Unit-2

Pharmacology-I

B.Pharma 4 Semester Notes

UNIT-II

- **General Pharmacology**
  - **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 (pharmacokinetic and pharmacodynamic)**
  - **Drug discovery and clinical evaluation of new drugs** -Drug discovery phase, preclinical evaluation phase, clinical trial phase, phases of clinical trials and pharmacovigilance.

Pharmacodynamics:

It is the branch of pharmacology which is derived drom two word Pharmacodynamics.

The term,

Pharmaco = Drugs

Dynamics = Effect

It means the drug which produce the different-2 action inside the body.

Principles of Drug Action:

- Drug action is the pharmaco-dynamic parameter in which the study of drug effects and their action is described. One drug alters or inhibits the action of another drug.
- Drugs don't produce new functions to any cells/ tissues/organ they just alter the effect of the specific activity.

There are following action:-

1. Stimulation
2. Depression
3. Irritation
4. Replacement
5. Cytotoxic

1. Stimulation

- Stimulation is defined as the enhancement of the level of activity of specialized cells.

Example:

- Adrenaline stimulates the heart.
- Pilocarpine stimulates salivary gland.
- CNS stimulant action is produced by a high dose of picrotoxin.

2. Depression

- Depression is defined as the selective reduction of the activity of specialized cells.

Example:

- CNS depressant action is produced by barbiturates.
- Quinidine depresses the heart.
- Acetylcholine stimulates intestinal smooth muscles but depresses SA node in the heart.

3. Irritation

- This predicate a non-selective, often toxic effect on the specialized cells(epithelial cells, connective tissue). Strong irritation can also lead to inflammation, corrosion, necrosis etc.

4. Replacement

- Replacement is defined as the use of natural metabolites, hormones, or their derivatives in the state of deficiency.

Example:

- Levodopa is used in parkinsonism.
- Insulin is used in diabetes mellitus.
- Iron is used in anemia.

5. Cytotoxic Action

- Cytotoxic action is the toxic action on cancer cells or on the growing parasites without significantly affecting the host cells that are used for the diagnosis of infection and neoplasms.

Example:

- Penicillin
- Zidovudine
- Cyclophophamide
- Chloroquine

Mechanism of Drug Action

- The steps and path followed by the drug to produce its pharmacological action are called the mechanism of action.
- It involves- "HOW, WHERE & WHEN".
- Most of the drugs produce their effects by interacting with the target molecules and shows the action.
- Drug gives its action through four main functional proteins
  1. Enzymes
  2. Ion Channels
  3. Transporters
  4. Receptors

1. Enzymes-

- Almost all biological reactions are carried out under catalytic influences of enzymes. So when drug interact with it can either increase or decrease the rate of enzyme activity and also the biological activity.

Enzyme Induction: When drug bind with enzyme and increase its activity is known as enzyme induction.

Enzyme Inhibitor: When any drugs decrease the activity of enzyme is known as enzyme inhibition

- Competitive (structurally same as substrate so fight for same binding sites)
- Non-Competitive (It decrease the enzyme activity by binding with adjacent site or allosteric site).

2. Ion Channels:

- There are many ion channels in our body which helps transmembrane signaling and regulate intracellular ionic composition.
- Drugs can affect ion channels. Drugs can also affect ion movement by directly binding on channel.

Eg:

- Quinidine blocks the myocardial NA+ ion channel.
- Ethosuccimide inhibits T- type Ca2+ion-channel.
- Phenytoin modulates Na+ ion channel.
- Nicorandil opens ATP-sensitive K+ channel.

3. Transporters

- Transporters are the protein that is membrane-bound and transports the drugs inside and outside of the cell.
- Many drugs interact with transporters and bind with them & show their specific actions.
- They are also known as carriers.

Examples:

- Reserpine blocks the vesicular uptake of nor-epinephrine.
- Furosemide inhibits Na+Ka+2Cl- co-transporter in ascending loop of Henle.
- Probenecid restricts the active transport of uric acid, penicillins in renal tubules.
- Hydrochlorothiazide restricts the Na+Cl- symporter in distal tubule.

4. Receptors

- Receptors are proteins or binding site which present on surface and inside the cells, drugs bind with it activate it and give its pharmacological response.

Or

- These are proteins or macromolecules that bind to drugs, hormones, or neurotransmitters, initiating a biological response. Receptors can be found on the cell surface or within the cell.

Agonist:

- An agent which receptor to produce effects.
- Agonist are those legand molecule which have similar structure and action to the natural drug there affinity 100% and efficacy is also 100%.

Antagonist:

- A chemical substance that binds to and blocks the activation of certain receptors on cells, preventing a biological response.
- An agent which inhibit the action of agonist.
- Thoes legand molecule whose affinity is 100% but efficacy 0% so they bind with the receptor completely but produce no response.

Receptor Theories:

- Induced fit theory
- Occupation theory
- Rate theory
- Two State model

Induced fit theory:

- It is based on **Lock-and-key theory:** Proposed by Emil Fischer, it suggests a specific fit between a drug (key) and its receptor (lock) for interaction and action.

Occupation Theory:

- According to this theory, pharmacological response is depend on that now much drug occupied the receptors.
- Pharmacological Effect of Drugs × Na of Receptor Occupied
- Maximum response occurs when all the receptors are occupied.

Rate Theory:

- According to this theory The response is proportional to the rate of drug-receptor formation.

$$Pharmacological\ effect\ of\ drugs \times Formation\ of\ Drug - receptor\ Complex$$

- The more drug bind with receptors the more receptors will be activated.

Drug Receptors Interactions:

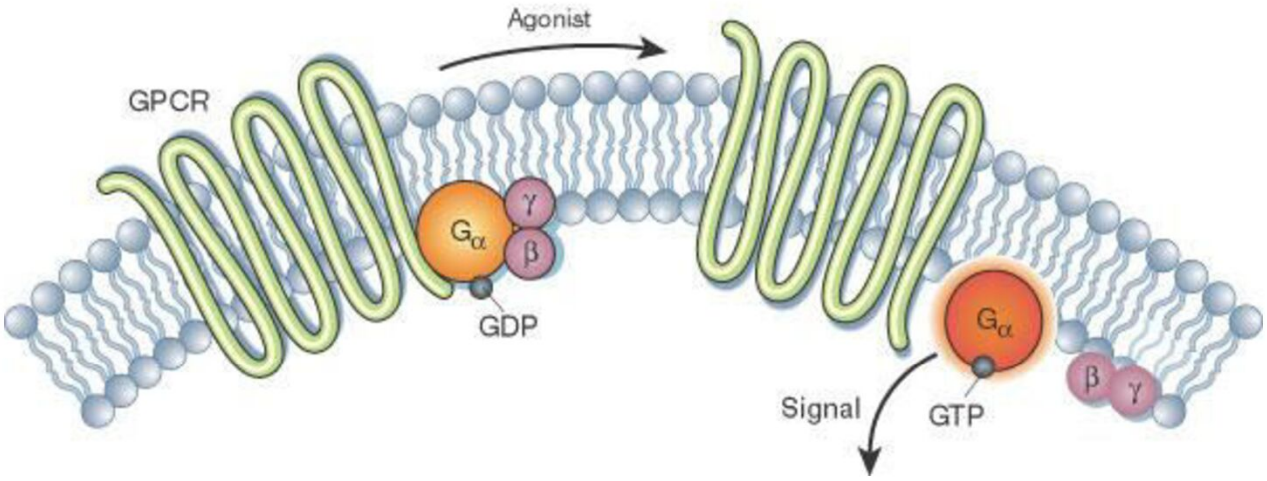
- The drug bind with receptor is known as drug- receptor interaction.
- Drug + Receptor = Drug Receptor = Response
- Drug is of different types of the basis of their action:

Classification of Receptors:

- G-protein-coupled receptors
- Ion channel receptor,
- Enzyme linked receptors,
- JAK-STAT binding receptor
- Receptors that regulate transcription factors

G-protein-coupled receptors

- G protein-coupled receptor (GPCR), protein located in the cell membrane that binds extracellular substances and transmits signals from these substances to an intracellular molecule called a G protein (guanine nucleotide-binding protein).
- GPCR receptor is a family of cell membrane Receptor which is Activated by G-Protein this receptor is made up by seven helical sparing membrane which are connected each other.
- In this helical channels three segment run in extra cellular and three run intra cellular when drug agonist by is bind with the amine group of extra cellular then G-Protein is Activated and G-protein bind with the receptor and produce action.



The GPCR receptor produce action by following three pathways:

1. Adenylyl Cyclase Pathway cAMP Systems
2. Phospholipase DAG Pathway
3. Ion Channel Regulation

1. Adenylyl Cyclase Pathway cAMP Systems:

- Activation of Ac result in intracellular accumulation of second messenger cAMP which function through alters the function of many enzymes, ion channels trans proteins and structural proteins.

2. Phospholipase DAG Pathway:

- Activation of phospholipase, Hydrolysis the membrane Pip to Generate IP and DAG. IP mobilizes Cat and DAG inhances protein kinase activation by ca^{+}

3. Ion Channel Regulation:

- The activated G-Protein can also open or ionic channels specific for Ca^{+}, k or Na without the intervention of any second messenger like cAMP or IP and bring about depolarization Hyperpolarization changes in Intracellular ca^{+}

Ion channel receptor:

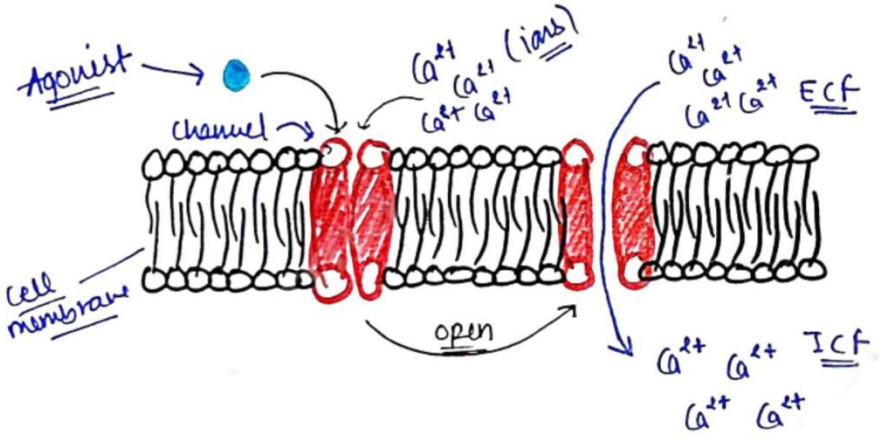
- Also known as ligand gated ion channel.
- These are cell surface receptor.
- Ion selective channel for Na^{+}, K^{+},Ca^{2+} or Cl^{-}

Mechanism:

- Drug (Agonist) bind with ion channel and open the channel.
- Ion move inside the cytosol (Intracellular)
- Changes in ionic composition
- Responses such as depolarization/Hyper polarization.

Receptor includes in this category

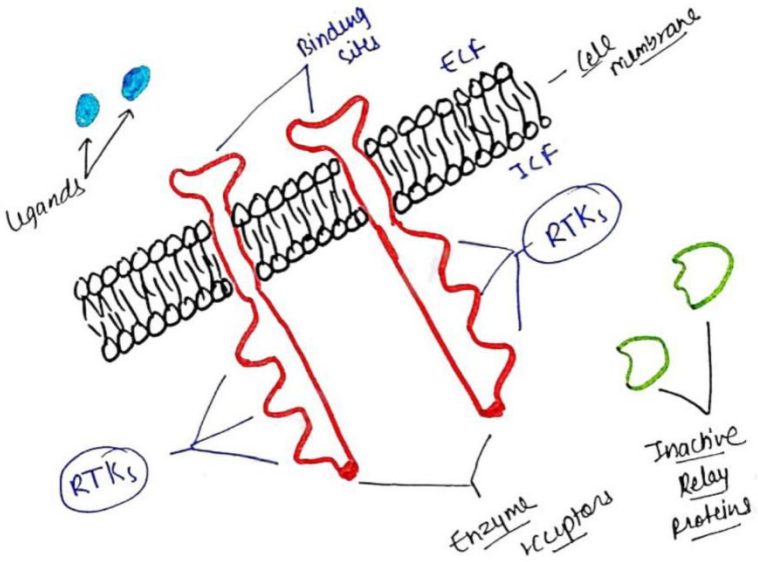
- Nicotinic cholinergic, $GABA_A$, etc.



- In these receptors the agonist directly operates ion channel (no requirement of secondary messenger)
- The onset and offset of responses through this class of receptors is the fastest (in milliseconds)

Transmembrane Enzyme Linked Receptor:

- These are plasma membrane receptors.
- Made up of single transmembrane chain, which has ligand binding domain in extracellular and 'Receptor tyrosine kinases' (RTKs) intracellular as a catalytic site with enzymatic property.



- Mostly peptide hormone are bind with receptor as a ligands.
- When no ligands bind, Receptors are in monomeric state and "Receptor tyrosine kinase" (RTKs) are in inactive form.

Mechanism:

Ligand bind with receptor (Hormone bind)

↓

Monomeric receptors move laterally in the membrane and form diamers.

↓

Dimerisation activates RTKs & RTKs activity of the intracellular domain

↓

Autophosphorylate tyrosine residue on each other

↓

Increase affinity for protein

↓

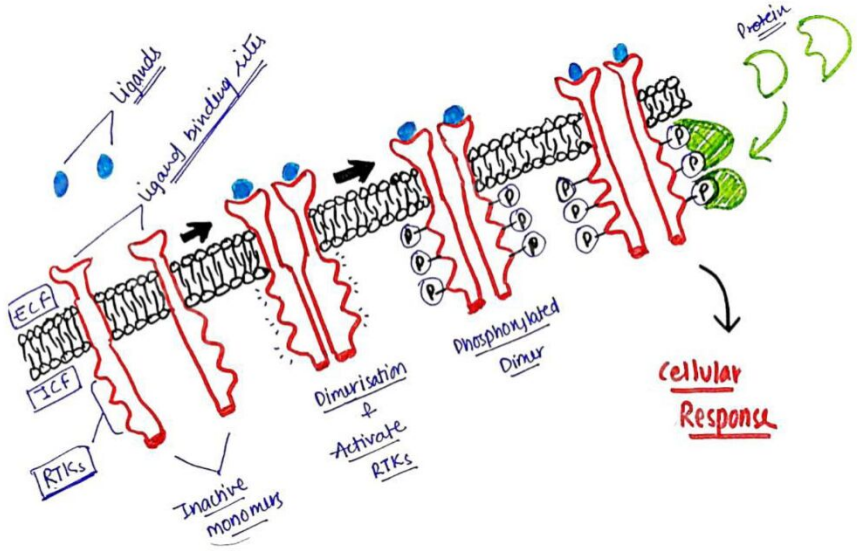
Protein bind on RTKs

↓

Responses

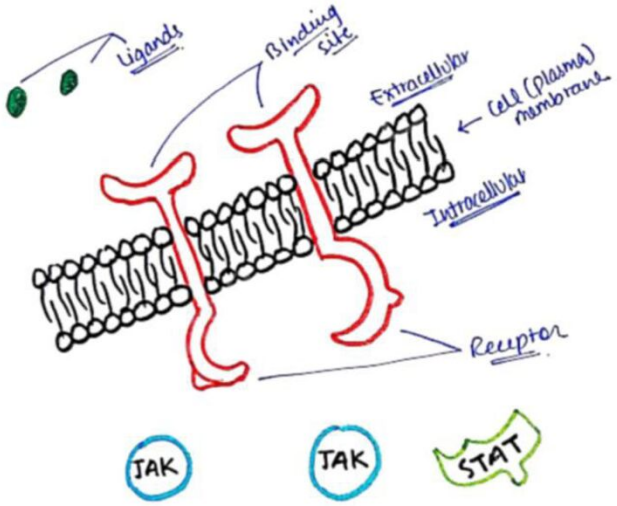
↓

Cellular Responses



Transmembrane JAK-STAT Binding Receptor:

- Similar as RTK's receptor, but they do not having any catalytic domain.



- Many cytokines, growth hormone, prolactin, interferons etc. act through this type of receptor.

Mechanism:

Agonist binds and induced dimerization

↓

Which after the intracellular domain conformation to increase its affinity for a cytosolic tyrosine protein kinase JAK (Janus kinase)

↓

On binding, JAK gets activated and phosphorylate tyrosine residues of the receptor

↓

Which now bind another free moving protein STAT (Signal transducer and activator of transcription) which is also phosphorylated by JAK

↓

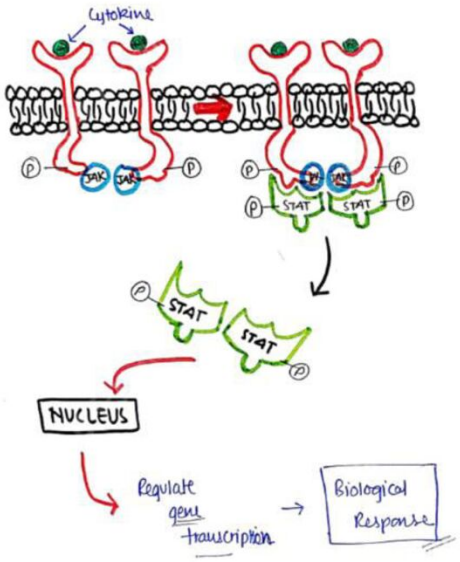
Pair of phosphorylated STAT dimerize

↓

Translocate to the nucleus to regulate gene transcription

↓

Biological Responses



Receptor regulating gene Expression:

- These are intracellular receptor which are present inside the cell.
- They contain soluble protein which responds to lipid soluble chemical messengers that penetrates the cell.
- The receptor protein is inherently capable of binding to specific gene, but it attached proteins HSP-90 or any other to prevent it from adopting the configuration needed for binding to DNA.

Mechanism:

Hormone binds near the carboxy terminus of the receptor

↓

The restricting proteins (HSP-90) are released

↓

The receptor dimerizes and the DNA binding regulatory segment folds into requisite

↓

The liganded receptor dimer moves to the nucleus and bind other co-activator/ co-repressor proteins (which have capacity to alter gene function)

↓

(Transcriptions) Specific mRNA is synthesized or repressed on the template of the gene

↓

This mRNA moves to Ribosome

↓

Synthesis of specific

↓

Regulate activity of target cells

- All steroidal hormone (Glucocorticoids, mineralocorticoids, androgens, estrogens, progesterone), thyroxine, Vitamin D and Vitamin A function in manner.

Dose Response Relationship:

Dose:

- Dose is defined as the minimum amount of the drug which is requires for the effect in body is called dose.

Response:

- Response may be defined as the all pharmacological effect which produce after binding of the drug with receptor is called response.

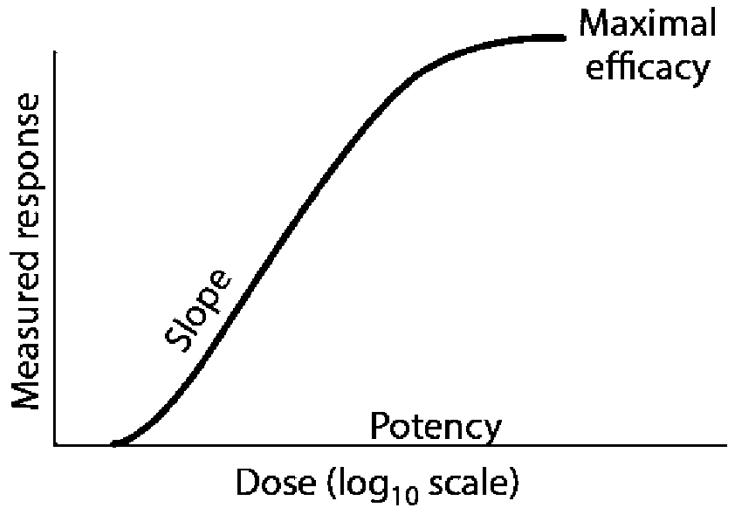
In dose response relationship it depends upon two component.

1. Drug plasma concentration Relationship
2. Plasma concentration response relationship

The response is quantitatively directly proportional to the plasma concentration as much as plasma concentration of drug is increase there response will also be increase and if the drug plasma concentration is decrease the response will also be decrease.

Dose response curve:

- The pharmacological effect of a drug depends on its concentration at the site of action, which, in turn, is determined by the dose of the drug administered. Such a relationship is called 'dose-response relationship'.
- Initially, the extent of response increases with increase in dose till the maximum response is reached.
- When a drug is administered systemically, the dose-response relationship has two components: dose-plasma concentration relationship and plasma concentration response relationship



Type:

Graded dose response relationship

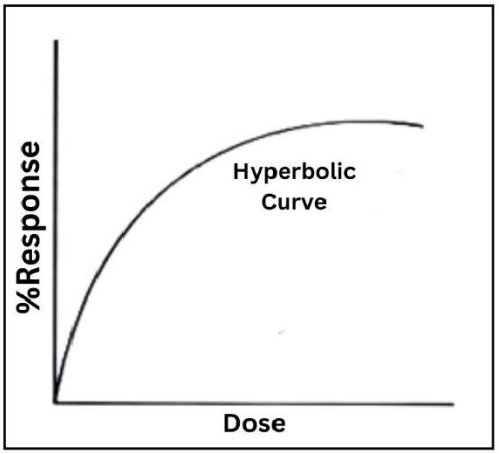
Quantal dose response relationship

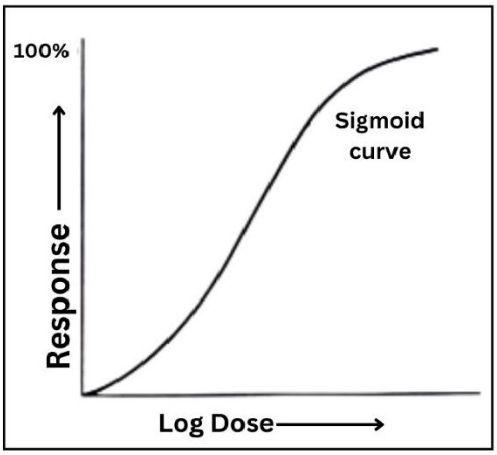
- The graded dose response curve has the shape of a rectangular hyperbola.
- After the maximum effect has been obtained, further increase in doses does not increase the response.
- If dose is plotted on a logarithmic scale, the curve becomes sigmoid.

Advantages of plotting log DRC are:

1. Wide range of doses can be displayed on the graph

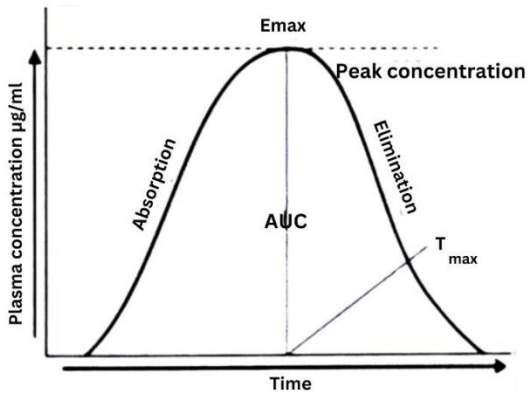
2. Easy to compare agonists and study antagonists





ii. Quantal dose response relationship

- Certain responses can only be all-or- none (e.g. vomiting) and when represented on the dose response curve, the curve appears bell-shaped and it indicates the percentage of responders.
- It is used to calculate ED_{50} and LD_{50}



Therapeutic Index:

The ratio of the dose that produces a toxic (Lethal) effect to the desired therapeutic effect.

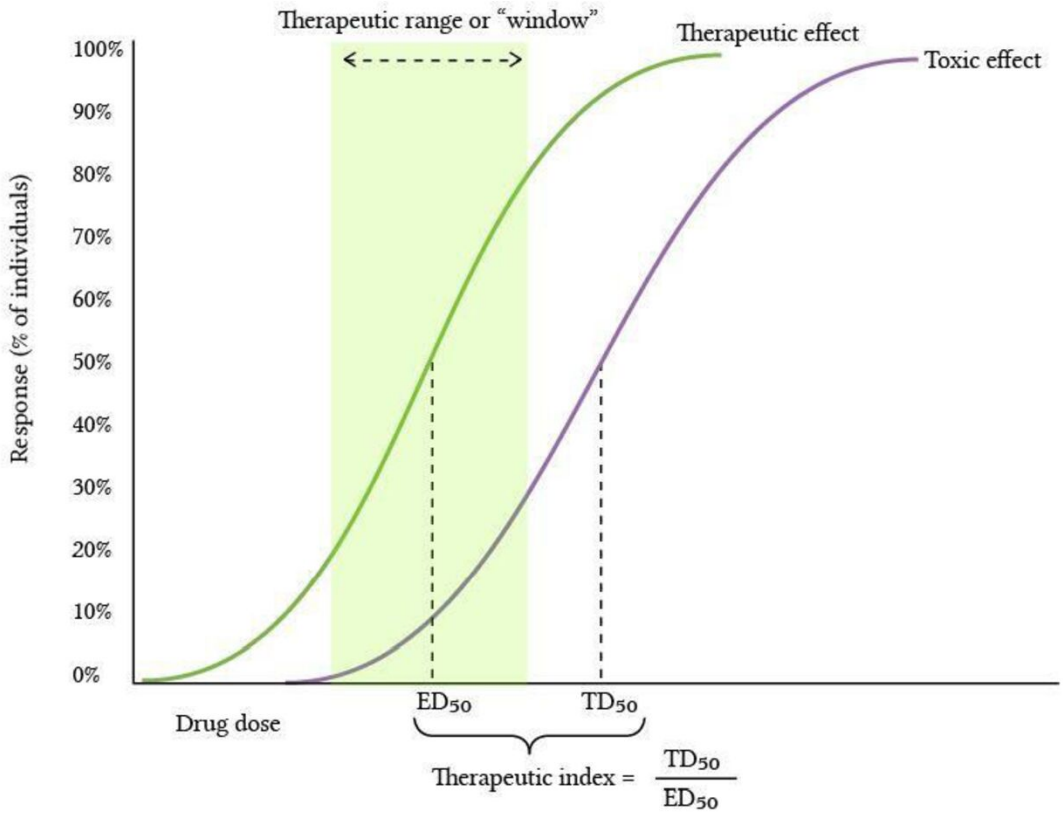
$$Therapeutic\ Index = \frac{LD_{50}}{ED_{50}}$$

Where,

LD_{50} = That dose which kills 50% recipients (animals)

ED_{50} = That dose which produced specified effect and curved 50% individuals.

- It produced a maximum effects with minimum side effects.
- It helps to decide the dose for patients of any drug.
- Therapeutic index is a quantitative measurement of the relative safety of a drug



Dose response curve for therapeutic index

Combined Effects Of Drugs:

- When two or more drug given in combination then they either increase the effect of drug or they decrease the effect of drug.
- On the basic their effect of combination is of two type:-

1. Synergistic
2. Antagonistic

1. Synergistic Effect:

- When the two different drug are given in combination then they enhance the action of each other and the effect of drug is increase is called synergistic effect.

It is of two types:-

a. Addition
b. Supra addition

a. Addition:

The effect of the two drugs is in the same direction and simply adds up.

Effect of A+B = Effect of A+ Effect of B

Combination of drugs	Additive action
Aspirin +Paracetamol	Analgesic / Antipyretic
Ephedrine + Theophylline	Bronchodilator

b. Supra Addition:

The effect of combination is greater than the individual effects of the components

Effect of A + B > Effect of A + Effect of B

Combination of drugs	Supra Additive action
Adrenaline + Cocaine/Desipramine	Neuronal uptake
Acetylcholine + Physostigmine	breakdown of Acetylcholine

2. Antagonistic

When the two different drug are given in combination then they inhibit the action of each other and the effect of drug is decrease or stop is called Antagonistic effect.

It is of two type:

a. Competitive Antagonism

- Antagonist shape is similar as agonist and bind with the same receptor and inactivate receptor.

b. Non-competitive Antagonism

- Antagonist bind with another site (allosteric) of receptor and inactive it so drug does not give any effect
- Eg: Diazepam → Bicuculline etc.

Factors Modifying Drug Action:

1. Body size
2. Age - (Paediatric & Geriatric)
3. Sex (Male & Female)
4. Species and Race
5. Genetic- P'genomicsand P'genetics
6. Physiological state - GI disease, Congestive Disease, Kidney & Liver disease
7. Diet and environmental factor
8. Psychological factors
9. Tolerance & Resistance
10. Pregnancy & Lactation
11. Route of drug administration

Adverse drug reactions.

- WHO has defined an adverse drug reaction as "any response to a drug that is noxious and unintended and that occurs at therapeutic doses used in man for prophylaxis, diagnosis or therapy.'

Or

- Adverse drug reactions is an undesirable effect of drug in our body which we dose not want.
- It may include all kind of noxious effect such as trivial, serious, even fatal
- Adverse effects may develop instantly or only after prolonged medication or even after stoppage of the drugs.

Cause of adverse drug reaction :-

- Incorrect dose intake
- Overdosing
- Allergies to particular drug
- Interaction with other drug or food items
- Drug combination with alcohol
- Idiosyncrasy

Factors Affecting Adverse Drug Reactions:

A. Patient related factor:
- Age
- Sex
- Genetic influences
- Concurrent disease (renal, cardiac)
- Previous adverse effect
- Compliance with dose regimen
- Total number of medications
- Misc. (diet, smoking, environmental exposure).

B. Drug related factor:
- Dose
- Duration
- Inherent toxicity of
- Pharmacodynamics properties
- Pharmacokinetics properties

Types of Adverse Drug Reaction.

They are 6 types:

a. Type A
b. Type B
c. Type C
d. Type D

e. Type E
f. Type F

Type A:

- It is also known as augmented reaction. These reactions occurs in case when amount of drug is increase in body.
- This type of adverse drug reaction can be minimize by using dose adjustment or other combination of drugs.
- **Effects:** Include side effects, toxic effects and consequences of drug withdrawl.
- They are more common, dose related and mostly preventable, predictable and may be reversible.

Examples:

Benzodiazepines → Sedation

Insulin → Hypoglycemia etc.

Type B:

- Also known as bizarre reaction.
- This types of reaction occurs suddenly with unknown reason and effect of drug is not known.
- They are less common, not tolerated and are an abnormal reaction to drug.
- They could be idiosyncratic (genetically mediated) reactions or allergic reactions (immunologically mediated).
    (a) Idiosyncrasy is genetically determined abnormal reaction to a drug, e.g. Primaquine & Sulfonamides induce hemolysis in patients with G6PD deficiency.
    (b) Allergic reactions to drugs (see below) are immunologically-mediated reactions which are not related to therapeutic effects of drug. The drug or its metabolite acts as an antigen to induce antibody formation.

Type-C (continuous or chronic use) reactions:

- It occur on prolonged use of drugs and both dose and duration of drug use influence these ADRs.
- Eg.- chloroquine retinopathy, Cushing's syndrome, analgesic nephropathy.

Type-D (delayed effects):

- Occur long after stopping treatment, after years.
- Eg.- leukemia after treatment of Hodgkin's lymphoma

Type-E (end of use):

- It occurs due to sudden discontinuation of a drug after prolonged use.

Eg.-

- Angina after sudden withdrawal of atenolol.
- Withdrawal syndrome to opioids.

Type F (Failure of efficacy):

- This type of ADRs occurs when drug failed to show their efficacy.
- In this drug does not show their own response.

Example:

- Counter fit medicines
- Drug interactions
- Antagonism, etc

Drug interactions (pharmacokinetic and pharmacodynamic)

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

Types of drug Interaction:

- Drug-drug interaction
- Drug Food Interaction
- Drug Chemical Interaction
- Drug Laboratory test Interaction
- Drug Disease Interactions

Drug-drug interaction - Drug interactions occur when one drug alters the pharmacological effect of another drug. The pharmacological effect of one or both drugs may be increased or decreased, or a new and unanticipated adverse effect may be produced.

Drug-food interaction - A drug-food interaction occurs when your food and medicine interfere with one another. Interactions can happen with both prescription and over-the-counter medicines. These include antacids, vitamins, and iron pills. Not all medicines are affected by food.

Drug-chemical interaction - It occurs when certain chemical like alcohol or tobacco interacts with the ingested drug.

Drug-Laboratory test interaction - True drug-lab test interactions are the result of a drug altering the test specimen, or direct interference from the drug itself reacting with the test reagents.

Drug-disease interaction - DDSIs is a situations where pharmacotherapy used to treat a disease causes worsening of another disease in a patient.

Mechanism of drug interactions:

The three mechanism by which an interaction can develop are-

1. Pharmaceutical interaction
2. Pharmacokinetic Interaction
3. Pharmacodynamics Interaction

1. Pharmaceutical interaction:

- Pharmaceutical Interaction also called as incompatibility. It is a physiochemical interaction that occurs when drugs are mixed in IV (Intravenous). Infusions causing precipitation or inactivation of active principles.
- Ex: Ampicillin, Chlorpromazine and barbiturates interact with dextram in solutions and are broken down or from chemical compounds.

2. Pharmacokinetic Interaction:

- These interactions are those in which ADME properties of the object drugs is altered by the precipitant and hence such interactions are also called ad ADME interactions.
- The resultant effect is altered plasma concentration of the object drug.

These are classified as:

a) Absorption interactions
b) Distribution interactions
c) Metabolism Interaction
d) Excretion Interaction

a) Absorption interactions:

Absorption interaction 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.

b) Distribution interactions:

- Distribution interaction are where the distribution pattern of the drug is altered .
- The major mechanism for distribution interaction is alteration of plasma drug binding.

c) Metabolism interactions:

- Metabolism interaction are those where the metabolism of object drug is altered.
- Hepatic microsomal enzyme induction and inhibition can both result in drug interactions.
- It is most significant interaction in comparison to other drug interaction and can be fatal.

d) Excretion interactions:

- When drugs compete for the same renal tubular transport system, they prolong each other's duration of action, e.g. penicillin and probenecid.
- These are divided into two excretory mechanisms: Renal & Bile excretion.

3. Pharmacodynamics Interaction:

- Pharmacodynamics Interaction are those in which the activity of the object drugs at its site of action is altered by the precipitant.

Eg. Atropin opposes the effect of physostigmine

Effects

1. Synergism (When two or more drug is given in combination, then the action of one drug is increased by other)

2. Antagonism (When two or more drug are given in combination then one drug decrease the action of another).

Drug discovery and clinical evaluation of new drugs -Drug discovery phase, preclinical evaluation phase, clinical trial phase, phases of clinical trials and pharmacovigilance.

Drug discovery:

- In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery.
- It is the process in which new medicines are identified and introduced into market.

It involves two stages:

1. Drug discovery

2. Drug development

- It will take approx. 10-15 year and lots of money for a new drug.
- In an ancient times, drug have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery.
- But now a days drug is discovered on the basis of disease.

Drug discovery and development involves total six steps:

A. Drug discovery Phase

1. Target identification
2. Target validation
3. Lead identification
4. Lead optimization

B. Drug Development Phase

5. Preclinical trials
6. Clinical trials

A. Drug Discovery Phase:

In drug discovery phase we have we have to identified the disease or problem then identified the drug which is used to cure that disease.

1. Target identification:

- Target identification is the second process of drug discovery in this phase basically we find out the organ of body where the disease is occur and in that particular organ find out the particular receptor.

2. Target Validation:

- Now in this step choose target is analysze and validate that above information is correct or not.
- Short listed the causes and affect of disease.Also check the druggability (can a target actually bind to the drug)

3. Lead Identification:

- In this step, identified the drugs that is actually used to cure that disease (lead compound)
- It can be synthesized in laboratory.
- Identified that drug which have potential to bind to the identified target successfully.
- Approx 5000-10000 compound should be choose.

4. Lead optimization:

- After successfully choose lead compounds, now optimize it.
- Modify compounds for increase its effectiveness and safety.
- Drugs can be optimize through various methods:-

Functional group modification

- SAR
- QSAR
- Approx 250 compounds send for the pre-clinical trials.

B. Drug development phase:-

In this phase, drug is develop for the market use.

I. **Pre-clinical evaluation phase**
II. **Clinical trial phase**

I. Preclinical Evaluation Phase:

- The main goals of pre-clinical studies are to determine the safe dose for first-in-man study and assess a product's safety profile.
- After the lead optimization and lead findings the testing of these drugs on animal is called preclinical testing.
- Onan average, only one in 5,000 compounds which enter drug discovery to the stage of clinical development becomes an approved drug.
- Each class of product may undergo different types of pre-clinical research.
- Drugs may undergo pharmacodynamic (PD), pharmacokinetic (PK) and toxicological testing.
- This data allows researchers to estimate safe starting dose of the drug for clinical trials in humans.

- While performing pre-clinical studies, Good Laboratory Practices (GLPs) are followed.

II. Clinical trial phase:

- Set of procedures in medical research and drug development to study the safety and efficacy of new drug.
- Essential get marketing approval from regulatory authorities.
- May require upto 7 years.

Phases of clinical trials:

Phase-I

- Clinical pharmacologic evaluation.
- First stage of testing in human 20-80 healthy volunteers.
- The main purpose of this phase to check the safety and side effect (toxicity) of the drug.
- In this phase study of pharmacokinetic, Pharmacodynamics, Pharmacological effect, tolerability, side effects and toxicity at different doses.

Phase-II

- This phase is also called therapeutic exploration & dose ranging.
- Phase II trials are performed on subjects in large groups (20-300) and are designed to assess the efficiency of the drugs, once its initial safety has been confirmed in Phase I trials.
- Also, during this phase, safety assessments of Phase I are continued on volunteers and patients in a larger group.
- Phase II studies historically have recorded lowest success rate.

Phase IIA and Phase IIB are the into which Phase II studies are sometimes divided two divisions:

I. **Phase IIA:** The dosing requirements (how many drug should be given) are assessed.
II. **Phase IIB:** The efficacy [how well the drug works at the prescribed dose(s)] of a drug is assessed.

Phase III:

- This phase is also called therapeutic confirmation/comparison.
- Phase III studies are randomised controlled multicentre trials on a large patient groups ranging from 300-3000.
- These studies are aimed at being the definitive assessment of effectiveness of the drug.

Purpose:

- Long term safety

- Tolerability-common side effects.
- Drug interaction
- Assessment of safety and efficacy.

Phase IV:

- This phase is also called Postmarketing surveillance/data gathering studies.
- In this phase collect data of drug that drug is safe or not.

Purpose:

- Perform Quality of life trails
- Collection of long term safety information.

Pharmacovigilance:

- The science and activity relating to the detection, Assessment, Under
- WHO defines "Pharmacovigilance is the pharmacological a science related to detection, assessment, understanding and prevention of adverse drug reactions particularly long term and short term adverse effects of medicines".

Objectives of Pharmacovigilance:

- To improve patient care and safety in relation to the use of medicines.
- To contribute to assessment of benefit, harm, effectiveness and risk of medicines.
- Encourage the safe, rational and more effective (including cost effective) use of medicines,
- To promote understanding, education and clinical training in p'vigilance and its effective communication to health professionals and the public.
- To detect problems related to use of medicines & communicate the findings in a timely manner.