E-CONTENT FOR COMPLETE COURSE

e-book:

PHARMACEUTICAL ORGANIC CHEMISTRY –I

(BP202T)

(For B.Pharm 2nd Semester Student)

Editor: Dr.Alok Kumar Dash

Institute Of Pharmacy

V.B.S.P.University,Jaunpur,U.P.

Email:dr.alokdash@gmail.com

COURSE CONTENT:

General methods of preparation and reactions of compounds superscripted with asterisk (*) to be explained To emphasize on definition, types, classification, principles/mechanisms, applications, examples and differences

UNIT-I

- **Classification, nomenclature and isomerism**

Classification of Organic Compounds
Common and IUPAC systems of nomenclature of organic compounds
(up to 10 Carbons open chain and carbocyclic compounds)
Structural isomerisms in organic compounds

UNIT-II

- **Alkanes*, Alkenes* and Conjugated dienes***

SP_3 hybridization in alkanes, Halogenation of alkanes, uses of paraffins.
Stabilities of alkenes, SP_2 hybridization in alkenes
E_1 and E_2 reactions – kinetics, order of reactivity of alkyl halides, rearrangement of carbocations, Saytzeffs orientation and evidences. E_1 verses E_2 reactions, Factors affecting E_1 and E_2 reactions. Ozonolysis, electrophilic addition reactions of alkenes, Markownikoff's orientation, free radical addition reactions of alkenes, Anti Markownikoff's orientation. Stability of conjugated dienes, Diel-Alder, electrophilic addition, free radical addition reactions of conjugated dienes, allylic rearrangement

UNIT-III

- **Alkyl halides***

SN_1 and SN_2 reactions - kinetics, order of reactivity of alkyl halides, stereochemistry and rearrangement of carbocations.
SN_1 versus SN_2 reactions, Factors affecting SN_1 and SN_2 reactions
Structure and uses of ethylchloride, Chloroform, trichloroethylene, tetrachloroethylene, dichloromethane, tetrachloromethane and iodoform.

- **Alcohols*-** Qualitative tests, Structure and uses of Ethyl alcohol, Methyl alcohol, chlorobutanol, Cetosteryl alcohol, Benzyl alcohol, Glycerol, Propylene glycol

UNIT-IV

- **Carbonyl compounds* (Aldehydes and ketones)**

Nucleophilic addition, Electromeric effect, aldol condensation, Crossed Aldol condensation, Cannizzaro reaction, Crossed Cannizzaro reaction, Benzoin condensation, Perkin condensation, qualitative tests, Structure and uses of Formaldehyde, Paraldehyde, Acetone, Chloral hydrate, Hexamine, Benzaldehyde, Vanilin, Cinnamaldehyde.

UNIT-V

- **Carboxylic acids***

Acidity of carboxylic acids, effect of substituents on acidity, inductive effect and qualitative tests for carboxylic acids ,amide and ester
Structure and Uses of Acetic acid, Lactic acid, Tartaric acid, Citric acid, Succinic acid. Oxalic
acid, Salicylic acid, Benzoic acid, Benzyl benzoate, Dimethyl phthalate, Methyl salicylate and
Acetyl salicylic acid

- **Aliphatic amines* -** Basicity, effect of substituent on Basicity. Qualitative test, Structure and uses of Ethanolamine, Ethylenediamine, Amphetamine

CHAPTER-1

TOPIC- Introduction to Medicinal Chemistry

Email: dr.alokdash@gmail.com

Introduction to Medicinal Chemistry

1. Definition and Scope

Medicinal Chemistry is a branch of chemistry that deals with the **design, discovery, development, and synthesis of pharmaceutical agents (drugs)**. It combines **organic chemistry**, **biochemistry**, **pharmacology**, and **pharmacokinetics** to understand how chemical compounds interact with biological systems.

Medicinal chemistry not only focuses on the **synthesis of bioactive molecules** but also on understanding the **mechanism of action**, **structure–activity relationship (SAR)**, and **toxicity** of drug compounds.

2. Interdisciplinary Nature

Medicinal chemistry is an **interdisciplinary science** that integrates:

- **Organic Chemistry**: Designing and synthesizing new molecules
- **Pharmacology**: Understanding drug action and target interactions
- **Biochemistry**: Mechanism of action at molecular and cellular levels
- **Molecular Biology**: Role of genes and proteins in drug action
- **Pharmaceutics**: Formulation and delivery of drugs
- **Toxicology**: Safety and side-effect profiling

3. Goals of Medicinal Chemistry

- Discover **new therapeutic agents** from natural or synthetic sources
- Improve **efficacy** and **potency** of existing drugs
- Reduce **toxicity** and **side effects**
- Enhance **bioavailability** and **pharmacokinetic properties**
- Understand **drug-receptor interactions**
- Modify drugs to overcome **resistance** (e.g., antibiotics, antivirals)

4. Drug Discovery and Development Process

a) Target Identification and Validation

- Identify a **biological molecule** (enzyme, receptor, gene) associated with a disease.

b) Lead Compound Identification

- Find a **lead molecule** that shows desired activity through **high-throughput screening**, **natural products**, or **computational modeling**.

c) Lead Optimization

- Modify the structure to improve **activity**, **selectivity**, **solubility**, **stability**, and **safety**.

d) Preclinical and Clinical Studies

- Test in vitro and in vivo for **efficacy and toxicity**.
- Clinical trials (Phases I–IV) for human safety and approval.

5. Key Concepts in Medicinal Chemistry

a) Structure–Activity Relationship (SAR)

- Study of how **chemical structure** affects **biological activity**.
- Helps guide drug design by determining essential functional groups.

b) Pharmacokinetics (ADME)

- **Absorption**: How the drug enters the bloodstream.
- **Distribution**: How the drug reaches tissues and organs.
- **Metabolism**: How the drug is broken down (usually in the liver).
- **Excretion**: How the drug is eliminated from the body.

c) Pharmacodynamics

- Describes how the drug **interacts with its biological target** and produces a therapeutic effect.

d) Drug-Receptor Interactions

- Drugs bind to specific biological targets like enzymes or receptors.
- Types of interactions: hydrogen bonding, ionic, van der Waals, hydrophobic, covalent.

6. Types of Drugs Based on Source

Source	Example
Natural Products	Morphine, Quinine
Synthetic Drugs	Aspirin, Ibuprofen
Semi-synthetic	Ampicillin, Erythromycin
Biotechnological	Insulin, Monoclonal antibodies

7. Physicochemical Properties in Drug Design

- **Lipophilicity (log P)**: Affects membrane permeability.
- **Ionization (pKa)**: Influences solubility and absorption.
- **Molecular weight**: Smaller molecules often have better bioavailability.
- **Hydrogen bond donors/acceptors**: Influence target binding.

8. Prodrugs

- **Prodrugs** are inactive compounds that are metabolized in the body to release the **active drug**.
- Improve **solubility**, **absorption**, or **target specificity**.
- Example: **Enalapril** (prodrug) → **Enalaprilat** (active ACE inhibitor)

9. Drug Resistance and Medicinal Chemistry

Medicinal chemistry plays a vital role in overcoming **drug resistance** (e.g., antibiotic resistance in bacteria) by:

- Designing **new analogs** of existing drugs
- Developing **multi-target agents**
- Using **combinatorial chemistry** to rapidly generate compound libraries

10. Role in Modern Medicine

Medicinal chemistry is central to the development of:

- **Antibiotics**
- **Anticancer agents**
- **Antivirals (e.g., for HIV, COVID-19)**
- **Anti-inflammatory and analgesic drugs**
- **CNS agents (e.g., antidepressants, antipsychotics)**
- **Cardiovascular drugs**

Summary

Aspect	Details
Definition	Design and development of bioactive chemical agents
Disciplines Involved	Organic chemistry, pharmacology, molecular biology
Key Concepts	SAR, ADME, pharmacodynamics, drug-receptor interactions
Applications	Drug discovery, optimization, safety evaluation
Outcome	Therapeutic agents with high efficacy and low toxicity

CHAPTER-2

TOPIC- History and development of medicinal chemistry

Email: dr.alokdash@gmail.com

History and Development of Medicinal Chemistry

1. Introduction

Medicinal chemistry is the science concerned with the design, synthesis, and development of pharmaceutical agents. It integrates principles from **organic chemistry**, **pharmacology**, **biochemistry**, and **molecular biology** to discover and optimize therapeutic compounds.

2. Ancient Period

- Early civilizations like **India, China, Egypt**, and **Greece** used herbs, minerals, and animal extracts.
- **Ayurvedic** and **Traditional Chinese Medicine (TCM)** laid foundational concepts.
- Key contributors:
  - **Charaka** and **Sushruta** (India)
  - **Hippocrates** (Greece): emphasized natural healing
  - **Dioscorides**: compiled *De Materia Medica*, a pharmacopoeia

3. Medieval Period – Alchemical Era

- Alchemy introduced chemical techniques like **distillation, extraction**, and **calcination**.
- **Avicenna (Ibn Sina)** advanced medical knowledge through works like *The Canon of Medicine*.
- Focus shifted to **mineral remedies** and **chemical cures**.

4. Renaissance to Early Modern Period (1500–1800)

- **Paracelsus** (16th century) introduced the idea that "the dose makes the poison."

- Shifted medicine from mysticism to **chemical-based therapies**.
- First isolation of natural **alkaloids** like **morphine**, **quinine**, and **caffeine**.
- Beginnings of **pharmacognosy** (study of natural products).

5. 19th Century

- **Friedrich Wöhler** synthesized **urea**, bridging organic and inorganic chemistry.
- Structural theories of **benzene** and organic compounds emerged.
- First **synthetic drugs** like **chloral hydrate** were developed.
- Rise of **systematic organic synthesis** and **SAR (structure–activity relationship)** studies.

6. Early 20th Century

- **Paul Ehrlich** introduced the concept of the **magic bullet** and developed **Salvarsan** for syphilis.
- **Sulfa drugs** were discovered, starting the **antibacterial era**.
- Advancements in the synthesis of **hormones**, **vitamins**, and **analgesics**.

7. Post-War Period (1940s–1970s)

- **Penicillin**, **streptomycin**, and other **antibiotics** revolutionized medicine.
- Development of **drug receptor theory** and **enzyme inhibition concepts**.
- Regulatory frameworks (e.g., **FDA**) were established after tragedies like **thalidomide**.

8. Late 20th Century

- **Biotechnology boom**: recombinant insulin, monoclonal antibodies.
- **Combinatorial chemistry** and **high-throughput screening (HTS)** emerged.
- **Computer-aided drug design (CADD)** became standard in early-stage development.

9. 21st Century – Precision Medicine Era

- **Human Genome Project** enabled **targeted drug discovery**.
- Rise of **AI and machine learning** in drug repurposing and design.
- **mRNA vaccines**, **CRISPR gene editing**, and **personalized medicine** redefine therapeutic approaches.

Timeline Summary

Era	Key Development
Ancient	Herbal medicine, natural remedies
Medieval	Alchemy, mineral therapies
1500–1800	Isolation of active compounds
1800s	Organic chemistry, SAR, synthetic drugs
Early 1900s	Magic bullet theory, sulfa drugs
Mid 1900s	Antibiotics, receptor theory, drug safety regulations

Era	Key Development
Late 1900s	Biotech, HTS, CADD
2000s–Present	Genomics, AI, personalized therapies

🔬 Conclusion

The evolution of medicinal chemistry reflects humanity's journey from **plant-based remedies** to **data-driven drug design**. Today, it stands at the intersection of **biology, chemistry, and informatics**, advancing toward safer, more effective, and personalized treatments.

CHAPTER-3

TOPIC- Physicochemical properties in relation to biological action

Email: dr.alokdash@gmail.com

Physicochemical Properties in Relation to Biological Action

1. Introduction

In medicinal chemistry, the **physicochemical properties** of a drug profoundly influence its **absorption, distribution, metabolism, excretion (ADME)**, and **biological activity**. These properties determine how a drug behaves in the **biological environment**, including how well it binds to its target, how it moves through membranes, and how it is processed by the body.

Understanding these properties is essential for **drug design, formulation, and therapeutic effectiveness**.

2. Key Physicochemical Properties

2.1. Lipophilicity (Partition Coefficient - log P)

- **Definition**: The ability of a compound to dissolve in lipids vs. water.
- Measured by the **partition coefficient (log P)**:

  $$\log P = \log \left(\frac{\text{[Drug in octanol]}}{\text{[Drug in water]}} \right) \log P = \log([\text{Drug in octanol}][\text{Drug in water}])$$

- **Relevance**:
  - Influences **membrane permeability**
  - Affects **oral absorption** and **CNS penetration**
  - Determines **distribution** in lipophilic tissues (e.g., brain, fat)
- **Examples**:
  - Drugs with **moderate log P (1–3)** show optimal **bioavailability**.
  - **Too lipophilic**: high tissue retention, poor solubility.
  - **Too hydrophilic**: poor membrane permeability.

2.2. Ionization (pKa and pH)

- **Definition**: Degree to which a drug is ionized at a given pH.
- Governed by the **Henderson–Hasselbalch equation**:

  $$pH=pKa+\log([A^-][HA])\text{pH} = \text{pKa} + \log \left(\frac{\text{[A}^-\text{]}}{\text{[HA]}} \right)pH=pKa+log([HA][A−])$$

- **Relevance**:
  - Ionized drugs are **more water-soluble**, but **less membrane-permeable**.
  - Non-ionized drugs are **more lipophilic**, enhancing **absorption**.
- **Absorption Sites**:
  - Weak acids absorbed better in the **stomach** (acidic pH)
  - Weak bases absorbed better in the **intestine** (basic pH)
- **Examples**:
  - **Aspirin** (weak acid): absorbed in stomach
  - **Morphine** (weak base): better absorbed in small intestine

2.3. Molecular Size and Weight

- **Relevance**:
  - Affects **passive diffusion** through biological membranes
  - Optimal MW for oral drugs: **<500 Da**
- **High MW**: poor permeability and oral bioavailability
- **Small molecules**: easily absorbed and distributed
- **Lipinski's Rule of Five** includes molecular weight as a critical factor in drug-likeness.

2.4. Hydrogen Bonding Capacity

- Involves **hydrogen bond donors (HBD)** and **acceptors (HBA)**.
- **Relevance**:
  - Affects **solubility** and **membrane permeability**
  - Excessive hydrogen bonding can **hinder CNS penetration**
- **Optimal Range**:
  - HBD ≤ 5
  - HBA ≤ 10
- Drugs with appropriate hydrogen bonding can have **better receptor binding affinity** without compromising absorption.

2.5. Aqueous Solubility

- **Definition**: Ability of a drug to dissolve in water.
- **Relevance**:
  - Critical for **dissolution**, **absorption**, and **bioavailability**
  - Poor solubility can lead to **precipitation**, **erratic absorption**, and **low efficacy**
- Affected by:
  - **Ionization state**
  - **Functional groups**
  - **Crystal form or polymorph**
- **Solution**: Use of **salts**, **prodrugs**, or **formulation techniques** to enhance solubility.

2.6. Chemical Stability

- **Relevance**:
  - Affects **shelf-life**, **bioavailability**, and **formulation**
  - Instability may lead to degradation, reduced potency, or toxic by-products
- Influencing factors:
  - **pH**
  - **Temperature**
  - **Oxidation/reduction potential**
- **Examples**:
  - **Penicillin G** is unstable in acid → limited oral bioavailability.
  - Stabilized forms (e.g., prodrugs) are used for better effectiveness.

3. Combined Influence on Biological Action

Property	Biological Impact
Log P	Permeability, tissue distribution, CNS access
pKa/Ionization	Site of absorption, membrane crossing ability
Molecular Weight	Transport through membranes, oral bioavailability
H-bonding	Receptor binding, solubility, permeability
Solubility	Absorption rate, dosage form design
Stability	Drug potency and safety during storage and use

4. Drug Design and Optimization

- **Medicinal chemists** modify physicochemical properties to enhance:
  - **Target binding affinity**
  - **Pharmacokinetics**
  - **Solubility and stability**
  - **Minimization of side effects**
- **Strategies include**:
  - Addition/removal of **polar groups**
  - **Bioisosteric replacement**
  - Converting drugs into **prodrugs**

- Using **salt forms**

5. Lipinski's Rule of Five

A guideline to predict **oral bioavailability**:

1. Not more than 5 hydrogen bond donors
2. Not more than 10 hydrogen bond acceptors
3. Molecular weight < 500 Da
4. Log P < 5

Drugs that violate more than one rule are likely to have **poor absorption** or **permeability**.

Summary

- Physicochemical properties like **lipophilicity, ionization, solubility, hydrogen bonding**, and **molecular weight** play a crucial role in determining a drug's **biological performance**.
- A balance between **water solubility** and **lipid solubility** is essential for optimal **absorption and activity**.
- These properties guide **drug design**, **formulation**, and **optimization** to ensure efficacy and safety.

CHAPTER-4

TOPIC- Drug Metabolism

Email: dr.alokdash@gmail.com

Drug Metabolism

1. Introduction

Drug metabolism refers to the **biochemical modification** of pharmaceutical substances by living organisms, usually through specialized enzymatic systems. It primarily occurs in the **liver**, though other organs like the **intestine**, **lungs**, **skin**, and **kidneys** also contribute.

Metabolism transforms **lipophilic drugs** into more **polar**, **water-soluble metabolites** that can be easily **excreted** from the body, mainly via urine or bile.

2. Objectives of Drug Metabolism

- **Enhance drug excretion** by converting lipophilic drugs into hydrophilic forms.
- **Terminate pharmacological activity** by inactivating drugs.
- Occasionally, **activate prodrugs** into their therapeutically active forms.
- **Detoxify** or sometimes **bioactivate** xenobiotics into toxic compounds.

3. Sites of Drug Metabolism

Organ	Function
Liver	Primary site (via CYP450 enzymes)
Intestine	First-pass metabolism
Kidneys	Minor role in biotransformation
Lungs	Important for volatile drugs
Skin	Limited enzymatic activity

4. Principles of Drug Metabolism

Drug metabolism is generally divided into **two phases**:

5. Phase I Reactions (Functionalization Reactions)

These reactions introduce or expose a **functional group** (–OH, –NH_2, –SH, –COOH) on the drug molecule.

Types of Phase I Reactions:

Reaction Type	Description	Examples
Oxidation	Addition of oxygen or removal of hydrogen	Hydroxylation, dealkylation

Reaction Type	Description	Examples
Reduction	Addition of hydrogen	Nitro → amine, ketone → alcohol
Hydrolysis	Breaking ester/amide bonds using water	Esterase-mediated hydrolysis

Key Enzymes:

- **Cytochrome P450 monooxygenases (CYP450)** – major enzymes
- **Flavin-containing monooxygenases (FMOs)**
- **Alcohol and aldehyde dehydrogenases**
- **Esterases and amidases**

Example:

- **Codeine** is O-demethylated to **morphine** (active metabolite).

6. Phase II Reactions (Conjugation Reactions)

These reactions involve **conjugating** the functional group (from Phase I or already present) with **endogenous molecules** to increase **hydrophilicity** and **excretion**.

Types of Phase II Reactions:

Conjugation Type	Conjugating Agent	Example
Glucuronidation	Glucuronic acid	Morphine-glucuronide
Sulfation	Sulfate	Paracetamol sulfate
Acetylation	Acetyl-CoA	Isoniazid → acetylisoniazid
Methylation	S-adenosyl methionine	Adrenaline → metanephrine
Amino acid conjugation	Glycine, glutamine	Salicylic acid → salicyluric acid
Glutathione conjugation	Glutathione (GSH)	Detoxification of reactive species

Enzymes:

- **UDP-glucuronosyltransferases (UGTs)**
- **Sulfotransferases (SULTs)**
- **N-acetyltransferases (NATs)**
- **Methyltransferases**

7. Prodrugs and Bioactivation

Some drugs are **inactive as administered** and require metabolism to become active.

Examples:

- **Enalapril** → Enalaprilat (active ACE inhibitor)

- **Cyclophosphamide** → active cytotoxic metabolites

Bioactivation can also result in **toxic metabolites** (e.g., **acetaminophen** overdose → hepatotoxic NAPQI).

8. Factors Affecting Drug Metabolism

A. Genetic Factors (Pharmacogenetics)

- **Polymorphisms** in CYP enzymes (e.g., CYP2D6, CYP2C9)
- **Slow vs. fast metabolizers** affect efficacy and toxicity
- Example: CYP2D6 poor metabolizers → poor response to codeine

B. Physiological Factors

Factor	Effect on Metabolism
Age	Neonates and elderly have reduced metabolism
Sex	Hormonal differences can affect metabolism
Diet/Nutrition	Low protein diets impair enzyme function

C. Pathological Conditions

- **Liver disease** (e.g., cirrhosis) reduces enzyme activity
- **Renal failure** may affect Phase II conjugate excretion

D. Enzyme Induction and Inhibition

Enzyme Inducers	Effect
Rifampicin, phenobarbital	↑ Metabolism, ↓ drug levels

Enzyme Inhibitors	Effect
Cimetidine, erythromycin	↓ Metabolism, ↑ toxicity

E. Drug–Drug Interactions

- Competing substrates may **inhibit metabolism** (e.g., warfarin + fluconazole).
- Important in **polypharmacy**, especially in elderly or chronic patients.

F. Environmental and Lifestyle Factors

- **Smoking** induces CYP1A2 (affecting theophylline)
- **Alcohol** affects both Phase I and II enzymes
- **Pollutants** can alter enzyme expression

G. Stereochemistry (Stereochemical Aspects)

Chirality of drugs plays a key role in metabolism:

- **Enantiomers** may have different **metabolic rates** and **pathways**
- **Stereoselective metabolism** affects:
    - **Efficacy**: One enantiomer may be active
    - **Toxicity**: The other may be inactive or toxic

Examples:

- **Warfarin**: S-enantiomer is more potent, metabolized by CYP2C9
- **Thalidomide**: R-form is sedative, S-form is teratogenic
- **Propranolol**: S-enantiomer is more active and metabolized faster

Summary Table

Phase	Reaction Type	Purpose	Enzymes
Phase I	Oxidation, reduction, hydrolysis	Introduce functional group	CYP450, esterases, dehydrogenases
Phase II	Conjugation (e.g., glucuronidation, acetylation)	Enhance excretion	UGTs, SULTs, NATs, GSTs

🧪 Conclusion

Drug metabolism is a crucial determinant of a drug's **duration**, **intensity**, and **toxicity**. Understanding **Phase I and II reactions**, as well as the **genetic, physiological, and chemical factors** affecting metabolism, is essential for **rational drug design**, **dose optimization**, and **predicting drug interactions**.

CHAPTER-5

TOPIC- Drugs acting on Autonomic Nervous System

Email: dr.alokdash@gmail.com

Drugs Acting on the Autonomic Nervous System (ANS)

1. Introduction

The **Autonomic Nervous System (ANS)** is a part of the **Peripheral Nervous System (PNS)** that controls **involuntary physiological functions** such as **heart rate**, **blood pressure**, **digestion**, **respiration**, and **glandular secretions**. It operates without conscious control and is divided into two major branches:

- **Sympathetic Nervous System (SNS)** – "fight or flight"
- **Parasympathetic Nervous System (PNS)** – "rest and digest"

Drugs acting on the ANS either **mimic** (agonists) or **block** (antagonists) the effects of neurotransmitters like **acetylcholine** and **norepinephrine** at **cholinergic** and **adrenergic receptors**, respectively.

2. Classification of Autonomic Drugs

I. Cholinergic Drugs (Parasympathomimetics)

Act on cholinergic receptors and mimic **acetylcholine**.

A. Direct-acting Cholinergic Agonists

- Bind directly to **muscarinic** or **nicotinic receptors**
- Examples:
  - **Pilocarpine** – used in glaucoma
  - **Bethanechol** – used for urinary retention

B. Indirect-acting Cholinergic Agonists (Anticholinesterases)

- Inhibit **acetylcholinesterase**, increasing ACh levels
- Examples:
  - **Neostigmine**, **Physostigmine** – used in myasthenia gravis
  - **Donepezil**, **Rivastigmine** – used in Alzheimer's disease

II. Anticholinergic Drugs (Parasympatholytics)

Block muscarinic receptors, inhibiting parasympathetic activity.

A. Muscarinic Antagonists

- Examples:
  - **Atropine** – used in bradycardia, organophosphate poisoning
  - **Hyoscine (Scopolamine)** – motion sickness
  - **Ipratropium**, **Tiotropium** – used in COPD, asthma

B. Ganglion Blockers

- Act on nicotinic receptors at autonomic ganglia
  - Rarely used clinically

C. Neuromuscular Blockers

- Used in anesthesia to cause muscle relaxation
  - **Succinylcholine**, **Pancuronium**

III. Adrenergic Drugs (Sympathomimetics)

Mimic the action of **norepinephrine** and **epinephrine**.

A. Direct-acting Adrenergic Agonists

Receptor Selectivity	Examples	Uses
α_1	Phenylephrine	Nasal decongestant
α_2	Clonidine	Hypertension, withdrawal symptoms
β_1	Dobutamine	Acute heart failure
β_2	Salbutamol, Terbutaline	Asthma, premature labor
Non-selective	Epinephrine, Norepinephrine	Anaphylaxis, cardiac arrest

B. Indirect-acting Adrenergic Agonists

- Promote **release of NE** or **inhibit reuptake**
- Examples:
  - **Amphetamine**, **Tyramine** – CNS stimulants
  - **Cocaine** – inhibits reuptake of NE

C. Mixed-acting Adrenergic Agonists

- Examples: **Ephedrine** – used in nasal congestion

IV. Adrenergic Antagonists (Sympatholytics)

Block adrenergic receptors and inhibit sympathetic activity.

A. Alpha Blockers

Type	Examples	Uses
Non-selective (α_1, α_2)	Phentolamine, Phenoxybenzamine	Pheochromocytoma, hypertension crisis
Selective α_1	Prazosin, Terazosin	Hypertension, BPH

B. Beta Blockers

Type	Examples	Uses
Non-selective (β_1, β_2)	Propranolol	Hypertension, angina, tremors
Selective β_1	Atenolol, Metoprolol	Hypertension, post-MI, heart failure
With α-blocking activity	Labetalol, Carvedilol	Hypertensive emergencies, heart failure

3. Neurotransmitters in the ANS

System	Neurotransmitter	Receptors
Sympathetic (pre-ganglionic)	Acetylcholine	Nicotinic (N)
Sympathetic (post-ganglionic)	Norepinephrine	Adrenergic (α, β)
Parasympathetic (pre- and post-ganglionic)	Acetylcholine	Nicotinic (N) and Muscarinic (M)
Adrenal medulla	Acetylcholine	Nicotinic – releases Epinephrine

4. Clinical Applications of ANS Drugs

Drug Class	Example	Use
β_2-agonists	Salbutamol	Bronchial asthma
β-blockers	Metoprolol	Hypertension, angina
α-blockers	Prazosin	BPH, hypertension
Muscarinic agonists	Pilocarpine	Glaucoma
Anticholinergics	Atropine	Bradycardia, organophosphate poisoning
Anticholinesterases	Neostigmine	Myasthenia gravis

5. Side Effects and Precautions

- **Adrenergic agonists**: tachycardia, hypertension, tremors
- **Adrenergic blockers**: bradycardia, fatigue, bronchospasm

- **Cholinergic agonists**: diarrhea, salivation, hypotension
- **Anticholinergics**: dry mouth, blurred vision, constipation, urinary retention

Summary

Drug Group	Action	Examples
Cholinergic Agonists	Stimulate PNS	Pilocarpine, Bethanechol
Anticholinergics	Inhibit PNS	Atropine, Ipratropium
Adrenergic Agonists	Stimulate SNS	Epinephrine, Salbutamol
Adrenergic Antagonists	Inhibit SNS	Propranolol, Prazosin

🧪 Conclusion

Drugs acting on the **autonomic nervous system** play critical roles in managing conditions like **hypertension, asthma, cardiac arrhythmias, glaucoma**, and **neuromuscular disorders**. A thorough understanding of their **mechanism of action**, **receptor selectivity**, and **clinical applications** is essential for safe and effective pharmacological therapy.

CHAPTER-6

TOPIC- Adrenergic Neurotransmitters

Email: dr.alokdash@gmail.com

Adrenergic Neurotransmitters

1. Introduction

Adrenergic neurotransmitters are chemical messengers of the **sympathetic nervous system**. The most important ones include:

- **Norepinephrine (NE)** – primary neurotransmitter released at sympathetic nerve endings.
- **Epinephrine (Epi)** – hormone and neurotransmitter released by the adrenal medulla.
- **Dopamine (DA)** – precursor to NE and a neurotransmitter in CNS and periphery.

These neurotransmitters are classified as **catecholamines**, owing to their **catechol (benzene with two hydroxyl groups)** and **amine** functional groups.

2. Biosynthesis of Catecholamines

Catecholamines are synthesized from the amino acid **tyrosine** through a series of enzymatic reactions:

Stepwise Pathway:

1. **Tyrosine**
   ↓ *(Tyrosine hydroxylase)*
   L-DOPA (rate-limiting step)
2. **L-DOPA**
   ↓ *(DOPA decarboxylase)*
   Dopamine

3. **Dopamine**
   ↓ *(Dopamine β-hydroxylase)*
   Norepinephrine
4. **Norepinephrine**
   ↓ *(Phenylethanolamine-N-methyltransferase - PNMT)*
   Epinephrine *(in adrenal medulla only)*

Location:

- **Tyrosine hydroxylase**: Cytoplasm of nerve terminals
- **Dopamine β-hydroxylase**: Stored vesicles
- **PNMT**: Cytosol of adrenal medulla cells

3. Storage and Release

- **Dopamine and norepinephrine** are stored in **synaptic vesicles**.
- Upon nerve stimulation, they are released by **exocytosis**.
- NE acts on **postsynaptic adrenergic receptors**, and its action is terminated by **reuptake** or **enzymatic degradation**.

4. Catabolism of Catecholamines

Catecholamines are inactivated by **enzymatic degradation** primarily by:

- **Monoamine Oxidase (MAO)** – in nerve terminals and mitochondria
- **Catechol-O-Methyl Transferase (COMT)** – in liver and kidney

Major Metabolic Pathways:

- NE/Epinephrine
  → via **COMT and MAO**
  → **Vanillylmandelic acid (VMA)** → excreted in urine
- Dopamine
  → **Homovanillic acid (HVA)**

Clinical Use:

- **VMA levels in urine** help diagnose **pheochromocytoma**, a catecholamine-secreting tumor.

5. Adrenergic Receptors

Adrenergic receptors (adrenoceptors) are **G protein-coupled receptors (GPCRs)** classified into:

- **α-receptors (α_1 and α_2)**
- **β-receptors (β_1, β_2, β_3)**

Each type is distributed in specific tissues and mediates different physiological responses.

6. Alpha (α) Adrenergic Receptors

α_1 Receptors – *Post-synaptic, Gq protein-coupled*

Location	Action
Vascular smooth muscle	Vasoconstriction → ↑ BP
Pupillary dilator muscle	Mydriasis (pupil dilation)
Bladder and prostate	Contraction → urinary retention
Liver	Glycogenolysis → ↑ blood glucose

Clinical Note: Blocked by **prazosin**, used in hypertension and BPH.

α_2 Receptors – *Pre-synaptic, Gi protein-coupled*

Location	Action
CNS	↓ Sympathetic outflow → ↓ BP
Presynaptic nerve terminals	Inhibits NE release (negative feedback)
Platelets	Promotes aggregation

Clinical Note: Stimulated by **clonidine**, used to treat hypertension.

7. Beta (β) Adrenergic Receptors

All β-receptors are **Gs protein-coupled**, activating **adenylate cyclase** and increasing **cAMP**.

β_1 Receptors

Location	Action
Heart	↑ Heart rate and contractility
Kidney	↑ Renin release → ↑ BP

Clinical Note: Blocked by **metoprolol**, used in angina, hypertension, heart failure.

β_2 Receptors

Location	Action
Bronchial smooth muscle	Bronchodilation
Uterus	Relaxation (tocolytic effect)
Liver	Glycogenolysis and gluconeogenesis
Skeletal muscle	Vasodilation, tremors

Clinical Note: Stimulated by **salbutamol**, used in asthma and premature labor.

β₃ Receptors

Location	Action
Adipose tissue	Lipolysis
Urinary bladder	Relaxation (treats overactive bladder)

Clinical Note: Stimulated by **mirabegron**, used in overactive bladder syndrome.

Summary Table

Biosynthesis and Degradation of Catecholamines

Step	Enzyme
Tyrosine → L-DOPA	Tyrosine hydroxylase
L-DOPA → Dopamine	DOPA decarboxylase
Dopamine → NE	Dopamine β-hydroxylase
NE → Epi	PNMT
Catabolism	MAO and COMT → VMA (urine)

Adrenergic Receptor Actions

Receptor	Tissues	Effects
α_1	Vessels, eye, bladder	Vasoconstriction, mydriasis, retention
α_2	CNS, nerve terminals, platelets	↓ NE release, ↓ BP, platelet aggregation
β_1	Heart, kidney	↑ HR, ↑ renin
β_2	Lungs, uterus, liver, muscle	Bronchodilation, uterine relaxation
β_3	Fat, bladder	Lipolysis, bladder relaxation

🧪 Conclusion

Understanding the **biosynthesis and metabolism** of catecholamines and the **receptor distribution and functions** of α and β adrenergic receptors is essential in designing and using **sympathomimetic and sympatholytic drugs**. These receptors are critical targets in treating **cardiovascular**, **respiratory**, and **urological** disorders.

CHAPTER-7

TOPIC- Sympathomimetic Agents: SAR and Classification

Email: dr.alokdash@gmail.com

Sympathomimetic Agents: SAR and Classification

Structure–Activity Relationship (SAR) of Sympathomimetic Agents

1. **Core Structure**: Most sympathomimetics are based on the **phenylethanolamine nucleus**.
2. **Aromatic Ring Substituents**:
   - **3,4-dihydroxy substitution** (catechol) enhances potency and receptor affinity (e.g., epinephrine).
   - **Absence or modification** of hydroxyl groups can increase **α-selectivity** or oral bioavailability.
3. **Amine Substitution**:
   - Small alkyl groups (e.g., methyl) favor **α-activity**.
   - Bulky groups (e.g., isopropyl, tert-butyl) increase **β2-selectivity**.
4. **α-Carbon Substitution**:
   - Inhibits metabolism by MAO.
   - Increases **CNS penetration**.
5. **β-Hydroxyl Group**:
   - Required for direct receptor activity.
   - Decreases CNS penetration.

Direct-Acting Sympathomimetic Agents

CHAPTER-8

TOPIC- Adrenergic Antagonists – Alpha Adrenergic Blockers

Email: dr.alokdash@gmail.com

Adrenergic Antagonists – Alpha Adrenergic Blockers

1. Introduction

Adrenergic antagonists, also known as **adrenoceptor blockers** or **sympatholytics**, are drugs that inhibit the **actions of catecholamines** (such as norepinephrine and epinephrine) by blocking **alpha (α) or beta (β) adrenergic receptors**.

This section focuses on **alpha-adrenergic blockers**, which inhibit **α_1 and/or α_2 receptors**, leading to **vasodilation**, **decreased blood pressure**, and **modulation of sympathetic tone**.

2. Classification of Alpha Adrenergic Blockers

Type	Receptor Target	Examples
Non-selective reversible	α_1 and α_2	Phentolamine, Tolazoline
Non-selective irreversible	α_1 and α_2	Phenoxybenzamine
Selective α_1 blockers	α_1	Prazosin, Terazosin, Doxazosin
Partial agonists / Mixed	α/serotonin	Dihydroergotamine, Methysergide

3. Individual Agents

1. Tolazoline

Type: Non-selective α-blocker (reversible)
Mechanism: Competitive antagonist of both α_1 and α_2 receptors
Actions:

- Vasodilation, decreases peripheral resistance
- Reflex tachycardia due to α_2 blockade (↑ NE release)

Therapeutic Use:

- Previously used in **persistent pulmonary hypertension in newborns**
- Limited clinical use today due to non-selectivity and side effects

2. Phentolamine

Type: Non-selective α-blocker (reversible)
Mechanism: Competitively blocks α_1 and α_2 receptors
Pharmacological Actions:

- Reduces blood pressure (vasodilation)
- Increases NE release via α_2 blockade → **tachycardia**

Therapeutic Use:

- **Pheochromocytoma** (tumor of adrenal medulla)
- **Reversal of soft tissue anesthesia** (with vasoconstrictor)
- **Hypertensive crisis** due to MAOI + tyramine interaction

Side Effects:

- Tachycardia, arrhythmia, postural hypotension

3. Phenoxybenzamine

Type: Non-selective α-blocker (irreversible)
Mechanism: Alkylates α-receptors permanently (covalent bonding)
Duration: Long-acting (up to 24–48 hours)

Pharmacological Effects:

- Reduces peripheral vascular resistance
- Reflex tachycardia from α_2 blockade

Therapeutic Use:

- **Preoperative management of pheochromocytoma**
- **Bladder outlet obstruction** (rare)

Adverse Effects:

- Hypotension, reflex tachycardia, nasal congestion, GI upset

4. Prazosin

Type: Selective α_1-blocker
Mechanism: Blocks α_1 receptors → vasodilation without reflex tachycardia
Pharmacological Actions:

- ↓ Arterial and venous tone
- ↓ Blood pressure (especially diastolic)

Therapeutic Use:

- **Hypertension**
- **Benign prostatic hyperplasia (BPH)** – relaxes smooth muscle in prostate and bladder neck

Advantages:

- Minimal effect on heart rate
- Improves lipid profile

Side Effects:

- First-dose hypotension, dizziness, fatigue

5. Dihydroergotamine

Type: Partial α-blocker; also acts on serotonin (5-HT) receptors
Mechanism:

- Weak α-adrenergic antagonism
- Potent vasoconstrictor through serotonergic action

Therapeutic Use:

- **Acute migraine attacks**
- **Orthostatic hypotension**

Cautions:

- May cause vasospasm or hypertension in overdose
- Contraindicated in **coronary artery disease**

6. Methysergide

Type: Ergot derivative; serotonin antagonist with α-blocking activity
Mechanism:

- Weak α-blocker
- Antagonist at 5-HT_2 receptors

Therapeutic Use:

- **Prophylaxis of migraine and cluster headache**
- Not for acute attacks

Adverse Effects:

- Retroperitoneal fibrosis, hallucinations, GI disturbances

4. Clinical Applications of Alpha Blockers

Condition	Drug of Choice / Useful Drugs
Pheochromocytoma	Phenoxybenzamine, Phentolamine
Hypertension	Prazosin (as adjunct therapy)
BPH	Prazosin (and newer agents like Tamsulosin)
Migraine	Methysergide, Dihydroergotamine
Drug-induced vasospasm	Tolazoline, Phentolamine (historical)

5. Side Effects of Alpha Blockers

- **Orthostatic hypotension**
- **Reflex tachycardia** (especially with α_2 blockers)
- **Nasal congestion**
- **Dizziness, headache**
- **GI upset**
- **Tolerance** (in long-term use)

Summary Table

Drug	Type	Uses
Tolazoline*	Non-selective reversible	Vasospasm (historical)
Phentolamine	Non-selective reversible	Pheochromocytoma, hypertensive crises
Phenoxybenzamine	Non-selective irreversible	Pheochromocytoma (pre-op)
Prazosin	Selective α_1 blocker	Hypertension, BPH
Dihydroergotamine	Partial α-blocker, 5-HT agonist	Migraine
Methysergide	5-HT_2 antagonist, weak α-blocker	Migraine prophylaxis

CHAPTER-9

TOPIC- Cholinergic Neurotransmitters

Email: dr.alokdash@gmail.com

Cholinergic Neurotransmitters

1. Introduction

Cholinergic neurotransmitters are chemical messengers that use **acetylcholine (ACh)** to transmit nerve impulses across synapses. Acetylcholine is the principal neurotransmitter of the **parasympathetic nervous system**, **somatic motor neurons**, **preganglionic fibers of the sympathetic and parasympathetic nervous systems**, and certain pathways in the **central nervous system (CNS)**.

2. Biosynthesis of Acetylcholine (ACh)

Acetylcholine is synthesized in the **cytoplasm of cholinergic neurons** via a single-step reaction:

Step:

Choline+Acetyl-CoA→Choline Acetyltransferase (ChAT)Acetylcholine (ACh)+CoA\text{Choline} + \text{Acetyl-CoA} \xrightarrow{\text{Choline Acetyltransferase (ChAT)}} \text{Acetylcholine (ACh)} + \text{CoA}Choline+Acetyl-CoACholine Acetyltransferase (ChAT)Acetylcholine (ACh)+CoA

Key Components:

- **Choline**: Derived from dietary sources and membrane phospholipids.
- **Acetyl-CoA**: Provided by mitochondrial metabolism.
- **Choline acetyltransferase (ChAT)**: Specific enzyme found only in cholinergic neurons.

Storage:

- ACh is packaged into **synaptic vesicles** via **vesicular ACh transporter (VAChT)** and stored until nerve impulse triggers release.

3. Release of ACh

When an action potential reaches the nerve terminal:

- **Calcium influx** through voltage-gated channels triggers vesicle fusion with the presynaptic membrane.
- ACh is released into the synaptic cleft by **exocytosis**.
- It then binds to **cholinergic receptors** on the **postsynaptic membrane**.

4. Catabolism (Breakdown) of Acetylcholine

Acetylcholine has a **short half-life** in the synaptic cleft due to rapid breakdown by the enzyme **acetylcholinesterase (AChE)**.

Reaction:

Acetylcholine→AcetylcholinesteraseCholine+Acetate\text{Acetylcholine} \xrightarrow{\text{Acetylcholinesterase}} \text{Choline} + \text{Acetate}AcetylcholineAcetylcholinesteraseCholine+Acetate

- **Choline** is actively **reuptaken** into the presynaptic neuron for reuse.
- **Acetate** diffuses away.

Location:

- AChE is located at **neuromuscular junctions**, **ganglia**, and **CNS synapses**.

5. Cholinergic Receptors

Cholinergic receptors are classified into two major types:

1. Muscarinic Receptors (mAChRs) – G protein-coupled receptors

2. Nicotinic Receptors (nAChRs) – Ligand-gated ion channels

6. Muscarinic Receptors

- Found primarily in **parasympathetic target organs** and **CNS**.
- Activated by **acetylcholine** and **muscarine** (a mushroom alkaloid).
- Blocked by **atropine**.

Subtypes: M1 to M5

Receptor	Location	Function
M1	CNS, gastric glands	Cognitive function, gastric acid secretion
M2	Heart (atria, SA node)	↓ Heart rate and contractility
M3	Smooth muscle, glands, eye	Contraction (bronchi, bladder), secretion, miosis
M4	CNS (striatum)	Inhibitory role in dopamine pathways
M5	CNS (dopaminergic neurons)	Vasodilation via NO release

7. Nicotinic Receptors

- Found in **autonomic ganglia**, **neuromuscular junctions**, and **CNS**.
- Activated by **acetylcholine** and **nicotine**.
- Blocked by **hexamethonium** (ganglia) and **tubocurarine** (NMJ).

Subtypes:

- **Nn (Neuronal type)** – autonomic ganglia and CNS
- **Nm (Muscle type)** – neuromuscular junction (skeletal muscle)

Receptor	Location	Function
Nn	Autonomic ganglia, adrenal medulla, CNS	Ganglionic transmission, catecholamine release
Nm	Neuromuscular junction	Skeletal muscle contraction

8. Distribution Summary

Receptor Type	Location	Major Effects
M1	CNS, gastric parietal cells	Excitatory (neurons), ↑ gastric secretion
M2	Heart (atria, nodes)	↓ Heart rate and force of contraction
M3	Smooth muscle (bronchi, GI, bladder), eyes	Contraction, secretion, miosis
Nn	Autonomic ganglia, adrenal medulla, CNS	Ganglionic transmission, NE/E release
Nm	Skeletal muscle	Muscle contraction

9. Clinical Relevance

Cholinergic Agonists:

- **Pilocarpine**: M3 agonist for glaucoma
- **Bethanechol**: Enhances bladder and GI motility

Anticholinergics:

- **Atropine**: Muscarinic blocker for bradycardia, organophosphate poisoning
- **Ipratropium**: Bronchodilator for COPD

Cholinesterase Inhibitors:

- **Neostigmine**: Reverses muscle relaxants
- **Donepezil**: Alzheimer's disease

Summary Table

Acetylcholine Metabolism

Process	Enzyme	Product
Synthesis	Choline acetyltransferase	Acetylcholine
Catabolism	Acetylcholinesterase	Choline + Acetate

Receptor Overview

Receptor	Type	Location	Effect
M1	Muscarinic	CNS, stomach	↑ cognition, acid secretion
M2	Muscarinic	Heart	↓ heart rate
M3	Muscarinic	Smooth muscle, glands	↑ secretion, bronchoconstriction
Nn	Nicotinic	Ganglia, CNS	Ganglionic transmission
Nm	Nicotinic	Neuromuscular junction	Muscle contraction

🧪 Conclusion

Acetylcholine is a key neurotransmitter in the **parasympathetic nervous system** and the **neuromuscular junction**. Its synthesis, storage, release, and rapid degradation are tightly regulated. The actions of ACh are mediated via **muscarinic and nicotinic receptors**, each with distinct subtypes, locations, and physiological roles. Understanding these pathways is essential for the **rational use of cholinergic and anticholinergic drugs** in therapy.

CHAPTER-10

TOPIC- Cholinergic Neurotransmitters

Email: dr.alokdash@gmail.com

Cholinergic Neurotransmitters

1. Introduction

Cholinergic neurotransmitters are chemical messengers that use **acetylcholine (ACh)** to transmit signals across **synapses and neuromuscular junctions**. ACh plays a crucial role in both the **peripheral nervous system (PNS)** and **central nervous system (CNS)** and is the primary neurotransmitter of the **parasympathetic nervous system**.

2. Biosynthesis of Acetylcholine

Acetylcholine (ACh) is synthesized in the **cytoplasm** of **cholinergic neurons** by the enzyme **choline acetyltransferase (ChAT)**.

Biosynthesis Reaction:

Choline+Acetyl-CoA→Choline AcetyltransferaseAcetylcholine (ACh)+Coenzyme A\text{Choline} + \text{Acetyl-CoA} \xrightarrow{\text{Choline Acetyltransferase}} \text{Acetylcholine (ACh)} + \text{Coenzyme A}Choline+Acetyl-CoACholine Acetyltransferase Acetylcholine (ACh)+Coenzyme A

Key Components:

- **Choline**: Obtained from diet or recycled via high-affinity choline transporter.
- **Acetyl-CoA**: Derived from mitochondria.
- **Choline Acetyltransferase**: Exclusively found in cholinergic neurons.

Storage:

- Once synthesized, ACh is packaged into **synaptic vesicles** by **vesicular ACh transporter (VAChT)** and stored until released by exocytosis.

3. Release and Synaptic Action

- An **action potential** reaching the nerve terminal causes **Ca^{2+} influx**.
- This triggers **exocytosis** of vesicles, releasing ACh into the **synaptic cleft**.
- ACh binds to **cholinergic receptors** on the **postsynaptic membrane**, eliciting a response.

4. Catabolism (Breakdown) of Acetylcholine

Enzyme Involved: Acetylcholinesterase (AChE)

- Located in the **synaptic cleft** and **red blood cells**.
- **Rapidly hydrolyzes** ACh into **choline** and **acetic acid**.

Reaction:

Acetylcholine→AChECholine+Acetate\text{Acetylcholine} \xrightarrow{\text{AChE}} \text{Choline} + \text{Acetate}AcetylcholineAChECholine+Acetate

Fate of Choline:

- Reabsorbed into the presynaptic terminal via **high-affinity choline transporter (CHT)** and recycled.

5. Cholinergic Receptors

There are two major types of **cholinergic receptors**:

1. **Muscarinic Receptors (mAChRs)** – G-protein-coupled receptors
2. **Nicotinic Receptors (nAChRs)** – Ligand-gated ion channels

6. Muscarinic Receptors (mAChRs)

- Activated by **muscarine** (a natural alkaloid from mushrooms)
- Blocked by **atropine**
- **Five subtypes**: M1 to M5

Subtypes and Distribution:

Receptor	Location	Function
M1	CNS, gastric glands	Cognitive function, increases gastric acid secretion
M2	Heart (atria, SA node)	Slows heart rate, reduces atrial contractility
M3	Smooth muscle, glands, eyes	Contraction (bronchi, bladder), secretion, miosis

Receptor	Location	Function
M4	CNS (striatum)	Inhibitory control of dopamine pathways
M5	CNS (dopaminergic neurons)	Modulates reward system, cerebral blood flow

Signaling Pathways:

- **M1, M3, M5**: Couple to **Gq proteins**, increase **IP_3/DAG**, raise intracellular Ca^{2+}.
- **M2, M4**: Couple to **Gi proteins**, inhibit adenylate cyclase, decrease cAMP.

7. Nicotinic Receptors (nAChRs)

- Activated by **nicotine**
- Blocked by **curare-type compounds** (e.g., tubocurarine)
- Found at **autonomic ganglia**, **adrenal medulla**, **neuromuscular junction**, and in the **CNS**

Subtypes:

Receptor Type	Location	Function
Nn (neuronal)	Autonomic ganglia, adrenal medulla, CNS	Ganglionic transmission, NE/Epi release
Nm (muscle)	Neuromuscular junction (skeletal muscle)	Muscle contraction

Structure:

- **Pentameric structure** composed of five subunits (e.g., α, β, γ, δ, ε).
- Binding of two ACh molecules opens a **cation channel**, allowing **Na^+ influx** and **membrane depolarization**.

8. Distribution Summary

System	Receptor Type	Tissue	Physiological Role
Parasympathetic	Muscarinic (M1–M3)	Heart, lungs, GI tract, glands	Secretion, motility, heart rate modulation
Somatic (motor)	Nicotinic (Nm)	Skeletal muscle	Voluntary muscle contraction
Sympathetic	Nicotinic (Nn)	Autonomic ganglia, adrenal medulla	Sympathetic ganglionic transmission
CNS	M1–M5, Nn	Brain regions	Memory, learning, motor control, reward system

9. Clinical Relevance

Condition	Drug Class	Examples
Myasthenia gravis	AChE inhibitors	Neostigmine, Pyridostigmine
Alzheimer's disease	CNS AChE inhibitors	Donepezil, Rivastigmine
Glaucoma	Muscarinic agonists	Pilocarpine
Motion sickness	Muscarinic antagonists	Scopolamine
Bradycardia	Muscarinic antagonist	Atropine
Anesthesia (muscle relaxation)	Nicotinic antagonists	Rocuronium, Vecuronium

Summary Table

Process	Key Enzyme	Outcome
Biosynthesis of ACh	Choline acetyltransferase	ACh formed from choline + acetyl-CoA
Storage	Vesicular ACh transporter	ACh stored in vesicles
Release	Ca^{2+}-mediated exocytosis	ACh released into synaptic cleft
Action	Muscarinic/Nicotinic receptors	Signal transmission
Degradation	Acetylcholinesterase	ACh → choline + acetate

🧪 Conclusion

Acetylcholine plays a central role in regulating both **autonomic and somatic nervous functions**. Its effects are mediated by **muscarinic** and **nicotinic** receptors distributed throughout the body and brain. A thorough understanding of ACh metabolism and receptor pharmacology is crucial for the **diagnosis and treatment** of disorders like **myasthenia gravis**, **glaucoma**, **Alzheimer's disease**, and for effective **anesthetic** and **neuromuscular management**.

CHAPTER-11

TOPIC-

Parasympathomimetic Agents

Email: dr.alokdash@gmail.com

Parasympathomimetic Agents

1. Introduction

Parasympathomimetic agents, also known as **cholinergic agonists**, are drugs that **mimic the actions of acetylcholine (ACh)** on **muscarinic** and **nicotinic** receptors. They enhance the effects of the **parasympathetic nervous system**, which is responsible for "rest and digest" physiological functions.

These agents are broadly classified as:

- **Direct-acting agents**: Act directly on muscarinic/nicotinic receptors.
- **Indirect-acting agents** (Cholinesterase inhibitors): Inhibit **acetylcholinesterase**, increasing endogenous ACh levels.

2. Structure-Activity Relationship (SAR) of Parasympathomimetic Agents

Common Features of Choline Esters and Alkaloids:

1. **Quaternary ammonium group (N^+)**: Required for receptor binding (ionic interaction).
2. **Ester functional group (–COO–)**: Hydrolyzable, mimics acetylcholine.
3. **Ethylene bridge (2-carbon separation)**: Maintains optimal distance between nitrogen and ester oxygen for receptor activation.

4. **Hydrophilicity**: Most agents are polar, limiting CNS penetration unless they are tertiary amines (e.g., pilocarpine).
5. **Substitutions**:
    - **Methyl substitution** on β-carbon increases **muscarinic selectivity** (e.g., methacholine).
    - **Carbamate group** (–NHCOO–) in carbachol and bethanechol **resists hydrolysis**, prolonging duration of action.

3. Direct-Acting Parasympathomimetics

These agents bind and activate **muscarinic and/or nicotinic receptors**.

1. Acetylcholine

- **Receptors**: M and N (non-selective)
- **Limitation**: Rapidly hydrolyzed by acetylcholinesterase
- **Use**: Intraocular solution for miosis during ophthalmic surgery

2. Methacholine

- **SAR**: β-methyl group increases muscarinic selectivity
- **Use**: Diagnosis of **bronchial hyperreactivity (asthma challenge test)**

3. Carbachol*

- **SAR**: Carbamate ester → resistant to cholinesterase
- **Receptors**: Muscarinic + nicotinic (non-selective)
- **Use**: **Glaucoma**, ophthalmic surgeries for miosis

4. Bethanechol

- **SAR**: β-methyl + carbamate group → muscarinic selective and cholinesterase-resistant
- **Use**: **Urinary retention**, **gastrointestinal atony** (post-op)

5. Pilocarpine

- **Natural alkaloid** (tertiary amine) → crosses BBB
- **Use**: **Glaucoma**, **xerostomia** (dry mouth in Sjögren's syndrome)
- **Side Effects**: Sweating, salivation, bradycardia

4. Indirect-Acting Parasympathomimetics (Cholinesterase Inhibitors)

These drugs inhibit **acetylcholinesterase (AChE)** and increase endogenous ACh at synapses. They are categorized into:

A. Reversible Inhibitors

Drug	Structure	Uses
Physostigmine	Tertiary amine alkaloid	**Glaucoma**, antidote for anticholinergic toxicity (e.g., atropine overdose)
Neostigmine*	Quaternary ammonium	**Myasthenia gravis**, post-op GI/bladder atony
Pyridostigmine	Quaternary ammonium	**Myasthenia gravis** (longer acting than neostigmine)
Edrophonium chloride	Simple alcohol with quaternary ammonium	Diagnosis of **myasthenia gravis** (Tensilon test)
Tacrine hydrochloride	CNS-penetrant AChE inhibitor	**Alzheimer's disease** (discontinued due to hepatotoxicity)
Ambenonium chloride	Longer-acting quaternary compound	Myasthenia gravis

B. Irreversible Inhibitors (Organophosphates)

These **covalently bind AChE**, inactivating the enzyme permanently unless reactivated early.

Drug	Use / Note
Isofluorophate	Long-acting miotic (rarely used now)
Echothiophate iodide	Used in **chronic glaucoma** (rare)
Parathione	Insecticide; highly toxic to humans
Malathion	Insecticide; used in **lice treatment** (less toxic in humans due to hepatic detoxification)

Antidote:

- **Pralidoxime (2-PAM)**: Reactivates phosphorylated AChE (effective only before "aging" of enzyme complex)
- **Atropine**: Competitive muscarinic antagonist used to control symptoms

5. Therapeutic Applications

Condition	Drugs Used
Glaucoma	Pilocarpine, Carbachol, Physostigmine
Myasthenia gravis	Neostigmine, Pyridostigmine, Ambenonium
Alzheimer’s disease	Tacrine (discontinued), Donepezil
Urinary retention	Bethanechol
Anticholinergic toxicity	Physostigmine
Reversal of neuromuscular block	Neostigmine
Diagnosis of myasthenia gravis	Edrophonium
Organophosphate poisoning	Atropine + Pralidoxime

Summary Table

Direct-Acting Agents

Drug	Muscarinic/Nicotinic	Use
Acetylcholine	Non-selective	Ophthalmic surgery (miosis)
Methacholine	Muscarinic > Nicotinic	Asthma diagnosis
Carbachol*	Non-selective	Glaucoma
Bethanechol	Muscarinic selective	Urinary/GI atony
Pilocarpine	Muscarinic	Glaucoma, xerostomia

Reversible AChE Inhibitors

Drug	Key Feature	Use
Physostigmine	CNS penetration	Atropine toxicity
Neostigmine*	Peripheral action	Myasthenia gravis, GI atony
Pyridostigmine	Longer acting	Myasthenia gravis
Edrophonium	Short-acting	Diagnosis of MG
Tacrine	CNS active, hepatotoxic	Alzheimer's (obsolete)
Ambenonium	Long-acting	MG

Irreversible AChE Inhibitors

Drug	Use
Isofluorophate	Old glaucoma treatment
Echothiophate	Glaucoma (rare)
Parathione	Insecticide, toxic
Malathion	Lice treatment

🧪 Conclusion

Parasympathomimetic agents play a crucial role in managing disorders involving **cholinergic deficiency or dysfunction**. Understanding their **chemical structure**, **mechanism**, and **clinical application** enables targeted therapy in conditions like **glaucoma**, **myasthenia gravis**, **urinary retention**, and **Alzheimer's disease**. Reversible agents are widely used, while irreversible agents are largely toxic or of historical significance.

CHAPTER-12

TOPIC- Cholinesterase Reactivator and Cholinergic Blocking Agents

Email: dr.alokdash@gmail.com

Cholinesterase Reactivator and Cholinergic Blocking Agents

1. Cholinesterase Reactivator: Pralidoxime Chloride (2-PAM)

Background:

Organophosphate poisoning (e.g., from pesticides like parathion) leads to **irreversible inhibition** of acetylcholinesterase (AChE) via phosphorylation, causing **accumulation of acetylcholine** and overstimulation of cholinergic receptors.

Mechanism of Action:

- **Pralidoxime (2-PAM)** is a **nucleophilic oxime compound** that **reactivates phosphorylated AChE** before the enzyme undergoes "aging."
- It cleaves the bond between the organophosphate and the **serine residue** in the AChE active site.

Phosphorylated AChE+2-PAM→Free AChE+Phosphate–2-PAM complex\text{Phosphorylated AChE} + \text{2-PAM} \rightarrow \text{Free AChE} + \text{Phosphate–2-PAM complex}Phosphorylated AChE+2-PAM→Free AChE+Phosphate–2-PAM complex

Therapeutic Use:

- **Organophosphate poisoning**
- **Nerve agent exposure**
- Administered along with **atropine** (to block muscarinic effects)

Pharmacological Notes:

- Ineffective if aging has occurred
- Poor CNS penetration due to quaternary nitrogen (no blood–brain barrier crossing)

2. Cholinergic Blocking Agents (Anticholinergics)

These drugs competitively block **muscarinic receptors (M_1–M_5)**, preventing acetylcholine from binding and exerting its effect on **smooth muscles**, **secretory glands**, and the **CNS**.

3. Structure–Activity Relationship (SAR) of Cholinolytic Agents

Cholinolytics (muscarinic antagonists) generally follow the **structure of acetylcholine**, but with modifications that prevent activation and instead promote receptor blocking.

Key SAR Features:

Feature	Role in Activity
Ester or ether oxygen	Maintains hydrogen bonding with muscarinic receptor
Tertiary or quaternary amine	Tertiary amines (e.g., atropine) cross BBB; quaternary (e.g., ipratropium) do not
Hydrophobic side chains	Enhance receptor affinity and lipophilicity
Rigid ring systems (tropane ring)	Provide conformational constraint for binding
Bulky aromatic or aliphatic groups	Improve muscarinic receptor affinity and antagonism

4. Solanaceous Alkaloids and Their Analogues

These are **naturally occurring anticholinergics** from the Solanaceae family and their **synthetic analogues**. They are primarily **muscarinic receptor antagonists**.

1. Atropine Sulfate

- **Structure**: Racemic mixture of hyoscyamine; tropane ring with ester linkage to tropic acid.
- **Mechanism**: Competitive antagonist at **M_1–M_5 receptors**
- **Pharmacological Effects**:
  - Mydriasis (pupil dilation)
  - Tachycardia (↑ heart rate)
  - Inhibition of salivary, bronchial, and sweat secretions
  - Antispasmodic effects on GI and urinary tracts
- **Therapeutic Uses**:
  - Bradycardia
  - Organophosphate poisoning (with 2-PAM)
  - Pre-anesthetic (reduce secretions)
  - Antidote to **cholinesterase inhibitors**

- **Side Effects**: Dry mouth, blurred vision, urinary retention, CNS stimulation (in high doses)

2. Hyoscyamine Sulfate

- **Structure**: Levo-isomer of atropine; more potent
- **Uses**:
  - GI and urinary antispasmodic
  - Used in **IBS**, **renal colic**, and **Parkinson's adjunct therapy**
- **Note**: Greater CNS effects compared to atropine

3. Scopolamine Hydrobromide

- **Structure**: Similar to atropine; contains **epoxide bridge**
- **CNS Effects**: More **centrally sedative** than atropine
- **Therapeutic Uses**:
  - Motion sickness (transdermal patch)
  - Pre-anesthetic sedative
  - Anti-emetic
- **Side Effects**: Drowsiness, amnesia, dry mouth

4. Homatropine Hydrobromide

- **Semi-synthetic derivative** of atropine
- **Shorter duration** and less potent
- **Uses**:
  - Eye drops for **diagnostic mydriasis and cycloplegia**
- **Advantages**: Faster onset and recovery compared to atropine

5. Ipratropium Bromide ★

- **Structure**: Quaternary ammonium derivative of atropine
- **Action**: Localized **bronchodilation** without systemic absorption
- **Mechanism**: Blocks **M_3 receptors** in bronchial smooth muscle
- **Use**:
  - **COPD**, **asthma**, **bronchitis** (inhaled form)
- **Advantages**:
  - Minimal systemic/CNS side effects
  - Shorter duration than tiotropium

Summary Table

Drug	Type	Key Features / Uses
Pralidoxime chloride	Cholinesterase reactivator	Organophosphate antidote (peripheral)
Atropine sulfate	Tertiary amine alkaloid	Antidote for AChE inhibitors, bradycardia
Hyoscyamine sulfate	Levo-isomer of atropine	IBS, urinary spasm
Scopolamine	CNS-acting anticholinergic	Motion sickness, pre-anesthesia
Homatropine	Semi-synthetic derivative	Ophthalmic use (mydriasis)
Ipratropium bromide	Quaternary amine derivative	COPD, asthma (inhaled), minimal CNS effects

🧪 Conclusion

Cholinergic blocking agents derived from solanaceous alkaloids form the cornerstone of therapy for conditions involving **excess cholinergic activity**, such as **organophosphate poisoning**, **bronchospasm**, and **GI/urinary spasms**. Understanding their **structure-activity relationship** helps in the rational design of **CNS-penetrating vs. peripherally acting drugs**. **Pralidoxime**, as a reactivator of cholinesterase, plays a life-saving role in **toxicological emergencies**.

CHAPTER-13

TOPIC- Synthetic Cholinergic Blocking Agents

Email: dr.alokdash@gmail.com

Synthetic Cholinergic Blocking Agents

1. Introduction

Synthetic cholinergic blocking agents are **antimuscarinic drugs** that inhibit the action of **acetylcholine (ACh)** at **muscarinic receptors**, thereby blocking **parasympathetic nerve impulses**. These drugs are synthetically derived and offer **enhanced selectivity**, **reduced CNS penetration**, or **specific organ targeting**, depending on their chemical structure.

They are widely used in:

- **Ophthalmology**
- **Gastrointestinal disorders**
- **Respiratory conditions**
- **Parkinsonism**
- **Anesthesia adjuncts**

2. Classification of Synthetic Anticholinergic Agents

Group	Examples	Uses
Ophthalmic agents	Tropicamide, Cyclopentolate	Mydriasis, cycloplegia
GI & antispasmodic	Clidinium, Dicyclomine, Methantheline, Propantheline, Glycopyrrolate	GI spasm, peptic ulcer
CNS/Parkinsonism agents	Benztropine, Orphenadrine, Biperiden, Procyclidine, Ethopropazine	Parkinson's disease, drug-induced EPS
Other uses	Tridihexethyl chloride, Isopropamide	Antisecretory, adjunct in ulcers

3. Individual Agents and Their Pharmacological Profile

A. Ophthalmic Anticholinergics

1. Tropicamide

- **Mechanism**: Short-acting muscarinic antagonist (primarily M_3)
- **Use**: Produces **mydriasis** and **cycloplegia** for ophthalmic exams
- **Onset**: Rapid (15–30 minutes); duration ~4–6 hours
- **Advantage**: Safer than atropine due to shorter action

2. Cyclopentolate Hydrochloride

- **Mechanism**: Muscarinic receptor blocker
- **Use**: Induces mydriasis and cycloplegia for pediatric eye exams
- **Duration**: Longer than tropicamide (up to 24 hours)

B. Antispasmodic and GI-specific Agents

3. Clidinium Bromide

- **Use**: Adjunct in **peptic ulcers** and **IBS** to reduce GI secretions and motility
- **Often combined with**: **Chlordiazepoxide** for anxiety-related GI issues

4. Glycopyrrolate Bromide

- **Quaternary ammonium compound**: Does **not cross BBB**
- **Use**:
  - Pre-anesthetic to reduce **salivary and bronchial secretions**
  - Treat **peptic ulcers**
- **Advantage**: Minimal CNS effects

5. Dicyclomine

- **Tertiary amine**: Can cross BBB mildly
- **Use**: Antispasmodic for **intestinal cramping**, **IBS**, **colic**
- **Mechanism**: Anticholinergic + direct smooth muscle relaxant

6. Methantheline Bromide

- **Use**: Antisecretory agent in **peptic ulcer**
- **Quaternary ammonium**: Peripheral effects, no CNS action

7. Propantheline Bromide

- **Use**: Treat **peptic ulcer disease**, **urinary incontinence**
- **Effects**: ↓ GI secretions, ↓ GI motility

C. CNS-Acting Anticholinergics (Parkinsonism and EPS)

8. Benztropine Mesylate

- **Mechanism**: Centrally acting anticholinergic + antihistaminic
- **Use**:
  - **Parkinson's disease**
  - **Drug-induced extrapyramidal symptoms (EPS)** from antipsychotics
- **Caution**: Sedation, confusion in elderly

9. Orphenadrine Citrate

- **Dual action**: Anticholinergic + skeletal muscle relaxant
- **Use**:
  - Muscle spasms
  - Adjunct for Parkinsonism

10. Biperiden Hydrochloride

- **Use**:
  - Idiopathic **Parkinson's disease**
  - Drug-induced EPS
- **Effect**: Restores dopamine-cholinergic balance in basal ganglia

11. Procyclidine Hydrochloride

- **Mechanism**: Central anticholinergic
- **Use**:
  - **Parkinsonism**
  - **Dystonia** and **tremors** from antipsychotics
- **Advantage**: Fewer peripheral side effects

12. Ethopropazine Hydrochloride

- **Similar to procyclidine**
- **Use**: Parkinsonism, dystonia
- **Property**: More sedative effect

D. Miscellaneous Agents

13. Tridihexethyl Chloride

- **Use**: Adjunct in **peptic ulcer**
- **Mechanism**: Blocks M receptors in GI tract

14. Isopropamide Iodide

- **Use**: Adjunct in **GI disorders** and **respiratory secretion control**
- **Feature**: Does not cross BBB

4. Pharmacokinetic and Pharmacodynamic Considerations

Feature	Tertiary Amines	Quaternary Ammonium Salts
CNS Penetration	Yes (e.g., benztropine, dicyclomine)	No (e.g., glycopyrrolate, methantheline)
Duration of Action	Short to moderate	Typically longer
Onset	Rapid in tertiary; slower in quaternary	Slower onset
Use in elderly	Caution with CNS-active drugs	Safer with quaternary drugs

5. Side Effects of Synthetic Anticholinergics

Common anticholinergic side effects (mnemonic: "**Dry as a bone, hot as a hare, blind as a bat, red as a beet, mad as a hatter**"):

- **Dry mouth**
- **Constipation**
- **Blurred vision**
- **Urinary retention**
- **Tachycardia**
- **CNS effects**: confusion, hallucinations (tertiary amines)

Summary Table

Drug	Class/Use	Key Notes
Tropicamide	Ophthalmic	Short-acting mydriatic
Cyclopentolate	Ophthalmic	Longer mydriasis

Drug	Class/Use	Key Notes
Clidinium	GI antispasmodic	Paired with chlordiazepoxide
Glycopyrrolate	Antisecretory	No CNS effects
Dicyclomine	GI spasmolytic	IBS relief, mild CNS activity
Methantheline bromide	Peptic ulcer	No CNS effects
Propantheline bromide	GI/urinary antispasmodic	Peripheral action
Benztropine mesylate	CNS acting	Parkinsonism, antipsychotic EPS
Orphenadrine citrate	Muscle relaxant + anticholinergic	CNS depressant
Biperiden HCl	CNS acting	EPS, Parkinsonism
Procyclidine HCl	CNS acting	EPS, Parkinsonism
Tridihexethyl chloride	GI adjunct	Antisecretory
Isopropamide iodide	GI/respiratory	No CNS effects
Ethopropazine HCl	CNS acting	Sedative anticholinergic

🧪 Conclusion

Synthetic cholinergic blocking agents are a diverse group of **muscarinic antagonists** developed to optimize **receptor selectivity**, **CNS penetration**, and **therapeutic specificity**. Their applications range from treating **GI spasms**, **Parkinson's disease**, and **motion sickness** to facilitating **ophthalmic examinations** and **pre-anesthetic preparation**. Proper agent selection, based on **pharmacodynamic and pharmacokinetic** profiles, is crucial for therapeutic success and safety.

CHAPTER-14

TOPIC- Drugs Acting on Central Nervous System

Email: dr.alokdash@gmail.com

Drugs Acting on Central Nervous System

Section A: Sedatives and Hypnotics

I. Benzodiazepines

Mechanism of Action:

- Enhance the effect of **GABA** at **GABA-A receptors**.
- Produce **sedative**, **anxiolytic**, **muscle relaxant**, **anticonvulsant**, and **hypnotic** effects.

Structure-Activity Relationship (SAR):

- **Benzodiazepine ring** is essential for activity.
- **Electron-withdrawing group** at position **7** (e.g., Cl, NO_2) enhances potency.
- Ring fusion at **positions 1 and 2** increases binding affinity.
- Substituents at **position 1 (N)** and **position 5 (aromatic ring)** affect potency, duration of action, and metabolism.

Key Drugs:

1. **Chlordiazepoxide** – First benzodiazepine; anxiolytic.
2. **Diazepam*** – Long-acting; used for anxiety, muscle spasm, seizures.
3. **Oxazepam** – Shorter-acting; used in elderly.
4. **Clorazepate** – Prodrug; converted to desmethyldiazepam.
5. **Lorazepam** – Intermediate-acting; for anxiety and sedation.
6. **Alprazolam** – Used for panic disorder and anxiety.
7. **Zolpidem** – Non-benzodiazepine hypnotic (acts on GABA-A).

II. Barbiturates

Mechanism of Action:

- Potentiate GABA activity at **GABA-A receptors**, leading to **CNS depression**.

Structure-Activity Relationship (SAR):

- Core structure: **Barbituric acid**.
- Substituents at **5th position** affect lipid solubility and duration.
- Branched chains = shorter duration; longer chains = prolonged action.

Key Drugs:

1. **Barbital*** – One of the first hypnotics.
2. **Phenobarbital** – Long-acting; used as anticonvulsant.
3. **Mephobarbital** – Epilepsy treatment.
4. **Amobarbital** – Intermediate-acting sedative.
5. **Butabarbital** – Short-acting.
6. **Pentobarbital** – Used for anesthesia induction.
7. **Secobarbital** – Hypnotic, quick onset.

III. Miscellaneous Hypnotics

A. Amides and Imides

- **Glutethimide** – Barbiturate-like action; obsolete due to toxicity.

B. Alcohol and Carbamate Derivatives

- **Meprobamate** – Muscle relaxant and anti-anxiety drug.
- **Ethchlorvynol** – Rapid-acting sedative with dependence risk.

C. Aldehyde Derivatives

- **Triclofos sodium** – Pediatric sedative (prodrug of chloral hydrate).
- **Paraldehyde** – Used in **alcohol withdrawal seizures** and as a sedative.

Clinical Notes

- Benzodiazepines are **preferred over barbiturates** due to safety.
- All agents vary in **onset**, **duration**, and **abuse potential**.
- Careful use is required in elderly due to CNS sensitivity.

IV. Pharmacokinetics of Sedative-Hypnotics

Understanding the **onset, duration, metabolism, and elimination** of these agents is crucial for their safe use.

1. Benzodiazepines

- **Absorption**: Well absorbed orally.
- **Distribution**: Highly protein-bound; cross the blood-brain barrier.
- **Metabolism**: Liver metabolism via **CYP450 enzymes**, especially **CYP3A4**.
- **Excretion**: Renal, as inactive or less active metabolites.

Drug	Half-life	Remarks
Diazepam	Long (>30 hours)	Active metabolites prolong action
Lorazepam	Intermediate	Direct conjugation → safer in liver disease
Alprazolam	Short-acting	Used in panic disorders
Oxazepam	Short-acting	No active metabolites; preferred in elderly

2. Barbiturates

- **Metabolism**: Extensive hepatic metabolism.
- **Enzyme induction**: Induce CYP enzymes → drug interactions.
- **Excretion**: Mostly renal.

Drug	Duration	Use
Phenobarbital	Long (1–2 days)	Anticonvulsant
Secobarbital	Short (~3–8 hrs)	Sleep inducer (obsolete)
Pentobarbital	Short	Anesthetic induction

V. Clinical Uses of Sedatives and Hypnotics

Indication	Preferred Drug Class	Notes
Anxiety Disorders	Benzodiazepines (e.g., alprazolam)	Short-term use only
Insomnia	Zolpidem, Short BZDs	Minimal hangover effect
Pre-operative Sedation	Midazolam, Lorazepam	Amnestic effect useful
Epilepsy	Phenobarbital, Clonazepam	Long-acting agents preferred
Muscle Spasm	Diazepam, Meprobamate	Central action
Alcohol Withdrawal	Diazepam, Lorazepam	Prevent seizures, reduce autonomic symptoms
Status Epilepticus	Diazepam, Lorazepam (IV)	Emergency management

VI. Comparative Advantages and Disadvantages

Benzodiazepines

- ✅ High safety margin
- ✅ Lower risk of fatal overdose (when used alone)
- ❌ Tolerance and dependence on long-term use
- ❌ CNS depression when combined with alcohol/opioids

Barbiturates

- ✅ Effective for seizures
- ❌ Narrow therapeutic index
- ❌ High risk of respiratory depression and addiction
- ❌ Induce liver enzymes → drug interactions

Z-drugs (e.g., Zolpidem)

- ✅ Selective for sleep-inducing GABA-A sites
- ✅ Minimal hangover and memory impairment
- ❌ Risk of parasomnias (e.g., sleep-walking)
- ❌ Tolerance with prolonged use

Miscellaneous Hypnotics

- ❌ Less predictable pharmacokinetics
- ❌ Older agents (e.g., glutethimide, paraldehyde) are largely obsolete due to toxicity

VII. Side Effects and Toxicity

Class	Common Side Effects	Serious Effects
Benzodiazepines	Drowsiness, ataxia, cognitive impairment	Dependence, withdrawal seizures
Barbiturates	Sedation, hypotension, respiratory depression	Coma, death (in overdose), enzyme induction
Zolpidem	Dizziness, sleep behaviors (walking, eating)	Rare psychosis, hallucination
Meprobamate	CNS depression, rash	Physical dependence, withdrawal symptoms
Paraldehyde	GI irritation, garlic-like breath odor	Hepatotoxicity, respiratory depression

VIII. Antidotes and Management of Overdose

1. Benzodiazepine Overdose

- **Antidote**: **Flumazenil**

- Competitive antagonist at GABA-A receptor BZD binding site
- Administered IV; fast onset
- **Caution**: May precipitate seizures in chronic BZD users or mixed overdose

2. Barbiturate Overdose

- **Supportive care**: Maintain airway, breathing, circulation
- **No specific antidote**
- **Alkalinization of urine** may enhance elimination (for phenobarbital)

Quick Revision Table

Drug Class	Prototype	Action Site	Use
Benzodiazepines	Diazepam	GABA-A (BZD site)	Anxiety, insomnia
Barbiturates	Phenobarbital	GABA-A (barbiturate site)	Seizures, anesthesia
Z-hypnotics	Zolpidem	GABA-A (α1 subunit)	Insomnia
Carbamates	Meprobamate	GABA enhancement	Anxiolytic, muscle relaxant
Aldehydes	Triclofos, Paraldehyde	Unknown	Pediatric sedation, seizures

🧠 Final Notes

- **Short-term use** is preferred to avoid **tolerance and dependence**.
- In elderly, **short-acting agents** (e.g., oxazepam, lorazepam) are safer.
- Avoid combination with **alcohol**, **opioids**, or other CNS depressants.
- Regular monitoring is essential for patients on **chronic therapy**.

CHAPTER-15

TOPIC- Sedatives and Hypnotics

Email: dr.alokdash@gmail.com

A. Sedatives and Hypnotics

1. Introduction

Sedatives and hypnotics are drugs that **depress CNS activity**, leading to:

- **Sedation**: A calming effect, often with reduced anxiety and alertness.
- **Hypnosis**: Induction of sleep resembling natural sleep.

They are used in the treatment of **insomnia**, **anxiety**, **epilepsy**, and as **pre-anesthetic medications**.

The three major classes include:

1. **Benzodiazepines**
2. **Barbiturates**
3. **Miscellaneous agents** – structurally diverse

2. Benzodiazepines

Benzodiazepines act by **potentiating GABAergic neurotransmission** at **GABA-A receptors**, which are **ligand-gated chloride channels**. They increase the frequency of Cl^- channel opening, **hyperpolarizing the neuron** and reducing excitability.

Structure–Activity Relationship (SAR) of Benzodiazepines

- Core structure: **1,4-benzodiazepine ring**
- **Electron-withdrawing group** (e.g., Cl or NO_2) at **position 7** increases potency.
- **N-1 substitution** and **position 2 modifications** affect metabolism and duration.
- **Fused aromatic rings** increase binding affinity.
- Triazolo/imidazo fusion leads to higher potency (e.g., **alprazolam**).

Key Benzodiazepines

Drug	Properties & Uses
Chlordiazepoxide	First BZD; used for anxiety, alcohol withdrawal.
Diazepam*	Long-acting; anxiolytic, muscle relaxant, anticonvulsant.
Oxazepam	Short-acting; safe in elderly and liver dysfunction.
Clorazepate	Prodrug; metabolized to desmethyldiazepam.
Lorazepam	Intermediate-acting; ideal for elderly and liver disease patients.
Alprazolam	Short-acting; used in panic and anxiety disorders.
Zolpidem	Non-benzodiazepine acting on BZD receptor (α1 subtype); used as a hypnotic.

3. Barbiturates

Barbiturates are **CNS depressants** that enhance GABA action by **increasing the duration** of Cl^- channel opening at **GABA-A receptors**. In high doses, they can also directly activate the GABA receptor.

Structure–Activity Relationship (SAR) of Barbiturates

- Parent nucleus: **Barbituric acid** (inactive)
- **Substitutions at position 5** (usually alkyl or aryl) increase lipophilicity and activity.
- **Branched chains** → shorter onset and duration (e.g., **pentobarbital**).
- **Saturation** of the 5,5-substituents enhances hypnotic action.
- **Sulfur substitution** at C2 (thiobarbiturates) increases lipid solubility.

Key Barbiturates

Drug	Duration	Clinical Use
Barbital*	Long-acting	Early hypnotic; now obsolete
Phenobarbital	Long-acting	Anticonvulsant
Mephobarbital	Long-acting	Seizures
Amobarbital	Intermediate	Pre-anesthetic sedation
Butabarbital	Short-acting	Hypnotic
Pentobarbital	Short-acting	Anesthetic, euthanasia
Secobarbital	Ultra-short	Former hypnotic; now rarely used

4. Miscellaneous Sedative-Hypnotics

These include compounds that **do not structurally resemble benzodiazepines or barbiturates**, yet exert **CNS depressant effects**.

A. Amides and Imides

Glutethimide

- Non-barbiturate hypnotic with **barbiturate-like action**.

- Inhibits **CNS activity** through modulation of GABA pathways.
- Now obsolete due to **high abuse potential** and **respiratory depression**.

B. Alcohol and Carbamate Derivatives

1. Meprobamate

- **Carbamate derivative**
- Acts on **GABA-A receptors** similar to barbiturates.
- Anxiolytic and muscle relaxant properties.
- Has been replaced by benzodiazepines due to **addiction risk**.

2. Ethchlorvynol

- **Alcohol derivative**
- Short-acting sedative-hypnotic
- Acts on **reticular activating system (RAS)**
- Withdrawn in many countries due to **dependence** and **narrow therapeutic index**.

C. Aldehyde and Derivatives

1. Triclofos Sodium

- **Chloral hydrate derivative**
- **Pediatric sedative** for procedures (oral solution).
- Metabolized to **trichloroethanol**, the active sedative component.
- Safer and more palatable than chloral hydrate.

2. Paraldehyde

- Cyclic **trimer of acetaldehyde**
- Used in **status epilepticus**, **delirium tremens**
- Strong odor; administered rectally or IM.
- Side effects: **respiratory depression**, **acidosis**, and **liver damage**.

5. Comparison of Sedative-Hypnotic Classes

Class	Action	Key Features
Benzodiazepines	↑ GABA-A action (frequency)	High safety margin, lower overdose risk
Barbiturates	↑ GABA-A action (duration), GABA-mimetic	Narrow safety margin, enzyme inducer
Z-drugs	Selective for GABA-A α1 subunit	Preferred for insomnia, fewer side effects
Glutethimide	Barbiturate-like	Rarely used, toxic
Meprobamate	GABA modulation	Obsolete due to dependence
Triclofos	Sedative (chloral hydrate derivative)	Pediatric use

Class	Action	Key Features
Paraldehyde	CNS depressant	Emergency use only; outdated

6. Adverse Effects

Category	Benzodiazepines	Barbiturates	Others
CNS	Sedation, amnesia	Drowsiness, ataxia	Confusion, delirium (elderly)
Respiratory	Rare (unless IV overdose)	Respiratory depression	Severe with glutethimide
Dependence	Moderate	High	High (especially paraldehyde)
Enzyme Induction	No	Yes	No
Withdrawal Symptoms	Anxiety, seizures	Life-threatening seizures	Restlessness, insomnia

Summary Table

Drug	Class	Main Use	Special Note
Diazepam	Benzodiazepine	Anxiety, seizures, sedation	Long half-life
Zolpidem	Non-BZD hypnotic	Short-term insomnia	Low rebound insomnia
Phenobarbital	Barbiturate	Seizures	Enzyme inducer
Glutethimide	Imide	Hypnotic (historical)	Withdrawn in many countries
Meprobamate	Carbamate	Anxiety, muscle relaxant	High abuse potential
Triclofos sodium	Aldehyde derivative	Pediatric sedative	Oral, palatable
Paraldehyde	Aldehyde polymer	Status epilepticus, alcohol withdrawal	IM or rectal use

🧠 Conclusion

Sedatives and hypnotics play a vital role in **anxiety management**, **sleep induction**, **preoperative care**, and **seizure control**. Over time, the transition from **barbiturates to benzodiazepines and Z-drugs** has improved **safety, selectivity**, and **tolerability**. However, attention to **dose**, **duration**, and **drug dependence** is critical for rational use.

CHAPTER-16

TOPIC- Antipsychotic Drugs

Email: dr.alokdash@gmail.com

Antipsychotic Drugs

1. Introduction

Antipsychotic drugs are primarily used in the treatment of:

- **Schizophrenia**
- **Bipolar disorder**
- **Severe psychotic depression**
- **Acute psychosis**
- **Tourette's syndrome**

These agents are broadly classified into:

A. Typical (First-generation) Antipsychotics

- Mainly **D_2 receptor antagonists**
- Effective on **positive symptoms** (delusions, hallucinations)
- High risk of **extrapyramidal side effects (EPS)**

B. Atypical (Second-generation) Antipsychotics

- Block **D_2 + 5-HT_2A receptors**
- Effective on both **positive and negative symptoms**
- Lower incidence of EPS

2. Phenothiazines

Phenothiazines are **tricyclic antipsychotics** with a **phenothiazine nucleus**.

Structure:

- **Three-ring system** with a **nitrogen** in the central ring and a **side chain** at position 10.
- Substituents and the nature of the side chain determine potency and receptor profile.

3. SAR of Phenothiazines

Position	Modification	Effect
Ring A	Electron-withdrawing group at C-2	Enhances dopamine receptor binding
Ring B	Nitrogen in thiazine ring	Essential for activity
Ring C	Substituted aromatic or aliphatic groups	Alters potency and duration
Side chain	3-carbon linker to terminal amine	Optimal length for D_2 binding
Terminal nitrogen	Varies (aliphatic, piperidine, piperazine)	Influences potency, side effect profile

Types Based on Side Chain

Side Chain Type	Potency	Examples
Aliphatic	Low	Promazine, Chlorpromazine
Piperidine	Moderate	Thioridazine
Piperazine	High	Trifluoperazine, Prochlorperazine

Important Phenothiazines

Drug	Properties & Clinical Use
Promazine hydrochloride	Low potency, high sedation, anticholinergic side effects
Chlorpromazine hydrochloride*	Prototype drug; used in schizophrenia, nausea, hiccups
Triflupromazine	Potent antiemetic and tranquilizer
Thioridazine hydrochloride	Moderate potency; high anticholinergic and cardiac side effects
Piperacetazine hydrochloride	High-potency tranquilizer
Prochlorperazine maleate	Used in **nausea**, **vertigo**, **psychotic disorders**
Trifluoperazine hydrochloride	High potency; used in schizophrenia and anxiety

4. Ring Analogues of Phenothiazines

These analogues retain the **antipsychotic profile** but have slight changes in ring structure to enhance **efficacy**, **receptor binding**, or **tolerability**.

A. Thioxanthenes

- Sulfur in the phenothiazine ring is retained, but **nitrogen is replaced with a double bond** to a carbon.

Drug	Use
Chlorprothixene	Sedative antipsychotic

Drug	Use
Thiothixene	High-potency antipsychotic; less sedation

B. Dibenzoxazepines and Dibenzodiazepines

These are **atypical** or **second-generation** agents with action on **D_2 and 5-HT_2A receptors**.

Drug	Type	Key Features
Loxapine succinate	Dibenzoxazepine	Intermediate between typical and atypical profiles
Clozapine	Dibenzodiazepine	Highly effective in **resistant schizophrenia**; risk of **agranulocytosis**

5. Fluorobutyrophenones

This class has a **butyrophenone backbone** with a fluorine atom and a tertiary amine or piperidine ring.

Mechanism of Action:

- Strong **D_2 receptor antagonists**
- Minimal anticholinergic activity

Drug	Use
Haloperidol	Schizophrenia, Tourette's syndrome, agitation
Droperidol	Pre-anesthetic agent; antiemetic
Risperidone	Atypical agent; D_2 and 5-HT_2A blocker

6. β-Amino Ketones

These are less common but retain **D_2 antagonist** properties.

Drug	Features
Molindone hydrochloride	Effective in schizophrenia, fewer metabolic side effects; withdrawn in some markets

7. Benzamides

Selective **D_2 receptor antagonists**, especially effective in the **limbic system** with fewer motor side effects.

Drug	Use
Sulpiride	Schizophrenia, **depression at low doses**
Amisulpride (not listed but related)	Used in Europe; minimal extrapyramidal effects

8. Clinical Uses of Antipsychotics

Condition	Preferred Drug Classes
Schizophrenia	Typical & Atypical Antipsychotics
Bipolar mania	Atypicals (e.g., risperidone, olanzapine)
Acute psychosis	Haloperidol, olanzapine
Nausea and vomiting	Prochlorperazine, chlorpromazine
Tourette's syndrome	Haloperidol, pimozide
Resistant schizophrenia	Clozapine

9. Adverse Effects of Antipsychotics

Effect Type	Common Drugs Involved	Features
Extrapyramidal symptoms (EPS)	High-potency typicals (e.g., haloperidol)	Parkinsonism, dystonia, akathisia, tardive dyskinesia
Anticholinergic effects	Low-potency typicals (e.g., chlorpromazine, thioridazine)	Dry mouth, blurred vision, constipation
Endocrine	All D_2 blockers	Hyperprolactinemia → gynecomastia, amenorrhea
Sedation	Chlorpromazine, clozapine	H1 receptor blockade
Agranulocytosis	Clozapine	Requires regular CBC monitoring
Cardiotoxicity	Thioridazine, ziprasidone	QT prolongation
Weight gain, diabetes	Olanzapine, clozapine	Atypicals more commonly associated

Quick Comparison Table

Class	Example	Receptor Activity	Key Feature
Phenothiazines	Chlorpromazine	D_2 >> 5-HT_2A	High sedation, anticholinergic
Thioxanthenes	Thiothixene	D_2 selective	High potency, fewer EPS
Dibenzodiazepines	Clozapine	D_4 > D_2, 5-HT_2A	Effective in resistant cases
Butyrophenones	Haloperidol	D_2 potent	High EPS risk
Atypicals	Risperidone, Clozapine	D_2 + 5-HT_2A	Treats both +ve and -ve symptoms
Benzamides	Sulpiride	D_2 (limbic selective)	Low EPS

🧠 Conclusion

Antipsychotics are central to the management of psychotic disorders. Their **diverse structures**—from **tricyclic phenothiazines** to **heterocyclic and benzamide derivatives**—define their **pharmacological properties**, **efficacy**, and **side effect profiles**. While **typicals** are effective for **positive symptoms**, **atypicals** are better for **negative symptoms and cognitive deficits** with **fewer EPS**. A comprehensive understanding of SAR and classification enables rational drug selection and patient-specific treatment.

CHAPTER-17

TOPIC- Anticonvulsants

Email: dr.alokdash@gmail.com

Anticonvulsants

1. Introduction

Anticonvulsants (antiepileptic drugs or AEDs) are used to **prevent or reduce the severity of seizures**. Seizures are episodes of **abnormal, excessive neuronal activity** in the brain. Anticonvulsants work by modulating excitatory and inhibitory neurotransmission to **stabilize neuronal membranes**.

2. Mechanisms of Anticonvulsant Action

Anticonvulsants exert their effects through one or more of the following mechanisms:

Mechanism	Examples
Na^+ channel inactivation	Phenytoin, Carbamazepine, Valproate
Ca^{2+} channel blockade (T-type)	Ethosuximide, Valproate
Enhancement of GABAergic inhibition	Phenobarbital, Benzodiazepines, Valproate
Reduction of glutamate excitation	Lamotrigine, Felbamate
SV2A protein modulation (vesicle release)	Levetiracetam

3. Structure–Activity Relationship (SAR) of Anticonvulsants

General SAR Insights

1. **Aromatic rings and hydrophobic substituents** enhance CNS penetration.
2. **Electronegative groups** improve activity but may affect toxicity.
3. **Hydantoin or barbiturate rings** provide structural rigidity and influence duration of action.
4. Substitution on **nitrogen** or **aromatic rings** alters potency and pharmacokinetics.

4. Barbiturates

Barbiturates enhance **GABA-A receptor-mediated chloride influx**, increasing neuronal inhibition.

Phenobarbitone (Phenobarbital)

- Long-acting anticonvulsant.
- Used for generalized tonic-clonic and partial seizures.
- **SAR**:
    - Substitutions at C-5 increase lipophilicity and CNS activity.
    - Phenyl or alkyl groups enhance potency.

Methabarbital

- N-methyl derivative of phenobarbital.
- Less potent and longer-acting.

5. Hydantoins

Hydantoins block **voltage-gated sodium channels**, stabilizing the neuronal membrane.

Phenytoin* (Prototype)

- Effective in generalized tonic-clonic and partial seizures.
- **SAR**:
    - Diphenyl substitution at position 5 is essential.
    - A hydrogen at N3 is required for activity.

Mephenytoin

- Less commonly used due to hepatotoxicity.

Ethotoin

- Lower efficacy, fewer side effects than phenytoin.

6. Oxazolidine Diones

Used primarily for **absence seizures**, they block **T-type Ca^{2+} channels** in the thalamus.

Trimethadione

- First-line drug for **absence seizures** (petit mal).
- **Side Effects**: Photophobia, teratogenicity

Paramethadione

- Less effective and more toxic than trimethadione.

7. Succinimides

Also used in **absence seizures**, succinimides selectively block **T-type Ca^{2+} channels**.

Ethosuximide*

- Drug of choice for absence seizures.
- Few sedative effects; well-tolerated.

Phensuximide

- Less effective than ethosuximide.

Methsuximide

- Used in refractory absence seizures.

SAR of Succinimides:

- N-alkyl substitutions modulate duration and potency.
- Methyl substitution improves selectivity for T-channels.

8. Ureas and Monoacylureas

Phenacemide

- Used for **refractory epilepsy**.
- Withdrawn in many countries due to severe toxicity.

Carbamazepine* (Monoacylurea derivative)

- Acts by blocking **Na^+ channels**.
- Also used in **bipolar disorder** and **trigeminal neuralgia**.

SAR:

- Tricyclic structure essential for activity.
- Iminostilbene nucleus critical for anticonvulsant effects.

9. Benzodiazepines

Benzodiazepines **enhance GABA-A receptor activity**, increasing Cl^- channel opening.

Clonazepam

- Used in **absence**, **myoclonic**, and **infantile spasms**.

- Tolerance may develop with long-term use.

SAR:

- Electronegative substituent at position 7 (e.g., Cl) is critical.
- Fused benzodiazepine ring system is essential.

10. Miscellaneous Anticonvulsants

Primidone

- Prodrug converted to **phenobarbital** and **PEMA** (active metabolites).
- Used in tonic-clonic and partial seizures.

Valproic Acid

- Multiple mechanisms:
  - Na^+ channel inactivation
  - GABA-T inhibition (increasing GABA)
  - T-type Ca^{2+} channel blockade
- Used for **all seizure types**, **migraine**, and **bipolar disorder**.

Gabapentin

- Structural analogue of GABA but acts by **blocking voltage-gated Ca^{2+} channels** ($\alpha_2\delta$ subunit).
- Used for **partial seizures**, **neuropathic pain**.

Felbamate

- Antagonizes **NMDA receptor** and **modulates GABA-A** receptors.
- Reserved for **refractory epilepsy** due to risk of **aplastic anemia** and **hepatic failure**.

Comparison of Major Anticonvulsants

Drug	Mechanism	Indications
Phenobarbital	Enhances GABA-A activity	GTC, partial seizures
Phenytoin	Blocks Na^+ channels	GTC, partial seizures
Ethosuximide	Blocks T-type Ca^{2+} channels	Absence seizures
Carbamazepine	Na^+ channel blocker	GTC, partial, trigeminal neuralgia
Clonazepam	GABA-A enhancement	Absence, myoclonic, infantile spasms
Valproic acid	Multiple (GABA ↑, Na^+ & Ca^{2+} block)	Broad-spectrum (GTC, absence, myoclonic)
Gabapentin	Modulates Ca^{2+} channels ($\alpha_2\delta$)	Partial seizures, neuropathic pain
Felbamate	NMDA blocker + GABA-A modulator	Refractory epilepsy

11. Adverse Effects of Anticonvulsants

Drug/Class	Major Side Effects
Phenytoin	Gingival hyperplasia, hirsutism, ataxia, teratogenicity
Phenobarbital	Sedation, cognitive impairment, enzyme induction
Valproic acid	Hepatotoxicity, pancreatitis, weight gain, teratogenic
Carbamazepine	Hyponatremia, aplastic anemia, liver enzyme induction
Ethosuximide	GI upset, fatigue, rare blood dyscrasias
Clonazepam	Drowsiness, dependence, tolerance
Felbamate	Aplastic anemia, hepatotoxicity
Gabapentin	Sedation, dizziness, edema

12. Rational Use & Monitoring

- **Therapeutic drug monitoring** (TDM) is required for phenytoin, valproate, carbamazepine.
- **Hepatic and renal function** should be assessed before initiating therapy.
- Some anticonvulsants (e.g., valproate, phenytoin) are **teratogenic** and should be avoided in pregnancy if possible.

🧠 Conclusion

Anticonvulsants represent a structurally diverse group of drugs, each with distinct **mechanisms of action**, **SAR profiles**, and **clinical uses**. A thorough understanding of these differences helps in tailoring treatment to **seizure type**, **patient tolerance**, and **comorbid conditions**. Ongoing research is focused on **novel targets** and **better safety profiles**.

CHAPTER-18

TOPIC- Drugs Acting on the Central Nervous System – General Anesthetics

Email: dr.alokdash@gmail.com

Drugs Acting on the Central Nervous System – General Anesthetics

1. Introduction

General anesthetics are agents that induce a reversible loss of consciousness and sensation, used primarily during surgical and diagnostic procedures. They work by **depressing the central nervous system (CNS)** to various degrees, affecting consciousness, memory, and pain sensation.

General anesthetics are classified into:

- **Inhalational anesthetics** – gases or vapors absorbed via lungs.
- **Intravenous anesthetics** – drugs administered directly into circulation.

2. Mechanism of Action of General Anesthetics

While the precise mechanisms are still under investigation, most general anesthetics:

- **Enhance inhibitory GABAergic neurotransmission** at **GABA-A receptors**
- **Suppress excitatory NMDA receptor activity**
- Disrupt ion channels, especially potassium and calcium channels, leading to **neuronal hyperpolarization**

3. Inhalation Anesthetics

These are **volatile liquids or gases** administered through the respiratory tract.

General Properties:

Property	Effect
Blood-gas partition coefficient	Determines speed of induction and recovery
MAC (Minimum Alveolar Concentration)	Reflects potency (lower MAC = higher potency)

A. Halothane*

- **Type**: Volatile liquid
- **Potency**: High (MAC ~0.75%)
- **Onset**: Slow (blood-gas coefficient ~2.3)
- **Mechanism**: GABA-A receptor enhancement; K^+ channel modulation
- **Clinical Use**: Pediatric anesthesia (historically)
- **Adverse Effects**:
    - **Hepatotoxicity (Halothane hepatitis)**
    - **Cardiac arrhythmias**
    - Sensitizes heart to catecholamines

B. Methoxyflurane

- **Type**: Volatile liquid
- **Potency**: Very high
- **Use**: Rare now (used in obstetrics, Australia)
- **Adverse Effects**:
    - **Nephrotoxicity** due to fluoride ion release
    - Slow induction and recovery (blood-gas ~12)

C. Enflurane

- **Type**: Halogenated ether
- **Potency**: Moderate
- **Use**: General anesthesia (now replaced)
- **Adverse Effects**:
    - CNS stimulation → **seizure-like EEG**
    - **Renal toxicity** (fluoride ions)

D. Sevoflurane

- **Type**: Halogenated ether
- **Potency**: Moderate (MAC ~2%)
- **Use**: **Induction in pediatrics** due to non-pungent smell
- **Adverse Effects**:
    - Rare nephrotoxicity (Compound A formation)
    - Cardiovascular stability

E. Isoflurane

- **Type**: Halogenated ether
- **Use**: Widely used inhalational anesthetic
- **Properties**:
  - Good muscle relaxation
  - Pungent odor → not used for induction
- **Adverse Effects**:
  - Hypotension
  - Minimal cardiac sensitization

F. Desflurane

- **Type**: Fluorinated ether
- **Use**: Outpatient anesthesia (fast recovery)
- **Properties**:
  - Low blood solubility → rapid onset and offset
  - Requires **heated vaporizer**
- **Adverse Effects**:
  - Airway irritation
  - Sympathetic stimulation

Summary of Inhalational Agents

Agent	MAC	Blood-Gas Solubility	Special Note
Halothane	0.75%	High	Hepatotoxic; cardiac sensitization
Methoxyflurane	0.16%	Very high	Nephrotoxic; obsolete
Enflurane	1.68%	Moderate	CNS excitation, renal toxicity
Isoflurane	1.15%	Moderate	Cardiovascular stable
Sevoflurane	2.0%	Low	Best for induction in children
Desflurane	6.0%	Very low	Rapid recovery, airway irritant

4. Ultra Short-Acting Barbiturates

These are intravenous agents with **ultra-short durations** (due to redistribution) and are used for **induction** of anesthesia.

A. Methohexital Sodium*

- **Use**: Rapid induction of anesthesia, electroconvulsive therapy (ECT)
- **Onset**: 30–40 seconds
- **Duration**: 5–10 minutes
- **Mechanism**: GABA-A agonist → CNS depression
- **Advantages**:
  - Rapid recovery
  - Less hangover effect
- **Adverse Effects**:
  - Laryngospasm
  - Excitatory movements (myoclonus)

B. Thiopental Sodium

- **Prototype ultra-short barbiturate**
- **Use**: Induction of anesthesia, emergency seizure control
- **Onset**: 20–40 seconds
- **Duration**: 5–10 minutes
- **Properties**:
    - Rapid redistribution terminates action
    - Does not provide analgesia

C. Thiamylal Sodium

- Similar to thiopental; rarely used now
- Shorter duration; used in rapid sequence intubation

5. Dissociative Anesthetics

Ketamine Hydrochloride

- **Mechanism**: **NMDA receptor antagonist**
- Produces **"dissociative anesthesia"**: patients appear conscious but are unresponsive to pain and external stimuli

Features	Notes
Analgesia	Excellent
Cardiovascular effect	↑ BP and HR (stimulates SNS)
Respiratory function	Maintained
Uses	Short procedures, pediatric, battlefield, burn dressings
Adverse Effects	Emergence delirium, hallucinations

Comparison Table of General Anesthetics

Class	Example	Onset	Duration	Main Use
Inhalation	Sevoflurane	Medium	Medium	Pediatric induction
Inhalation	Isoflurane	Slow	Long	Maintenance
Barbiturate (IV)	Thiopental sodium	20–40 sec	5–10 mins	Induction
Barbiturate (IV)	Methohexital sodium*	Very rapid	Very short	ECT induction

Class	Example	Onset	Duration	Main Use
Dissociative	Ketamine	30–60 sec (IV)	10–15 mins	Analgesic procedures, children

6. Adverse Effects Summary

Agent/Class	Adverse Effects
Halothane	Hepatotoxicity, arrhythmias
Methoxyflurane	Nephrotoxicity
Enflurane	Seizures, renal toxicity
Sevoflurane	Rare nephrotoxicity
Desflurane	Airway irritation
Thiopental	No analgesia, respiratory depression
Methohexital	Myoclonus, excitation
Ketamine	Hallucinations, increased ICP

🧠 Conclusion

General anesthetics vary in **onset**, **duration**, **mechanism**, and **side effect profiles**. Inhalation agents like **sevoflurane** are ideal for **induction**, while IV agents like **thiopental** or **ketamine** are used for **rapid action** and **special scenarios**. A strong grasp of their **pharmacology, safety, and clinical utility** is essential for optimizing patient care in surgical and emergency settings.

CHAPTER-19

TOPIC- Narcotic and Non-Narcotic Analgesics

Email: dr.alokdash@gmail.com

Narcotic and Non-Narcotic Analgesics

1. Introduction

Pain is a complex physiological experience modulated by various pathways. Analgesics are classified into:

- **Narcotic (opioid) analgesics** – act on opioid receptors in the CNS.
- **Non-narcotic analgesics** – primarily NSAIDs, which inhibit prostaglandin synthesis.

2. Narcotic (Opioid) Analgesics

Opioids are natural or synthetic compounds that produce **analgesia**, **euphoria**, and **sedation** by acting on **μ (mu), κ (kappa), and δ (delta)** opioid receptors.

2.1 SAR of Morphine and its Analogues

Morphine is a pentacyclic compound with a phenanthrene nucleus.

Essential Structural Features:

Feature	Effect
Phenolic OH (C3)	Critical for analgesic activity
Alcoholic OH (C6)	Modifies potency and duration
Double bond (C7=C8)	Saturation increases potency
Tertiary amine (C17)	N-substituents modify receptor activity (agonist vs antagonist)

Modifications and Effects:

- **C3 OH methylation → Codeine** (less potent, oral bioavailability ↑)
- **C6 OH acetylation → ↑ lipophilicity → Heroin** (faster CNS penetration)
- **N17 substitution with bulky groups → Antagonist activity** (e.g., naloxone)

2.2 Morphine and Related Opioids

Drug	Features & Use
Morphine sulfate	Prototype opioid; severe pain, MI, cancer
Codeine	Less potent; used as antitussive
Meperidine hydrochloride	Synthetic opioid; short-acting; causes mydriasis
Anileridine hydrochloride	Piperidine derivative; more potent than meperidine
Diphenoxylate hydrochloride	Weak opioid; combined with atropine in antidiarrheal (Lomotil)
Loperamide hydrochloride	OTC antidiarrheal; acts peripherally on μ-receptors
Fentanyl citrate*	Highly potent, lipophilic; used in anesthesia, transdermal patch
Methadone hydrochloride*	Long-acting; used in opioid dependence and chronic pain
Propoxyphene hydrochloride	Withdrawn in many countries due to cardiac risk
Pentazocine	Mixed agonist-antagonist; used in moderate to severe pain
Levorphanol tartrate	Potent synthetic analogue of morphine

2.3 Narcotic Antagonists

Drug	Mechanism & Use
Nalorphine hydrochloride	Partial agonist-antagonist; historical use
Levallorphan tartrate	Antidote for opioid toxicity; less potent
Naloxone hydrochloride	Pure μ-antagonist; used in opioid overdose

3. Non-Narcotic Analgesics / Anti-inflammatory Agents

These are **NSAIDs** and other **non-opioid** drugs used for:

- **Pain**
- **Fever**
- **Inflammation**

Their main mechanism is the **inhibition of cyclooxygenase (COX-1 and COX-2)** enzymes, reducing **prostaglandin synthesis**.

3.1 Salicylates

Drug	Details
Sodium salicylate	Anti-inflammatory, less GI irritation
Aspirin	Irreversible COX inhibitor; analgesic, antipyretic, anti-platelet

3.2 Fenamates

Drug	Properties
Mefenamic acid*	NSAID with antipyretic and anti-inflammatory actions
Meclofenamate	Derivative of mefenamic acid; longer action

3.3 Acetic Acid Derivatives

Drug	Use & Features
Indomethacin	Potent; used in gout and PDA closure
Sulindac	Prodrug; fewer GI side effects
Tolmetin	Similar to ibuprofen; short-acting
Zomepirac	Withdrawn (toxic); powerful analgesic
Diclofenac	Widely used; potent COX-2 inhibitor
Ketorolac	Potent analgesic (parenteral); short-term post-op pain

3.4 Propionic Acid Derivatives

Drug	Notes
Ibuprofen*	Most commonly used NSAID; OTC; fewer GI side effects
Naproxen	Longer half-life; preferred for chronic pain

3.5 Oxicams

Drug	Notes
Piroxicam	Long half-life; once daily dosing; used in arthritis

3.6 Para-aminophenol Derivatives

Drug	Details
Phenacetin	Withdrawn due to nephrotoxicity
Acetaminophen (Paracetamol)	Analgesic and antipyretic; **no anti-inflammatory** effect

3.7 Pyrazolone Derivatives

Drug	Use
Antipyrine	Obsolete; antipyretic
Phenylbutazone	Anti-inflammatory; **used in ankylosing spondylitis**

4. Summary Table of NSAIDs

Drug Class	Prototype	Key Effects
Salicylates	Aspirin	Analgesic, antipyretic, anti-inflammatory
Fenamates	Mefenamic acid	Antipyretic, menstrual pain
Acetic acids	Diclofenac	Strong anti-inflammatory, arthritis use
Propionic acids	Ibuprofen	Mild pain, OTC, well-tolerated
Oxicams	Piroxicam	Long-acting NSAID
Para-aminophenols	Acetaminophen	Antipyretic; minimal GI side effects
Pyrazolones	Phenylbutazone	Potent; limited due to adverse effects

5. Adverse Effects

Opioids:

- Respiratory depression
- Constipation
- Tolerance, dependence
- Nausea, vomiting
- CNS depression

NSAIDs:

- GI ulceration
- Renal toxicity
- Hepatotoxicity (especially acetaminophen)
- Cardiovascular risks (COX-2 selective)

🧠 Conclusion

Both **narcotic** and **non-narcotic** analgesics are critical tools in the management of pain and inflammation. Opioids are indispensable in **moderate to severe pain**, but require careful monitoring due to **addiction risks**. NSAIDs are widely used for **inflammatory conditions**, but long-term use is limited by **gastrointestinal and cardiovascular risks**. A deep understanding of their **structure-activity relationships**, **mechanisms**, and **side effects** ensures safe and effective therapeutic use.