensive have potential to interfere with sexual function in males but not in females.

Species and race: Among human beings some racial differences have been observed, e.g. blacks require higher and mongols require lower concentrations of atropine and ephedrine to dilate their pupil. B-blockers are less effective as antihypertensive in Afro-Caribbeans. Indians tolerate thiacetazone better than whites. Considering the widespread use of chloramphenicol in India and Hong Kong, relatively few cases of aplastic anaemia have been reported compared to its incidence in the west. Similarly, quiniodochlor related cases of sub-acute myelooptic neuropathy (SMON) occurred in epidemic proportion in Japan, but there is no confirmed report of its occurrence in India despite extensive use.

Route of administration: Route of administration governs the speed and intensity of drug response. Parenteral administration is often resorted to for more rapid, more pronounced and more predictable drug action. A drug may have entirely different uses through different routes, e.g. magnesium sulfate given orally causes purgation, applied on sprained joints—decreases swelling, while intravenously it produces CNS depression and hypotension.

Environmental factors and several: Environmental factors affect drug responses. Exposure to insecticides, carcinogens, tobacco smoke and consumption of charcoal broiled meat are well known to induce drug metabolism. Type of diet and temporal relation between drug ingestion and meals can alter drug absorption. Time of administration Subjective effects of a drug may be markedly influenced by the setup in which it is taken. Hypnotics taken at night and in quiet, familiar surroundings may work more easily. It has been shown that corticosteroids taken as a single morning dose cause less pituitary-adrenal suppression.

Psychological factor: Efficacy of a drug can be affected by patient's beliefs, attitudes and expectations. This is particularly applicable to centrally acting drugs, e.g. a nervous and anxious patient requires more general anesthetic; alcohol generally impairs performance but if punishment (which induces anxiety) is introduced, it may actually improve performance by relieving anxiety.

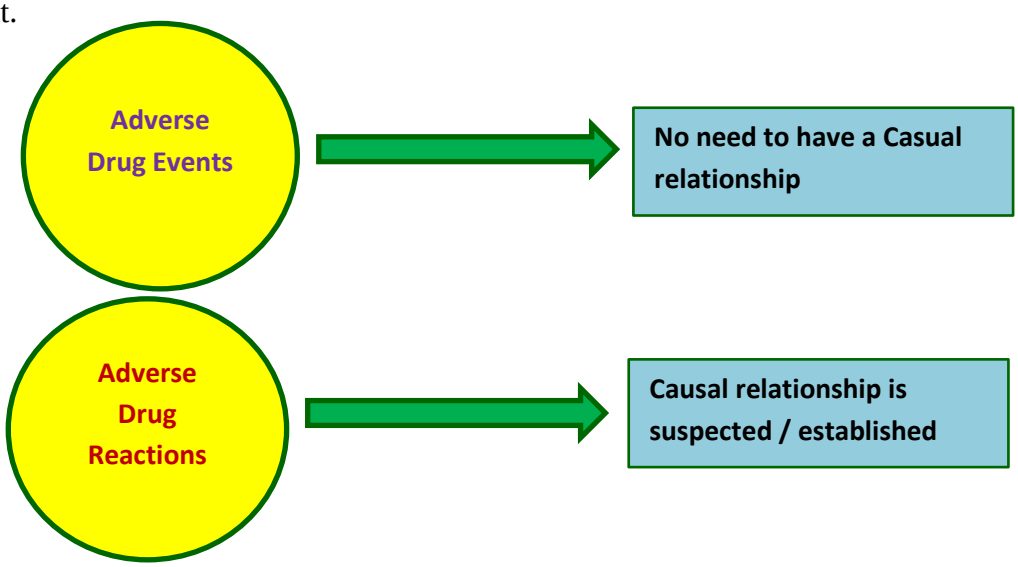
Disease: Not only drugs modify disease processes, several diseases can influence drug disposition and drug action. Certain g.i. diseases can alter absorption of orally administered drugs. Similarly liver disease can alter the metabolism of the drug and Kidney disease can alter the excretion of the drug.

Other drugs: Drugs can modify the response to each other by pharmacokinetic or pharmacodynamics interaction between them.

ADVERSE DRUG REACTIONS

Adverse Drug Reaction: Any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates In future use of same drug

Adverse Events: Any unwanted medical occurrence that may present during treatment a pharmaceutical product but which does not necessarily have causal relationship with this treatment.



Classification of ADRs

ADRs is very important as safe use of the medicinal product is critical issue for pharmaceutical, industry, doctors, pharmacist and public. ADR may occur immediately or after prolonged use after termination.

1. **Type A (Augmented) Reactions**
2. **Type B (Bizarre) Reactions**
3. **Type C(Continuing) Reactions**
4. **Type D(Delayed) Reactions**
5. **Type E(End of use) Reactions**
6. **Type F(Failure of Therapy) Reactions**

1. Type A (Augmented) Reactions

Dose related

Extension of Pharmacological effect.

Also called predictable or anticipated events.

Most frequent or less serious

Eg. Respiratory depression with opioids

2. Type B (Bizarre) Reactions

Non dose related

Also called pharmacologically unexpected, unpredictable of Idiosyncratic reaction

Generally more serious and less frequent

Eg. Skin rashes with antibiotics

3. Type C(Continuing) Reactions

Dose & time related

Associated with long term use

Eg. NSAID induced renal failure

4. Type D(Delayed) Reactions

Apparent only sometime after use of drug

Timing of these may make them more difficult to detect.

e.g. Thalidomide in first trimester caused phocoelia limb defects.

5. Type E (End of use) Reactions

Associated with the withdrawal of a medicine

e.g. Insomnia, anxiety & perceptual disturbances following withdrawal of benzodiazepines.

6. Type F(Failure of Therapy) Reaction

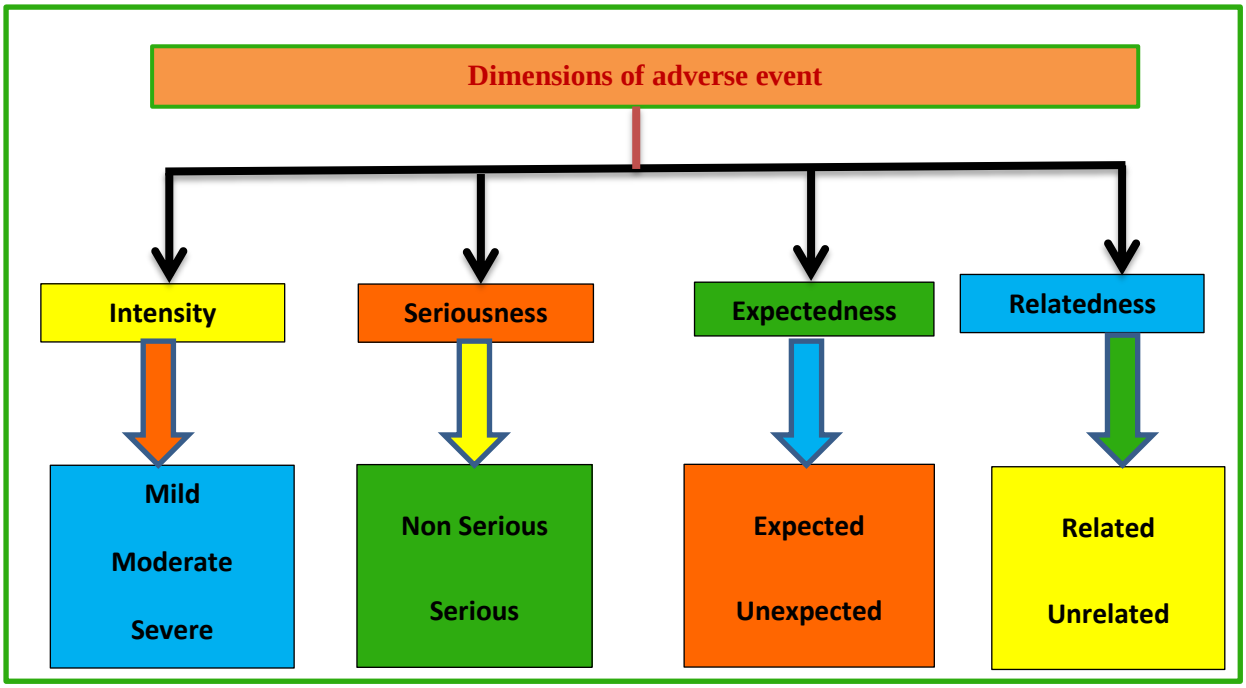
Failure of therapy which can be due to diverse causes such as inadequate information on the consumption, quality of drug etc.

e.g. Anti-tubercular therapy

Prevention of ADR

- By taking following steps, chances of ADR can be minimized/ prevented:-
- Avoid inappropriate drugs in the context of clinical conditions
- Use right dose, route, frequency based on patient variables
- Elicit medication history and history of allergy
- Rout of drug interactions
- Adopt right technique of medication and follow adequate monitoring

Dimensions of AE



The tern s**evere** is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infraction). The event itself, may be of relatively minor medical significance (such as severe headache) While the term **serious** is based on patient's event outcome or action criteria.

Several terms commonly used to describe the adverse effect of drug therapy:-

Side effects

Side effect as name indicates it is the side wise effect along with main effect of drug which was taken intentionally. Side effects are often associated with the therapeutic effect and it is well known in advance prior to drug administration**.**

Drug toxic effects

Toxic effect is the result of excessive pharmacological action of drug due to over dosage or prolonged use. Over usage may be intentional or relative related with therapeutic dose. The effects are predictable and dose related.

Drug Abuse

Drug abuse is a somehow misuse of drug. In this case people use the drug not for the intended or prescribed purpose but for other narcotic purpose. There are several examples- codeine was a good antitussive drug but few people used that for narcotic purpose.

Intolerance

It is the appearance of characteristic toxic effects of a drug in an individual at a therapeutic dose.

It is a converse of tolerance and indicates a low threshold of individual to the action of drug.

Idiosyncrasy

It is genetically determined abnormal reactivity to a chemical. The drugs interact with some unique feature of the individual, not found in majority of subjects, and produce the uncharacteristic.

Drug Allergy

It is an immunologically mediated reaction producing stereo type symptoms which are unrelated to the Pharmacodynamics profile of the drug, generally occur even with much smaller dose and have different time course of onset and duration. This is also called drug hypersensitivity.

Drug dependence

Drug capable of altering mood and feeling are liable to repetitive use to derive euphoria, withdrawal from reality, social adjustment etc. drug dependence is a state in which use of drug for personal satisfaction is accorded a high priority than other basic needs. It is of several types- psychological dependence, physiological dependence.

Photosensitivity

It is a cutaneous reaction resulting from drug induced sensitization of the skin to UV radiation. This may of two types- phototoxic and photo allergic.

Drug withdrawal

Physical and mental symptoms that occur after stopping or reducing intake of a drug. The characteristics of withdrawal depend on what drug is being discontinued.

Teratogenicity

It refers to the capacity of drug to cause fetal abnormalities when administered to the pregnant woman. This may cause disturbance in the organogenesis.

Carcinogenicity

The term carcinogen denotes a chemical substance or a mixture of chemical substances which induce cancer of increase incidence.

Mutagenicity

It refers to the capacity of drug to cause genetic defects and cancer respectively. Usually oxidation of the drug results in the production of reactive intermediate which affects gene and may cause structural changes, in the chromosome.

Drug induces disease

It is defined as the unintended effect of a drug that results in mortality or morbidity with symptoms sufficient to prompt a patient to seek medical attention and to require hospitalization and may persist even after the offending drug has been withdrawn.

DRUG INTERACTIONS (PHARMACOKINETIC AND PHARMACODYNAMICS

DEFINITION

Drug interaction is defined as the pharmacological activity of one drug is altered by the concomitant use of another drug or by the presence of some other substance.

The Drug whose Activity is effected by such an Interaction is called as a **"Object drug."** The agent which precipitates such an interaction is referred to as the **"Precipitant".**

Types of drug Interactions

1. Drug-drug interactions.
2. Drug-food interactions.
3. Chemical-drug interactions.
4. Drug-laboratory test interactions.
5. Drug-disease interactions.

The Net effect of a Drug Interaction is:

- Generally quantitative i.e. increased or decreased effect.
- Seldom qualitative i.e. Rapid or slower effect.
- Precipitation of newer or increased adverse effect.

Drug interactions are:

- Mostly undesirable
- Rarely desirable (beneficial): for eg.,enhancement of activity of penicillin's when administered with probenecid**.**

Factors contributing to drug interactions:

1. Multiple drug therapy.
2. Multiple prescribers.
3. Multiple pharmacological effects of drug.
4. Multiple diseases/predisposing illness.
5. Poor patient compliance.
6. Advancing age of patient.
7. Drug-related factors.

Mechanisms of drug interactions: The three mechanisms by which an interaction can develop are-

1. Pharmaceutical interactions.
2. Pharmacokinetic interactions.
3. Pharmacodynamic interactions.

Pharmaceutical interactions:

Also called as incompatibility. It is a physicochemical interaction that occurs when drugs are mixed in i.v . Infusions causing precipitation or inactivation of active principles. Example:- Ampicillin ,chlorpromazine & barbiturates interact with dextran in solutions and are broken down or from chemical compounds.

Pharmacokinetic Interactions:

"These interactions are those in which ADME properties of the object drug are altered by the precipitant and hence such interactions are also called as ADME interactions". The resultant effect is altered plasma concentration of the object drug. These are classified as:

1. Absorption interactions
2. Distribution interactions
3. Metabolism interactions
4. Excretion interactions.

Absorption interactions

Are those where the absorption of the object drug is altered. The net effect of such an interaction is:

- Faster or slower drug absorption.
- More, or, less complete drug absorption.

Major mechanisms of absorption interactions are:

1. Complexation and adsorption.
2. Alteration in GI pH.
3. Alteration in gut motility.
4. Inhibition of GI enzymes.
5. Alteration of GI micro flora.
6. Malabsorption syndrome.

ABSORPTION INTERACTIONS		
Object drug	**Participant**	**Influence on object drug**
Complexation & adsorption		
Ciprofloxacin, pencillamine	Antacids, food & minerals supplements containing al, mg, fe, zn & ca^{2+} ions	Formation of poorly soluble and absorbable complex with such heavy metal ions.
Alteration of GI pH		
Sulphonamides, Aspirin, ferrous sulphate	Antacids Sodium bicarbonate, Calcium carbonate	Enhanced dissolution and absorption rate. Decreased dissolution and enhance absorption
Alteration of gut motility		
Aspirin, Diazepam, levodopa, mexiletine	Metoclopramide	Rapid gastric emptying, increased rate of absorption.
levodopa, Mexiletine lithium carbonate,	anti-cholinergic delayed gastric emptying	decreased rate of absorption
Alteration of GI micro flora		
Digoxin	anti-biotic	Increased bioavailability due to destruction of bacterial flora that inactivates digoxin in lower intestine.
Malabsorption syndrome		
vitamin a,b12, digoxin	Neomycin	Inhibition of absorption due to mal.

DISTRIBUTION INTERACTIONS: Are those where the distribution pattern of the object drug is altered: The major mechanism for distribution interaction is alteration in protein-drug binding.

Competitive displacement interactions		
Object drug	**Participant0**	**Influence on object drug**
Displaced drug Displacer		
Anti-coagulants	Phenylbutazone, Chloral hydrate	Increased clotting time. Increased risk of hemorrhage.
lbutamide	lphonamides	Increased hypoglycemic effect

METABOLISM INTERACTIONS: Are those where the metabolism of the object drug is altered. Mechanisms of metabolism interactions include:

1. Enzyme induction: Increased rate of metabolism.

2. Enzyme inhibition: Decreased rate of metabolism. It is the most significant interaction in comparison to other interactions and can be fatal.

Metabolism interactions		
Object drug	**Precipitant**	**Influence on object drug**
Enzyme Induction		
Corticosteroids, Oral contraceptives, Coumarins, phenytoin	Barbiturates	Decreased plasma levels; decreased efficacy of object drugs
Oral contraceptives, Oral hypoglycemic	rifampicin	decreased plasma levels
Enzyme Inhibition		
Tyramine rich food	MAO inhibitors	Enhanced absorption of unmetabolized tyramine
Coumarins	metronidazole phenyl butanone	increased anti-coagulant activity

EXCRETION INTERACTIONS: Are these where the excretion pattern of the object drug is altered.

Excretion Interactions		
Object drug	**Precipitant**	**Influence on object drug**
Changes in active tubular secretion		
Penicillin, cephalosporin, and nalidixic acid	probenicid	Elevated plasma levels of acidic drugs
Changes in urine pH		
Amphetamine	Antacids, Thiazides, Acetazolamide	Increased passive reabsorption of basic drugs. Increased risk of toxicity
Changes in renal blood flow		
Lithium Bicarbonate	NSAIDS	Decreased renal clearance of lithium. Risk of toxicity

Major mechanisms of excretion interactions are-

- Alteration in renal blood flow
- Alteration of urine PH
- Competition for active secretions
- Forced diuresis

PHARMACODYNAMIC INTERACTIONS:

Are those in which the activity of the object drug at its site of action is altered by the precipitant. Such interactions may be direct or indirect. These are of two types

1. Direct pharmacodynamics interactions.
2. Indirect pharmacodynamics interactions.

Direct pharmacodynamics interactions:

In which drugs having similar or opposing pharmacological effects are used concurrently. The three consequences of direct interactions are

1. Antagonism.
2. Addition or summation.
3. Synergism or potentiation.

Antagonism: The interacting drugs have opposing actions Example: Acetylcholine and noradrenaline have opposing effects on heart rate.

Addition or summation: The interacting drugs have similar actions and the resultant effect is the some of individual drug responses Example: CNS depressants like sedatives and hypnotics etc

Synergism or potentiation: It is an enhancement of action of one drug by another Example: Alcohol enhances the analgesics activity of aspirin**.**

Indirect pharmacodynamics interaction:

In which both the object and the precipitant drugs have unrelated effects. But the latter in some way alerts the effects but latter in some way alerts the effects of the former.

Example: salicylates decrease the ability of the platelets to aggregate thus impairing the Homeostasis if warfarin induced bleeding occurs.

Reducing the risk of drug interactions:

- Identify the patient's risk factors.
- Take through drug history.
- Be knowledge about the actions of the drugs being used.
- Consider therapeutic alternatives.

- Avoid complex therapeutic regiments when possible.
- Educate the patient.
- Monitor therapy.

Consequences of drug interactions:

The consequences of drug interactions may be:

Major: Life threatening.

Moderate: Deterioration of patients' status.

Minor: Little effect.

Influence of smoking on drug interactions:

Smoking increases the activity of drug metabolizing enzymes in the liver, with the result that certain therapeutic agents. Example: Diazepam, propoxyphene, theophylline, olanzapine. Are metabolized more rapidly, and their effect is decreased

Influence of alcohol on drug interaction:

Chronic use of alcohol beverages may increases the rate of metabolism of drugs such as warfarin and phenytoin, probably by increasing the activity of hepatic enzymes.

- Acute use of alcohol by non-alcoholic individuals may cause an inhibition of hepatic enzymes.
- Use of alcoholic beverages with sedatives and other depressants drugs could result in an excessive depressant response.

Influence of Food on Drug Interaction:

Food affects the rate and extent of absorption of drugs from the GI tract. Example: Many anti biotic should be given at least 1hr before or 2hr after meals to achieve Optimal absorption.

- The type of food may be important with regard to the absorption of concurrently administered Drugs. Example: Dietary items such as milk and other dairy products that contain calcium may decrease. The absorption of tetracycline and flour quinolone derivatives.
- Diet also may influence urinary pH values.

DRUG DISCOVERY AND CLINICAL EVALUATION OF NEW DRUGS

Drug Development Process

Drug development is basically bringing out a new product into the market. On average it takes about 10-15 years to develop a drug from its discovery to getting approved for marketing it available in the market for its usage.

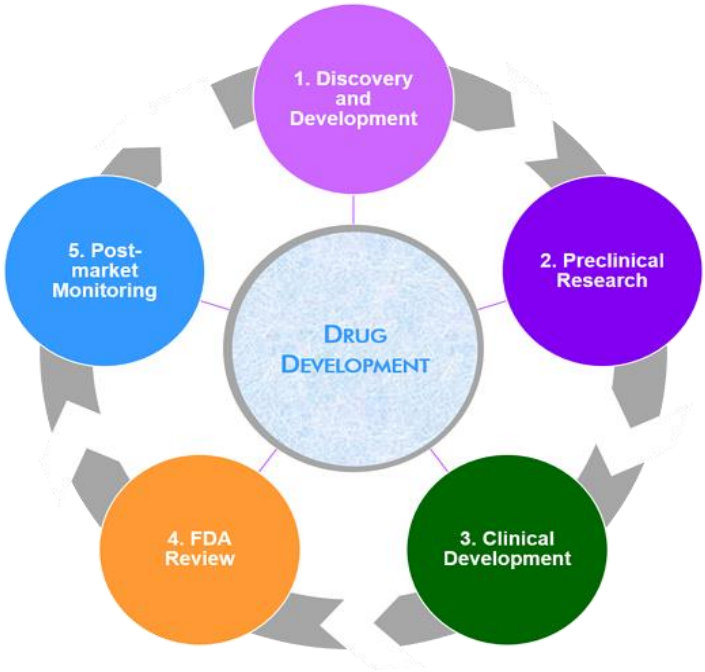
Drug Development process can be divided into:

Discovery Phase

Pre-Clinical Phase

Clinical Phase

Market Phase

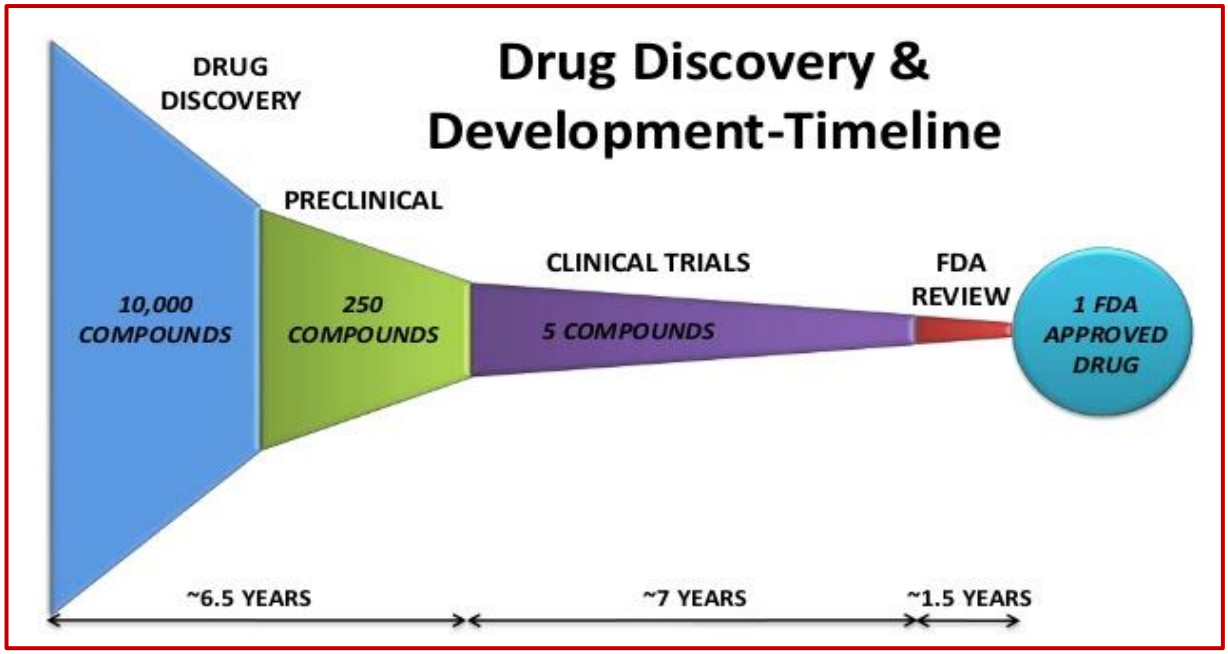


Drug Discovery

In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery.

- But now we know diseases are controlled at molecular and physiological level.
- Also shape of a molecule at atomic level is well understood.

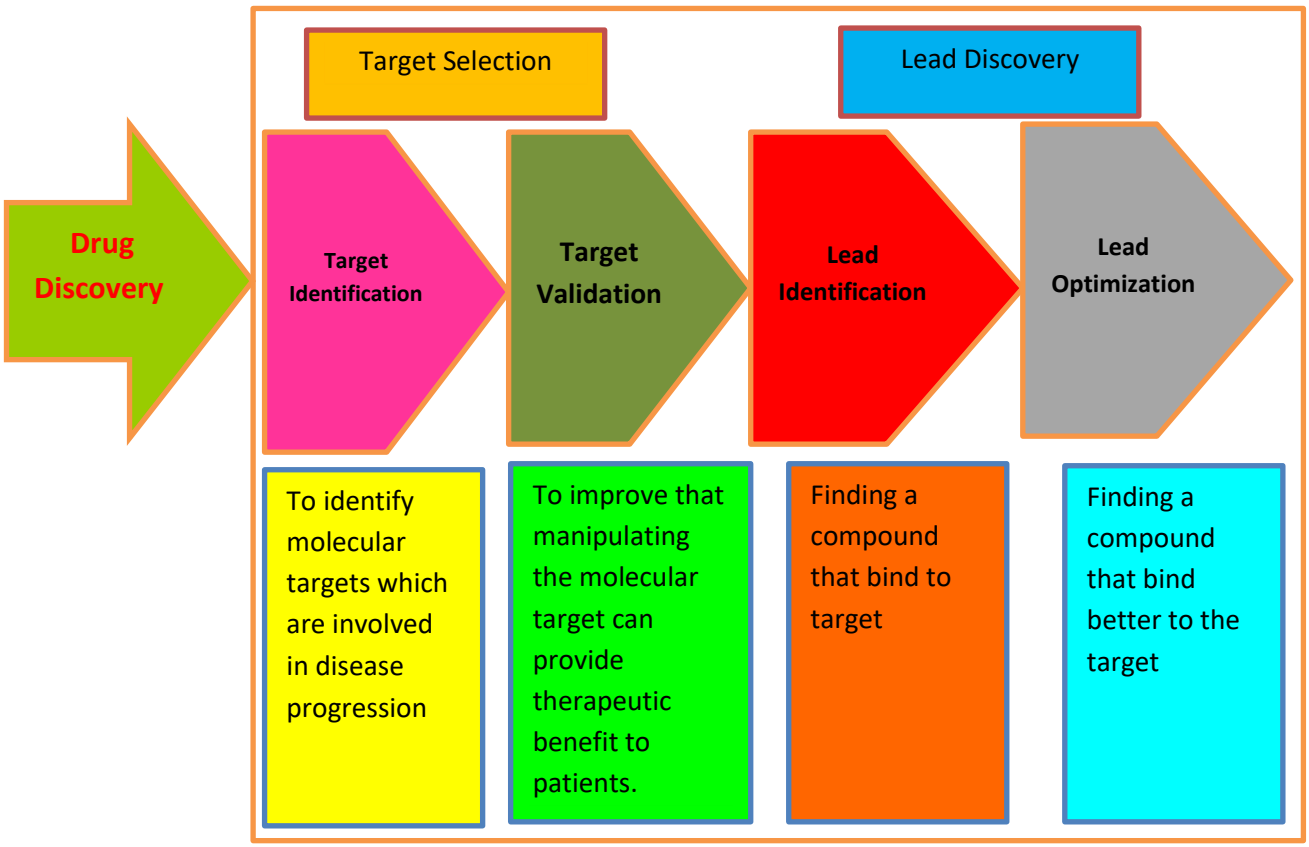
"A process that starts with the identification of disease and therapeutic target of interest and include methodology, assay development ,lead identification and characterization in vitro ,formulation and animal pharmacological studies ,pharmacokinetics and safety studies in animals and clinical studies in the human ."



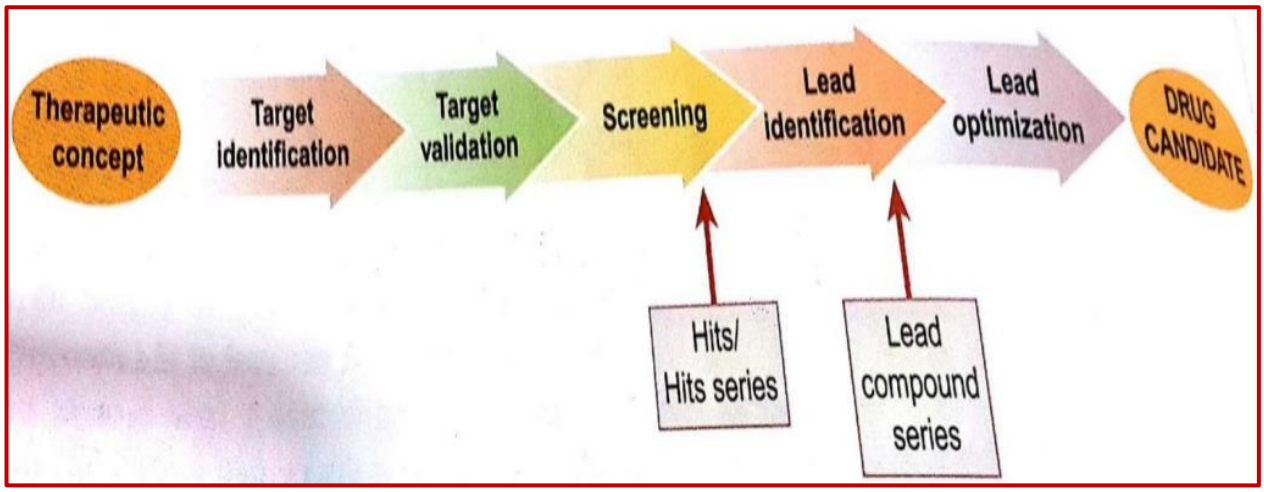
Drug Discovery

DRUG DISCOVERY PHASES

Discovery phase is the first phase of drug development process which includes the following:



Discovery phase overview

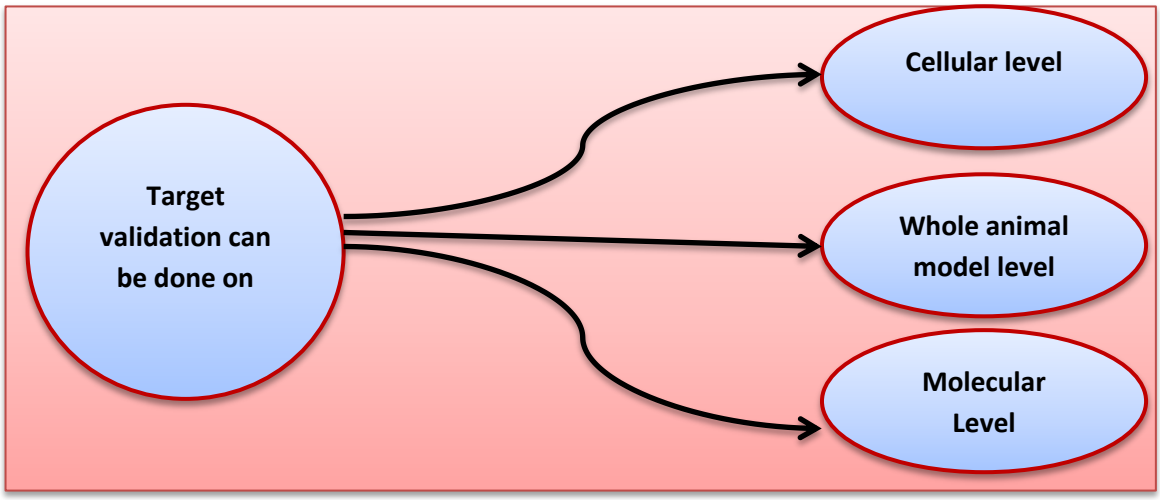


TARGET SELECTION

Target selection in drug discovery is defined as the decision to focus on finding an agent with a particular biological action that is anticipated to have therapeutic utility

Target identification: to identify molecular targets that is involved in disease progression.

Target validation: to prove that manipulating the molecular target can provide therapeutic benefit for patients.



Target Validation

LEAD DISCOVERY

Lead compound is a chemical that has pharmacological/biological activity likely to be therapeutically useful, but may still have sub-optimal structure that structure that requires modification to fit better to the target.

Lead Identification: Find a compound that bind to target.

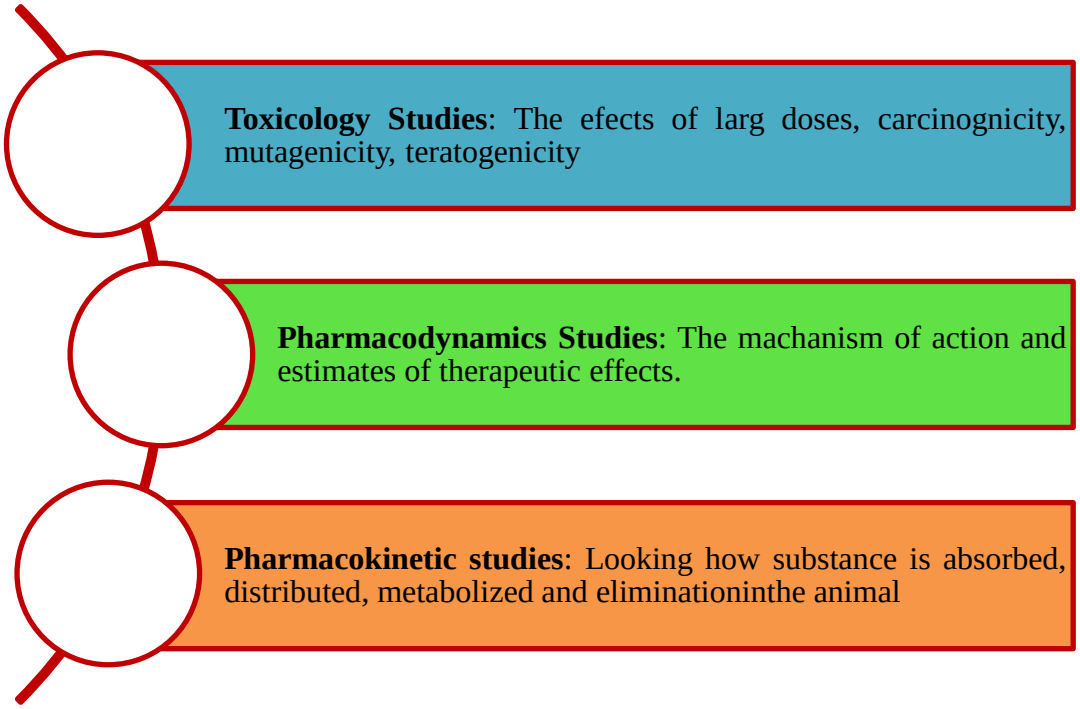
Lead optimization: Find compound that bind better to the target.

PRE-CLINICAL PHASE

In this phase, research in animal model, ex vivo and in vivo experiments takes place to check the safety and efficacy of new potential compound which is carried out according to regulatory guidelines. Major areas are:

- Pharmacodynamics studies in vivo in animals, In vitro preparation
- Absorption, distribution , elimination studies (pharmacokinetics)
- Acute, sub-acute, chronic toxicity studies (toxicity profile)
- Therapeutic index (safety & efficacy evaluation)

Animal Studies comprises of:-



OBJECTIVES OF PRECLINICAL STUDIES

- The purpose of pre-clinical study is to develop adequate data to decide that it is reasonably safe to proceed with human trials of the drug.
- Means, a laboratory test of a new drug or a new medical device, usually done on animal subjects, to see if the treatment really works and if it is safe to test on humans
- However the main objective is to collect the data to submit to the FDA for IND filing.

IND APPLICATION FILING

Once preclinical studies have indicated the safety and efficacy of a drug an IND application has to be filed with the regulatory authorities. For obtaining regulatory Approval for Phase I, phase II and Phase III clinical evaluation. Contents of IND application:

- Preclinical Data (All data from animal studies)
- Information on composition and source of drug
- Chemical and manufacturing information
- Proposed clinical plans and protocol
- Ethical Committee Clearance

CLINICAL PHASE

The clinical studies test the potential treatments (drug, device or biologics like vaccines human volunteers or patients to see whether they should be further investigated or approved for the wider use in general population.

Types of clinical trial

- Randomized
- Blinded or open label
- Prospective or retrospective
- Placebo
- Pilot study.
- Cross-over study.

Randomized: Subjects have equal chance to be assigned to one of two or more groups just like tossing of coin. – One group gets the most widely accepted treatment (standard treatment) – The other gets the new treatment being tested – All groups are as alike as possible; removes the probability of bias.

Open label trial Doctor and patient know which drug is given

Blinded clinical trial

Single Blind: the patient doesn't know which treatment he/she is getting

Double Blind: neither doctor nor patient knows

Prospective: Patients are enrolled for the study before any treatment begins Progress of patients is monitored during course of treatment

Retrospective: Past case records & other statistical data are used for analysis Investigator has to rely on methods employed & data available

Placebo Study:

It is an inert medicament given in the garb of medicine.

It resembles the active drug in physical properties but does not have any pharmacological activity.

The new treatment is tested against a placebo.

Pilot Study:

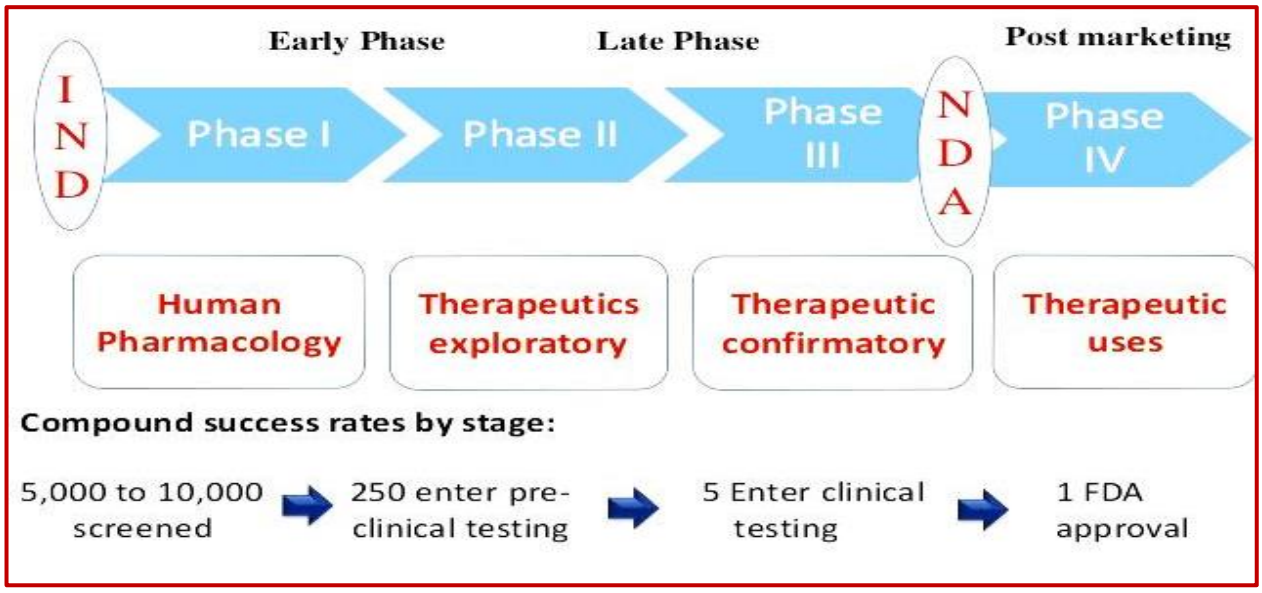
A small study that helps to develop a bigger study.

Advantage

- ✓ To find out possible difficulties
- ✓ To help with design of the bigger, more pivotal study.

Cross-Over Study: Two types of treatment are studied in the same group. • Before giving 1st treatment baseline observations are made for certain period – "Run-in period". • When one treatment is over, before starting 2nd treatment some time is allowed for the effect of treatment to completely wash out – "Wash-out period".

PHASE OF CLINICAL TRIALS



PHASE 0 STUDY /MICRODOSING

- Study of new drug in micro doses to derive PK information in human before undertaking phase I studies is called PHASE O
- Micro dose: Less than 1/100 of the dose of a test substance calculated to produce pharmacological effect with a max dose ≤100 micrograms

Objective:

- ➢ To obtain preliminary Pharmacokinetic data.
- ➢ Preclinical Data: Sub acute toxicity study in one species by two routes of administration.

Advantages:

Less chances of adverse effects

Short duration

Less no. of volunteers

Reduced cost of development

Reduced drug development time

Limitations:

- ✓ Study mainly based on PK parameters - not efficacy and safety based
- ✓ Agents having different kinetic characteristics between micro dose and full dose are not evaluated by phase 0 trials
- ✓ The laboratory parameters are very limited and expensive, researchers have to depend on BA/BE labs

PHASE I CLINICAL TRIAL

- First stage of testing in human subjects.
- Designed to assess the safety, tolerability, PK and PD of drug.
- 20-80 healthy volunteers; Duration: 6-12 months.
- Patients: Anticancer drugs, AIDS therapy.
- The aim of a Phase I trial is to determine the maximum tolerated dose (MTD) of the new treatment.
- Kinds of Phase I:
- SAD: Single ascending dose studies.
- MAD: Multiple ascending dose studies.
- Food Effect: Investigates differences in absorption caused by food.
- SUBJECTS: • Healthy human volunteers: Commonly used.
- Patient Volunteers: Cytotoxic drugs, AIDS therapy -Patients in advanced stage of disease.

LIMITATIONS:

Trial restricted to homogenous subjects.

Performance extrapolated to heterogeneous market place.

PHASE II CLINICAL TRIAL

- It is a Therapeutic Exploratory Trial consists of 100-500 Subjects.
- To confirm effectiveness, monitor side effects, & further evaluate safety.
- First in patients (who have the disease that the drug is expected to treat).

- Duration: 6 months to several years.
- Optimum dose finding:
- Dose efficacy relationship
- Therapeutic dose regimen
- Duration of therapy
- Frequency of administration
- Therapeutic window
- For New Actions of a marketed drug, start with Phase II (Phase I exemption obtained).

Phase II Study Types:

Phase IIA: Designed to assess dosing requirements.

Phases IIB: Designed to study efficacy.

PHASE III CLINICAL TRIALS

- It is a Therapeutic confirmatory trial.
- Target population: several 1000 to 3000 patients.
- Duration: Takes a long time, up to 5 years.
- To establish efficacy of the drug against existing therapy in larger number of patients, method of usage, & to collect safety data etc.
- To assess overall and relative therapeutic value of the new drug Efficacy, Safety and Special Properties

Subtypes:

Phase IIIA: To get sufficient and significant data.

Phase IIIB: Allows patients to continue the treatment, Label expansion, additional safety data. Phase III B studies are known as "label expansion" to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing.

End of Clinical Trial Activities

- Sponsor: Expert Committee review of Efficacy, safety and potential sales (Profit).
- Go-No Go decision to file new drug application with DCGI.
- Expert review by DCGI's Committee
- DCGI approval.
- NCE marketed Phase IV begins 2021.

NDA: New Drug Application

NDA Refers to New Drug Application. Formal proposal for the FDA/DCGI to approve a new drug for sale. Sufficient evidences provided to FDA/DCGI to establish:

- Drug is safe and effective.
- Benefits outweigh the risks.
- Proposed labeling is appropriate.

NDA contains all of the information gathered during preclinical to phase III.

PHASE IV CLINICAL TRIALS

Post Marketing Surveillance (PMS). No fixed duration / patient population. Helps to detect rare ADRs, Drug interactions and also to explore new uses for drugs [Sometimes called Phase V].

Periodic Safety Update Reports : To be submitted by the manufacturer every 6 months for 2 yrs and then annually for next 2 yrs after marketing approval.

Harmful effects discovered may result in a drug being no longer sold, or restricted to certain uses

Objectives of phase IV:

Confirm the efficacy and safety profile in large populations during practice.

Detect the unknown/rare adverse drug reaction/s.

Evaluation of over-dosage.

Identifications of new indications.

Dose refinement: Evaluation of new formulations, dosages, durations of treatment.

Reporting of ADR:

The ADR can be reported to a formal reporting system such as: WHO International System USFDA- Medwatch UK- Yellow card system INDIA- National Pharmacovigilance Programme (CDSCO)

PHARMACOVIGILANCE

Pharmaco (Greek) = drug or medicine **Vigilare (Latin) = To watch, keep awake or alert**

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. (As per WHO guidelines)

Overall Process

Discover

Develop

Proof of Safety

Proof of Evidence

Submit

Clinical trial

A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of, and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their efficacy and safety.

Clinical Trials: Snap shot

Clinical Trials

	Preclinical Testing		Phase I	Phase II	Phase III		FDA		Phase IV
Years	3.5		1	2	3		2.5	12 Total	
Test Population	Laboratory and animal studies	File IND at FDA	20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers	File NDA at FDA			Additional Post marketing testing required by FDA
Purpose	Assess safety and biological activity		Determine safety and dosage	Evaluate effectiveness, look for side effects	Verify effectiveness, monitor adverse reactions from long-term use		Review process / Approval		
Success Rate	5,000 compounds evaluated		5 enter trials				1 approved		

Adverse Event

Any untoward medical occurrence that may present during treatment with a pharmaceutical product at any dose, but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction

A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. (WHO).

Serious Adverse Event

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect?
- is any other important medical event?

History of Pharmacolvigilance

1848: The Lancet starts collecting notifications of side effects after a death caused by anesthesia.

1906: US Federal Food and Drug Act require that pharmaceuticals be “pure” and “free of any contamination”.

1937: USA: 107 lethal cases after diethylenglycol was mistakenly used to solubilize sulphanilamides.

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1906: US Federal Food and Drug Act require that pharmaceuticals be “pure” and “free of any contamination”.

1937: USA: 107 lethal cases after diethylenglycol were mistakenly used to solubilize sulphanilamides.

1967: Start of WHO Programme for International Drug Monitoring.

1976: Drugging of the Americas: inadequacy of safety information.

1990: ICH - elaboration of intra-regional requirements for safety starts

The thalidomide tragedy

20th Century

1962 – A new sleeping pill is found to have caused birth defects in thousands of babies born in Western Europe. Terratogenic effects in new borns.

Dr. Frances Kelsey, FDA kept Thalidomide off the U.S. Market

Sulfanilamide tragedy

Sulfanilamide had been used safely for some time in tablet and powder form to treat streptococcal infections

S.E. Massengill Co., a pharmaceutical company dissolved the drug in diethylene glycol and sold it in the liquid form after testing for flavor and colour

Toxicity testing was not done and resulted in deaths of 100 children in 1937

The company was sued for misbranding

The current status WHO International drug monitoring programme was laid in 1971.

2000:

WHO UMC provided guidelines for setting up a pharmacovigilance center.

CIOMS and ICH were established for development of pharmacovigilance world wide.

The UK 'yellow card' system for the reporting of suspects adverse effects came into being in1964

1968 WHO drug monitoring programme was laid

Classical example of serious and unexpected adverse reactions

Medicine	Adverse reaction
Aminophenazone(amidopyrine)	Agranulocytosis
Chloramphenicol	Aplastic anaemia
Clioquinol	Myelooptic neuropathy (SMON)
Erythromycin estolate	Cholestatic hepatitis
Fluothane	Hepatocellular hepatitis
Methyldopa	Haemolytic anaemia
Oral contraceptives	Thromboembolism
Practolol	Sclerosing peritonitis
Reserpine	Depression

Pharmacovigilance

When a medicine is released into the market there is still uncertainty about the safety of the product.

Once marketed, the drug is openly available for the use of large population, which brings a major safety concern.

In order to prevent unnecessary sufferings by patients, it is essential to have a drug safety monitoring system in place in every country.

Thalidomide disaster

Thalidomide was first marketed in the late 1950s as a sedative and was used in the treatment of nausea in pregnant women.

Within a few years of the widespread use of thalidomide in Europe, Australia, and Japan, approximately 10,000 children were born with phocomelia, leading to the ban of thalidomide in most countries in 1961.

The thalidomide tragedy also brought into sharp focus the importance of rigorous and relevant testing of pharmaceuticals prior to their introduction into the marketplace

Need of Pharmacolvigilance

Unreliability of preclinical data

Well controlled conditions

Small and specific sample size

Pressure from various groups to reduce time to approval

Changing pharmaceutical marketing strategies

Aggressive marketing

Direct to customer advertising

Launch in many countries at a time

Changing physician and patient preferences

Increasing use of newer drugs

Increasing use of drugs to improve quality of life

Shift of supervised to self-administered therapy

Easy accessibility

Increasing conversion of prescription drugs to OTC drugs

Easy access by internet

Easy availability of complimentary medicines

Easy availability of substandard drugs

The scope of Pharmacolvigilance

- To improve patient care and safety
- To improve public health and safety
- To contribute to the assessment of benefit, harm, effectiveness and risk of medicines
- To promote education and clinical training
- To promote effective communication to the public.
- To promote rationale and safe use of medicines.

Goals of Pharmacolvigilance

- Early detection of unknown safety problems
- Detection of increase in frequency of ADR's
- Identification of risk factors
- Quantifying risks
- Preventing patients from being affected unnecessarily

Aim of Pharmacolvigilance

- Improve patient care and safety in relation to the use of medicines and all medical & paramedical interventions.
- Improve public health and safety in relation to the use of medicines.
- Contribute to the assessment of benefit, harm, effectiveness and risk of medicines.
- Encouraging their safe, rational and more effective (including cost-effective) use.
- Promote understanding, education and clinical training in Pharmacolvigilance and its effective communication to the public.

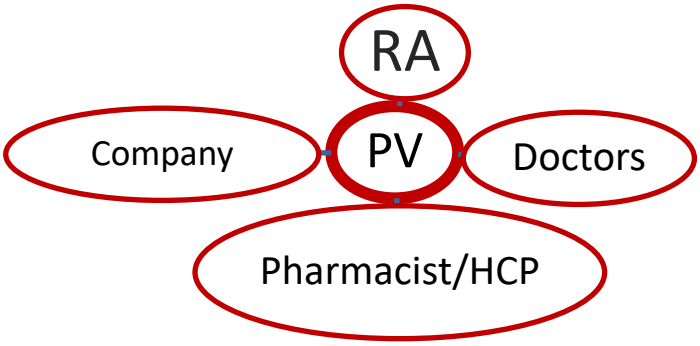
PHARMACOVIGILANCE- A SHARED RESPONSIBILITY

Company – legally and morally responsible for monitoring their product.

Regulatory authorities – are responsible for the safety of the drugs they license

Doctors – responsible to patients

Pharmacist & nurse – responsible to patients



Sources of Pharmacolvigilance

- Pre-clinical studies
- Clinical studies (pre- and post-marketing)
- Spontaneous adverse reaction reporting
- National
- International
- Epidemiological studies
- Case-control (one effect/many risk factors)
- Cohort (one risk factor/many possible effects)
- Data collected for other purposes
- Routine statistics
- Databases of prescription and outcomes

Why is Pharmacolvigilance important

"Dying from a disease is sometimes unavoidable. But, dying from an adverse drug reaction is unacceptable".

-Dr Vladimir Lepakhin

Why is Pharmacolvigilance important?

- Bottlenecks in clinical studies
- Monitoring by Health Authorities
- To Increase in awareness among the physicians and the patients about adverse event reporting for better quality of life
- Early detection of unknown safety problems
- Detection of ADR's with increase in frequency.
- Identification of risk factors
- Quantification of risks
- Prevention of patients' unnecessary sufferings

Minimum Safety Information

- An identifiable patient
- An identifiable reporter
- A suspect drug or biological product
- An adverse event

Sources of adverse event reports

Pre-clinical studies

Clinical studies (Pre-post marketing)

Spontaneous Reports Literature, Internet, Consumers/HCPs &Other Sources –Lay press/ Media

Epidemiological studies

1.Case control

2.Cohort studies

Data collected for other purposes

1.Routine statistics

2.Databases for prescription and outcomes

ORGANIZATIONS WHICH PLAY A KEY ROLE IN PHARMACOVIGILANCE

World Health Organization (WHO)

International Conference on Harmonization (ICH)

Council for International Organizations of Medical Sciences (CIOMS)

The International Society of Pharmacovigilance (ISoP)

Key regulatory agencies

United States Food and Drugs Administration (USFDA)

European Medicines Agency (EMA)

Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK)

Pharmaceuticals and Medical Devices Agency (PMDA) in Japan

Health Canada

Therapeutic Goods Administration (TGA) in Australia

Chinese Food and Drug Administration (CFDA)

LONG ANSWER TYPE QUESTIONS (10 Marks)

1. Explain signal transduction mechanism and explain G-Protein coupled receptor
2. Define drug interaction. Explain pharmacokinetic and pharmacodynamics type of drug interaction with suitable examples.
3. Explain drug discovery process and elaborate different phases of clinical trial.

SHORT ANSWER TYPE QUESTIONS (5 Marks)

1. Define receptors. Explain various types of receptors family in short
2. Write short notes on adverse drug reaction with suitable examples.
3. What are various factors modifying drug action.
4. Write short notes on dose response relationship
5. What do you understand by combined effect of drugs? Give your answer with example.
6. What is Trans- membrane enzyme linked receptor.
7. What do you understand by mechanism of drug action?
8. Explain pharmacokinetic and pharmacodynamics in short along with their related examples**.**
9. Explain Pharmacolvigilance. Why it is important?
10. Explain combined effect of drugs with suitable examples
11. Explain essential drug concept

VERY SHORT ANSWER TYPE QUESTIONS (2 Marks)

1. Write a note on pharmacodynamics drug interaction.
2. Write a note on pharmacokinetic drug interaction.
3. Write a note on preclinical evaluation.
4. Write a note on drug interactions.
5. Define Pharmacolvigilance.
6. Enlist receptor theory.
7. Define phase of clinical trials.
8. Define therapeutic Index.
9. Write a note on drug discovery.
10. Write a note on ADR.
11. Enlist different type of receptor.