Cholinergic drugs
Cholinergic neurons

They are found in:
CNS, adrenal medulla, autonomic ganglia
(sympath. And parasympath )
Neurotransmission

1-Synthesis.
2-Storage.
3-Release.
4-Binding to Receptors.
5-Recycling.
Cholinergic receptors

1- Muscarinic Receptors (M 1-5).
2- Nicotinic Receptors (Nn, Nm).
Location (Of Musc. Receptors)

Nervous system contain all 5 sub types.
M1: Gastric parietal cell (increase gas. Acid)
M2: Heart (S A node, Contractility)
M3: Smooth muscle (eye, Gut, bladder wall, sphincters, bronchi and exocrine gland).
Nicotinic Receptors

These are:

Nn: Neuronal type ganglionic receptors they found in the CNS, Autonomic gang. And adrenal medulla).

Nm: Muscle type or end plate receptors, found in the skeletal m. (neuromuscular junction.)
Cholinergic drugs
agonists (cholinomimetics)

1-Direct acting cholinomimetic.
2-Indirect acting cholinomimetic (C E inhibitors).
1-Direct acting cholinomimetic
They act by binding directly to cholinreceptor.
Have longer duration of action than Ach.
The effects include the action of generalized stimulation. Such as
Salivation
Profuse sweating
Flashing
Bronchospasm
Diarrhea and abdominal pain
Is therapeutically of no importance because its rapid inactivation by Ach E. have both musc. And nicotinic activity.

**Pharmacological action:**

**CVS:** decrease HR and C.O.

- **B.V.:** vasodilation
- **B. P.:** hypotension
Respiratory system: Bronchospasm, increase bronchial secretion.

GIT: Increase

  Salivary secretion

  intestinal secretion and motility

  Relaxation of sphinctors


Eye: miosis (constriction of pupil)
Carbachol (carbachol)

Has both M and N action.

**Pharmacological action:**
It has some selectivity on s.m. of the Gut and urinary bladder.

It can cause release of adrenalin from adrenal medulla by its nic action.

Applied topically to the eye (cornea), it cause miosis and decrease I.O.P. (treat glaucoma).

**Uses:**
Its rarely used therapeutically except for glaucoma.
Bethanecole

It's not metabolised by AchE but inactivated by other esterases.

Its major action on s.m. of G.I.T. and urinary bladder.

Uses:

Pilocarpine

Not metabolized by AchE.
It’s the drug of choice in the emergency lowering of IOP of both narrow angle and wide angle glaucoma.

Side effect:
Sweating and salivation.
Indirect acting cholinomimetics (ChE inhibitors)

ChE enz that cleaves Ach to choline and acetate. Inhibition of this enz. Prolong the life time of the endogenous Ach.

These inhibitors are either reversible or irreversible agents:

A- The reversible are:
1- Physostigmine
2- Neostigmine
3- Pyridostigmine
4- Edrophonium
5- Tacarin
Physostigmin

Has a wide range of action because it stimulate not only musc. and Nm receptors it can enter and stimulate CNS.

Duration of action about 2-4 hr.

**Uses:**
1- Atony of intestine
2- Atony of Bladder
3- glaucoma
4- As antidote of drug with anticholinergic action such as atropine and TCA.
5- Alzheimer dementia.

**Side effect:**
Rarely seen with therapeutic doses (convulsion, bradycardia, sk. M. paralysis).
Neostigmine

Compared to phys. It does not enter CNS
Its duration of action is similar to that of physo.

Uses:
1- Atony of intestine
2- Atony of Bladder
3- As antidote for tubocurarine and other competitive N-M blocking agents.
4- Symptomatic treatment of Myasthenia gravis.
Pyridostigmine

Slower in onset
Longer duration of action (3-6 hrs)
Used in chronic management of Myasthenia gravis.

Edrophonium

Its action is brief (10-20 min)

Uses:
1. To diagnose Myasthenia gravis.
2. To differentiate Myasthenia crisis from a cholinergic crisis.

Tacarin

Is centrally acting
Used to treat dementia.
B- Irreversible Ch E inhibitors(synthetic organophosphorous compounds)

- They bind to AchE resulting in a long-lasting increase in Ach at all sites where it is released.
- Restoration of AchE activity requires the synthesis of new enzymes, which may take weeks.
- Many of these are extremely toxic or insecticides.
- Absorbed through the skin, GIT, and by inhalation.
Action (typical features of poisoning)

1- Generalized cholinergic stimulation.
2- Paralysis of motor function (m. weakness).
3-CNS effect  
(miosis, anxiety, headache, convulsion, resp. failure and even death).

Treatment:
Atropin in high dose given IM or IV immediately and repeated every 15-60min until HR become more than 70 beat/min
Some time Mechanical ventilation may be needed to assist the respiratory m.
These drugs are:

1- Isoflurophate. (glaucoma)
2- Echothiophate (glaucoma)

Nerve gases:

3- Paraoxon
4- Tuban
5- Sarin
6- Soman
Cholinergic antagonists

1- Muscarinic receptor blockers.

2- Nicotinic receptor blockers (Ganglionic blockers) (Nn).

3- N-M blockers:
   a- Competitive (non-depolarizing)
   b- Noncompetitive (polarizing)
Muscarinic receptor blockers

1- Atropine

Its a competitive antagonist of mus. Receptors in both central and peripheral N.S.

Its DoA is 4hr. But locally last for days.

**Action:**

- **CVS:**
  - heart: at low doses (brady cardia)
  - at high doses (tacky cardia)

- **B.V.:** at high dose cause vasodilation.

- **Resp.:** bronchial m. relaxation.

- **U.T.:** decrease motility and urinary retention may occur.

- **G.I.T.:** decrease tone and peristalsis.

- **Eye:** mydriatic agent (increase IOP).

- **Exocrine gland:** Decrease:
  - salivary sec.
  - sweat gland sec.
  - lacrimal gland sec.
  - bronchial sec.
Therapeutic uses

1- Ophthalmic: topical atropine (mydriasis)
2- Anti-spasmodic.
3- Anti-secretory agent (to block sec. preop.)
4- For bradycardia following M.I.
5- Antidote for cholinomimetic agents.

**Side effect:**

Dry mouth and eye, constipation, retention of urine, tachy cardia, blurred vision and attacks of glaucoma in pat. With narrow angle glaucoma. CNS: restlessness, confusion, hallucination resp. and circulatory collapse and death.
2- Homatropine
3- Tropicamide
4- cyclopentolate
used topically as mydriatics
5- Ipratropium: (used by inhalation as bronchodilator in asthma and COPD.
6- Hyosine (scopolamine):
Structurally related to atropine but has greater effect on CNS and longer DOA.

**Uses:**
1- prevention of motion sickness (D.O.C)
2- anti emetic

**Side effect:**
Similar to that of atropine.
7- Hyoscine buty bromide (anti-spasmodic agent).
8- Propantheline (s.m. relaxant for IBS).
10- Pirenzepine (dec. acid sec.) (for DU)
11- Flafoxate (selectivity on urin. Bladder used in urinary incontinance and frequency).

Drugs that improve both termer and rigidity of Parkinson disease.

12- Benzhexol, Orphenadrine and Benztropin
Ganglionic Blockers (Nn blockers)

These specifically act on Nic. Receptors in the autonomic gang.
Rarely used therapeutically.
They often serves in experimental pharmacology.

These includes:
1- Nicotine
2- Trimethaphan
3- Mecamylamine
Nicotine: Is the active ingredient in tobacco. Is not currently used therapeutically except in smoking cessation therapy.

**Action:**

Low doses causes (tachycardia, increase B.P., vasoconstriction).

High doses (decrease B.P. and motor activity of both bowel and urinary bladder).
Trimethaphan:
Is short acting competitive gang. Blockers. Must be given by IV infusion.
Used for emergency lowering B.P. when other agent can not be used.

Mecamylamine:
Its a competitive ganglionic blocker. Is effective orally.
Its DOA after single dose is 10min.
N-M blockers Drugs (Nm receptors blockers)

- They are structural analogue of Ach and act either competitive antagonist (non-depolarizing type or agonist(depolarizing type) at Nm- end plate of sk.m. causing blockade of cholinergic transmission bet. Motor nerve endings and Nm receptors.
- All these drugs are injected IV.
a- Competitive (non-depolarizing)

- Are poorly absorbed by GIT (thus given IV)
- Are poorly penetrate cell mem. And don’t enter CNS (water soluble).
- They compete and prevent Ach from binding Nm receptors. Thus they prevent depolarization of the m. cell membrane and inhibit m. contraction.
- Their action can be over come by increasing Ach concentration in the synaps (by ChEI like Neostigmin….ect) and thus the DOA of Nm blockade can be shortened.
- The sequence of paralysis 1- cont. m. of the face and eye 2- there after the limbs 3- neck 4- the trunk 5- then the intercostal m. And lastly the diaphragm.
Uses:
They used as ajuvant drugs in anesthesia during surgery to relax sk. M..

Drug interaction:
• Antagonize their action (chEI)
• Potentiate their action (Halothan, aminoglycosides, Ca-channel blockers).

**Tubocurarine** (time of max. blockade 2min.)

Side effect:
May induce histamine release, hotness.

**Atracuriam** (3min.):
Its used in mechanical ventilation of critically ill patient and its suitable for short surgical procedures.

**Mivacurium** (2min):
Useful for short surgical procedures.

**Rocurinum** (1min):
Rapid onset of action (useful for indotrachial intubation).
Noncompetitive (Depolarizing Nm blocking drugs)

Suxamethonium (succinyl choline):
Mechanism of action:
Is agonist drug that activate Nm receptors on sk. M.-end plate causes depolarization (sk. M. cont.) by its first application (because suxam. Is not destroyed by AchE).
It persist at high conc. In the synsps and the intial depolarization persists, By time there is resistance to this continious depolarization due to Nm desensitization and thus flaccid paralysis ocurre.

Uses:
1- Useful in rapid indotrachial intubation (rapid onset and short DOA).
2- During ECT treatment to induce sk m. relax.

Side effect:
1- Hyperthermia (malignant hyperthermia).
2- Apnoea