CHOLINERGICS AND ANTI-CHOLINERGICS

PROFESSOR DR. IMAD A-J THANNOON
Nervous System Divisions

Nervous System

Central Nervous System (CNS)
Brain and spinal cord

Peripheral Nervous System (PNS)
Nerves outside of brain and spinal cord

Sensory

Motor

Somatic or Voluntary (skeletal muscles)

Autonomic (smooth and cardiac muscles and glands)

Parasympathetic Branch (homeostasis, daily maintenance)

Sympathetic Branch (alert system)
Objectives:
To discuss the physiology of parasympathetic system
To discuss the parasympathomimetic drugs both synthetic & natural, direct and indirect.
To discuss anticholinergic drugs both antimuscarinic and antinicotinic.
**Autonomic Nervous System: (AN)**

The ANS is the major Involuntary, unconscious, automatic portion of the Nervous system.

**Spinal roots of origin:**

The parasympathetic preganglionic motor fibers originate in the cranial nerve nuclei (III, VII, IX, X) and the sacral segment (usually S2-S4) of the cord.

The sympathetic preganglionic fibers originate in the thoracic (T1-T12) and lumbar (L1-L5) segments of the spinal cord.
Location of the ganglia

Most of the sympathetic ganglia are located in 2 paravertebral chains that lie along the spinal column.

Most of the parasympathetic ganglia are located in the organs innervated, more distant from the spinal cord.

Length of pre and postganglionic fibers: Because of the location of the ganglia, the preganglionic sympathetic fibers are short and the postganglionic fibers are long. The opposite is true for the parasympathetic system: i.e. preganglionic fibers are long and postganglionic are short.

Primary transmitters

Acetylcholine (Ach) is the primary transmitter in all autonomic ganglia and at the parasympathetic postganglionic neuron-effector cell synapses.
Figure 6–2. Characteristics of transmitter synthesis adrenergic nerve terminals are shown from the top down. 
Choline acetyltransferase; ACh, acetylcholine; AChE.
Synthesis and storage of transmitters:
Ach is synthesized by the enzyme choline acetyl transferase from acetyl CoA and choline.

Termination of action of transmitters:
The action of Ach in the synapse is normally terminated by metabolism to acetate and choline by the enzyme acetylcholinesterase. The products are not excreted but are recycled in the body.

Cholinoceptors:
Also referred to as cholinergic receptors these receptors respond to Ach and its analogues, these receptors are subdivided as follows

a. Muscarinic receptors:
These receptors respond to muscarins as well as Ach. Muscarinic receptors of 3 well defined subtypes:
M_1 N.endings
M_2 Heart & some N.endings
M_3 sm.m, glands and endothelium

b. Nicotinic receptors:
These receptors respond to nicotine as ell as Ach of 2 major subtype.
N_N in autonomic ganglia
N_M N.m endplant.
Effects of stimulation of cholinoceptors in autonomic ganglia at the postganglionic endings

Eye:
* miosis & spasm of the ciliary m, so the eye is accommodated for near vision.
* ↓I.O.P

Exocrine glands:
↑secretion especially of salivary, lachrymal, bronchial, and sweat gland.

Heart:
bradycardia with A-v block & eventually cardiac arrest.

Bronchi:
bronchoconstriction with↑↑ secretion.

Alimentary tract:
* ↑motor activity & exocrine secretion and colicky pain may occur.
* Sphincter tone is reduced & patient may defecate unconsciously & lowering oesph. sphincter tone create a risk of regurgitation & inhalation.

Bladder and uterus:
contraction & the drug promote micturation.

N-m junction:
m.fasciculation.
CNS:

Sti followed by depression, mental excitement with confusion, restlessness, insomnia, tremors & even convulsions.

Bd vessels:

there is stimulation of cholinergic vasodilator N-endings, in addition to the more important dilating action on arterioles and capillaries mediated through noninnervated receptors.

Note:

The actions of Ach and substances acting like it at autonomic ganglia and the N-m junction are described as nicotinic because they are like the stimulated effect of nicotine.

The actions at postganglionic cholinergic endings and those noninnervated receptors on blood vessels are described as muscarinic because they resemble those of the alkaloid muscarine.
Parasympathetic Responses

- Eye: constrict pupil
- Lungs: constrict bronchioles and increase secretions
- Heart: decreased heart rate
- Blood vessel: dilate
- Gastrointestinal: increase peristalsis and secretions
- Salivary gland: increased salivation
- Bladder: contracts

Spinal cord

PNS (Parasympathetic) stimulates various organs and systems in the body.
cholinergic (cholinomimetic) drugs

Direct acting
- Cholinesters
- Nicotin alkaloids
  - Short acting edrophonium
  - Intermediate and long Acting carbamates (physostigmine, neostigmine)

Indirect acting (anticholinesterases)
- Very long acting Organophosphate Echthiophate
Cholinesters:

Carbachol:
its actions are most pronounced on the bladder and bowel, so its use is still these organs e.g. after surgery (its not destroyed by cholinesterase).

Bethanechol:
also not destroyed by Colinesterase It acts chiefly on the bowel and bladder & it is preferable to carbachol because of the partial selectivity.

Alkaloid with cholinergic effects:

Nicotine:
It is available as either gum or as patches used as an adjunct to stop tobacco smoking.
They deliver a lower dose of nicotine than cigarettes and the patches are slightly better tolerated than the gum, which needs to be chewed for 20-30 min. of every hour, with avoidance of beverages (coffee, carbonated drink), that reduce acidity of saliva and therefore absorption.
Note: Nicotine acts to stimulate dopamine release in mesolimbic dopamine pathway (reward center).
Pilocarpine:
Acts directly on end organs innervated by postganglionic Ns (parasympathetic system and sweat gland).

The Chief clinical use of pilocarpine is to ↓ I.O.P in chronic simple glaucoma as an adjust to a topical B-blocker.
oral pilocarpine is available to the treatment of xerostomia (dry mouth) in sjogren's synd. or following irradiation of head & neck tumors.
The commonest adverse effect is sweating.

Arecoline:
is an alkaloid, produce mild dependence it sti the brain.

Muscarine:
Is of no therapeutic use. It presents in small amounts in the Fungus Amanita muscaria.
Anticholinesterases

Of these agents:

**Physostigmine:**
- *is an alkaloid from the seeds of the plant physostigma*
- *it is used synergistically with pilocarpine to decrease I.O.P also used in Alzheimer dementia. Dose: tab. 15mg inj. 2.5mg, is the maintenance drug of choice for patients with Myasthenia gravis. Slow release.*

**Neostigmine:**
- *t1/2 2h*
- *it is synthetic reversible cholinesterase inhibitor.*
- *its action is more prominent on the N-m junction and GIT than on C.V.S and eye. That is why its main use is in the management of myasthenia gravis and to stimulate the bowels and bladder after surgery and as antidote to competitive N-m blocking agents. oral dose 5-30 mg 3-4 times a daily. S.c 0.5-2 mg(Poorly absorbed orally so requires larger doses than when given parenterally. Often combined with atropine to reduce the unwanted muscarinic effects.*
Pyridostigmine:
*is similar to Neostigmine but of less effect and slower onset and slightly longer duration of action. The only anticholinesterase capable of crossing the blood brain barrier. Is more lipid soluble. Used as an antidote for overdosage of anticholinergics such as: atropine, antihistamines, TCA, phenothiazines.
*used in the treatment of myasthenia gravis.

Edrophonium:
*is structurally related to Neostigmine but its action is brief.
*it is used to diagnose myasthenia gravis and to differentiate a myasthenia crisis (weakness due to inadequate anticholinesterase treatment or severe disease) from a cholinergic crisis (weakness caused by over treatment with anticholinesterase).
*the actions of 3mg I.V are lost in 5 min.

Metriphonate:
Is used for urinary schistosomiasis.
Indirect Acting Agents used to treat Alzheimer’s disease

- Donepezil (Aricept)—said to delay progression of the disease by up to 55 weeks. Does not cause liver toxicity.
- Galantamine (Reminyl)—newest drug
- Rivastigmine (Exelon) long acting. Twice a day dosing.
- Tacrine (Cognex)—hepatoxic. Elevated liver enzymes usu. Within 18 wks. > in women.
Toxicity of Irreversible Anticholinesterase Agents

- These agents are lipid soluble
- Can enter the body by the eye, skin, respiratory system and GI tract.
- Case in point, organophosphate insecticides (malathion, parathion) or nerve gases (sarin, tabun, soman)
- These agents cause excessive cholinergic stimulation (muscarinic) and neuromuscular blockade
Pesticides of the carbamate type act by reversible inhibition of cholinesterase whereas organophosphorus compounds inhibit the enzyme almost or completely irreversibly (so recovery depends on the formation of new enzyme this process may take weeks, although clinical recovery is usually evident within days). Of these substances GA (tabun), GB (sarin) and GD (soman) called nerve gas, although they are volatile liquids.

**Note:** where there is known risk of exposure, prior use of pyridostigmine, which occupies cholinesterase reversibly for few hours, completely protect them from access.

**Note:** organophosphate are absorbed through the skin, the GIT and by inhalation.
Clinical Features of poisoning:

1. Excessive salivation, Nausea, Vomiting, abdominal cramps diarrhoea.
2. Excessive bronchial secretion, bronchoconstriction, cough, wheezing and dyspnoea.
4. Involuntary micturation.
5. Sweating.
7. Miosis, anxiety, headache, convulsion, respirating failure.

Death is due to actions on CNS, paralysis of respiratory m. and excessive bronchial secretion & constriction.
Treatment:
1. Contaminated clothing should be removed and the skin washed.
2. In case of ingestion-gastric lavage is needed.
3. Atropine 2mg I.m or I.V repeated every 15-60 min until dryness of the mouth and a Heart rate in excess of 70 beat/min.
   Atropine antagonise the parasympathomimetic effect of the poison ie due to stimulus at postganglionic N-endings (muscarinic effects). N-m block is not relieved as atropine does not antagonise Ach. at the nicotinic sites.
4. Mechanical ventilation may therefore be needed to assist the respiratory ms.
5. Diazepam for convulsions if present.
6. Atropine eye drops may relieve headache caused by miosis.
7. Enzyme reactivation.
   These substances hasten the destruction of the accumulated Ach and unlike atropine they have both antinicotinic and antimuscaric effects. pralidoxime 1.g 4hr I.m or diluted by slow I.v infusion
   Efficacy is best if it is administered within 12 hr. Of the poisoning. M-power may improve within 30 min.
Myasthenia gravis

* Synaptic transmission at the N-m junction is impaired.
* Most cases appear to have autoimmune basis as up to 90% of patients have a raised titer of auto antibodies to Ach receptors.

Pathogenesis:
* Clinical features of MG are caused by special Abs, which either block or causes lysis of the Ach receptor.
* Cholinoceptors exist for about 7ds in normal individuals but for only 1d in MG patient.
* The thymus gland is in some way involved in the pathogenesis as 3/4 of the patient have either thymitis or a thymoma.

Diagnosis:
Is made by edrophonium which dramatically and transiently (5min) relieves m-weakness. A syringe loaded with 10mg endophonium, 2mg given i.v, if there is no improvement within 30 sec. The remaining 8mg are injected.
Clinical manifestations

Primary = easy fatigability of skeletal muscle during activity.

Muscles involved: eyes and eyelids, chewing, swallowing, speaking, and breathing.

Fluctuating weakness: usually strong in the morning, progressively weaker with activity.
Clinical manifestations

Variable course

May be precipitated by emotional stress, pregnancy, menses, secondary illness, trauma, temperature extremes, hypokalemia, ingestion of drugs with neuromuscular blocking agents, surgery.
Treatment:
1- Immuno suppression aim is to eliminate Ach. Receptor Abs, prednisolone induces improvement in 80% of cases. The dose should be slowly using an alternate day regimen, improvement to occur may take weeks also Azathioprine may be used as steroid-sparing agent.
2. Thymectomy to be done once the clinical state allows and unless there is a powerful C/I to surgery.
3. Symptomatic drugs: Its aim is to ↑↑ the concent of Ach at the N-m junction with anticholinesterases.
   Pyridostigmine starting 60mg orally /6h (of smoother action then neostigmine is more rapid in onset).

Lambert-eaton syndrome

* Her similar symptoms to those in MS occur in association with carcinoma. In the syndromes there is a deficiency of Ach release.
* Patients with this syndrome do not respond well to anticholinesterases.
* Diaminopyridine ↑ N-transmitter release it need to be taken orally 4-5 times daily with reported adverse effects of insomnia and seizures.
Specific Conditions—Cholinergic vs. Myasthenic Crisis

- Myasthenic crisis requires more anticholinesterase drug whereas cholinergic crisis requires discontinuation of the anticholinesterase drugs.
- Diagnosis can be made by evaluating patient response to their medication (s/s one hour after medication often is cholinergic crisis, s/s 3 or more hours after medication often is myasthenic crisis).
Drug induced disorders of N-m Transmission

1. Abs *aminoglycosides (neomycin, streptomycin, gemtamicin)
   *polypeptides (colistin, polymyxin B)
   *Quinolones, ciprofloxacin.
   It appears that the Abs both interfere with the release of Ach & also here a competitive curare-like effect on the Ach receptors.

2. C.V.S- quinidine, procainamide, lignocaine
   -B-blockers e.g propranolol, oxprenolol.
   -Acts by interfering with Ach release and may aggravate or revel MG.

3. Other drugs: - penicillamine specially in patient with Rhoid arthritis to form Abs to the Ach receptor and a synd indistinguishable from MG.
   -Phenytoin may induce or aggravate MG possibly by depressing Ach release.
   -Lithium may impair synaptic N-transition.
Anticholinergic drugs

- Antimuscarinic
  - M1-selective
  - Non-selective
- Antinicotinic
  - ganglion blockers
  - N-m blockers
Atropine

Atropine is an alkaloid found in *atropa belladona*

It is a competitive antagonist for the muscarinic acetylcholine receptor

Because it’s a tertiary amine atropine is relatively lipid soluble and cross BBB and it’s well distributed through the CNS
Atropine

Duration of action is 4 to 8 hours except in the eyes where it reaches 72 hours or longer.

Initial single doses in adults vary from around 0.5 mg to 1 mg.

40% metabolized in the liver, 60% excreted unchanged in the urine.
Anitmuscarinic drugs

Competitively block the binding of Ach to receptors at the postgangtion cholinergic ending and at the noninnervated receptor on blood vessels. They also block effects of Ach in the CNS.

Atropine:
* $t_{1/2}$ 2h
* It is an alkaloid plant atropa belladonna.

Clinical effects:
1. Exocrine glands all secretions excepts milk are ↓↓; Dry mouth and dry eyes are common.
   - Gastric acid secretion is ↓↓ so as total volume of gastric secretion (so $H^+$ concentration PH may be little altered)
   - Sweating is inhibited
   - Bronchial secretions are ↓↓& become viscid.

2. Sm.m is relaxed
   - In GIT, ↓ in tone and peristalsis.
   - Bronchi, relaxes Bronchial Sm.m which is useful in some asthmatics
     - urinary retention may be induced especially in presence of BPH.
3. Ocular effects Mydriasis with ↑ l.o.p this is due to dilated iris blocking drainage of the l.o fluids from the angle of the anterior chamber.
   The ciliary m is paralyzed & so the eye is accommodated for far-vision.
**Note:**
* After atropinisation normal pupillary reflexes may not be regained for 2 wks.
* Atropine is a cause of unequal sized and unresponsive Pupils.
4. C.V.S
* It↓ vagal tone thus ↑ HR & enhancing conduction in the bundle of His, effects which are less marked in the elderly in whom vagal tone is low.

**Note:** transient vagal stimulation, probably in the CNS, may cause bardoardycardia.

* Atropine has no significant effect on peripheral blood vessels in therapeutic dose but with poising, there is marked vasodilatation.

**Note:** Atropine opposes the effects of all cholinergic drug on the CNS, at postganglionic cholinergic N-endings & on the peripheral blood vessels.

It dose not oppose cholinergic effects at the N-m junction or significantly at the autonomic ganglia.

**PK:**
Atropine is readily observed from the GIT & can also be given by injection. It is part destroyed in the liver & in part excreted unchanged by the kindred.

**Dose:**
0.25-2.0 mg orally or 0.4-1 mg 1.v
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration of Effect in eye (Days)</th>
<th>Usual Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>7-10</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Hyoscine</td>
<td>3-7</td>
<td>0.25</td>
</tr>
<tr>
<td>Homatropine</td>
<td>1-3</td>
<td>2-5</td>
</tr>
<tr>
<td>Cyclopentolate</td>
<td>1</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Tropicamide</td>
<td>0.25</td>
<td>0.5-1</td>
</tr>
</tbody>
</table>
CHOLINOCEPTOR-BLOCKING DRUGS

MUSCARINIC ANTAGONISTS

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Sedation, hallucination, drowsiness, antimotion sickness action, antiparkinson action, amnesia</td>
</tr>
<tr>
<td>EYE</td>
<td>Mydriasis, cyclopegia, lacrimal glands become dry and sandy</td>
</tr>
<tr>
<td>HEART</td>
<td>Initial bradycardia at low doses then tachycardia</td>
</tr>
<tr>
<td>RESPIRATORY</td>
<td>Bronchodilation, decrease in bronchial secretions</td>
</tr>
<tr>
<td>GIT</td>
<td>Relaxation, decrease motility, antidiarrheal, prolongs gastric emptying time</td>
</tr>
<tr>
<td>GUT</td>
<td>Relaxation of the bladder wall, urinary retention</td>
</tr>
<tr>
<td>GLANDS</td>
<td>Decrease secretion, salivation, lacrimation, sweating</td>
</tr>
<tr>
<td>SKELETAL MUSCLES</td>
<td>None</td>
</tr>
</tbody>
</table>
Poisoning with atropine

Features:
1. Dry mouth with dysphasia.
2. Mydriasis, blurred vision.
3. Hot flushes, dry skin with hyperthermia (CNS effect + absence of sweating).
4. Restlessness, anxiety, excitement, hallucinations, delirium, mania. The cerebral excitation is followed by depression and coma.

Treatment:
by giving activated charcoal to adsorb the drug, diazepam for excitement. Cooling agents (ice bags, cooling blankets, tepid baths). In severe cases use Physostigmine:
   Antidote
   Abolishes delirium & coma

Dose:
I/V – Adults: 1-4 mg
Children: 0.5-1 mg
Parkinson’s Disease

- Useful in those with minimal side effects
- Those who cannot take Levodopa
- Helpful in decreasing salivation, spasticity and tremors
- Benzhexol and orphendrine, used in the treatment of parkinsonism
Preop

- Help prevent vagal stimulation and potential bradycardia
- Reduce respiratory secretions as well
- Produce amnesia
Clinical use of antimuscarinic drugs

1. For their action on CNS:
   a. Benzhexol, orphenadrine, against rigidity and tremor in parkinsonism
   b. Promethazine, as antiemetic.
   c. Hyoscine to prevent or reduce motion sickness.
   d. Hyoscine sedative action, so used in anesthetic premedication.

2. For their peripheral effects:
   a. Atropine, homatropine, and cyclopentolate used to dilate the pupils and paralyze ocular accommodation. If it is desired to dilate the pupil and to spare accommodation, a sympathomimetic e.g. phenylphrine is used.
   b. In the respiratory tract, ipratropium is an effective bronchodilator.
Respiratory

- In bronchospasm whether related to asthma or COPD
- Atrovent very useful for its bronchodilating effects
- Ipratropium: is used by inhalation as bronchodilator and can be useful when cough is a pronounced symptom in an asthmatic patient. Dose 0.4-2ml of a 0.02% solution up to 4.t.d. Aerosol 1-2 puffs 3-4 t.d. Nebulizer solution 250 microgram/ml.
Primarily, the site of bronchodilation action of inhaled $\beta_2$-adrenergic agonists is mainly the bronchiolar smooth muscle. Atropinic drugs cause bronchodilation by blocking cholinergic constrictor tone, act primarily in large airways.

**Anticholinergics in asthma**

- Ipratropium
- Tiotropium
Homatropine
Tropicamide
3. For actions on GIT:
   dicyclomine, hyoscine butylbromide used against spasm of m. and hypermotility.

4. In the urinary tract:
   Flavoxate, propantheline and oxybutynin, are used to relieve m-spasm accompanying infection in cystitis and for detrusor instability.

5. C.V.S:
   atropine is useful in bradycardia following M.I.

6. Cholinergic poisoning:
   Atropine is an important antagonist of both central nervous parasympathominetic and vasodilator effects. Its also used to block muscarinic effects when cholinergic drugs such a Neostigmine are used for their effect on the N-m junction in MG.
Contraindications

- BPH
- Myasthenia gravis
- Hyperthyroidism
- Glaucoma
- Tachydysrhythmias
- Not in situations whereby delaying of gastric emptying is a concern
Nicotinic antagonists

a. Ganglion blocking agents

hexamethionin, mecamylamine and other ganglion-blocker were extensively used in the treatment of hypertension, but unfortunately, the adverse effect of ganglion blocked are so severe (both sympathetic and parasympathetic divisions are blocked), that patients are unable to tolerate long term treatment with them. Duration of action is about 10 h after a single administration.

Trimethaphan is the only Ganglion-blocker still in clinical use; it is poorly lipid soluble inactive orally and has a short half-life. It is used I.V to treat severe accelerated hypertension (malignant hypertension) and to produce controlled hypotension.
GANGLION-BLOCKING DRUGS

- Hexamethonium
- Trimetaphan
- Tubocurarine
- Pancuronium
- Atracurium
- Vecuronium
<table>
<thead>
<tr>
<th>Effector site</th>
<th>Predominant tone</th>
<th>Effect of ganglionic Blockade (side effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweet glands</td>
<td>Sympathetic</td>
<td>Reduced sweating (anhidrosis)</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Parasympathetic</td>
<td>Reduced salivaion (dryness of mouth)</td>
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<td>Reduced lacrimation (dry sandy eyes)</td>
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<td>Vascular vessel</td>
<td>Sympathetic</td>
<td>Failure to erection (impotence)</td>
</tr>
<tr>
<td>Male genital organs</td>
<td>Parasympathetic</td>
<td>Failure to ejaculate (impotence)</td>
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<tr>
<td>Urinary bladder</td>
<td>Parasympathetic</td>
<td>Decreased tone &amp; motility, decreased secretions</td>
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<td>Gastrointestinal (GI)</td>
<td>Parasympathetic</td>
<td>Mydriasis (photophobia)</td>
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<td>Ciliary Muscle</td>
<td>Parasympathetic</td>
<td>Cycloplegia (blurred vision)</td>
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<td>Eye</td>
<td>Sympathetic</td>
<td>Dilation (Postural Hypotension)</td>
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<td>Heart (SA node)</td>
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<td>Veins</td>
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<td>Parasympathetic</td>
<td>Decreased tone &amp; motility, decreased secretions</td>
</tr>
<tr>
<td>Vestibular</td>
<td>Sympathetic</td>
<td>Dilation (Postural Hypotension)</td>
</tr>
<tr>
<td>Pituitary gland</td>
<td>Parasympathetic</td>
<td>Tachycardia (palpitation)</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>Sympathetic</td>
<td>Vasodilation, Hypotension</td>
</tr>
<tr>
<td>Skin</td>
<td>Sympathetic</td>
<td>Reduced sweating (anhidrosis)</td>
</tr>
</tbody>
</table>
# Ganglion blockers

<table>
<thead>
<tr>
<th>Effector organs</th>
<th>Dominant system</th>
<th>Effects of ganglionic blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterioles/veins</td>
<td>SANS</td>
<td>Vasodilatation, hypotension</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>SANS</td>
<td>Anhydrosis</td>
</tr>
<tr>
<td>Genitals</td>
<td>PANS/SANS</td>
<td>Impotence</td>
</tr>
<tr>
<td>Heart</td>
<td>PANS</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Iris</td>
<td>PANS</td>
<td>Mydriasis</td>
</tr>
<tr>
<td>Ciliary</td>
<td>PANS</td>
<td>Cycloplegia</td>
</tr>
<tr>
<td>Bladder</td>
<td>PANS</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Salivary</td>
<td>PANS</td>
<td>Xerostomia</td>
</tr>
<tr>
<td>GIT</td>
<td>PANS</td>
<td>Constipation</td>
</tr>
</tbody>
</table>
Note:
As ganglion-blocking agents interrupts sympathetic control of venous-pooling, postural hypotension.

**B-N-M blocking agents:**

these drugs are important for producing complete sk-m relaxation in surgery by specific blockade of the N-M junction. They enable light level of anesthesia to be employed with adequate relaxation of the muscles of the abdomen and diaphragm, they also relax the vocal cords and allow the passage of a tracheal tube. Patients who have received a m-relaxant should always have their respiration assisted or controlled until the drug have been inactivated or antagonized.
Glaucoma
Glaucoma

Glaucoma is increased intraocular pressure.

Intraocular pressure is determined by the balance between fluid input & drainage out of the globe

----- aqueous humor produced by ciliary epithelium and drained at the filtration angle of the anterior chamber.

Objective of glaucoma therapy: --- increase outflow & or decrease production of aqueous humor.
<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Methods of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholinomimetics</strong></td>
<td>Ciliary muscle contraction, opening of trabecular meshwork; increased outflow</td>
<td>Topical drops or gel; plastic film slow-release insert</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td></td>
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<tr>
<td>Carbachol</td>
<td></td>
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<tr>
<td>Physostigmine</td>
<td></td>
<td></td>
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<tr>
<td>Echothiophate</td>
<td></td>
<td></td>
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<tr>
<td>Demecarium</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alpha agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unselective</td>
<td>Increased outflow</td>
<td>Topical drops</td>
</tr>
<tr>
<td>Epinephrine, dipivefrin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alpha₂-selective</strong></td>
<td>Decreased aqueous secretion</td>
<td>Topical, postlaser only</td>
</tr>
<tr>
<td>Apraclonidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brimonidine</td>
<td></td>
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</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td>Decreased aqueous secretion from the ciliary epithelium</td>
<td>Topical drops</td>
</tr>
<tr>
<td>Timolol</td>
<td></td>
<td></td>
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<tr>
<td>Betaxolol</td>
<td></td>
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<tr>
<td>Carteolol</td>
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<tr>
<td>Levobunolol</td>
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<tr>
<td>Metipranolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>Decreased secretion due to lack of HCO₃⁻</td>
<td>Topical</td>
</tr>
<tr>
<td>Dorzolamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brinzolamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetazolamide</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Dichlorphenamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methazolamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prostaglandins</strong></td>
<td>Increased outflow</td>
<td>Topical</td>
</tr>
<tr>
<td>Latanoprost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unoprostone</td>
<td></td>
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</tbody>
</table>