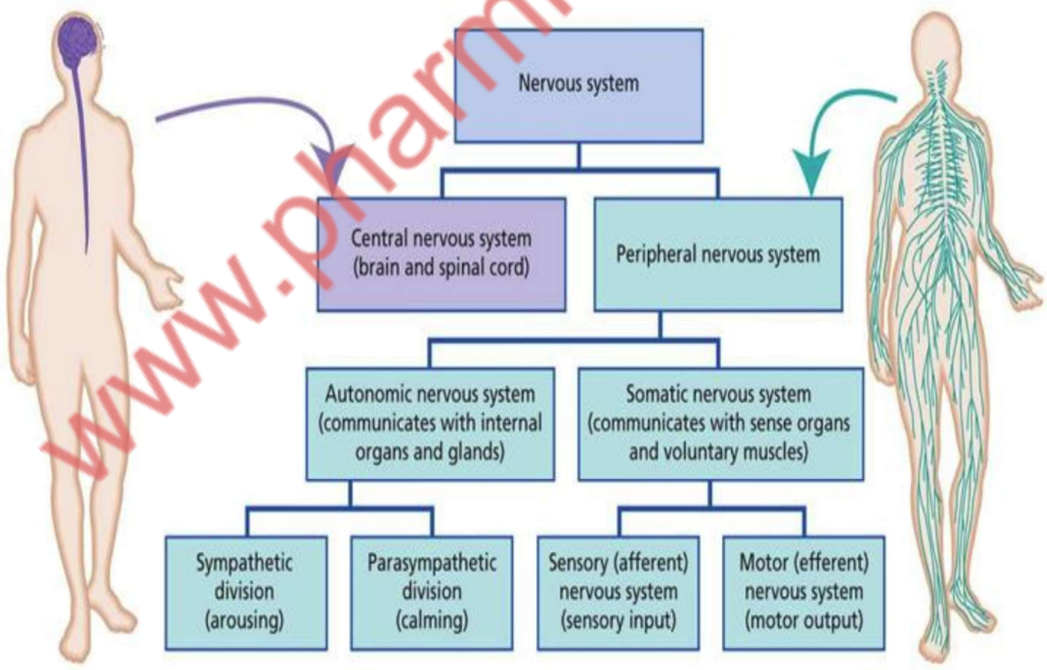
UNIT 3 (PHARMACOLGY-1)

❖ Pharmacology of Drugs Acting on the Peripheral Nervous System

The peripheral nervous system (PNS) plays a critical role in relaying signals between the central nervous system (CNS) and the rest of the body. It is composed of sensory and motor neurons that allow for voluntary and involuntary responses, as well as autonomic regulation of internal organs. Drugs that affect the PNS are used for a variety of therapeutic purposes, ranging from pain management to the treatment of disorders like hypertension and asthma.

The pharmacology of drugs acting on the PNS involves understanding how these substances interact with neurotransmitters, receptors, and various components of the PNS to modify physiological processes. Drugs can either stimulate or inhibit specific receptors, modulate neurotransmitter release, or mimic the action of endogenous molecules. The major systems affected by PNS-targeting drugs include the autonomic nervous system (ANS), which governs involuntary bodily functions, and the somatic nervous system, which controls voluntary movements.



Organization and Functions of ANS

Introduction of ANS

The Autonomic Nervous System (ANS) is a critical component of the peripheral nervous system that regulates involuntary physiological functions. It maintains homeostasis by controlling the activity of internal organs, smooth muscles, and glands. Unlike the somatic nervous system, which governs voluntary movements, the ANS operates below the level of consciousness to manage functions such as heart rate, digestion, respiratory rate, and pupil dilation.

1. Historical Perspective

The concept of the ANS has evolved over centuries. Early anatomists like Thomas Willis and Johannes Wepfer contributed to the understanding of the nervous system's role in regulating bodily functions. The term "autonomic" was coined in the 19th century to describe this system's ability to function independently of conscious control.

❖ Anatomy of the Autonomic Nervous System

❖ Structural Organization

The ANS comprises three main divisions:

- **Sympathetic Nervous System (SNS):** Originates in the thoracolumbar region of the spinal cord (T1-L2). It prepares the body for "fight or flight" responses during stressful situations.
- **Parasympathetic Nervous System (PNS):** Arises from the brainstem and sacral spinal cord (S2-S4). It promotes "rest and digest" activities, conserving energy and facilitating maintenance functions.
- **Enteric Nervous System (ENS):** Often referred to as the "second brain," the ENS is a complex network of neurons embedded within the gastrointestinal tract. It independently regulates digestive processes but communicates with the CNS via the ANS.

❖ Neuroanatomy

Each division of the ANS follows a two-neuron pathway:

- **Preganglionic Neurons:** Originate in the CNS and synapse in autonomic ganglia.
- **Postganglionic Neurons:** Extend from the ganglia to target organs.

Neurotransmitters play a pivotal role in synaptic transmission:

- **Acetylcholine (ACh):** Released by all preganglionic neurons and postganglionic neurons of the PNS.
- **Norepinephrine (NE):** Released by most postganglionic neurons of the SNS.

- **Epinephrine (E):** Released by the adrenal medulla into the bloodstream.

❖ Functional Aspects of the Autonomic Nervous System

Sympathetic Nervous System

The SNS is activated during stressful situations, initiating the "fight or flight" response:

- **Cardiovascular Effects:** Increases heart rate and contractility, leading to elevated blood pressure.
- **Respiratory Effects:** Dilates bronchial passages to enhance airflow.
- **Metabolic Effects:** Stimulates glycogenolysis and lipolysis, providing energy substrates.
- **Gastrointestinal Effects:** Inhibits digestion by decreasing peristalsis and sphincter relaxation.
- **Pupillary Effects:** Dilates pupils (mydriasis) to improve vision in low-light conditions.

Parasympathetic Nervous System

The PNS promotes "rest and digest" activities, conserving energy:

- **Cardiovascular Effects:** Decreases heart rate and contractility.
- **Respiratory Effects:** Constricts bronchial passages.
- **Gastrointestinal Effects:** Stimulates digestion by increasing peristalsis and glandular secretions.
- **Pupillary Effects:** Constricts pupils (miosis) for near vision.

Enteric Nervous System

The ENS autonomously regulates gastrointestinal functions:

- **Motility:** Controls peristalsis and segmentation.
- **Secretion:** Regulates enzyme and hormone release.
- **Blood Flow:** Modulates splanchnic circulation.

Neurotransmitters and Receptors

4.1 Cholinergic System

- **Acetylcholine (ACh):** The primary neurotransmitter in cholinergic transmission.
- **Receptors:**
  - **Nicotinic Receptors:** Found in autonomic ganglia and neuromuscular junctions.
  - **Muscarinic Receptors:** Located in target organs of the PNS.

4.2 Adrenergic System

- **Norepinephrine (NE) and Epinephrine (E):** Primary neurotransmitters in adrenergic transmission.
- **Receptors:**
  - **Alpha (α) Receptors:** α_1 (vasoconstriction) and α_2 (inhibition of neurotransmitter release).
  - **Beta (β) Receptors:** β_1 (increased heart rate and contractility), β_2 (bronchodilation), and β_3 (lipolysis).

☑ Neurohumoral Transmission, Co-Transmission, and Classification of Neurotransmitters

🧠 I. Neurohumoral Transmission

◇ What is it?

Neurohumoral transmission is the process by which **nerve cells (neurons)** send **messages** to other cells (like muscles, glands, or other nerves) using **chemicals** called **neurotransmitters**.

Instead of passing electricity directly, **nerve impulses (electrical signals)** are converted to **chemical messages** at special points called **synapses**.

📋 Key Terms:

- **Neuron** – Nerve cell
- **Neurotransmitter** – Chemical messenger
- **Synapse** – Gap between two nerve cells
- **Receptor** – Protein on target cell where neurotransmitter binds

🔄 Steps of Neurohumoral Transmission (With Diagram Summary)

1. Synthesis of Neurotransmitter

- The nerve cell produces neurotransmitters from **basic building blocks** (called precursors).
- E.g., Acetylcholine is synthesized from **choline + acetyl-CoA**.

2. Storage in Synaptic Vesicles

- The neurotransmitters are packed into small **membrane-bound vesicles** inside the nerve terminal.
- These vesicles protect the neurotransmitters and keep them ready for release.

3. Arrival of Nerve Impulse (Action Potential)

- An electrical signal travels along the neuron and reaches the end (**axon terminal**).
- This causes **calcium ions (Ca^{2+})** to enter the neuron.

4. Release of Neurotransmitter

- The calcium ions trigger the vesicles to **fuse with the membrane** and release the neurotransmitter into the **synaptic cleft** (the gap between neurons).

5. Binding to Receptors

- The neurotransmitter crosses the synaptic cleft and **binds to specific receptors** on the post-synaptic cell (next nerve/muscle/gland).
- This binding causes changes inside the target cell.

6. Generation of Response

- Depending on the neurotransmitter and receptor type:
  - It can **excite** the cell (start an action)
  - Or **inhibit** the cell (stop/prevent an action)

7. Termination of Signal

- The action must stop quickly to avoid overactivation.
- This happens by:
  - **Enzymatic breakdown** (e.g., ACh is broken by acetylcholinesterase)
  - **Reuptake** (neurotransmitter is taken back into the neuron)
  - **Diffusion** (it drifts away)

Example: Acetylcholine at Neuromuscular Junction

- ACh is released from the motor neuron.
- It binds to **nicotinic receptors** on the muscle.
- The muscle **contracts**.
- ACh is then destroyed by **acetylcholinesterase (AChE)** to stop the signal.

II. Co-Transmission

What is it?

Co-transmission means that **one neuron can release more than one type of neurotransmitter at the same time**.

Earlier, we thought one neuron = one neurotransmitter (Dale's principle). But now we know many neurons use **multiple chemical signals**.

Why is it important?

- The **primary neurotransmitter** gives the main effect.
- The **co-transmitter** can:
  - **Modulate** the effect (make it stronger or weaker)
  - Act on **different receptors**
  - Cause **longer-lasting effects**

Example:

A **cholinergic neuron** may release:

- **Acetylcholine (ACh)** → causes fast response
- **Vasoactive intestinal peptide (VIP)** → causes slower, sustained relaxation of smooth muscles

Examples Table:

Nerve Type	Primary Neurotransmitter	Co-Transmitters
Cholinergic	Acetylcholine (ACh)	ATP, VIP
Adrenergic	Noradrenaline (NA)	Neuropeptide Y
Dopaminergic	Dopamine	Substance P, CCK

III. Classification of Neurotransmitters

Neurotransmitters can be classified based on:

A. Chemical Structure

1. Small Molecules
2. Neuropeptides
3. Gaseous neurotransmitters
4. Purines

B. Excitatory or Inhibitory Action

- **Excitatory** = stimulates target cell (e.g., Glutamate, ACh)
- **Inhibitory** = suppresses target cell (e.g., GABA, Glycine)

Detailed Classification:

1. Small Molecule Neurotransmitters

Group	Examples	Function
ACh	Acetylcholine	Muscle movement, parasympathetic control
Amino Acids	Glutamate, GABA, Glycine	CNS activation/inhibition
Biogenic Amines	Dopamine, Noradrenaline, Adrenaline, Serotonin, Histamine	Mood, alertness, hormone control

2. Neuropeptides

- Made of 2 or more amino acids
- Act slowly but effects last longer
- Modulate pain, emotions, stress, appetite

Example	Function
Substance P	Pain signaling
Endorphins/Enkephalins	Natural painkillers
Neuropeptide Y	Appetite, stress
Somatostatin	Inhibits hormone release

3. Purines

- **ATP** and **Adenosine**
- Released with other neurotransmitters
- Involved in pain, heart rate, and neuromodulation

◇ 4. Gaseous Neurotransmitters

- **Nitric oxide (NO)** and **Carbon monoxide (CO)**
- Not stored in vesicles – made on demand
- Act by **diffusing** into nearby cells

Gas	Role
NO	Blood vessel relaxation, memory
CO	Modulation in CNS

📝 Important Points to Remember

Topic	Key Fact
Neurohumoral Transmission	Chemical signal sent across synapse using neurotransmitters
Co-Transmission	One neuron → multiple transmitters
ACh	Released at neuromuscular junctions
GABA and Glycine	Inhibitory neurotransmitters
Glutamate	Most common excitatory neurotransmitter
Neuropeptides	Long-term modulators (e.g., pain, stress)
NO (Nitric Oxide)	Gas neurotransmitter, causes vasodilation.

🧠 Autonomic Nervous System (ANS) Drug Categories

These drugs affect the autonomic nervous system in **four major ways**:

Action Type	Parasympathetic (Cholinergic)	Sympathetic (Adrenergic)
Stimulate	Parasympathomimetic	Sympathomimetics
Inhibit (Block)	Parasympatholytic	Sympatholytic

Parasympathomimetic –

Definition

Parasympathomimetic (also called **cholinergic agonists**) are drugs that **mimic or enhance the effects of acetylcholine (ACh)**, the neurotransmitter of the **parasympathetic nervous system (PNS)**.

These drugs **activate cholinergic receptors** to produce **"rest-and-digest"** responses in various organs.

Overview of the Parasympathetic Nervous System (PNS)

- Part of the **autonomic nervous system** (along with the sympathetic system).
- Controls involuntary functions: digestion, urination, salivation, etc.
- Main neurotransmitter: **Acetylcholine (ACh)**
- Receptors:
    1. **Muscarinic receptors (M1–M5)** – found in smooth muscles, heart, glands.
    2. **Nicotinic receptors** – found in autonomic ganglia, adrenal medulla, skeletal muscles.

Classification of Parasympathomimetic

I. Based on Mechanism of Action

1. Direct-Acting Parasympathomimetic

- These drugs **bind directly to cholinergic receptors** (mainly muscarinic or nicotinic).
- They **mimic the action of acetylcholine**.

Examples:

Drug	Receptor Type	Major Use
Acetylcholine	Muscarinic & Nicotinic	Experimental only (short action)
Bethanechol	Muscarinic	Urinary retention, atonic bladder
Pilocarpine	Muscarinic	Glaucoma, dry mouth
Carbachol	Both (strong)	Glaucoma (topical use)
Methacholine	Muscarinic	Diagnosis of bronchial asthma

2. Indirect-Acting Parasympathomimetic

- These **inhibit the enzyme acetylcholinesterase (AChE)**, which breaks down ACh.
- More ACh remains in the synapse, leading to **enhanced parasympathetic effects**.

a. Reversible AChE inhibitors

Drug	Use
Neostigmine	Myasthenia gravis, postoperative ileus

Drug	Use
Pyridostigmine	Long-term management of myasthenia gravis
Physostigmine	Anticholinergic poisoning
Edrophonium	Diagnosis of myasthenia gravis (Tensilon test)
Donepezil, Rivastigmine, Galantamine	Alzheimer's disease treatment

b. Irreversible AChE inhibitors (Organophosphates)

Compound	Use
Malathion, Parathion	Insecticides (toxic to humans)
Echothiophate	Glaucoma (obsolete)

📊 Pharmacological Actions of Parasympathomimetic

◇ Eyes

- Miosis (pupil constriction)
- Improves drainage of aqueous humor (↓ intraocular pressure)
- Accommodation for near vision

◇ Heart

- ↓ Heart rate (bradycardia)
- ↓ AV conduction
- ↓ Cardiac output

◇ Blood Vessels

- Generally, **no direct effect**, unless injected in high doses (some vasodilation via endothelial M3 receptors)

◇ Respiratory Tract

- Bronchoconstriction
- ↑ Bronchial secretions

◇ Gastrointestinal Tract

- ↑ Peristalsis
- ↑ Gastric and pancreatic secretions
- May cause abdominal cramps

◇ Urinary Bladder

- Contracts detrusor muscle
- Relaxes sphincter → facilitates urination

◇ Exocrine Glands

- ↑ Salivation, lacrimation, sweating, nasal & GI secretions

💉 Receptor Subtypes and Actions

Receptor	Location	Effect
M1	CNS, gastric glands	Memory, gastric acid secretion
M2	Heart	↓ Heart rate and conduction
M3	Smooth muscles, glands, eyes	Contraction, secretion
M4, M5	CNS (less understood)	CNS modulation
Nicotinic	Autonomic ganglia, NMJ	Autonomic response, muscle contraction

💊 Therapeutic Uses of Parasympathomimetic

Condition	Drug(s) Used
Glaucoma	Pilocarpine, Carbachol
Urinary retention	Bethanechol
Dry mouth (xerostomia)	Pilocarpine
Myasthenia gravis	Neostigmine, Pyridostigmine
Alzheimer's disease	Donepezil, Rivastigmine
Anticholinergic poisoning	Physostigmine
Diagnostic (asthma)	Methacholine

⚠ Adverse Effects of Parasympathomimetic

Mnemonic: SLUDGE-M

- **S** – Salivation
- **L** – Lacrimation
- **U** – Urination
- **D** – Diarrhoea
- **G** – GI upset
- **E** – Emesis (vomiting)
- **M** – Miosis, Muscle cramps

Other side effects:

- Hypotension
- Bradycardia
- Sweating

- Bronchospasm (dangerous in asthmatics)

❌ **Contraindications**

Do not use parasympathomimetic in:

- **Asthma or COPD** → bronchoconstriction risk
- **Bradycardia or AV block**
- **Peptic ulcer disease** → increased acid secretion
- **Parkinsonism** (for indirect cholinergic agents)
- **Urinary obstruction** or intestinal obstruction

💊 **Cholinergic Crisis**

Occurs due to **overdose of cholinergic drugs** (especially organophosphates or neostigmine).

Symptoms:

- SLUDGE symptoms + muscle paralysis + respiratory depression

Treatment:

- **Atropine**: Blocks muscarinic receptors
- **Pralidoxime (2-PAM)**: Reactivates AChE (if given early)

🌿 1. Parasympatholytic (Anticholinergics)

☑ **Definition:**

Drugs that **block the action of acetylcholine** on **muscarinic receptors**. They **inhibit parasympathetic activity**.

🔬 **Mechanism:**

- **Competitive antagonists** at **muscarinic receptors (M1–M5)**.
- Some drugs may also block **nicotinic receptors** at ganglia or neuromuscular junctions (e.g., ganglion blockers, muscle relaxants).

💊 **Examples of Parasympatholytic**

Drug	Use
Atropine	Bradycardia, organophosphate poisoning
Hyoscine (Scopolamine)	Motion sickness, pre-anesthetic
Ipratropium, Tiotropium	Asthma, COPD (inhalers)
Oxybutynin, Tolterodine	Overactive bladder
Cyclopentolate	Eye exams (mydriasis, cycloplegia)

📊 Effects on Organs

Organ/System	Effect of Parasympatholytic
Eye	Mydriasis (pupil dilation), cycloplegia
Heart	↑ Heart rate (tachycardia)
Lungs	Bronchodilation
GI Tract	↓ Motility, constipation
Bladder	Urinary retention
Glands	↓ Secretions (dry mouth, dry eyes)

⚠ Side Effects (Mnemonic: "Dry as a bone, blind as a bat, hot as a hare, mad as a hatter")

- Dry mouth (xerostomia)
- Blurred vision (cycloplegia)
- Tachycardia
- Constipation
- Urinary retention
- Confusion (especially in elderly)

❌ Contraindications

- Glaucoma (may raise intraocular pressure)
- BPH (benign prostatic hyperplasia)
- Elderly with dementia or cognitive decline
- Paralytic ileus

2. Sympathomimetics (Adrenergic Agonists)

☑ Definition:

These drugs **mimic or enhance the effects of the sympathetic nervous system** by activating **adrenergic receptors (alpha, beta).**

🔬 Types of Receptors

Receptor	Location	Effect
α1	Blood vessels, eye, bladder	Vasoconstriction, mydriasis, urine retention
α2	CNS (presynaptic), pancreas	↓ Sympathetic outflow, ↓ insulin
β1	Heart	↑ Heart rate and contractility

Receptor	Location	Effect
β2	Bronchi, uterus, liver, vessels	Bronchodilation, uterine relaxation, glycogenolysis
β3	Fat cells	Lipolysis

Classification

A. Direct-acting Sympathomimetics

Drug	Receptor Activity	Uses
Epinephrine	α1, α2, β1, β2	Anaphylaxis, cardiac arrest
Norepinephrine	α1, α2, β1	Shock (↑ BP)
Dopamine	D1, β1, α1 (dose-dependent)	Shock, heart failure
Dobutamine	β1	Acute heart failure
Salbutamol	β2	Asthma, COPD
Phenylephrine	α1	Nasal decongestant, hypotension
Clonidine	α2	Hypertension

B. Indirect-acting Sympathomimetics

Drug	Mechanism	Use
Amphetamine	↑ NE release	ADHD, narcolepsy
Cocaine	Inhibits NE reuptake	Local anaesthesia
Tyramine	Releases stored NE (dietary amine)	Causes hypertensive crisis in MAOI users

Therapeutic Effects

System	Effect
Heart	↑ HR and contractility (β1)
Blood vessels	Vasoconstriction (α1) or dilation (β2)
Bronchi	Bronchodilation (β2)

System	Effect
Eyes	Mydriasis (α1)
Metabolism	↑ Glucose, ↑ lipolysis

⚠ **Adverse Effects**

- Tachycardia
- Hypertension
- Anxiety, tremors
- Arrhythmias
- Headache
- Hyperglycaemia

⛔ 3. Sympatholytic (Adrenergic Blockers)

☑ **Definition:**

These are drugs that **inhibit the effects of the sympathetic nervous system** by **blocking adrenergic receptors**.

🛍 Classification

A. Alpha Blockers

Drug	Type	Use
Prazosin	α1 selective	Hypertension, BPH
Phentolamine	Non-selective	Pheochromocytoma diagnosis
Phenoxybenzamine	Non-selective (irreversible)	Pheochromocytoma (pre-op)

Effects:

- Vasodilation
- ↓ BP
- Reflex tachycardia

B. Beta Blockers

Drug	Selectivity	Use
Propranolol	Non-selective	Hypertension, angina, tremors
Atenolol, Metoprolol	β1-selective	Heart disease, hypertension

Drug	Selectivity	Use
Carvedilol, Labetalol	α + β blocker	Heart failure, hypertensive emergency

Effects:

- ↓ HR and BP
- ↓ cardiac workload
- ↓ renin release

❌ **Adverse Effects**

Alpha Blockers	Beta Blockers
Postural hypotension	Bradycardia
Reflex tachycardia	Fatigue, depression
Nasal congestion	Bronchospasm (non-selective types)
Sexual dysfunction	Hypoglycaemia masking in diabetics

💊 Neuromuscular Blocking Agents (NMBAs)

🦴 Peripheral Skeletal Muscle Relaxants

These drugs act at the **neuromuscular junction (NMJ)** to **cause muscle relaxation or paralysis**, mainly during surgeries or medical procedures.

🧠 **What is the Neuromuscular Junction (NMJ)?**

- The **NMJ** is a synapse between a **motor neuron and a skeletal muscle fiber**.
- **Acetylcholine (ACh)** is released from the nerve ending → binds to **nicotinic receptors** on the muscle → causes depolarization → muscle contracts.

🧬 **Classification of Neuromuscular Blocking Agents**

Type of Agent	Mechanism	Example Drugs
Depolarizing Blockers	Initially depolarize, then block NMJ	**Succinylcholine (Suxamethonium)**
Non-Depolarizing Blockers	Compete with ACh at nicotinic receptors	**Tubocurarine, Atracurium, Vecuronium, Rocuronium**

Mechanism of Action

1. Depolarizing Neuromuscular Blockers

- **Mimic ACh**, bind to **nicotinic receptors** and **continuously stimulate** them.
- This causes **initial contractions (fasciculations)** followed by **flaccid paralysis**.
- Only drug used clinically: **Succinylcholine**.

Phases of Action:

- **Phase I (Depolarizing):** Persistent depolarization → no repolarization → paralysis.
- **Phase II (Desensitizing):** Receptors become unresponsive.

Note: Phase I is not reversed by cholinesterase inhibitors.

2. Non-Depolarizing Neuromuscular Blockers

- **Competitive antagonists** of ACh at **nicotinic receptors**.
- Prevent ACh from activating the receptor → no depolarization → no contraction.

Can be reversed by cholinesterase inhibitors (e.g., neostigmine).

Comparison Table

Feature	Depolarizing (Succinylcholine)	Non-depolarizing (e.g., Vecuronium)
Action	Persistent stimulation → block	Competitive inhibition
Onset	Rapid (30–60 seconds)	Slower
Duration	Short (5–10 min)	Intermediate to long
Fasciculations	Yes (initial)	No
Reversible by AChE inhibitors	No (Phase I), Yes (Phase II)	Yes
Common Use	Rapid intubation	General anesthesia muscle relaxation

Examples of Non-Depolarizing Agents

Drug	Duration	Special Features
Tubocurarine	Long-acting	Histamine release → ↓BP
Atracurium	Intermediate	Safe in liver/kidney disease
Vecuronium	Intermediate	Widely used in anesthesia
Rocuronium	Rapid onset	Succinylcholine alternative
Pancuronium	Long-acting	↑ Heart rate (vagolytic effect)

💉 Reversal Agents for Non-Depolarizing Blockade

Drug	Mechanism
Neostigmine	Inhibits acetylcholinesterase → ↑ ACh
Sugammadex	Encapsulates rocuronium/vecuronium → direct reversal

⚠ Adverse Effects

Drug	Adverse Effects
Succinylcholine	Hyperkalemia, malignant hyperthermia, apnea, muscle pain
Tubocurarine	Histamine release → hypotension
All NMBAs	Respiratory paralysis if ventilation support is not provided

💡 Peripheral Skeletal Muscle Relaxants

These include **neuromuscular blocking agents**, as well as some **peripherally acting agents that work differently**.

☑ Skeletal Muscle Relaxants:

Type	Action Site	Examples
Central	CNS (spinal cord/brain)	Baclofen, Diazepam, Tizanidine
Peripheral (NMBAs)	NMJ	Succinylcholine, Vecuronium

Type	Action Site	Examples
Direct-acting	Muscle itself	Dantrolene

Direct-acting Skeletal Muscle Relaxant

Dantrolene

- **Inhibits calcium release** from sarcoplasmic reticulum in skeletal muscle.
- **Reduces muscle contraction** directly at muscle fiber.
- Used in **malignant hyperthermia** and **chronic spasticity** (e.g., in MS, cerebral palsy).

Clinical Uses of NMBAs & Peripheral Relaxants

Use	Drugs Used
Muscle relaxation during surgery	Vecuronium, Atracurium
Rapid sequence intubation	Succinylcholine
Mechanical ventilation	Rocuronium, Pancuronium
Treatment of seizures (adjunct)	Diazepam
Malignant hyperthermia	Dantrolene
Electroconvulsive therapy	Succinylcholine (prevent injuries)

Local Anesthetic Agents

1. Introduction

Local anaesthetics (LAs) are drugs that **reversibly block nerve conduction** when applied locally to nerve tissues, **without causing loss of consciousness**. They are primarily used for **temporary pain relief** during minor surgical, dental, or diagnostic procedures.

2. Mechanism of Action

Local anaesthetics block **voltage-gated sodium (Na^+) channels** in the neuronal membrane.

- This **prevents depolarization** and **inhibits action potential propagation**, leading to **loss of sensation** in the area.

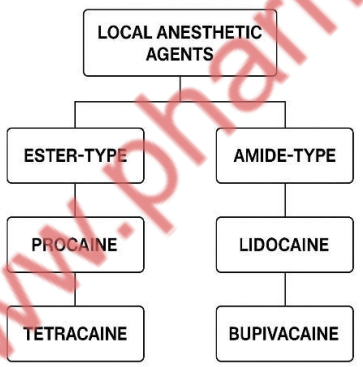
◇ **Steps:**

1. LA penetrates the nerve membrane in uncharged (lipid-soluble) form.
2. Inside the neuron, it becomes charged (ionized).
3. The ionized form binds to Na^+ channels and **blocks sodium influx**, stopping impulse conduction.

3. Classification of Local Anaesthetics

A. Based on Chemical Structure

Type	Examples	Metabolism Site
Ester-linked	Procaine, Tetracaine	Plasma (pseudocholinesterase)
Amide-linked	Lidocaine, Bupivacaine	Liver (CYP450 enzymes)



4. Ideal Properties of a Local Anesthetic

- Reversible nerve block
- Rapid onset and adequate duration
- Low systemic toxicity
- Non-irritating to tissues

- Stable in solution and sterilizable

5. Pharmacokinetics

- **Absorption**: Depends on dose, vascularity of area, and vasoconstrictors (e.g., epinephrine).
- **Distribution**: Highly protein-bound drugs have longer duration (e.g., bupivacaine).
- **Metabolism**:
  - Esters – rapidly hydrolyzed in plasma
  - Amides – metabolized in liver
- **Excretion**: Mainly via kidneys

6. Adjuvants Used with Local Anesthetics

- **Epinephrine (vasoconstrictor)**: Prolongs action, reduces systemic absorption, and decreases bleeding.

7. Routes of Administration

- **Topical**: Surface anesthesia (e.g., lidocaine gel)
- **Infiltration**: Into tissues (e.g., for dental procedures)
- **Nerve block**: Around specific nerves
- **Spinal**: Into CSF (subarachnoid space)
- **Epidural**: Outside the dura mater (in labor pain)

8. Commonly Used Local Anesthetics

Drug	Type	Uses	Onset/Duration
Lidocaine	Amide	Dental, minor surgery, arrhythmia	Rapid/Intermediate
Bupivacaine	Amide	Long procedures, labor analgesia	Slow/Long
Procaine	Ester	Infiltration, dental anesthesia	Slow/Short
Tetracaine	Ester	Spinal anesthesia	Slow/Long

9. Adverse Effects

A. CNS Toxicity:

- Restlessness, tremors
- Convulsions
- CNS depression → coma

B. Cardiovascular Toxicity:

- Hypotension
- Arrhythmias (especially with **bupivacaine**)

C. Allergic Reactions:

- More common with **ester**-type agents

10. Contraindications

- Known hypersensitivity
- Severe liver dysfunction (for amides)
- Heart block or severe bradycardia (for certain types)

11. Recent Advances

- **Eutectic mixtures** (e.g., EMLA cream – lidocaine + prilocaine)
- **Liposome-encapsulated LAs** (e.g., Exparel – bupivacaine)

Drugs Used in Myasthenia Gravis and Glaucoma

1. Myasthenia Gravis (MG)

Overview:

Myasthenia Gravis is a chronic autoimmune neuromuscular disorder characterized by weakness and rapid fatigue of voluntary muscles. It results from antibodies against the nicotinic acetylcholine receptors (AChRs) at the neuromuscular junction, leading to impaired transmission of nerve impulses to muscles.

Treatment Approach:

The primary treatment is to improve neuromuscular transmission by **inhibiting acetylcholinesterase (AChE)** — the enzyme that breaks down acetylcholine (ACh) — thereby increasing ACh availability at the neuromuscular junction.

Drugs Used:

Drug Category	Drug Name	Mechanism of Action	Notes
Acetylcholinesterase inhibitors (AChEIs)	Pyridostigmine (most commonly used)	Inhibits AChE → increases ACh levels at neuromuscular junction → improves muscle contraction	Oral or IV; preferred for long-term management
	Neostigmine	Same as above, used mainly in acute settings or diagnosis	Shorter duration than pyridostigmine
Immunosuppressants	Prednisone, Azathioprine	Suppress immune system to reduce antibody production against AChR	Used in severe or refractory cases
Other treatments	Plasmapheresis, IVIG	Remove circulating antibodies or modulate immune response	Used in crisis or before surgery

Mechanism Diagram: Acetylcholinesterase Inhibitor Action in MG

Nerve terminal releases ACh

⬇

ACh binds to nicotinic receptors on muscle

⬇

Normal: ACh broken down by AChE

⬇

In MG: fewer receptors

⬇

weak signal

⬇

AChE inhibitor blocks AChE

⬇

More ACh available

⬇

Improved muscle contraction

Glaucoma

Overview:

Glaucoma is a group of eye diseases characterized by increased intraocular pressure (IOP), leading to optic nerve damage and vision loss. The goal of treatment is to lower IOP either by decreasing aqueous humor production or increasing its outflow.

Drugs Used:

Drug Category	Drug Name	Mechanism of Action	Notes
Prostaglandin analogs	Latanoprost, Bimatoprost	Increase uveoscleral outflow of aqueous humor → lowers IOP	First-line treatment
Beta-blockers	Timolol, Betaxolol	Decrease aqueous humor production by ciliary body	Used as monotherapy or with prostaglandins
Alpha-2 agonists	Brimonidine	Decrease aqueous humor production and increase uveoscleral outflow	Can cause allergic reactions
Carbonic anhydrase inhibitors	Acetazolamide (oral), Dorzolamide (topical)	Decrease aqueous humor production by inhibiting carbonic anhydrase	Oral form used in emergencies
Cholinergic agonists (miotics)	Pilocarpine	Increase trabecular meshwork outflow by contracting ciliary muscle	Used less due to side effects

Mechanism Flowchart: Glaucoma Drug Action

Increased IOP

Optic nerve damage

Vision loss

Treatment:

Decrease aqueous humor production

| ├─ Beta-blockers (Timolol)

| ├─ Alpha-2 agonists (Brimonidine)

| └─ Carbonic anhydrase inhibitors (Acetazolamide)

|

|--- Increase aqueous humor outflow

├─ Prostaglandin analogs (Latanoprost) via uveoscleral pathway

└─ Cholinergic agonists (Pilocarpine) via trabecular meshwork

Result: Lower IOP → Protect optic nerve → Preserve vision

Diagram: Aqueous Humor Dynamics and Drug Sites of Action

Ciliary body (produces aqueous humor)

→ Anterior chamber

→ Outflow via:

- Trabecular meshwork (conventional pathway)

- Uveoscleral pathway (unconventional)

Drugs:

- Beta-blockers, CA inhibitors, alpha-2 agonists ↓ production at ciliary body
- Prostaglandin analogs ↑ uveoscleral outflow
- Pilocarpine ↑ trabecular meshwork outflow by contracting ciliary muscle

Summary Table

Disease	Drug Category	Examples	Mechanism	Clinical Use
Myasthenia Gravis	Acetylcholinesterase inhibitors	Pyridostigmine, Neostigmine	Inhibit AChE → ↑ ACh at NMJ	Improve muscle strength
	Immunosuppressants	Prednisone, Azathioprine	Suppress antibody production	Severe/refractory MG
Glaucoma	Prostaglandin analogs	Latanoprost	↑ Uveoscleral outflow	First-line therapy
	Beta-blockers	Timolol, Betaxolol	↓ Aqueous humor production	Used alone or combined
	Alpha-2 agonists	Brimonidine	↓ Production, ↑ outflow	Adjunct therapy
	Carbonic anhydrase inhibitors	Acetazolamide, Dorzolamide	↓ Aqueous humor production	Emergency or adjunct
	Cholinergic agonists	Pilocarpine	↑ Trabecular outflow	Less common due to side effects