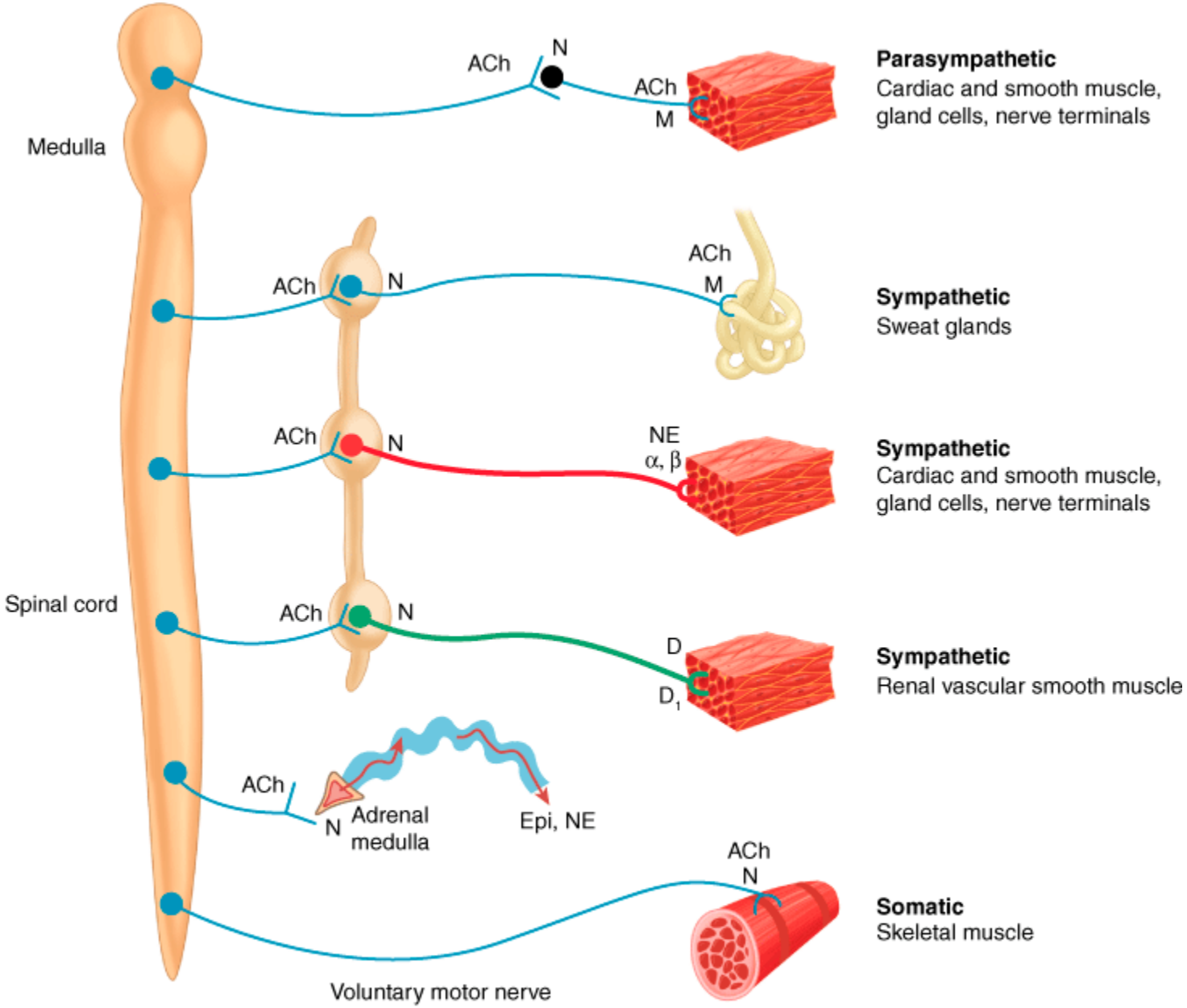
CHOLINOCEPTOR-BLOCKING DRUGS

OVERVIEW

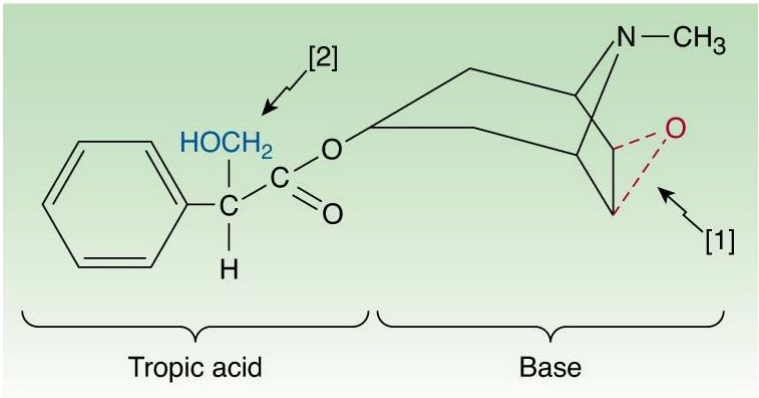
- Cholinergic antagonists are subdivided according to their physiological site of action:
  1. **Muscarine antagonists**
  2. **Ganglionic blockers**
  3. **Neuromuscular-blocking drugs**

- **Muscarinic antagonists** are **sometimes** called ***parasympatholytic*** because **they block** the **effects of parasympathetic autonomic discharge**….exceptions! So, the term **"antimuscarinic" is preferable**



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Muscarinic antagonists (*ANTIMUSCURINIC*)



- The class of drugs includes:

- **Naturally occurring alkaloids:**

ATROPINE *(hyoscyamine)* is found in:

- ***Atropa belladonna***, or *deadly nightshade*
- ***Datura stramonium***, *or jimsonweed (thorn apple)*

SCOPOLAMINE *(l-hyoscine)* occurs in *Hyoscyamus niger*, or *henbane*

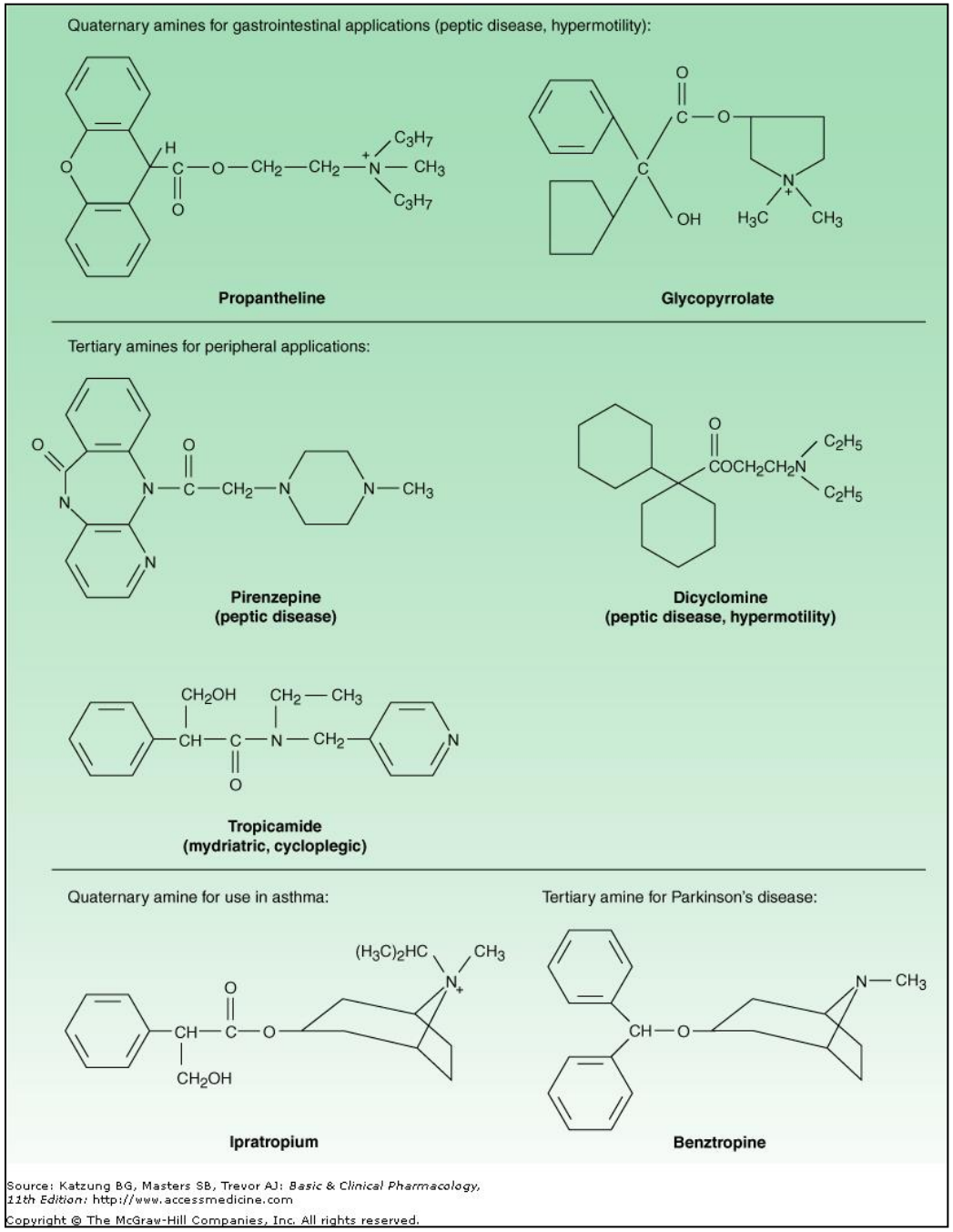
Muscarinic antagonists (*ANTIMUSCURINIC*)

- **Semisynthetic and fully synthetic molecules:**

- The **tertiary members** (Fig. 8–2) are often **used** for their **effects** on the **eye or the CNS** (many antihistaminic, antipsychotic, and antidepressant have similar structures and antimuscarinic effects)

- **Quaternary amine agents** produce more **peripheral** effects and **reduced CNS effects**

- ***EX.: IPRATROPIUM, OXITROPIUM, HOMATROPINE*** & ***TROPICAMIDE***)



ABSORPTION & DISTRIBUTION

- **Natural alkaloids** and most **tertiary** antimuscarinic drugs…..**well absorbed** from the **gut** and **conjunctival** membranes
- Well distributed **into the CNS** (*scopolamine*)
- Just **10-30% of** a dose of a **quaternary** antimuscarinic drug is **absorbed** after oral administration….**poorly distributed**

Muscarinic antagonists (*ANTIMUSCURINIC*)

METABOLISM & EXCRETION

- ~ **50% of** the dose is **excreted unchanged** in the urine
- The rest **50% appears** in the urine as hydrolysis and **conjugation p**roducts

- The drug's **effect** on **parasympathetic function declines rapidly** in all organs **except the eye**....
  - Effects on the **iris and ciliary muscle** persist for ≥**72 hours**

Muscarinic antagonists (***ANTIMUSCURINIC***)

MECHANISM OF ACTION

- Atropine ***reversibly*** blocks the ***muscarinic*** receptor

- Classically, were viewed as muscarinic antagonists….
  - **recent evidence** indicates them as **inverse agonists** (**shift** the **equilibrium** to the **inactive state of the receptor**)

Muscarinic antagonists(*ANTIMUSCURINIC*)

MECHANISM OF ACTION

- **Tissues most sensitive to atropine** are
  - the salivary,
  - bronchial,
  - and sweat glands

- **Least sensitive:** secretion of acid by the ***gastric parietal cells***

- Atropine does not distinguish among the M_1, M_2, and M_3 subgroups of muscarinic receptors

- In contrast, synthetic antimuscarinic drugs are **moderately selective** for **one or another** of these subgroups (table 8-1)

- In most tissues, antimuscarinic agents **block exogenously** administered **cholinoceptor agonists more effectively** than **endogenously** released acetylcholine

I. Muscarinic antagonists
Organ system effect

A. Central nervous system (CNS)

1) Atropine:

- At therapeutic doses (0.2 to 2 mg) has minimal central effects

2) Scopolamine:….more marked central effects…

- At therapeutic doses can cause CNS depression manifested as drowsiness in sensitive individuals,

- At higher doses it can produce a constellation of responses collectively termed the ***'central anticholinergic syndrome'*** cause excitement, agitation, hallucinations, and coma

I. Muscarinic antagonists
Organ system effect

A. Central nervous system (CNS)

- Decrease the Parkinsonian tremor in combination with a dopamine precursor drug (levodopa)
  - ……**benztropine**

- Effective in preventing or reversing vestibular disturbances (**motion sickness**) that appear to involve muscarinic cholinergic transmission
  - …..***scopolamine***

I. Muscarinic antagonists
Organ system effect

B. The eye

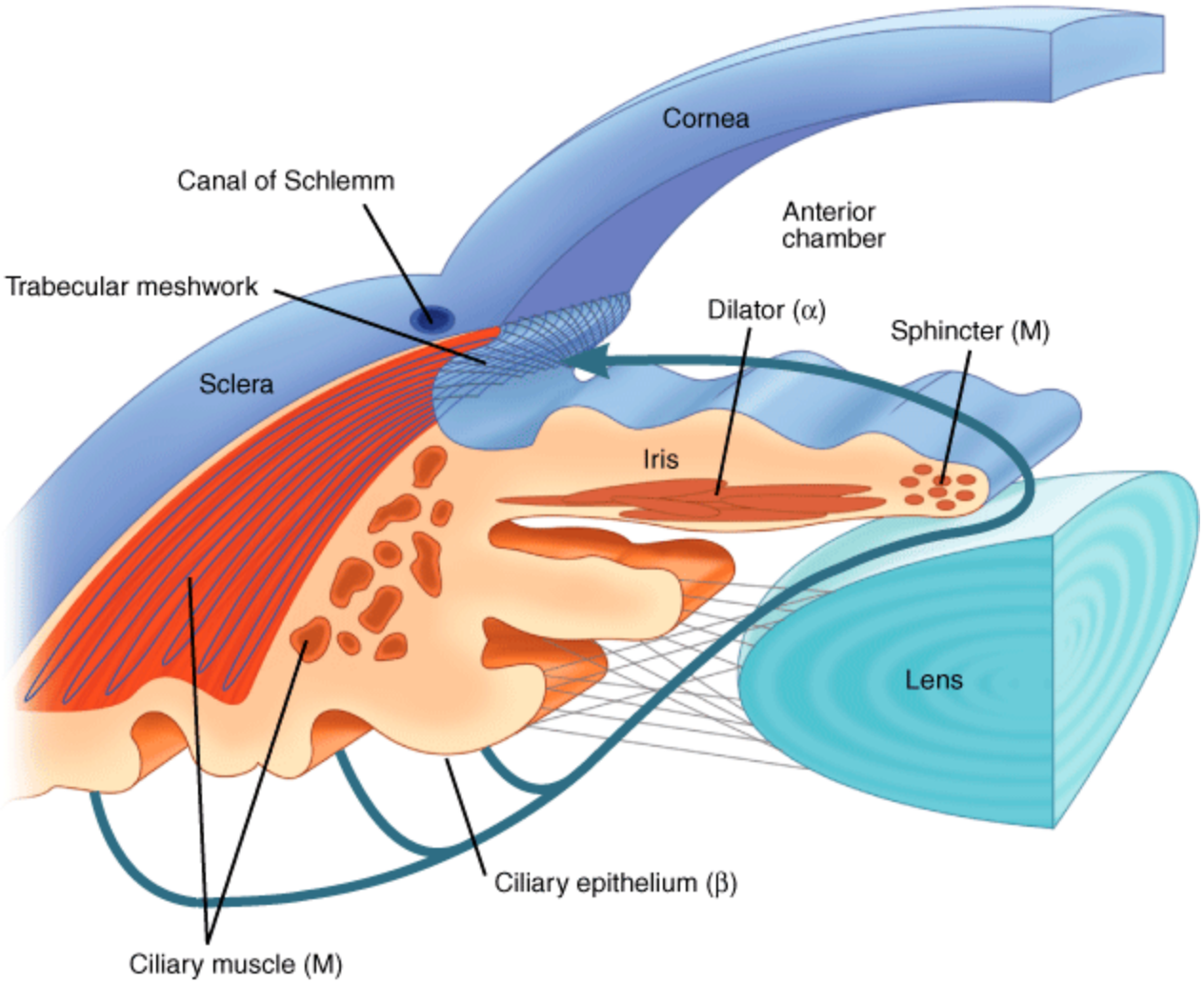
1. **Mydriasis**: (**unopposed sympathetic dilator** activity)

2. **Cycloplegia:** weaken contraction of the **ciliary muscle** resulting in loss of the ability to accommodate (the fully atropinized eye cannot focus for near vision)

   - Both mydriasis and cycloplegia are useful in ophthalmology.

   - **Hazardous….may induced glaucoma in patients with a narrow anterior chamber angle**

3. **Reduce lacrimal secretion** (dry or "sandy" eyes)



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

I. Muscarinic antagonists
Organ system effect

C. Cardiovascular system

- The **sinoatrial node** is very sensitive to muscarinic receptor blockade:
  - **At low doses (0.4 to 0.6 mg):** the predominant effect is a decreased heart rate (**bradycardia**) due to block of presynaptic M_1 receptors (autoceptors), thus permitting increased acetylcholine release
  - **Moderate to high doses (≥ 1mg):** progressively cause **tachycardia** by **blocking vagal slowing effects on M_2** receptors on **the SA node**
- Muscarinic effects on **atrial muscle** are similarly blocked, but these effects are of no clinical significance except in **atrial flutter and fibrillation**

C. Cardiovascular system

- The **ventricles** are less affected by antimuscarinic drugs at therapeutic levels…..**less degree of vagal** control

- No direct parasym. innervation of **blood vessels**

- However, **parasympathetic nerve** stimulation **dilates coronary** arteries and **almost all vessels (M_3)**….**Atropine can block this vasodilation**

- **At toxic doses**, (and in **some individ**uals at normal doses), antimuscarinic agents **cause cutaneous vasodilation**, especially in the upper portion of the body

- **The net cardiovascular effects of atropine:**
  - **tachycardia with little effect on BP**

I. Muscarinic antagonists
Organ system effect

D. Respiratory system

- **Bronchodilation** and **reduce secretion** in normal individuals and patients with airway diseases

E. Gastrointestinal tract

- **Inhibition of salivation** (**low doses**)….[**dry mouth** ADE in parkinsonian patients receiving Tx]

- **Inhibition of acid secretion** (**high doses of atropine**)

- **Reduction of GIT motility** (prolong emptying time and intestinal transit time)
  - **Diarrhea may be stopped**.
  - However, this intestinal "paralysis“ is **tempora**ry; **ENS usu**ally reestablish at least some peristalsis after **1–3 days of Tx.**

I. Muscarinic antagonists
Organ system effect (Cont'd)

E. Genitourinary tract

- Atropine and its analogs **relaxes smooth muscle of the ureters and bladder wall and slows voiding**

- Useful in **Tx of spasm** induced by mild **inflammation**, **surgery,** and certain neurologic conditions,
  - **but** can **precipitate** urinary **retention in men** with **prostatic hyperplasia**

- **The antimuscarinic drugs have no significant** effect on the uterus

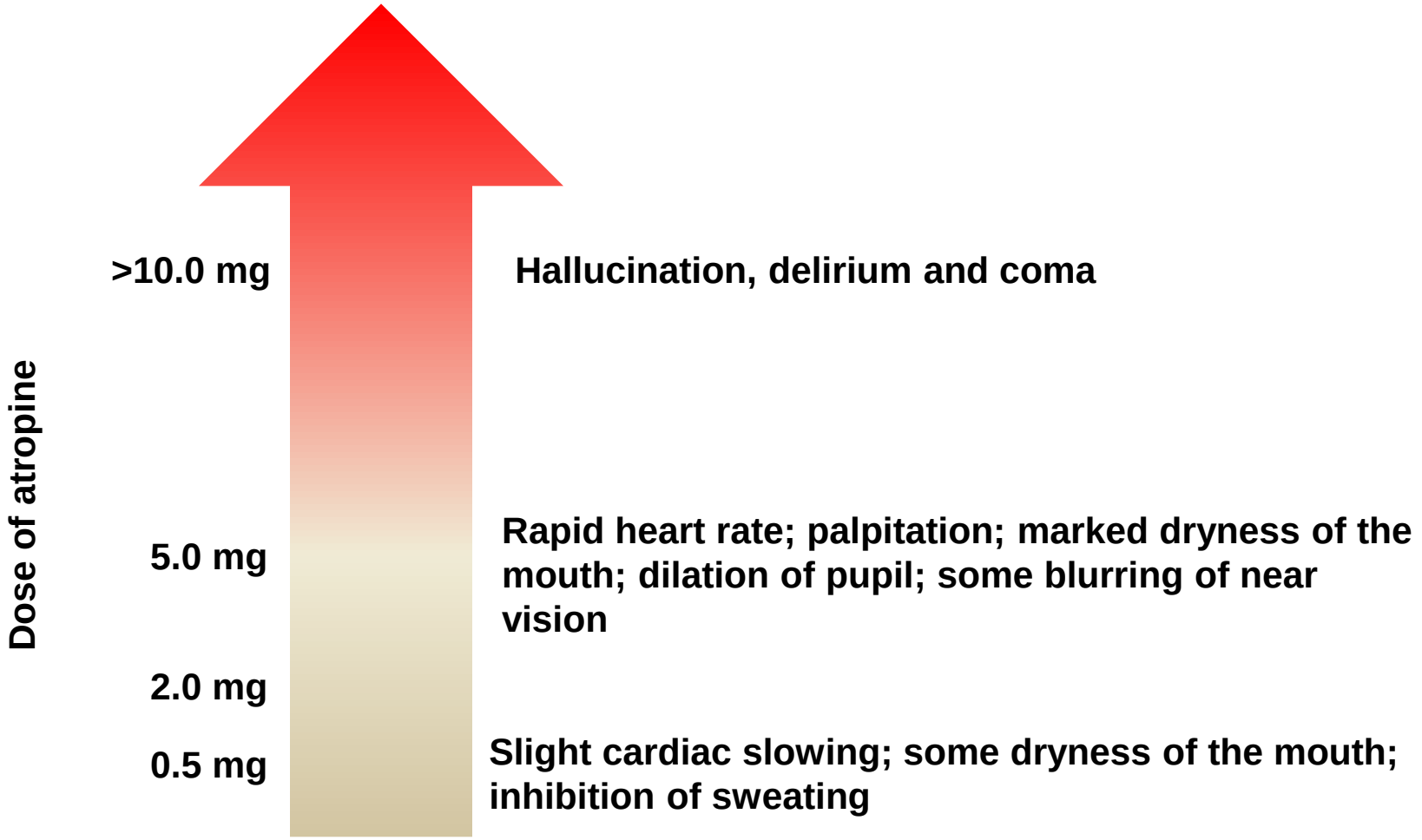
I. Muscarinic antagonists
Organ system effect

F. Sweat Glands

- Sympathetic cholinergic fibers innervate eccrine sweat glands, and their muscarinic receptors are readily accessible to antimuscarinic drug
  - .....***Atropine suppresses thermoregulatory sweating***

- In **adults**, body **temperature is elevated** by this effect only **if large doses** are administered,
  - but in infants and children even ordinary doses may cause "atropine fever"

Dose-dependent effect of atropine



I. Muscarinic antagonists
Clinical uses

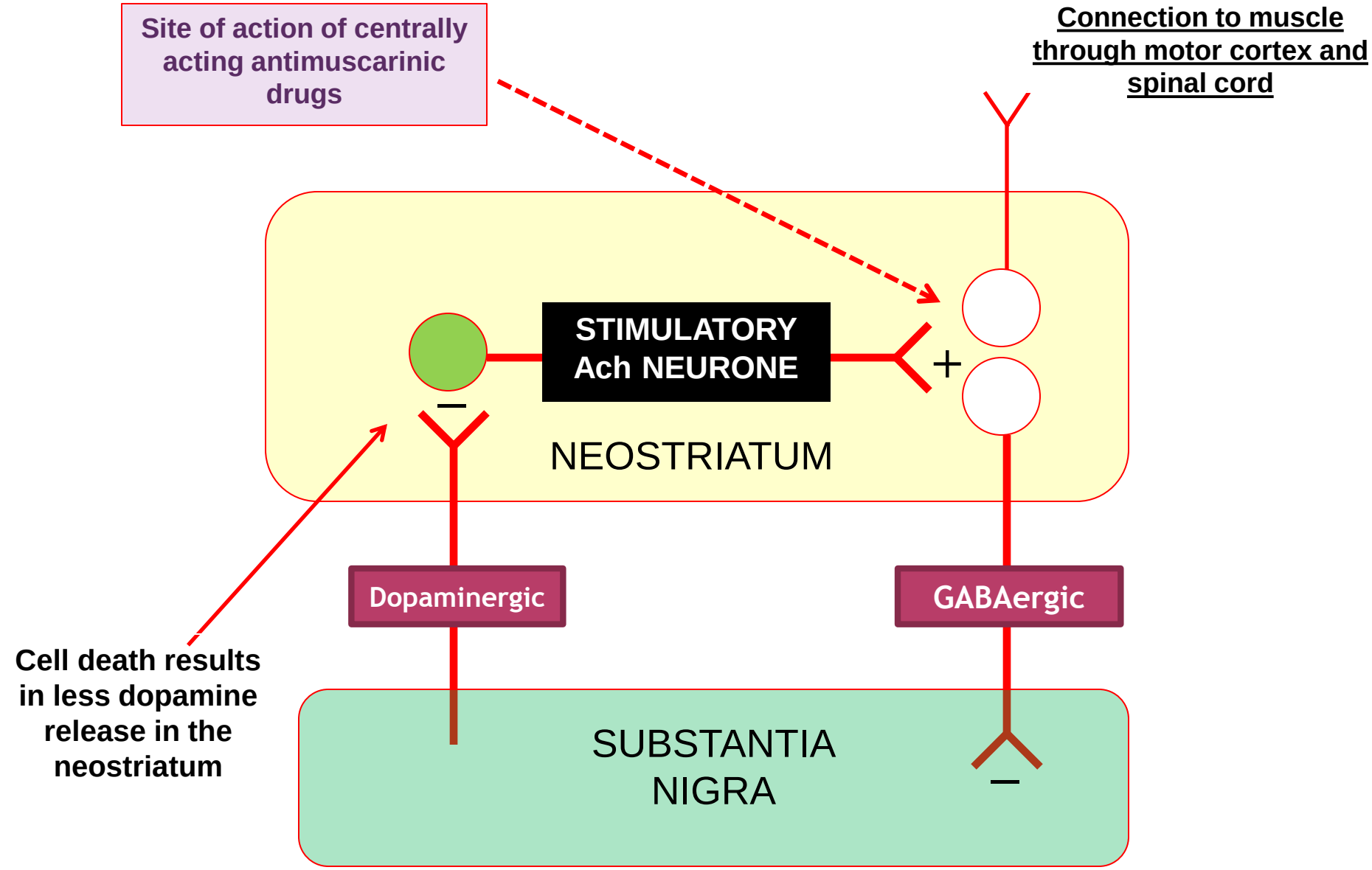
A. Central Nervous System Disorders

1. **Parkinson's Disease:**

- Parkinsonian tremor and rigidity seem to result
  - from a *relative* excess of cholinergic activity
  - because of a deficiency of dopaminergic activity in the basal ganglia-striatum system

- Blockage of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission

- Centrally acting agents such as ***benztropine*** play only an adjuvant role in antiparkinsonism therapy


Site of action of centrally acting antimuscarinic drugs
Connection to muscle through motor cortex and spinal cord
STIMULATORY Ach NEURONE
+
−
NEOSTRIATUM
Dopaminergic
GABAergic
Cell death results in less dopamine release in the neostriatum
SUBSTANTIA NIGRA
−

I. Muscarinic antagonists
Clinical uses

A. Central Nervous System Disorders

2. **Motion Sickness:**

- Vestibular disturbances appear to involve muscarinic cholinergic transmission

- ***Scopolamine*** is used in the **prevention of motion sickness**. Can be given:
  - by injection
  - by mouth or
  - as transdermal patches

- ADEs: cause **significant sedation and dry mouth**

B. Ophthalmologic Disorders (**eye drops or ointment**)

- Agents used: ***Atropine, scopolamine, cyclopentolate and tropicamide***

- Accurate measurement of **refractive error** in **uncooperative patients** (requires **ciliary paralysis**)

- **Ophthalmoscopic examination** of the **retina** is greatly facilitated **by mydriasis**

- **<u>Antimuscarinic poisoning</u>**!....
  - .....**Drug loss** from the **conjunctival sac** via the **nasolacrimal duct** into the nasopharynx can be diminished by the use of the **ointment form rather than drops**

TABLE 8–2 **Antimuscarinic drugs used in ophthalmology.**

Drug	Duration of Effect (days)	Usual Concentration (%)
Atropine	7–10	0.5–1
Scopolamine	3–7	0.25
Homatropine	1–3	2–5
Cyclopentolate	1	0.5–2
Tropicamide	0.25	0.5–1

I. Muscarinic antagonists
Clinical uses

B. Ophthalmologic Disorders

- **The mydriatic** and **cycloplegic** actions of **atropine** and **scopolamine**
  - can persist for **a week** after **topical application** to the eye

- **Shorter-acting drugs**, such as **cyclopentolate** and **tropicamide**, are now **favored** for this application
  - because **complete recovery of accommodation occurs within hours**

I. Muscarinic antagonists
Clinical uses

C. Respiratory disorders

- Atropine and synthetic analogs **reduce secretion** in both the upper and lower respiratory tracts.
  - This effect may provide **some symptomatic relief** of **acute rhinitis** associated **with hay fever**

- ***Ipratropium* & *tiotropium*** used as an **inhalational** drug in **asthma** & chronic obstruction pulmonary disease (**COPD**)…inhalational drug

D. Cardiovascular disorders (limited clinical application)

- Atropine may be considered in the initial treatment of patients with acute myocardial infarction
  - in whom excessive vagal tone causes sinus or nodal bradycardia

- **Rare individuals** may experience **faintness** as a result of **vagal discharge** in response to **pressure on the neck**, (eg, tight collar). **"hyperactive carotid sinus reflexes"**
  - Such individuals may benefit from the use of atropine or a related antimuscarinic agent

I. Muscarinic antagonists
Clinical uses

E. Gastrointestinal disorders

- **Common traveler's diarrhea and hypermotility:** antimuscarinics can provide **some relief** in these conditions

- **Often combined** with an **opioid antidiarrheal** drug, an **extremely effective therapy** (e.g. LAMOTIL®: *atropine* & *diphenoxylate* combination)

I. Muscarinic antagonists
Clinical uses

F. Urinary Disorders

- In the treatment of **urinary urgency** caused by minor **inflammatory bladder** disorders

- To relieve **bladder spasm** after **urologic surgery**

- To decrease **involuntary voiding** in patients with **neurologic disease**:
  - *Oxybutynin, darifenacin, solifenacin, tolterodine, fesoterodine)* (all are **selective M_3 antagonists**),
  - *trospium* (a nonselective antagonist) are used in these situation

TABLE 8–3 **Antimuscarinic drugs used in gastrointestinal and genitourinary conditions.**

Drug	Usual Dosage
Quaternary amines	
Anisotropine	50 mg tid
Clidinium	2.5 mg tid–qid
Glycopyrrolate	1 mg bid–tid
Isopropamide	5 mg bid
Mepenzolate	25–50 mg qid
Methantheline	50–100 mg qid
Methscopolamine	2.5 mg qid
Oxyphenonium	5–10 mg qid
Propantheline	15 mg qid
Tridihexethyl	25–50 mg tid–qid
Trospium	20 mg bid
Tertiary amines	
Atropine	0.4 mg tid–qid
Darifenacin	7.5 mg qd
Dicyclomine	10–20 mg qid
Oxybutynin	5 mg tid
Oxyphencyclimine	10 mg bid
Propiverine	15 mg bid–tid
Scopolamine	0.4 mg tid
Solifenacin	5 mg qd
Tolterodine	2 mg bid

I. Muscarinic antagonists
Clinical uses

G. **Cholinergic poisoning: cholinesterase inhibitor insecticides, wild mushrooms** and **chemical warfare "nerve gases"**

- Both nicotinic and muscarinic effects of the cholinesterase inhibitors can be life-threatening.
  - **No effective method for directly blocking the nicotinic effects**

1. **Antimuscarinic therapy:** a tertiary (not quaternary) amine drug must be used (preferably atropine) to treat the CNS effects
   - **Massive doses of atropine** may be required **over a long period** of time to counteract the poison

2. **Cholinesterase Regenerator Compounds:** to treat **organophosphorus** poisoning. These oxime agents include pralidoxime (PAM) and diacetylmonoxime (DAM)

I. Muscarinic antagonists
Clinical uses

3. ***Pretreatment* with reversible inhibitors:**

- "prophylaxis" to prevent binding of the irreversible organophosphate inhibitor.
- pyridostigmine or physostigmine just in situations in which possibly lethal poisoning is anticipated, eg, chemical warfare (+ atropine)

H. Mushroom poisoning:

- Caused by the ingestion of mushrooms of ***Inocybe* genus**
- Characterized by **rapid onset signs** (within 15–30 minutes) (nausea, vomiting, diarrhea, urinary urgency, vasodilation, reflex tachycardia (occasionally bradycardia), sweating, salivation, and sometimes bronchoconstriction
- **Antidote: atropine**
- (***Amanita phalloids, A. virosa***) **show delayed onset** poisoning (6-12hr)…renal & hepatic failure! (**atropine useless**)

I. Muscarinic antagonists
Adverse effects

- "Dry as a bone, blind as a bat, red as a beet, mad as a hatter"

- **At higher doses**: dry mouth, constipation, 'sandy eyes', blurred vision, tachycardia, hot and flushed skin, agitation, and delirium

- Children, especially infants, are very sensitive to the **hyperthermic effects** of atropine

- Poisoning caused by high doses of **quaternary antimuscarinic** drugs is associated with all of the peripheral signs of parasympathetic blockade but **few or none of the CNS** effects of atropine
  - These more polar drugs may cause significant ganglionic blockade, however, with marked orthostatic hypotension

I. Muscarinic antagonists

Contraindications

- Contraindications to the use of antimuscarinic drugs are relative, not absolute

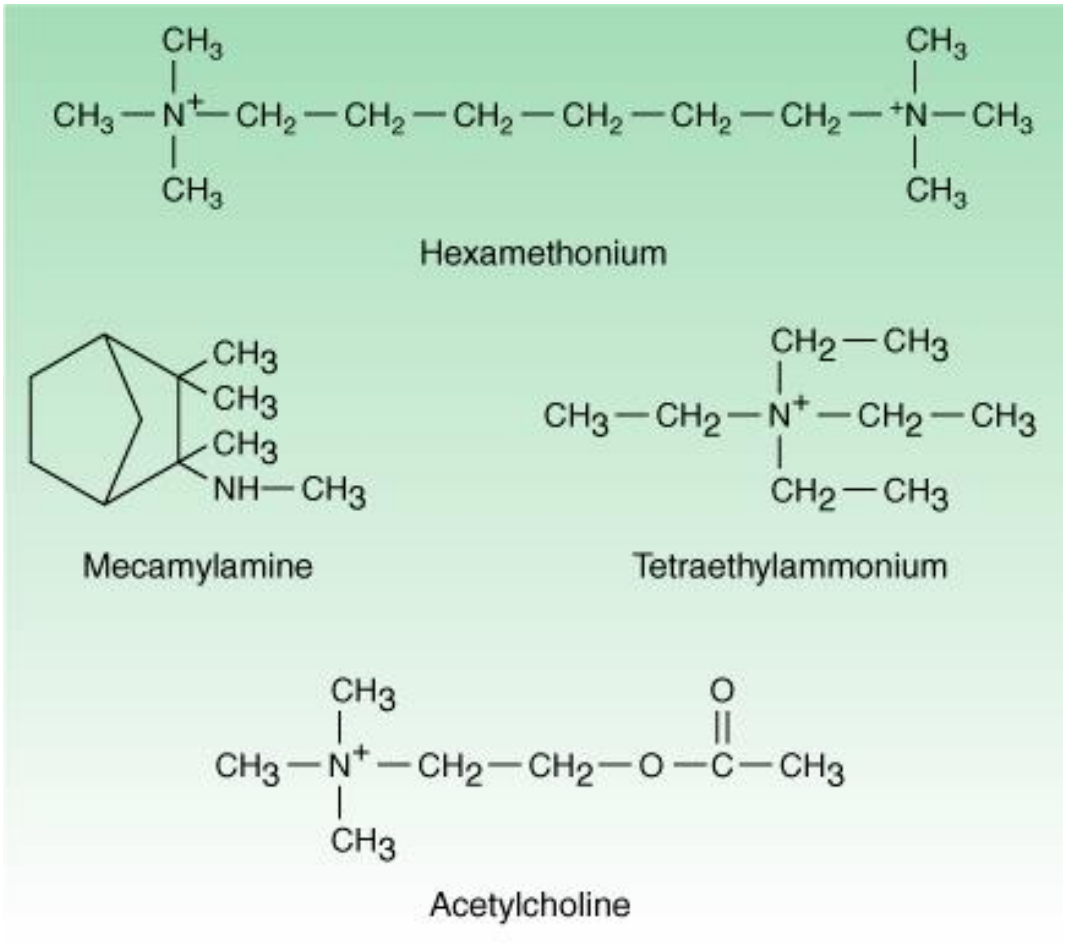
- Antimuscarinic drugs are contraindicated:
  - ✓ in patients with **glaucoma**
  - ✓
  - ✓ **elderly patients** with a **history of prostatic hyperplasia**
  - ✓ may ***increase*** **symptoms** in patients with **gastric ulcer** because the antimuscarinic drugs **slow gastric emptying,**
  - ✓ !!!(should never be used to treat acid-peptic disease)

II. Ganglion-Blocking Drugs

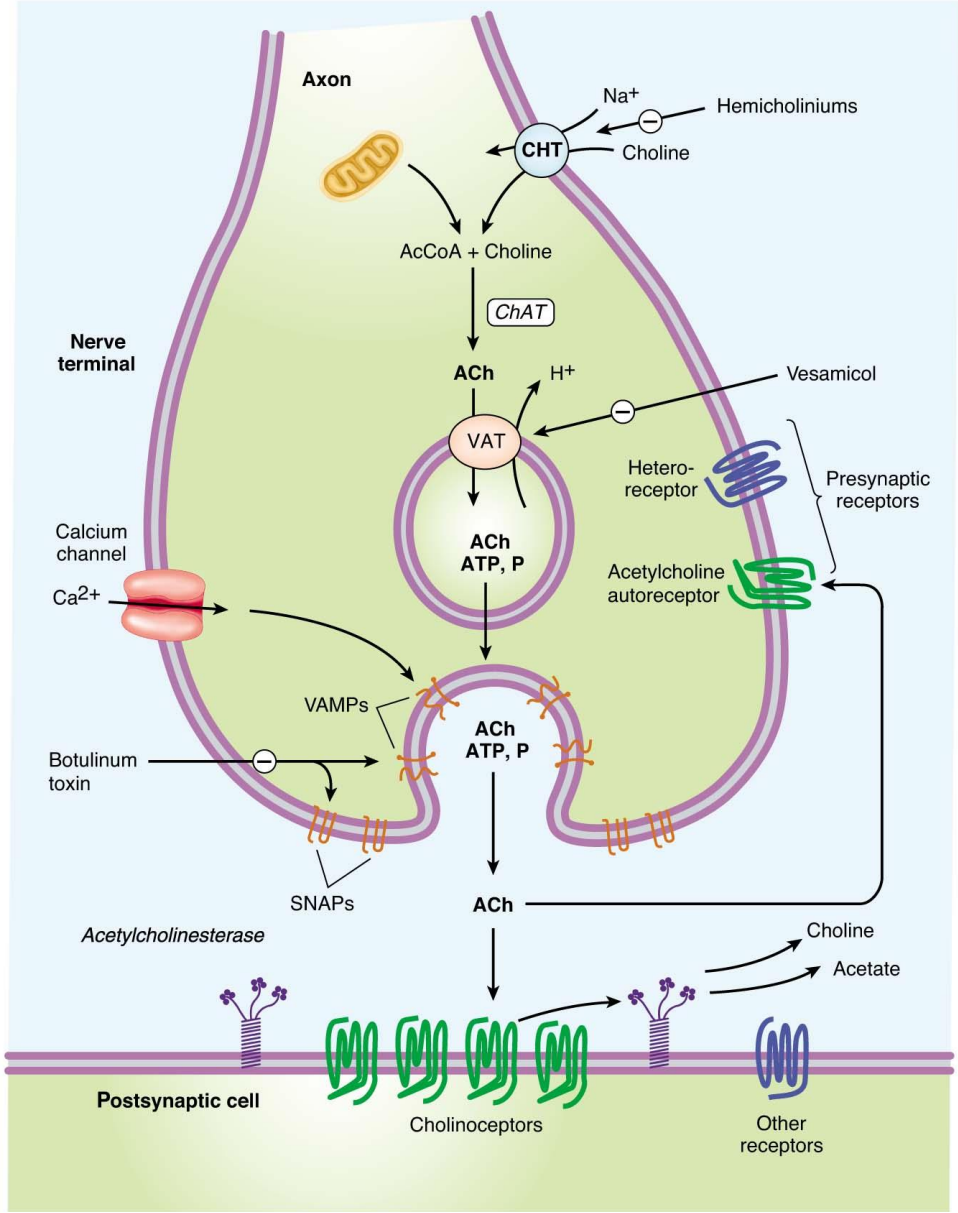
- These drugs **block the entire output of the ANS** (block **gangilionic nicotinic erceptors**):
  - the **responses** observed are **complex and unpredictable** (used in **pharmacological research**!)
- The **net effect (response)** produced by ganglionic blocking drugs depends largely on the **relative proportion** of the **total autonomic input coming from sympathetic** and **parasympathetic nerves** to **the organ**

1. **Non-depolarizing competitive antagonists** (nicotinic blocker)

2. Nicotine, and even acetylcholine itself (if amplified with a cholinesterase inhibitor) can produce **depolarizing ganglion block**
3. Botulinum toxin & hemicholinium



- All are Synthetic amines (quaternary or tertiary) amines
- Hexamethonium: was used for tx HTN
- Decamethonium similar…analogue
- **Mecamylamine: 2ndry amine…more absorbed** from GIT


Axon
Na+
Hemicholiniums
CHT
Choline
AcCoA + Choline
ChAT
Nerve terminal
ACh
H+
Vesamicol
VAT
Hetero-receptor
Presynaptic receptors
Calcium channel
ACh ATP, P
Acetylcholine autoreceptor
Ca2+
VAMPs
ACh ATP, P
Botulinum toxin
SNAPs
ACh
Acetylcholinesterase
Choline
Acetate
Postsynaptic cell
Cholinoceptors
Other receptors

II. Ganglion-Blocking Drugs
Organ system effects

A. Central nervous system

- Mecamylamine, a secondary amine that readily enters the CNS causing:
  - **sedation,**
  - **tremor,**
  - **choreiform movements, (movement disorder)**
  - **and mental aberrations**

B. Eye

- **Moderate dilation** of the pupil because parasympathetic tone usually dominates this tissue

- **Cycloplegia** with loss of accommodation (same reason)

II. Ganglion-Blocking Drugs
Organ system effects (Cont'd)

C. Cardiovascular System

- **Vascular:** the blood vessels receive chiefly vasoconstrictor fibers from the sympathetic nervous system…
  - **decrease arteriolar and venomotor tone…orthostatic and postural hypotension**

- **Cardiac** effects include:
  - **diminished contractility and**
  - **a moderate tachycardia** (SA node usually dominated by parasympathetic nervous system)

D. Gastrointestinal Tract

- **Secretion is reduced**
- **Motility is profoundly inhibited**, and constipation can be marked

II. Ganglion-Blocking Drugs
Organ system effects (Cont'd)

E. Other Systems

- **Genitourinary tract:**
  - **difficulty in urination**,
  - precipitate **urinary retention** in men with prostatic hyperplasia
  - **Sexual dysfunction**

- **Sweat glands: thermoregulatory sweating is reduced by** the ganglion-blocking drugs
- ……However, **hyperthermia is not a** problem except in **very warm environments**,
  - because **direct cutaneous vasodilation** is usually **sufficient to maintain a normal body temperature**

II. Ganglion-Blocking Drugs
Organ system effects (Cont'd)

F. Response to Autonomic Drugs

- Patients receiving **ganglion-blocking drugs** are fully responsive to **autonomic drugs** acting on **muscarinic, α-, & β-adrenergic receptors** because these effector cell receptors **are not blocked**

- In fact, responses may be **exaggerated or even reversed**

II. Ganglion-Blocking Drugs
Clinical uses

- **Ganglion blockers are used infrequently because:**
  - the responses observed are **complex**
  - and **unpredictable,**
  - making it **impossible to** achieve **selective action**

- ***Mecamylamine*** blocks central nicotinic receptors and has been studied as transdermal patch to reduce nicotine craving in patients **attempting to quit smoking**

- ***Trimethaphan*** is occasionally used for **control hypertension** during **plastic, neurological, and ophthalmological** surgery
  - to **minimize hemorrhage** in the **operative field**,
  - to **reduce blood loss**,
  - and **to facilitate surgery** on **blood vessels**

II. Ganglion-Blocking Drugs
Toxicity

1) **Mild untoward ADRs:** visual disturbances, dry mouth, conjunctival suffusion, urinary hesitancy, decreased potency, subjective chilliness, moderate constipation, occasional diarrhea, abdominal discomfort, anorexia, heartburn, nausea, eructation, and bitter taste and the signs and symptoms of syncope caused by postural hypotension

2) **Severe ADRs:**
    1) marked hypotension,
    2) constipation,
    3) syncope,
    4) paralytic ileus,
    5) urinary retention,
    6) and cycloplegia