Cholinergic drugs
### DIRECT ACTING

- Acetylcholine
- Bethanechol
- Carbachol
- Cevimeline
- Nicotine
- Pilocarpine

### INDIRECT ACTING (reversible)

- Ambenonium
- Donepezil
- Edrophonium
- Galantamine
- Neostigmine
- Physostigmine
- Pyridostigmine
- Rivastigmine

### INDIRECT ACTING (irreversible)

- Echothiophate

### REACTIVATION OF ACETYLCHOLINESTERASE

- Pralidoxime

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**Figure 4.1**

Summary of cholinergic agonists.
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.
• Cholinergic receptors (cholinoceptors) 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 cholinoreceptors.

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.
Figure 4.5
Comparison of the structures of some cholinergic agonists.
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.
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), 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.
PHOSPHORYLATION OF ENZYME

- Enzyme inactivated
- Pralidoxime (2-PAM) can remove the inhibitor

Active site of acetylcholinesterase

RSH

Acetylcholinesterase (inactive)

H₂O

Acetylcholinesterase (irreversibly inactive)

Acetylcholinesterase (active)

2-PAM

Figure 4.10
Covalent modification of acetylcholinesterase by echothiophate. Also shown is the reactivation of the enzyme with pralidoxime. R = (CH₃)₃N⁺−CH₂−CH₂−; RSH = (CH₃)₃N⁺−CH₂−CH₂−S−H.
**Isofluorophate:**

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 isofluorophate.

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 4.11
Summary of actions of some cholinergic agonists. CNS = central nervous system.
Cholinergic antagonists
Figure 5.2
Sites of actions of cholinergic antagonists.
Cholinergic antagonists:
They are also called anticholinergic drugs or cholinergic blockers, this group include:

1. **Antimuscarinic** agents (atropine, ipratropium, scopolamine)
2. **Ganglionic** blockers (mecamylamine, nicotine, trimethaphan)
3. **Neuromuscular** blockers (atracutium, metocurine, mivacurium, pancuronium, succinylcholine, tubocurarine, and vecuronium)
Antimuscarinic agents: These agents block muscarinic receptors and inhibit muscarinic functions, they are useful in different clinical situations, they have no actions on skeletal neuromuscular junctions or autonomic ganglia because they do not block nicotinic receptors.
Figure 5.3

Competition of *atropine* and *scopolamine* with acetylcholine for the muscarinic receptor.
Atropine:
A belladonna alkaloid has a high affinity for muscarinic receptors, it is a competitive inhibitor of muscarinic receptors preventing ACH from binding to that site.
Atropine is both central and peripheral muscarinic blocker, its action lasts about 4 hours, when used topically in the eye its action lasts for days.
**Actions:**

Eye: It cause dilation of the pupil (mydriasis), unresponsiveness to light, and cycloplegia (inability to focus for near vision), if used in patients with glaucoma, it will cause dangerous elevation in IOP.
Respiratory system: Bronchodilatation and reduce secretion.

CNS: Sedation, amnesia, at high doses cause agitation, hallucination, and coma.
**GIT:** Reduce motility so it is effective as antispasmodic.

**Urinary system:** Reduce motility and cause urine retention so used in treatment of nocturnal enuresis in children, it **dangerous** to be used in patients with **benign prostatic hypertrophy** due to its effect in producing urine retention.
CVS: Its actions depend on the dose, at low dose lead to bradycardia due to central activation of vagus nerve, but recently this effect is due to blockade of M1 receptors on the inhibitory prejunctional neurons so increase ACH release. At higher doses of atropine there will be blockade of cardiac receptors on SA node and this will increase heart rate (tachycardia), blood pressure is not affected but at toxic doses atropine will cause dilatation of cutaneous blood vessels.
Secretions: It blocks the salivary gland secretion and produce dry mouth (xerostomia), blocks the Lacrimal glands secretion and cause eye dryness (xerophthalmia), blocks the bronchial secretion, and blocks the secretion of sweat gland and increase body temperature.
Clinical uses:

Antispasmodic agent: Relax GIT and bladder. 
Mydriatic and cycloplegic agent in the eye to permit measurement of refractive errors.
Antidote for cholinergic agonists: To treat organophosphorus poisoning (present in insecticides), and mushroom poisoning.
Antisecretory agent: To block the secretion of upper and lower respiratory tracts prior to surgery.
Dry mouth, blurred vision, tachycardia, and constipation.

CNS restlessness, confusion, hallucination, and delirium, this may progress to circulatory and respiratory collapse and death.

It is very risky in individuals with glaucoma and BPH so careful history is required.
Figure 5.4
Dose-dependent effects of atropine.
Scopalnine (hyoscine): A belladonna alkaloid produce peripheral effects similar to atropine, it has greater actions on CNS and longer duration of action. It is one of the most effective antimotion sickness, it is effective also in blocking short term memory, it produce sedation but at higher doses cause excitement.
Figure 5.6
Adverse effects commonly observed with muscarinic antagonists.
• Ipratropium: It is inhaled derivative of atropine useful in treating asthma and COPD in patients unable to take adrenergic agonist. Other agents like homatropine, cyclopentolate, and tropicamide used mainly in ophthalmology.
Ganglionic blockers:

- They act on **nicotinic** receptors of the autonomic ganglia.

- They have **no selectivity** toward the parasympathetic or sympathetic ganglia.

➤ **The effect of these drugs is complex and unpredictable** so rarely used therapeutically, used mainly in experimental pharmacology.
Nicotine

• It is component of cigarette smoke, has many undesirable actions.

• Depending on the dose, nicotine depolarizes ganglia resulting first in stimulation then followed by paralysis of all ganglia.

• The stimulatory effects are complex include (at low dose):
  1- Increase in blood pressure and heart rate (due to release of the transmitter from adrenergic terminals and adrenal medulla).

Increase peristalsis and secretions.
On large dose, nicotine:

The blood pressure falls because of ganglionic blockade, activity both in GIT and UB musculature decrease.
Figure 5.8
Neurochemical effects of nicotine.
GABA = γ-aminobutyric acid.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic uses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscarinic blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Trihexyphenidyl Benztpine</td>
<td>● Treatment of Parkinson’s disease</td>
</tr>
<tr>
<td>Darifenacin</td>
<td></td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>● Treatment of overactive urinary bladder</td>
</tr>
<tr>
<td>Oxybutynin</td>
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<tr>
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<td>Trosipium</td>
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</tr>
<tr>
<td>Cyclopentolate Tropicamide</td>
<td>● In ophthalmology, to produce mydriasis and cycloplegia prior to refraction</td>
</tr>
<tr>
<td>Atropine*</td>
<td>● To treat spastic disorders of the GI tract</td>
</tr>
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<td></td>
<td>● To treat organophosphate poisoning</td>
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<tr>
<td></td>
<td>● To suppress respiratory secretions prior to surgery</td>
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<tr>
<td></td>
<td>● To treat bradycardia</td>
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<tr>
<td>Scopolamine</td>
<td>● To prevent motion sickness</td>
</tr>
<tr>
<td>Ipratropium Tiotropium</td>
<td>● Treatment of COPD</td>
</tr>
<tr>
<td><strong>Ganglionic blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>● Smoking cessation</td>
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</table>

**Figure 5.7**  
Summary of cholinergic antagonists.  
*Contraindicated in angle-closure glaucoma. GI = gastrointestinal; COPD = chronic obstructive pulmonary disease.
Neuromuscular blocking drugs:

- Drugs that block cholinergic transmission between motor nerve ending and the nicotinic receptors on the neuromuscular end plate of the skeletal muscle.

- They are structural analogs of ACH.
They are useful in surgery to produce complete muscle relaxation to avoid higher anesthetic doses to achieve similar muscular relaxation.
They are of 2 types:

1- **Antagonist (nondepolarizing type).**
   (isoquinoline derivative e.g. atracurium, tubocurarine) or steroid derivative e.g. pancuronium, vecuronium)

2- **Agonist (depolarizing type) at** the receptors on the end plate of the NMJ (e.g. Succinylcholine).
Figure 5.9
Mechanism of action of competitive neuromuscular-blocking drugs.
NMB drugs minimally absorbed when given orally

Vecuronium and rocuronium and metabolites appear mainly in bile

Most drugs excreted primarily unchanged in urine

Neuromuscular-blocking drugs

Figure 5.10
Pharmacokinetics of the neuromuscular-blocking drugs. IV = intravenous.
Non depolarizing (competitive) blockers

**mechanism of action:**

- At low dose: they combine with nicotinic receptors and prevent binding with ACH so prevent depolarization of muscle cell membrane and inhibit muscular contraction.
- Their action can be overcome by administration of acetylcholinesterase inhibitors such as neostigmine or edrophonium.
At high doses: Block the ion channel of the end plate so lead to weakening of neuromuscular transmission and reduce the ability of acetylcholinesterase inhibitors to reverse the effect of nondepolarizing muscle relaxants.
Pharmacological actions:

They cause first paralysis of the small contracting muscles of face, followed by fingers, then after limbs, neck and trunk muscles are paralyzed, then the intercostal muscles are affected, and lastly the diaphragm is paralyzed.
Therapeutic uses:

Are adjuvant drugs in anesthesia during surgery to relax skeletal muscles.
Side effects:

- Histamine release, ganglionic blockade and hypotension.
- Postoperative muscle pain and hyperkaleamia.
- Increase IOP and intra-gastric pressure.
- Malignant hyperthermia.
Figure 5.11
Onset and duration of action of neuromuscular-blocking drugs.

- **Atracurium**: 1.2-40 min
  - Cisatracurium spontaneously degrades in plasma and is the only nondepolarizing neuromuscular blocker whose dose need not be reduced in patients with renal failure. It is often used in patients with multisystem organ failure because its metabolism is independent of hepatic or renal function. Cisatracurium is useful in mechanical ventilation of critically ill patients.
- **Cisatracurium**: 1-90 min
- **Vagolytic (increased heart rate)**
- **Pancuronium**: 3-86 min
- **Rocuronium**: 1-43 min
- **Succinylcholine**: 1.1-8 min
- **Vecuronium**: 2-44 min

Postoperative muscle pain is common; hyperkalemia and increased intraocular and intragastric pressure may occur. Drug may trigger malignant hyperthermia. Rapid onset makes succinylcholine useful for tracheal intubation in patients with gastric contents.
Drug interactions:

– Cholinesterase inhibitors: They can overcome the effect of nondepolarizing NM blockers at high doses.

– Haloginated hydrocarbone anesthetics: Enhance their actions by exerting stabilizing action at the NMJ.

– Aminoglycoside antibiotics: Inhibit ACH release from cholinergic nerves by competing with calcium ions, they synergize with all competitive blockers and enhance the blockade.

– Calcium channel blockers: Increase the effect of both depolarizing and nondepolarizing agents.
Depolarizing agents:

Mechanism of action:

- **Succinylcholine** attach to nicotinic receptors and acts like acetylcholine to depolarize NMJ.

- This drug persist at high concentration at synaptic cleft and attach to the receptor for long time, it cause initially opening of the sodium channel associated with the nicotinic receptor which cause receptor depolarization and this lead to transient twitching of the muscle (fasciculation).

- The continuous binding of the agent to the receptor renders the receptor incapable to transmit further impulses, then there will be gradual repolarization as the Na⁺ channels will be closed and this causes resistance to depolarization and a flaccid paralysis.
PHASE I
Membrane depolarizes, resulting in an initial discharge that produces transient fasciculations followed by flaccid paralysis.

Nicotinic receptor at a neuromuscular junction

Succinylcholine

Na⁺

Depolarized

PHASE II
Membrane repolarizes, but receptor is desensitized to the effect of acetylcholine.

Succinylcholine

Na⁺

Repolarized

Figure 5.12
Mechanism of action of depolarizing neuromuscular-blocking drugs.
Pharmacological action

- Initially produce short lasting muscle fasciculation, followed within a few minutes by paralysis.
- The duration of action of acetylcholine is short since it is broken rapidly by plasma cholinesterase.
Therapeutic uses:

• 1. Because its rapid onset of action and short duration of action it is useful when rapid endotracheal intubation is required during the induction of anesthesia.
• 2. Electroconvulsive shock treatment (ECT).
• Succinylcholine given by continuous i.v infusion because of it is short duration on action (due to rapid hydrolysis by plasma cholinesterase).
Side effects:

1- Hyperthermia: When halothane used as an anesthetic, succinylcholine may cause malignant hyperthermia with muscle rigidity and hyperpyrexia in genetically susceptible individuals.

This treated by rapidly cooling the patient and by administration of dantroline which blocks Ca release and thus reduce heat production and relaxing the muscle tone.
Apnea: A genetically related deficiency of plasma cholinesterase or presence of an atypical form of the enzyme can cause apnea lasting 1-4 hours due to paralysis of the diaphragm.

It is managed by mechanical ventilation.