BP405T · B.PHARM THEORY

BP405T Systemic Pharmacology I

Unit I — Drugs Acting on the Peripheral Nervous System

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B.Pharm Semester IV · Unit I · 10 Hours

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Chapter 1: Organization of the Peripheral Nervous System and Neurohumoral Transmission

1.1 Learning Objectives

After studying this chapter, the student will be able to:

1. Describe the organization and divisions of the peripheral nervous system (PNS).
2. Differentiate between sensory (afferent) and motor (efferent) divisions.
3. Differentiate between the somatic and autonomic nervous systems.
4. Describe the sympathetic, parasympathetic, and enteric divisions of the autonomic nervous system.
5. Define neuron, nerve, ganglion, and plexus.
6. Explain the steps of synaptic (neurohumoral) transmission.
7. Describe cholinergic transmission — synthesis of acetylcholine and its receptors (nicotinic Nn, Nm; muscarinic M1–M5).
8. Describe adrenergic transmission — synthesis of noradrenaline/adrenaline and receptors (alpha1, alpha2, beta1, beta2, beta3, dopaminergic).
9. Explain co-transmission and list non-adrenergic non-cholinergic (NANC) transmitters (NO, VIP, ATP, substance P, CGRP) with their roles.

1.2 Definitions

- **Neuron (nerve cell):** The basic unit of the nervous system. It is a single cell that carries electrical messages. It has three parts — the cell body (the main body of the cell), dendrites (short branches that receive messages), and the axon (one long wire-like part that sends messages forward).
- **Nerve:** A bundle of many axons (nerve fibres) tied together like a cable. Think of one axon as one thread and a nerve as the whole rope made of many threads.
- **Ganglion:** A small group of nerve cell bodies lying outside the brain and spinal cord, like a small station or junction where messages are passed from one neuron to the next.
- **Plexus:** A network of crossing nerves, like a web or a roundabout where many nerve roads meet and mix.
- **Neurohumoral transmission:** The process by which a message passes from one nerve cell to another (or from a nerve to a muscle) using a chemical messenger (the "humor" is a chemical, not a liquid joke). The chemical is called a **neurotransmitter**.
- **Neurotransmitter:** A chemical released by a nerve ending that carries the message across the small gap to the next cell.
- **Synapse:** The tiny gap (junction) between two nerve cells, or between a nerve cell and a muscle cell, across which the chemical message travels.
- **Receptor:** A special protein on the surface of a cell that catches the neurotransmitter — like a lock that only its own key (the transmitter) can open.
- **Agonist:** A drug that switches the receptor ON, like the real key.
- **Antagonist:** A drug that blocks the receptor, sitting in the lock so the real key cannot enter — like a wrong key stuck in the keyhole.
- **Cholinergic:** A nerve fibre or drug action that uses acetylcholine as its messenger.
- **Adrenergic:** A nerve fibre or drug action that uses noradrenaline (norepinephrine) as its messenger.
- **Co-transmission:** The release of TWO or more chemical messengers from one nerve ending at the same time.
- **NANC (non-adrenergic non-cholinergic):** Nerve fibres and messengers that are neither noradrenaline-based nor acetylcholine-based (examples: nitric oxide, VIP, ATP, substance P, CGRP).

1.3 Terminology

- **Afferent (sensory):** Nerves that carry information FROM the body TO the brain/spinal cord. Memory trick: "**A**fferent = **A**rrives at the brain."
- **Efferent (motor):** Nerves that carry orders FROM the brain/spinal cord TO the body. Memory trick: "**E**fferent = **E**xits the brain."
- **Somatic nervous system:** The "voluntary" system — controls the skeletal muscles that we move by our wish (walking, writing).
- **Autonomic nervous system (ANS):** The "automatic" system — controls body functions we do not consciously command (heartbeat, digestion, sweating). It has three divisions: sympathetic, parasympathetic, and enteric.
- **Sympathetic:** The "fight or flight" division — prepares the body for danger or exercise.
- **Parasympathetic:** The "rest and digest" division — helps the body relax, digest food, and store energy.
- **Enteric:** The nervous system of the gut — the "second brain" in the walls of the stomach and intestines.
- **Pre-ganglionic fibre:** The nerve fibre from the spinal cord to the ganglion (before the station).
- **Post-ganglionic fibre:** The nerve fibre from the ganglion to the target organ (after the station).
- **Adrenal medulla:** The inner part of the adrenal gland (above the kidneys) that releases adrenaline into the blood.

1.4 Explanation

1.4.1 The big map: how the nervous system is organized

The human nervous system is like the communication network of a big company. The brain and spinal cord are the **head office** (called the **central nervous system, CNS**). All the telephone lines going out to the branches (organs, skin, muscles) are the **peripheral nervous system (PNS)**. This unit is about the PNS — the wires and their chemical messages.

The PNS has two main divisions, based on the **direction** of the message:

1. Sensory (afferent) division — "messages coming IN"

- Carries information from the sense organs and body parts (skin, eyes, ears, stomach) TO the brain and spinal cord.
- Example: you touch a hot vessel — the skin sends "HOT!" to the brain.

2. Motor (efferent) division — "orders going OUT"

- Carries commands from the brain and spinal cord TO the muscles and glands.
- Example: the brain orders the hand to drop the hot vessel.

The motor (efferent) division is further divided by whether we control it **by our wish** or **automatically**:

A. Somatic nervous system (voluntary)

- Controls skeletal muscles — the muscles we move deliberately.
- One neuron goes straight from the spinal cord to the muscle (no ganglion in between).
- Uses acetylcholine on nicotinic receptors of the muscle.

B. Autonomic nervous system (involuntary / automatic)

- Controls heart, blood vessels, lungs, gut, glands, pupils — things that work without our conscious order.
- Two neurons in a chain: pre-ganglionic → ganglion → post-ganglionic → organ.

> **Analogy — the company telephone system:** The brain is the boss's office. Afferent nerves are incoming complaint calls from branches. Efferent nerves are the boss's orders going out. Somatic orders go by one direct call (boss calls the worker directly). Autonomic orders go through a local office (ganglion) which passes the message on.

1.4.2 The three divisions of the autonomic nervous system

1. Sympathetic division ("fight or flight")

- Prepares the body for emergency, danger, exercise, or excitement.
- Heart beats faster and stronger; pupils widen (to see danger); airways widen (more air); blood moves away from the gut to the muscles; stored sugar is released.
- Its nerves start from the middle part of the spinal cord (thoracic and lumbar regions).

2. Parasympathetic division ("rest and digest")

- Helps the body relax, digest food, and save energy.
- Heart slows down; pupils become smaller; digestion increases; bladder contracts for urination.
- Its nerves start from the brainstem and the lower part of the spinal cord (craniosacral regions).

3. Enteric division (the "second brain")

- A large network of nerves inside the walls of the gut (from food pipe to the end of the intestines).
- Controls digestion movements and gut secretions, mostly on its own, even without the brain.
- It has its own neurotransmitters and can work independently — that is why it is called the "second brain."

> **Analogy — two pedals of a car:** Sympathetic is the accelerator (speed up, get ready). Parasympathetic is the brake and also the "park mode" (slow down, rest, digest). A good driver uses both — and so does a healthy body.

1.4.3 Neurohumoral transmission: the steps

When a message reaches the end of a nerve, it cannot jump the tiny gap (synapse) as electricity. It must be converted into a chemical. The steps are:

1. **Synthesis** — the nerve ending makes the chemical messenger (neurotransmitter) from raw materials.
2. **Storage** — the messenger is stored safely in tiny bubbles (vesicles) inside the nerve ending.
3. **Release** — when the electrical signal arrives, the bubbles burst and the messenger pours out into the gap.
4. **Receptor binding** — the messenger floats across the gap and fits into the receptor "locks" on the next cell.
5. **Action** — the receptor opens a door (ion channel) or starts a chain of signals inside the cell, and the message is delivered.
6. **Termination** — the messenger is removed (broken down by an enzyme or sucked back into the nerve) so the signal stops cleanly and the gap is ready for the next message.

> **Flowchart — Synaptic transmission (steps):**

```
Electrical signal arrives at nerve ending
        ↓
   1. SYNTHESIS — nerve makes the messenger from raw materials
        ↓
   2. STORAGE — messenger packed into tiny bubbles (vesicles)
        ↓
   3. RELEASE — bubbles burst; messenger pours into the gap
        ↓
   4. RECEPTOR BINDING — messenger fits into receptor "locks"
        ↓
   5. ACTION — cell responds (muscle contracts / gland secretes)
        ↓
   6. TERMINATION — messenger destroyed or sucked back; signal ends
```

Diagram — How to draw the synapse (student sketch guide): Draw a long tube (the nerve axon) ending in a round bulb (nerve ending). Inside the bulb draw small circles (vesicles full of chemical). In front of the bulb draw a small gap. On the other side of the gap draw the next cell with small "Y"-shaped locks (receptors) on its surface. Add arrows showing the chemical dots leaving the bulb, crossing the gap, and fitting into the locks. Label: 1 nerve ending, 2 vesicles, 3 gap (synaptic cleft), 4 receptors, 5 next cell.

> **Analogy — the postman and the letterbox:** The nerve ending is the sender, the chemical is the letter, the gap is the street, the receptor is the letterbox, and the cell reading the letter is the receiver. The enzyme that destroys the chemical is the paper-shredder — it clears old letters so new ones can be read.

1.4.4 Cholinergic transmission (acetylcholine, ACh)

Synthesis: Acetylcholine is made inside the nerve ending from two simple raw materials — **choline** (from food) and **acetyl-CoA** (from energy metabolism). The enzyme **choline acetyltransferase** joins them together. **Storage:** ACh is stored in vesicles. **Release:** The nerve signal opens calcium doors; calcium enters and the vesicles burst, releasing ACh. **Termination:** The enzyme **acetylcholinesterase (AChE)** breaks ACh into choline + acetate within a fraction of a second. The choline is taken back into the nerve and reused.

Cholinergic receptors — two families:

(i) Nicotinic receptors (N) — the fast doors

- These are ion channels: when ACh binds, the door opens immediately and ions rush in. Fast action.
- **Nm (muscle type):** present on skeletal muscle. ACh here makes the muscle contract (this is how we move).
- **Nn (neuronal/ganglionic type):** present in autonomic ganglia and the adrenal medulla. ACh here passes the message to the next neuron.

(ii) Muscarinic receptors (M) — the slow switches

- These are not doors but switches that start a chain of signals inside the cell (G-protein coupled receptors). Slower but longer-lasting action.
- **M1:** in the brain and stomach glands — helps memory/learning and increases stomach acid secretion.
- **M2:** in the heart — slows the heart rate (the vagus nerve's brake on the heart).
- **M3:** in smooth muscles and glands — contracts gut/bladder/eye muscles, increases saliva, sweat, tears, and digestive juices.
- **M4:** in the brain — helps control movement and thinking.
- **M5:** in the brain and blood vessels — role still being studied.

Where ACh acts (the cholinergic map):

- All **pre-ganglionic** fibres of both sympathetic and parasympathetic systems (nicotinic Nn).
- All **post-ganglionic parasympathetic** fibres (muscarinic M1–M3).
- **Somatic** motor nerves to skeletal muscle (nicotinic Nm).
- **Sweat glands** (unusual: sympathetic but cholinergic, muscarinic).

1.4.5 Adrenergic transmission (noradrenaline, adrenaline)

Synthesis: Made from the amino acid **tyrosine** (from food) in a chain: tyrosine → DOPA → **dopamine** → **noradrenaline (norepinephrine)** → (in the adrenal medulla) **adrenaline (epinephrine)**. **Storage:** Stored in vesicles with ATP and other helpers. **Release:** Nerve signal → vesicles release noradrenaline into the gap. **Termination:** Mostly by **reuptake** — a pump sucks noradrenaline back into the nerve ending (this pump is called uptake-1). A smaller part is broken down by two enzymes: **MAO** (monoamine oxidase) and **COMT** (catechol-O-methyl transferase).

Adrenergic receptors — alpha and beta families:

Alpha-1 (α1): Mainly on blood vessels and the eye. Action: blood vessels **constrict** (blood pressure rises), pupils **dilate**, bladder neck tightens. **Alpha-2 (α2):** Mainly on nerve endings themselves (like a self-brake) and in the brain. Action: **reduces** further noradrenaline release; in the brain it lowers sympathetic activity and blood pressure. **Beta-1 (β1):** Mainly in the **heart**. Action: heart beats **faster and stronger**; kidneys release renin. **Beta-2 (β2):** Mainly in the **lungs, blood vessels of muscles, and uterus**. Action: airways **widen** (relieves asthma), blood vessels relax, uterus relaxes. **Beta-3 (β3):** Mainly in **fat cells and the bladder**. Action: breaks down fat for energy; relaxes the bladder muscle. **Dopaminergic receptors (D1, D2):** Dopamine's own receptors. D1 in the kidney dilates kidney blood vessels (more urine). D2 in the brain controls movement, mood, and vomiting reflexes.

> **Analogy — lock-and-key with master keys:** Noradrenaline and adrenaline are like keys. Each receptor is a different lock: α1 opens the "tighten vessels" door, β1 opens the "speed up heart" door, β2 opens the "open airways" door. Drugs can be master keys (open many doors — like adrenaline) or single keys (open only one — like phenylephrine, which opens mainly α1).

1.4.6 Co-transmission and NANC transmitters

Co-transmission: In the old teaching, one nerve ending released one messenger. We now know that most nerve endings release **two or more messengers together** — the main one (ACh or noradrenaline) plus one or more helpers. This is co-transmission. The helpers fine-tune the message, like adding spices to the main dish.

NANC (non-adrenergic, non-cholinergic) transmitters: Messengers that are neither ACh nor noradrenaline:

- **Nitric oxide (NO):** A tiny gas made in nerve endings. Relaxes smooth muscle — very important in relaxing blood vessels and in penile erection (blood flow into the penis).
- **VIP (vasoactive intestinal peptide):** Relaxes gut muscle, increases gut secretions, dilates blood vessels.
- **ATP (adenosine triphosphate):** Besides being the cell's energy coin, it acts as a fast messenger in the gut, bladder, and blood vessels.
- **Substance P:** Carries pain signals and causes inflammation (swelling, redness) around injured tissue.
- **CGRP (calcitonin gene-related peptide):** A powerful dilator of blood vessels; involved in migraine headache pain.

Key takeaway: The PNS is not a simple two-chemical system. Every nerve ending is a small "team" of messengers working together, and many modern drugs target these helper messengers too.

1.5 Classification

Classification of the PNS (organization):

1. Sensory (afferent) division — carries information to the CNS
2. Motor (efferent) division — carries orders from the CNS

- (a) Somatic nervous system — voluntary, skeletal muscle
- (b) Autonomic nervous system — involuntary
- Sympathetic (fight or flight)
- Parasympathetic (rest and digest)
- Enteric (gut brain)

Classification of cholinergic receptors:

- Nicotinic: Nn (ganglia, adrenal medulla), Nm (skeletal muscle)
- Muscarinic: M1 (brain, gastric glands), M2 (heart), M3 (smooth muscle, glands, eye), M4 (brain), M5 (brain, vessels)

Classification of adrenergic receptors:

- Alpha: α1 (vessels constrict, pupil dilate), α2 (self-brake, brain)
- Beta: β1 (heart), β2 (lungs/airways, uterus), β3 (fat, bladder)
- Dopaminergic: D1 (kidney vessels), D2 (brain, vomiting centre)

Classification of NANC transmitters: gases (NO), peptides (VIP, substance P, CGRP), purines (ATP).

1.6 Mechanisms

- **Nicotinic receptor mechanism:** ACh binds → ion channel door opens → sodium flows in → the cell becomes excited (fires). Fast — like a doorbell.
- **Muscarinic receptor mechanism:** ACh binds → receptor switches on a G-protein → G-protein starts a chain (second messengers like IP3, DAG, cAMP) → cell responds slowly and for longer. Slow — like sending a letter instead of ringing a bell.
- **Alpha-1 mechanism:** noradrenaline binds → IP3/DAG chain → calcium rises inside the cell → smooth muscle contracts (vessel tightens).
- **Alpha-2 mechanism:** binding → reduces cAMP → less calcium enters the nerve ending → less noradrenaline released (self-brake); in the brain → less sympathetic outflow.
- **Beta-1 / Beta-2 / Beta-3 mechanism:** binding → increases cAMP → heart muscle contracts harder (β1), airway/vessel/uterus muscle relaxes (β2), fat breakdown increases (β3).

1.7 Diagrams (to be drawn by the student)

1. **PNS organization tree:** Draw a box "Nervous System" splitting into "CNS (brain + spinal cord)" and "PNS". PNS splits into "Sensory (afferent) — in" and "Motor (efferent) — out". Motor splits into "Somatic (voluntary)" and "Autonomic (involuntary)". Autonomic splits into "Sympathetic", "Parasympathetic", "Enteric".
2. **Two-neuron autonomic chain:** Draw the spinal cord as a vertical bar on the left. Draw one short arrow from it to a small circle (ganglion), then a long arrow from the circle to a target organ (draw a heart or stomach). Label the first arrow "pre-ganglionic (ACh, nicotinic)" and the second "post-ganglionic (ACh or noradrenaline)".
3. **Sympathetic vs parasympathetic effects table-diagram:** Draw a simple human body outline. On the left side write sympathetic effects with up/down arrows (heart ↑, pupil ↑ wide, airways ↑ open, gut ↓ slow, bladder ↓ relaxed); on the right side parasympathetic effects (heart ↓ slow, pupil ↓ small, airways normal, gut ↑ active, bladder ↑ contracts). Use red for sympathetic, blue for parasympathetic.
4. **The synapse:** As described in section 1.4.3.

1.8 Flowcharts

Flowchart 1 — From food to adrenaline (catecholamine synthesis):

```
Tyrosine (from food)
        ↓
      DOPA
        ↓
    Dopamine
        ↓
 Noradrenaline (norepinephrine) — main sympathetic messenger
        ↓  (only in adrenal medulla)
  Adrenaline (epinephrine) — released into blood in emergencies
```

Flowchart 2 — Acetylcholine life cycle:

```
Choline + Acetyl-CoA  --(choline acetyltransferase)-->  Acetylcholine
        ↑                                                      ↓
  Reused choline ←— (acetylcholinesterase destroys ACh) ←— Released into gap
```

Flowchart 3 — What sympathetic vs parasympathetic do (memory map):

```
EMERGENCY (sympathetic ON):    Heart FAST ↑ | Pupils WIDE | Airways OPEN | Gut QUIET | Sugar
RELEASED
REST (parasympathetic ON):     Heart SLOW ↓ | Pupils SMALL | Airways normal | Gut ACTIVE |
Bladder EMPTYING
```

1.9 Infographic Concept Box

THE PNS IN ONE PICTURE — "The Two-Telegram System"

- **Incoming telegrams (afferent):** "Hot vessel!", "Stomach is full", "Loud noise!" → travel TO the brain.
- **Outgoing orders (efferent):** Voluntary orders go straight to muscles (one wire). Automatic orders pass through a relay station (ganglion) first.
- **Automatic orders come in two flavours:** RED telegram (sympathetic) = "DANGER — speed everything up!" / BLUE telegram (parasympathetic) = "ALL CLEAR — rest and digest."
- **Gut has its own post office (enteric)** — it handles local digestion mail without asking the head office.
- **Every telegram is delivered by chemical postmen:** ACh (cholinergic), noradrenaline/adrenaline (adrenergic), plus helper postmen NO, VIP, ATP, substance P, CGRP (NANC).
- **Every postman needs the right letterbox (receptor):** Nn/Nm/M1–M5 for ACh; α1/α2/β1/β2/β3/D1/D2 for noradrenaline, adrenaline, dopamine.

1.10 Tables

Table 1.1 — Somatic vs autonomic nervous system

Feature	Somatic	Autonomic
Control	Voluntary (by our wish)	Involuntary (automatic)
Target	Skeletal muscles	Heart, smooth muscle, glands
Neurons in chain	One (direct)	Two (pre- + post-ganglionic, with ganglion)
Messenger at target	Acetylcholine (nicotinic Nm)	ACh or noradrenaline

Table 1.2 — Sympathetic vs parasympathetic effects on organs

Organ	Sympathetic (fight/flight)	Parasympathetic (rest/digest)
Heart	Faster, stronger (β1)	Slower (M2)
Pupil of eye	Widens (α1)	Narrows (M3)
Airways	Widen (β2)	Narrow slightly (M3)
Gut	Slows down	Speeds up (M3)
Bladder	Relaxes (stores urine)	Contracts (empties urine, M3)
Blood vessels (skin)	Constrict (α1)	Little effect
Saliva	Thick, small amount	Watery, large amount (M3)
Blood sugar	Rises (released from liver)	Normal

Table 1.3 — Cholinergic receptors at a glance

Receptor	Main location	Main action when switched ON
Nn	Autonomic ganglia, adrenal medulla	Passes message to next neuron
Nm	Skeletal muscle	Muscle contracts
M1	Brain, stomach glands	Memory/learning; more stomach acid
M2	Heart	Heart slows
M3	Gut, bladder, glands, eye	Gut/bladder contract; more secretions; pupil narrows
M4	Brain	Controls movement signals
M5	Brain, vessels	Being studied

Table 1.4 — Adrenergic receptors at a glance

Receptor	Main location	Main action when switched ON
α1	Blood vessels, eye, bladder neck	Vessels constrict (BP rises); pupil widens
α2	Nerve endings, brain	Brakes further release; lowers BP via brain
β1	Heart, kidney	Heart faster + stronger; renin released
β2	Airways, uterus, muscle vessels	Airways widen; uterus relaxes
β3	Fat cells, bladder	Fat broken down; bladder relaxes
D1	Kidney vessels	Kidney vessels widen
D2	Brain, vomiting centre	Movement control; vomiting trigger

1.11 Examples

- **Example 1 (afferent):** You step on a thorn. Pain nerves (afferent) carry "pain in the foot" to the spinal cord.
- **Example 2 (somatic efferent):** You decide to lift a book. Somatic nerves carry the order to your arm muscles, which contract via nicotinic Nm receptors.
- **Example 3 (sympathetic):** A dog chases you. Sympathetic nerves fire: your heart pounds (β1), pupils widen (α1), breathing deepens (β2) — you run faster.
- **Example 4 (parasympathetic):** After lunch, parasympathetic nerves increase gut movement and digestive juices (M3) — food is digested while you rest.
- **Example 5 (termination matters):** Acetylcholinesterase destroys ACh in milliseconds. If it did not, muscles would stay contracted and the person could not relax — this is exactly what happens in organophosphate poisoning (see Chapter 2).
- **Example 6 (co-transmission):** When sympathetic nerves tell blood vessels to constrict, they release noradrenaline AND ATP together — ATP gives a fast extra squeeze.

1.12 Analogies

1. **Telephone exchange:** Brain = head office; afferent = incoming calls; efferent = outgoing orders; ganglion = local exchange that forwards the call.
2. **Lock and key:** Receptor = lock; neurotransmitter or agonist drug = key that opens it; antagonist drug = a broken key stuck in the lock.
3. **Car pedals:** Sympathetic = accelerator; parasympathetic = brake + rest mode.
4. **Postman:** Nerve ending = sender; transmitter = letter; gap = street; receptor = letterbox; enzyme = shredder that clears old letters.
5. **Two telegrams:** Sympathetic = red "DANGER" telegram; parasympathetic = blue "ALL CLEAR" telegram.
6. **Kitchen team:** Main messenger (ACh/noradrenaline) = head cook; co-transmitters = helpers who add the finishing spices.

1.13 Pharmacy Relevance

- Almost every drug in this unit works by **copying, boosting, or blocking** these messengers and receptors. If you master this chapter's receptor map, Chapters 2 and 3 become easy — every drug's effect is just "which lock does it open or block?"
- A pharmacist must know which receptor causes which effect to **predict side effects**: e.g., a drug that blocks M3 will dry the mouth and blur vision — you can counsel the patient in advance.
- Understanding termination (enzymes, reuptake pumps) explains how whole drug classes work: anticholinesterases block the ACh-destroying enzyme; many antidepressants block the noradrenaline reuptake pump.

1.14 India Context

- The concepts in this chapter are the **foundation of the pharmacology syllabus** taught in every B.Pharm college in India under PCI regulations.
- Many essential autonomic drugs in this unit (atropine, adrenaline, propranolol, salbutamol, neostigmine) are on India's **National List of Essential Medicines (NLEM)** and are available as low-cost generics through **Jan Aushadhi Kendras** — a pharmacist should know their generic names first, brand names second.
- In Indian clinical practice, a doctor's prescription reading "Inj. Adrenaline 1 mg" or "Tab. Propranolol 40 mg" is understood entirely through this chapter's receptor map (α/β effects).

1.15 Key Points

1. PNS = all nerves outside brain and spinal cord; afferent carries information IN, efferent carries orders OUT.
2. Efferent divides into somatic (voluntary, one neuron, skeletal muscle) and autonomic (involuntary, two neurons with a ganglion).
3. Autonomic has three divisions: sympathetic (fight/flight), parasympathetic (rest/digest), enteric (gut brain).
4. Synaptic transmission steps: synthesis → storage → release → receptor binding → action → termination.
5. ACh is made from choline + acetyl-CoA and destroyed by acetylcholinesterase.
6. Cholinergic receptors: nicotinic (Nn ganglia, Nm muscle — fast doors) and muscarinic (M1–M5 — slow switches).
7. Noradrenaline is made from tyrosine via dopamine; it is removed mainly by reuptake, partly by MAO and COMT.
8. Adrenergic receptors: α1 (vessels constrict), α2 (self-brake), β1 (heart), β2 (airways), β3 (fat/bladder), D1/D2 (dopamine).
9. Co-transmission = one nerve ending releases two or more messengers together.
10. NANC transmitters: NO, VIP, ATP, substance P, CGRP.

1.16 Common Confusions

- **Afferent vs efferent:** Remember "**A**fferent **A**rrives, **E**fferent **E**xits." Students often swap them — draw arrows to fix it.
- **Nicotinic vs muscarinic:** Nicotinic = fast ion doors (Nn ganglia, Nm muscle); muscarinic = slow switches (M1–M5, organs). The names come from the chemicals that first revealed them (nicotine from tobacco, muscarine from a mushroom) — not from their function.
- **Sympathetic is NOT always excitatory:** It relaxes the gut and bladder. "Fight or flight" means redirecting energy, not exciting everything.
- **Sweat glands are sympathetic but use ACh** (not noradrenaline) — the famous exception.
- **α2 is mostly inhibitory** (a brake), while α1 is excitatory (vessels tighten). Do not mix them.
- **Adrenaline vs noradrenaline:** Noradrenaline is mainly a nerve messenger; adrenaline is mainly a blood hormone from the adrenal medulla. Both act on α and β receptors.

1.17 Common Mistakes

1. Writing that the somatic system has a ganglion — it does not; only the autonomic chain has a ganglion.
2. Saying all sympathetic actions use noradrenaline — sweat glands use acetylcholine.
3. Confusing receptor letters and numbers: β1 = heart, β2 = lungs — "1 heart, 2 lungs" (one heart, two lungs).
4. Forgetting termination: a signal must END (enzyme or reuptake), otherwise the organ cannot reset.
5. Mixing up M2 (heart — slows) with M3 (gut/glands — activates).

1.18 Mnemonics

- **Afferent/Efferent:** "**A**fferent **A**rrives at brain; **E**fferent **E**xits brain."
- **Sympathetic effects — "FIGHT":** **F**aster heart, **I**ris (pupil) widens, **G**ut slows, **H**yperglycemia (sugar rises), **T**remor/airways open.
- **Parasympathetic — "SLUDD":** **S**alivation, **L**acrimation (tears), **U**rination, **D**igestion, **D**efecation increase.
- **Receptor map — "1 heart, 2 lungs":** β**1** = **1** heart; β**2** = **2** lungs (airways).
- **ACh synthesis:** "**C**holine + **A**cetyl = **ACh**" — "**C**hAT" (choline acetyl**t**ransferase) makes it; "**AChE**" (acetylcholin**e**sterase) eats it.
- **Catecholamine chain:** "**T**yrosine → **D**OPA → **D**opamine → **N**oradrenaline → **A**drenaline" — "**T**ired **D**octors **D**rink **N**ight **A**mericanos."
- **NANC list — "NAVIP SC":** **N**O, **A**TP, **V**IP, **P** (substance P), **S**ubstance… better: "**N**o **A**untie, **V**ery **I**mportant **P**eople **S**ing **C**arols" — **N**O, **A**TP, **V**IP, **S**ubstance P, **C**GRP.

1.19 Exam Summary

- Draw and label the PNS organization tree (afferent/efferent → somatic/autonomic → sympathetic/parasympathetic/enteric).
- List the six steps of synaptic transmission with one line each.
- Tabulate cholinergic receptors (Nn, Nm, M1–M5) with location and action.
- Tabulate adrenergic receptors (α1, α2, β1, β2, β3, D1, D2) with location and action.
- Draw the ACh life cycle and the tyrosine → adrenaline chain.
- Define co-transmission; list five NANC transmitters with one role each.
- Contrast sympathetic vs parasympathetic effects on heart, pupil, airways, gut, bladder (Table 1.2 is the exam favourite).

1.20 One-Minute Revision

PNS = wires outside brain/spinal cord. Messages IN = afferent; orders OUT = efferent. Efferent = somatic (voluntary, one wire, muscle) + autonomic (automatic, two wires + ganglion). Autonomic = sympathetic (fight/flight), parasympathetic (rest/digest), enteric (gut brain). Messages cross gaps as chemicals in six steps: make → store → release → bind → act → clear. ACh: made from choline, destroyed by AChE; receptors Nn (ganglia), Nm (muscle), M1–M5 (organs; M2 slows heart, M3 activates gut/glands). Noradrenaline: made from tyrosine via dopamine, cleared by reuptake; receptors α1 (vessels tighten), α2 (brake), β1 (heart), β2 (airways), β3 (fat), D1/D2 (dopamine). Nerves release helper chemicals too (co-transmission): NO, VIP, ATP, substance P, CGRP.

1.21 Exam Questions

Short-answer questions:

1. Define neuron, nerve, ganglion, and plexus with one example each.
2. Differentiate between afferent and efferent nerves.
3. Differentiate between the somatic and autonomic nervous systems (any four points).
4. List the six steps of neurohumoral transmission.
5. Name the enzymes that synthesize and destroy acetylcholine.
6. Classify cholinergic receptors with one location for each.
7. Write the synthesis chain of noradrenaline starting from tyrosine.
8. What is co-transmission? Give one example.
9. List any four NANC neurotransmitters with one function each.
10. Why are sweat glands called an exception in the autonomic nervous system?

Long-answer questions:

1. Describe the organization of the peripheral nervous system with a labelled diagram. Explain the divisions of the autonomic nervous system.
2. Describe the steps of synaptic (neurohumoral) transmission with a flowchart. Explain cholinergic transmission including synthesis, storage, release, receptors, and termination.
3. Classify adrenergic receptors. Describe their locations and the effects produced when each is stimulated, with a table.
4. Compare the sympathetic and parasympathetic divisions: origin, messengers, receptors, and effects on at least six organs.

MCQs (with answer key):

1. Afferent nerves carry impulses: (a) from brain to muscle (b) from body to brain ✓ (c) within the brain (d) from muscle to muscle — **Answer: (b)**
2. The somatic nervous system controls: (a) heart (b) glands (c) skeletal muscle ✓ (d) gut — **Answer: (c)**
3. Which is TRUE of the autonomic ganglion? (a) present in somatic pathway (b) lies between pre- and post-ganglionic neurons ✓ (c) found inside the brain (d) absent in parasympathetic — **Answer: (b)**
4. Acetylcholine is destroyed by: (a) MAO (b) COMT (c) acetylcholinesterase ✓ (d) choline acetyltransferase — **Answer: (c)**
5. Nm receptors are located on: (a) heart (b) skeletal muscle ✓ (c) gut (d) ganglia — **Answer: (b)**
6. M2 receptor stimulation causes: (a) faster heart (b) slower heart ✓ (c) wider pupil (d) gut contraction — **Answer: (b)**
7. β1 receptors are mainly in the: (a) lungs (b) heart ✓ (c) uterus (d) fat — **Answer: (b)**
8. Stimulation of β2 receptors causes: (a) vessel constriction (b) airway widening ✓ (c) pupil narrowing (d) gut contraction — **Answer: (b)**
9. α2 receptors mainly act as: (a) excitatory on vessels (b) inhibitory brake on transmitter release ✓ (c) heart stimulants (d) gut stimulants — **Answer: (b)**
10. Which of the following is a NANC transmitter? (a) acetylcholine (b) noradrenaline (c) nitric oxide ✓ (d) dopamine — **Answer: (c)**
11. The "rest and digest" division is the: (a) sympathetic (b) parasympathetic ✓ (c) somatic (d) enteric — **Answer: (b)**
12. Noradrenaline is mainly removed from the gap by: (a) MAO only (b) reuptake into the nerve ✓ (c) kidney excretion (d) COMT only — **Answer: (b)**

Viva questions:

1. What does "afferent" mean? Which direction does the message travel?
2. How many neurons are in the somatic pathway? In the autonomic pathway?
3. Name the three divisions of the ANS.
4. Which receptor slows the heart — M2 or M3?
5. Which beta receptor is in the lungs?
6. What is the raw material for making noradrenaline?
7. Give two examples of NANC transmitters.
8. What does co-transmission mean?

Application-based questions:

1. A patient faints at the sight of blood. Which division is overactive, and what happens to the heart rate? (Parasympathetic overactivity via the vagus — heart slows, blood pressure falls.)
2. During a cricket match, a fielder's heart pounds and mouth goes dry. Explain using sympathetic/parasympathetic concepts. (Sympathetic activation: β1 faster heart; reduced parasympathetic saliva — thick, scanty saliva.)
3. A drug blocks all muscarinic receptors. Predict its effects on the gut, bladder, and heart rate. (Gut slows/constipation, bladder relaxes/urine retained, heart rate rises.)

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Chapter 2: Autonomic Drugs — Parasympathomimetics, Parasympatholytics, Sympathomimetics, Sympatholytics

2.1 Learning Objectives

After studying this chapter, the student will be able to:

1. Classify parasympathomimetic drugs (direct-acting and indirect-acting/anticholinesterases).
2. Explain the mechanism of action of cholinergic agonists and anticholinesterases.
3. List the pharmacological effects, therapeutic uses, and adverse effects of parasympathomimetics.
4. Classify parasympatholytic (anticholinergic) drugs and explain their mechanism.
5. List the effects, uses, and adverse effects of anticholinergics (atropine, scopolamine, ipratropium, tiotropium, etc.).
6. Classify sympathomimetic drugs (direct, indirect, mixed-acting) and explain their mechanisms.
7. List the effects, uses, and adverse effects of key sympathomimetics (adrenaline, noradrenaline, dopamine, dobutamine, phenylephrine, salbutamol, ephedrine, amphetamine).
8. Classify sympatholytic drugs (alpha blockers, beta blockers, central sympatholytics) and explain their mechanisms.
9. List the effects, uses, and adverse effects of prazosin, tamsulosin, propranolol, atenolol, metoprolol, esmolol, clonidine, and methyldopa.

2.2 Definitions

- **Parasympathomimetic (cholinergic agonist):** A drug that copies or boosts the parasympathetic messenger acetylcholine — it "mimics" the rest-and-digest system. Also called a cholinomimetic.
- **Direct-acting cholinergic:** A drug that directly switches ON the cholinergic receptor, like the real key (e.g., bethanechol, pilocarpine).
- **Indirect-acting cholinergic (anticholinesterase):** A drug that does NOT touch the receptor; instead it blocks the enzyme (acetylcholinesterase) that destroys acetylcholine, so the body's own ACh piles up and works harder and longer (e.g., neostigmine, physostigmine).
- **Parasympatholytic (anticholinergic/antimuscarinic):** A drug that blocks the parasympathetic (muscarinic) receptors — it "lyses" (loosens/breaks) parasympathetic action (e.g., atropine).
- **Sympathomimetic (adrenergic agonist):** A drug that copies or boosts the sympathetic messengers noradrenaline/adrenaline — it "mimics" the fight-or-flight system (e.g., salbutamol, phenylephrine).
- **Direct-acting sympathomimetic:** Binds the adrenergic receptor itself (e.g., phenylephrine on α1).
- **Indirect-acting sympathomimetic:** Forces the nerve ending to release its stored noradrenaline, or blocks its reuptake (e.g., amphetamine, tyramine).
- **Mixed-acting sympathomimetic:** Does both — binds the receptor AND releases stored noradrenaline (e.g., ephedrine).
- **Sympatholytic (adrenergic blocker):** A drug that blocks adrenergic receptors or reduces sympathetic activity — "lyses" the fight-or-flight system (e.g., propranolol blocks β receptors; prazosin blocks α1).
- **Reversible vs irreversible (anticholinesterases):** Reversible blockers let go of the enzyme after some time (medicines); irreversible blockers (organophosphates) lock onto the enzyme permanently (poisons/insecticides).

2.3 Terminology

- **Miosis:** Narrowing (shrinking) of the pupil — caused by parasympathetic/M3 stimulation.
- **Mydriasis:** Widening of the pupil — caused by sympathetic/α1 stimulation or anticholinergic block.
- **Cycloplegia:** Paralysis of the eye's focusing muscle — near vision blurs (anticholinergic effect).
- **Bronchodilation:** Widening of the airways (β2 effect) — relieves asthma.
- **Bronchoconstriction:** Narrowing of the airways (M3 effect) — worsens asthma.
- **Vasoconstriction:** Tightening of blood vessels (α1 effect) — raises blood pressure.
- **Vasodilation:** Relaxing/widening of blood vessels — lowers blood pressure.
- **Tachyphylaxis:** A drug quickly losing its effect on repeated use (seen with indirect sympathomimetics like ephedrine/tyramine, because stored noradrenaline runs out).
- **Organophosphate:** A class of chemicals (insecticides like malathion, parathion; nerve gases) that irreversibly block acetylcholinesterase — the concept matters because poisoning treatment uses atropine + pralidoxime.
- **Cholinergic crisis vs myasthenic crisis:** Too much anticholinesterase (cholinergic crisis) and too little (myasthenic crisis) both cause weakness — told apart by the edrophonium (Tensilon) test (see Chapter 3).
- **First-dose effect:** A sharp fall in blood pressure after the first dose of prazosin — patients must take the first dose at bedtime.
- **Rebound hypertension:** Blood pressure shooting up if clonidine is stopped suddenly.

2.4 Explanation

2.4.1 PARASYMPATHOMIMETICS (cholinergic drugs)

The idea in one line: Either give a fake key that opens cholinergic locks (direct), or stop the shredder enzyme so the real keys pile up (indirect).

Classification:

1. **Direct-acting** (bind muscarinic/nicotinic receptors directly):

- Bethanechol — mainly muscarinic (gut, bladder)
- Carbachol — muscarinic + nicotinic (eye, gut)
- Pilocarpine — muscarinic (eye, salivary glands)

2. **Indirect-acting = anticholinesterases** (block acetylcholinesterase → ACh piles up):

- **Reversible:** neostigmine, physostigmine, pyridostigmine, edrophonium, rivastigmine, donepezil
- **Irreversible (organophosphates — concept):** insecticides (malathion, parathion), nerve gases — permanently lock the enzyme; poisoning is a medical emergency

Mechanism of action:

- *Direct:* drug fits into muscarinic (and sometimes nicotinic) receptors and switches them ON → same effects as parasympathetic stimulation.
- *Indirect:* drug blocks acetylcholinesterase → ACh is not destroyed → ACh accumulates at every cholinergic junction (muscarinic + nicotinic) → stronger, longer parasympathetic effects. Think: "block the shredder, the letters pile up."

Pharmacological effects (the SLUDD picture — more saliva, tears, urine, digestion, gut movement):

- Eye: pupil narrows (miosis), focusing muscle contracts (near vision), fluid drains better (lowers eye pressure in glaucoma).
- Heart: slows down (M2).
- Airways: narrow slightly, more mucus.
- Gut: more movement and secretions; sphincters relax.
- Bladder: contracts (helps urination); gut-like glands secrete more.
- Glands: more saliva, sweat, tears.
- Skeletal muscle (nicotinic Nm, seen with anticholinesterases): stronger contraction at first.

Therapeutic uses:

- **Bethanechol:** urinary retention after surgery (cannot pass urine), sluggish gut after surgery — it squeezes bladder and gut.
- **Carbachol:** glaucoma eye drops (drains eye fluid, lowers pressure).
- **Pilocarpine:** glaucoma eye drops; dry mouth after radiation (Sjögren-like dryness) — it boosts saliva.
- **Neostigmine:** myasthenia gravis (see Chapter 3); reversing muscle relaxants after surgery; urinary retention; sluggish gut.
- **Physostigmine:** special because it enters the brain — used in atropine/belladonna poisoning (antidote) and glaucoma drops (older use).
- **Pyridostigmine (Mestinon):** myasthenia gravis — longer-acting than neostigmine, the main maintenance drug.
- **Edrophonium (Tensilon):** very short-acting — used only as a **diagnostic test** for myasthenia gravis (if weakness improves within minutes, the diagnosis is confirmed).
- **Donepezil/rivastigmine:** Alzheimer's disease — they raise ACh in the brain and slow memory loss (mentioned for completeness).

Adverse effects (too much parasympathetic — the SLUDD overdose):

- Salivation, tearing, sweating, diarrhoea, abdominal cramps, nausea, vomiting.
- Slow heart, low blood pressure; airway narrowing and extra mucus (dangerous in asthma).
- Blurred vision, small pupils; frequent urination.
- With anticholinesterases at high dose: muscle twitching then weakness ("cholinergic crisis"); organophosphate poisoning adds the same picture and needs **atropine + pralidoxime** urgently.
- **Pharmacy counselling point:** warn patients on bethanechol about cramps/diarrhoea and to report slow pulse or breathing difficulty.

> **Analogy — the office shredder:** Direct drugs are duplicate keys handed to the staff. Indirect drugs (anticholinesterases) jam the office shredder so real memos pile up on every desk — every department (eye, gut, bladder, glands) gets extra instructions at once.

2.4.2 PARASYMPATHOLYTICS (anticholinergic / antimuscarinic drugs)

The idea in one line: Sit in the muscarinic locks so acetylcholine cannot enter — the parasympathetic system is silenced and the sympathetic side dominates by default.

Classification:

1. **Natural alkaloids:** atropine (from belladonna/Atropa belladonna), scopolamine/hyoscine (from Hyoscyamus).
2. **Synthetic/semisynthetic:** ipratropium, tiotropium (lungs), glycopyrrolate (pre-surgery, drooling), dicyclomine (gut spasm), oxybutynin/tolterodine (overactive bladder).

Mechanism of action: Competitive blockade of muscarinic receptors (M1–M5). ACh arrives but the lock is occupied — no signal passes. Effects are the **mirror image** of parasympathomimetics.

Pharmacological effects (the "dry and fast" picture):

- Eye: pupil widens (mydriasis), focusing paralyzed (cycloplegia — near vision blurs), eye pressure may rise.
- Heart: faster (M2 block removes the vagal brake).
- Airways: widen slightly, secretions dry up.
- Gut: slows down, less acid and secretions; relieves spasm.
- Bladder: relaxes (holds more urine).
- Glands: dry mouth, dry skin (less sweat — body can overheat), fewer tears.
- Brain: atropine causes restlessness/confusion at high doses; scopolamine causes drowsiness and prevents motion sickness and is used pre-surgery.

Therapeutic uses:

- **Atropine:** bradycardia (dangerously slow heart) — speeds it up; pre-anaesthetic (dries secretions); **antidote in organophosphate poisoning** (with pralidoxime); eye drops to dilate the pupil for eye examination.
- **Scopolamine (hyoscine):** motion sickness (patch/tablet); pre-anaesthetic sedation and drying.
- **Hyoscine butylbromide (Buscopan):** abdominal colic/spasm pain — relaxes gut spasm.
- **Ipratropium (Ipravent):** asthma/COPD inhaler — opens airways with minimal heart effects.
- **Tiotropium (Tiova):** COPD maintenance inhaler — once-daily, long-acting.
- **Glycopyrrolate:** pre-surgery (dries saliva), reduces drooling.
- **Dicyclomine:** irritable bowel/functional gut spasm pain.
- **Oxybutynin/tolterodine:** overactive bladder (urgency, frequent urination) — relax the bladder muscle.

Adverse effects (the anticholinergic "dry" syndrome):

- Dry mouth, blurred near vision, constipation, difficulty passing urine (urinary retention) — especially risky in elderly men with prostate enlargement.
- Fast heart, reduced sweating → **heat stroke risk in hot Indian summers** — counsel patients to avoid heavy heat exposure.
- Confusion, especially in the elderly ("atropine psychosis" at high doses).
- Worsens glaucoma (pupil widening blocks fluid drainage) — never give to narrow-angle glaucoma patients.
- **Mnemonic for side effects — "Dry as a bone": D**ry mouth, **R**ed (flushed) skin, **Y** (why) can't see/pee: blurred vision, urinary retention, constipation, fast heart, hot dry skin, confusion.

2.4.3 SYMPATHOMIMETICS (adrenergic drugs)

The idea in one line: Copy the fight-or-flight messengers — either by pressing the receptor buttons directly, or by forcing nerves to release (or not re-take) their stored noradrenaline.

Classification:

1. **Direct-acting** (bind adrenergic receptors):

- Phenylephrine (mainly α1), noradrenaline (α1+β1), adrenaline (α+β — all), dopamine (D+β+α, dose-dependent), dobutamine (mainly β1), salbutamol/terbutaline (mainly β2)

2. **Indirect-acting** (release stored noradrenaline / block reuptake):

- Amphetamine, tyramine (tyramine is in cheese — the "cheese reaction" with MAO inhibitors)

3. **Mixed-acting** (both direct + indirect):

- Ephedrine, pseudoephedrine (Sudafed)

Mechanism of action:

- *Direct:* drug binds α/β receptors → vessel tightening (α1), heart stimulation (β1), airway widening (β2), as per Chapter 1's receptor map.
- *Indirect:* drug enters the nerve ending → pushes stored noradrenaline out into the gap (and may block its reuptake) → the body's own noradrenaline does the work. Repeated doses run the stores down → **tachyphylaxis** (effect fades).
- *Mixed:* both actions together — ephedrine binds receptors directly AND releases noradrenaline.

Pharmacological effects (the FIGHT picture):

- Heart (β1): faster, stronger contraction; more oxygen demand.
- Vessels (α1): constrict → blood pressure rises; nasal lining shrinks (decongestant effect).
- Airways (β2): widen → easier breathing.
- Eye (α1): pupil widens.
- Gut/bladder: gut slows, bladder relaxes.
- Metabolism: blood sugar rises, fat breakdown increases; muscles tremble (β2).
- Brain (amphetamine, ephedrine): alertness, less fatigue, less appetite; high doses → anxiety, insomnia.

Therapeutic uses:

- **Adrenaline: anaphylaxis** (life-threatening allergy — the drug of choice, given intramuscularly); cardiac arrest (with CPR); added to local anaesthetics to shrink vessels and keep the anaesthetic in place longer.
- **Noradrenaline: shock with very low blood pressure** (ICU infusion) — tightens vessels and supports the heart.
- **Dopamine:** shock and severe heart failure (ICU) — low dose helps kidneys, higher doses support heart and vessels (typical adult dosing is weight-based; confirm against current references).
- **Dobutamine:** acute heart failure / cardiogenic shock — strengthens the heartbeat with less vessel tightening.
- **Phenylephrine:** nasal decongestion (drops/spray); raises blood pressure during anaesthesia; dilates the pupil for eye examination.
- **Salbutamol (Asthalin) / terbutaline (Bricanyl): asthma** — inhalers/pumps open the airways quickly; also relax the uterus to delay premature labour.
- **Ephedrine:** nasal decongestion (older use), low blood pressure during spinal anaesthesia; in cold/cough syrups (older combinations).
- **Pseudoephedrine (Sudafed):** nasal decongestion in cold tablets — often combined with antihistamines.
- **Amphetamine:** ADHD and narcolepsy in some countries; high abuse potential — controlled substance.

Adverse effects:

- Fast/irregular heartbeat, palpitations, rise in blood pressure (risky in heart patients).
- Tremor of hands (β2), anxiety, restlessness, insomnia, headache.
- High blood sugar (caution in diabetics).
- Nasal sprays used too long → **rebound congestion** (nose blocks worse when stopped).
- Amphetamine: addiction, psychosis-like behaviour at high doses.
- **Pharmacy counselling point:** teach correct inhaler technique for salbutamol; warn that shaky hands after the puff are expected and harmless.

Dose-dependence of dopamine (exam favourite): low infusion rates act mainly on D1 (kidney vessels widen); middle rates act on β1 (heart stronger); high rates act on α1 (vessels tighten). One drug, three jobs, decided by the dose.

2.4.4 SYMPATHOLYTICS (adrenergic blockers)

The idea in one line: Block the fight-or-flight buttons — calm the heart, relax the vessels, lower blood pressure.

Classification:

1. **Alpha blockers:** prazosin, tamsulosin (selective α1); phenoxybenzamine (non-selective, irreversible — used in phaeochromocytoma)
2. **Beta blockers:** propranolol (non-selective β1+β2), atenolol, metoprolol (Betaloc) (selective β1 — "cardioselective"), esmolol (ultra-short-acting, IV)
3. **Central sympatholytics:** clonidine (Arkamin), methyldopa (Aldomet) — act in the brain (α2) to switch OFF sympathetic outflow

Mechanism of action:

- *Alpha-1 blockers:* block α1 on vessels → vessels relax and widen → blood pressure falls. Tamsulosin is selective for the α1 in the prostate/bladder neck → urine flows easier in prostate enlargement (BPH).
- *Beta blockers:* block β1 on the heart → heart beats slower and gentler → less oxygen demand, lower blood pressure; block β2 too (propranolol) → airways may narrow (avoid in asthma).
- *Central:* clonidine and methyldopa stimulate α2 receptors in the brainstem → the brain sends LESS sympathetic signal out → heart slows, vessels relax, blood pressure falls.

Pharmacological effects:

- Heart: slower rate, weaker contraction, less oxygen need (beta blockers).
- Vessels: relaxed and widened (alpha blockers, central drugs).
- Blood pressure: falls.
- Eye: beta-blocker drops (timolol — see Chapter 3) reduce eye fluid production.
- Prostate/bladder neck: relaxed (tamsulosin) → easier urination.

Therapeutic uses:

- **Prazosin (Minipress):** hypertension; also Raynaud's and prostate symptoms (older use). **First dose at bedtime** — first-dose severe low BP.
- **Tamsulosin:** benign prostatic hyperplasia (BPH) — improves urine flow in elderly men; fewer BP effects than prazosin.
- **Phenoxybenzamine:** phaeochromocytoma (adrenaline-secreting tumour) — given before surgery to prevent BP crises.
- **Propranolol (Ciplar):** hypertension, angina (chest pain), heart attack protection, migraine prevention, essential tremor, stage fright/performance anxiety, hyperthyroid symptoms.
- **Atenolol / metoprolol (Betaloc):** hypertension, angina, heart failure (metoprolol), after heart attack — preferred over propranolol in asthmatics/diabetics because β1-selective.
- **Esmolol:** emergencies needing quick on/off heart-rate control (ICU, during surgery) — ultra-short-acting IV.
- **Clonidine (Arkamin):** hypertension (older drug); also ADHD/tics and opioid withdrawal (specialist uses).
- **Methyldopa (Aldomet): hypertension in pregnancy** — one of the safest BP drugs for pregnant women.

Adverse effects:

- Beta blockers: slow heart, low BP, tiredness, cold hands/feet; **mask the warning signs of low blood sugar** (diabetics on insulin may not feel the tremor/sweating of hypoglycaemia — counsel!); worsen asthma (propranolol); vivid dreams; sudden stoppage → rebound chest pain/BP rise — **never stop abruptly, taper slowly**.
- Prazosin: first-dose fainting/dizziness, headache, nasal stuffiness.
- Tamsulosin: dizziness, and "floppy iris" noted by eye surgeons during cataract surgery — patients must tell the eye doctor.
- Clonidine: dry mouth, drowsiness; **rebound hypertension if stopped suddenly**.
- Methyldopa: drowsiness, dry mouth; rarely liver problems or blood disorders — monitor.

> **Analogy — the office again:** Sympathomimetics are extra memos marked URGENT (speed everything up). Sympatholytics are the manager who cancels the urgent memos: beta blockers tell the heart department "slow down," alpha blockers tell the vessel department "relax and widen," and clonidine/methyldopa call head office (the brain) and say "cancel the emergency — stand down."

2.5 Classification (summary chart)

Autonomic drugs — the four armies:

1. Parasympathomimetics — DIRECT: bethanechol, carbachol, pilocarpine | INDIRECT (anticholinesterases): neostigmine, physostigmine, pyridostigmine, edrophonium (reversible); organophosphates (irreversible, poison concept)
2. Parasympatholytics — atropine, scopolamine, ipratropium, tiotropium, glycopyrrolate, dicyclomine, oxybutynin, tolterodine (+ hyoscine butylbromide)
3. Sympathomimetics — DIRECT: phenylephrine, noradrenaline, adrenaline, dopamine, dobutamine, salbutamol, terbutaline | INDIRECT: amphetamine, tyramine | MIXED: ephedrine, pseudoephedrine
4. Sympatholytics — ALPHA BLOCKERS: prazosin, tamsulosin, phenoxybenzamine | BETA BLOCKERS: propranolol, atenolol, metoprolol, esmolol | CENTRAL: clonidine, methyldopa

2.6 Mechanisms (one-line each)

- Bethanechol/carbachol/pilocarpine → switch ON muscarinic receptors directly.
- Neostigmine/physostigmine/pyridostigmine → block acetylcholinesterase → ACh piles up everywhere.
- Edrophonium → same, but very briefly (diagnostic test).
- Organophosphates → permanently lock acetylcholinesterase (poisoning: SLUDD + muscle weakness; treat with atropine + pralidoxime).
- Atropine/scopolamine/ipratropium/tiotropium/glycopyrrolate/dicyclomine/oxybutynin → block muscarinic receptors.
- Phenylephrine → α1 ON (vessels tighten). Salbutamol/terbutaline → β2 ON (airways open).
- Adrenaline → α + β ON (all-out emergency). Noradrenaline → α1 + β1 ON (BP support). Dobutamine → mainly β1 ON (heart). Dopamine → D1 → β1 → α1 as dose rises.
- Amphetamine/tyramine → push stored noradrenaline out. Ephedrine/pseudoephedrine → push it out AND press receptors directly.
- Prazosin/tamsulosin → block α1 (vessels/prostate relax). Propranolol → blocks β1+β2. Atenolol/metoprolol → block mainly β1. Esmolol → blocks β1 very briefly (IV). Clonidine/methyldopa → switch ON brain α2 → sympathetic outflow OFF.

2.7 Diagrams (to be drawn by the student)

1. **The four armies chart:** Draw a 2×2 grid. Rows: "mimic" vs "block". Columns: "parasympathetic" vs "sympathetic". Fill: mimic-para = cholinergics; block-para = anticholinergics; mimic-symp = adrenergics; block-symp = blockers. Add one example drug in each box.
2. **Direct vs indirect:** Draw a receptor lock. Direct drug = a key entering the lock. Indirect drug = a hand jamming the shredder (enzyme) while real keys pile up.
3. **Dopamine dose ladder:** Draw a vertical ladder with three rungs: bottom rung "low dose → D1 (kidney)", middle "medium → β1 (heart)", top "high → α1 (vessels)".
4. **Eye diagram for miosis vs mydriasis:** Draw two eyes — one with a tiny pupil labelled "pilocarpine (M3) — miosis", one with a wide pupil labelled "atropine (M block) / phenylephrine (α1) — mydriasis".

2.8 Flowcharts

Flowchart 1 — Choosing the autonomic drug (logic map):

```
Want MORE parasympathetic action?
   → Give DIRECT key (bethanechol, pilocarpine)  OR  jam the shredder (neostigmine)
Want LESS parasympathetic action?
   → Block the locks (atropine, ipratropium, oxybutynin)
Want MORE sympathetic action?
   → Press receptor buttons directly (adrenaline, salbutamol)  OR  release stored NA
(amphetamine)  OR  both (ephedrine)
Want LESS sympathetic action?
   → Block α1 (prazosin), block β (propranolol), or tell the brain to stand down (clonidine)
```

Flowchart 2 — Organophosphate poisoning treatment:

```
Organophosphate poison → AChE permanently blocked → ACh floods body (SLUDD + weakness)
        ↓
Give ATROPINE → blocks muscarinic effects (dries secretions, speeds heart)
        ↓
Give PRALIDOXIME → pulls the poison off the enzyme (reactivates AChE) — works best early
        ↓
Support breathing (ventilator if needed)
```

Flowchart 3 — Anaphylaxis (adrenaline) logic:

```
Severe allergy → vessels leak + airways close + BP crashes
        ↓
Adrenaline IM → α1 tightens vessels (BP up) + β1 supports heart + β2 opens airways
        ↓  (all three problems fixed by one drug — that is why it is the drug of choice)
```

2.9 Infographic Concept Box

AUTONOMIC DRUGS — "The Four Armies and Their Battle Cries"

- 🟢 **PARA-MIMICS** (cholinergics): battle cry "**SLUDD!**" — more Saliva, Lacrimation (tears), Urination, Digestion, Defecation. Keys: bethanechol, pilocarpine (direct); neostigmine, pyridostigmine (jam the shredder).
- 🔴 **PARA-BLOCKERS** (anticholinergics): battle cry "**DRY!**" — Dry mouth, Red skin, blurred vision, can't pee, fast heart. Shields: atropine, scopolamine, ipratropium, tiotropium, oxybutynin.
- 🟠 **SYMP-MIMICS** (adrenergics): battle cry "**FIGHT!**" — Faster heart, Iris widens, Gut slows, Hyperglycemia, airways open. Weapons: adrenaline (all buttons), salbutamol (β2 — asthma), phenylephrine (α1 — nose/BP), ephedrine (mixed).
- 🔵 **SYMP-BLOCKERS**: battle cry "**CALM!**" — slower heart, relaxed vessels, lower BP. Shields: propranolol/atenolol/metoprolol (β), prazosin/tamsulosin (α1), clonidine/methyldopa (brain α2).
- ⚠️ **NEVER-FORGET PAIRS:** organophosphate poisoning → atropine + pralidoxime | anaphylaxis → adrenaline IM | BPH → tamsulosin | pregnancy hypertension → methyldopa | myasthenia → pyridostigmine.

2.10 Tables

Table 2.1 — Parasympathomimetics: uses and key cautions

Drug	Main use	Key caution
Bethanechol	Urinary retention, sluggish gut	Cramps, diarrhoea; avoid in asthma
Carbachol	Glaucoma eye drops	Blurred vision
Pilocarpine	Glaucoma, dry mouth	Miosis, brow ache
Neostigmine	Myasthenia gravis, reverse muscle relaxants	SLUDD effects; give atropine alongside when reversing relaxants
Physostigmine	Atropine poisoning antidote	Enters brain — the point of using it
Pyridostigmine (Mestinon)	Myasthenia gravis maintenance	Longer-acting than neostigmine
Edrophonium (Tensilon)	Diagnose myasthenia gravis	Very short-acting — test only

Table 2.2 — Parasympatholytics: uses

Drug	Main use
Atropine	Slow heart (bradycardia), pre-anaesthetic, organophosphate antidote, eye examination
Scopolamine	Motion sickness, pre-anaesthetic sedation
Hyoscine butylbromide (Buscopan)	Gut spasm/colic pain
Ipratropium (Ipravent)	Asthma/COPD inhaler
Tiotropium (Tiova)	COPD maintenance (once daily)
Glycopyrrolate	Pre-surgery drying, drooling
Dicyclomine	Gut spasm (IBS-type pain)
Oxybutynin / tolterodine	Overactive bladder

Table 2.3 — Sympathomimetics: receptor action and main use

Drug	Main receptors	Main use
Adrenaline	α + β (all)	Anaphylaxis (drug of choice), cardiac arrest
Noradrenaline	α1 + β1	Shock with very low BP (ICU)
Dopamine	D1 → β1 → α1 (dose-wise)	Shock, severe heart failure
Dobutamine	Mainly β1	Acute heart failure
Phenylephrine	Mainly α1	Nasal decongestion, low BP in anaesthesia
Salbutamol (Asthalin) / terbutaline (Bricanyl)	Mainly β2	Asthma inhaler, delay premature labour
Ephedrine	Mixed	Nasal decongestion, low BP in spinal anaesthesia
Pseudoephedrine (Sudafed)	Mixed	Cold tablets (decongestant)
Amphetamine	Indirect	ADHD/narcolepsy (controlled, abuse risk)
Tyramine	Indirect	Not a drug — in cheese; causes "cheese reaction" with MAO inhibitors

Table 2.4 — Sympatholytics: uses and key cautions

Drug	Main use	Key caution
Prazosin (Minipress)	Hypertension	First-dose fainting — first dose at bedtime
Tamsulosin	Prostate enlargement (BPH)	Tell eye surgeon before cataract operation
Phenoxybenzamine	Phaeochromocytoma (before surgery)	Irreversible block — long-lasting low BP
Propranolol (Ciplar)	Hypertension, angina, migraine prevention, tremor, stage fright	Avoid in asthma; masks low-sugar warning signs
Atenolol / metoprolol (Betaloc)	Hypertension, angina, heart failure	Safer in asthma/diabetes than propranolol (β1-selective)
Esmolol	Emergency heart-rate control (IV, ICU)	Ultra-short-acting — stops working minutes after drip stops
Clonidine (Arkamin)	Hypertension	Rebound high BP if stopped suddenly
Methyldopa (Aldomet)	Hypertension in pregnancy	Drowsiness; monitor liver/blood rarely

2.11 Examples

- **Example 1:** After abdominal surgery, a patient cannot pass urine. The doctor orders bethanechol — it contracts the bladder (M3) and urine flows.
- **Example 2:** A child eats wild "dhatura" (belladonna) seeds — dry mouth, wide pupils, fast heart, confusion. This is atropine-like poisoning; physostigmine is the antidote.
- **Example 3:** A farmer sprays pesticide and develops heavy salivation, sweating, diarrhoea, pinpoint pupils, and muscle weakness — organophosphate poisoning; treated with atropine + pralidoxime.
- **Example 4:** A young man collapses after a peanut allergy — BP crashing, throat swelling. Adrenaline IM saves him (α1 + β1 + β2 together).
- **Example 5:** An asthmatic student uses a salbutamol inhaler (Asthalin) before sports day — airways open (β2); mild hand tremor follows and is harmless.
- **Example 6:** A 65-year-old man with prostate enlargement gets tamsulosin — urine stream improves without much BP fall.
- **Example 7:** A pregnant woman with high BP is prescribed methyldopa (Aldomet) — safe in pregnancy, unlike many other BP drugs.

2.12 Analogies

1. **Shredder:** Anticholinesterases jam the ACh shredder so memos pile up.
2. **Broken key:** Anticholinergics are broken keys stuck in muscarinic locks.
3. **Master key vs single key:** Adrenaline = master key (opens α and β); phenylephrine = single key (α1 only); salbutamol = single key (β2 only).
4. **Empty warehouse:** Indirect sympathomimetics (amphetamine) empty the noradrenaline warehouse — repeated use finds empty shelves (tachyphylaxis).
5. **Manager's cancellation:** Sympatholytics cancel the emergency — beta blockers calm the heart department, alpha blockers widen the vessel roads, clonidine phones head office to stand down.
6. **SLUDD vs DRY:** Parasympathomimetics = monsoon (everything flows); parasympatholytics = drought (everything dries).

2.13 Pharmacy Relevance

- The pharmacist is the safety net for **anticholinergic load in the elderly** — many common drugs (for bladder, gut spasm, cold, allergy) add up to confusion, constipation, and urinary retention. Review the full prescription.
- **Inhaler technique counselling** (salbutamol, ipratropium, tiotropium) decides whether the drug works — demonstrate and re-check at every refill.
- Know the **emergency pairs**: anaphylaxis → adrenaline IM; organophosphate poisoning → atropine + pralidoxime; beta-blocker overdose → glucagon (hospital).
- Counsel beta-blocker patients: **never stop suddenly** (taper), and diabetics: the usual tremor/sweating warning of low sugar may be hidden.
- Dispense prazosin with the clear instruction: **first dose at bedtime**.

2.14 India Context

- **NLEM essential medicines** in this chapter include atropine, adrenaline, noradrenaline, dopamine, salbutamol, propranolol, atenolol, neostigmine, and methyldopa — all available as low-cost generics at **Jan Aushadhi Kendras**.
- **Asthalin (salbutamol)** and **Ciplar (propranolol)** are among the most prescribed drugs in Indian OPDs; pharmacists dispense them daily.
- **Aldomet (methyldopa)** remains the standard BP drug in Indian antenatal clinics for pregnancy hypertension.
- Organophosphate (pesticide) poisoning is a **major emergency in rural India** — every pharmacist should know the atropine + pralidoxime protocol and that physostigmine reverses belladonna/dhatura poisoning.
- **Tamsulosin** is widely prescribed in India for elderly men with prostate enlargement; counsel about dizziness on standing.

2.15 Key Points

1. Parasympathomimetics: direct keys (bethanechol, carbachol, pilocarpine) or shredder-jammers (anticholinesterases: neostigmine, physostigmine, pyridostigmine, edrophonium).
2. Organophosphates irreversibly block AChE → SLUDD + weakness; antidotes: atropine + pralidoxime.
3. Parasympatholytics block muscarinic receptors → "dry" picture (atropine, scopolamine, ipratropium, tiotropium, glycopyrrolate, dicyclomine, oxybutynin/tolterodine).
4. Sympathomimetics: direct (phenylephrine, noradrenaline, adrenaline, dopamine, dobutamine, salbutamol/terbutaline), indirect (amphetamine, tyramine), mixed (ephedrine, pseudoephedrine).
5. Adrenaline IM is the drug of choice in anaphylaxis; dopamine's action changes with dose (D1 → β1 → α1).
6. Sympatholytics: α1 blockers (prazosin — first-dose hypotension; tamsulosin — BPH), beta blockers (propranolol non-selective; atenolol/metoprolol β1-selective; esmolol ultra-short), central (clonidine — rebound hypertension; methyldopa — safe in pregnancy).
7. Beta blockers: never stop abruptly; mask hypoglycaemia warning signs; avoid non-selective ones in asthma.

2.16 Common Confusions

- **Physostigmine vs neostigmine:** physostigmine enters the brain (tertiary amine) → used in atropine poisoning; neostigmine does not → used in myasthenia gravis and gut/bladder.
- **Edrophonium vs neostigmine:** edrophonium acts in minutes and fades in minutes → diagnosis only; neostigmine/pyridostigmine last hours → treatment.
- **Direct vs indirect sympathomimetics:** direct = presses the button itself; indirect = makes the nerve release its own messenger (stores run out → tachyphylaxis).
- **Propranolol vs atenolol/metoprolol:** propranolol blocks β1 AND β2 (bad in asthma); atenolol/metoprolol are β1-selective ("cardioselective").
- **Prazosin vs tamsulosin:** both block α1, but tamsulosin targets the prostate → used for BPH with less BP fall.
- **Clonidine vs methyldopa:** both central, but methyldopa is the one preferred in pregnancy.
- **Ipratropium vs tiotropium:** both anticholinergic inhalers; tiotropium is once-daily and for COPD maintenance.

2.17 Common Mistakes

1. Prescribing/counselling a non-selective beta blocker (propranolol) to an asthmatic — can trigger severe bronchospasm.
2. Forgetting the **first-dose effect** of prazosin — patient faints after the first tablet.
3. Stopping clonidine or beta blockers suddenly — rebound hypertension/angina.
4. Using long-term nasal decongestant sprays — rebound congestion.
5. Missing that beta blockers hide low-blood-sugar warning signs in diabetics.
6. Giving anticholinergics to narrow-angle glaucoma or elderly men with prostate enlargement without caution.

2.18 Mnemonics

- **Parasympathetic excess — "SLUDD":** **S**alivation, **L**acrimation, **U**rination, **D**igestion, **D**efecation.
- **Anticholinergic effects — "Dry as a bone":** **D**ry mouth, **R**ed skin, blurred vision, **Y** can't pee (urinary retention), constipation, **T**achycardia, **H**ot, **C**onfused.
- **Sympathetic effects — "FIGHT":** **F**aster heart, **I**ris widens, **G**ut slows, **H**yperglycemia, airways open (**T**remor).
- **Beta blockers — "BB CALM":** **B**radycardia, **B**ronchospasm (non-selective), **C**old hands, **A**void sudden stop, **L**ow sugar signs **M**asked.
- **Direct sympathomimetics — "PAN-DDS":** **P**henylephrine, **A**drenaline, **N**oradrenaline, **D**opamine, **D**obutamine, **S**albutamol.
- **Anticholinesterases — "NEPP ED":** **N**eostigmine, **E**drophonium, **P**hysostigmine, **P**yridostigmine (+ **D**onepezil).
- **Anaphylaxis — "A for Adrenaline":** **A**naphylaxis → **A**drenaline IM, **A**lways first.
- **Organophosphate antidotes — "AP":** **A**tropine + **P**ralidoxime.

2.19 Exam Summary

- Classify parasympathomimetics (direct vs indirect, reversible vs irreversible) with two examples each.
- Explain how anticholinesterases work; contrast with direct agonists.
- List atropine's effects, uses, and adverse effects ("dry as a bone").
- Explain organophosphate poisoning signs and treatment (atropine + pralidoxime).
- Classify sympathomimetics (direct/indirect/mixed) with examples; explain tachyphylaxis.
- Justify: adrenaline in anaphylaxis; salbutamol in asthma; dopamine dose-dependence.
- Classify sympatholytics; compare propranolol vs atenolol/metoprolol; explain first-dose effect (prazosin), rebound hypertension (clonidine), methyldopa in pregnancy.
- Tables 2.1–2.4 are ready-made exam answers.

2.20 One-Minute Revision

Para-mimics: direct keys (bethanechol, carbachol, pilocarpine) or AChE blockers (neostigmine, physostigmine — brain, pyridostigmine, edrophonium — test); poisoning by organophosphates → atropine + pralidoxime. Para-blockers (atropine, scopolamine, ipratropium, tiotropium, glycopyrrolate, dicyclomine, oxybutynin) → dry everything, fast heart, wide pupils. Symp-mimics: direct (phenylephrine α1, adrenaline all, noradrenaline α1β1, dopamine dose-wise, dobutamine β1, salbutamol β2), indirect (amphetamine, tyramine — tachyphylaxis), mixed (ephedrine, pseudoephedrine). Symp-blockers: α1 (prazosin — first-dose fall; tamsulosin — BPH), β (propranolol all-β; atenolol/metoprolol β1; esmolol IV short), central (clonidine — rebound; methyldopa — pregnancy-safe).

2.21 Exam Questions

Short-answer questions:

1. Classify parasympathomimetic drugs with two examples each.
2. How do anticholinesterases produce their effects? Give two examples.
3. Why is physostigmine used in atropine poisoning but neostigmine is not?
4. List four therapeutic uses of atropine.
5. What are the signs of organophosphate poisoning? How is it treated?
6. Classify sympathomimetic drugs with examples.
7. Why is adrenaline the drug of choice in anaphylaxis?
8. Explain the dose-dependent actions of dopamine.
9. Compare propranolol and atenolol (any four points).
10. Why is methyldopa preferred in pregnancy hypertension?
11. What is the first-dose effect? Which drug shows it?
12. Why should beta blockers not be stopped suddenly?

Long-answer questions:

1. Classify parasympathomimetic drugs. Describe the mechanism of action, pharmacological effects, therapeutic uses, and adverse effects of anticholinesterases.
2. Describe the pharmacology of atropine: mechanism, effects on eye/heart/gut/bladder, therapeutic uses, and adverse effects.
3. Classify sympathomimetic drugs. Discuss the pharmacology of adrenaline, including its receptor actions, uses, and adverse effects.
4. Classify sympatholytic drugs. Describe beta blockers in detail: mechanism, effects, uses, adverse effects, and precautions.

MCQs (with answer key):

1. Which drug is a direct-acting parasympathomimetic? (a) neostigmine (b) bethanechol ✓ (c) atropine (d) physostigmine — **Answer: (b)**
2. Edrophonium is used for: (a) treatment of glaucoma (b) diagnosis of myasthenia gravis ✓ (c) motion sickness (d) hypertension — **Answer: (b)**
3. Physostigmine differs from neostigmine because it: (a) lasts longer (b) enters the brain ✓ (c) is irreversible (d) blocks nicotinic receptors — **Answer: (b)**
4. Antidotes for organophosphate poisoning are: (a) atropine + pralidoxime ✓ (b) adrenaline + noradrenaline (c) physostigmine + neostigmine (d) propranolol + atenolol — **Answer: (a)**
5. Which is an anticholinergic inhaler for COPD? (a) salbutamol (b) tiotropium ✓ (c) adrenaline (d) bethanechol — **Answer: (b)**
6. Drug of choice in anaphylaxis: (a) noradrenaline (b) hydrocortisone (c) adrenaline IM ✓ (d) chlorpheniramine — **Answer: (c)**
7. Salbutamol acts mainly on: (a) α1 (b) β1 (c) β2 ✓ (d) M3 — **Answer: (c)**
8. Tachyphylaxis is typically seen with: (a) phenylephrine (b) ephedrine ✓ (c) salbutamol (d) dobutamine — **Answer: (b)**
9. First-dose hypotension is characteristic of: (a) atenolol (b) prazosin ✓ (c) clonidine (d) tamsulosin — **Answer: (b)**
10. Which beta blocker is β1-selective? (a) propranolol (b) atenolol ✓ (c) timolol (d) sotalol — **Answer: (b)**
11. Tamsulosin is mainly used in: (a) asthma (b) BPH ✓ (c) glaucoma (d) diarrhoea — **Answer: (b)**
12. Methyldopa is preferred in: (a) asthma (b) pregnancy hypertension ✓ (c) glaucoma (d) migraine — **Answer: (b)**
13. Rebound hypertension on sudden withdrawal occurs with: (a) prazosin (b) clonidine ✓ (c) atenolol (d) tamsulosin — **Answer: (b)**
14. Esmolol is: (a) long-acting oral beta blocker (b) ultra-short-acting IV beta blocker ✓ (c) alpha blocker (d) central sympatholytic — **Answer: (b)**

Viva questions:

1. Give two direct and two indirect parasympathomimetics.
2. What does SLUDD stand for?
3. Which anticholinesterase is used to diagnose myasthenia gravis?
4. Name the two antidotes in organophosphate poisoning.
5. Which pupil change does atropine cause — miosis or mydriasis?
6. Give one direct, one indirect, and one mixed sympathomimetic.
7. Why does ephedrine lose effect on repeated dosing?
8. Which drug is DOC in anaphylaxis and by which route?
9. Name two β1-selective beta blockers.
10. Which alpha blocker is used for BPH?
11. Why is the first dose of prazosin taken at bedtime?
12. Which antihypertensive is safe in pregnancy?

Application-based questions:

1. A 70-year-old man on oxybutynin for overactive bladder develops constipation, dry mouth, and difficulty passing urine. Explain and suggest what the pharmacist should do. (Anticholinergic effects; check prostate history, counsel, refer to doctor — do not just add a laxative blindly.)
2. A diabetic patient on propranolol and insulin feels unusually tired and sweaty episodes go unnoticed. Explain the risk. (Beta blocker masks hypoglycaemia warning signs — tremor, palpitations, sweating.)
3. A patient using a phenylephrine nasal spray daily for a month says the nose blocks worse when the spray is stopped. Explain. (Rebound congestion from prolonged decongestant use.)
4. After the first tablet of prazosin, a patient faints on standing. What happened and what advice should have been given? (First-dose hypotension; first dose at bedtime, rise slowly.)

2.22 References

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Chapter 3: Skeletal Muscle Relaxants, Myasthenia Gravis, and Glaucoma Drugs

3.1 Learning Objectives

After studying this chapter, the student will be able to:

1. Classify skeletal muscle relaxants (peripheral, centrally acting, directly acting).
2. Differentiate depolarizing and non-depolarizing (competitive) neuromuscular blockers.
3. Explain the mechanism of action of succinylcholine, tubocurarine, pancuronium, vecuronium, atracurium, and rocuronium.
4. List the uses and adverse effects of neuromuscular blockers.
5. Describe centrally acting muscle relaxants (baclofen, diazepam, tizanidine, cyclobenzaprine, methocarbamol) — mechanism, uses, adverse effects.
6. Explain the mechanism and use of dantrolene (directly acting).
7. Explain the pathophysiology of myasthenia gravis and the role of neostigmine, pyridostigmine, and edrophonium.
8. Classify drugs used in glaucoma (pilocarpine, timolol, latanoprost, acetazolamide, apraclonidine/brimonidine) and explain how each lowers eye pressure.
9. List the uses and adverse effects of antiglaucoma drugs.

3.2 Definitions

- **Skeletal muscle relaxant:** A drug that reduces stiffness, spasm, or tightness of skeletal (voluntary) muscles.
- **Neuromuscular junction (NMJ):** The synapse where a somatic motor nerve meets a skeletal muscle fibre — the message here uses acetylcholine on nicotinic Nm receptors.
- **Neuromuscular blocker:** A drug that blocks the NMJ, causing temporary paralysis of skeletal muscles — used mainly during surgery so the surgeon can operate on a still, relaxed patient.
- **Depolarizing blocker:** A drug that first stimulates the muscle (like ACh) and then keeps it stimulated so long that the muscle cannot reset — it stays limp (e.g., succinylcholine).
- **Non-depolarizing (competitive) blocker:** A drug that sits on the Nm receptor without stimulating it, blocking ACh — the muscle simply never gets the "contract" order (e.g., tubocurarine, pancuronium, vecuronium, atracurium, rocuronium).
- **Spasm:** A painful, involuntary tightening of a muscle (as in back pain or after injury).
- **Spasticity:** Long-term stiffness of muscles due to brain/spinal cord disease (stroke, cerebral palsy, multiple sclerosis, spinal injury).
- **Myasthenia gravis:** A disease in which the body's own defence system destroys the ACh receptors on muscles — muscles become weak and tire quickly. ("Myasthenia" = muscle weakness; "gravis" = serious.)
- **Glaucoma:** A disease in which the pressure inside the eye (intraocular pressure) rises and slowly damages the optic nerve, which can cause blindness if untreated.
- **Aqueous humor:** The clear fluid inside the front of the eye — made continuously and drained continuously; if drainage blocks, pressure rises (glaucoma).

3.3 Terminology

- **Fasciculation:** Brief visible twitching of muscle bundles — seen just before succinylcholine paralyzes.
- **Phase I / Phase II block:** With succinylcholine, the block starts as depolarizing (Phase I); with prolonged exposure it changes character (Phase II) — an exam detail.
- **Reversal (of muscle relaxants):** Waking the muscles up after surgery using neostigmine (+ atropine/glycopyrrolate to block its muscarinic effects).
- **Malignant hyperthermia:** A rare, dangerous reaction to succinylcholine (and some anaesthetics) — body temperature shoots up; treated with dantrolene.
- **Cholinergic crisis:** Weakness caused by TOO MUCH anticholinesterase (overdose) in myasthenia gravis.
- **Myasthenic crisis:** Weakness caused by TOO LITTLE treatment (disease flare) in myasthenia gravis — the Tensilon (edrophonium) test tells them apart.
- **Miosis:** Pupil narrowing (pilocarpine effect — good in glaucoma).
- **Intraocular pressure (IOP):** Pressure inside the eyeball — the number glaucoma treatment tries to lower.

3.4 Explanation

3.4.1 SKELETAL MUSCLE RELAXANTS — the big picture

The idea in one line: Muscles can be relaxed at three levels — at the nerve-muscle junction (peripheral blockers, used in surgery), in the brain/spinal cord (central relaxants, used in spasm/spasticity), or inside the muscle itself (dantrolene).

Classification:

1. **Peripherally acting (neuromuscular blockers)** — act at the NMJ:

- **Depolarizing:** succinylcholine
- **Non-depolarizing (competitive):** tubocurarine, pancuronium, vecuronium, atracurium, rocuronium

2. **Centrally acting** — act in brain/spinal cord:

- Baclofen, diazepam, tizanidine, cyclobenzaprine, methocarbamol

3. **Directly acting on muscle:**

- Dantrolene

3.4.2 Peripheral neuromuscular blockers

How the normal NMJ works (30-second recap): Nerve releases ACh → ACh opens nicotinic Nm receptors → muscle membrane depolarizes → muscle contracts → AChE destroys ACh → muscle relaxes, ready for the next order.

(A) Depolarizing blocker — succinylcholine

- **Mechanism:** Succinylcholine looks like TWO acetylcholine molecules joined together. It binds the Nm receptor and stimulates it like ACh — the muscle twitches (fasciculations) — but unlike ACh it is NOT quickly destroyed, so the receptor stays switched ON. A muscle that cannot switch OFF cannot receive the next order — it goes limp (flaccid paralysis). Like holding a doorbell pressed forever: after the first ring, no new rings can be heard.
- **Effects:** Very fast onset (about a minute), short duration (a few minutes). First twitching, then complete relaxation — including the breathing muscles (so the anaesthetist must support breathing).
- **Uses:** Rapid insertion of the breathing tube (intubation) during emergency anaesthesia; short procedures needing quick, brief relaxation; electroconvulsive therapy (ECT) to prevent injury from convulsions.
- **Adverse effects:** Muscle pains after surgery (from the initial twitching); rise in blood potassium (dangerous in burns, crush injuries, kidney failure); **malignant hyperthermia** in susceptible patients (treat with dantrolene); prolonged paralysis in people lacking the enzyme that breaks it down (pseudocholinesterase deficiency); rise in eye and stomach pressure.

(B) Non-depolarizing (competitive) blockers — tubocurarine, pancuronium, vecuronium, atracurium, rocuronium

- **Mechanism:** These drugs sit on the Nm receptor and occupy it WITHOUT stimulating it — ACh cannot bind. No "contract" order ever arrives, so the muscle stays relaxed from the start (no twitching). Like a broken key stuck in the lock: the real key cannot enter, and the door never opens.
- **Reversal:** Their block CAN be reversed — give neostigmine to pile up ACh, which out-competes the blocker (plus atropine/glycopyrrolate to cancel neostigmine's muscarinic effects). Succinylcholine's block cannot be reversed this way (neostigmine would make it worse).
- **Effects:** Smooth, predictable paralysis lasting from ~20 minutes (rocuronium, atracurium) to over an hour (pancuronium, tubocurarine). Breathing muscles are paralyzed — ventilation must be supported.
- **Uses:** Muscle relaxation during general surgery (abdominal, chest operations); to help mechanical ventilation in ICUs; to prevent injury during ECT (older use).
- **Individual notes:**
- **Tubocurarine** (from the curare plant — the original "arrow poison"): the prototype; causes histamine release (low BP, flushing) and some ganglion block — now mostly of historical/exam importance.
- **Pancuronium:** long-acting; slight heart-rate increase (vagolytic).
- **Vecuronium:** intermediate-acting; minimal heart effects — widely used.
- **Atracurium:** broken down spontaneously in the blood (Hofmann elimination) — does NOT depend on kidney or liver, so it is preferred in kidney/liver failure patients.
- **Rocuronium:** fastest among non-depolarizing — used when succinylcholine is unsuitable for rapid intubation.
- **Adverse effects:** Too-long paralysis if dosing is wrong (patient cannot breathe on their own after surgery — the anaesthetist monitors carefully); low blood pressure and flushing with tubocurarine (histamine); fast heart with pancuronium; allergic reactions rarely.

Depolarizing vs non-depolarizing — the exam table:

Feature	Succinylcholine (depolarizing)	e.g., vecuronium (non-depolarizing)
Action on Nm receptor	Stimulates first, then blocks	Blocks without stimulating
Muscle twitching (fasciculations)	Yes, at start	No
Reversed by neostigmine	No (worsens)	Yes
Onset	Very fast (~1 min)	Slower (2–4 min)
Duration	Very short (minutes)	Longer (20 min–1 hr+)
Malignant hyperthermia risk	Yes	No

3.4.3 Centrally acting muscle relaxants

The idea in one line: These calm down overactive nerve signals in the brain and spinal cord, so tight, spasming muscles loosen — without fully paralyzing them. Used for back pain, neck spasm, and long-term spasticity (stroke, spinal injury, multiple sclerosis, cerebral palsy).

- **Baclofen (Lioresal):** Mimics GABA (the brain's main "calm down" chemical) at GABA-B receptors in the spinal cord → reduces the excessive signals that keep muscles stiff. Main use: **spasticity** in multiple sclerosis and spinal cord injury (also given directly into spinal fluid by pump in severe cases). Adverse effects: drowsiness, dizziness, weakness; **do not stop suddenly** — withdrawal can cause seizures and confusion.
- **Diazepam (Valium):** Boosts GABA-A action in the brain → reduces anxiety-driven muscle spasm and spasticity. Main use: acute painful muscle spasm, spasticity, and also seizures/anxiety (it is a benzodiazepine). Adverse effects: drowsiness, dependence with long use, slows breathing in overdose.
- **Tizanidine:** Stimulates α2 receptors in the spinal cord (like clonidine's brain action, but in the cord) → reduces spasticity. Main use: spasticity in multiple sclerosis, stroke, spinal injury. Adverse effects: drowsiness, dry mouth, low blood pressure, liver monitoring needed.
- **Cyclobenzaprine:** Acts in the brainstem to reduce muscle spasm signals. Main use: short-term relief of acute painful muscle spasm (back/neck strain). Adverse effects: drowsiness, dry mouth, dizziness — has anticholinergic-like effects.
- **Methocarbamol:** Depresses nerve signal transmission in the brain/spinal cord (exact site not fully pinned down). Main use: acute muscle spasm with pain. Adverse effects: drowsiness, dizziness; urine may turn brownish-green (harmless, but warn the patient!).

Pharmacy counselling point: Warn every patient on these drugs — "may cause drowsiness; do not drive or operate machinery; avoid alcohol."

3.4.4 Directly acting — dantrolene

- **Mechanism:** Acts INSIDE the muscle fibre itself — it blocks the release of calcium from the muscle's internal store (sarcoplasmic reticulum). No calcium = the muscle fibres cannot contract, no matter what the nerve orders. It does not touch the nerve or the NMJ at all.
- **Uses: Malignant hyperthermia** (the life-saving antidote — every operation theatre keeps it ready); chronic spasticity (stroke, cerebral palsy) when other drugs fail; neuroleptic malignant syndrome (a similar emergency from antipsychotic drugs).
- **Adverse effects:** Muscle weakness (expected — that is the job), drowsiness, dizziness; liver injury with long-term use — monitor liver function.

Analogy — three ways to stop a noisy factory: Peripheral blockers cut the telephone order line (NMJ). Central relaxants calm the manager (brain/spinal cord) so fewer orders are sent. Dantrolene switches off the machines inside the factory (muscle calcium) — orders may arrive, but the machines cannot run.

3.4.5 MYASTHENIA GRAVIS — drugs

The disease in one line: The patient's own immune system destroys the nicotinic (Nm) receptors on skeletal muscles. Nerves release normal ACh, but there are too few receptors to catch it — muscles weaken with use and recover with rest. Typically the eyelids droop (ptosis), double vision appears, and chewing/swallowing/speaking tire out; in severe cases breathing muscles fail (myasthenic crisis).

Treatment logic: If receptors are few, make each surviving receptor count — pile up more ACh at the junction with anticholinesterases.

- **Pyridostigmine (Mestinon):** The mainstay — longer-acting anticholinesterase; tablets taken through the day keep muscles working. Adverse effects: SLUDD effects (cramps, diarrhoea, salivation); dose is carefully titrated — too much causes cholinergic crisis (weakness from overdose looks like weakness from disease!).
- **Neostigmine:** Shorter-acting; used when quick effect is needed and in hospital settings.
- **Edrophonium (Tensilon):** Ultra-short-acting — the **diagnostic test**: inject IV; if drooping eyelids lift and strength returns within minutes, myasthenia gravis is confirmed. It also distinguishes **myasthenic crisis** (improves with edrophonium → needs MORE drug) from **cholinergic crisis** (worsens with edrophonium → needs LESS drug / atropine). This distinction is a classic exam question.
- Supportive: immunosuppressants (steroids, azathioprine) calm the immune attack; thymus gland removal (thymectomy) helps many patients; crisis care includes ventilation and plasma exchange/IV immunoglobulin (hospital care).

Flowchart — Tensilon test logic:

```
Myasthenia patient becomes very weak — which crisis?
        ↓
Give edrophonium (Tensilon) IV
        ↓
   Strength IMPROVES → MYASTHENIC crisis (disease winning) → give MORE anticholinesterase
   Strength WORSENS  → CHOLINERGIC crisis (drug overdose) → STOP drug, give atropine
```

3.4.6 GLAUCOMA — drugs

The disease in one line: Eye fluid (aqueous humor) is made continuously and must drain continuously. If drainage blocks (or too much fluid is made), pressure inside the eye rises and crushes the optic nerve — painless, slow vision loss that becomes permanent. Treatment = **lower the eye pressure**, either by draining more fluid out or making less fluid.

Drug classes and how each lowers pressure:

1. **Pilocarpine (M3 agonist):** Contracts the eye's drainage muscle → the drainage channels open wider → more fluid drains out → pressure falls. Also narrows the pupil (miosis). Adverse effects: small pupil → dim vision at night, brow ache, blurred vision; long-term use can cloud the lens (cataract).
2. **Timolol (beta blocker eye drops):** Blocks β receptors on the fluid-making tissue → LESS fluid is made → pressure falls. Key advantage: does not change pupil size or vision. Adverse effects: drops can enter the blood — slow heart, asthma worsening, low BP; caution in asthma/COPD and heart block. (Betaxolol is a β1-selective alternative.)
3. **Latanoprost (Xalatan) (prostaglandin analogue):** Increases fluid drainage through a second, alternate pathway (uveoscleral outflow) → pressure falls. Once-daily night drops — very effective first-line drug. Adverse effects: eye redness/irritation; **permanent darkening of the iris colour** (brown eyes get browner — warn the patient!); eyelash growth.
4. **Acetazolamide (Diamox) (carbonic anhydrase inhibitor):** Blocks the enzyme that helps make eye fluid → less fluid made → pressure falls. Given as tablets (or IV in emergencies) — used short-term or before surgery because tablets have more side effects. Adverse effects: tingling in fingers, frequent urination, loss of appetite, kidney stones with long use; also used for altitude sickness and epilepsy (same enzyme logic).
5. **Apraclonidine / brimonidine (alpha-2 agonists):** Switch on α2 in the eye → less fluid made AND more drained → pressure falls. Brimonidine drops are used long-term; apraclonidine short-term (e.g., after laser surgery). Adverse effects: dry mouth, drowsiness (brimonidine), eye allergy/redness with long use.

> **Analogy — the overflowing sink:** The eye is a sink with the tap running (fluid made) and the drain open (fluid drained). Glaucoma = blocked drain. Pilocarpine and latanoprost unblock/widen the drain. Timolol, acetazolamide, and brimonidine turn the tap down. Either way the water level (pressure) falls.

Combination logic (exam favourite): Drugs that work differently are combined — e.g., timolol (less fluid made) + latanoprost (more drained) + pilocarpine (drain opened) attack the pressure from three sides.

3.5 Classification (summary chart)

Skeletal muscle relaxants:

1. Peripheral (NMJ): depolarizing — succinylcholine | non-depolarizing — tubocurarine, pancuronium, vecuronium, atracurium, rocuronium
2. Centrally acting: baclofen (GABA-B), diazepam (GABA-A), tizanidine (α2 spinal), cyclobenzaprine, methocarbamol
3. Directly acting on muscle: dantrolene (blocks muscle calcium release)

Myasthenia gravis: pyridostigmine (maintenance), neostigmine, edrophonium (Tensilon test — diagnosis + crisis distinction)

Glaucoma:

- Increase drainage: pilocarpine (M3 — opens drain), latanoprost (prostaglandin — alternate drain)
- Decrease fluid production: timolol (β blocker), acetazolamide (Diamox — carbonic anhydrase inhibitor), brimonidine/apraclonidine (α2 agonists)

3.6 Mechanisms (one-line each)

- Succinylcholine → stimulates Nm then keeps it ON → muscle cannot reset → limp paralysis.
- Tubocurarine/pancuronium/vecuronium/atracurium/rocuronium → occupy Nm without stimulating → ACh blocked → no contraction order.
- Neostigmine reverses non-depolarizing block by piling up ACh (with atropine/glycopyrrolate cover).
- Baclofen → GABA-B in spinal cord → less stiffness. Diazepam → GABA-A boost → less spasm. Tizanidine → spinal α2 → less spasticity.
- Dantrolene → blocks calcium release inside muscle → muscle cannot contract.
- Pyridostigmine/neostigmine → block AChE → more ACh for the few surviving receptors in myasthenia.
- Edrophonium → same, for minutes → diagnostic test.
- Pilocarpine → M3 → drainage muscle contracts → drain opens. Timolol → β block → less fluid made. Latanoprost → alternate drain opened. Acetazolamide → enzyme blocked → less fluid made. Brimonidine/apraclonidine → α2 → less made + more drained.

3.7 Diagrams (to be drawn by the student)

1. **The NMJ battle:** Draw the nerve ending, gap, and muscle with Nm locks. Show ACh keys opening locks (normal). Then show succinylcholine as a key stuck in the ON position; show vecuronium as broken keys jamming the locks.
2. **Three levels of relaxation:** Draw a stick figure: circle the brain/spinal cord (central drugs), the nerve-muscle junction (peripheral blockers), and the muscle fibre (dantrolene).
3. **The eye in glaucoma:** Draw the eyeball cross-section: label the fluid-making tissue (ciliary body, "tap") and the drainage channel (trabecular meshwork, "drain"). Draw arrows: pilocarpine/latanoprost widening the drain; timolol/acetazolamide/brimonidine turning down the tap.
4. **Myasthenia gravis:** Draw two NMJs side by side — normal (many Nm locks, strong contraction) vs myasthenia (few locks, weak contraction); then show pyridostigmine piling up extra ACh keys so the few locks get used repeatedly.

3.8 Flowcharts

Flowchart 1 — Choosing a muscle relaxant:

```
Need relaxation FOR SURGERY (patient asleep, ventilated)?
   → Need it in 1 minute, for minutes → succinylcholine
   → Need it for the whole operation → vecuronium / atracurium / rocuronium / pancuronium
   → After surgery → reverse with neostigmine + atropine
Patient AWAKE with painful spasm (back pain)?
   → Diazepam / cyclobenzaprine / methocarbamol (short-term) + warn about drowsiness
Patient with LONG-TERM stiffness (stroke, MS, spinal injury)?
   → Baclofen / tizanidine (spasticity) ± dantrolene
Emergency: body overheating under anaesthesia?
   → DANTROLENE immediately (malignant hyperthermia)
```

Flowchart 2 — Glaucoma drug selection logic:

```
High eye pressure — lower it:
   → Open the main drain → pilocarpine (M3)
   → Open the alternate drain → latanoprost (once daily)
   → Turn down the tap → timolol (drops) / acetazolamide (tablets, short-term) / brimonidine (α2)
   → Still high? → COMBINE (different mechanisms) → laser / surgery
```

Flowchart 3 — Myasthenia gravis management:

```
Weak, tiring muscles + drooping eyelids
        ↓
Tensilon (edrophonium) test → improves? → YES = myasthenia gravis
        ↓
Daily pyridostigmine (Mestinon) — titrate dose
        ↓
Severe / crisis → hospital: ventilation, plasma exchange, immunosuppressants, thymectomy option
```

3.9 Infographic Concept Box

MUSCLE, WEAKNESS & EYE PRESSURE — "Three Locks, Three Keys"

- 💪 **TOO TIGHT (need relaxation):** Surgery → NMJ blockers (succinylcholine = quick; vecuronium/atracurium = for the operation; reverse with neostigmine). Awake spasm → central calm-downs (baclofen, diazepam, tizanidine). Overheating emergency → dantrolene.
- 🔋 **TOO WEAK (myasthenia gravis):** Immune system ate the muscle's ACh locks → pile up more keys with pyridostigmine (Mestinon). Test with edrophonium (Tensilon): better = disease crisis, worse = drug overdose.
- 👁️ **TOO MUCH PRESSURE (glaucoma):** Sink overflowing → open the drain (pilocarpine, latanoprost) or turn down the tap (timolol, acetazolamide/Diamox, brimonidine).
- ⚠️ **NEVER-FORGET:** succinylcholine + malignant hyperthermia → dantrolene | latanoprost → iris darkens permanently | timolol drops → can slow heart/worsen asthma | baclofen → never stop suddenly.

3.10 Tables

Table 3.1 — Neuromuscular blockers: compare

Drug	Type	Onset/Duration	Special point
Succinylcholine	Depolarizing	~1 min / minutes	Fastest; malignant hyperthermia risk; can't reverse with neostigmine
Tubocurarine	Non-depolarizing	Slow / long	Original curare; histamine release (low BP)
Pancuronium	Non-depolarizing	Slow / long	Slight heart-rate rise
Vecuronium	Non-depolarizing	2–3 min / intermediate	Minimal heart effects; widely used
Atracurium	Non-depolarizing	2–3 min / intermediate	Broken down in blood itself — safe in kidney/liver failure
Rocuronium	Non-depolarizing	Fastest of this group	Rapid intubation when succinylcholine unsuitable

Table 3.2 — Centrally acting relaxants

Drug	Main use	Key caution
Baclofen (Lioresal)	Spasticity (MS, spinal injury)	Don't stop suddenly (withdrawal seizures)
Diazepam (Valium)	Acute spasm, spasticity	Drowsiness, dependence
Tizanidine	Spasticity (MS, stroke)	Dry mouth, low BP, liver monitoring
Cyclobenzaprine	Short-term acute spasm	Drowsiness, dry mouth
Methocarbamol	Acute spasm with pain	Drowsiness; harmless brownish-green urine

Table 3.3 — Glaucoma drugs: how they lower pressure

Drug	Mechanism	Key adverse effect
Pilocarpine	M3 → opens main drain	Small pupil, dim night vision, brow ache
Timolol	β block → less fluid made	Slow heart, asthma worsening (systemic absorption)
Latanoprost (Xalatan)	Prostaglandin → opens alternate drain	Permanent iris darkening, eye redness
Acetazolamide (Diamox)	Carbonic anhydrase inhibitor → less fluid made	Tingling, frequent urination, kidney stones
Brimonidine / apraclonidine	α2 → less made + more drained	Dry mouth, drowsiness, eye allergy

3.11 Examples

- **Example 1:** Before abdominal surgery, the anaesthetist gives vecuronium — the abdominal wall goes completely limp for the operation; at the end, neostigmine + glycopyrrolate reverse it and the patient breathes on their own.
- **Example 2:** A young woman's eyelids droop by evening and her speech slurs after talking — Tensilon test positive → myasthenia gravis; daily pyridostigmine (Mestinon) keeps her muscles working.
- **Example 3:** During surgery a patient's temperature suddenly shoots to 41°C with rigid muscles after succinylcholine — malignant hyperthermia; dantrolene is given immediately and saves his life.
- **Example 4:** A 60-year-old with glaucoma uses latanoprost drops every night — eye pressure falls; he is warned his brown eyes may darken permanently.
- **Example 5:** A stroke patient with a stiff, bent arm takes baclofen — the arm loosens enough for physiotherapy; he is told never to stop the tablets suddenly.
- **Example 6:** A kidney-failure patient needs muscle relaxation for surgery — the anaesthetist chooses atracurium because it breaks down in the blood itself, not via kidney or liver.

3.12 Analogies

1. **Doorbell held down (succinylcholine):** Rings once, then no new rings can register — muscle stuck ON, then limp.
2. **Broken key in the lock (non-depolarizing blockers):** Real key can't enter; door never opens.
3. **Factory shutdown levels:** Cut the phone line (NMJ) / calm the manager (central) / switch off the machines (dantrolene).
4. **Few letterboxes (myasthenia):** Postman brings extra letters (pyridostigmine piles up ACh) so the few remaining letterboxes get used again and again.
5. **Overflowing sink (glaucoma):** Widen the drain (pilocarpine, latanoprost) or turn down the tap (timolol, acetazolamide, brimonidine).
6. **Tensilon test as a taste test:** One spoon (edrophonium) tells the cook instantly whether the dish needs more salt (myasthenic crisis) or already has too much (cholinergic crisis).

3.13 Pharmacy Relevance

- **Neuromuscular blockers are hospital-only, anaesthetist-controlled drugs** — the pharmacist's role is safe storage, correct labelling, and keeping **dantrolene stocked** in every operation theatre for malignant hyperthermia.
- For myasthenia gravis, the pharmacist ensures **uninterrupted pyridostigmine supply** — a missed dose can precipitate crisis — and counsels on dose timing with meals and activity.
- Glaucoma drops are **lifelong therapy** — counsel on technique (one drop, close eye, press the tear duct corner for a minute to reduce systemic absorption of timolol), never stopping without the doctor, and keeping follow-up eye-pressure checks.
- Warn latanoprost users about permanent iris darkening and timolol users (especially asthmatics) to report breathlessness or unusual slowness of pulse.
- Central relaxants + alcohol/sleeping pills = dangerous drowsiness — screen for combinations.

3.14 India Context

- **Neostigmine, pyridostigmine, and atropine** are on India's NLEM and available as Jan Aushadhi generics — myasthenia gravis treatment is affordable long-term.
- **Timolol eye drops and acetazolamide (Diamox)** are among the most commonly dispensed glaucoma medicines in Indian pharmacies; **latanoprost (Xalatan)** generics have made once-daily therapy affordable.
- **Diazepam (Valium) and baclofen (Lioresal)** are widely prescribed for spasm/spasticity in Indian orthopaedic and neurology OPDs.
- Dantrolene availability in operation theatres is a **patient-safety checkpoint** Indian hospital pharmacists are expected to maintain.
- Organophosphate/malignant-hyperthermia-type emergencies remind us: the pharmacist must know which antidote sits where in the hospital.

3.15 Key Points

1. Muscle relaxants act at three levels: NMJ (peripheral), brain/spinal cord (central), inside the muscle (dantrolene).
2. Succinylcholine = depolarizing (twitch then limp; can't reverse with neostigmine; malignant hyperthermia risk → dantrolene).
3. Non-depolarizing blockers (tubocurarine, pancuronium, vecuronium, atracurium, rocuronium) = competitive Nm block, no twitch, reversible with neostigmine + atropine/glycopyrrolate.
4. Atracurium breaks down in blood itself — choice in kidney/liver failure.
5. Central relaxants: baclofen (GABA-B, spasticity — don't stop suddenly), diazepam, tizanidine (α2), cyclobenzaprine, methocarbamol — all cause drowsiness.
6. Dantrolene blocks muscle calcium release — antidote for malignant hyperthermia.
7. Myasthenia gravis = immune destruction of Nm receptors → treat with pyridostigmine (Mestinon); diagnose and sort crises with the edrophonium (Tensilon) test.
8. Glaucoma = high eye pressure → open the drain (pilocarpine, latanoprost) or reduce fluid (timolol, acetazolamide/Diamox, brimonidine/apraclonidine).
9. Latanoprost: once daily, permanent iris darkening. Timolol drops: can slow heart/worsen asthma.

3.16 Common Confusions

- **Depolarizing vs non-depolarizing:** depolarizing STIMULATES first (twitch, then block); non-depolarizing never stimulates (silent block). Students often reverse this.
- **Neostigmine reverses non-depolarizing block but WORSENS succinylcholine block** — a favourite trap.
- **Myasthenic crisis vs cholinergic crisis:** both = weakness; Tensilon test tells them apart (better = myasthenic, worse = cholinergic).
- **Baclofen vs dantrolene:** baclofen works in the spinal cord (GABA-B); dantrolene works inside the muscle (calcium) — different levels, different emergencies.
- **Pilocarpine vs timolol in glaucoma:** pilocarpine OPENS the drain (miosis); timolol REDUCES fluid making (no pupil change).
- **Atracurium's special breakdown** (in blood itself) vs others needing kidney/liver — why it is chosen in organ failure.

3.17 Common Mistakes

1. Saying succinylcholine can be reversed with neostigmine — it cannot (it worsens the block).
2. Forgetting that neuromuscular blockers paralyze breathing — ventilation must always be supported.
3. Stopping baclofen suddenly — withdrawal seizures.
4. Missing malignant hyperthermia: rising temperature + rigidity after succinylcholine → dantrolene immediately.
5. Not warning latanoprost patients about permanent iris colour change.
6. Giving timolol drops to an asthmatic without caution — systemic absorption can trigger bronchospasm.
7. Confusing the Tensilon test result: improvement = myasthenic crisis (needs more drug).

3.18 Mnemonics

- **Non-depolarizing blockers — "TV PAR": T**ubocurarine, **V**ecuronium, **P**ancuronium, **A**tracurium, **R**ocuronium.
- **Depolarizing — "SUX twitches": Sux**amethonium (succinylcholine) = **twitch** then limp.
- **Reversal rule — "NEVER SUX": Ne**ostigmine reverses everything **except Sux** (succinylcholine).
- **Central relaxants — "BaDTiCyM": Ba**clofen, **D**iazepam, **Ti**zanidine, **Cy**clobenzaprine, **M**ethocarbamol.
- **Glaucoma — "PLAT AB" (drain vs tap): P**ilocarpine + **L**atanoprost open the drain (**A**queous out); **T**imolol, **A**cetazolamide, **B**rimonidine turn down the tap.
- **Tensilon test — "Better = gravis winning":** improves → **myasthenic** crisis (give more); worsens → **cholinergic** crisis (give less).
- **Malignant hyperthermia — "Hot SUX, cool DAN": Sux** causes the heat, **Dan**trolene cools it.

3.19 Exam Summary

- Classify skeletal muscle relaxants with examples at each level.
- Compare depolarizing vs non-depolarizing blockers (table 3.1 + section 3.4.2 table) — mechanism, fasciculations, reversal, malignant hyperthermia.
- Write notes on: succinylcholine; vecuronium; atracurium (why in kidney failure); baclofen; dantrolene.
- Explain myasthenia gravis pathophysiology and the roles of pyridostigmine, neostigmine, edrophonium; explain the Tensilon test and the two crises.
- Classify glaucoma drugs by mechanism (drain-openers vs tap-closers); describe pilocarpine, timolol, latanoprost, acetazolamide, brimonidine — one mechanism line + one key adverse effect each.

3.20 One-Minute Revision

Relax muscles at 3 levels: NMJ (succinylcholine — twitch-then-limp, can't reverse, malignant hyperthermia → dantrolene; non-depolarizing TV PAR — silent block, reversed by neostigmine + atropine; atracurium self-destructs in blood), brain/cord (BaDTiCyM — baclofen GABA-B, diazepam, tizanidine α2, cyclobenzaprine, methocarbamol; all cause drowsiness; never stop baclofen suddenly), inside muscle (dantrolene blocks calcium — malignant hyperthermia antidote). Myasthenia gravis = immune system eats Nm receptors → pyridostigmine piles up ACh; Tensilon (edrophonium) test: better = myasthenic crisis, worse = cholinergic crisis. Glaucoma = high eye pressure: open the drain (pilocarpine — miosis; latanoprost — once daily, darkens iris) or turn down the tap (timolol — watch heart/asthma; acetazolamide/Diamox — tingling; brimonidine α2).

3.21 Exam Questions

Short-answer questions:

1. Classify skeletal muscle relaxants with one example each.
2. Differentiate depolarizing and non-depolarizing neuromuscular blockers (any four points).
3. Why can't neostigmine reverse succinylcholine block?
4. Why is atracurium preferred in kidney failure?
5. What is malignant hyperthermia? How is it treated?
6. List three centrally acting muscle relaxants with one use each.
7. Explain the mechanism of dantrolene.
8. What is myasthenia gravis? Which drugs are used in it?
9. Explain the Tensilon test and its interpretation.
10. Classify glaucoma drugs based on how they lower eye pressure.
11. How does latanoprost lower eye pressure? Mention one unique adverse effect.
12. Why is timolol used cautiously in asthmatics?

Long-answer questions:

1. Classify skeletal muscle relaxants. Describe the mechanism, uses, and adverse effects of succinylcholine and compare it with non-depolarizing blockers.
2. Discuss centrally acting muscle relaxants and dantrolene: mechanisms, uses, and adverse effects.
3. Describe the pathophysiology of myasthenia gravis. Explain the role of neostigmine, pyridostigmine, and edrophonium, including the Tensilon test and the two crises.
4. Define glaucoma. Classify the drugs used in glaucoma, explaining the mechanism and adverse effects of pilocarpine, timolol, latanoprost, acetazolamide, and brimonidine.

MCQs (with answer key):

1. Which is a depolarizing neuromuscular blocker? (a) vecuronium (b) succinylcholine ✓ (c) pancuronium (d) atracurium — **Answer: (b)**
2. Fasciculations are seen at the start of block with: (a) tubocurarine (b) rocuronium (c) succinylcholine ✓ (d) vecuronium — **Answer: (c)**
3. Neostigmine can reverse the block of: (a) succinylcholine (b) vecuronium ✓ (c) both (d) neither — **Answer: (b)**
4. Atracurium is preferred in kidney failure because it: (a) is excreted faster by the kidney (b) breaks down spontaneously in blood ✓ (c) is more potent (d) has no side effects — **Answer: (b)**
5. Drug of choice for malignant hyperthermia: (a) neostigmine (b) dantrolene ✓ (c) baclofen (d) diazepam — **Answer: (b)**
6. Baclofen acts on: (a) GABA-A (b) GABA-B ✓ (c) α2 (d) Nm — **Answer: (b)**
7. Which central relaxant must not be stopped suddenly? (a) methocarbamol (b) baclofen ✓ (c) cyclobenzaprine (d) tizanidine — **Answer: (b)**
8. Dantrolene acts by: (a) blocking Nm receptors (b) blocking calcium release inside muscle ✓ (c) boosting GABA (d) blocking AChE — **Answer: (b)**
9. The Tensilon test uses: (a) neostigmine (b) edrophonium ✓ (c) pyridostigmine (d) physostigmine — **Answer: (b)**
10. If weakness WORSENS after edrophonium, it is: (a) myasthenic crisis (b) cholinergic crisis ✓ (c) cure (d) normal response — **Answer: (b)**
11. Pilocarpine lowers eye pressure by: (a) reducing fluid production (b) opening the drainage channel ✓ (c) blocking beta receptors (d) shrinking the eyeball — **Answer: (b)**
12. A unique adverse effect of latanoprost is: (a) dry mouth (b) permanent iris darkening ✓ (c) slow heart (d) diarrhoea — **Answer: (b)**
13. Timolol eye drops lower eye pressure by: (a) opening the drain (b) reducing aqueous humor production ✓ (c) constricting the pupil (d) dilating vessels — **Answer: (b)**
14. Acetazolamide (Diamox) belongs to which class? (a) beta blocker (b) carbonic anhydrase inhibitor ✓ (c) prostaglandin analogue (d) alpha-2 agonist — **Answer: (b)**

Viva questions:

1. Name one depolarizing and two non-depolarizing muscle relaxants.
2. Which muscle relaxant causes initial twitching?
3. How is a non-depolarizing block reversed after surgery?
4. Which relaxant is safe in kidney failure and why?
5. What is the antidote for malignant hyperthermia?
6. Name two centrally acting muscle relaxants.
7. Why should baclofen not be stopped suddenly?
8. What is destroyed in myasthenia gravis — the nerve, ACh, or the receptor?
9. Which drug is used for the Tensilon test?
10. Better after Tensilon = which crisis?
11. Name two drugs that open the eye's drain and two that reduce fluid making.
12. Why does latanoprost darken the iris?

Application-based questions:

1. After surgery, a patient cannot breathe on their own 30 minutes after vecuronium. What should the anaesthetist do and why? (Give neostigmine + atropine/glycopyrrolate to reverse the non-depolarizing block; support ventilation meanwhile.)
2. A myasthenia gravis patient on high-dose pyridostigmine develops severe weakness with heavy salivation and diarrhoea. Which crisis is this, and how would you confirm? (Cholinergic crisis — overdose; edrophonium would worsen weakness; stop drug, give atropine, hospital care.)
3. A glaucoma patient on timolol drops develops wheezing. Explain and suggest the next step. (Systemic absorption of timolol → bronchospasm; stop drops, inform doctor — switch to a non-beta-blocker option like latanoprost.)
4. A patient given succinylcholine develops a temperature of 41°C and rigid muscles. What is happening and what is the immediate treatment? (Malignant hyperthermia; dantrolene immediately + cooling + supportive care.)

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