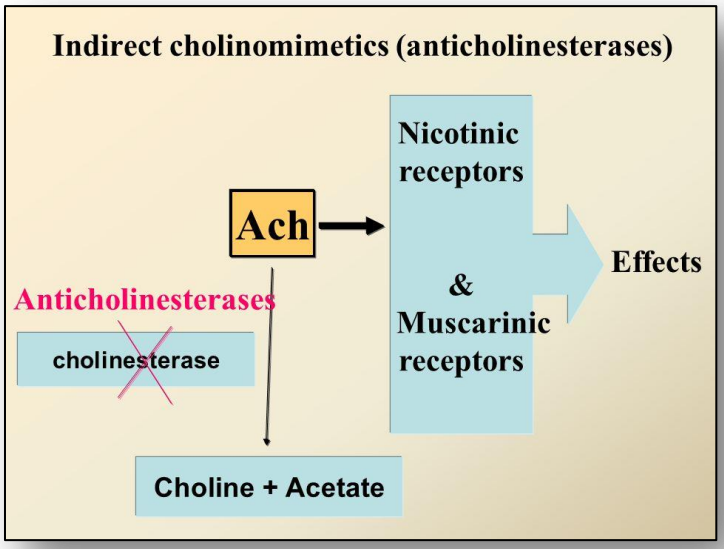
Indirect-Acting Cholinergic Agonists (Anticholinesterase Agents) or (Cholinesterase Inhibitors):

They inhibit the enzyme cholinesterases, which is responsible for hydrolysis of acetylcholine. Thus, ACh is not metabolized, gets accumulated at muscarinic and nicotinic sites, and produces cholinergic effects. Hence, anticholinesterases are called indirectly acting cholinergic drugs.



A/ Reversible anticholinesterases:

Physostigmine:

- it is found naturally in plants.
- Physostigmine stimulates the muscarinic and nicotinic sites of the ANS, and the nicotinic receptors of the NMJ.
- Muscarinic stimulation can cause contraction of GI smooth muscles, miosis, bradycardia, and hypotension. Nicotinic stimulation can cause skeletal muscle twitches, fasciculations, and skeletal muscle paralysis (at higher doses).
- It is intermediate-acting agent with a duration of action is about 30 minutes to 2 hours.

- Physostigmine can enter and stimulate the cholinergic sites in the CNS.
- Physostigmine is used *in the treatment of overdoses of drugs with anticholinergic actions, such as atropine, and *to reverse the effects of NMBs.

Neostigmine:

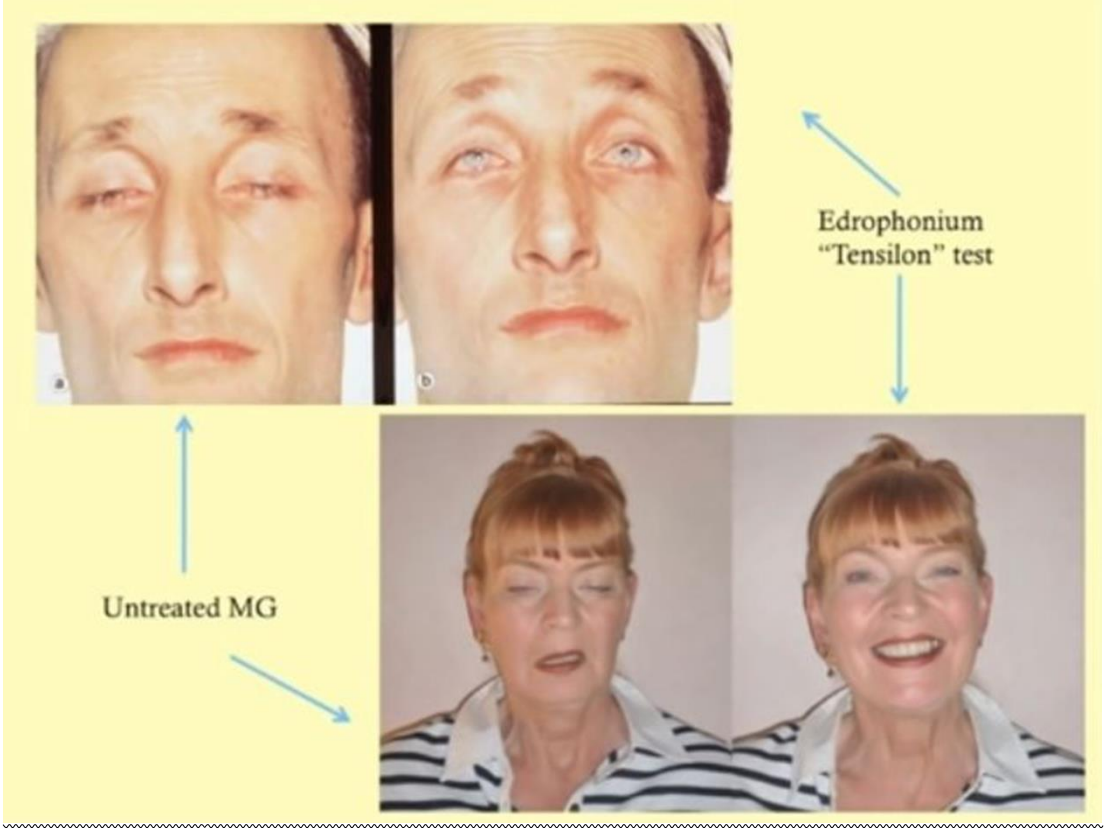
- It is a synthetic compound.
- Unlike physostigmine, neostigmine has a quaternary nitrogen. Therefore, it is more polar, is absorbed poorly from the GI tract, and does not enter the CNS. Its effect on skeletal muscle is greater than physostigmine, and it can stimulate contractility before it paralyzes.
- Neostigmine has an intermediate duration of action, usually 30 minutes to 2 hours.
- *It is used to stimulate the bladder and GI tract and *as an antidote for competitive neuromuscular-blocking agents. *Neostigmine is also used to manage symptoms of myasthenia gravis.
- Adverse effects of neostigmine include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.
- Neostigmine does not cause CNS side effects and is not used to overcome toxicity of central-acting antimuscarinic agents such as atropine.
- Neostigmine is contraindicated when intestinal or urinary bladder obstruction is present.

Pyridostigmine:

- It is another cholinesterase inhibitor.
- *It used in the chronic management of myasthenia gravis.
- Its duration of action is intermediate (3 to 6 hours) but longer than that of neostigmine.
- Adverse effects are similar to those of neostigmine.

***Edrophonium*:**

- It has a short duration of action of 10 to 20 minutes due to rapid renal elimination.
- Edrophonium is a quaternary amine, and its actions are limited to the periphery.
- *It is used in the diagnosis of myasthenia gravis, an autoimmune disease caused by antibodies to the nicotinic receptor at the NMJ. This causes the degradation of the nicotinic receptors, making fewer receptors available for interaction with ACh. Intravenous injection of edrophonium leads to a rapid increase in muscle strength in patients with myasthenia gravis. Care must be taken, because excess drug may provoke a cholinergic crisis (atropine is the antidote). *Edrophonium may also be used to assess cholinesterase inhibitor therapy, for differentiating cholinergic and myasthenic crises, and *for reversing the effects of nondepolarizing neuromuscular blockers (NMBs) after surgery.
- Due to the availability of other agents, edrophonium use has become limited.



Irreversible Anticholinesterase Agents:

- A number of synthetic organophosphate compounds have the ability to bind **covalently** to AChE. The result is a long-lasting increase in ACh at all sites where it is released.
- Many of these drugs are extremely toxic and were developed by the military as nerve agents.
- Related compounds, such as ***parathion*** and ***malathion***, are used as insecticides. They are used as agricultural insecticides in the United States, which has led to numerous cases of accidental poisoning with these agents. In addition, they are frequently used for suicidal and homicidal purposes.
- ***Organophosphate*** nerve gases such as sarin are used as agents of warfare and chemical terrorism.

- Toxicity with these agents is manifested as nicotinic and muscarinic signs and symptoms (cholinergic crisis). Depending on the agent, the effects can be peripheral or can affect the whole body.
- Signs and symptoms of organophosphate poisoning:

1. Muscarinic effects: Profuse sweating, salivation, lacrimation, increased tracheobronchial secretions, bronchospasm, vomiting, abdominal cramps, miosis, bradycardia, hypotension, involuntary urination and defecation.
2. Nicotinic effects: Twitchings, fasciculations, muscle weakness and paralysis is due to prolonged depolarization.
3. Central effects: Headache, restlessness, confusion, convulsions, coma, and death occurs usually due to respiratory failure.

- Treatment of organophosphate poisoning:

➢ *Atropine* competitively blocks the muscarinic side effects of these agents. The ability of atropine to enter the central nervous system (CNS) is of particular importance in treating central toxic effects of anticholinesterases.

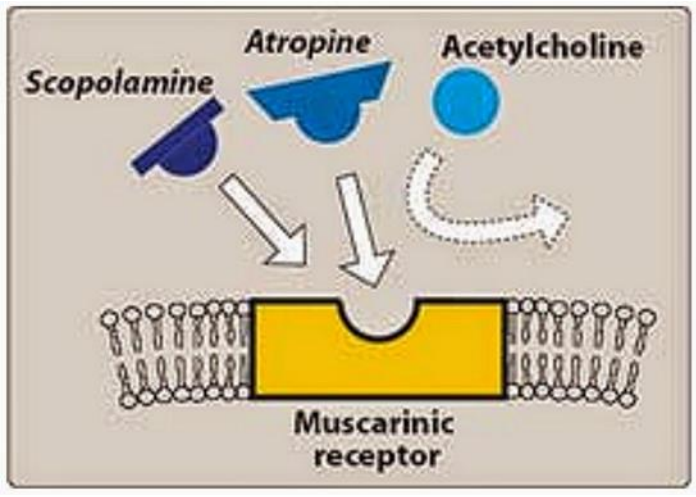
- *Diazepam* is also administered to reduce the persistent convulsion caused by these agents.
- ***Pralidoxime*** can reactivate inhibited AChE. It can reverse both muscarinic and nicotinic peripheral effects of organophosphates, but not the CNS effects.
- General supportive measures, such as maintenance of patent airway, oxygen supply, and artificial respiration, may be necessary as well.

CHOLINERGIC ANTAGONISTS:

Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.

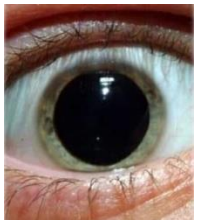
I. Muscarinic Blockers: Commonly known as anticholinergic drugs, these agents (for example, ***atropine*** and ***scopolamine***) block muscarinic receptors, causing inhibition of muscarinic functions. In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating the salivary and sweat glands.

Atropine :



- It binds competitively to muscarinic receptors to prevent ACh from binding.
- Atropine acts both centrally and peripherally.

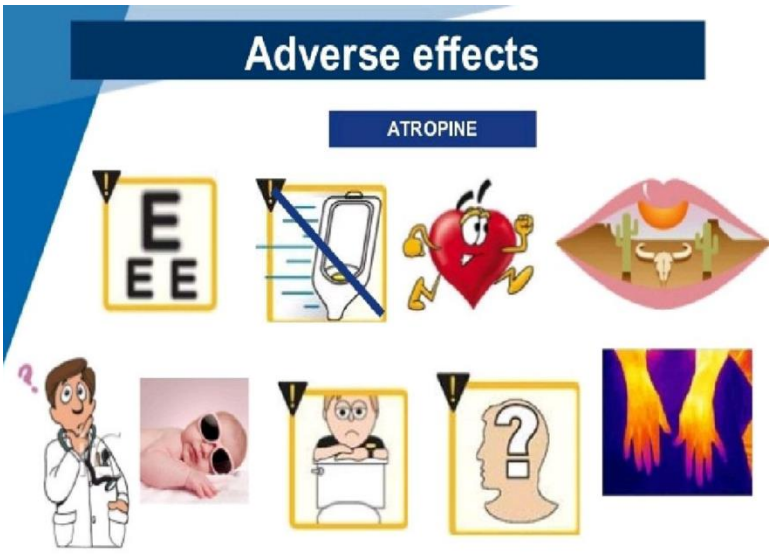
- General actions last about 4 hours; however, effects of topical administration in the eye may persist for days.
- Atropine blocks muscarinic activity in the eye, resulting in mydriasis (dilation of the pupil), unresponsiveness to light, and cycloplegia (inability to focus for near vision). In patients with angle-closure glaucoma, intraocular pressure may rise dangerously.



- Atropine can be used as an antispasmodic to reduce activity of the GIT (antispasmodic). Doses of atropine that reduce spasms also reduce saliva secretion, ocular accommodation, and urination. These effects decrease compliance with atropine.

- Atropine is sometimes used as an antisecretory agent to block secretions in the respiratory tract prior to surgery.
- Atropine produces divergent effects on the cardiovascular system, depending on the dose. At low doses, the predominant effect is a slight decrease in heart rate.
- Atropine blocks muscarinic receptors in the salivary glands, producing dryness of the mouth (xerostomia). Sweat and lacrimal glands are similarly affected. [Note: Inhibition of secretions of sweat glands can cause elevated body temperature, which can be dangerous in children and the elderly.]
- Atropine is used for the treatment of organophosphate (insecticides, nerve gases) poisoning, of overdose of clinically used anticholinesterases such as physostigmine, and in some types of mushroom poisoning (certain mushrooms contain cholinergic substances that block cholinesterases).
- The ability of atropine to enter the central nervous system (CNS) is of particular importance in treating central toxic effects of anticholinesterases.
- Depending on the dose, atropine may cause dry mouth, blurred vision, “sandy eyes,” tachycardia, urinary retention, and constipation. Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death.
- Low doses of cholinesterase inhibitors, such as ***physostigmine***, may be used to overcome atropine toxicity. Atropine may also induce urinary retention. The

drug may be dangerous in children, because they are sensitive to its effects, particularly to rapid increases in body temperature.



Scopolamine :

- Scopolamine has greater action on the CNS and a longer duration of action as compared to atropine.
- Scopolamine is used *for the prevention of motion sickness and postoperative nausea and vomiting. For motion sickness, it is available as a topical patch that provides effects for up to 3 days. [Note: As with all drugs used for motion sickness, it is much more effective prophylactically than for treating motion sickness once it occurs].
- Adverse effects are similar to atropine.

Ipratropium: It is used for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) also used in the acute management of bronchospasm in asthma.
It is delivered via inhalation. Because of the positive charge, these drugs do not enter the systemic circulation or the CNS, restricting effects to the pulmonary system.

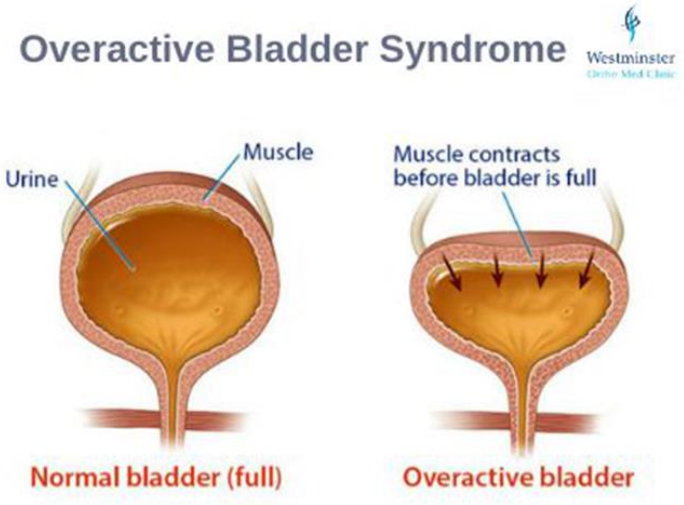
Tiotropium: is a long-acting muscarinic antagonists. It is used for maintenance treatment of bronchospasm associated with (COPD) and chronic management of

asthma. It is delivered via inhalation. Because of the positive charge, these drugs do not enter the systemic circulation or the CNS, restricting effects to the pulmonary system.

Tropicamide and ***cyclopentolate*****:** These agents are used as ophthalmic solutions for mydriasis and cycloplegia. Their duration of action is shorter than that of atropine. *Tropicamide* produces mydriasis for 6 hours and *cyclopentolate* for 24 hours.

Benztropine and ***trihexyphenidyl*****:** are useful as adjuncts with other antiparkinson agents to treat Parkinson disease and other types of parkinsonian syndromes, including antipsychotic-induced extrapyramidal symptoms.

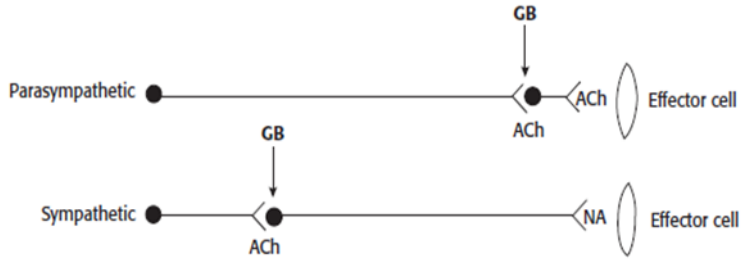
Oxybutynin: and other antimuscarinic agents for overactive bladder competitively block muscarinic (M_3) receptors in the bladder, intravesical pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced. Antimuscarinic actions at M3 receptors in the GI tract, salivary glands, CNS, and eye may cause adverse effects. ***Darifenacin*** and ***solifenacin*** are relatively more selective M3 muscarinic receptor antagonists.



II. Nicotinic Blockers:

a/ Ganglionic Blockers:

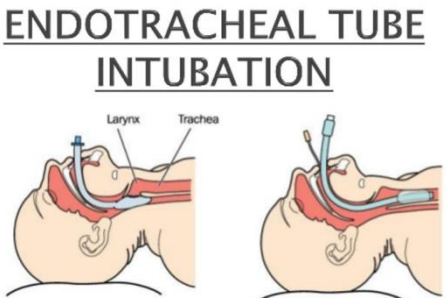
- Example ***nicotine***
- They act at N_N receptors of the autonomic ganglia (block both parasympathetic and sympathetic ganglia) and produce widespread complex effects therefore, ganglionic blockade is rarely used therapeutically, but often serves as a tool in experimental pharmacology.



b/ Neuromuscular Blockers:

- These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on skeletal muscle.
- They possess some chemical similarities to Ach and
- act either as antagonists (nondepolarizing) or as agonists (depolarizing) at the receptors on the endplate of the NMJ.
- Neuromuscular blockers (NMBs) are clinically useful to:

1. facilitate rapid intubation when needed due to respiratory failure.
2. to facilitate endotracheal intubation and provide complete muscle relaxation at lower anesthetic doses during surgery. This increases the safety of anesthesia.
3. in the intensive care unit (ICU) as adjuvant therapy to facilitate intubation and mechanical ventilation in critically ill patients.



(i) Nondepolarizing (competitive) blockers:

- The first known NMB was ***curare***, which Amazon hunters used to paralyze prey. The development of ***tubocurarine*** followed, but it has been replaced by

agents with fewer adverse effects, such as ***cisatracurium***, ***mivacurium***, ***pancuronium***, ***rocuronium***, and ***vecuronium***.

- They compete with ACh at the receptor without stimulating it, thus preventing depolarization of the muscle cell membrane and inhibiting muscular contraction. *Their competitive action can be overcome by administration of cholinesterase inhibitors, such as ***neostigmine*** and ***edrophonium***, which increase the concentration of ACh in the NMJ. Clinicians employ this strategy to shorten the duration of neuromuscular blockade.
- Muscles have differing sensitivity to blockade by competitive agents. Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers, limbs, neck, and trunk muscles. Next, the intercostal muscles are affected and, lastly, the diaphragm. The muscles recover in the reverse manner.
- All NMBs are injected IV or occasionally IM.
- Aminoglycoside antibiotics such as ***gentamicin*** and ***tobramycin*** inhibit ACh release from cholinergic nerves by competing with calcium ions. They synergize with competitive blockers, enhancing neuromuscular blockade.
- Calcium channel blockers may increase the neuromuscular blockade of competitive blockers.

(ii) Depolarizing agents:

- Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh.
- However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can more persistently depolarize the muscle fibers.
- ***Succinylcholine*** is the only depolarizing muscle relaxant in use today.
- It causes initial fasciculations and later flaccid paralysis due to prolonged depolarization
- The duration of action is dependent on diffusion from the motor end plate and hydrolysis by plasma cholinesterase (also called butyrylcholinesterase or pseudocholinesterase). Genetic variants in which plasma cholinesterase levels are low or absent lead to prolonged neuromuscular respiratory paralysis with prolonged apnoea this is referred to as ‘succinylcholine apnoea’. There is no antidote available.
- *Succinylcholine* can cause histamine release.