UNIT-III

Cholinergic and Anticholinergic Drug

The nervous system is divided into the somatic nervous system, which controls organs under voluntary control (mainly muscles) and the autonomic nervous system (ANS) which regulates individual organ function and homeostasis, and for the most part is not subject to voluntary control. The autonomic nervous system is also known as the visceral or automatic system. The ANS is predominantly an efferent system transmitting impulses from the central nervous system (CNS) to peripheral organ systems. The autonomic nervous system consists of sensory neurons and motor neurons that innervates between the central nervous system (especially the hypothalamus and medulla oblongata) and various internal organs such as the heart, lungs, viscera, glands (both exocrine and endocrine). Thus it is responsible for monitoring conditions in the internal environment and bringing about appropriate changes in them. The ANS is divided into two separate divisions called the parasympathetic and sympathetic systems, on the basis of anatomical and functional differences. Both of these systems consist of myelinated preganglionic fibres which make synaptic connections with unmyelinated postganglionic fibres, and it is these which then innervate the effector organ. These synapses usually occur in clusters called ganglia. The main nerves of the parasympathetic system are the tenth cranial nerve, the vagus nerve, which originate in the medulla oblongata. Other preganglionic parasympathetic neurons also extend from the brain as well as from the lower tip of the spinal cord. Each preganglionic parasympathetic neuron synapses with just a few postganglionic neurons, which are located near or in the effector organ, a muscle or major gland. Acetylcholine (ACh) is the neurotransmitter of all the pre and many of the postganglionic neurons of the parasympathetic system. Parasympathetic stimulation causes slowing down of
the heart beat, lowering of blood pressure, constriction of the pupils, increased blood flow to the skin and viscera, peristalsis of the GI tract

**Biosynthesis and catabolism of acetylcholine:** The chemical transmitter at both pre and postganglionic synapses in the parasympathetic system is acetylcholine (Ach). Ach is also the neurotransmitter at sympathetic preganglionic synapses, some sympathetic postganglionic synapses, the neuromuscular junction (somatic nervous system), and at some sites in the CNS. Acetylcholine is the most widespread autonomic transmitter present in the body.

(a) Synthesis of acetylcholine (ACH). It was first synthesized by Bayer in 1867. Acetylcholine virtually has no therapeutic effect because of its differences of action and susceptibility to hydrolysis by acetylcholinesterase and plasma butyrylcholinesterase. The synthesis of acetylcholine involves the reaction of choline with active acetyl (CoA). The active acetyl CoA being formed by the combination of acetate with Coenzyme A (CoA). The reaction between acetyl Coenzyme A and choline is catalyzed by the enzyme cholineacetylase. There is considerable evidence that the enzyme cholineacetylase is synthesized within the neuronal perikaryon, then transferred along the axon to its terminals where the formation of acetylcholine is believed to occur.
Metabolism

Storage and release of ACh. ACh is stored in synaptic vesicles, which is released as discrete “Quanta” in response to depolarization of the nerve terminal and an increased influx of Ca++. When a nerve impulse occurs, depolarization of nerve terminal causes influx of Ca++, which facilitates the fusion of the axonal and vesicular storage membranes, and release formed acetylcholine into the synaptic cleft by exocytosis. The released acetylcholine combines with the receptors at target organ, remains bound for less than a millisecond and is quickly hydrolysed by acetylcholinesterase enzyme into choline and acetate.
Cholinergic receptors (Muscarinic & Nicotinic) and their distribution

Acetylcholine Receptors. There are number of different ACh receptors throughout the body. Acetylcholine acts on two different classes of receptors-nicotinic receptors and muscarinic receptors (widely distributed within both peripheral and central nervous systems).

Nicotinic Receptors. Nicotinic receptors are selectively activated by nicotine and blocked by tubocurarine or hexamethonium. These are rosette like pentameric structures which enclose a ligand gated cation channel, their activation causes opening of the channel and rapid flow of cations resulting in depolarization and generation of action potential. On the basis of location and selectivity. They are divided into two types;

N1 : These are present at skeletal muscle endplate and mediate skeletal muscle contractions. They are selectively stimulated by phenyltrimethyl ammonium and are blocked by tubocurarine.

N2 : These are present in ganglionic cells, adrenal medullary cells, in spinal cord and in certain areas of brain. They are primarily stimulated by dimethylphenylpiperazine and blocked by hexamethonium.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Membrane Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle (N_m)</td>
<td>Skeletal neuromuscular junction (post-junctional)</td>
<td>Excitatory; end plate depolarization; contraction (skeletal muscle)</td>
</tr>
<tr>
<td>(α_1)_2β_1δ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(α_1)_2β_1γδ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuronal (N_p)</td>
<td>Autonomic ganglia; adrenal medulla</td>
<td>Excitatory; depolarization firing of postganglionic neuron; depolarization &amp; secretion of catecholamines</td>
</tr>
<tr>
<td>(α_3)_2β_4_3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central neuronal (CNS)</td>
<td>CNS; pre- &amp; postjunctional</td>
<td>Pre- &amp; postsynaptic excitation; prejunctional control of transmitter release</td>
</tr>
<tr>
<td>(α_2) (α-bungarotoxin insensitive)</td>
<td></td>
<td></td>
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<tr>
<td>(α_3) (α-bungarotoxin sensitive)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS; pre- and postsynaptic</td>
<td>Same as central neuronal</td>
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</table>
Muscarinic Receptors. Although five muscarinic receptors have been identified, helpfully labelled M1 to M5, only three are well-characterised. The prototype agonist for these receptors is muscarine, derived from the poisonous fly agaric, Amanita muscaria.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Tissue location</th>
<th>Function</th>
</tr>
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</table>
| M1       | CNS, gastric and salivary glands, autonomic ganglia, enteric nerves               | ↑ Cognitive function  
         |                                                                                  | ↑ Seizure activity, ↑ Secretions  
         |                                                                                  | ↑ Autonomic ganglia depolarization  
         |                                                                                  | ↓ DA release and locomotion         |
| M2       | Autonomic nerve terminals; CNS; heart; smooth muscle                              | ↑ Smooth muscle contraction  
         |                                                                                  | Neural inhibition in periphery via autoreceptors and heteroreceptor  
         |                                                                                  | ↓ Ganglionic transmission  
         |                                                                                  | Neural inhibition in CNS, ↓ Heart rate  
         |                                                                                  | ↑ Tremors hypothermia & analgesia   |
| M3       | CNS (< other mACHRs), smooth muscle, glands, heart                               | ↑ Smooth muscle contraction (e.g., bladder)  
         |                                                                                  | ↑ Salivary gland secretion  
         |                                                                                  | ↑ Food intake, body fat deposits  
         |                                                                                  | Inhibits dopamine release  
         |                                                                                  | Synthesis of nitric oxide           |
| M4       | CNS                                                                              | Inhibition of autoreceptor- and heteroreceptor-mediated transmitter release in CNS, Analgesia, Cataleptic activity;  
         |                                                                                  | Facilitates dopamine release       |
| M5       | Low levels in CNS & periphery; predominate mACHRs in dopaminergic neurons of substantia nigra & ventral tegmentum area | Mediates dilation of cerebral arteries  
         |                                                                                  |Facilitates dopamine release       
         |                                                                                  |Augments drug seeking behavior and reward |

M1 receptors are mainly found in the nervous system. They mediate excitatory effects, lowering transmembrane potential by a decrease in K+ ion conductance; as an added wrinkle, they mediate increased gastric acid secretion seen with vagal stimulation. M1 receptors work via phospholipase C, increasing IP3 and DAG levels.

M2 receptors mediate the cardiac effects of vagal stimulation. They are inhibitory (hyperpolarizing membranes by increasing potassium conductance).

M2 receptors are found presynaptically in a variety of situations. This fits on cardiac cells and smooth muscle. M2 receptors lower intracellular cAMP levels.
M3 receptors are responsible for all the other effects of parasympathetic stimulation, as they are the cholinergic excitatory receptors found on glands and smooth muscle. M3 receptors are similar to M1 in their use of phospholipase C. Physiology is however never simple, vascular smooth muscle relaxes in some situations due to M3 receptor stimulation. This relaxation is mediated by endothelial release of nitric oxide (NO), and occurs in some vascular beds that appear devoid of parasympathetic innervation.

M4 are similar to M2. M5 receptors seem similar to M1 and M3 in their effects.

CHOLINOMIMETIC (PARASYMPATHOMIMETIC) DRUGS

The cholinomimetic or parasympathomimetic or cholinergic drugs are those which cause a muscarinic action on the receptors of the effector organs provided by the post-ganglionic cholinergic nerves. Invariably, these drugs exert their action in two different ways, namely: direct action, whereby they act on the cholinoceptive receptors like acetylcholine; indirect action, by rendering the cholinesterase enzymes inactive and preserving endogenously secreted acetylcholine, e.g., anticholinesterase drugs like physostigmine (naturally occurring neostigmine and pyridostigmine (synthetic).

SAR OF CHOLINERGIC DRUGS
1. Substitutions at \(\alpha\)-carbon with respect to ester group

1. May be a hydrogen atom, a hydroxyl group, a hydroxymethyl group, or a carboxamide
2. Hydroxyl group or a hydroxymethyl group, the antagonist usually is more potent

\(R_2\) and \(R_3\) should be carbocyclic or heterocyclic rings (phenyl, cyclohexyl, cyclopentyl) for maximal antagonist potency

Substitution of naphthalene rings at \(R_2\) and \(R_3\) affords inactive compounds, because of steric hindrance at the muscarinic receptor.

Bigger \(R_2\) and \(R_3\) groups bind to the hydrophobic region outside the Ach receptor site

The hydroxyl group at \(R_1\) presumably increases binding strength by participating in a hydrogen bond interaction at the receptor.

2. Changes at ester group

This substituent may also be an ether oxygen, or it may be absent completely.

Ester group provides most potent anticholinergic activity
3. Substitution at the amine group

Compounds possessing the quaternary ammonium group exhibit nicotinic antagonist activity at high doses.

Quaternary ammonium compounds possess most potent anticholinergic activity

Methyl, ethyl, propyl, or isopropyl groups are tolerated

Tertiary amines also possess antagonist activity, presumably by binding to the receptor in the protonated form.

Quaternary ammonium drugs are primarily used in the treatment of ulcers or other conditions for which a reduction in gastric secretions and reduced motility of the gastrointestinal tract are desired

4. Changes at R4 position

Optimum chain length is 2-4 carbons. Two carbon chain possess the most antagonistic activity.
Classification:-

Cholinomimetic drugs may be broadly classified under the following two categories.

1. Direct acting agents:
   b. Natural alkaloids: Pilocarpine.

2. Indirect acting/ Cholinesterase inhibitors
   a. Reversible: Physostigmine, Neostigmine*, Tacrine hydrochloride

i. Acetylcholine chloride (Miochol)

![Chemical Structure]

(2-Acetoxyl ethyl)-trimethyl ammonium chloride

Synthesis

Trimethyl amine

2-Chloroethyl acetate

Acetyl choline chloride

Properties and uses: It is a white or almost white crystalline powder or colourless crystals, very hygroscopic in nature, slightly soluble in methylene chloride, soluble in water and alcohol. It is a topical ophthalmic drug to induce miosis, during certain intraocular surgical procedures, such as cataract surgery, iridectomy, penetrating keratoplasty, and other anterior-segment surgery. Systemically administered Ach is rapidly hydrolyzed by acetylcholinesterase, hence, it has no clinical use. It is a cardiac depressant and effective vasodilator.

Storage: It should be stored in well closed ampoules and protected from light. Dose: Topically as a 1% solution.
**Carbachol**

![Chemical structure of Carbachol]

**Synthesis**

**Route 1: From Ethylene chlorohydrin**

\[\text{Ethylene chlorohydrin} + \text{Phosgene} \rightarrow \text{Chloro ethyl chloroformate} \]

\[\text{Chloro ethyl chloroformate} \rightarrow \text{NH}_3 \text{ether} \rightarrow \text{Chloro ethyl urethane} \]

\[\text{Chloro ethyl urethane} \rightarrow \text{Carbachol} \]

**Properties and uses:** It is a white crystalline, hygroscopic powder, soluble in water, sparingly soluble in alcohol, insoluble in acetone. It is an ester of carbamic acid, the terminal methyl group of Ach is replaced by amino group. It possesses both muscarinic and nicotinic properties by cholinergic receptor stimulation. It is more slowly hydrolyzed by acetylcholinesterase. It is used for its miotic actions in the treatment of glaucoma to reduce intraocular pressure.
ii. Bethanechol chloride  (Synonym: Urecholine, Myetonachol, Bethacol, Urotonin)


\[
\text{H}_2\text{N} \text{COO} \text{C} \text{C} \text{N} \text{CH}_3 \text{Cl} \\
\text{CH}_3 \text{H} \text{H} \text{CH}_3 \text{H} \text{H} \text{CH}_3 \text{H}
\]

2-[(Amino carbonyl) oxy] N, N, N trimethyl propan ammonium chloride

**Properties and uses:** It is a white crystalline hygroscopic powder, and it exhibits polymorphism, soluble in water and alcohol. It has pharmacological properties similar to those of methacholine. The presence of −Cl gives prolonged activity due to steric hindrance. It produces smooth muscle contractions. It is not well absorbed from the gastro-intestinal tract. It can be given subcutaneously, but not by intramuscular (IM) or intravenous (IV) because of its severe side effects. It is used to relieve urinary retention and abdominal distention after surgery. This is one of the postvagotomy gastric drug.

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3. Methacholine

**Properties and uses:** It is highly deliquescent, has faint fishy odour, and aqueous solutions are neutral, soluble in water, alcohol, and CHCl₃. It is used to treat Reynaud’s syndrome and glaucoma. Dose: For usual paroxysmal tachycardia, 10 to 25 mg; by S.C. for peripheral vascular disease 10 to 25 mg.
4. Pilocarpine.

Properties and uses: It is a white or almost white crystalline powder or colourless crystals, hygroscopic, very soluble in water and in alcohol. Pilocarpine is an alkaloid obtained from the dried leaflets of Pilocarpus jaborandi and Pilocarpus microphyllus in which it occurs to the extent of about 0.5% together with other alkaloids. Pilocarpine is a nonselective agonist on the muscarinic receptors. It acts on M3 receptors in smooth muscles and cause contractions in the gut, trachea, and eyes. It is used for the treatment of symptoms of dry mouth caused by radiotherapy for cancer of head and neck and the symptoms associated with Sjogren’s syndrome.

Storage: It should be stored in well-closed airtight containers, and protected from light.

Dose: Topically 0.1 ml of 0.5 to 6% solution into the conjunctival sac 1 to 5 times/day. Dosage forms: Pilocarpine hydrochloride eye drops B.P.

2. Reversible & Irreversible:

1. Physostigmine
Properties and uses: It exists as a white or almost white crystalline powder, hygroscopic, very soluble in water, and freely soluble in alcohol. It gradually becomes red when exposed to air and light; the colour develops more quickly when the substance is also exposed to moisture. Aqueous solutions are unstable. It melts at about 145°C with decomposition. It is an alkaloid obtained from the dried ripe seeds of *Physostigma venenosum*. It occurs as a white, odourless, microcrystalline powder, slightly soluble in H2O, freely soluble in alcohol, CHCl3 and fixed oils. Physostigmine is an oldest anticholinesterase agent. It is used in the treatment of glaucoma. It can penetrate the blood brain barrier and is employed to antagonize the toxic CNS effects of antimuscarinic drugs, tricyclic depressants, H1 antihistamines, and benzodiazepines. It is also used in the treatment of Alzheimer’s disease.

Storage: It should be stored in well-closed airtight glass container and protected from light.

2. Neostigmine*

![Chemical structure of neostigmine]

Synthesis
Properties and uses: It exists as white, odourless, crystalline powder with a bitter taste, freely soluble in water, alcohol, and insoluble in ether. Its solutions are neutral to litmus. It acts as a cholinesterase inhibitor.

Storage: It should be stored in well-closed airtight container and protected from light.

Dosage forms: Neostigmine bromide tablets I.P., Neostigmine methyl sulphate injection I.P., Neostigmine tablets B.P.
3. Pyridostigmine

**Properties and uses:** It exists as white, crystalline powder with a characteristic odour and bitter taste, soluble in water, alcohol, chloroform, slightly soluble in hexane, and insoluble in ether. It is hygroscopic in nature. It is used in the treatment of myasthenia gravis and it antagonizes the effects of neuromuscular blocking (NMB) agents.

Storage: It should be stored in well-closed airtight container, protected from light. The sterile substance should be stored in airtight, tamper-proof containers, and protected from light.

Dose: Initially, 60 mg every 4 to 8 h, but 120 to 300 mg 6 times/day is the usual dose.

Dosage forms: Pyridostigmine tablets B.P.

4. Edrophonium chloride
Properties and uses: It exists as a white crystalline powder, soluble in water and alcohol, insoluble in methylene chloride. On parenteral administration, edrophonium has a more rapid onset and shorter duration of action than neostigmine, pyridostigmine, or ambenonium. It is used as an antiarrhythmic drug in paroxymal atrial tachycardia. It is also used in the diagnosis of myasthenia gravis.

Assay: Dissolve the sample in a mixture of equal volumes of acetic anhydride and anhydrous acetic acid. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: By I.V. 2 to 10 mg; usually 2 mg is injected initially and if no adverse reaction takes place within 30 sec, the remaining 8 mg may be injected.

Dosage form: Edrophonium injection B.P.

5. Tacrine hydrochloride

![Tacrine hydrochloride structure](image)

**IUPAC name:** 1,2,3,4-tetrahydro-9-aminoacridine hydrochloride.

- **MOA:** It is a non-classical reversible cholinesterase inhibitor that binds to both acetylcholinesterase and butyryl cholinesterase.

- **Metabolism:** It is metabolized by CYP1A2 to the 2-, 3- & 4-hydroxy metabolites. Major metabolite 4-hydroxytacrine, is most active. Its elimination half-life is between 1.5 and 4 hours, metabolites are excreted via urine.

- **Uses:** It is used in the treatment of Alzheimer disease. It is also used in mild to moderate Alzheimer dementia.
6. Ambenonium chloride

![Chemical structure of Ambenonium chloride]

**Properties and uses:** It exists as a white crystalline powder, soluble in water and alcohol, insoluble in methylene chloride. On parenteral administration, edrophonium has a more rapid onset and shorter duration of action than neostigmine, pyridostigmine, or ambenonium. It is used as an antiarrhythmic drug in paroxymal atrial tachycardia. It is also used in the diagnosis of glaucoma.

7. Isofluorphate

![Chemical structure of Isofluorphate]

8. Echothiaphate iodide

![Chemical structure of Echothiaphate iodide]

**Properties and uses:** It exists as a white crystalline powder, soluble in water and alcohol, insoluble in methylene chloride. On parenteral administration, edrophonium has a more rapid onset and shorter duration of action than neostigmine, pyridostigmine, or ambenonium. It is used as an antiarrhythmic drug in paroxymal atrial tachycardia. It is also used in the diagnosis of glaucoma.
9. Parathione

10. Malathion.

CHOLINESTERASE REACTIVATOR:

Drugs used to reverse the inactivation of cholinesterase caused by organophosphates or sulfonates. They are an important component of therapy in agricultural, industrial, and military poisonings by organophosphates and sulfonates.

1. Pralidoxime chloride.
CHOLINERGIC BLOCKING AGENTS

Cholinergic Blocking agents: Cholinergic antagonists inhibit the actions of endogenous acetyl choline and muscarinic agonists at muscarinic receptor sites in peripheral tissues and in the CNS. These drugs are highly specific reversible competitive antagonists for muscarinic ACh receptors. The pharmacological effects are blockage of parasympathetic stimulation at effector organs. They are rapidly absorbed from the gastrointestinal tract, slowly absorbed when applied locally on eye or skin. The potent anticholinergics are used to control the secretion of saliva and gastric acid, slow down gut motility, and to prevent vomiting. They also have a limited therapeutic use for the treatment of Parkinson’s disease.

SAR of cholinolytic agents

1. Anticholinergic agents are bulky. They combine with muscarinic receptors and shield the binding site from acetylcholine. The general structure of the compounds in this category is

2. Substituent R1 should be carbocyclic or heterocyclic ring for maximal antagonist activity.
3. Substituent R2 should be a hydrogen atom, hydroxy group, hydroxymethyl group, or methyl group.
4. The nature of the group X effects only the duration of action, the physicochemical properties and the side effects of the drug molecule but not its ability to bind with the receptor.
5. There is a limitation for the N-substitution. Optimal potency is associated with 2-3 ethyl groups.
6. The stereochemistry at the benzylic carbon is critical for muscarinic antagonist activity. Any compound that can place the phenyl group in the same absolute configuration as depicted in the general formula above will have potent muscarinic antagonist activity.
7. The phenyl ring cannot tolerate any substituent than F at the p-position without losing its antagonist activity.
8. A negative site for binding of the positive charged N; quaternary amines have formal positive charge while tertiary amines have a positive charged proton.

9. Atropine is a racemic mixture (equal number of d- and l-isomers) and like most chemicals acting on the peripheral nervous system, atropine is stereospecific; l-isomer (l-hyoscyamine) is 250 times more active than the d-isomer.
10. The presence of an N-methyl group on atropine or scopolamine changes the activity of the ligand, possibly by preventing a close interaction between the ligand and the membrane or lipophilic sites on the receptor. The methyl group also prevents the penetration into the brain.

**Therapeutic uses of anticholinergic drugs**

1. Peripheral: Therapeutic uses following inhibition of parasympathetic transmission, e.g., mydriasis with cycloplegia, decrease saliva production,
decrease motility of smooth muscle, inhibition of vagal transmission to heart, decrease bronchial secretions, decrease in urinary incontinence, etc.

2. Central: Anti-parkinson and anti-motion sickness

3. If anticholinergic drugs are non-quaternary amine derivatives, they will cross the bloodbrain barrier. They may have therapeutic actions, or side effects, involving the central nervous system; if anticholinergic drugs are quaternary amines, they will not cross the blood brain barrier, thus they are devoid of CNS activity.

4. Expected ‘side effects’ of anticholinergic therapy include: peripheral-photophobia, cycloplegia, dry mouth, tachycardia, difficult urination, red skin (‘atropine flush’), and increase in skin temperature, central-sedation or excitement.

SOLANACEOUS ALKALOIDS AND ANALOGUES

Scopolamine is an alkaloid isolated from various members of solanaceae. It is an optically active compound and levofl ox (−) Scopolamine is slightly water miscible viscous liquid. Scopolamine occurs as Scopolamine hydrobromide salt, which is a colorless, odorless, water soluble powder.

1. Atropine sulphate

Properties and uses: It is a white crystalline powder or colourless crystals, freely soluble in alcohol and well soluble in water. It is the tropine ester of racemic tropic acid and is optically inactive. The greater molar potency of
Atropine helps it to block several moles of acetylcholine. The umbrella-like atropine molecule may mechanically or electrostatically inactivate adjacent receptors on the cell surface so that these receptors are also unavailable for acetylcholine or other parasympathomimetic stimulants. Atropine has all the actions and uses of antimuscarinic drugs.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: In Bradycardia: Adult: 500 μg every 3–5 min totally 3 mg.


2. **Hyoscyamine sulphate**

![Hyoscyamine molecular structure](image)

**Properties and uses:** Hyoscyamine sulphate is available as white, crystalline powder or colorless needles, very soluble in water, sparingly soluble or soluble in alcohol, practically insoluble in ether. It melts at about 203°C, with decomposition. It should be stored in an airtight container, protected from light.

Use: Hyoscyamine is an anticholinergic drug used to treat peptic ulcers.
3. Scopolamine hydrobromide

Properties and uses: It exists as colourless or white crystals or white granular powder, odourless, slightly efflorescent in dry air, and is an anhydrous salt, soluble in water or alcohol and in chloroform, insoluble in ether. Scopolamine is the levo component of the racemic mixture that is known as Hyoscine. It is effective in the prevention of motion sickness. It is a competitive blocking agent of the parasympathetic nervous system like atropine, but it differs markedly from atropine in its action on the higher nerve centres.

4. Homatropine hydrobromide

Properties and uses: It is a white crystalline powder or colourless crystals, sparingly soluble in alcohol, but freely soluble in water. It is used topically on the ciliary structure of the eye and to effect mydriasis.

Storage: It should be stored in well-closed airtight containers, protected from light.

Dose: Topically for adult, to the conjunctiva, 1 drop of a 2%–5% solution given three times at 10 min intervals.

Dosage forms: Homatropine eye drops B.P.
5. Ipratropium bromide*.

Properties and uses: It is a white or almost white crystalline powder, freely soluble in methanol, soluble in water, but slightly soluble in ethanol. It is used in the inhalation therapy to produce dilation of bronchial smooth muscle for acute asthmatic attacks. It produces broncho-dilation by competitive inhibition of cholinergic receptors bound to the smooth muscles of the bronchioles.

Assay: Dissolve the sample in water and add 3 ml of dilute nitric acid. Titrate with 0.1 M silver nitrate and determine the end point potentiometrically.

Dose: For inhalation reversible airways obstruction and COPD, maximum dose is 320 μg daily as nebulized solution.

Dosage forms: Ipratropium Nebuliser solution B.P., Ipratropium powder for inhalation B.P., Ipratropium pressurized inhalation B.P.
Synthetic cholinergic blocking agents:

1. Tropicamide

![Tropicamide molecule](image)

**Properties and uses:** Tropicamide is (RS)-N-ethyl-2-phenyl-N-(4-pyridylmethyl) hydrocyralamide. It is white, crystalline powder, slightly soluble in water, freely soluble in alcohol and in methylene chloride. It is an effective anticholinergic drug for ophthalmic use. It antagonizes M4 receptors.

2. Cyclopentolate hydrochloride

![Cyclopentolate molecule](image)

**Properties and uses:** It exists as white crystalline powder, soluble in water, methanol, and ethanol, but insoluble in toluene. Cyclopentolate is usually employed as eye drops to cause cycloplegia and mydriasis. It acts much faster than atropine and possesses a relatively shorter duration of action.

**Dose:** Topically for adult, 1 drop of 1 or 2% solution to the conjunctiva; for refraction 1 drop of a 0.5% solution repeated after 5 to 15 min.

**Dosage forms:** Cyclopentolate eye drops B.P.
3. Clidinium bromide

**Uses:** Used as a bronchodilator in asthmatic conditions. It has a longer lasting effect as compared to β-agonists.

4. **Dicyclomine hydrochloride**

   ![Chemical Structure of Dicyclomine]

   **Properties and uses:** It exists as a white, crystalline powder with a bitter taste, soluble in water and chloroform. Dicyclomine HCl behaves both as an antimuscarinic and a nonspecific antispasmodic agent. It was first introduced...
in 1950 and had minimized the adverse effects associated with the atropine type of compounds. Dicyclomine has spasmolytic effect on various smooth muscle spasms particularly those associated with the gastrointestinal (GI) tract. It is also used in dysmenorrhoea, pylorospasm, and biliary dysfunction.

Dose: By oral or I.M. 10 to 20 mg per day in four divided dose.

5. Glycopyrrolate

![Glycopyrrolate](image)

**Properties and uses:** It exists as a white, crystalline powder with a bitter taste, soluble in water and alcohol. It is used for suppressing gastric secretion and in the treatment of peptic ulcer and gastrointestinal disorder associated with spasm.

6. Methantheline bromide

![Methantheline bromide](image)
7. Propantheline bromide

Properties and uses: It is a white or yellowish-white powder, slightly hygroscopic, soluble in water, in alcohol, and in methylene chloride. It is beneficial for the treatment of peptic ulcer, due to the decreased gastric motility by this drug, and it may relieve the pain in this condition.

Assay: Dissolve the sample in acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight container, and protected from light.

Dose: The usual initial dose is 15 mg thrice/day before meals; and 30 mg at bedtime.

Dosage forms: Propantheline bromide tablets I.P., Propantheline tablets B.P.

8. Benztropinemesylate

Properties and uses: It is a white crystalline powder, insoluble in ether, but soluble in water and ethanol. It has anticholinergic, antihistaminic, and local anaesthetic activities. It is used in the treatment of Parkinsons’s disease.

Dosage forms: Benztropine injection B.P., Benztropine tablets B.P.
9. Orphenadrine citrate

**Properties and uses:** It is a white or almost white crystalline powder, sparingly soluble in water, slightly soluble in alcohol. It is used for the symptomatic treatment of Parkinson’s disease. It is also used as a skeletal muscle relaxant.

**Storage:** It should be stored in well-closed containers. If the substance is sterile, it should be stored in a sterile, airtight, tamper-proof container, and protected from light.

**Dose:** The initial oral dose is 100 mg twice/day; I.M. or I.V. 60 mg every 12 hrs.

10. Biperidine hydrochloride

**Properties and uses:** It is a white crystalline powder, slightly soluble in methylene chloride, in water, and in alcohol. It has a relatively strong musculotrophic action, which is about equal to that of papaverine, in comparison with most synthetic anticholinergic drugs. It is used in all types of Parkinson’s disease.
Assay: Dissolve the sample in alcohol and titrate with 0.1 M alcoholic potassium hydroxide and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: For parkinsonism, 2 mg 3 or 4 times/day.

11. Procyclidine hydrochloride*

Properties and uses: It exists as white crystalline powder, and it has been used for peripheral effects that are similar to methantheline. Its clinical usefulness lies in its ability to relieve voluntary muscle spasticity through its central action. Procyclidine is used in the treatment of Parkinson’s disease.

Dose: The initial oral dose is 7.5 mg/day in 3 or 4 divided doses after meals; maintenance dose is usually 20 to 30 mg per day.

Dosage forms: Procyclidine injection B.P., Procyclidine tablets B.P.
12. Tridihexethyl chloride

Properties and uses: It is a white crystalline powder, slightly soluble in water, sparingly soluble in alcohol and in methylene chloride. It is used as antispasmodic and antiparkinsonian agent. Trihexylphenidyl is more effective than levodopa against Parkinson’s tremor.

Assay: Dissolve the sample in alcohol and add 0.01 M hydrochloric acid. Perform potentiometric titration using 0.1 M sodium hydroxide.

Dose: Initial oral dose is 1 mg on first day, followed by 2 mg daily after 3 to 5 days; maintenance dose, 6 to 10 mg/day in 3 to 4 divided doses but not exceeding 20 mg/day.

Dosage forms: Trihexylphenidyl tablets B.P.

13. Isopropamide iodide.

Properties and uses: Isopropamide iodide is pale yellow coloured, bitter taste crystalline powder. It is sparingly soluble in water and freely soluble in chloroform and alcohol. Isopropamide is a potent anticholinergic drug. It has antispasmodic and antisecretory effects. It is used in the treatment of peptic ulcer.

![Chemical Structure of Ethopropazine Hydrochloride]