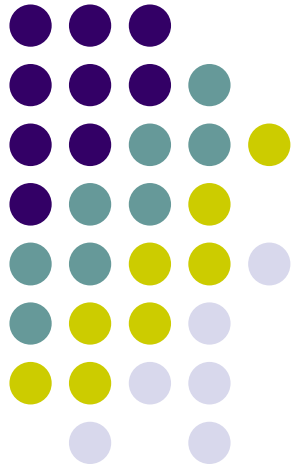
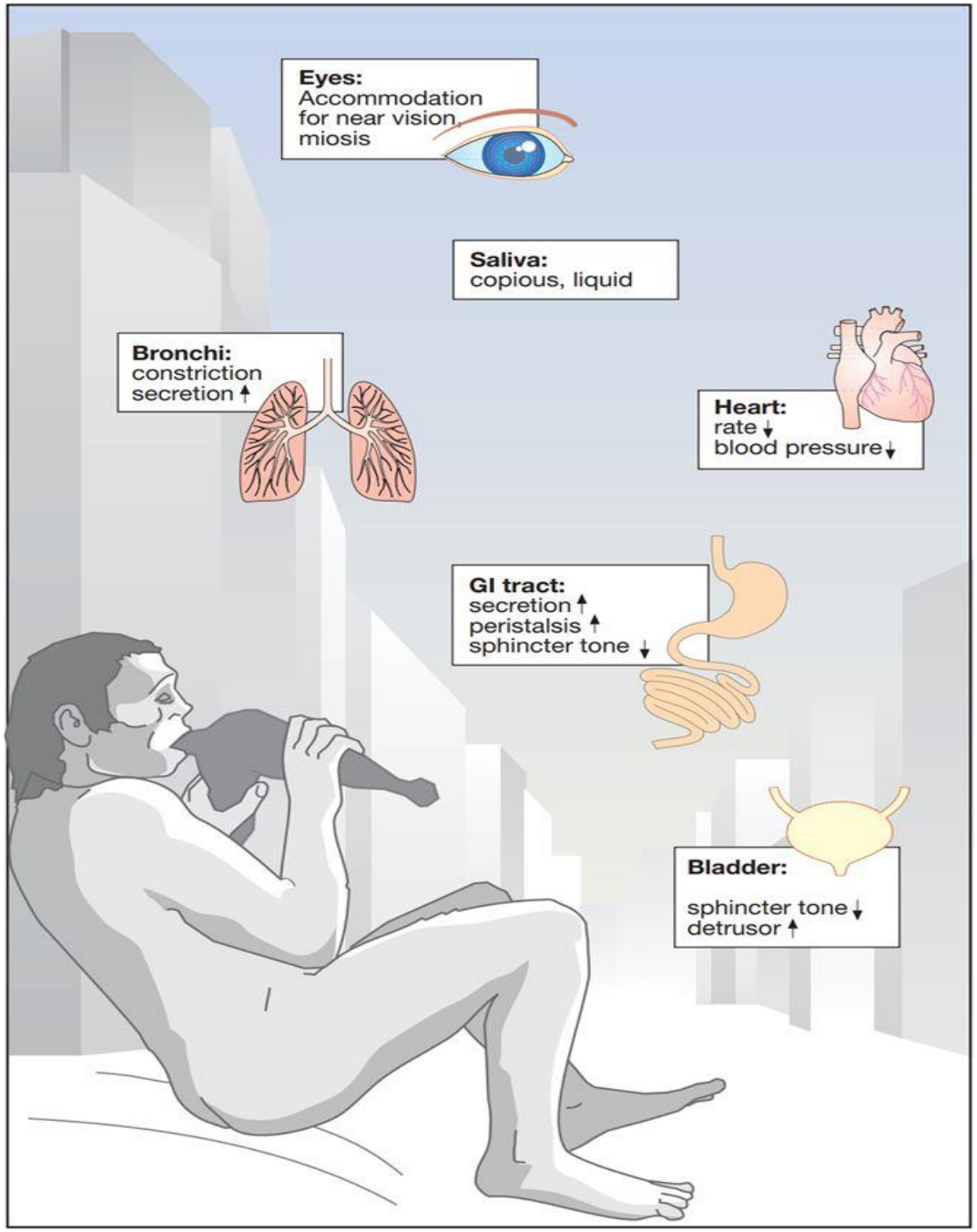
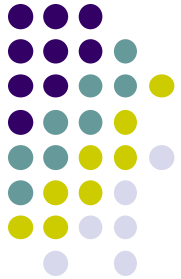
Parasympatholytics Anticholinergics

Dr. Asma Inam




Eyes:
Accommodation
for near vision
miosis
Saliva:
copious, liquid
Bronchi:
constriction
secretion ↑
Heart:
rate ↓
blood pressure ↓
GI tract:
secretion ↑
peristalsis ↑
sphincter tone ↓
Bladder:
sphincter tone ↓
detrusor ↑

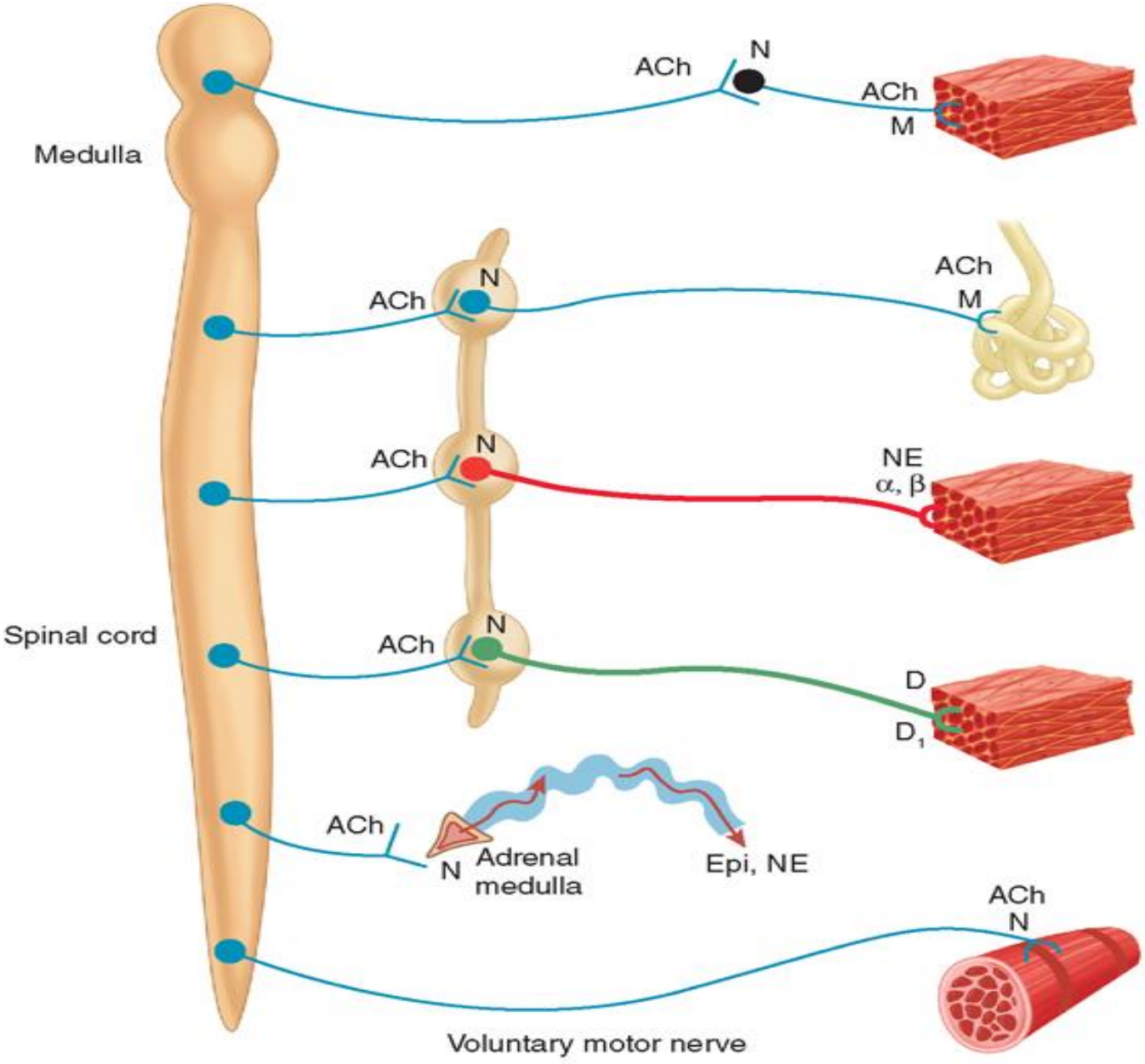
Cholinergic Antagonists: (Cholinergic blockers or anticholinergic drugs)



- They block the various types of cholinergic receptors.

1. **Antimuscarinic Drugs:**
   - They block the action of Acetylcholine at muscarinic receptors and also effects of parasympathetic nerve stimulation.

2. **Ganglion Blocking drugs:**
   - They block the action of Acetylcholine at autonomic ganglia. (Nicotinic receptors).
3. **Neuromuscular blocking drugs:**
   - They block the effect of Acetylcholine at N.M junction.



Source: Trevor AJ, Katzung BG, Kruidering-Hall M, Masters SB: *Katzung & Trevor's Pharmacology: Examination & Board Review*, 10th Edition: www.accesspharmacy.com

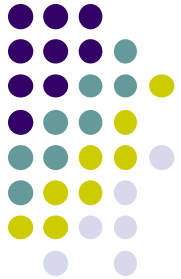
Classification:

- **Natural alkaloids:**
  - Atropine
  - Hyoscine
- **Semisynthetic compounds:**
  - Atropine methonitrate
  - Hyoscine methobromide
  - Hyoscine butylbromide
  - Homatropine methylbromide
- **Synthetic compounds:**
  - **Mydriatic and Cycloplegics:**
    - **Cyclopentolate**
    - **Tropicamide**
  - **Spasmolytics (antispasmodics)**
    - **Propantheline**
    - **Isopropamide**
    - **Ipratropium**
    - **Glycopyrrolate**
    - **Pirenzepine**
  - **Anti-Parkinsonism Agents:**
    - **Trihexyphenidyl**
    - **Benztropine**
    - **Biperiden**
    - **Procyclidne**
    - **Orphendrine**

- For urinary incontinence:
- Fesoterodine
- Tolterodine
- Dorifenacin
- Solifenacin
- Oxybutynin

- For Asthma and COPD
- Ipratropium
- Tiotropium

Antimuscarinic Drugs



- They reduce or abolish (block) the muscarinic receptor mediated effects of parasympathetic nervous system.

- The dosed required to block the responses to parasympathetic stimulation are greater than those required to block effects of exogenously administered drugs.

Some drugs have anti-muscarinic action as their secondary effects, such as anti-histamines, anti-depressants and anti-psychotic drugs.

ANTIMUSCARINIC DRUGS

- These drugs, for example atropine and hyoscine, block muscarinic receptors. In addition these drugs block the sympathetic neurons that are cholinergic, such as those innervating sweat glands.

ATROPINE (Prototype)

Source

Plant	Alkaloid
Atropa Belladonna	Atropine
Datura stramonium	Atropine
Atropa Acuminata	Atropine
Hyoscyamus niger	Hyoscine
Scopolia Carniolica	Hyoscine

Atropine

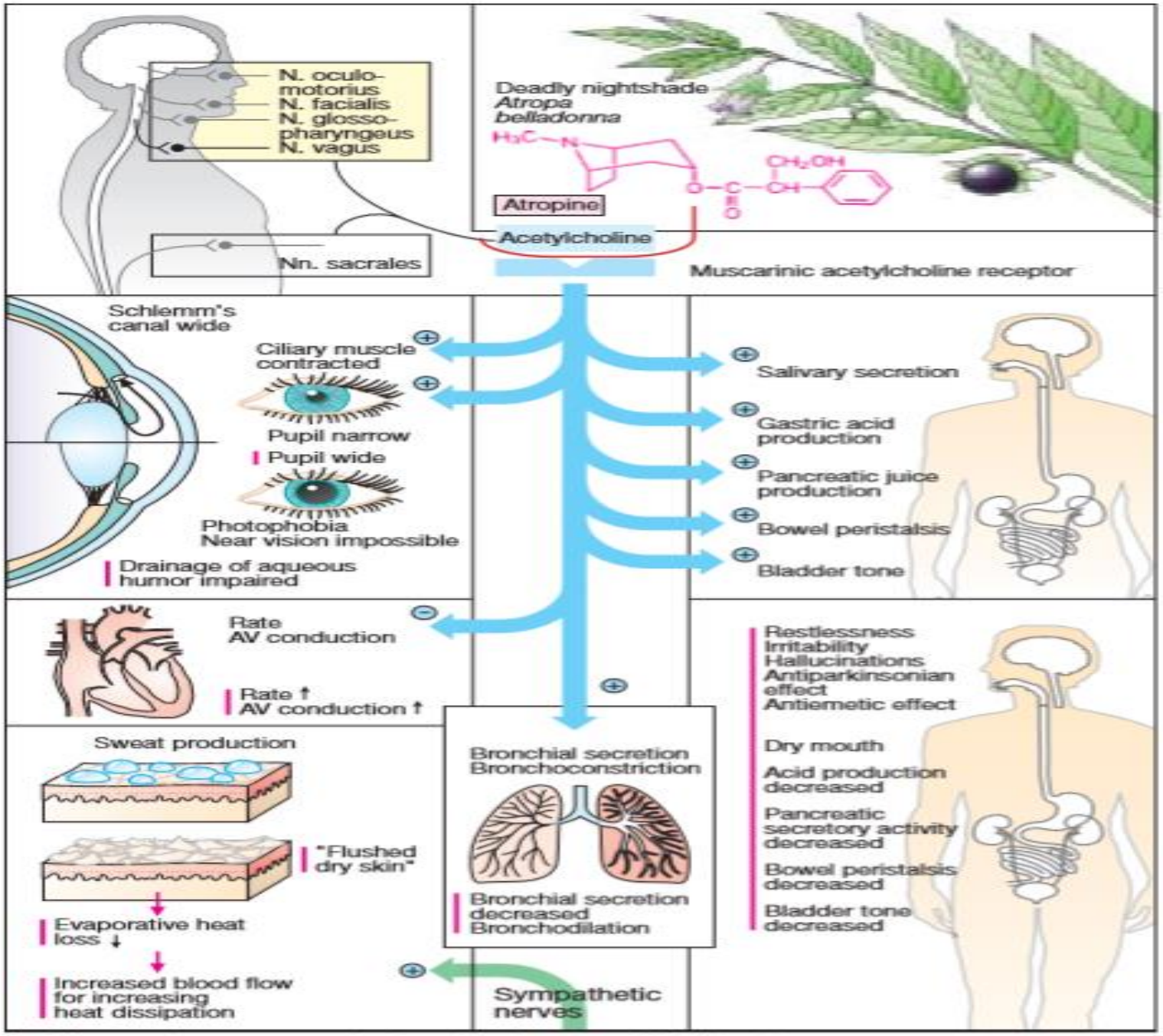
- **Chemistry:** atropine is a tertiary ammonium alkaloid ester of tropic acid with an organic base, tropine. Hyoscine is an ester of tropic acid with an organic base, scopine.

- **Mechanism of Action:** Atropine is a competitive antagonist of acetylcholine at muscarinic receptors. The action of atropine is reversible and can be overcome by increasing the concentration of acetylcholine or any other muscarinic agonist or by the use of anticholinesterase.

Atropa belladona

Atropine

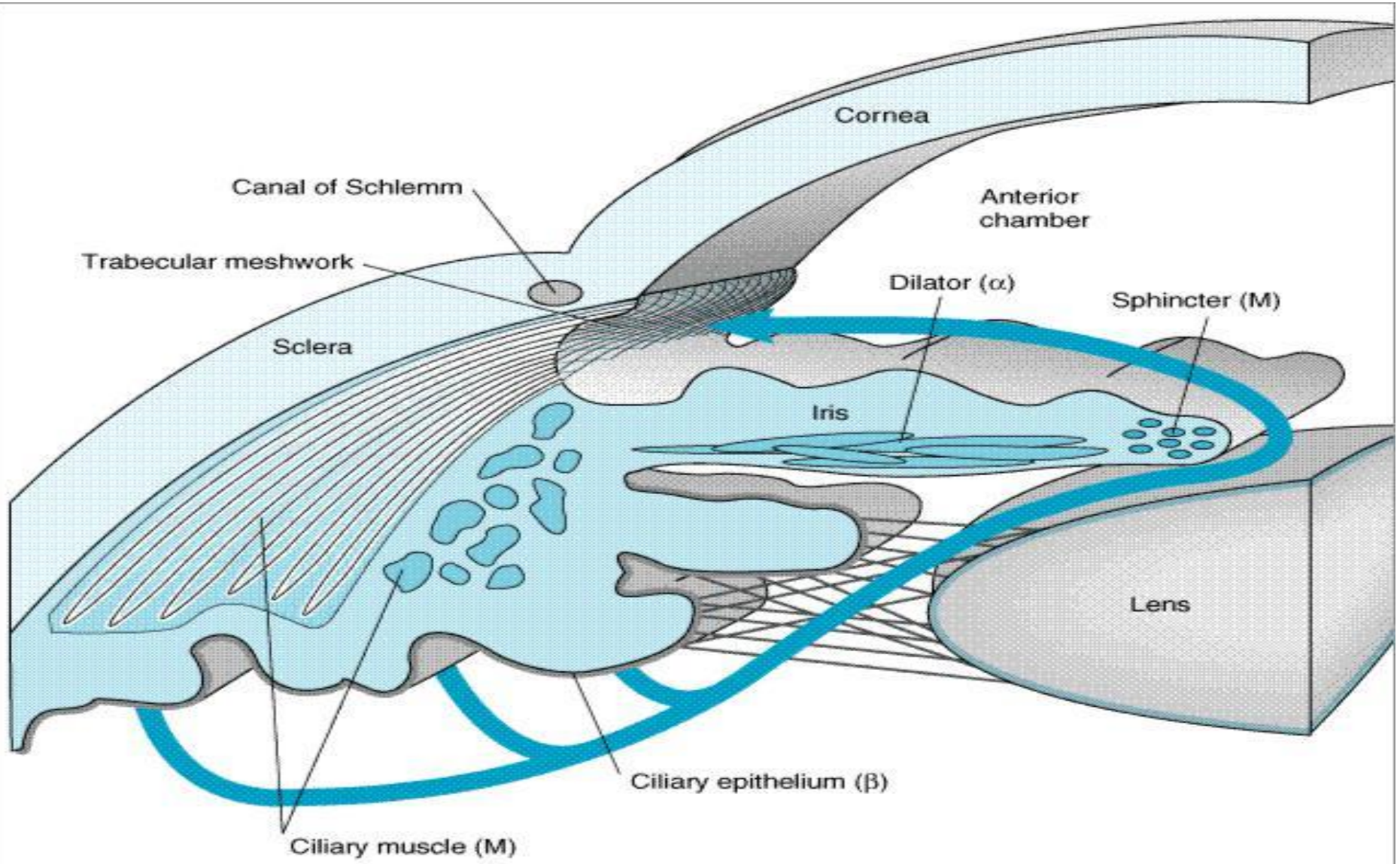
- **Pharmacokinetics:**
- lipid soluble.
- Rapidly absorbed from GIT and mucous membranes (conjunctiva).
- cross BBB (Blood-Brain Barrier) and placental barrier.
- half- life about 4 hrs.
- metabolized in liver. About half of the dose is secreted unchanged in urine.

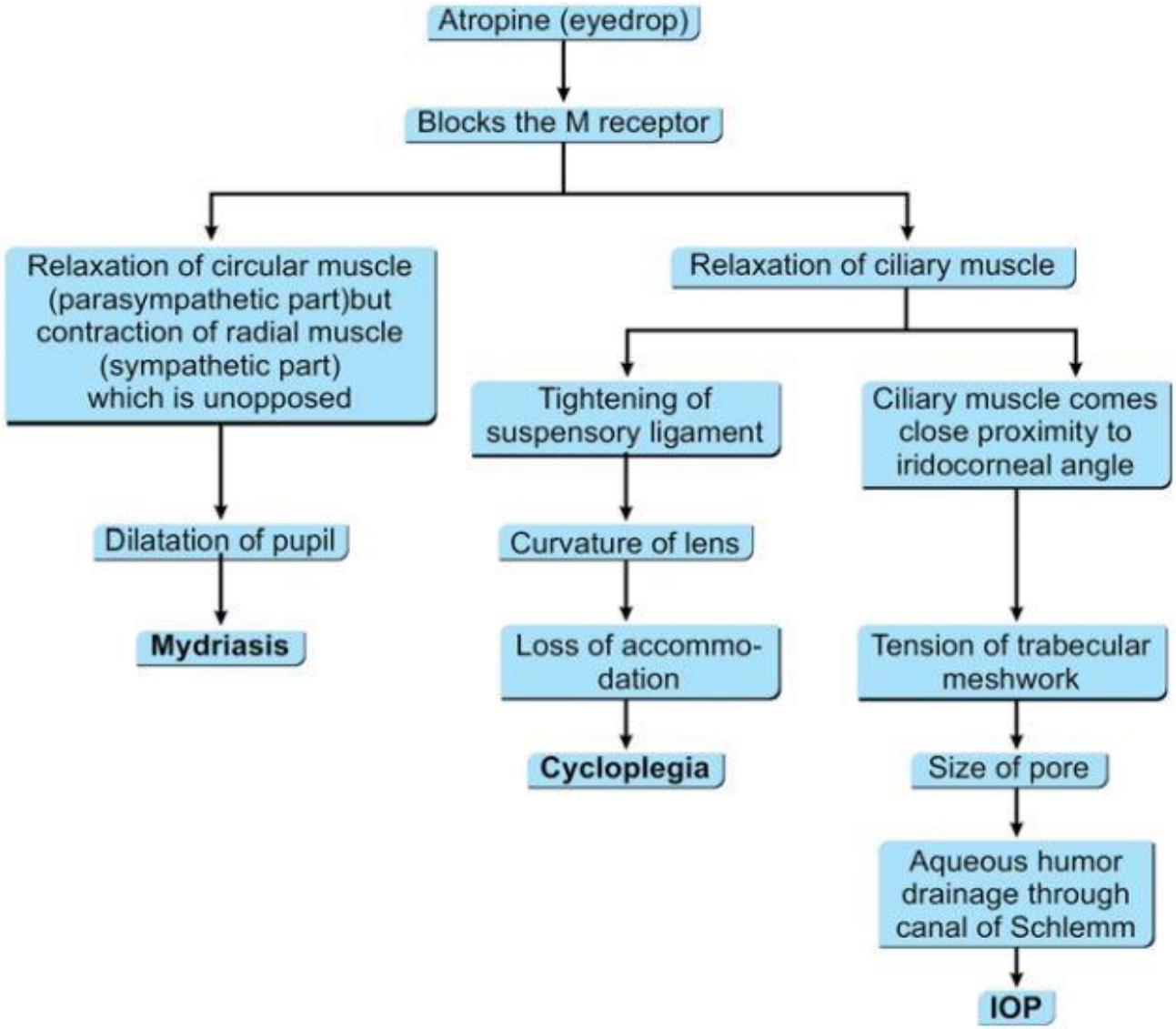


A. Effects of parasympathetic stimulation and blockade

Atropine

- **Pharmacological Actions**
  - **Eye:** Atropine blocks muscarinic receptors of circular muscles, causing their relaxation. The unopposed action of dilator pupillae (radial) muscles causes *'mydriasis'*. Light reflex is abolished and this caused photophobia.
  - The ciliary muscle is relaxed with paralysis (loss) of accommodation; the lens becomes flat and fixed for far (distant) vision. This is called cycloplegia.


Cornea
Canal of Schlemm
Anterior chamber
Trabecular meshwork
Dilator (α)
Sphincter (M)
Sclera
Iris
Lens
Ciliary epithelium (β)
Ciliary muscle (M)


Atropine (eyedrop)
Blocks the M receptor
Relaxation of circular muscle (parasympathetic part)but contraction of radial muscle (sympathetic part) which is unopposed
Dilatation of pupil
Mydriasis
Relaxation of ciliary muscle
Tightening of suspensory ligament
Curvature of lens
Loss of accommo-dation
Cycloplegia
Ciliary muscle comes close proximity to iridocorneal angle
Tension of trabecular meshwork
Size of pore
Aqueous humor drainage through canal of Schlemm
IOP

- There is increase in the intra-ocular pressure because the iris crowded back into the anterior chamber of the eye interferes with the drainage of aqueous humor.

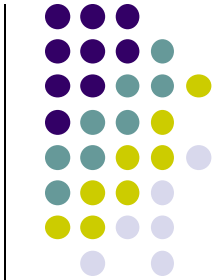
- In elderly patients with shallow anterior chamber, atropine can precipitate acute congestive glaucoma. Effects of atropine can occur after local or systemic administration.

Synthetic Atropine substitutes

- They include mydriatic, cycloplegic, Spasmolytics and antiparkinsonian drugs.

Drug	Duration of Mydriasis (Days)	Duration of Cycloplegia (Days)
Atropine	7-10	7-12
Cyclopentolate HCl	1	¼ - 1
Homatropine HBr	1-3	1-3
Hyoscine HBr	3-7	3-7
Tropicamide	¼	¼

Atropine



Gastrointestinal Tract:

- markedly reduces salivary secretions.
- Mouth becomes dry and swallowing becomes difficult.
- Gastric secretion is reduced in volume but H+ concentration remains unaltered.
- *'Pirenzepine'*, a M1 – muscarinic antagonist, does reduce gastric acid secretion in doses that do not antagonize other systems.
- reduces motility of the GIT..
- decrease in the tone as well as amplitude and frequency of peristaltic contractions.

Atropine

Gall Bladder:

mild antispasmodic effect on bile ducts and gall bladder

- cannot overcome the spasm of bile ducts induced by morphine.

Urinary Tract:

- decreases tone and amplitude of contractions of ureter and urinary bladder.
- Detrusor muscle is relaxed and sphincter contracts.
- urinary retention especially in elderly males with enlarged prostate.

Atropine

- **Respiratory Tract:**
- Atropine acts on the bronchial glands and bronchial smooth muscles. It reduces the secretions of the respiratory tract

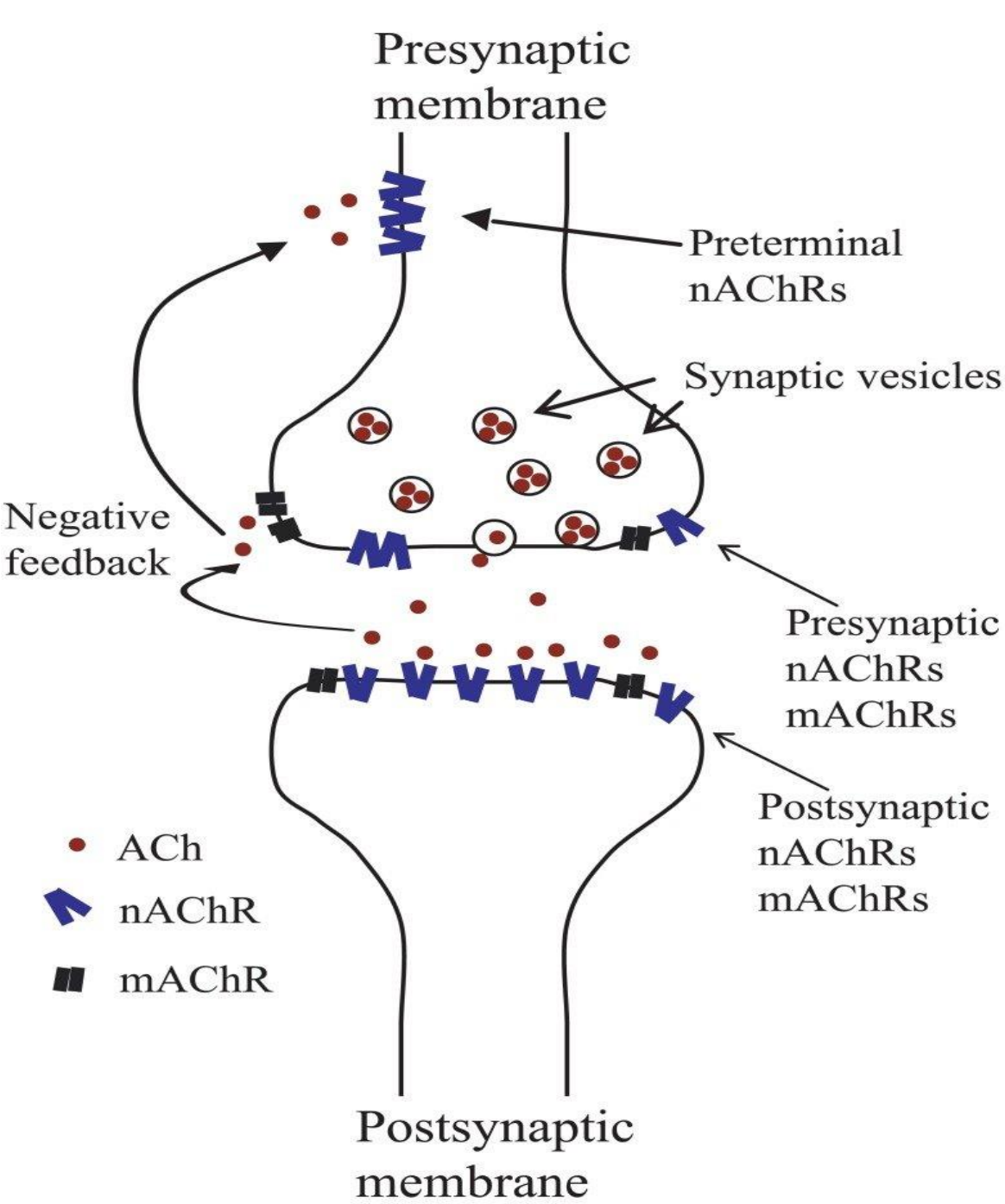
used a preanesthetic medication.

- Anesthetics, especially the Ether, stimulate bronchial secretions, which result in reflex bronchospasm.
- Atropine causes bronchodilatation resulting in increase in the rate and depth of respiration.
- Ipratropium bromide, a synthetic quaternary antimuscarinic compound used by inhalation.

Atropine

Cardiovascular System:

- biphasic action on the heart.
- causes transient bradycardia, especially noticeable at low doses. This initial bradycardia occurs due to:
- Blockade of pre-synaptic M1 receptors on post-ganglionic parasympathetic neurons.
- This is followed by tachycardia due to blockade of cardiac M2 receptors on SA node and AV node.


Presynaptic membrane
Preterminal nAChRs
Synaptic vesicles
Negative feedback
Presynaptic nAChRs mAChRs
Postsynaptic nAChRs mAChRs
ACh
nAChR
mAChR
Postsynaptic membrane

Continued ….

- used as pre-anesthetic medication as it may prevent excessive vagal slowing of the heart during anesthesia.
- In large doses there may be dilatation of cutaneous blood vessels (atropine flush) in face and neck, which may be due to direct action, unrelated to cholinergic innervation.

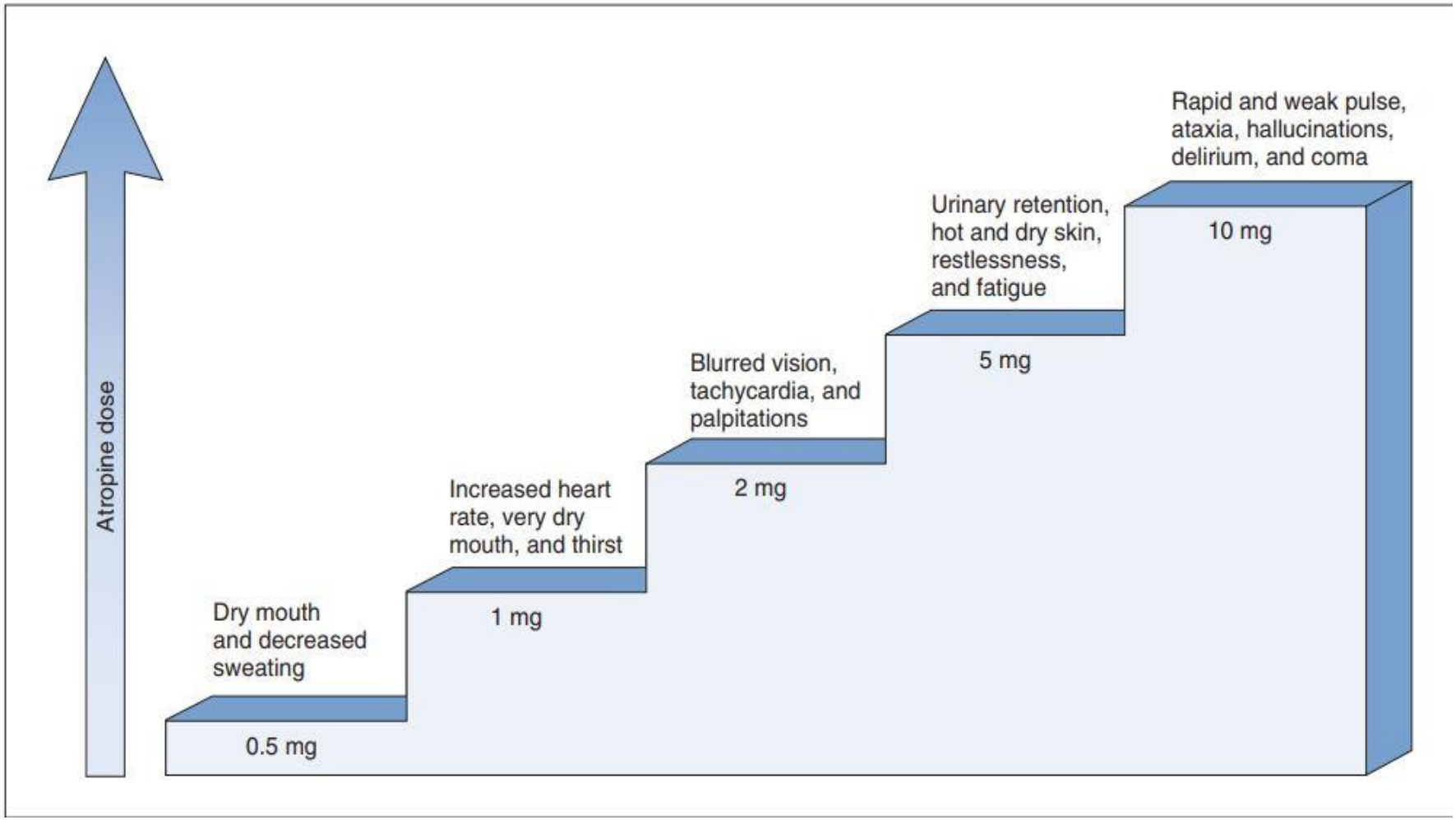
Sweat Glands:

- Sweat gland of the skin are innervated by sympathetic cholinergic fibers,
- blocked by atropine resulting in no sweating and no heat loss; there is rise in the body temperature. Infants and small children are more sensitive 'Atropine fever'.

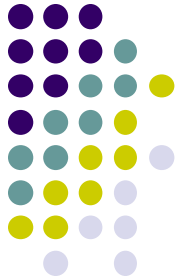
Central Nervous System:

- Atropine stimulates CNS. Large doses cause restlessness, irritability, hallucinations, and delirium.
- Stimulation is followed by depression. Atropine reduces tremors and rigidity in Parkinsonism, where there is cholinergic activity.

Dose dependent effects of Atropine



THERAPEUTIC USES OF ANTIMUSCARINIC DRUGS



Eye Conditions:

- Short-acting antimuscarinic drugs are used to produce mydriasis and cycloplegia.
- When only mydriasis is required, a sympathomimetic drug like phenylephrine is used.
- Longer acting drugs like atropine may be used alternately with a miotic agent to break the adhesions in uveitis and iritis.

Continued uses

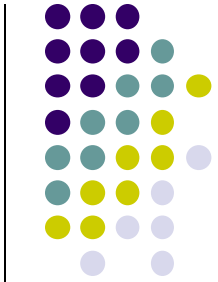
Gastrointestinal System:

- Antisecretory: Used in peptic ulcer
- Antispasmodic: used in intestinal colic, ulcerative colitis, biliary colic.

Genitourinary System:

- Used in ureteric colic, cystitis, incontinence of urine. (nocturnal enuresis).

Cardiovascular and respiratory system:



- Preanesthetic medication: useful in preventing:
  - Increased secretions of respiratory tract due to irritant effects of anesthesia.
  - Vagal effects of some anesthetics
- Bronchial asthma: Ipratropium is used by inhalation.
- Extreme bradycardia associated with:
  - Hyperactive carotid sinus reflex.
  - vasovagal syndrome.
  - sinoatrial arrest.
  - A-V block

Continued uses…

Central Nervous system

- Parkinsonism
- Motion sickness – hyoscine butyl bromide – prevention
- Twilight sleep: Hyoscine (scopolamine) in combination with narcotic analgesic pethidine is used in obstetrics to produce relaxed state associated with amnesia and analgesia called '*twilight sleep'*.

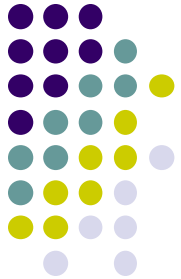
Uses continued …

- In the treatment of organophosphorus compound Poisoning.
- In treatment of mushroom poisoning.
- In treatment of myasthenia gravis, to antagonize the muscarinic effects of neostigmine.

Spasmolytics:

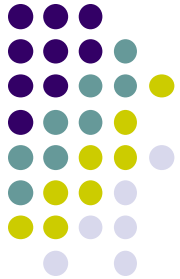
- They are quaternary ammonium compounds. Given orally. Used for gastrointestinal and genitourinary conditions. They reduce gastric motility, pylorospasm and gastric secretion.
- **Ipratropium Bromide**
- It is used as a bronchodilator, by inhalation. It does not interfere with the functions of ciliated epithelium of bronchial tree. So it can be used in chronic obstructive pulmonary diseases (COPD).
- **Pirenzepine**
- It is a tertiary amine. It is selective antagonist of M1 receptors, which are present in the intra-mural plexus of the stomach and reduced gastric secretions without interference with M2 receptor. It is used in the treatment of peptic ulcer.
- **Antiparkinsonism Agents**
- Have weak peripheral anticholinergic action, cross Blood-Brain barrier and act on the basal ganglia.

Semisynthetic Derivatives



- **Atropine Methonitrate:**
  - It is a quaternary derivative of atropine. It is used in congenital hypertrophic pyloric stenosis and pylorospasm in children.
- **Hyoscine Methobromide:**
  - It is a quaternary derivative of hyoscine. It is used in peptic ulcer, renal colic and cystitis.
- **Hyoscine Butylbromide:**
  - It is used for esophageal and gastrointestinal spastic conditions, peptic ulcer, spasm of ureter and bile duct.
- **Homatropine Methylbromide:**
  - Used topically as mydriatic and cycloplegic. It is also used orally to treat the spasm of GIT, bile duct and ureter.

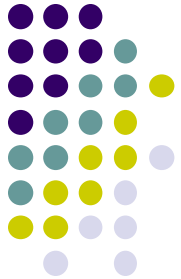
Precautions with Atropine-like drugs



- In patients over 40 years of age, with shallow anterior chamber, systemic or topical administration of these drugs may precipitate acute congestive glaucoma.
- In patients with enlarged prostate there may be retention of urine.
- In coronary artery disease atropine may precipitate angina.

- In patients with gastric ulcer, if it is given alone, delay in gastric emptying-time will expose the ulcer to acid for longer time.

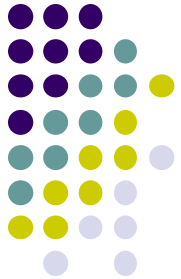
Poisoning of Antimuscarinic Drugs



- **Symptoms and signs:** They are due to peripheral blockade of muscarinic receptors and the actions on CNS.
- ***Peripheral muscarinic effects:***
- Dry mouth, dysphagia, thirst, constipation, pupils dilated, loss of accommodation, photophobia.
- Skin – Dry, hot, hyperpyrexia, rash in face and neck, Atropine flush.
- Palpitations
- Dysuria, retention of urine.

- ***Central nervous system effects:***
- They are not seen with semisynthetic and synthetic derivatives. They are:
- Excitement, restlessness, delirium, disorientation, hallucinations. This is followed by depression of vasomotor center and respiratory center.

Treatment



- Treatment of hyperpyrexia – ice bag, artificial respiration, oxygen.
- Removal of unabsorbed drug by gastric lavage with $KMnO_4$ or activated charcoal.
- To counteract excitement and convulsions – diazepam.
- Specific treatment – Physostigmine I/V.

ANTICHOLINERGIC SIDE EFFECTS

Hot as a hare

Dry as a bone

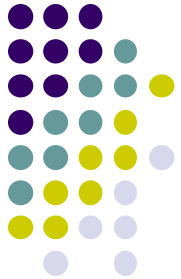
sketchymedicine.com

Blind as a bat

Red as a beet

Mad as a hatter

Ganglion blockers



- Hexamethonium
- Mecamylamine(smoking cessation)
- Trimethaphan

- Block nicotinic receptors competitively (PSM,SM)
- Used to treat hypertension

TABLE 8–2 Effects of ganglion-blocking drugs.

Organ	Effects
CNS	Antinicotinic action may include reduction of nicotine craving and amelioration of Tourette's syndrome (mecamylamine only)
Eye	Moderate mydriasis and cycloplegia
Bronchi	Little effect; asthmatics may note some bronchodilation
Gastrointestinal tract	Marked reduction of motility, constipation may be severe
Genitourinary tract	Reduced contractility of the bladder;impairment of erection (parasympathetic block) and ejaculation (sympathetic block)
Heart	Moderate tachycardia and reduction in force and cardiac output at rest; block of exercise-induced increases
Vessels	Reduction in arteriolar and venous tone, dose-dependent reduction in blood pressure; orthostatic hypotension usually marked
Glands	Reductions in salivation, lacrimation, sweating, and gastric secretion
Skeletal muscle	No significant effect