PARASYMPATHOLYTICS
(ANTICHOLINERGIC DRUGS)

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PARASYMPATHETIC RECEPTORS

- Muscarinic
  - M1
  - M2
  - M3
- Nicotinic
  - Nn (Ganglion, Adrenal medulla)
  - Nm (NMJ)

REMEMBER THIS NEUMONIC=

QIQ the ion channel

- M_1 ======= Gq
- M_2 ======= Gi
- M_3 ======Gq
- N ===== ion channel

Molecular Mechanisms of Action

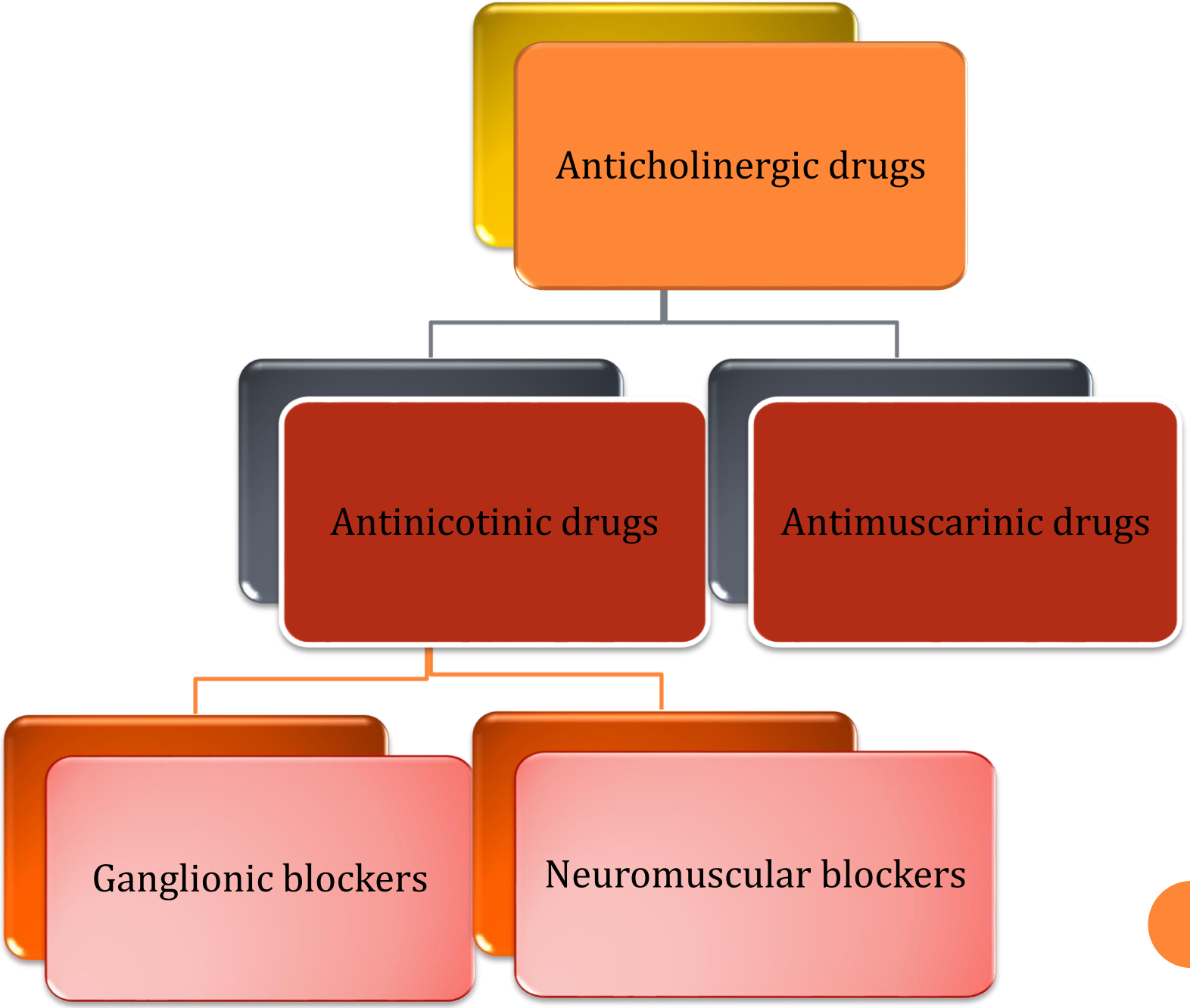
Receptors	G protein	Post receptor mechanism
M1	Gq	IP3, DAG cascade
M2	Gi	↓ cAMP
M3	Gq	IP3, DAG cascade
Nn, Nm	Ion channel	Na/K depolarization

Receptors	Location	Actions
M1	CNS Autonomic ganglia	• Inc learning & memory
	Gastric glands	• Promote glandular secretions
M2	Heart	• Depress SA node, AV node & heart muscles activity
M3	Smooth muscles	• Inc smooth muscle contraction
	Exocrine glands	• Inc exocrine gland secretion
	Endothelial cells	• Vasodilation by EDRF release
Nn	Autonomic ganglia, adrenal medulla	• Stimulates both sympathetic and parasympathetic actions
Nm	Neuromuscular junction	• Skeletal Muscle contraction

ANTI-CHOLINERGIC AGENTS

An **anticholinergic** agent is a substance that blocks the neurotransmitter acetylcholine in the central and the peripheral nervous system.

They inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells.


Anticholinergic drugs
Antinicotinic drugs
Antimuscarinic drugs
Ganglionic blockers
Neuromuscular blockers

ANTI MUSCRINIC

NON SPECIFIC ATROPINE

SPECIFIC RECEPTOR BLOCKERS

- **Pirenzipine(M1)**
- **Darifenacine (M3)**
- **Solifenacine (M3)**
- **Oxybutynin (M3)**
- **Tolterodine(M3)**
- **Trospium (M3)**

Anti-muscarinic agents

CLASSIFICATION

ON THE BASIS OF ORIGIN

Natural Alkaloids

(Extract of Belladona)

Atropine

(Extract of Hyocyamus)

Hyoscine/scopolamine

Semisynthetic

Homatropine Encatropine
Methylatropine
Methscopoline

Synthetic Tropicamide
Glycopyrrolate
Pirenzeline

CLINICAL CLASSIFICATION

MYDRIATICS & CYCLOPLEGICS

Homatropine

Cyclopentolate

Tropicamide

BRONCHODILATORS

Ipratropium

Tiotropium

ANTISPASMODIC (GIT)

Hyoscine (buscopan)

Dicyclomine

Glycopyrolate

ANTI-SECRETORY (GIT)

Pirenzepine

Propantheline

VESICO SELECTIVE (BLADDER)

Oxybutynin, Trospium

Solifenacin, Darifenacin, Tolterodine

ANTIPARKINSONIAN

Benztropine

Biperidin

Trihexyphenidyl

Procyclidine

ATROPINE

Atropine is the prototype drug.

- **It is a tertiary amine.**

PHARMACOKINETIC

- Source= From a plant, Atropa belladonna. Belladonna (Italian)= Beautiful lady
- Absorption= Lipid soluble & cross membrane barriers
- Distributed widely including BBB and placental barrier.
- Eliminated partly by the liver & kidneys
- 1/3 is excreted unchanged in the urine
- T ½ life is 2 hours
- Duration of action = 4 to 8 hours, except in the eye (it lasts more than 72 hours)

PHARMACODYNAMIC

- MOA:
  - Interaction with muscarinic receptors:
  - Reversible, competitive
- Receptor selectivity:
  - Atropine: selective for muscarinic receptors
  - But, ***pirenzepine a selective antagonist for m1-receptors*** (stomach parietal cells)
- Tissue selectivity:
  - Atropine: salivary, sweat and bronchial glands
  - Pirenzepine (telenzepine, more effective): acid secretion from parietal cells (stomach)
  - Scopolamine: more effective on vestibular disturbances (eg. Motion sickness)

Pharmacological Effects

CNS

- In small/ therapeutic doses:

Atropine has no or very slight stimulatory effect on CNS.

- At high doses:
  - Atropine causes strong CNS stimulantion i.e cortical excitation, restlessness, disorientation, hallucinations and delirium later on followed by respiratory depression and coma.
  - Supresses vestibular apparatus (M receptors) and prevent impulse transmission to Vomiting center = Anti-motion sickness property.
  - Blocks the relative cholinergic over-activity in basal ganglia= suppresses tremor and rigidity of parkinsonism.

CVS

- **Low dose** Initial bradycardia due to blockage of pre-synaptic muscarinic inhibitory auto-receptors on cholinergic nerve endings.

- **Moderate dose** Tachycardia due to blockage of M2 receptors of heart, unopposed sympathetic activity.

VESSELS

- Most blood vessels receive no direct innervation from the parasympathetic system.
- However, parasympathetic nerve stimulation dilates coronary arteries (EDRF). Atropine can block this vasodilation at therapeutic doses.
- At toxic doses, antimuscarinic agents cause cutaneous vasodilation, especially in the upper portion of the body. The exact mechanism is unknown.

GIT

- Relax smooth muscles of GI tract
- Decrease motility and peristalsis
- Gastric emptying time prolonged
- Anti-spasmodic effect

- ↑ Sphincter contraction

- Result = constipation

- Decrease intestinal and gastric secretions

RESPIRATORY SYSTEM

- Some bronchodilatation
- Inhibition of bronchial secretion
- As Pre-anesthetic medication to reduce
  - -Bronchial secretions
  - -laryngospasm
  - -risk of airway obstructions
  - -postoperative pneumonia

EYE

- Blocks muscarenic innervations on the circular muscles (sphincter pupillae **(Mydriasis)**
- Paralysis of ciliary muscle (**cycloplegia):**
  - **Loss of accommodation**
  - **Photophobia**
  - **Blurred vision**
  - **Lasts for 7-10 days**

- Reduction of lacrimal secretion leading **dry sandy eye**

BODY TEMPERATURE

- Rise in body temperature occurs at higher doses. It is due to:
- ✓ Inhibition of sweating
- ✓ Stimulation of temperature regulating center in the hypothalamus.

- In adults, large doses of atropine can increase body temperature

- In infants and children, even ordinary doses may cause atropine fever

GENITO-URINARY TRACT

- It relaxes the Smooth muscles (detrusor) of bladder wall.
- But it increases the tone of trigone and sphincter of bladder.
- This results in urinary retention, specially in elderly with BPH.

EFFECTS ON GLANDS

- Markedly decreases sweat, salivary, lacrimal and tracheo-bronchial secretions
- Decrease secretion of acid, pepsin and mucus of stomach

CLINICAL USES

RESPIRATORY DISEASES

- Used in Asthma and COPD

Ipratropium and tiotropium .

These agents often are used with inhaled long-acting β2 adrenergic receptor agonists.

- Used in Rhinorrhea

Ipratropium is FDA-approved for use in nasal inhalers for the treatment of the rhinorrhea associated with the common cold or with allergic rhinitis.

CNS DISEASES

In prevention of motion sickness:

- Scopolamine is the most effective agent, it blocks M receptors in vestibular apparatus
- It can be given orally, by injection or as a transdermal patch (behind ear)

In the treatment of Parkinson disease:

- Deficiency of dopamine & relative increase in Ach in Substantia Nigra
- They mainly control the tremors and rigidity of parkinsonisn.
- Centrally acting anti-muscarinic agents are preffered.
- *Benztropine, Trihexyphenidyl, Biperiden*

CVS DISEASES

- Atropine is useful in counteracting bradycardia at moderate dose.
- Also in partial heart block in selected patients where increased vagal tone is responsible, e.g. in some cases of myocardial infarction, digitalis toxicity

OPTHALMIC DISEASES

As it Produces mydriasis and cycloplegia so:

- Mydriasis= fundus/retina examination.
- Mydriatics followed by miotic agents are used for breaking the adhesions between the iris and the lens (iridocyclitis).
- For accurate measurement of refractive errors.
  - Homatropine hydrobromide
  - Cyclopentolate hydrochloride
  - Tropicamide

GIT DISEASES

- In Peptic ulcer=Anti-secretory

Pirenzepine

Telenzepine

- Intestinal colic, renal colic and Diarrhea associated with irritation of the lower bowel may respond to atropine-like drugs.

Glycopyrrolate (M3-selective antagonists) is used to reduce GI tone and motility.

GENITARY URINARY DISEASES

These agents can lower intra-vesicular pressure, increase capacity, and reduce the frequency of contractions by antagonizing parasympathetic control of the bladder.

- Treatment of enuresis in children.

- Overactive urinary bladder due to post urologic surgeries can be successfully treated with muscarinic receptor antagonists.

- Oxybutynin
- Tolterodine
- Darifenacin, Solifenacin

Uses in Anesthesia

Atropine or **glycopyrrolate** is used as Pre-anesthetic medication to reduce

- -laryngospasm
- -Bronchial secretions
- -risk of airway obstructions
- -postoperative pneumonia
- -Vagal bradycardia due to anesthesia.(during surgery while touching the viscera there is inappropriate Vagal stimulation which sometimes lead to heart block)
- Postoperatively we give anticholinesterase to inhibit the effect of skeletal muscle relaxants. This also lead to increase in the concentration of ACH at the M2 receptors in the heart. Also neostigmine have muscarinic effects as well. Atropine is given to inhibit the effect of increased ACH.

USES IN POISONING

Organo-phosphate poisoning

- Atropine is not an actual antidote for organophosphate poisoning. It is often used along with oximes (cholinersterase reactivator)
- Atropine by blocking the action of acetylcholine at Muscarinic receptors, provide symptomatic relieve i.e SLUDGE syndrome (salivation, lacrimation, urination, diaphoresis, gastroint estinal motility, emesis) symptoms caused by organophosphate poisoning.

Curarine poisoning

- Used in curarine poisoning with neostigmine to counteract the muscarinic adverse effects of neostigmine.

Mushroom poisoning

- Some types of mushroom i.e inocybe species has strong muscarinic effects

Adverse Effects

- Eye
  - Blurred vision
  - May precipitate an acute attack of glaucoma in glaucoma patient
- Dry mouth
- Tachycardia
- Agitation, delirium, hallucination
- Elevation of body temperature, due to reduced sweating (Atropine fever, Hyperthermia, lethal in children)
- Flushing
- Constipation
- Urinary retention

Atropine Toxicity

- Atropine is incapacitating at doses of 10 to 20 mg per person.
- Its LD50 is estimated to be 453 mg per person
- Poisoned individuals manifest dry mouth, mydriasis, tachycardia, hot and flushed skin, agitation, and delirium for as long as a week.
- Body temperature is frequently elevated

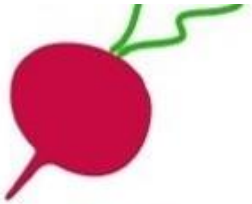
  - Hot as hare (due to hyperthermia)
  - Dry as bone (due to dryness of secretions)
  - Blind as a bat (mydriasis & cycloplegia)
  - Red as beet (VD of cutaneous Blood vessels & flushing, Fever)
  - Mad as hatter (CNS manifestations)

ANTICHOLINERGIC SIDE EFFECTS

Hot as a hare

Dry as a bone

Blind as a bat



Red as a beet

Mad as a hatter

Treatment

- **Physostigmine:**
- Used to counteract the CNS effects
- 1-4mg, iv. in adults
- 0.5-1mg iv. in children

- **Symptomatic:**
- Cold baths & sponges
- Catheterization if necessary
- Seizures: iv. diazepam

Contraindications (Relative)

- **Angle-closure glaucoma**
- **Prostatic hyperplasia** (Elderly men)
- **Gastric ulcer** (slow gastric emptying, may increase symptoms)
- **Infants & Children** (danger of hyperthermia, used cautiously)

ANTI-NICOTINIC AGENTS (GANGLION BLOCKERS)

GANGLION BLOCKERS

- They block the actions of Ach and similar agonists at the nicotinic receptors of both parasympathetic & sympathetic autonomic ganglions.

  - **Trimethaphan**
  - **Hexamethonium**
  - **Decamethonium**
  - **Mecamylamine**

- Due to a lot of side effects , they have very little clinical uses.

CLINICAL USES

- Mecamylamine
  - Reduce nicotine craving in patients attempting to quit smoking
- Trimethaphan
  - Occasionally used in the treatment of hypertensive emergencies and dissecting aortic aneurysm; to produce controlled hypotension, which can be of value in neurosurgery to reduce bleeding in the operative field

ADVERSE EFFECTS

- CNS - sedation , tremor , mental aberration
- Eye - Moderate dilation of pupils
- CVS - Orthostatic or postural hypotension, moderate tachycardia
- GIT - Constipation
- Urinary - Urinary retention
- Genital - sexual function is impaired (both erection & ejaculation)