Cholinoceptor -Blocking Drugs

Drugs that block muscarinic cholinoceptors.

Five subtypes of muscarinic receptor :

- **M1** on CNS neurons, sympathetic postganglionic cell bodies, and many **presynaptic** sites.
- **M2** in the **myocardium**, smooth muscle organs, and some neuronal sites.
- **M3** on effector cell membranes, especially **glandular** and **smooth muscle** cells.
- **M4** and **M5** play a greater role in the CNS than in the periphery.

Absorption

- Natural alkaloids (Solanaceae species, e.g. atropa belladona) & most tertiary antimuscarinic drugs are well absorbed
- **Scopolamine** is absorbed across the skin (transdermal).
- Quaternary antimuscarinic drugs 10–30% of a dose is absorbed after oral administration

Distribution

- Atropine and the other tertiary agents are widely distributed, reach CNS within 30 minutes to 1 hour.
- Scopolamine is rapidly and fully distributed into the CNS where it has greater effects than most other antimuscarinic drugs.
- In contrast, the quaternary derivatives are poorly taken up by the brain.

Metabolism and Excretion

Elimination of **atropine** occurs in two phases:

the *t*1/2 of the rapid phase is 2 hours and that of the slow phase is 13 hours.

About 50% of the dose is excreted unchanged in the urine (***the dextro form***, *levo isomer is* ***hyoscyamine***).

Most of the rest appears in the urine as hydrolysis and conjugation products.

The drug's effect on parasympathetic function declines rapidly in all organs **except the eye.**

Effects on the iris & ciliary muscle persist for 72 hours

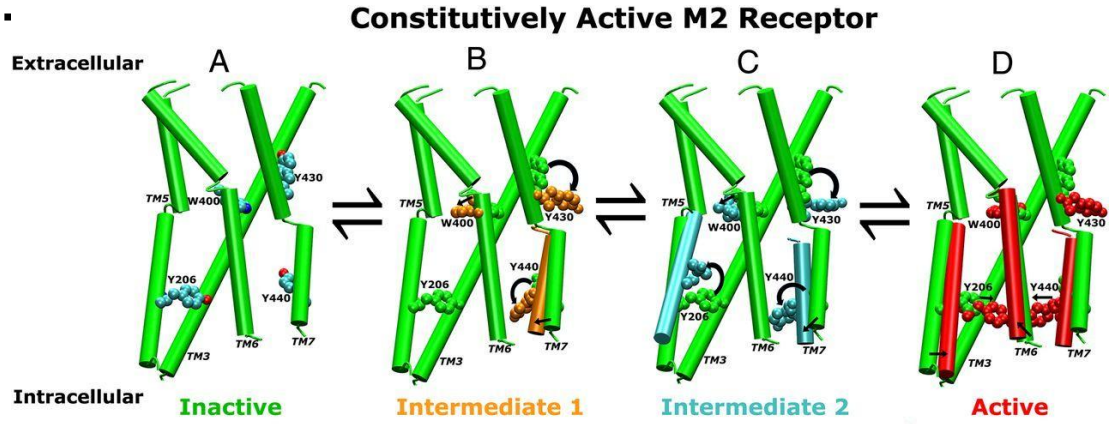
Mechanism of Action

Atropine causes reversible blockade of all M receptors.

Muscarinic receptors are **constitutively active**, and muscsrinic blockers are **inverse agonists** that shift the equilibrium to the inactive state of the receptor.

Inverse agonists include:

Atropine, pirenzepine, trihexyphenidyl & a methyl derivative of scopolamine



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

Secretion of acid by the gastric parietal cells is the least sensitive.

Antimuscarinic agents block exogenous cholinoceptor agonists more effectively than endogenously released

Organ System Effects

Central Nervous System

Atropine has minimal stimulant effects on CNS.

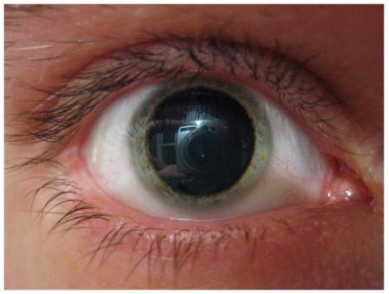
Scopolamine has more marked central effects, producing drowsiness and amnesia.

In toxic doses, scopolamine, and to a lesser degree atropine, can cause excitement, agitation, hallucinations, and coma.

The tremor of Parkinson's disease is reduced by centrally acting antimuscarinic drugs, and atropine—in the form of belladonna extract—was one of the first drugs used in the therapy of this disease.

Vestibular disturbances

Scopolamine is effective in preventing or reversing these disturbances.



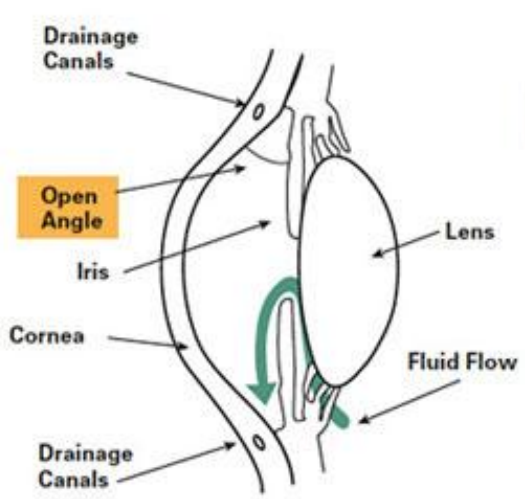
Eye

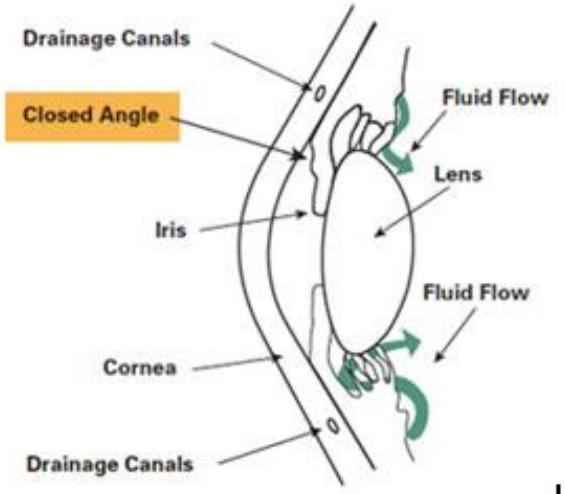
Atropine and other tertiary antimuscarinics cause an unopposed sympathetic dilator activity & **mydriasis**

Paralysis of the **ciliary muscle**, or **cycloplegia** resulting in **loss of accommodation** the fully atropinized eye cannot focus for near vision.

cause acute **glaucoma** in patients with a narrow anterior chamber angle.

Antimuscarinic drugs





reduce lacrimal secretion causing dry or "sandy" eyes.

Cardiovascular System

Atropine causes tachycardia by vagal block.

Lower doses often result in initial bradycardia before the effects of peripheral vagal block is seen.

This slowing may be due to block of M1 autoreceptors on vagal postganglionic fibers.

The ventricles are less affected

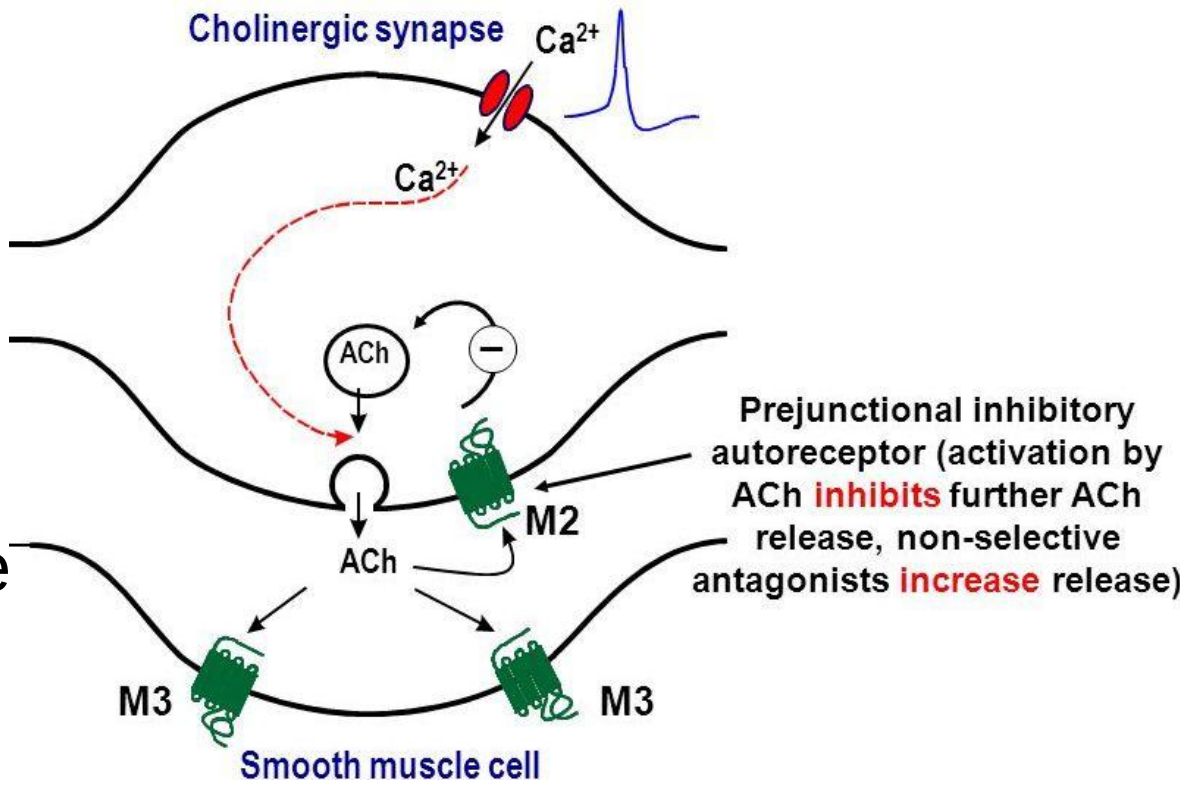
In toxic concentrations, it can cause intraventricular conduction block due to a local anesthetic action.

All blood vessels contain endothelial muscarinic receptors that mediate vasodilation .

These receptors are blocked by antimuscarinic drugs.

At toxic doses, antimuscarinic agents cause **cutaneous vasodilation**, especially in the the blush area. The mechanism is unknown.

Respiratory System



Atropine causes some bronchodilation & reduce secretion.

The effectiveness of nonselective antimuscarinic drugs in treating **bronchial asthma** is limited because block of **autoinhibitory M2** oppose the bronchodilation caused by block of **M3** receptors on airway.

Antimuscarinic drugs are frequently used before the administration of **inhalant anesthetics** to reduce the accumulation of secretions in the trachea.

Gastrointestinal Tract

Complete muscarinic block cannot totally abolish activity of GIT, since local hormones in the enteric nervous system also modulate GI functions.

Antimuscarinic drugs have marked effects on salivary secretion causing **dry mouth**

Gastric secretion is blocked less effectively: the volume and amount of acid, pepsin, and mucin are all reduced, but large doses of atropine may be required.

Basal secretion is blocked more effectively than that stimulated by food, nicotine, or alcohol.

Pirenzepine and **telenzepine**

M1 blockers. Reduce gastric acid secretion with fewer adverse effects than atropine

GI smooth muscle **motility** is affected from the stomach to the colon and both tone and propulsive movements are diminished.

Gastric emptying time is prolonged, and **intestinal transit time is lengthened**.

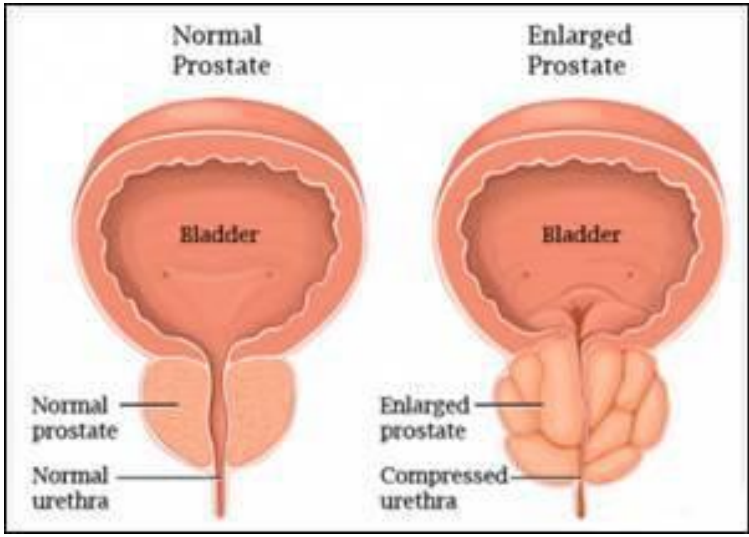
Diarrhea due to overdosage with muscarinic agents is readily stopped.

Diarrhea caused by nonautonomic agents can usually be temporarily controlled.

Genitourinary Tract

Relaxes smooth muscle of the ureters and bladder wall and slows voiding.

Useful in the **treatment of spasm** induced by mild inflammation, surgery, and certain neurologic conditions, but it can precipitate urinary retention in men who have **prostatic hyperplasia**



Sweat Glands

Atropine suppresses **sweating**.

In adults, body temperature is elevated only with large doses, but in infants and children even ordinary doses may cause "**atropine fever**."

Therapeutic Applications

Central Nervous System Disorders

Parkinson's Disease

useful as **adjunctive** therapy in some patients but with all of the adverse effects.

Motion Sickness

Scopolamine is as effective as any more recently introduced agent. Given by injection or by mouth or as a transdermal patch.

The **patch formulation** produces significant blood levels over 48–72 hours.

Useful doses by any route usually cause significant sedation and dry mouth.

Antimuscarinic Drugs Used in Ophthalmology.

Drug	Duration (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

Ophthalmologic Disorders

Antimuscarinic agents, as eye drops or ointment, produce mydriasis and cycloplegia are very helpful in doing a complete examination.

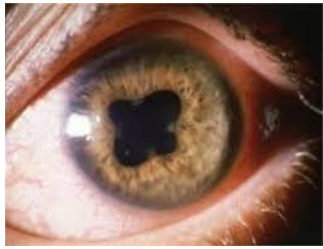
The shorter-acting drugs are preferred

Should never be used for mydriasis unless cycloplegia or prolonged action is required.

Alpha- adrenoceptor stimulant drugs, **phenylephrine**, produce a short mydriasis sufficient

for funduscopic examination.

Antimuscarinics also used to prevent **synechia.**



A **synechia** is an eye condition where the iris adheres to either the cornea or lens. The longer-lasting preparations, especially homatropine, are preferred.

Respiratory Disorders

Atropine was routinely used as a **preoperative** medication when anesthetics such as ether were used to decrease airway secretions and to prevent laryngospasm. Newer inhalational anesthetics are far less irritating to the airways.

Scopolamine also produces significant amnesia for the events associated with surgery and **obstetric delivery.**

Urinary retention and intestinal hypomotility following surgery are exacerbated by antimuscarinic drugs.

Ipratropium

a synthetic analog of atropine, is used as an inhalational drug in **asthma** with reduced systemic effects.

Ipratropium is also useful in chronic obstructive pulmonary disease (COPD) a condition that occurs more frequently in older patients, particularly chronic smokers.

Tiotropium

has a longer bronchodilator action and can be given once daily.

Cardiovascular Disorders

Marked reflex vagal discharge sometimes accompanies the pain of **myocardial infarction** (e.g., vasovagal attack) and may depress sinoatrial or atrioventricular node function sufficiently to impair cardiac output.

Atropine is used in this situation.

Rare individuals have **hyperactive carotid sinus reflexes** and may experience faintness or even syncope as a result of vagal discharge in response to pressure on the neck, e.g., from a tight collar.

Such individuals may benefit from the use of **atropine** or a related antimuscarinic agent.

Gastrointestinal Disorders

Antimuscarinic agents can provide some relief in the treatment of common **traveler's diarrhea** and other mild hypermotility.

They are often combined with an **opioid antidiarrheal drug**.

Atropine with **diphenoxylate**, (**Lomoti**l) is available in both tablet and liquid form.

Urinary Disorders

Provide symptomatic relief in the treatment of **urinary urgency** caused by minor inflammatory bladder disorders.

Oxybutynin

more selective for M3 receptors, is used to relieve bladder spasm after urologic surgery.

It reduce involuntary voiding in patients with neurologic disease.

Darifenacin

has greater selectivity for M3 receptors & long half-life

used in adults with urinary incontinence.

An alternative treatment for urinary incontinence refractory to antimuscarinic drugs is intrabladder injection of **botulinum toxin A**.

By interfering with the release of neuronal acetylcholine, botulinum toxin is reported to reduce urinary incontinence for several months after a single treatment.

Cholinergic Poisoning

Caused by cholinesterase inhibitor & wild mushrooms

Atropine is used to reverse the muscarinic effects, to treat the CNS effects as well as the peripheral effects of the organophosphate inhibitors.

Large doses of atropine may be needed to oppose the muscarinic effects of extremely potent agents like **parathion** and chemical warfare nerve gases.

1–2 mg of atropine sulfate may be given **IV** every 5–15 minutes until signs of effect (**dry mouth, reversal of miosis**) appear.

The drug is **repeated many times**, since the acute effects of the anticholinesterases may last 24–48 h.

1 g of atropine per day may be required for **one month** for full control of muscarinic excess.

Adverse Effects

Treatment with atropine or its congeners induces undesirable effects.

At higher concentrations, atropine causes block of all parasympathetic functions.

Poisoned individuals manifest:

dry mouth, mydriasis, tachycardia, hot and flushed skin, agitation, and delirium for as long as 1 week.

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

Deaths have followed doses as small as 2 mg.

Overdoses of atropine are treated **symptomatically**

When **physostigmine** is used, ***small*** doses are given *slowly* intravenously.

Symptomatic treatment may require temperature control with cooling blankets and **seizure** control with **diazepam.**

Poisoning by high doses of **quaternary antimuscarinic** drugs is associated with all of the peripheral signs but few or none of the CNS effects of atropine.

They may cause **ganglionic blockade** with marked orthostatic hypotension

Treatment of the antimuscarinic effects can be carried out with a quaternary cholinesterase inhibitor such as **neostigmine**.

Control of hypotension may require the administration of a sympathomimetic drug such as **phenylephrine.**

Contraindications

Glaucoma

Even systemic use of moderate doses may precipitate angle closure (and acute glaucoma) in patients with shallow anterior chambers.

Prostatic hyperplasia

In **elderly men**, antimuscarinic drugs should always be used with caution and should be avoided in those with a history of prostatic hyperplasia.

Nonselective antimuscarinic agents should never be used to treat acid-peptic disease.

Because the antimuscarinic drugs slow gastric emptying, they may *increase* symptoms in patients with gastric ulcer.