Autonomic Nervous System

- Parasympathomimetic drugs
- Parasympatholytics
- Sympathomimetics
- Sympatholytics

II-Indirect Cholinomimetics

[Cholinesterase Inhibitors or Anticholinesterases]

They are classified into:

	Reversible	Irreversible
Binding to Ch.E.	Loose	Firm
Activity of Ch.E.	Enzymes can regain activity	Enzymes cannot regain activity
Duration of action	Short	Long(till synthesis of new enzymes)
Examples	Physostigmine, neostigmine and neostigmine substitutes	Organophosphorus compounds

Cholinesterase Inhibition leads to increase in Ach percentage.

Toxicity: Overdose

Muscarinic : Bradycardia, hypotension, bronchospasm, miosis, vomiting, diarrhea and ↑↑ secretions.

Nicotinic : muscle twitches. → in any location

CNS: (with physostigmine only)

- Convulsions & collapse
- Coma
- Death from RC depression

Q) What an overdose of phyostigmine would do the CNS?

Treatment of toxicity:

1- Stomach wash.

2- Oxygen and artificial respiration. → Because the RS would be impaired and collapsed

3- Atropine.

4- Anticonvulsant in case of seizures.

According to the binding with Ch.E. enzymes:

For the ch.E Inhibitor

1- Bind reversible by electrostatic bond with **anionic** site (Negative charge) → Edrophonium

2- Bind reversibly with both **anionic & esteratic** sites

Physostigmine, neostigmine.

3- Phosphorylation of the esteratic site → Organophosphorus compounds

إضافة الفوسفور

(1) Reversible cholinesterase Inhibitors

	Physostigmine	neostigmine
Source & chemistry	Natural plant alkaloid Tertiary amine	Synthetic Quaternary ammonium compound
Absorption & distribution	Complete oral absorption Passes BBB	Partial oral absorption . Cannot pass BBB
Metabolism	Both are metabolized by cholinesterase	
Actions	***1-Muscarinic*** (eye): Miosis, accommodation for near vision, ↓↓ IOP, lid twithches, lacrimation] ***2- Nicotinic*** ⟶ Muscle twitches (Indirect action only) ***3- CNS***: Stimulation (convulsions in high doses)	***1-Muscarinic*** (mainly GIT& urinary tract) ***2- Nicotinic*** ⟶ Muscle twitches (direct & Indirect action) ***3- CNS:*** no action

Clinical uses:

Physostigmine :

A) Eye drops:

1- Glaucoma.

2- Counteracts action of mydriatics after fundus examination.

3- To cut recent adhesion between iris and lens [alternatively with mydriatics].

B) Alzheimer dementia **but** newer drugs are better.

C) Atropine toxicity: It antagonizes central and peripheral action **but** not preferred due to CNS toxicity

Neostigmine : Uses to cure

1- Reversal of paralysis induced by non-depolarizing neuromuscular blockers during surgical operations.

2- Postoperative retention of urine (Catheterization is better alternative).

3- Postoperative paralytic ileus.

4- Myasthenia gravis. ⇒ Severe Weakness of the Muscle

5- Antidote to atropine toxicity.

6- Glaucoma.

✱ Remember ⇒ Neostigmine is used to Inhibit the Ch.E. Aims for More Ach.

	Edrophonium	Pyridostigmine Ambenonium	Benzpyrinium	Demecarium
Selectivity	Skeletal muscle	Skeletal muscle	GIT & Urinary tract	Eye
Uses	1- Diagnosis of myasthenia gravis → improves 2- Treatment of myasthenia crisis 3- Differentiation between myasthenia crisis & cholinergic crisis: ▪ Myasthenia crisis improves ▪ Cholinergic crisis worsens	Treatment of myasthenia gravis (longer duration than neostigmine & more specific) Q) Why it is better drug than neostigmine?	1- Postoperative urine retention 2- Postoperative paralytic ileus	• Glaucoma

Myasthenia gravis

Muscle weakness and increased fatigability resulting from a failure of neuromuscular transmission due to formation antibodies against motor end plate → loss of nicotinic receptors.

Diagnosis: Edrophonium IV or neostigmine SC + Atropine [to block unwanted muscarinic actions] → improvement. so we know that the patient was suffering from Myasthenia gravis.

Treatment :

1- Neostigmine or Pyridostigmine + Atropine.

2- Adjuvant treatment : ephedrine or caffeine (potentiates neostigmine & facilitate NM transmission

3- Others : to decrease antibodies

- Steroids (e.g. prednisolone) or immunosuppressant drugs e.g. azathioprine.
- Plasmapharesis to wash antibodies.
- Thymectomy. => Responsible for Antibody-Antigen Reaction + lymphoid tissue development.

Drugs contraindicated in myasthenia gravis:

1-Skeletal muscle relaxants. 2- Aminoglycosides 3- β-blockers.

N.B.

- **Myasthenia crisis:** severe muscle weakness due to ***under treatment*** with anticholinesterase drugs → Edrophonium produces muscle improvement.
- **Cholinergic crisis:** severe muscle weakness due to ***over treatment*** with anticholinesterase drugs [sustained depolarization] → Edrophonium produces more weakness.

Alzheimer's disease

Alzheimer's disease (AD) is a common age-related dementia.

The main pathological features of AD comprise amyloid plaques & loss of neurons (***particularly cholinergic neurons of the basal forebrain***).

Drugs approved for the treatment of AD:

1- Cholinesterase inhibitors:

- **Tacrine** is a drug with anticholinesterase activity, has been used for the treatment of mild to moderate Alzheimer's disease but hepatotoxic.
- **Donepezil, galantamine, and rivastigmine** are newer, more selective and lack the hepatotoxic effect of tacrine.

2- Memantine [NMDA receptor antagonist] → inhibiting glutamate-induced excitotoxicity and neuronal damage. The drug improves cognitive function in moderate-to-severe AD.

(2) Irreversible cholinesterase Inhibitors

- Echothiophate &Isoflurophate ⟶ eye drops for glaucoma.
- Ware gases [e.g. sarin & soman].
- Thiophosphate insecticides [e.g. Parathion & Malathion]

Pharmacokinetics:

- All organophosphates (except for **echothiophate**) are well absorbed from the skin, lung, gut, and conjunctiva and distributed to all parts of the body, including CNS.
- The thiophosphate insecticides (parathion & malathion) are prodrugs. They are rapidly activated in insects and vertebrates. **Malathion** (not parathion)is rapidly metabolized by other pathways to **inactive products** in **birds** and **mammals** but **not in insects** (considered to be relatively safe).

N.B. Fish cannot detoxify malathion

Pharmacodynamics:

- They cause irreversible inhibition of cholinesterase by formation of ***covalent bond*** with its esteratic site.
- At first loose then non-competitive block [aged enzyme].
- Accumulation of huge amount of Ach ⟶ over-activation of cholinoceptors at NM junction and at autonomic and central nervous system.
- Their actions ended by resynthesis of new cholinesterases.

Organophosphorus poisoning

Causes :

1- **Occupational** inhalation or contamination of skin, clothes and food with insecticides.

2- **Suicidal.**

3- **Wars.**

Clinical manifestations:

- **Muscarinic :** Salivation, miosis, sweating, vomiting, colic, bradycardia and bronchospasm.
- **Nicotinic :** Muscle fasciculation then muscle weakness and paralysis.
- **CNS :** Confusion, convulsions the CNS depression.
- **Cause of death: Respiratory failure.**

Treatment:

1. Remove contaminated clothes and wash the skin by soap or NaHCO3.
2. Aspiration of secretion and artificial respiration.
3. Gastric lavage.
4. **Atropine** 1 mg IV every 10 minutes till full atropinization [dryness of mouth, mydriasis and tachycardia]. The patient is kept full atropinized for 24 hrs.

5. **Cholinesterase reactivators [oximes]:** in cases of Ach toxicity.

   ❖**Pralidoxime (PAM):** [30mg/kg bolus dose then 8mg/kg/hr IV infusion until clinical improvement] can break the bond between organophosphates and the enzyme, so the enzyme becomes free and hydrolyzes Ach at the receptors.

   ❖**Diacetylmonoxime (DAM):** like pralidoxime but can cross BBB and reactivate central cholinesterase.

6. Diazepam for convulsions, and artificial ventilation for respiratory failure.

Note:

- Early after intoxication and formation of organophosphate-enzyme complex (ionic bond) → spontaneous reactivation of the enzyme can occurs that can be hastened by oximes.
- Within a few hours, the organophosphate-enzyme complex loses one alkyl group renders it no longer susceptible to reactivation → ageing. So cholinesterase reactivators should be administered as early as possible.