Drugs That Affect the Autonomic Nervous System

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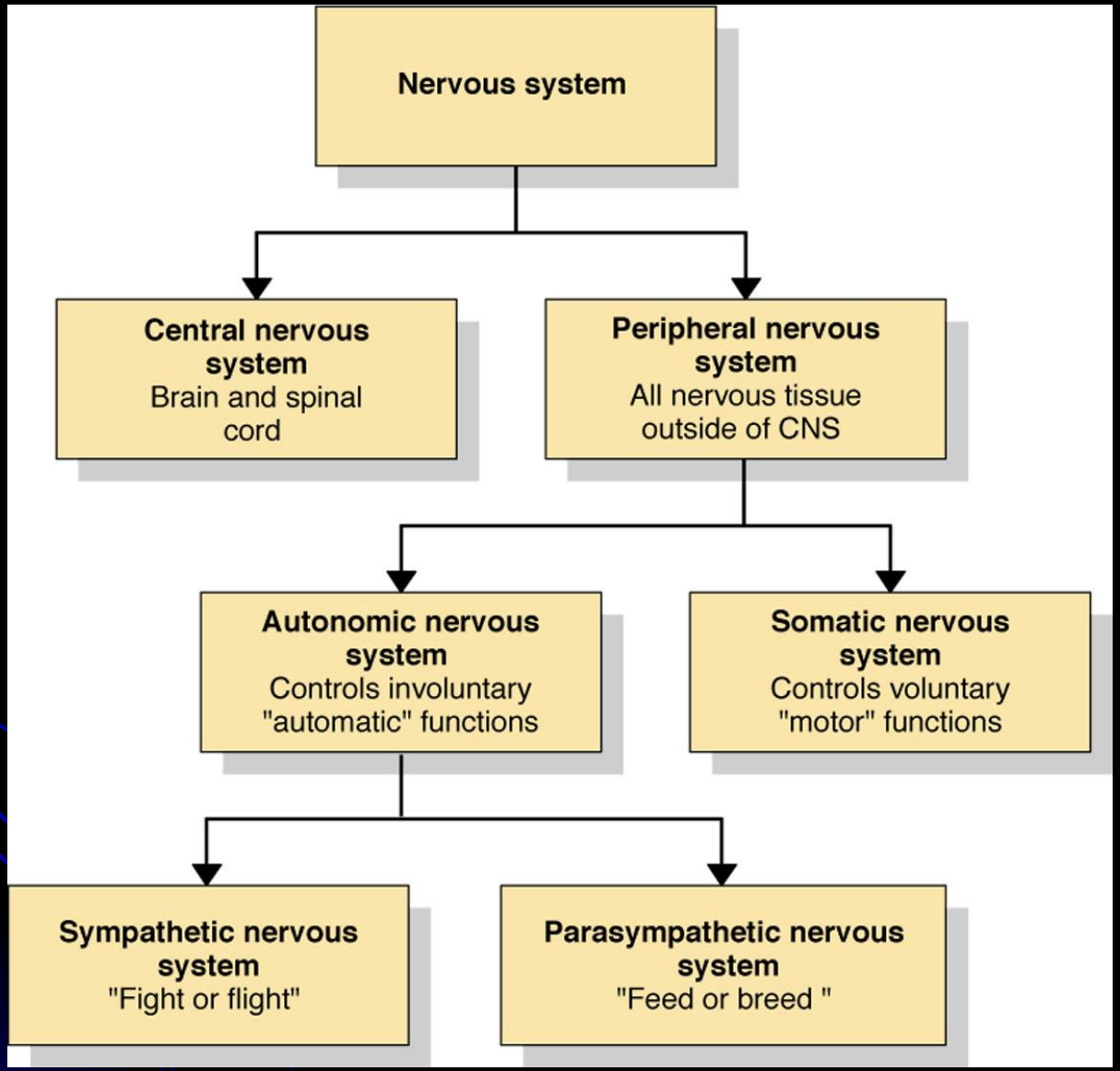
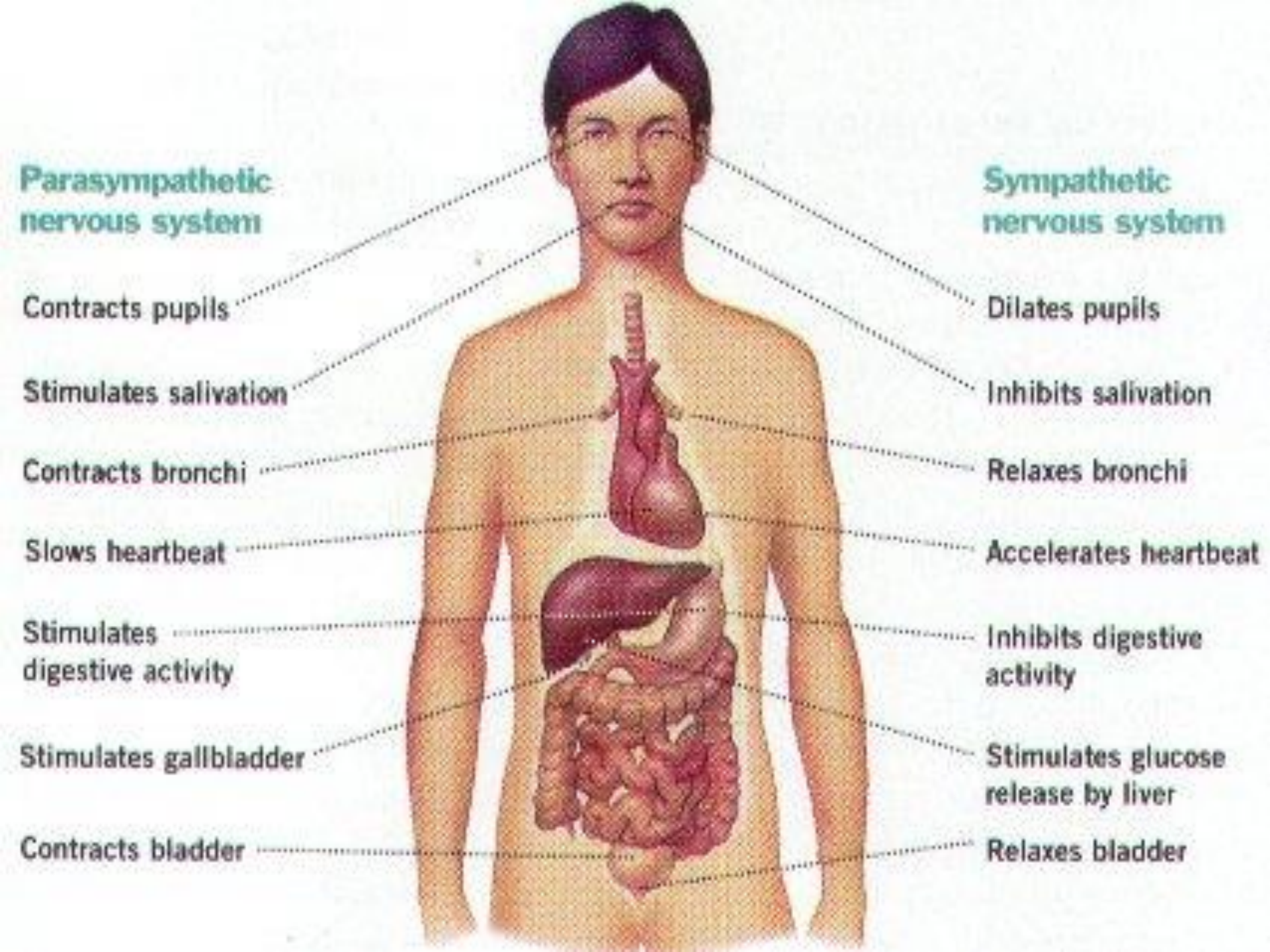

Nervous system
Central nervous system
Brain and spinal cord
Peripheral nervous system
All nervous tissue outside of CNS
Autonomic nervous system
Controls involuntary "automatic" functions
Somatic nervous system
Controls voluntary "motor" functions
Sympathetic nervous system
"Fight or flight"
Parasympathetic nervous system
"Feed or breed "

SUBDIVISIONS OF THE AUTONOMIC NERVOUS SYSTEM

- **Sympathetic nervous system**
  - Fight or Flight
  - Useful in highly stressful or emergency situations
- **Parasympathetic nervous system**
  - Maintains homeostasis
  - Works in “opposition” of the Sympathetic nervous system
  - “Rest and Digest”


Parasympathetic nervous system
Contracts pupils
Stimulates salivation
Contracts bronchi
Slows heartbeat
Stimulates digestive activity
Stimulates gallbladder
Contracts bladder
Sympathetic nervous system
Dilates pupils
Inhibits salivation
Relaxes bronchi
Accelerates heartbeat
Inhibits digestive activity
Stimulates glucose release by liver
Relaxes bladder

VOCABULARY "SYNONYMOUS" TERMS

- SYMPATHETIC
  - ADRENERGIC
  - SYMPATHOMIMETIC
    - MIMICS THE SYMPATHETIC SYSTEM
- PARASYMPATHETIC
  - CHOLINERGIC
  - PARASYMPATHOMIMETIC
    - MIMICS THE PARASYMPATHETIC NERVOUS SYSTEM

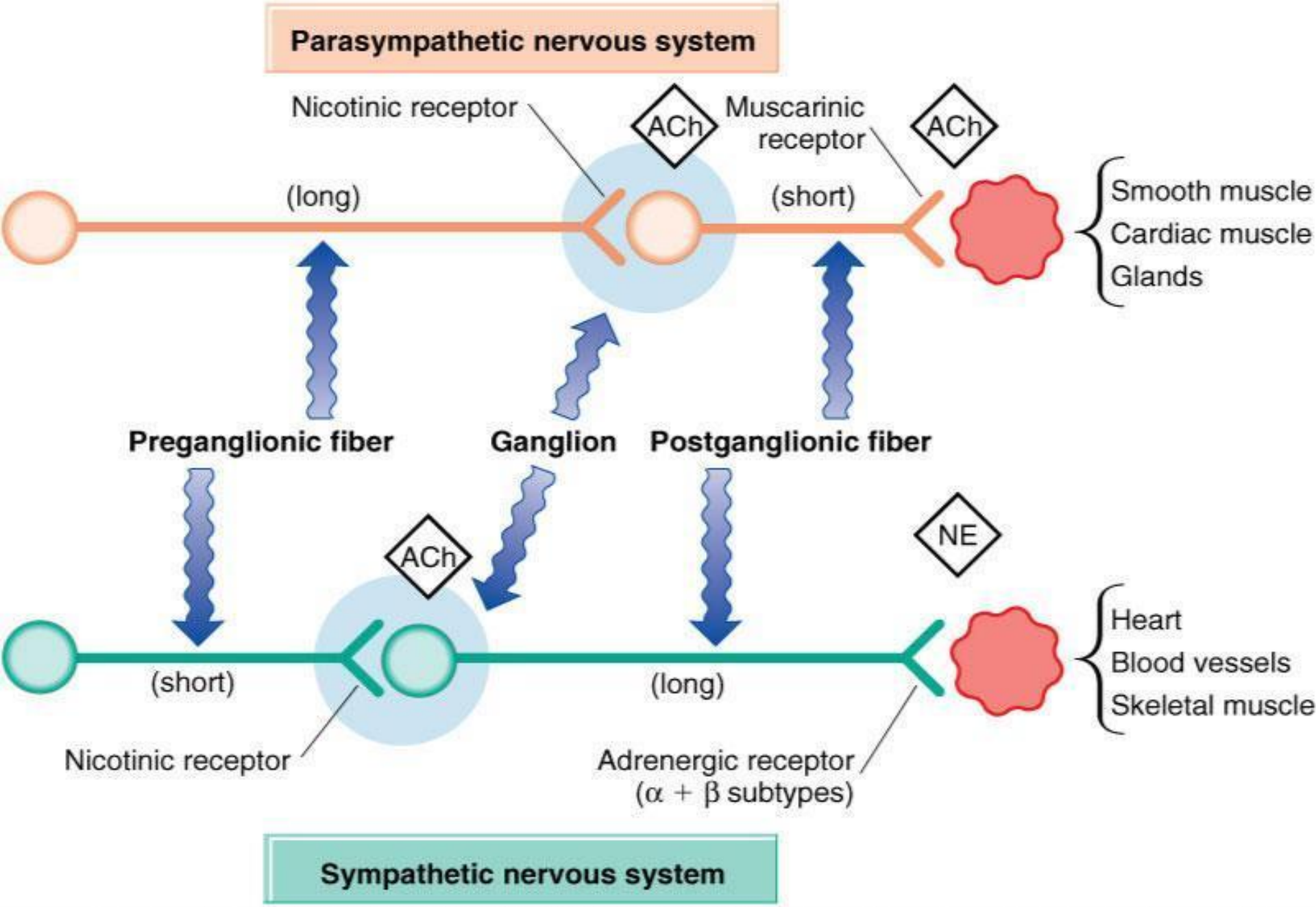
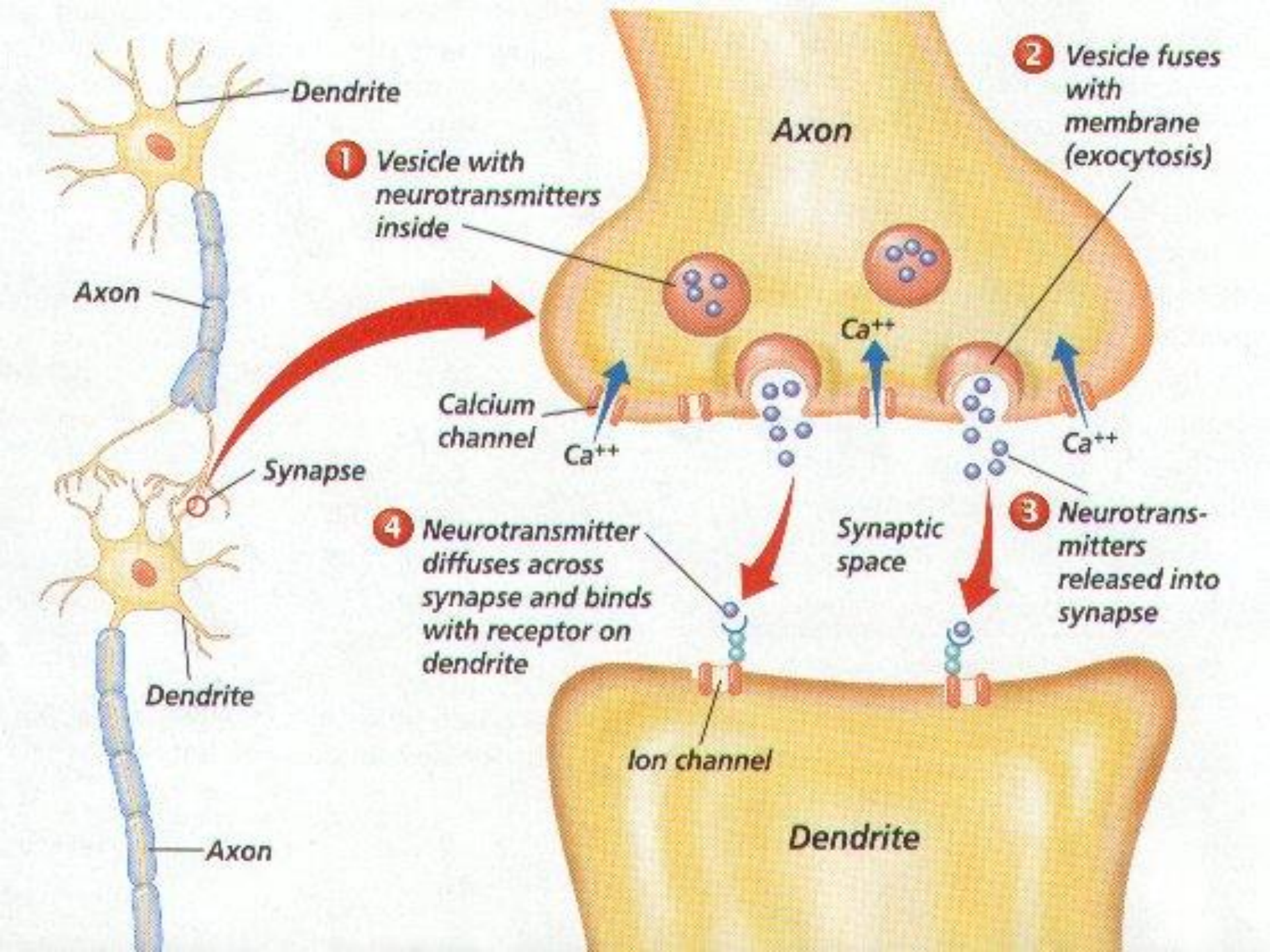


Fig. 19-1. The parasympathetic and sympathetic nervous systems and their relationship to one another. *ACh,* Acetylcholine; *NE,* norepinephrine.

Cholinergic Neurons

- Preganglionic fibers terminating in the adrenal medulla
- Preganglionic fibers of both parasympathetic & sympathetic nervous system
- Postganglionic fibers of the parasympathetic nervous system
- Voluntary muscles of the somatic nervous system


Dendrite
Axon
Synapse
Dendrite
Axon
1 Vesicle with neurotransmitters inside
Axon
2 Vesicle fuses with membrane (exocytosis)
Ca++
Calcium channel
Ca++
Ca++
3 Neurotrans-mitters released into synapse
Synaptic space
4 Neurotransmitter diffuses across synapse and binds with receptor on dendrite
Ion channel
Dendrite

Receptor Type	Other Names	Location	Structural Features
M_1		Nerves	G P C R (Metabotropic)
M_2	Cardiac M_2	Heart, nerves, smooth muscle	
M_3		Glands, smooth muscle, endothelium	
M_4		CNS	
M_5		CNS	
N_M	Muscle type, end plate receptor	Skeletal muscle neuromuscular junction	**Ion Channel (Ionotropic)**
N_N	Neuronal type, ganglion receptor	CNS postganglionic cell body, dendrites	

Drugs Affecting the Parasympathetic System:

- Cholinergics
- Anticholinergics
- Ganglionic Blocking Agents
- Neuromuscular Blocking Agents
- Ganglionic Stimulating Agents

Cholinergic Drugs

- Cholinergic drugs can be direct-acting (bind to and activate cholinergic receptors) or indirect-acting (inhibit cholinesterase which is the enzyme responsible for breaking down acetylcholine).

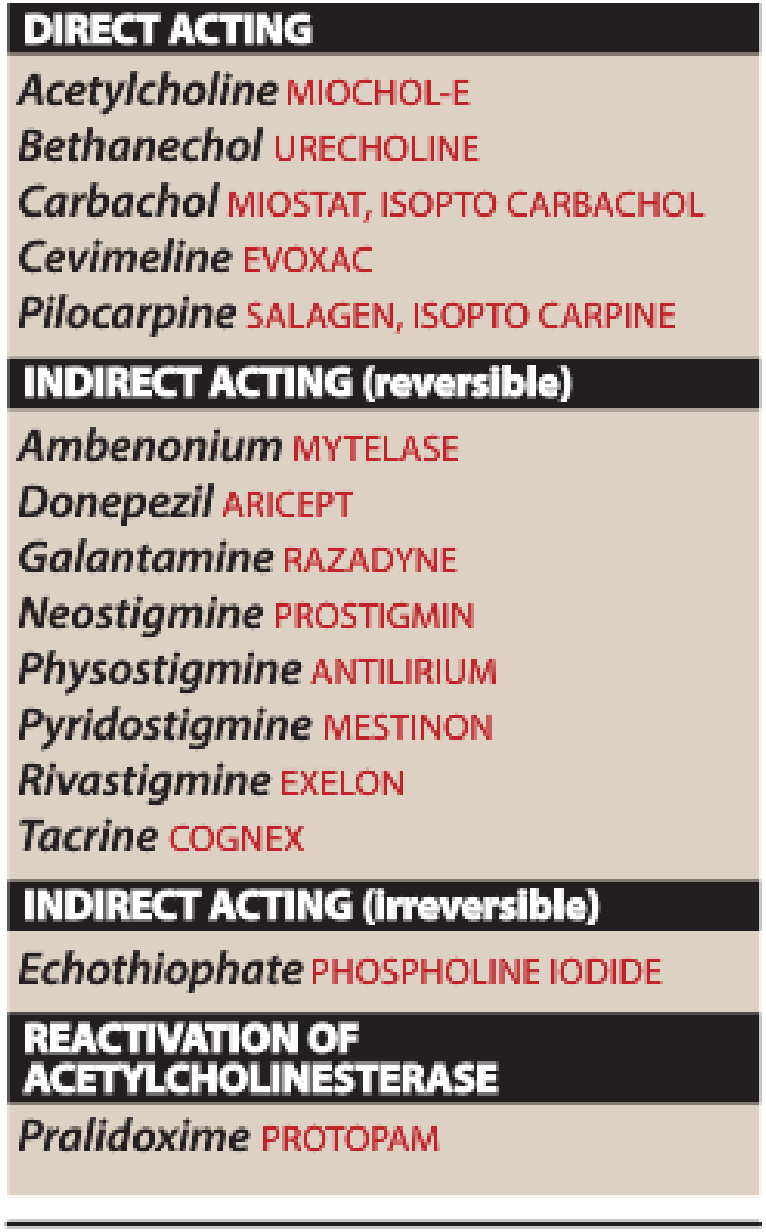
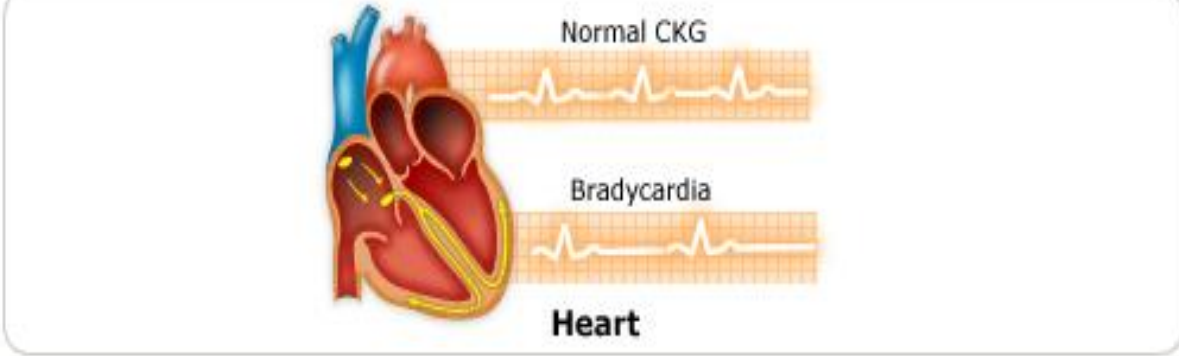


Figure 4.1
Summary of cholinergic agonists.

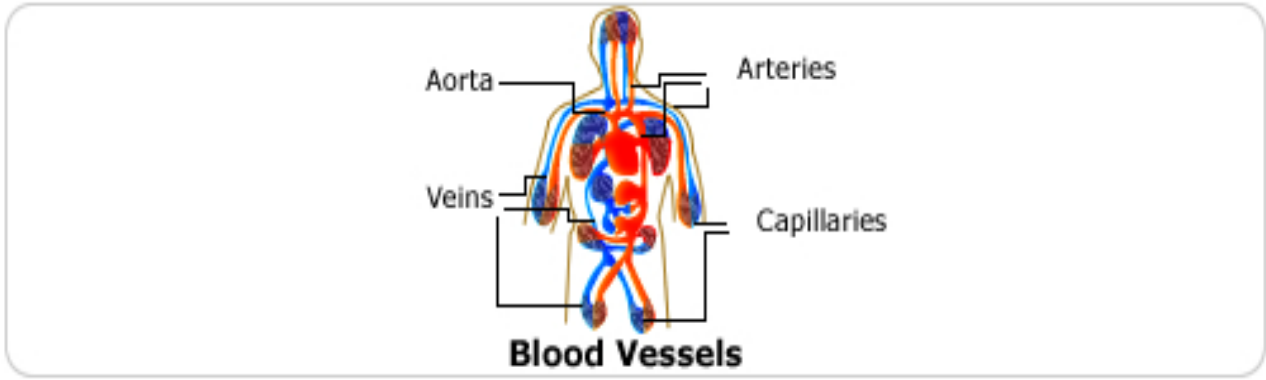
Ach on Heart



Effects produced by acetylcholine on the heart include:

- Negative chronotropic, inotropic and dromotropic action
- Cardiac depression
- Bradycardia

Ach on BV



Acetylcholine is a vasodilator that relaxes the smooth muscle of vasculature. It releases nitric oxide from the endothelium.

In the absence of endothelium, acetylcholine causes vasoconstriction.

Bethanechol

- It lacks nicotinic actions but does have strong muscarinic activity.
- Its major actions are on the smooth musculature on the bladder and GI tract.
- It has about a 1-hour duration of action.

Actions: Bethanechol directly stimulates muscarinic receptors, causing increased intestinal motility and tone.

It also stimulates the detrusor muscle on the bladder, whereas the trigone and sphincter are relaxed.

Therapeutic applications: In urologic treatment, bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention. Bethanechol may also be used to treat neurogenic atony as well as megacolon.

Carbachol

Actions: Carbachol has profound effects on both the cardiovascular and GI systems because of its ganglion-stimulating activity, and it may first stimulate and then depress these systems.

It can cause re-lease on epinephrine from the adrenal medulla by its nicotinic action.

Locally instilled into the eye, it mimics the effects of ACh, causing miosis and a spasm of accommodation in which the ciliary muscle of the eye remains in a constant state of contraction.

Therapeutic uses: Because of its high potency, receptor nonselectivity, and relatively long duration of action, carbachol is rarely used therapeutically except in the eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pres-sure.

Adverse effects: At doses used ophthalmologically, little or no side effects occur due to lack of systemic penetration (quaternary amine)

Pilocarpine

- Pilocarpine exhibits muscarinic activity and is used primarily in ophthalmology.

Actions:

Applied topically to the cornea, pilocarpine produces rapid miosis and contraction of the ciliary muscle. When the eye under-goes this miosis, it experiences a spasm of accommodation. The vision becomes fixed at some particular distance, making it impossible to focus

Pilocarpine is one of the most potent stimulators of secretions (secretagogue) such as sweat, tears, and saliva, but its use for producing these effects has been limited due to its lack on selectivity. The drug is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. Sjögren's syndrome, which is characterized by dry mouth and lack of tears, is treated with oral pilocarpine tablets

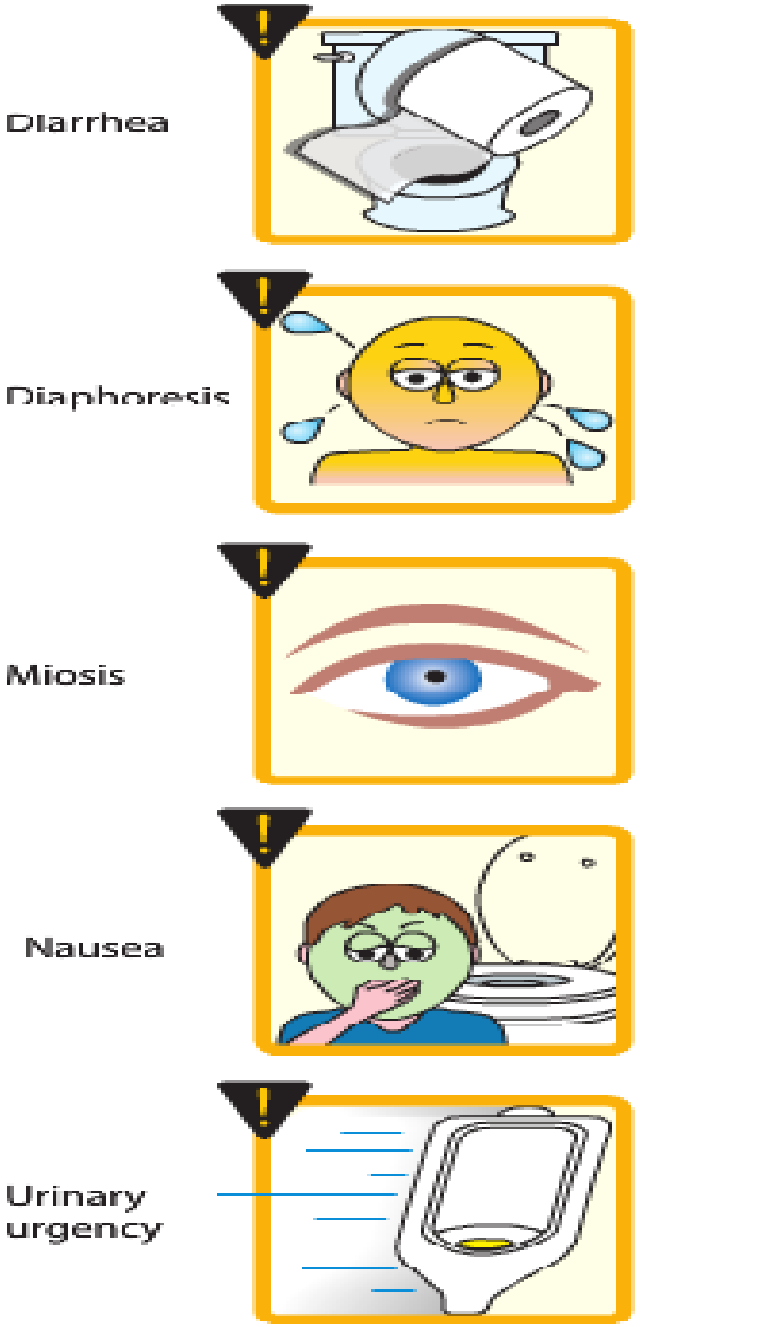
Therapeutic use in glaucoma:

Pilocarpine is used to treat glaucoma and is the drug of choice in the emergency lowering of intraocular pressure of both narrow-angle (or closed-angle) and wide-angle (also called open-angle) glaucoma. Pilocarpine is extremely effective in opening the trabecular meshwork around Schlemm's canal, causing an immediate drop in intraocular pressure as a result of the increased drainage of aqueous humor.

The miotic action of pilocarpine is also useful in reversing mydriasis due to atropine.

Adverse efects: Pilocarpine can enter the brain and cause CNS disturbances. Poisoning with this agent is characterized by exaggeration of various parasympathetic effects, including produce sweating (diaphoresis) and salivation. Parenteral atropine, at doses that can cross the blood-brain barrier, is administered to counteract the toxicity of pilocarpine.

Some adverse effects of cholinergic agonists



Indirect-Acting : Anticholinesterase

- REVERSIBLE (Anticholinesterases)
- IRREVERSIBLE (Organophosphate)

Indirect-Acting :

- REVERSIBLE (Anticholinesterases):
  - Physostigmine
  - Neostigmine
  - Pyridostigmine
  - Ambenonium
  - Edrophonium
  - Tacrine, Donezepil, Rivastigmine, Galantamine
- IRREVERSIBLE
  1. Organophosphates
     - Isoflurophate
     - Echothiophate
     - Malathion, Parathion
  2. Chemical Warfares
     - Sarin, Soman

Therapeutic uses and durations of action of cholinesterase inhibitors.

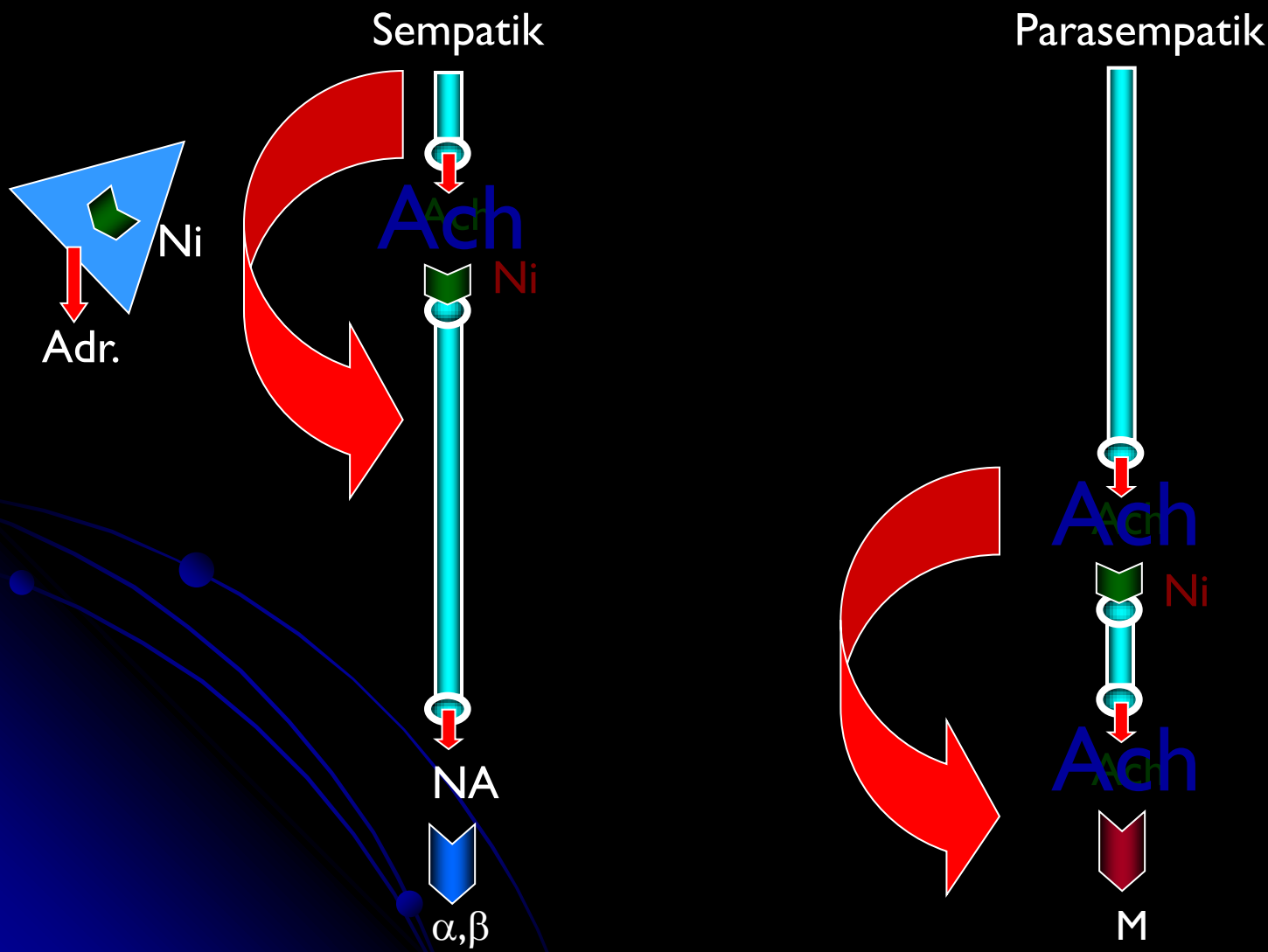
	Uses	Duration of Action
Alcohols		
Edrophonium	Myasthenia gravis, ileus, arrhythmias	15-5minutes
Carbamates and related agents		
Neostigmine	Myasthenia gravis, ileus	2-0.5hours
Pyridostigmine	Myasthenia gravis	6-3hours
Physostigmine	Glaucoma	2-0.5hours
Ambenonium	Myasthenia gravis	8-4hours
Demecarium	Glaucoma	6-4hours
Organophosphates		
Echothiophate	Glaucoma	100hours

PHYSOSTIGMINE (intermediate acting agent, Alkaloid, tertiary ammmonium grp)

- Enters the CNS
- Therapeutic Uses:
  1. Atony of intestines and bladder
  2. Glaucoma → lowers IOP (miosis and spasm of accomodation)-pilocarpine is more effective
  3. Antidote → atropine, phenothiazines, TCA

Adverse effects: convulsions (high doses), bradycardia, fall in cardiac output, paralysis of skeletal muscle (rarely seen therapeutic doses)

Fizostigmin



NEOSTIGMINE

- Quarternary ammonium grp. intermediate acting agent
- Does not enter the CNS → peripheral
- Its effect on skeletal muscle is greater than physostigmin
- Stimulation of bladder and GI tract

Therapeutic Uses:

1. Atony of intestines and bladder
2. Myasthenia gravis
3. Antidote for tubocurarine and other competitive NMBA

Adverse effects: salivation, flushing, ↓ BP, nausea, abdominal pain, diarrhea, bronchospasm

Contraindications: intestinal or urinary bladder obstruction, peritonitis or inflammatory bowel syndrome

PYRIDOSTIGMINE and AMBENONIUM

- DOA: PYRIDOSTIGMINE - 3 to 6 hrs (longer than neostigmin)
- AMBENONIUM – 4 to 8 hrs
- **Therapeutic Uses:**
  1. Myasthenia gravis
  2. Tubocurarine antidote
- **Adverse effects:** salivation, flushing, ↓ BP, nausea, abdominal pain, diarrhea, bronchospasm

EDROPHONIUM

- Quarternary amine
- **DOA:** 5 to 15 mins

Therapeutic Uses:

1. Diagnosis of Myasthenia gravis
2. To asses anticholinesterase therapy (differentiation of cholinergic and myasthenic crisis)
3. Tubocurarine antidote

- Adverse effects: salivation, flushing, ↓ BP, nausea, abdominal pain, diarrhea, bronchospasm

Tacrine, Donezepil, Rivastigmine, Galantamine

- Alzheimer disease → deficiency of cholinergic neurons in the CNS (none can stop its progression)
- *Tacrine* – hepatotoxic
- Adverse effect: GI distress

Indirect-Acting →IRREVERSIBLE :

ORGANOPHOSPHATES

- **ISOFLUROPHATE**
  - treatment of open angle glaucoma
- **ECHOTHIOPHATE**
  - Produce intense miosis → treatment of open angle glaucoma
- **PARATHION, MALATHION**
  - Insecticides

Sarin, Soman, Tabun

Chemical ware

ORGANOPHOSPHATE POISONING:

Signs & Symptoms

1. miosis
2. salivation, frothy secretions
3. sweating
4. bronchial constriction
5. vomiting and diarrhea
6. muscle fasciculation

ORGANOPHOSPHATE POISONING:

- Therapy:
  - maintenance of VS → respiration
  - Decontamination
  - Drugs: **Atropine + Pralidoxime**

ATROPINE sulfate

- → 1 to 2 mg IV every 5-15 min until muscarinic effect disappears (maximum of 1 gm per day)

PRALIDOXIME

- → A cholinesterase enzyme regenerator compound
- - 1 to 2 gm given over 30 min by IV infusion

Bethanechol

- Used in treatment of urinary retention
- Binds preferentially at muscarinic receptors

Physostigmine

- Increases intestinal and bladder motility
- Reduces intraocular pressure in glaucoma
- Reverses CNS and cardiac effects of tricyclic antidepressants
- Reverses CNS effects of *atropine*
- Uncharged, tertiary amine that can penetrate the CNS

Rivastigmine, galantamine, donepezil

- Used as first-line treatments for Azheimer disease, though confers modest benefit
- Have not been shown to reduce healthcare costs or delay institutionalization
- Can be used with *memantine* (N-methyl-D-aspartate antagonist) with moderate to severe disease

Carbachol

- Produces miosis during ocular surgery
- Used topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to *pilocarpine*

Neostigmine

- Prevents postoperative abdominal distention and urinary retention
- Used in treatment of myasthenia gravis
- Used as an antidote for *tubocurarine*
- Has long duration of action (2 to 4 hrs)

Echothiophate

- Used in treatment of open-angle glaucoma
- Has long duration of action (1 week)

Pilocarpine

- Reduces intraocular pressure in open-angle and narrow-angle glaucoma
- Binds preferentially at muscarinic receptors
- Uncharged, tertiary amine that can penetrate the CNS

Edrophonium

- For diagnosis of myasthenia gravis
- As antidote for tubocurarine
- Has short duration of action (10 to 20 min)

Acetylcholine

- Has no therapeutic uses

Figure 4.11
Summary of actions of some cholinergic agonists. CNS = central nervous system.

Cholinergic Agonists-summary

Pharmacodynamics:

- Mimic the action of acetylcholine on the neurons of target organs producing: salivation, bradycardia, vasodilation, constriction of bronchioles, increased GI activity, increased tone and contraction of the bladder muscles, and constriction of pupils.

Cholinergic Agonists-summary

Pharmacotherapeutics:

- Used to treat: atonic bladder conditions and post-operative and postpartum urinary retention; GI disorders such as post-operative abdominal distention and GI atony; reduce eye pressure in glaucoma patients and during eye surgery; and salivary hypofunction.

Cholinergic Agonists

Drug interactions/adverse reactions:

- Taken with other cholinergic drugs can increase the effects.
- Taken with cholinergic blocking drugs can reduce the effects.
- Can produce adverse effects in any organ innervated by the parasympathetic nerves.

Cholinergic Agonists

Cholinergic agents cause SLUDGE!

These effects are predictable by knowing PNS physiology

Salivation
Lacrimation
Urination
Defecation
Gastric motility
Emesis

Anticholinesterase Drugs-summary

Pharmacotherapeutics:

- Therapeutic uses include: reduce eye pressure; increase bladder tone; improve GI tone and peristalsis; promote muscular contraction; diagnose myasthenia gravis; an antidote to cholinergic blocking drugs; treat dementia due to Alzheimer's.

Anticholinesterase Drugs

Drug interactions/adverse reactions:

- Taken with other cholinergic drugs can increase the risk of toxicity.
- Nausea, vomiting, diarrhea, respiratory distress, and seizures.

Cholinergic Blockers

- Cholinergic blockers, anticholinergics, parasympatholytics, and antimuscarinic agents are all terms for the class of drugs that block the actions of acetylcholine in the PSNS.
- Cholinergic blockers allow the SNS to dominate and, therefore, have many of the same effects as the adrenergics.

Cholinergic Blockers

- Cholinergic blockers are competitive antagonists that compete with acetylcholine for binding at the muscarinic receptors of the PSNS, inhibiting nerve transmission.
- This effect occurs at the neuroeffector junctions of smooth muscle, cardiac muscle, and exocrine glands.
- Have little effect at the nicotinic receptors.

Cholinergic Blocking Drugs

- Interrupt parasympathetic nerve impulses in the central and autonomic nervous systems.
- Also referred to as anticholinergic drugs because they prevent acetylcholine from stimulating the muscarinic cholinergic receptors.
- Drugs include the belladonna alkaloids- the prototype is atropine.

Cholinergic Blocking Drugs

Pharmacokinetics:

- Absorbed from the eyes, GI tract, mucous membranes, and skin; when given IV atropine works immediately; distributed widely; cross the BBB; moderate protein-binding; metabolized by the liver; excreted by the kidneys.

Cholinergic Blocking Drugs

Pharmacodynamics:

- Can produce a stimulating or depressing effects depending on the target organ.
- In the brain low drug levels stimulate and high drug levels depress.

Cholinergic Blocking Drugs

Pharmacotherapeutics:

- Often used to treat GI disorders and complications.
- Atropine is administered pre-operative to reduce GI and respiratory secretions and prevent bradycardia caused by vagal nerve stimulation during anesthesia.

Cholinergic Blocking Drugs

- Other uses include treatment of motion sickness, Parkinson's, bradycardia, arrhythmias, pupil dilation, and organophosphate pesticide poisoning.

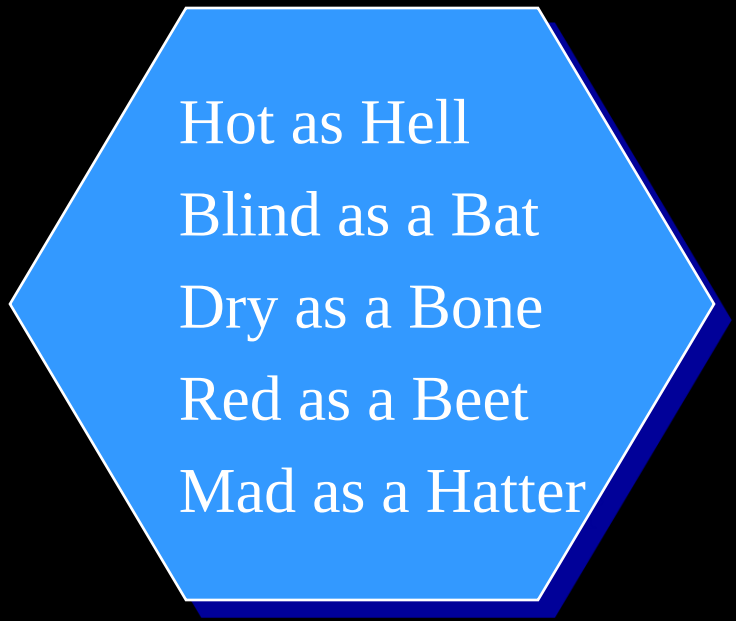
Cholinergic Blocking Drugs

- Dry mouth, reduced bronchial secretions, increased heart rate, and decreased sweating can occur.

Anticholinergics

- Muscarinic antagonists
  - Atropine
- Ganglionic antagonists
  - block nicotinic$_N$ receptors
  - *Turns off the ANS!*
  - trimethaphan (Arfonad®)
    - Hypertensive crisis

- Atropine Overdose
  - Dry mouth, blurred vision, anhidrosis



General effects of anticholinergic Drugs:

Restlessness
Irritability
Hallucinations
Antiparkinsonian effect
Antiemetic effect

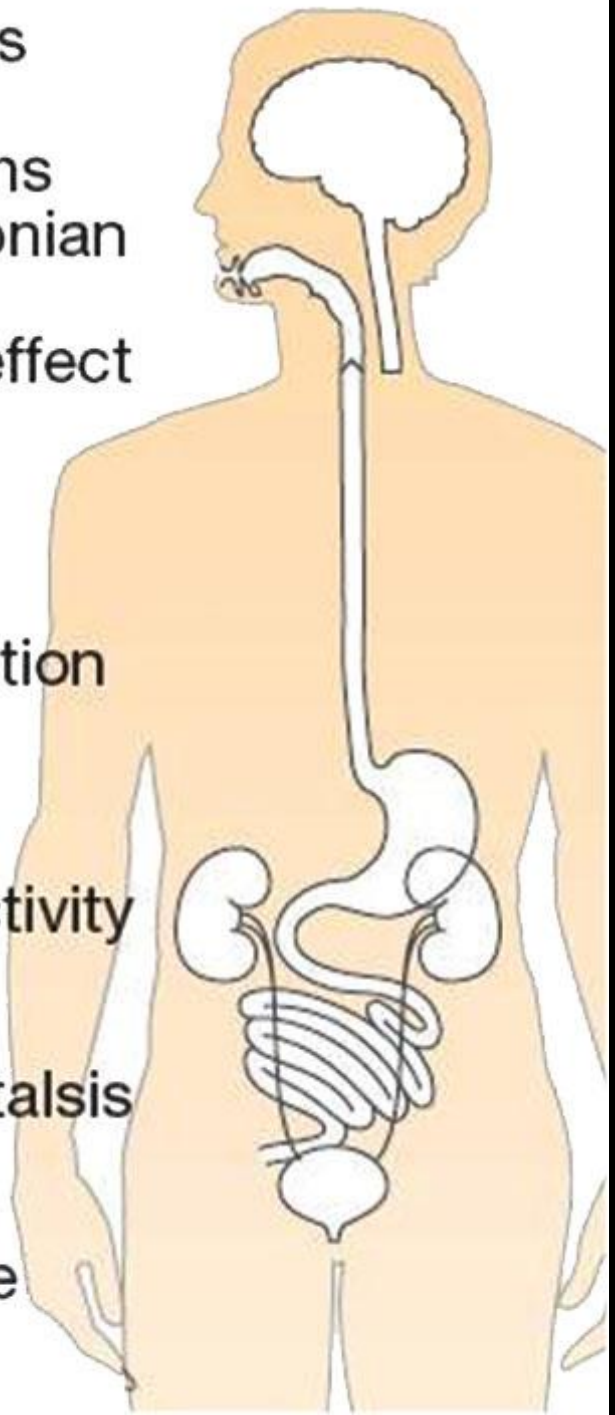
Dry mouth

Acid production decreased

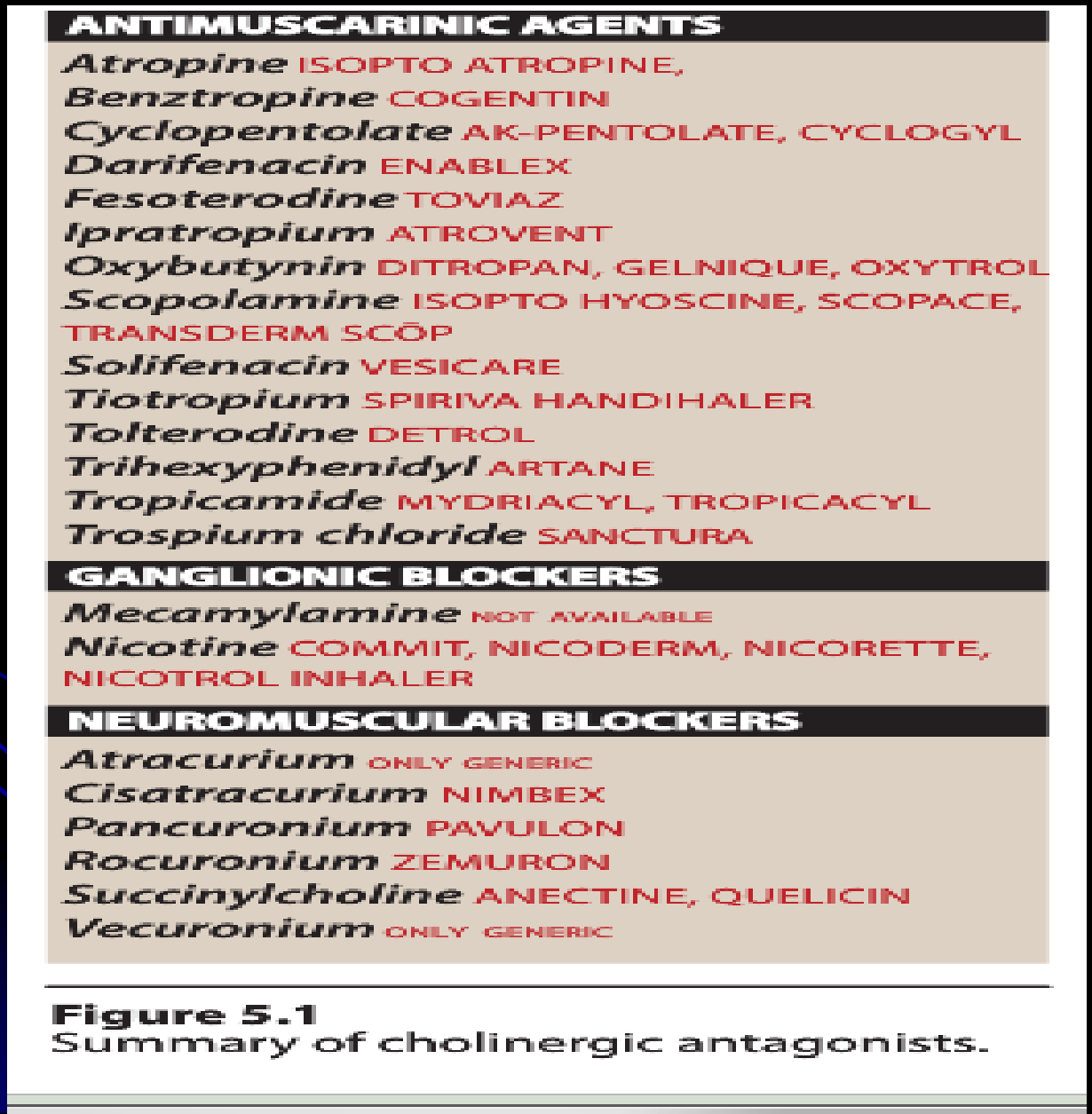
Pancreatic secretory activity decreased

Bowel peristalsis decreased

Bladder tone decreased



Cholinergic Antagonists



ANTIMUSCARINIC AGENTS

Atropine ISOPTO ATROPINE,
Benztropine COGENTIN
Cyclopentolate AK-PENTOLATE, CYCLOGYL
Darifenacin ENABLEX
Fesoterodine TOVIAZ
Ipratropium ATROVENT
Oxybutynin DITROPAN, GELNIQUE, OXYTROL
Scopolamine ISOPTO HYOSCINE, SCOPACE, TRANSDERM SCŌP
Solifenacin VESICARE
Tiotropium SPIRIVA HANDIHALER
Tolterodine DETROL
Trihexyphenidyl ARTANE
Tropicamide MYDRIACYL, TROPICACYL
Trospium chloride SANCTURA

GANGLIONIC BLOCKERS

Mecamylamine NOT AVAILABLE
Nicotine COMMIT, NICODERM, NICORETTE, NICOTROL INHALER

NEUROMUSCULAR BLOCKERS

Atracurium ONLY GENERIC
Cisatracurium NIMBEX
Pancuronium PAVULON
Rocuronium ZEMURON
Succinylcholine ANECTINE, QUELICIN
Vecuronium ONLY GENERIC

Figure 5.1
Summary of cholinergic antagonists.

ANTICHOLINERGIC DRUGS

1. **Natural alkaloids:** Atropine (spasmolytic, mydriatic), Hyoscine (Scopolamine), Scopoderm® TTS (antiemetic)

2. **Semisynthetic derivatives**
   - *Mydriatics*: Homatropine
   - *GI spasmolytics*: Hyoscine butyl bromide (Buscolysin®)

3. **Synthetic compounds**
   - *GI spasmolytics*: Oxyphenonium
   - *Antiulcus drugs*: Pirenzepine (M_1-blockers)
   - *Antiasthmatics*: Ipratropium and Tiotropium
   - *Antidisurics*: Flavoxate, Oxybutynyne, Trospium
   - *Mydriatics*: Tropicamide
   - *Antiparkinsonian (central M-cholinolytics)*: Benztropine, Biperiden, Trihexyphenidyl

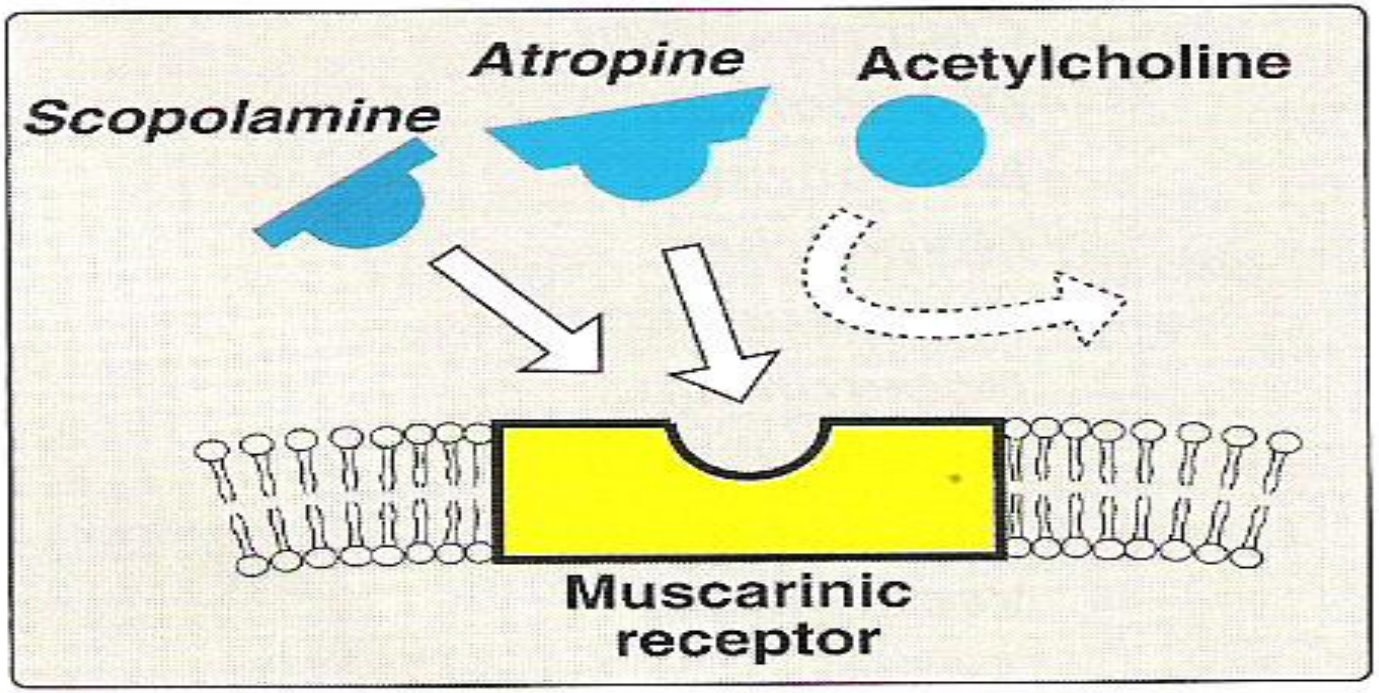


Figure 5.3
Competition of *atropine* and *scopolamine* with acetylcholine for the muscarinic receptor.

ATROPINE

- prototype
- Belladona alkaloid
- high affinity for muscarinic receptors
- central and peripheral muscarinic blocker

causes reversible (surmountable) blockade of the actions of cholinomimetics at muscarinic receptors

Unopposed sympathetic action

ATROPINE

- Actions:

1. CNS
   - minimal stimulant effect
2. Eye
   - mydriasis, unresponsiveness to light
   - *cycloplegia* → inability to focus for near-vision
3. GIT
   - antispasmodic → reduce GIT activity
4. GUT
   - reduce urinary bladder hypermotility
5. SECRETIONS
   - blocks salivary glands → antisialogogue
   - decrease also lacrimal & sweat glands secretion

ATROPINE

6. CVS

- divergent effects depending on dose

- Low dose – (-) M_1 → ↑ Ach release
- Higher dose – (-) M_2 on SA node → ↑ CR

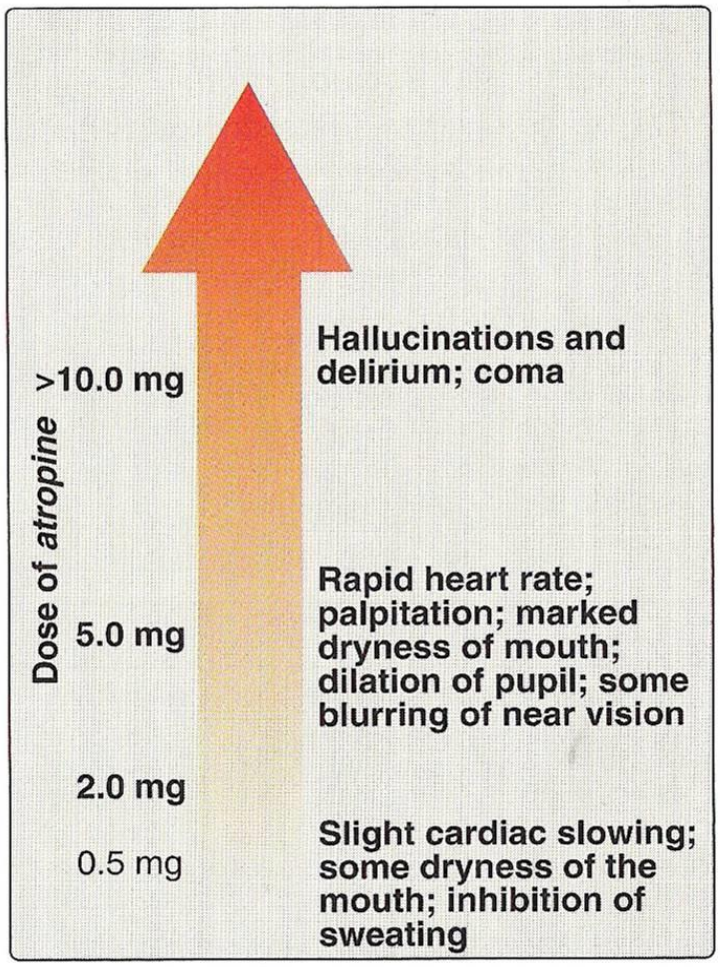


Figure 5.4
Dose-dependent effects of *atropine*.

- Effects in relation to dose:

Dose	Effects
0.5 mg	Slight cardiac slowing some dryness of mouth inhibition of sweating
1.0 mg	Definite dryness of mouth; thirst acceleration of heart, sometimes preceded by slowing mild pupillodilatation

Dose	Effects
2.0 mg	Rapid HR; palpitations marked dryness of mouth Dilated pupils; some blurring of vision
5.0 mg	All of the above symptoms marked; difficulty in speaking and swallowing; Restlessness and fatigue; Headache; dry, hot skin Difficulty in micturition Reduced intestinal peristalsis

Dose	Effects
10.0 mg and more	Above symptoms more marked Pulse rapid and weak Iris practically obliterated Vision very blurred Skin flushed, hot, dry, and scarlet Ataxia, restlessness and excitement Hallucinations and delirium Coma

ATROPINE

Therapeutic Uses:

1. Ophthalmic
   - Permits measurement of EOR
2. Antispasmodic
3. Antidote for cholinergic agonists
   - Organophosphate poisoning
   - Mushroom poisoning
   - acetylcholinesterase inhibitors
4. Antisecretory agent

SCOPOLAMINE

- Belladona alkaloid
- Peripheral effects similar to atropine
- Greater and longer CNS action
- Action:
  - Anti-motion sickness
  - Blocks short-term memory
  - Produces sedation, excitement
  - It may produce euphoria

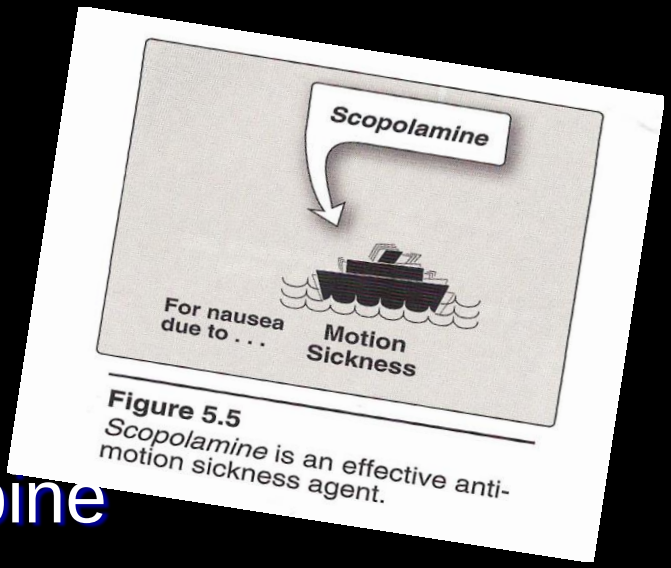


Figure 5.5
Scopolamine is an effective anti-motion sickness agent.

- Therapeutic Uses:
  - anti-motion sickness
  - adjunct in anesthesia procedures
  - > in obstetrics, + morphine → sedation
  - & amnesia

IPRATROPIUM (4X1) and TIOTROPIUM (1X1)

- Quarternary derivative of atropine
- Does not enter CNS
- Therapeutic Uses:
  - Treat asthma in patients who are unable to take adrenergic agonists
  - Management of COPD

TROPICAMIDE AND CYCLOPENTOLATE

- ✓ They are used for mydriasis and cycloplegia.
- ✓ Duration of action is shorter than atropin

BENZTROPINE AND TRIHEXYPHENIDYL

- ✓ Centrally acting antimuscarinic agents
- ✓ They have been used for in the treatment of parkinson disease (with the advent of other drugs- levodopa/carbidopa)

DARIFENASIN, FESOTERODINE, OXYBUTYNIN, SOLIFENACIN, TOLTERODINE, TROSPIUM

- ✓ These are used to treat overactive urinary bladder disease
- ✓ Intravesicular pressure is lowered, bladder capacity is increased, frequency of bladder contractions is reduced
- ✓ Side effects: dry mouth, constipation, blurred vision
- ✓ Oxybutinin is available as a transdermal system which is better tolerated because it causes less dry mouth than do oral formulations

Main interactions of anticholinergic drugs

- Absorption of more drugs is slowed because atropine delays gastric emptying. As a result the dose of levodopa, needed to control parkinsonism may have to be increased. But the extent of digoxin, and tetracyclines absorption may be increased.
- Antacids interfere with the absorption of anticholinergics.
- Antihistaminics, tricyclic antidepressants, phenothiazines, pethidine, etc. have anticholinergic property: additive side effects with atropinic drugs are possible.
- MAO inhibitors interfere with the metabolism of central antiparkinsonian drugs (biperiden and others): delirium may occur.

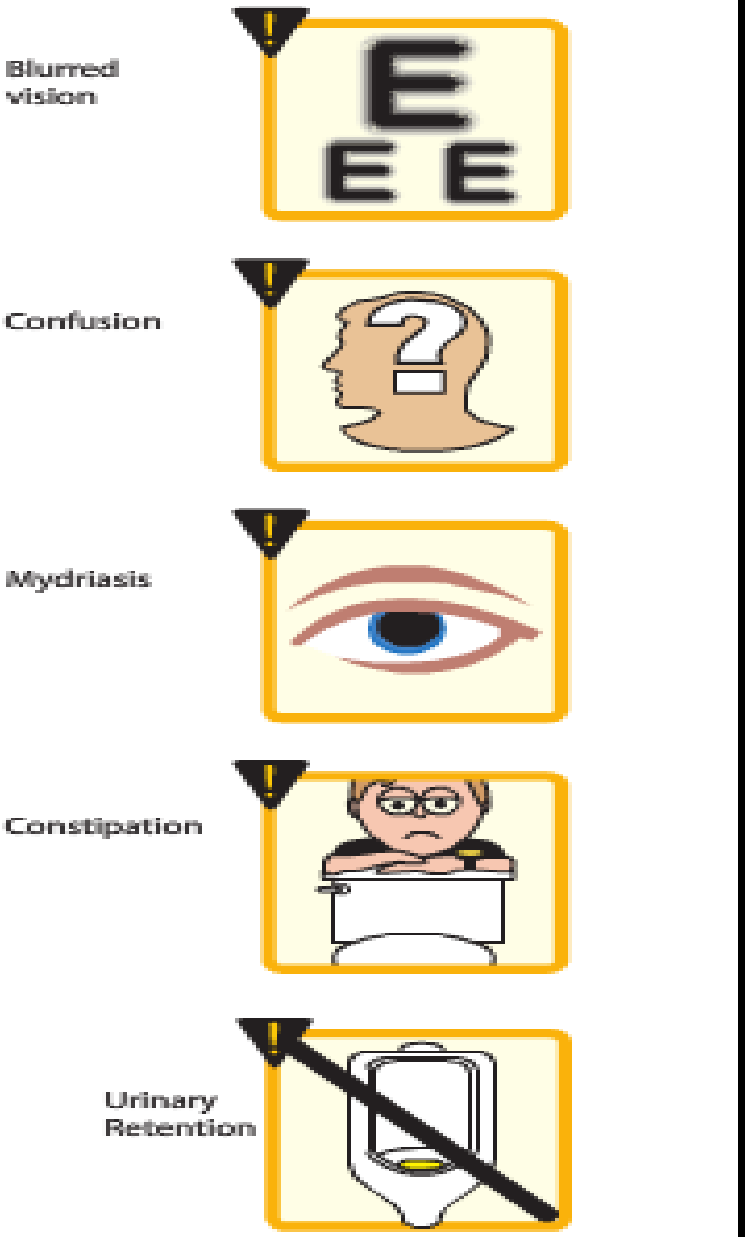
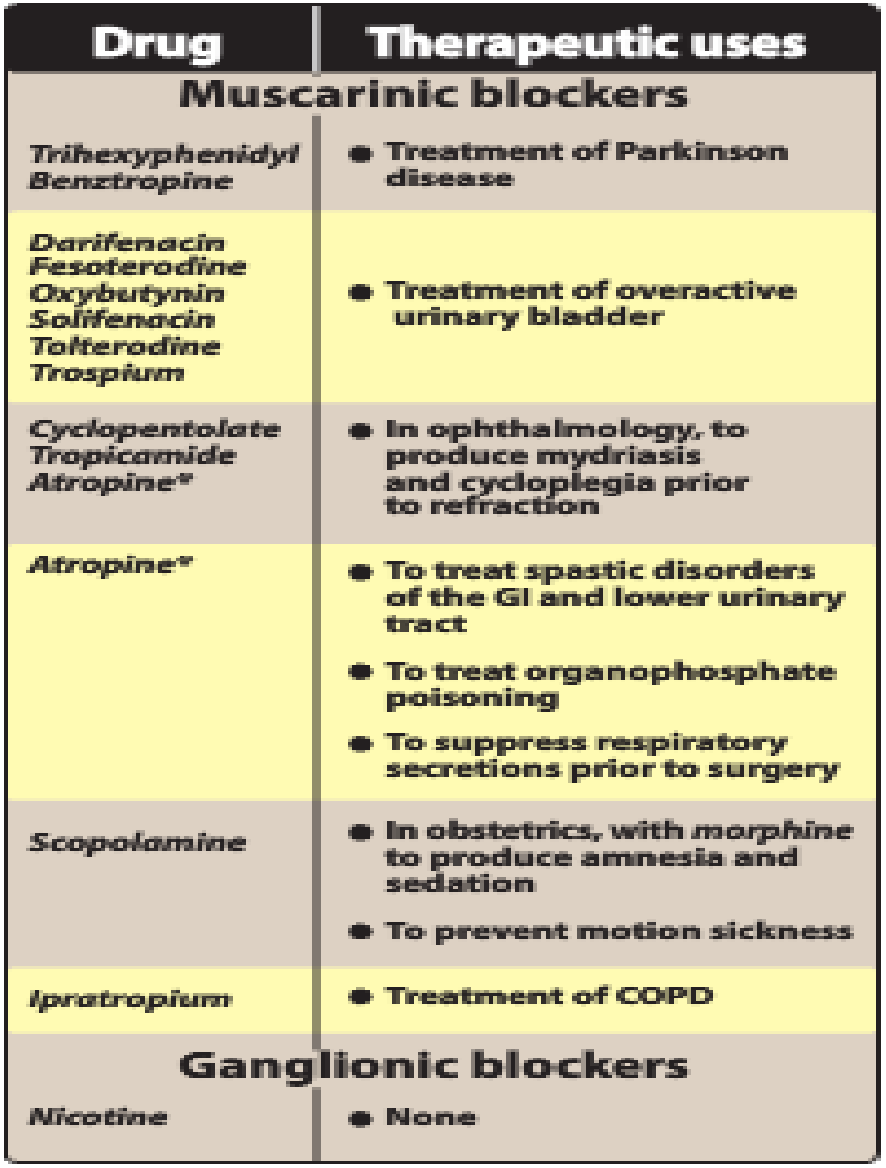


Figure 5.6
Adverse effects commonly observed with cholinergic antagonists.



Drug	Therapeutic uses
Muscarinic blockers	
Trihexyphenidyl *Benztropine*	• Treatment of Parkinson disease
Darifenacin *Fesoterodine* *Oxybutynin* *Solifenacin* *Tolterodine* *Trospium*	• Treatment of overactive urinary bladder
Cyclopentolate *Tropicamide* *Atropine**	• In ophthalmology, to produce mydriasis and cycloplegia prior to refraction
*Atropine**	• To treat spastic disorders of the GI and lower urinary tract • To treat organophosphate poisoning • To suppress respiratory secretions prior to surgery
Scopolamine	• In obstetrics, with *morphine* to produce amnesia and sedation • To prevent motion sickness
Ipratropium	• Treatment of COPD
Ganglionic blockers	
Nicotine	• None

Figure 5.7
Summary of cholinergic antagonists.
*Contraindicated in narrow-angle glaucoma.
GI = gastrointestinal; COPD = chronic obstructive pulmonary disease.

ATROPINE POISONING:

- **Manifestations are** dry mouth, mydriasis, tachycardia, hot and flushed skin,
- agitation, delirium and hyperthermia.

CONTRAINDICATIONS OF ANTIMUSCARINIC DRUGS:

- 1. Glaucoma, especially angle-closure glaucoma.
- 2. Prostatic hyperplasia.
- 3. Non selective antimuscarinic drugs should never be used to treat acid-peptic disease