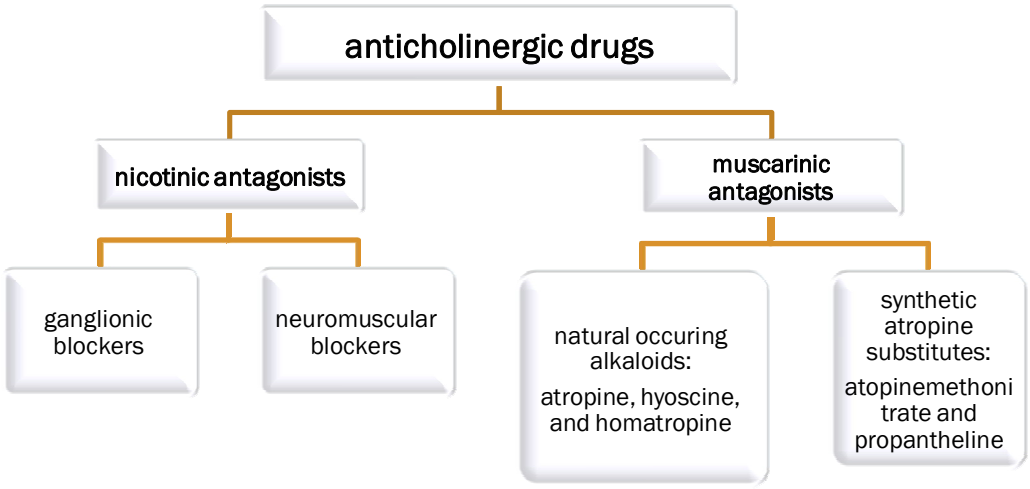
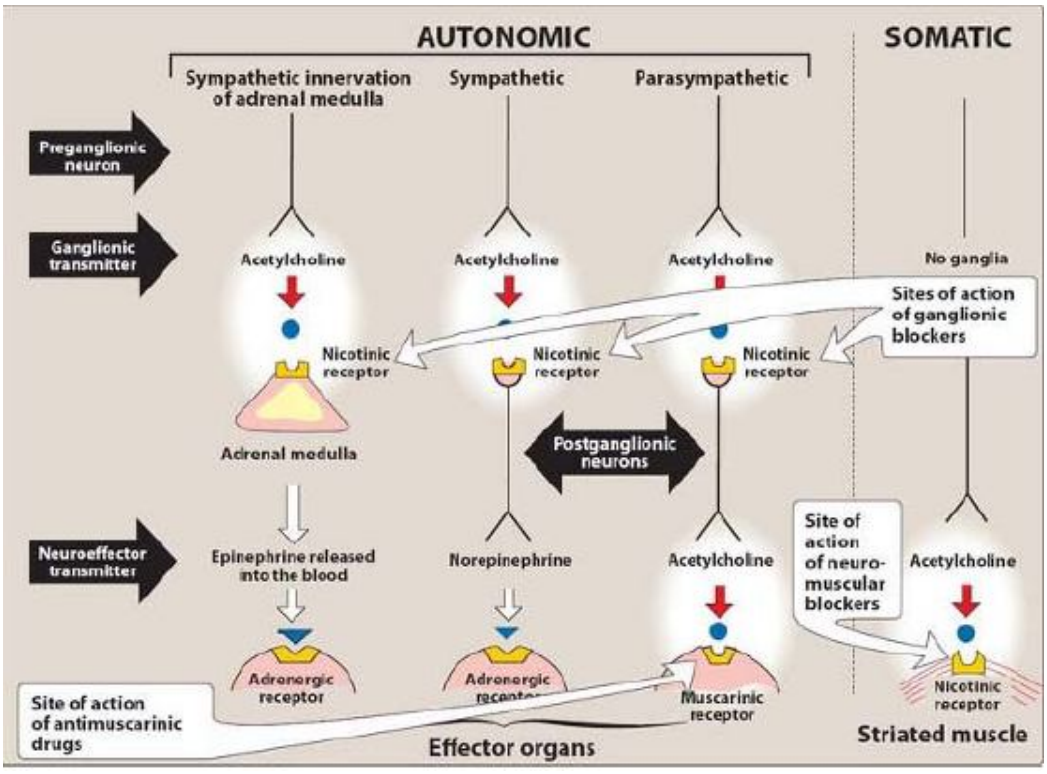
Ach Receptor Antagonist

Anticholinergic drugs: (Cholinoceptor antagonist)



NICOTINIC ANTAGONIST: Ganglionic blockers

- Little used nowadays, but they were first used as anti-hypertensive.
- They block the action of sympathetic and parasympathetic



Naturally occurring alkaloids (muscarinic)

- *E.g., atropine & hyosine*
  Atropine comes from a plant called Atropa Belladonna, Italian for (beautiful lady).

3°(tertiary) amine:

- Metabolized in the liver then excreted in urine after being converted to glucuronic acid derivatives.
  - 50% excreted unchanged (acidification will increase the excretion).
- Orally absorbed
- Crosses BBB - Non polar
- Has short duration of action on most organs.
  - half life 2 hours (except eyes:3-10days {*7 days*})
  - Ionized at physiologic pH

4° (quaternary) amine:

- Polar (don't cross BBB)
- Less absorbed
- E.g. atropine, methonitrate, propantheline.

Both tertiary and quaternary anticholinergic drugs are nonselective for muscarinic receptors, except **pirenzepine**, which is selective for M_1 receptors.

Mechanism of action:

- **Reversible competitive** blockers of Ach at all types of muscarinic receptors, thus they are **NON-SELECTIVE**.

Pharmacologic effects:

- Most sensitive organs to atropine are salivary, bronchial glands, and sweat glands

Organs Affected

- Intermediately effected organs are the heart, urinary tract, and bronchial muscles.
- The most resistant organs are gastric glands and pancreas

1. CNS

- At clinical dose>>>Initial stimulation followed by slower longer - lasting CNS.sedative action .
- Hyoscine will give an immediate sedative effect only
- Vagal nucleus (**CIC** stands for **C**ardiac **I**nhibitor **C**enter) : initial bradycardia (central action : Vagal stimulation) followed by tachycardia (receptor blocking).
  - Action Potential from CNS , stimulate Vagal (central) discharge to the heart and cause (Bradycardia)
  - Later on , the discharge became peripherally → blocks the receptors of the heart and cause (tachycardia) .
- Antimimetic effect (block vomiting center)
- Antiparkinsonian effect (block basal ganglia)
- Toxic dose: hyperthermia - excitement – hallucination(is a perception in absents of stimulus) .

2. Eye

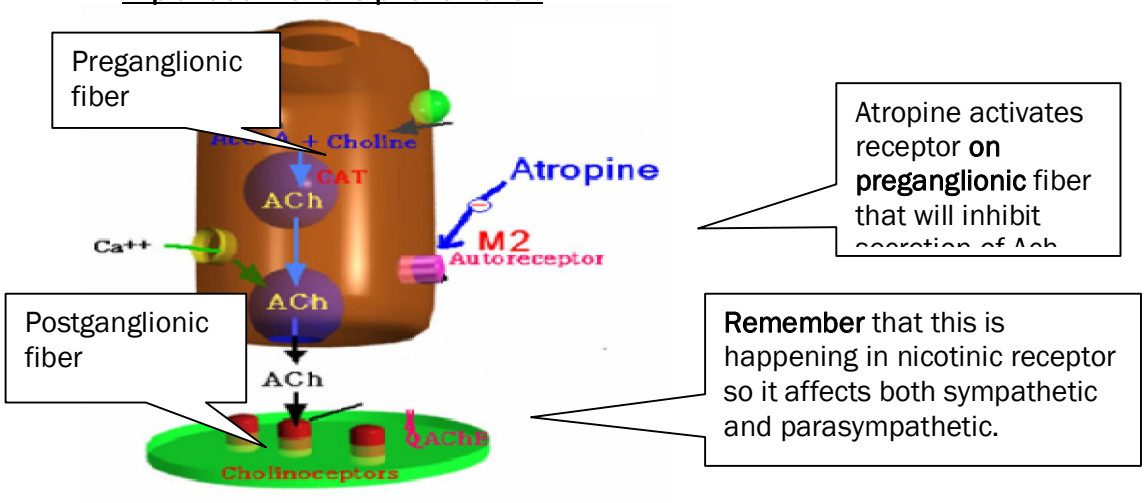
- Passive mydriasis (paralysis of sphincter pupillae).
- Indirect action by inhibiting parasympathetic lead to stimulation of sympathetic dilator activity.
- Cycloplagia (loss of accommodation to near vision) weaken of ciliary muscle lead to blurred vision. (fixed eye ball)
- Loss of light reflex lead to photophobia.
- I.O.P (intra-ocular pressur) contraindicated with glaucoma
    - Decrease lacrimal secretion→ sandy eye.

3. CVS

a. Heart

- Action on isolated heart *(in lab)* → tachycardia
- Action on human intact heart:Initial bradycardia followed by tachycardia.

Explanation for this phenomenon



- Increase in AV conduction (+ve dromotropic effect) and **Decrease** in conduction Time

b. Blood vessel

- Therapeutic dose: Decrease vasodilatation induced by cholinomimetics (M3)
- Toxic dose: cutaneous vasodilatation → atropine flush

4. Secretions

- Decrease salivary secretion → dry mouth
- Decrease sweating → dry skin →fever in infants & children (atropine fever)
- Decrease bronchial secretion → increase viscosity
- Decrease lacrimal secretion → sandy eye
- Decrease gastric secretion (less effective) → Decrease gastric motility

5. GIT

- Relaxation of smooth muscle (constipation)
- Decrease GIT motility → antispasmodic effect.
- Increase sphincter contractions.

6. Urinary tract

- Relaxation of ureter's smooth muscles.
- Sphincter concentration.
- Urinary retention

7. Bronchial muscles

- Bronchodilation. (bronchial relaxation)
- Decrease bronchial secretion → inc. viscosity

8. Genitourinary tract

- Antimuscarinic drug have no significant effect on human uterus

Use of anticholinergic drugs:

Bradycardia (myocardial infarction).

In this case **vagal discharge** accompanies the pain of myocardial infarction leading to bradycardia.

Preansthetic medication to :

- Decrease salivary and bronchial secretion. (preventing respiration of the secretions)
- Protect the heart from excessive vagal tone .(preventing bradycardia in the surgery)

Antispasmodic in renal and intestinal colics .

Cholinomimetics or organophosphourous poisoning .

- PAM is the most important one , and then the Atropin.
- They cause regeneration of the enzyme .

Adverse effect and toxicity:

- Blurred vision: mydriasis.
- Tachycardia
- Atropine flush.
- Constipation.
- Urinary retention
- Dryness of the mouth
- Sandy eye.
- Malignant hyperthermia. (severe fever due to peripheral action = inhibition of sweating or central action = hyperthermia)
- Hallucination (delirium) ,excitation(agitation), confusion (toxic dose).

These effects can be reversed by:

- Gastric lavage.
- Anticonvulsant.
- Cooling blanket.
- Antidote-physostigmine (IV slowly).
- Quaternary amine poisoning is reversed by quaternary cholinesterase inhibitor.
- Hypotension reversed by sympathomimetic.

Contraindiations:

- Glaucoma.
- Tachycardia secondary to thyrotoxicosis or cardiac insufficiency.
- Prostate hypertrophy in old patients reason is they cause urinary retention.
- Constipation and paralytic ileus.
- Children (hyperthermia). even if it is in therapeutic dose !
- Asthma patients (increased viscosity).
- Non selective amine are not used in case of ulcer.

Hyoscine (scopalamine):

Differences between hyoscine and atropine:

1. Rapid onset of action.
2. Short duration.
3. Less mydriatic action (2-4 days)
4. Has amensic action.
5. Less CVS effect.
6. More CNS depressant action (increase sedation- inhibition of vomiting center)
7. Hyoscine can be absorbed transdermally (prolong duration) used in horn players and travelers.

Uses :

1. Preansthetic medication
2. Antimemtic action (motion sickness)(induction of vomiting due to movement)

Synthetic atropine substitutes :

A. Eye :

it is used for fundus examination of the eye

- Atropine : 7 days
- Hometropine : 24 hours .
- Cyclopentalate : 12 hours .
- Iropicamide : 6 hours

B. GIT :

- Peptic ulcer → pirenzepine (selective M1 blocker)
- antispasmodic : hyoscine butyl bromide , oxyphenonium .

C. parkinsonism :

- benzotropine

D. bronchial asthma :

- ipartropium bromide .
- Quaternary (doesn't cross BBB → no CNS action)
- taken by inhalation (bronchodilator)
- local action
- little effect on viscosity

3.

Clinical Uses of Antimuscarinic Drugs

1. CNS

Parkinson's Disease:

Cause: imbalance between ↓dopamine and ↑Ach in basal ganglia.
Treatment: benzhexol (trihexyphenidyl), **benztropine** (tertiary amine) → ↓Ach(The previous drug can act mainly on CNS ; more selective)

Motion sickness

Cause: vestibular disorders.
Treatment: Scopolamine (should be taken before starting the journey).
Can be taken transdermally, orally, or parenterally.

2. Ophthalmologic disorder:

- We use antimuscarinic drugs in case of ophthalmoscopic examination of the retina to facilitate the operation by causing mydriasis

e.g.

Drug	Duration of Effect (days)
Atropine	7–10
Scopolamine	3–7
Homatropine	1–3
Cyclopentolate	1
Tropicamide	0.25

- **We mainly use:** Cyclopentolate or Tropicamide because they have shorter half-lives.
- **Side effect:** loss of accommodation.
- We can use sympathomimetic drugs for mydriasis without loss of accommodation.

3. Respiratory disorders

Preanesthetic Drugs

- Antimuscarinic drugs are used to prevent the accumulation of bronchial glandular secretion which is induced by anesthetics, which might lead to the suffocation of the unconscious patient.
- Also, antimuscarinic drugs used to protect the heart of excessive vagal tone.

Bronchial asthma

- Parasympathetic activation→ bronchial constriction.
- **Treatment:** ipratropium bromide
- **Characteristics:**
  1-quaternary (doesn't cross BBB)
  2-taken by inhalation (reduced systemic effect)
  3-little effect on viscosity

Chronic obstructive pulmonary disease (COPD)

We also use antimuscarinic drugs especially **tiotropium.**

4. GIT disorders

We use muscarinic blockers in these disorders:

1. hypermotility & ulcer to facilitate endoscopy (Pirenzepine)
2. biliary and renal colic
3. Traveler's Diarrhea. Commonly used drugs are opioid derivatives such as diphenoxylate.
4. Irritable Bowel Syndrome (use **dicyclomine)**

5. Urinary disorders

- Urinary urgency
- Urinary urgency is usually elicited in a minor inflammatory bladder disorder.
- **Side effect:** urinary retention

6. Hyperhydrosis (excessive sweating)

- Relief is incomplete (apocrine rather than eccrine sweat glands are involved).
- Atropine is used preferably.

7. Cholinergic Poisoning :

- By cholinomimetics or organophosphorus (insecticide).
- And in case of mushroom poisoning.

MCQs

1. **Your pharmacology laboratory has been given a new compound for screening. It is found to increase heart rate, dilate the pupil, reduce glandular secretions and decrease gastrointestinal motility. You would classify this compound as a(an):-**
    1. alpha agonist
    2. antimuscarinic
    3. beta agonist
    4. parasympathomimetic

2. **Mydriasis without loss of accommodation:-**
    atropine
    sympathomimetic
    Scopolamine
    Tropicamide
    cyclopentolate

3. **Current primary therapeutic rationale for using anticholinergic preoperative medication:-**
    sedation
    antisialagogue effects(decrease salivation)
    both
    Neither

4. **Preferred anticholinergic drug when sedation is the principal objective, preoperatively:-**
    atropine
    glycopyrrolate
    hyoscine

5. **Anticholinergic drug most likely to be used clinically to promote bronchodilation:-**
    IV atropine
    aerosolized atropine
    aerosolized ipratropium bromide
    Scopolamine

6. **Which of the following is not a side effect of the cholinoreceptor blocker (Atropine)?**
    A. Increased pulse
B. Urinary retention
C. Bronchospasm
D. Mydriasis

7. **A patient is brought into the emergency room. Upon examination you find the following: a high fever, rapid pulse, no bowel sounds and dilated pupils that do not respond to light. His lungs are clear. His face is flushed and his skin is dry. He is confused, disorientated and reports 'seeing monsters'. Based on these symptoms, you suspect he has been 'poisoned'. Which of the following, is the MOST obvious and BEST choice as an antidote?**

A. Atropine sulfate
B. Physostigmine
C. Neostigimine
D. Acetylcholine

8. **You are working in the post anesthesia care unit of a hospital. You have just received a patient back from surgery and you are monitoring his status. Knowing that the patient has received atropine, which of the following statements/observations is UNEXPECTED?**

A. The patient is complaining of extreme thirst.
B. The patient complains he is unable to clearly see the clock located just across from him.
C. The patient's heart rate is elevated.
D. The patient reports he has cramping and diarrhea.