Parasympatholytic Agents

- **Antimuscarinic**: eg. atropine
  - block Ach in parasympathetic effector junctions (muscarinic receptors)

- **Antinicotinic: Ganglia** eg. trimethapan
  - block Ach in ganglia (both parasympathetic and sympathetic, N_N or N_1-receptors)

- **Antinicotinic: NMJ** eg. curare, succinylcholine
  - block Ach in neuromuscular junctions (skeletal muscle relaxants, N_M or N_2-receptors)
Anticholinergic Effects on Organ Systems

- **Heart**: tachycardia, ↑ A-V nodal CV (M2-receptors)
- **Vasculature**: no effect, although toxic doses cause pronounced direct vasodilation (red blotches)
- **Smooth muscle**
  - GI tract, urinary tract: relaxation, ↓ secretion, ↓ motility
  - Lung: bronchial relaxation & ↓ bronchial secretions
  - Eye: mydriatic (sphincter relaxation), cyclopegic (ciliary muscle relaxation)
- **Secretions**
  - ↓ secretion: dry mouth, dry skin,
  - ↓ decreased gastric acid secretion
- **CNS**: agitation, delirium, confusion, elderly are more susceptible

Antimuscarinic Agents

- **Belladonna alkaloids**: well absorbed, CNS effects
  - atropine (7-10 d) - “belladonna”
  - homatropine (1-3 d) - iritis
  - scopolamine (3-7 d) - motion sickness
- **Synthetic antimuscarinics**
  - ipratropium (quaternary amine) – asthma, COPD
  - tiotropium - COPD
  - pirenzepine (tri-cyclic, M1-selective) - ulcer
  - benztropine - Parkinson’s disease
  - glycopyrrolate (quaternary amine)
  - cyclopentolate (tertiary amine)
  - propantheline (quaternary amine)
Deadly Nightshade

Mainly atropine
Devil’s apple
Stink weed
Devil’s cherries

Approx 5,000 per yr

Datura

Mainly scopolamine & hyoscyamine
Thorn apple
Jimson weed

Chronic Obstructive Pulmonary Disease (COPD)

Features:
- Damage to lungs
- Develops slowly
- No cure
- 4th US Cause of death
- Smoking common cause

Treatment (inhaled):
- Beta2-agonists
- M-receptor blockers (ipratropium, tiotropium)
- Glucocorticosteroids
- Oxygen
Other Parasympatholytics

Hemicholinium
- no clinical use
- inhibits uptake of choline into nerve terminal (rate limiting step)
- leads to decreased Ach synthesis

Botulinus toxin
- prevent release of Ach
- contamination of improperly prepared food

Clinical use: facial muscle spasms (blepharospasm, eye twitching or eye spasm) strabismus, wrinkles

Botulinum toxin
Inhibits Ach release
Single treatment can last 3-4 months

Facial wrinkles, FDA Approval: Apr 2002
Clinical uses of Antimuscarinic Agents

- respiratory (decrease bronchial secretion) ie. atropine
- Asthma, COPD ie. ipratropium, tiotropium
- ophthalmologic (mydriasis, cycloplegia) eg. iritis (ie. atropine)
- Parkinson’s disease ie. benztropine
- cardiovascular ie. atropine
- motion sickness ie. scopolamine
- GI disorders (peptic ulcers (pirenzepine), diarrhea)
- Rx pesticide poisoning (malathion) ie. atropine + 2-PAM
- Rx mushroom poisoning (muscarine) ie. atropine
- Rx nerve gases (Vx, sarin) ie. atropine + 2-PAM
Toxicity and treatment

• **Toxicity:**
  dry mouth, mydriasis, cycloplegia, tachycardia, hot flushed skin, agitation and delirium.

  High concentrations may cause ganglionic-blockade leading to hypotension

• **Treatment:**
  - quaternary cholinesterase inhibitor eg. neostigmine or physostigmine (cns action)
  - for hypotension: sympathomimetics ($\alpha$-agonist, eg.methoxamine)

Antimuscarinic Toxicity

Belladonna (beautiful lady)

• mad as a hatter: - CNS, delirium
• red as a beet: - direct vasodilation
• blind as a bat: - cycloplegia
• hot as hell (a hare): - ↓sweat, thermoregulation
• dry as a bone: - decreased secretions
Pharmacology of the Eye

“The eye is a good example of an organ with multiple ANS functions, controlled by several different autonomic receptors.” (Katzung)

Increased intraocular pressure: Untreated → blindness

Glaucoma:
- Open-angle (wide, chronic) – treated with beta-blockers and other agents
  - Closed-angle (narrow-angle) – dilated iris can occlude outflow. Pilocarpine or surgical removal of part of iris (iridectomy)

Glaucoma: Increased intraocular pressure: Untreated → blindness

Glaucoma:
- Open-angle (wide, chronic) – treated with beta-blockers and other agents
  - Closed-angle (narrow-angle) – dilated iris can occlude outflow
    Pilocarpine or surgical removal of part of iris (iridectomy)

Glaucoma treatment
1. α-Agonist: ↑Outflow
2. M-Agonists: ↑Outflow
3. β-Blocker: ↓Secretion
4. α2-Agonist: ↓Secretion
5. Prostaglandins: ↑Outflow
6. Carbonic acid inhibitors: ↓Secretion
Open Angle vs Closed Angle Glaucoma

Ach effects on smooth muscle in the eye

Contraction of sphincter muscle → miosis

Contraction of ciliary muscle for near vision
Glaucoma treatment

1. α-Agonist
   ↑Outflow

2. M-Agonists/AchEI
   ↑Outflow

3. β-Blocker
   ↓Secretion

4. α₂-Agonist
   ↓Secretion

5. Prostaglandins
   ↑Outflow

6. Carbonic acid inhibitors
   ↓Secretion

Prostaglandin analogues
(Latanoprost, Bimatoprost, Travoprost, Unoprostone)

Side effects:
- darkening of the iris
- lengthening and thickening of eyelashes
- intraocular inflammation
## Drugs used in glaucoma

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Effect</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinomimetics</td>
<td>Pilocarpine (acute DOC), physostigmine, echothiophate</td>
<td>Ciliary muscle contraction → opening of trabecular meshwork → ↑outflow</td>
<td>Topical</td>
</tr>
<tr>
<td><strong>Alpha Agonists: Unselective:</strong></td>
<td>Epinephrine, Dipivefrin, PE</td>
<td>↑ Outflow</td>
<td>Topical</td>
</tr>
<tr>
<td><strong>Alpha2-Selective Agonists:</strong></td>
<td>Apraclonidine, Brimonidine</td>
<td>↓ Aqueous secretion from the ciliary epithelium</td>
<td>Topical</td>
</tr>
<tr>
<td><strong>Beta-Blockers:</strong></td>
<td>Timolol, betaxolol, carteolol</td>
<td>↓ Aqueous secretion from the ciliary epithelium</td>
<td>Topical</td>
</tr>
<tr>
<td><strong>Diuretics: Carbonic acid inhib.</strong></td>
<td>Acetazolamide, Methazolamide, Dorzolamide, Brinzolamide</td>
<td>↓ Secretion due to lack of HCO₃⁻</td>
<td>Oral/Topical</td>
</tr>
<tr>
<td>**Prostaglandins: (PGF₂α) **</td>
<td>Latanoprost, Bimatoprost</td>
<td>↑ Outflow</td>
<td>Topical</td>
</tr>
</tbody>
</table>

## Effects of pharmacological agents on the pupil

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Drug</th>
<th>Pupillary Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Alpha agonist ie. phenylephrine</td>
<td>Dilation (mydriasis)</td>
</tr>
<tr>
<td>Normal</td>
<td>Muscarinic agonist ie. pilocarpine</td>
<td>Constriction (miosis) cycloplegia</td>
</tr>
<tr>
<td>Normal</td>
<td>Muscarinic antagonist ie. atropine</td>
<td>Mydriasis, cycloplegia</td>
</tr>
<tr>
<td>Horner’s syndrome</td>
<td>Cocaine</td>
<td>No dilation</td>
</tr>
<tr>
<td>Preganglionic Horner’s</td>
<td>Hydroxyamphetamine</td>
<td>Dilation</td>
</tr>
<tr>
<td>Postganglionic Horner’s</td>
<td>Hydroxyamphetamine</td>
<td>No dilation</td>
</tr>
<tr>
<td>Adie’s pupil</td>
<td>Pilocarpine</td>
<td>Constriction</td>
</tr>
<tr>
<td>Normal</td>
<td>Opioids (oral or intravenous)</td>
<td>Pinpoint pupils</td>
</tr>
</tbody>
</table>
Eye - Horner's Syndrome

Destruction of Sympathetic innervation to the iris
- loss of preganglionic fibers
- loss of postganglionic fibers
- parasympathetic innervation left unopposed

Horners Syndrome (note sagging left eyelid and miosis)

Question 3

The circles represent the size of the pupils of a patient's right and left eyes, both without treatment and with two different treatments. Which of the following is compatible with the findings shown for the left eye?

A. Blockade of \( \alpha \)-adrenergic rec.
B. Blockade of \( \beta \)-adrenergic rec.
C. Blockade of muscarinic rec.
D. Inhibition of cholinesterase
E. Sympathetic denervation

### Parasympathetic Summary

<table>
<thead>
<tr>
<th>Agonists</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ach</td>
<td>1. heart ⇒ bradycardia, ↓ contractility, ↓ conduction velocity in the AV node</td>
</tr>
<tr>
<td>2. Bethanecol</td>
<td>2. vasculature ⇒ mediate vasodilation via synthesis of NO by endothelial cells</td>
</tr>
<tr>
<td>3. Pilocarpine</td>
<td>3. smooth muscle ⇒ ↑ tone in intestine &amp; bladder, ↓ tone in sphincters</td>
</tr>
<tr>
<td>4. Methacholine</td>
<td>4. eye ⇒ contraction of sphincter (miosis) &amp; ciliary muscle for near vision</td>
</tr>
<tr>
<td>5. Exocrine glands</td>
<td>5. exocrine glands ⇒ ↑ sweating (SNS), salivation &amp; gastric acid secretion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antagonists</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Atropine - non-selective, long lasting</td>
<td>1. heart ⇒ tachycardia, ↑ AV node conduction</td>
</tr>
<tr>
<td>2. Scopolamine – CNS</td>
<td>2. vasculature ⇒ no effect (no cholinergic innervation)</td>
</tr>
<tr>
<td>3. Homatropine – shorter acting</td>
<td>3. smooth muscle ⇒ relaxation in GI &amp; urinary</td>
</tr>
<tr>
<td>4. Ipratropium - asthma</td>
<td>4. eye ⇒ mydriasis &amp; cycloplegia</td>
</tr>
<tr>
<td>5. Pirenzepine - M1 receptor selective (ulcer)</td>
<td>5. exocrine glands ⇒ dry mouth, dry skin, &amp; ↓ gastric acid secretion</td>
</tr>
<tr>
<td>6. CNS effects ⇒ belladonna toxicity (mad as a hatter, red as a beet, blind as a bat, hot as hell)</td>
<td></td>
</tr>
</tbody>
</table>

### Acetylcholinesterase Inhibitors

<table>
<thead>
<tr>
<th>Type</th>
<th>Agent</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly reversible (competitive)</td>
<td>Edrophonium ⇒ used for myasthenia gravis (aka Tensilon)</td>
<td></td>
</tr>
<tr>
<td>Slowly reversible (competing substrate, carboxylates enzyme)</td>
<td>1. Neostigmine ⇒ does not cross BBB; affects skeletal muscle most strongly; used for myasthenia gravis &amp; ileus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Physostigmine ⇒ crosses BBB, used for glaucoma and for treatment of belladonna poisoning</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Pyridostigmine ⇒ used for myasthenia gravis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Ambenonium ⇒ used for myasthenia gravis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Demercarium ⇒ used for glaucoma</td>
<td></td>
</tr>
<tr>
<td>Irreversible or very slowly reversible (phosphorylates enzyme)</td>
<td>Organophosphate insecticides, nerve gases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Echothiophate ⇒ used for glaucoma</td>
<td></td>
</tr>
</tbody>
</table>