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# PHARMACOLOGY - I

## UNIT 2

TOPIC :

- **General Pharmacology**
  - a. 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.
  - b. Adverse drug reactions.
  - c. Drug interactions (pharmacokinetic and pharmacodynamic)
  - d. Drug discovery and clinical evaluation of new drugs-Drug discovery phase, preclinical evaluation phase, clinical trial phase, phases of clinical trials and pharmacovigilance.

# Pharmacodynamics

- Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body and the mechanism by which these effects are produced.
- In simple terms: “*What the drug does to the body.*”
- It involves interaction of drugs with receptors, enzymes, ion channels, or non-receptor targets that ultimately produce therapeutic or toxic effects.

## Mechanism of Drug Action

Drugs produce their effects mainly by two mechanisms:

1. **Receptor Mediated Action**
2. **Non-Receptor Mediated Action**

### NON-RECEPTOR MEDIATED DRUG ACTION

#### 1. By Physical Action

Drugs may act due to their physical or physiochemical properties rather than interaction with a receptor.

- **Osmosis** → *Mannitol* (osmotic diuretic, reduces intracranial pressure).
- **Adsorption** → *Activated charcoal* (absorbs poisons in GIT during poisoning).
- **Radioactivity** → *Iodine-131 (I<sup>131</sup>)* in hyperthyroidism (radioactive destruction of thyroid tissue).
- **Mass of Drug (Bulk)** → *Bulk-forming laxatives* like Psyllium husk act by increasing fecal mass.

## 2. By Chemical Action

Drugs may act by producing chemical reactions in the body.

- **Neutralization of acids/bases** → *Antacids* (aluminum hydroxide, magnesium hydroxide neutralize gastric HCl).
- **Chelation** → *Dimercaprol* binds to arsenic/mercury in heavy metal poisoning.
- **Oxidizing Agents** → *Potassium permanganate* acts as antiseptic due to strong oxidation.

## 3. Through Enzymes

Drugs may modify enzyme activity.

- **Enzyme Activation** → Rare but some drugs activate enzymes.
  - Example: *Allopurinol* (acts on xanthine oxidase to reduce uric acid formation – uric acid lowering).
- **Enzyme Inhibition** → Very common mechanism.
  - **Competitive inhibition** → *Captopril* (inhibits ACE), *Neostigmine* (inhibits acetylcholinesterase).
  - **Non-competitive inhibition** → *Acetazolamide* (carbonic anhydrase inhibitor).

## 4. Through Ion Channels

Drugs can modulate movement of ions ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Cl}^-$ ) across cell membranes.

- **Blockers of voltage-gated channels** → *Local anesthetics* block  $\text{Na}^+$  channels to prevent nerve conduction.
- **Calcium channel blockers** → *Verapamil*, *Nifedipine* (reduce cardiac contractility and cause vasodilation).

## 5. Through Transporters

Some drugs act by inhibiting or modulating specific transport proteins (symporters, antiporters).

- **Example:** Selective serotonin reuptake inhibitors (*SSRIs like Fluoxetine*) block serotonin reuptake transporter, increasing serotonin availability in synaptic cleft.
- **Example:** Digoxin inhibits  $\text{Na}^+/\text{K}^+$  ATPase transporter in cardiac cells.

## 6. Through Antibody Production

Some drugs act through immunological mechanisms involving antibodies.

- **Vaccines** → Induce antibody production for protection against infections.
- **Monoclonal antibodies** → *Infliximab, Rituximab* used in autoimmune diseases and cancers.

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# RECEPTORS

- Macromolecules (mostly proteins) that bind drugs and mediate their effects.
- **Location:**
  - **Cell surface** → G-protein coupled receptors, ion channels, enzyme-linked receptors
  - **Cytoplasm** → Some steroid hormone receptors
  - **Nucleus** → Nuclear receptors for transcription regulation
- **Mechanism:**

Drug + Receptor → Drug Receptor Complex → Response

- **Function:** Conversion of a chemical signal (drug binding) into a cellular response.

## Classification of Receptors

Receptor Type	Mechanism / Function	Examples
<b>G-Protein Coupled Receptors (GPCRs)</b>	Activation of G-protein → second messenger cascade → physiological effect	β-adrenergic receptor, Muscarinic receptor
<b>Ion Channel Receptors</b>	Direct opening/closing of ion channels to change membrane potential	Nicotinic acetylcholine receptor, Voltage-gated $\text{Na}^+$ channels
<b>Enzyme-linked Receptors</b>	Binding of ligand activates intrinsic enzymatic activity or associated enzymes	Insulin receptor (tyrosine kinase), Guanylyl cyclase receptor
<b>JAK-STAT Receptors</b>	Ligand binding activates JAK kinases → phosphorylation of STAT → gene expression	Cytokine receptors (e.g., Interleukin receptors)
<b>Nuclear Receptors</b>	Ligand binds nuclear receptor → regulates gene transcription → protein synthesis	Steroid hormones (glucocorticoids, estrogen, thyroid hormone)

# G-Protein Coupled Receptors (GPCRs)

- GPCRs are a large family of cell membrane receptors that play a key role in cellular signal transduction.
- Other names: Metabotropic receptors, Heptahelical receptors, Serpentine receptors.
- Location: Cell surface (plasma membrane).
- Function: Convert extracellular signals (ligand binding) into intracellular responses via G-proteins and second messengers.

## Structure Of GPCRs

- **Receptor:** 7 transmembrane helices (heptahelical).
- **G-protein:** Heterotrimeric ( $\alpha$ ,  $\beta$ ,  $\gamma$  subunits)
- **Associated nucleotide:** GDP (inactive) / GTP (active)
- **Role of G-protein:** Acts as a **signal transducer**, linking receptor activation to intracellular effectors.

## Mechanism of Action

1. **Ligand binds GPCR**  $\rightarrow$  conformational change in receptor.
2. **G-protein activation:** GDP  $\rightarrow$  GTP on  $\alpha$  subunit.
3. **Activation of effector enzyme** (adenylate cyclase, phospholipase C) or ion channel.
4. **Generation of second messengers**  $\rightarrow$  cellular response.

**Major second messengers:** cAMP, IP<sub>3</sub>, DAG, Ca<sup>2+</sup>, cGMP

## Types Of G-Proteins

G-Protein	Effector Enzyme/Channel	Effect	Second Messenger
Gs	Adenylate cyclase	Activation	$\uparrow$ cAMP
Gi	Adenylate cyclase	Inhibition	$\downarrow$ cAMP
Gq	Phospholipase C	Activation	IP <sub>3</sub> + DAG
Go	Ion channels	Inhibition	Direct effect (no second messenger)



# Signaling Pathways

## 1. Adenylate Cyclase – cAMP Pathway (Gs / Gi)

- **Activated by:** Gs protein
- **Inhibited by:** Gi protein
- **Mechanism:**
  - Adenylate cyclase converts ATP → cAMP
  - cAMP activates protein kinase A (PKA)
  - PKA phosphorylates enzymes, ion channels, and structural proteins
- **Physiological Effects:**
  - Heart → ↑ contractility ( $\beta_1$  adrenergic)
  - Smooth muscle → relaxation ( $\beta_2$  adrenergic)
  - Liver → glycogenolysis
  - Adipose tissue → lipolysis

## 2. Phospholipase C – IP<sub>3</sub>/DAG Pathway (Gq)

- **Activated by:** Gq protein
- **Mechanism:**
  1. Phospholipase C hydrolyzes membrane phospholipids → IP<sub>3</sub> + DAG
  2. IP<sub>3</sub> → Ca<sup>2+</sup> release from endoplasmic reticulum → smooth muscle contraction, secretion
  3. DAG → activates protein kinase C (PKC) → modulates enzymes and ion channels
- **Physiological Effects:**
  - Smooth muscle contraction
  - Secretion in glands
  - Neuronal excitability regulation

### 3. Ion Channel Regulation (Direct G-protein effect)

- Some G-proteins regulate ion channels directly, without second messengers.
- Examples:
  - **G $\beta\gamma$  subunit** opens K<sup>+</sup> channels → slows heart rate (M<sub>2</sub> muscarinic receptor)
  - **N-type Ca<sup>2+</sup> channel inhibition** → reduces neurotransmitter release



# **Ion Channel Receptors (Ligand-Gated or Ionotropic Receptors)**

- Receptors directly linked to ion channels; drug binding opens or closes the channel without G-protein mediation.
- **Speed:** Fastest-acting receptors.
- **Mechanism:**
  - Drug binds to receptor → channel opens → ions ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Cl}^-$ ) flow → tissue response (depolarization/hyperpolarization)
- **Examples:**
  - **GABA receptors** →  $\text{Cl}^-$  influx → hyperpolarization → inhibitory effect
  - **NMDA receptors** →  $\text{Ca}^{2+}$  influx → excitatory neurotransmission

# **Enzymatic Receptors (Receptor Tyrosine Kinases)**

- Receptors with intrinsic enzymatic activity, usually tyrosine kinase, in their intracellular domain.
- **Mechanism:**
  1. Ligand binds extracellular domain
  2. Receptor dimerizes and autophosphorylates
  3. Initiates intracellular signaling cascade → physiological response
- **Examples:**
  - **Insulin receptor** → glucose uptake
  - **Prolactin receptor** → milk production
  - **Growth hormone receptor** → cell growth

# Nuclear Receptors

- Receptors located in cytoplasm or nucleus; lipid-soluble drugs pass through the membrane to bind.
- **Mechanism:**
  1. Drug binds nuclear receptor → receptor-drug complex enters nucleus
  2. Complex binds DNA → regulates gene transcription and translation
- **Types:**
  - **Cytoplasmic receptors** → steroid hormones (glucocorticoids, androgens)
  - **Nuclear receptors** → thyroid hormones, retinoic acid
- **Characteristics:**
  - Slowest-acting receptor type
  - Effects are long-lasting due to gene regulation

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# **JAK-STAT Receptors (Janus Kinase – Signal Transducer and Activator of Transcription)**

- Receptors that transmit extracellular signals to the nucleus using the JAK-STAT pathway, primarily for cytokines and growth factors.
- **Components:**
  1. **Receptor** → recognizes the signaling molecule
  2. **JAK (Janus kinase)** → enzyme associated with the receptor; phosphorylates tyrosine residues
  3. **STAT (Signal Transducer and Activator of Transcription)** → protein that carries the signal to the nucleus and regulates gene transcription
- **Mechanism:**
  1. Signaling molecule (e.g., cytokine or drug) binds to receptor.
  2. JAK is activated → phosphorylates tyrosine residues on receptor.
  3. STAT binds phosphorylated receptor → phosphorylated by JAK.
  4. STAT dimerizes → translocates to nucleus.
  5. Regulates gene transcription → cellular responses.
- **Key Points:**
  - Directly links extracellular signals to gene expression.
  - Important in immunity, growth, and hematopoiesis.

# Factors Affecting Drug Action

Drug action can be influenced by multiple factors, broadly classified as:

1. **Physiological Factors**
2. **Pharmacokinetic Factors**
3. **Drug-Related Factors**
4. **Environmental Factors**

## 1. Physiological Factors

- **Age:**
  - Infants and children: Immature organs → slower metabolism → stronger or prolonged effects.
  - Elderly: Reduced liver and kidney function → slower clearance → increased risk of toxicity.
- **Gender:**
  - Men and women may metabolize drugs differently due to hormones and body composition.
- **Body Weight:**
  - Higher body weight may require higher doses.
  - Fat-soluble drugs may stay longer in individuals with higher body fat.
- **Genetics:**
  - Inherited differences affect drug metabolism (fast or slow metabolizers).
- **Health Status:**
  - Liver or kidney disease reduces drug clearance → prolonged action and possible toxicity.

## 2. Pharmacokinetic Factors

- **Absorption:**
  - Some drugs require food for better absorption (e.g., fat-soluble vitamins).
  - Others work best on an empty stomach.
- **Distribution:**
  - Drugs binding to plasma proteins (e.g., Warfarin) → altered free drug levels and efficacy.
  - Tissue barriers like the **blood-brain barrier** limit drug access to certain organs.
- **Metabolism:**
  - Liver is the main site; rapid metabolism may require frequent dosing.
  - Slow metabolism prolongs drug action.
- **Excretion:**
  - Kidneys are primary for drug elimination.
  - Impaired kidney function → drugs accumulate → increased effects or toxicity.

## 3. Drug-Related Factors

- **Dose & Strength:**
  - Higher doses → stronger effects, but also higher risk of side effects.
- **Route of Administration:**
  - IV: Rapid action.
  - Oral: Slower, depends on absorption and first-pass metabolism.
  - Inhalation: Quick onset in lungs.
  - Topical: Local effect, slow systemic absorption.
- **Drug Interactions:**
  - **Synergistic:** Drugs enhance each other (e.g., Alcohol + sleeping pills → extreme drowsiness).
  - **Antagonistic:** Drugs reduce each other's effect (e.g., some antibiotics reduce efficacy of oral contraceptives).

## 4. Environmental Factors

- **Diet & Nutrition:**
  - Proper diet supports metabolism and drug efficacy.
  - Deficiencies (protein, vitamins) can alter drug effects.
- **Lifestyle:**
  - Smoking → increases metabolism of certain drugs.
  - Alcohol → may induce or inhibit drug metabolism.



# Dose-Response Relationship

The dose-response relationship describes how the amount of a drug (dose) affects the body's response. It helps in determining the optimal dose to achieve the desired therapeutic effect while minimizing toxicity and side effects.

## Key Components

- **Dose:** Quantity of drug administered.
- **Response:** Biological reaction, can be therapeutic or adverse.
- **Toxic Dose:** A high dose causing harmful or dangerous effects.

## Types of Dose-Response Relationships

### 1. Graded Dose-Response Relationship

- Response gradually increases with increasing dose.
- Example: Painkillers provide mild relief at a low dose, stronger relief at a moderate dose, and maximum relief at a high dose.

### 2. Quantal Dose-Response Relationship

- Measures the all-or-none response in a population.
- Example: A sleeping pill may work for some people at 5 mg, others at 10 mg, and almost everyone at 20 mg.

## Dose-Response Curve Phases

Phase	Description
Phase I	Dose too low → no observable response.
Phase II	Dose increases → desired therapeutic effect appears.
Phase III	Further dose increase → no additional beneficial effect, risk of toxicity increases.

## Important Parameter

- **EC<sub>50</sub>** (Effective Concentration 50):  
The dose or concentration of a drug that produces 50% of the maximum response.
  - Indicates potency of the drug.
  - Lower EC<sub>50</sub> → Higher potency.

## THERAPEUTIC INDEX (TI)

➤ The Therapeutic Index (TI) is a quantitative measure of a drug's safety. It compares the dose that produces toxicity to the dose that produces a therapeutic effect.

$$TI = \frac{TD_{50}}{ED_{50}}$$

Where:

- **TD50 (Toxic Dose 50):** Dose at which 50% of the population exhibits toxic effects.
- **ED50 (Effective Dose 50):** Dose at which 50% of the population experiences the desired therapeutic effect.

## Interpretation

- **High TI Drugs**
  - Large difference between toxic and therapeutic doses.
  - Safer, wider margin of safety.
  - **Example:** Penicillin
- **Low TI Drugs**
  - Narrow margin between toxic and therapeutic doses.
  - Requires careful monitoring.
  - **Example:** Warfarin, Digoxin

# Combined Effect of Drugs

When two or more drugs are administered simultaneously, their combined effect can be synergistic or antagonistic.

## Synergism

Synergism occurs when the effect of one drug is enhanced or modified by another drug.

### Types of Synergism

#### 1. Additive Effect

- The combined effect equals the sum of individual effects.
- **Formula:** Effect of A + B = Effect of A + Effect of B
- **Example:** Aspirin + Paracetamol (pain relief)

#### 2. Supra-Additive (Potentiation)

- The combination produces a greater effect than the sum of individual effects.
- **Example:** Sulfamethoxazole + Trimethoprim (antibiotics)

## Antagonism

Antagonism occurs when the effect of a drug is reduced or completely blocked by another drug.

### Types of Antagonism

#### 1. Chemical Antagonism

- One drug chemically interacts with another to neutralize its effect.
- **Example:** Protamine sulfate neutralizes the anticoagulant effect of heparin

#### 2. Pharmacokinetic Antagonism

- One drug affects the ADME of another, reducing its concentration.

- **Example:** Rifampicin induces liver enzymes, increasing metabolism of warfarin and reducing its effect

### 3. Physiological Antagonism

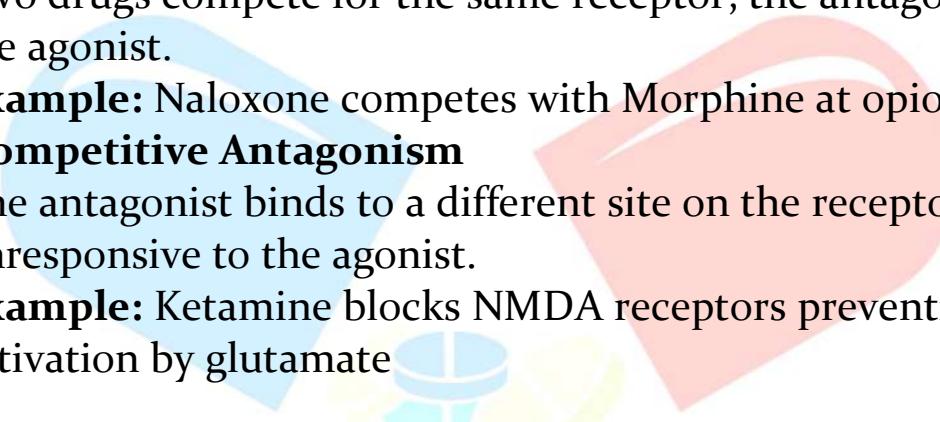
- Two drugs act on different pathways producing opposite physiological effects.
- **Example:** Adrenaline (increases BP) vs. Histamine (decreases BP)

### 4. Competitive (Receptor) Antagonism

- Two drugs compete for the same receptor; the antagonist blocks the agonist.
- **Example:** Naloxone competes with Morphine at opioid receptors

### 5. Non-Competitive Antagonism

- The antagonist binds to a different site on the receptor, making it unresponsive to the agonist.
- **Example:** Ketamine blocks NMDA receptors preventing activation by glutamate



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# Adverse Drug Reactions (ADRs)

Adverse drug reactions are harmful or unintended responses to a medication that occur at normal therapeutic doses used for treatment, diagnosis, or prevention of disease.

They can range from mild effects (like nausea) to severe effects (like organ damage or life-threatening allergic reactions).

## Types of ADRs

### 1. Type A – Augmented

- **Characteristics:**
  - Common and predictable
  - Dose-related
  - Caused by the known pharmacological effects of the drug
- **Examples:**
  - Bleeding with Warfarin
  - Hypoglycemia from Insulin

### 2. Type B – Bizarre

- **Characteristics:**
  - Rare and unpredictable
  - Not dose-related
  - Often due to allergies or genetic factors
- **Example:**
  - Anaphylaxis from Penicillin

### 3. Type C – Chronic

- **Characteristics:**
  - Associated with long-term use of drugs
- **Example:**
  - Adrenal suppression from long-term corticosteroids

## 4. Type D – Delayed

- **Characteristics:**
  - Appears after some time, even after stopping the drug
- **Example:**
  - Cancer caused by chemotherapeutic drugs

## 5. Type E – End of Use

- **Characteristics:**
  - Occurs when a drug is suddenly stopped (withdrawal)
- **Example:**
  - Seizures after stopping Benzodiazepines

## 6. Type F – Failure

- **Characteristics:**
  - Lack of drug effectiveness
  - Often due to drug interactions or inappropriate dosing
- **Example:**
  - Antibiotic resistance leading to treatment failure

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# Drug Interactions

Drug interactions occur when two or more drugs are taken together and alter each other's effectiveness or safety.

They are broadly classified into:

1. **Pharmacokinetic Interactions**
2. **Pharmacodynamic Interactions**

## 1. Pharmacokinetic Drug Interactions (PK Interactions)

These occur when one drug alters the absorption, distribution, metabolism, or excretion (ADME) of another drug, changing its concentration in the body.

### A. Absorption

- Some drugs can increase or decrease absorption of others.
- **Example:**
  - Antacids containing calcium, magnesium, or aluminum reduce absorption of tetracyclines, making them less effective.

### B. Distribution

- Drugs bind to plasma proteins (like albumin).
- If two drugs compete for the same binding site, free drug levels increase, which may lead to toxicity.
- **Example:**
  - Warfarin and aspirin both bind to albumin. Aspirin can displace Warfarin, increasing bleeding risk.

### C. Metabolism

- The liver metabolizes drugs using enzymes (e.g., CYP450).
- Drugs can induce or inhibit these enzymes, altering the metabolism of other drugs.

- **Example:**
  - Grapefruit juice inhibits CYP3A4, slowing metabolism of statins  
→ higher drug levels → potential toxicity.

## D. Excretion

- Drugs can affect **renal clearance** of other drugs.
- **Example:**
  - Probenecid **reduces excretion of penicillin**, leading to higher penicillin levels, sometimes therapeutically beneficial.

## 2. Pharmacodynamic Drug Interactions (PD Interactions)

These occur when two drugs act on the same target or biological pathway, leading to enhanced (synergistic) or reduced (antagonistic) effects.

- **Synergistic/Additive:** Drugs enhance each other's effect.
- **Antagonistic:** One drug reduces or blocks the effect of the other.



# Pharmacovigilance

Pharmacovigilance is the science and activities related to detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.

## Primary Goal:

- To improve patient safety
- To ensure maximum therapeutic benefit

## Activities Involved:

- Collecting and analyzing data from:
  - Clinical trials
  - Post-marketing reports
- Identifying potential risks associated with medications
- Implementing measures to **minimize adverse effects**

## NEW DRUG DEVELOPMENT

The process from synthesis/identification of a molecule to marketing a new drug.

- Duration: 10–20 years
- Cost: Very high

## Stages of New Drug Development:

1. **Synthesis/Isolation of Compounds** – identifying potential drug molecules
2. **Pre-Clinical Trials** – laboratory research and animal testing
3. **Permission for Clinical Trials** – regulatory approval
4. **Pharmaceutical Formulation** – standardization of chemical and dosage form
5. **Clinical Trials (Phase 0–III)** – testing in humans
6. **Grant of Marketing Permission** – after regulatory review
7. **Post-Marketing Surveillance (Phase IV)** – ongoing safety monitoring

# PRE-CLINICAL TRIALS

## Purpose:

Initial testing of a new drug before human trials to assess safety and efficacy

## Steps:

### 1. Laboratory Research

- Experiments using cell cultures or tissue samples
- Investigates biological effects and mechanism
- Identifies potential benefits and risks

### 2. Animal Testing

- Evaluates safety, efficacy, and pharmacokinetics
- Helps determine appropriate dosage
- Assesses potential harmful effects

# CLINICAL TRIALS

Research studies conducted in humans to evaluate safety, efficacy, and side effects

## Phases:

Phase	Purpose	Participants	Duration	Key Points
Phase 0	Microdosing, preliminary data	Very small group	Short	Early human PK/PD data
Phase 1	Safety, metabolism, pharmacodynamics	20–100 healthy volunteers	Few months	Establish safety profile
Phase 2	Therapeutic efficacy, dose range	100–300 patients with disease	6 months–several years	Evaluates effectiveness
Phase 3	Confirm efficacy, safety, tolerability, interactions	Hundreds to thousands of patients	3–5 years	Large-scale confirmatory trials
Phase 4	Post-marketing surveillance	General population	Ongoing	Monitors long-term effects and overall impact

