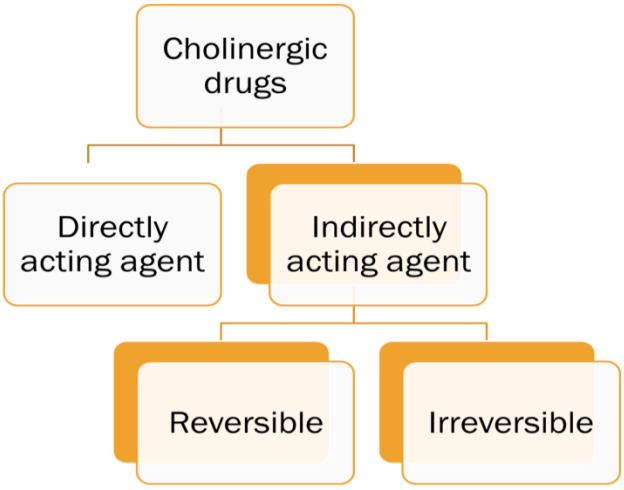
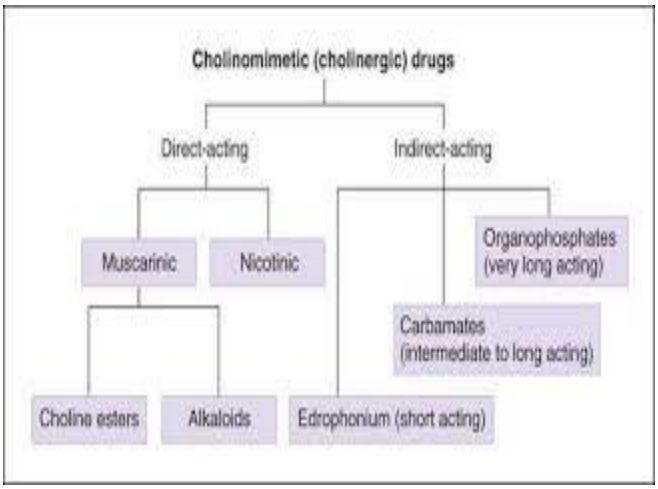
## Cholinergic Drugs

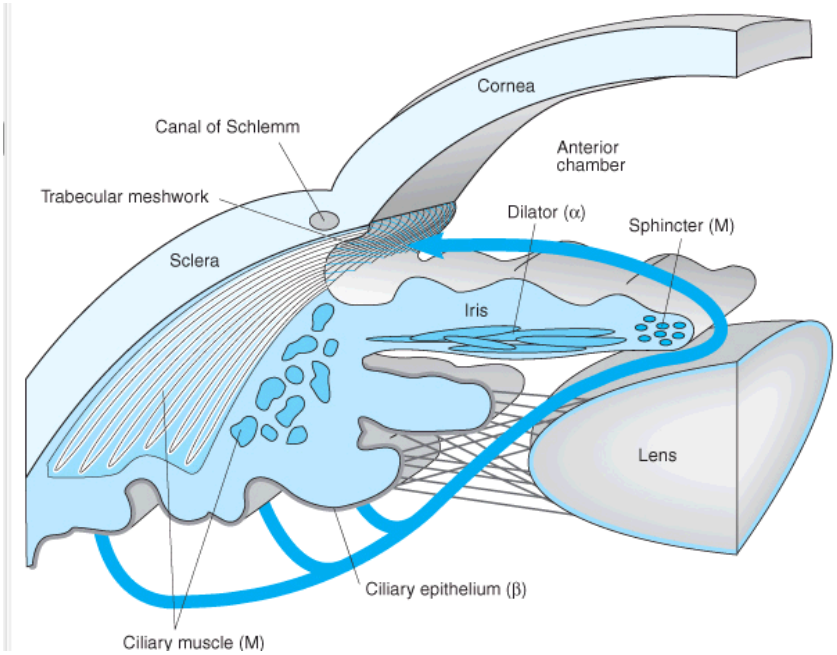



| Drug | Action | Selected therapeutic uses and important remarks |
|---|---|---|
| **Directly Acting Agents** | | |
| Bethanechol | Muscarinic receptors (activation) | Atonic bladder (in postpartum or postoperative non-obstructive urinary retention<br>Side-effects: generalised cholinergic stimulation* |
| Carbachol | Muscarinic & nicotinic $N_N$-receptors (activation) | Rarely used because of high potency and long duration of action, glaucoma, when used topically shows little or no adverse-effects |

Generalized cholinergic stimulation

DUMBBLESS




**Cevimeline and pilocarpine**

Cevimeline is synthetic drug Pilocarpine is a natural plant alkaloid.

Both drugs act as muscarinic agonists with no nicotinic effects.

Both drugs can be given orally to increase salivary secretion and decrease symptoms of dry mouth (xerostomia) associated with Sjögren syndrome.

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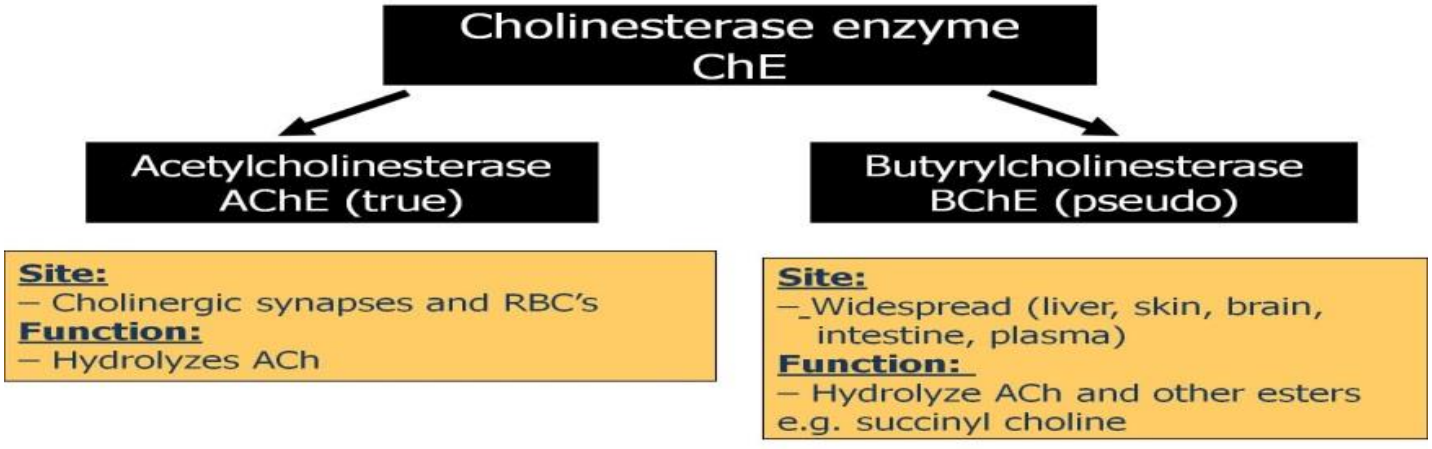
| Pilocarpine | Muscarinic receptors (activation) | Narrow (closed) and wide (open) angle glaucoma; it can enter the brain causing CNS-disturbances |



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| **Indirectly Acting (Reversible) Agents** | Inhibits AChE | |
| Physostigmine | | Atony of bladder and intestine, glaucoma, overdose with anticholinergics (e.g. atropine, phenothiazines and tricyclic antidepressants; it enters the brain, causes generalised cholinergic stimulation*; duration of action (0.5-2 hr) |
| Demecarium | | Glaucoma; duration of action (4-6 hr) |
| Neostigmine | | Atony of bladder and intestine, overdose with competitive neuromuscular blocking agents (e.g. tubocurarine), myasthenia gravis<br>Side-effects: generalised cholinergic stimulation<br>It poorly enters the CNS; duration of action (0.5-2 hr) |
| Pyridostigmine | | In chronic management of myasthenia gravis; duration of action (3-6 hr) |
| Ambenonium | | In chronic management of myasthenia gravis; duration of action (4-8 hr) |
| Edrophonium | | In the diagnosis of myasthenia gravis, postoperative paralytic ileus;<br>short duration of action (about 5-15 minutes) |

| | Physostigmine | Neostigmine |
|---|---|---|
| **Source** | Natural | Synthetic |
| **Chemistry** | Tertiary amine | Quaternary amine |
| **Oral absorption** | Complete | incomplete |
| **Passage through BBB** | Pass to CNS | Does not pass to CNS |
| **Actions** | 1. Muscarinic<br>2. Nicotinic<br>3. **CNS stimulaion** | 1. Muscarinic<br>2. Nicotinic<br>3. **Direct Sk m stimulant** |
| **Uses** | 1. **Locally** on eye in glucoma<br>2. **Systemically** in treatment of **atropine** poisoning | 1. **Myasthenia gravis**<br>2. **Antidote** to non-depolarizing NMB<br>3. **Antidote** to atropine( Periph)<br>4. Urinary retention, ileus<br>5. PAT (Heart)<br>6. Glaucoma |

Edrophonium
It acts as the same of neostigmine and pyridostigmine but has very short duration of action (5-15 minutes). It is used in the diagnosis of myasthenia gravis and to differentiate betwee muscle weakness due to insufficient treatment of myasthenia, or due to excessive treatment with AchE inhibitors (Tensilon test).

**Tensilon test:**
small doses of edrophonium improve muscle strength in untreated patients with myasthenia, but worsen muscle weakness if it was due to excessive dose of AChE inhibitors (excessive ACh stimulation at the neuromuscular junction results in muscle weakness due to maintained depolarization).

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| Tacrine<br>Donepezil<br>Rivastigmine<br>Galantamine | Inhibit AChE | Treatment of Alzheimer's disease. Tacrine has been replaced by the others because of its hepatotoxicity. None can stop the disease progression |

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| **Indirectly Acting (Irreversible) Agents (organophosphate, nerve agent)**<br>Isoflurophate (DFP)<br><br>Echothiophate | Covalently binds to AChE | In chronic management of open angle glaucoma (ointment, last for 1 week); it enters CNS, causes generalised cholinergic stimulation* (largely reversed by high dose of atropine); DFP ages in 6-8 hr<br>In chronic management of open angle glaucoma; duration of action (100 hr) |

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| **Reactivation of Acetylcholinesterase (AChE)**<br>Pralidoxime | Displaces organophosphate regenerating the enzyme | Poisoning with organophosphophorus compounds (before enzyme ageing occurs, i.e. loss of an alkyl group from the phosphorylated enzyme); it can reverse the effect of DFP except for those in CNS; less effective with newer nerve agents (enzyme ageing in seconds). |

## Case scenario

A 7-year-boy is brought to emergency department, he is lethargic and has excessive oral secretions and tearing. He has soiled his pants from urine and feces. His mother gave history of vomiting after a kid from school sprayed unidentified substance from his bottle while playing. The child was in good health before the incident. On physical examination constricted pupils are noticed, his blood pressure is 80/60 and heart rate is 46 beats/minute. Which drug is most likely to be effective in his condition?

1. Intravenous Corticosteroid
2. Intravenous Naloxone
3. Intravenous Atropine
4. Intravenous Edrophonium

## Cholinergic Blockers (Anticholinergic Drugs, cholinergic antagonists )

| Drug | Selected therapeutic uses and important remarks* |
|---|---|
| **Antimuscarinic agents** | |
| Atropine | In ophthalmology to produce mydriasis & cycloplegia prior to refraction (a single dose lasts for 7 days)<br>In spastic disorders of GI and lower urinary tracts<br>In organophosphate poisoning<br>In premedication prior to surgery, to suppress respiratory secretion in children |
| Homatropine | Cycloplegic for refraction in children (24 hr duration) |
| Tropicamide | Fundus examination (duration of 3 hr) |
| Scopolamine (hyoscine) | In obstetrics with morphine to produce amnesia and sedation<br>Motion sickness |
| Ipratropium | Asthma (inhalation) |
| Clidinium | With chlordiazepoxide (Librax®) in GI disorders like peptic ulcer, nervous dyspepsia, irritable bowel syndrome, spastic colitis, mild ulcerative colitis |

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| Isopropamide | With trifluoperazine (Stelabid®) in peptic ulcer, visceral spasm |
| Pirenzepine | Peptic ulcer (inhibits acid secretion), poorly enters the CNS, thus, no or little CNS side-effects |
| Propantheline | Peptic ulcer, irritable bowel syndrome, & urinary disorders of storage (urinary frequency, incontinence, nocturnal enuresis |
| Emepronium | Urinary disorders of storage (as above) |

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| CNS Agents<br>Benzotropine<br>Procyclidine<br>Benzhexol-HCl<br>Orphenadrine | (Centrally acting antimuscarinic antagonists)<br>Drug induced dystonias and Parkinson's disease |

***Dystonia*** *is a movement disorder in which a person's muscles contract uncontrollably.*

*A decrease in the dopaminergic activity (degenerative loss) is believed to be the underlying cause for Parkinson s disease*

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| Ganglionic blockers<br>Mecamylamine | |
| Trimethaphan | Moderately severe to severe hypertension<br>Short-term treatment of hypertension (emergency lowering of blood pressure, when other agents cannot be used) |

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| Neuromuscular blockers<br>Nondepolarising<br>(competitive agents)<br>Depolarising agents | See appropriate section in the chapter on CNS pharmacology (later on) |