Cholinergic drugs
<table>
<thead>
<tr>
<th>DIRECT ACTING</th>
<th>INDIRECT ACTING (reversible)</th>
<th>INDIRECT ACTING (irreversible)</th>
<th>REACTIVATION OF ACETYLCOLINESTERASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine MIOCHOL-E</td>
<td>Ambenonium MYTELASE</td>
<td>Echothiophate PHOSPHOLINE IODIDE</td>
<td>Pralidoxime PROTOPAM</td>
</tr>
<tr>
<td>Bethanechol URECHOLINE</td>
<td>Donepezil ARICEPT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbachol MIOSTAT, ISOPTO CARBACHOL</td>
<td>Edrophonium ENLON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cevimeline EVOXAC</td>
<td>Galantamine RAZADYNE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine NICORETTE</td>
<td>Neostigmine PROSTIGMIN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilocarpine SALAGEN, ISOPTO CARPINE</td>
<td>Physostigmine ANTILIRIUM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyridostigmine MESTINON</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rivastigmine EXELON</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4.1**
Summary of cholinergic agonists.
**Cholinergic drugs**

Are drugs act on receptors that are activated by acetylcholine (ACH) which is the neurotransmitter of the parasympathetic nervous system.

ACH is synthesized in the cholinergic neurons from choline and acetyl CoA then stored in synaptic vesicles then it will be release into synaptic gap to bind post synaptic receptors and lead to biological response.

ACH is metabolized by acetylcholine esterase enzyme that cleaves it to choline and acetate. Choline will be recaptured by uptake system back into the neuron and recycling will occur.
Figure 4.3
Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.
Cholinergic receptors (cholinoreceptors) are two families: muscarinic and nicotinic depending on their affinities to cholinomimetic agents (agents that mimic ACH actions).

Muscarinic receptors bind ACH and also recognize muscarine, they are located in autonomic effector organs such as heart, smooth muscle, brain, and exocrine glands.

Nicotinic receptors bind ACH and also recognize nicotine. They are located in the CNS, adrenal medulla, autonomic ganglia, and neuromuscular junction.
Figure 4.2
Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems.
Direct acting cholinergic agonists:
Are agents mimic the effect of ACH by binding directly to cholinoceptors.

They are synthetic esters of choline such as carbachol and bethanechol or naturally occurring alkaloids such as pilocarpine.

All of these drugs have longer duration of action than ACH.
ACH:
Is the neurotransmitter of the parasympathetic N.S and cholinergic nerves, it is therapeutically of no importance due to:

1. Multiplicity of actions.
2. Rapid inactivation by acetyl-cholinesterase.
3. Has both muscarinic and nicotinic activity.
**Actions:**

Decrease in **heart** rate and cardiac output: Due to SA node depression.

Decrease in **blood pressure**: It causes vasodilatation due to its effect on cholinergic receptors in blood vessels, it will lead to increase in intracellular nitric oxide (NO) which is called endothelium derived relaxing factor (EDRF).

**Other actions:**

**GIT**: Increase salivary secretion and increase intestinal motility and secretion.

**Respiratory**: stimulate bronchiolar secretions.

**Genitourinary tract**: Increase detrusor muscle tone.

**Eye**: Miosis (marked constriction of the pupil
Bethanechol:

Structurally related to ACH, has strong muscarinic activity but no nicotinic actions.

It directly stimulates muscarinic receptors of the GIT causing increase intestinal motility and tone, it also stimulates detrusor muscle of the bladder causing urine expulsion.
Clinical uses:
1. Atonic bladder stimulation such as in postpartum and post operative non obstructive urine retention.

Side effects: Sweating, salivation, flushing, hypotension, nausea, abdominal pain, diarrhea, and bronchospasm.
Figure 4.5
Comparison of the structures of some cholinergic agonists.
Carbachol:
Has both muscarinic and nicotinic actions, has strong effect on CVS and GIT, it causes release of epinephrine from adrenal medulla by its nicotinic action, using it locally on the eye cause Miosis.
**Clinical uses:**
Rarely used because of high potency and long duration of action except in the eye to cause Miosis and to decrease intraocular pressure.
Pilocarpine:
Mainly used in ophthalmology, it exhibit muscarinic activity, it produces rapid miosis and contraction of the ciliary muscle.

Clinical uses:
It is the drug of choice in the emergency lowering of intra-ocular pressure in case of glaucoma.
Side effects:
It can enter the brain and cause CNS disturbances, it stimulate profuse sweating and salivation.
Figure 4.7
Actions of pilocarpine and atropine on the iris and ciliary muscle of the eye.
Figure 4.6
Some adverse effects observed with cholinergic agonists.
Indirect acting cholinergic agonists:
Are drugs that exert cholinergic actions by prolonging the life time of ACH via inhibition of acetyl-cholinesterase enzyme, this results in accumulation of ACH in synaptic space and provoke response at all cholinoreceptors in the body including both muscarinic and nicotinic receptors as well as neuromuscular junction and the brain, these drugs are termed (anti-cholinesterases) which are reversible and irreversible.
Reversible anticholinesterase
Figure 4.3
Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.
This group include: physostigmine, neostigmine, pyridostigmine, and edrophonium, ambenonium, and demecarium.
The major therapeutic uses of the cholinomimetics are for diseases of the eye (glaucoma, accommodative esotropia), the gastrointestinal and urinary tracts (postoperative atony, neurogenic bladder), the neuromuscular junction (myasthenia gravis, curare-induced neuromuscular paralysis), and very rarely, the heart (certain atrial arrhythmias).
•Cholinesterase inhibitors are occasionally used in the treatment of atropine overdosage. Several newer cholinesterase inhibitors are being used to treat patients with Alzheimer's disease.
Figure 4.8
Mechanisms of action of indirect cholinergic agonists.
Physostigmine: It is an alkaloid which is nitrogenous compound found in plants, it is a reversible inhibitor of acetylcholinesterase and potentiate cholinergic activity through out the body. Physostigmine stimulates muscarinic and nicotinic receptors of ANS and nicotinic receptors of neuromuscular junction, its duration of action is 2-4 hours, it can enter and stimulate CNS.
Clinical uses:

1. Bladder and intestinal atony (increase their motility).
2. Glaucoma (decrease intraocular pressure).
3. **Overdose** of anticholinergic drugs like atropine, phenothiazines, and tricyclic antidepressants.
Side effects:
1. Convulsion at high doses.
2. Bradycardia.
3. Skeletal muscle paralysis due to inhibition of acetylcholinesterase at neuromuscular junction and ACH accumulation.
Neostigmine: Synthetic compound reversibly inhibits acetylcholinesterase, it does not enter CNS, it has greater effect on skeletal muscle that can increase contractility then paralysis.

Uses:
1. stimulate atonic bladder and intestine.
2. Antidote for neuromuscular blocking agents like tubocurarine.
3. Symptomatic treatment in myasthenia gravis.

Side effects: Salivation, flushing, hypotension, nausea, abdominal pain, diarrhea, and bronchospasm.
Pyridostigmine:
Used in chronic treatment of myasthenia gravis, its duration of action 3-6 hours.
Edrophonium:
Has short duration of action (10-20 minutes) used in diagnosis of myasthenia gravis (i.v injection of edrophonium lead to rapid increase in muscle strength).
**Edrophonium** is sometimes used as a diagnostic test for myasthenia. A 2 mg dose is injected intravenously after baseline muscle strength has been measured. If no reaction occurs after 45 seconds, an additional 8 mg may be injected. If the patient has myasthenia gravis, an improvement in muscle strength that lasts about 5 minutes can usually be observed.
Edrophonium is also used to assess the adequacy of treatment with the longer-acting cholinesterase inhibitors in patients with myasthenia gravis. If excessive amounts of cholinesterase inhibitor have been used, patients may become paradoxically weak because of nicotinic depolarizing blockade of the motor end plate.
Clinical situations in which severe myasthenia (myasthenic crisis) must be distinguished from excessive drug therapy (cholinergic crisis) usually occur in very ill myasthenic patients and must be managed in hospital with adequate emergency support systems such as mechanical ventilators.
Long-term therapy for myasthenia gravis is usually accomplished with pyridostigmine; neostigmine.

The doses are titrated to optimum levels based on changes in muscle strength. These drugs are relatively short-acting and therefore require frequent dosing (every 6 hours for pyridostigmine and every 4 hours for neostigmine.)
Irreversible anticholinesterase
Are synthetic organophosphorus compounds bind acetylcholinesterase covalently and inhibit it irreversibly, so there will be increase in ACH at all the sites of its release.
These drugs are extremely toxic and used in military as nerve agents (soman, sarin, VX), some agents like parathion and malathion used as insecticides.

The covalent phosphorus-enzyme bond is extremely stable and hydrolyzes in water at a very slow rate (hundreds of hours).

After the initial binding-hydrolysis step, the phosphorylated enzyme complex may undergo a process called aging.
This process apparently involves the breaking of one of the oxygen-phosphorus bonds of the inhibitor and further strengthens the phosphorus-enzyme bond. The rate of aging varies with the particular organophosphate compound.

If given before aging has occurred, strong nucleophiles like pralidoxime are able to break the phosphorus-enzyme bond and can be used as "cholinesterase regenerator".
Once aging has occurred, the enzyme-inhibitor complex is even more stable and is more difficult to break, even with oxime regenerator compounds.
**Isoflurophate:**

This drug cause permanent inactivation of acetylcholinesterase, the restoration of enzyme activity requires synthesis of new enzyme molecules.

It cause generalized cholinergic stimulation, paralysis of motor function leading to breathing difficulties, convulsion.

It cause intense miosis, atropine in high dose can reverse its muscarinic and central effects.
Clinical uses:

Available as ointment used topically for the treatment of glaucoma, the effect may last for one week after a single administration.

Echothiophate also is an irreversible inhibitor of acetylcholinesterase with the same uses of isofluropate.

The inhibited acetylcholinesterase can be reactivated by pralidoxime which is synthetic compound can regenerate new enzyme.
Organophosphorus poisoning
Acute intoxication must be recognized and treated promptly.

The dominant initial signs are those of muscarinic excess: miosis, salivation, sweating, bronchial constriction, vomiting, and diarrhea. Central nervous system involvement (cognitive disturbances, convulsions, and coma) usually follows rapidly, accompanied by peripheral nicotinic effects.
**Treatment:**
1. maintenance of vital **signs**—**respiration** in particular may be impaired;
2. decontamination to prevent further absorption—this may require removal of all clothing and washing of the skin in cases of exposure to dusts and sprays;
3. **atropine** parenterally in large doses, given as often as required to control signs of muscarinic excess.

Therapy often also includes treatment with **pralidoxime** and administration of **benzodiazepines** for seizures.
Figure 4.10
Covalent modification of acetylcholinesterase by echothiophate. Also shown is the reactivation of the enzyme with pralidoxime. $R = (\text{CH}_3)_2\text{N}^+\text{CH}_2\text{CH}_3$; $\text{RSH} = (\text{CH}_3)_2\text{N}^+\text{CH}_2\text{CH}_3\text{S}^-\text{H}$. 

PHOSPHORYLATION OF ENZYME
- Enzyme inactivated
- Pralidoxime (2-PAM) can remove the inhibitor
<table>
<thead>
<tr>
<th><strong>Bethanechol</strong></th>
<th><strong>Physostigmine</strong></th>
<th><strong>Rivastigmine, galantamine, donepezil</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Used in treatment of urinary retention</td>
<td>Increases intestinal and bladder motility</td>
<td>Used as first-line treatments for Alzheimer's disease, though confers modest benefit</td>
</tr>
<tr>
<td>Binds preferentially at muscarinic receptors</td>
<td>Reverses CNS and cardiac effects of tricyclic antidepressants</td>
<td>Have not been shown to reduce healthcare costs or delay institutionalization</td>
</tr>
<tr>
<td></td>
<td>Reverses CNS effects of atropine</td>
<td>Can be used with memantine (N-methyl-D-aspartate antagonist) with moderate to severe disease</td>
</tr>
<tr>
<td></td>
<td>Uncharged, tertiary amine that can penetrate the CNS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Carbachol</strong></th>
<th><strong>Neostigmine</strong></th>
<th><strong>Ecto thiophosphate</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Produces miosis during ocular surgery</td>
<td>Prevents postoperative abdominal distention and urinary retention</td>
<td>Used in treatment of open-angle glaucoma</td>
</tr>
<tr>
<td>Used topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to pilocarpine</td>
<td>Used in treatment of myasthenia gravis</td>
<td>Has long duration of action (100 hours)</td>
</tr>
<tr>
<td></td>
<td>Used as an antidote for competitive neuromuscular blockers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Has intermediate duration of action (0.5 to 2 hrs)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pilocarpine</strong></th>
<th><strong>Edrophonium</strong></th>
<th><strong>Acetylcholine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces intraocular pressure in open-angle and narrow-angle glaucoma</td>
<td>Used for diagnosis of myasthenia gravis</td>
<td>Used to produce miosis in ophthalmic surgery</td>
</tr>
<tr>
<td>Binds preferentially at muscarinic receptors</td>
<td>Used as an antidote for competitive neuromuscular blockers</td>
<td></td>
</tr>
<tr>
<td>Uncharged, tertiary amine that can penetrate the CNS</td>
<td>Has short duration of action (10 to 20 min)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4.11**
Summary of actions of some cholinergic agonists. CNS = central nervous system.