Drugs affecting the ANS:

1. The cholinergic drugs stimulating or blocking receptors that are activated by Ach.
2. The adrenergic drugs stimulating or blocking receptors that are stimulated by norepinephrine or epinephrine.

Drugs acting on the parasympathetic nervous system:

The cholinergic neuron:

ACh is the neurotransmitter in the preganglionic fibers terminating in the adrenal medulla, autonomic ganglia (both parasympathetic and sympathetic), postganglionic fibers of the parasympathetic division, postganglionic sympathetic division of sweat glands, cholinergic neurons innervate the muscles of the somatic system and also ACh plays an important role in the CNS.

Note: Patients with Alzheimer disease have a significant loss of cholinergic neurons. Acetylcholinesterase (AChE) inhibitors are used to treat this disease.

Neurotransmission at cholinergic neurons:

Neurotransmission in cholinergic neurons involves sequential steps:

Synthesis & storage of Ach:

- Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron (choline uptake is the rate-limiting step in ACh synthesis).
- Choline cannot diffuse through the membrane & it dose so by using an energy-dependent carrier system that cotransports sodium and can be inhibited by the drug **hemicholinium**.
- Choline interacts with acetyl coenzyme A (CoA) to form Ach.
- ACh is stored in the presynaptic vesicles

Release & binding of Ach to the receptor:

- When an action potential arrives at a nerve ending, an increase in the concentration of intracellular calcium occurs which promote the fusion of synaptic vesicles with the cell membrane and the release of Ach into the synaptic space.

Note:

Botulinum toxin can block the release of Ach, while **venom of black widow spider** causes the release of all stored Ach into the synaptic gap.

- The released ACh binds to either postsynaptic (muscarinic & nicotinic) or presynaptic receptors.
- Binding to a receptor leads to a biologic response.

Degradation of Ach & recycling of choline:

- ACh rapidly cleaves to choline and acetate by AChE found in the synaptic cleft terminating its effect.

Note: Pseudocholinesterase is found in the plasma but does not play a significant role in the termination of ACh's effect in the synapse.

- Choline may be recaptured & back into the neuron. There, it is acetylated into ACh that is stored until released by a subsequent action potential.

Cholinergic receptors (cholinoceptors):
Two families of cholinoceptors, muscarinic and nicotinic receptors are distinguished.

A. Muscarinic receptors:

- G protein–coupled receptors.
- Binds to Ach & muscarine (an alkaloid that is present in certain poisonous mushrooms), but they show only a weak affinity for nicotine.
- There are 5 subclasses of muscarinic receptors: M1, M2, M3, M4, & M5, only M1, M2 & M3 receptors have been functionally characterized.

Locations of muscarinic receptors: These receptors have been found on:

- Ganglia of the peripheral nervous system.
- Autonomic effector organs, such as the heart, smooth muscle, brain & exocrine glands.
- All the five subtypes have been found on neurons.
- Also M1 receptors are found on gastric parietal cells, M2 receptors on cardiac cells and smooth muscle & M3 receptors on the bladder, exocrine glands & smooth muscle.

Note: Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues, but at high concentration they may show some activity at nicotinic receptors.

Mechanisms of Ach signal transduction:

- The activated M1 or M3 receptors undergoes a conformational change & interacts with a G protein → activates phospholipase C → hydrolysis of IP2 → DAG & IP3.
- IP3 → ↑ intracellular Ca^{2+} → interact to stimulate or inhibit enzymes or to cause hyperpolarization, secretion, or contraction.
- DAG → activates protein kinase C→ phosphorylates numerous proteins within the cell.

M2 activation → stimulates a Gi protein → inhibits adenylyl cyclase & ↑ K^{+} conductance → ↓ HR & force of contraction.

Muscarinic agonists & antagonists:

- Muscarinic agonists & antagonists against specific subtypes receptor have been developed, they do not cause many of the side effects seen with the non-subtype-specific drugs.
- eg, **pirenzepine**, is an antimuscarinic with a greater affinity for the M1 receptors, such as in the gastric mucosa.
- However, **pirenzepine** rapid infusion produces a reflex tachycardia due to blockade of M2 receptors in the heart. Therefore, it's usefulness in the treatment of P.U is questionable.

- **Darifenacin,** is an antimuscarinic with a greater affinity for the M3 receptor it is used in the treatment of overactive bladder.

B. <u>Nicotinic receptors</u>:
- Recognize Ach & nicotine but show only a weak affinity for muscarine.
- Ligand-gated ion channel.
- Binding of two ACh molecules elicits a conformational change that allows the entry of Na^+ ions resulting in the depolarization of the effector cell.
- Nicotine at low concentration stimulates nicotinic receptor, while at high concentration it blocks this receptor.
- Located in the CNS, adrenal medulla, autonomic ganglia & NMJ.

Note:
Hexamethonium selectively blocks ganglionic nicotinic receptors, whereas **tubocurarine** selectively blocks nicotinic receptors at the NMJ

<u>Direct –acting cholinergic agonists (parasympathomimetics</u>):
- Mimic ACh effects by binding directly to cholinoceptors.
- Have longer durations of action than ACh.
- Classified into two groups:
  1. Choline esters: Ach & synthetic esters of choline, such as **carbachol** & **bethanechol**.
  2. Naturally occurring alkaloids, such as **pilocarpine**.

Notes:
1. **Pilocarpine** & **bethanechol** preferentially bind to muscarinic receptors (sometimes referred to as muscarinic agents).
2. Direct-acting agonists show little specificity in their actions, thus their clinical usefulness is limited.

<u>Acetylcholine</u>:
- Quaternary ammonium compound that cannot penetrate membranes.
- Has no therapeutic importance due to multiplicity of actions & rapid inactivation by the AchE.
- ACh has both muscarinic & nicotinic activity.

Ach actions:

1. Decrease HR & COP:

ACh act as vagomimic, eg. Ach IV injection produces a brief decrease cardiac rate (negative chronotropy) & stroke volume as a result of a reduction in the rate of firing at the SA node.

Note: The normal vagal activity regulates the heart by releasing ACh at the SA node.

2. Decrease BP:
- Injection of ACh causes vasodilation & lowering of Bp by an indirect mechanism of action.

- ACh activates M3 receptors found on endothelial cells of blood vessels, results in the production of NO, which in turn stimulates production of protein kinase G → hyperpolarization & smooth muscle relaxation.

Other actions:

- GIT, Ach increases salivary secretion & stimulates intestinal secretions & motility. It also enhances bronchiolar secretions & bronchcostriction.
- Genitourinary tract, ACh increases the tone of the detrusor muscle, while relaxes the trigone & sphincter result in expulsion of urine.
- Eye, ACh causes miosis (duo to pupillae sphincter muscle constriction) & near vision (duo to ciliary muscle contraction).
- ACh (1% solution) is used to produce miosis during ophthalmic surgery.