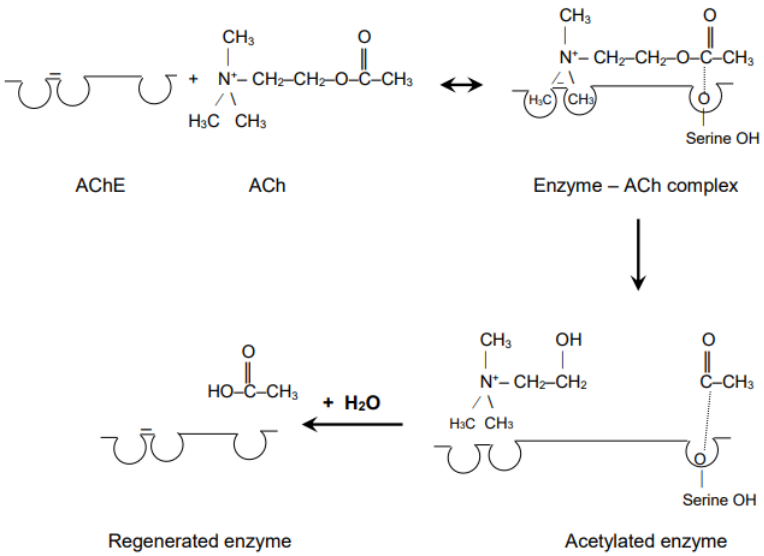
# Unit V: Introduction and classification of the drugs acting on: Autonomic nervous system

## (III) Cholinesterase Inhibitors:

These are indirect acting parasympathomimetic agents. They inactivate or inhibit AChE and pseudoChE and thereby intensify the activity of endogenous ACh.

**Acetylcholinesterase:** The active region of AChE forms a gorge which contains an aromatic anionic site formed by tryptophan and an esteratic site formed by serine, glutamate and histidine.

**Hydrolysis of ACh by AChE:** Hydrolysis of ACh involves electrostatic attraction of positively charged $N^+$ of ACh to the aromatic pocket and nucleophilic attack by serine –OH which is activated by the adjacent histidine leading to acetylation of the serine. The acetylated enzyme reacts with water to produce acetic acid and choline. The reaction is very fast.



**Reversible Inhibitors:**

**Mechanism of action:** These agents reversibly bind to the active sites of the enzyme, as they serve as alternate substrates for AChE. Edrophonium and tacrine attach only to the anionic site of the enzyme and tacrine inhibited enzyme does not involve hydrolysis of the inhibitor, but only its diffusion – so action is brief, whereas physostigmine and neostigmine bind to both anionic and esteratic sites of the enzyme. So, the carbamylation of the enzyme (with neostigmine and physostigmine) is of longer duration than the inhibition by edrophonium.

Thus, during the period where the enzyme inhibitor complex exists, the enzyme will not hydrolyze its natural substrate ACh.

1) **Physostigmine:** It is an alkaloid extracted from the dried ripe seeds of a vine, Physostigma venenosum which grows in tropical West Africa. It is also known as Calabar bean or "Ordeal bean". Now-a-days, physostigmine is used for its ability to constrict the pupil or as miotic and in the treatment of deadly nightshade poisoning.
2) **Neostigmine:** It is the salt of a synthetically produced substance structurally related to physostigmine. It is used as purgative and in the treatment of atony of urinary bladder.

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Table showing comparative features of Physostigmine and Neostigmine

| | Physostigmine | Neostigmine |
|---|---|---|
| 1. Source | Calabar bean | Synthetic |
| 2. Chemistry | Tertiary amine derivative | Quaternary ammonium compound |
| 3. Oral absorption | Good | Poor |
| 4. CNS actions | Present | Absent |
| 5. Applied to eye | Penetrates cornea | Poor penetration |
| 6. Direct action on cholinoceptors | Absent | Present |
| 7. Prominent effect on | Autonomic effectors | Skeletal muscle |
| 8. Important use | Miotic (in glaucoma) | Myasthenia gravis |
| 9. Dose | 0.5 – 1 mg (man) oral or parenteral<br>0.1 – 1% in eye drops. | 0.5 – 2.5 mg (man) i.m./ s.c |
| 10. Duration of action | Systemic - 4 to 6 hours<br>Eye – 6 to 24 hours | 4 to 6 hours. |

**Irreversible Inhibitors:**

**Mechanism of action:** Organophosphates act as irreversible inhibitors of the cholinesterases in mammals. These compounds irreversibly phosphorylate the esteratic site of both AChE and the non-specific or the pseudocholinesterase throughout the body. Endogenous ACh is not inactivated and the resulting effects are due to the excessive preservation and accumulation of endogenous ACh.

**Effects and toxicity:** Organophosphate poisoning produces diffuse cholinomimetic effects: profuse salivation, vomiting, defaecation, hypermotility of the GI tract, urination, bradycardia, hypotension, severe bronchoconstriction and excess bronchial secretions. These signs reflect excess activation of muscarinic receptors of post-ganglionic parasympathomimetic actions.

In addition to the muscarinic effects, skeletal muscle fasciculations, twitching and subsequently muscle paralysis occur. These effects are due to persistent excessive stimulation of the nicotinic receptors of skeletal neuromuscular junctions, resulting in the depolarizing type of striated muscle paralysis.

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Convulsions and frequently death are seen in organophosphate poisoning caused by the penetration of the agents into the CNS and subsequent intensification of the activity of ACh at CNS sites.

**Treatment of organophosphate poisoning:**

1) The first line of treatment consists of administration of atropine to counter muscarinic effects of ACh @ 0.2 to 0.5 mg/kg b.wt. (maximum dose = 1 mg/kg). It is administered as 0.15% solution of atropine in physiological saline.
2) The second line of treatment involves the use of oxime reactivators such as diacetyl monoxime (DAM), 2-pyridine aldoxime methiodide (2-PAM or pralidoxime), obidoxime etc. which reactivate the phosphorylated AChE enzyme and greatly accelerates clinical recovery. It also serves to reduce the quantity of atropine required. The usefulness of oxime reactivators is limited to a short period (minutes or hours depending on the compound) because the enzyme phosphate complex becomes resistant when a further group is removed by hydrolysis, a change known as "ageing".

**Therapeutic use of Irreversible inhibitors:**

(i) The only drug indication is the relief of glaucoma where a single instillation of dyflos (di-isopropylfluorophosphate) or echothiopate acts for several weeks.

(ii) Organophosphates and carbamates are used as insecticides for the control of insect vectors and ectoparasites.

## ❖ Anticholinergic Drugs (Parasympatholytics):

These drugs block muscarinic receptors only, so better known as antimuscarinic agents.

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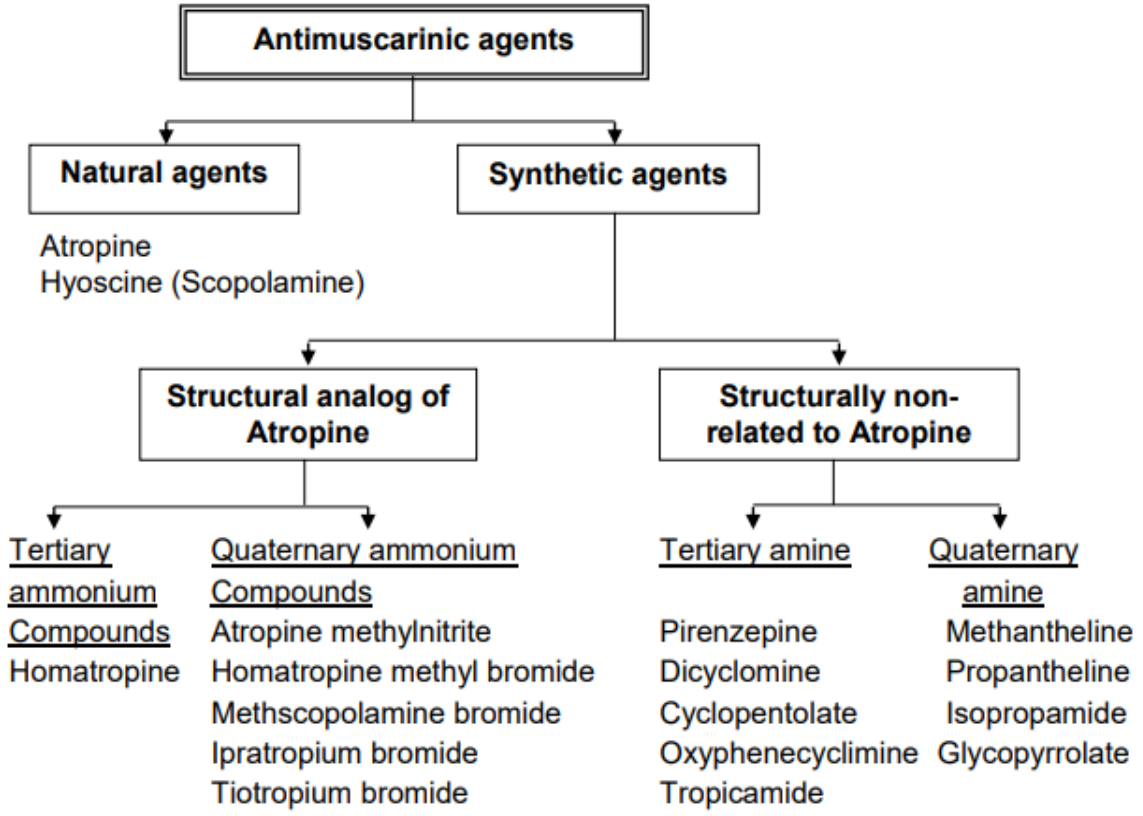
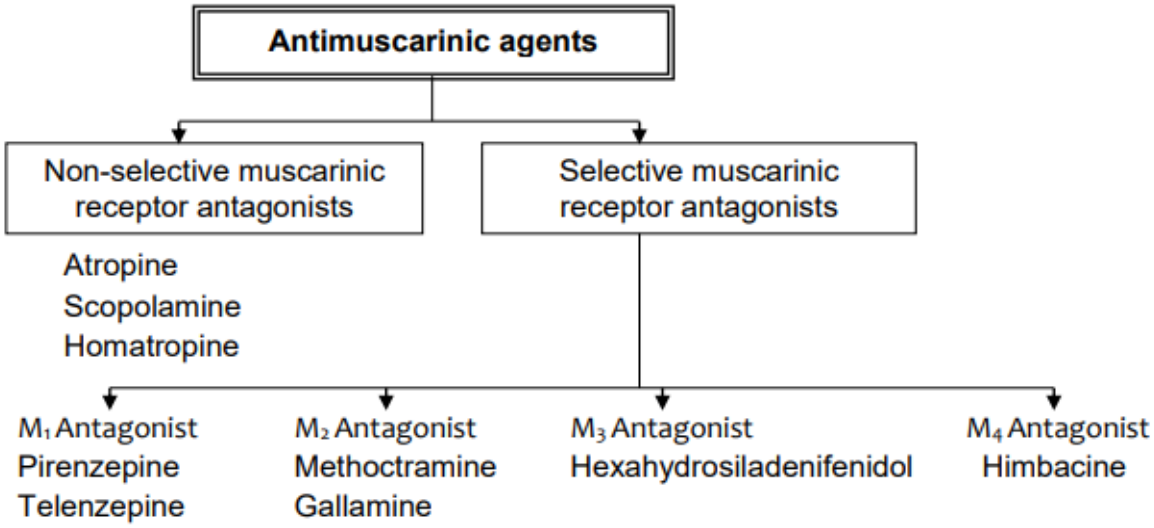
**CLASSIFICATION:**

**(I) Classification based on Origin & Structure:**




**(II) Classification based on Mode of Action:**




**Mechanism of action of muscarinic blockers:** Atropine and related drugs block the cholinergic muscarinic receptors by acting as competitive antagonists of ACh or other direct acting cholinergic drugs.