# Cholinergic Antagonists

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The cholinergic antagonists (also called cholinergic blockers, parasympatholytics or anticholinergic drugs) bind to cholinoceptors, but they do not trigger the usual receptor-mediated intracellular effects.

The most useful of these agents selectively block muscarinic synapses of the parasympathetic nerves.

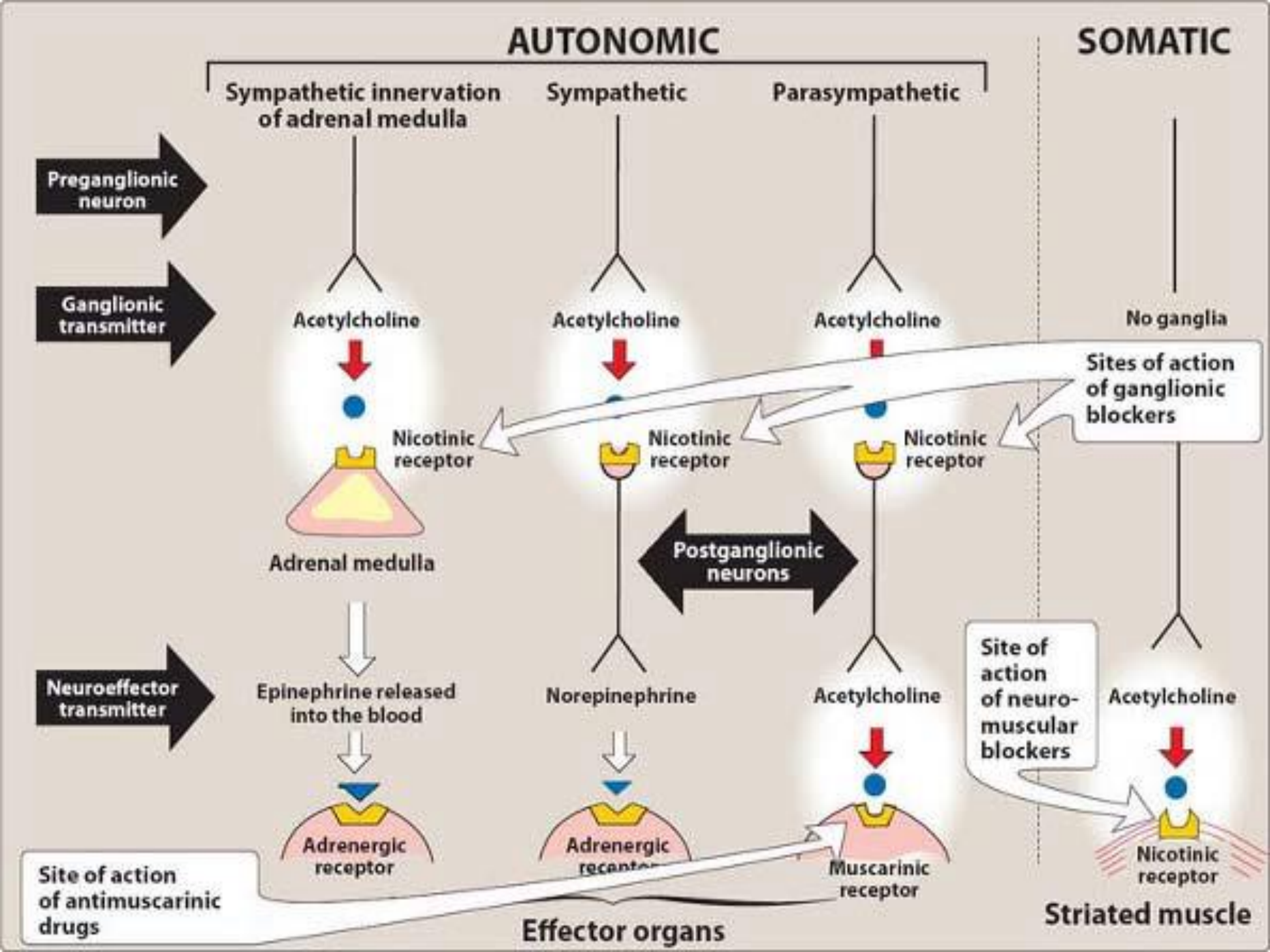
The effects of parasympathetic innervation are thus interrupted, and the actions of sympathetic stimulation are left unopposed.

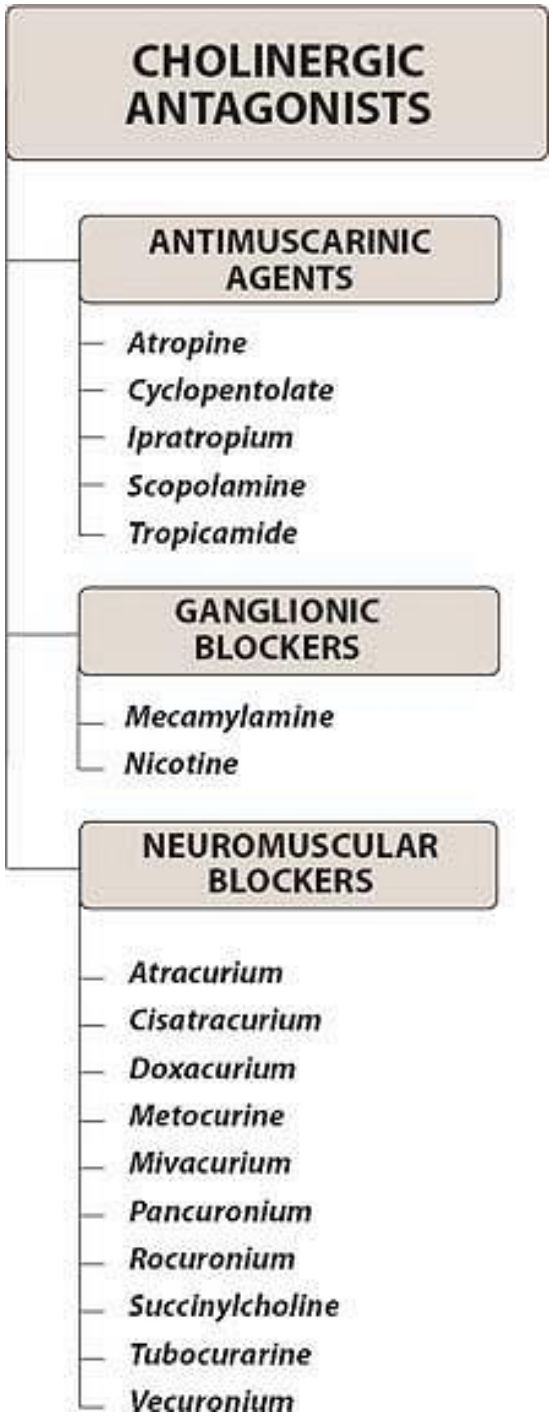
A second group of drugs, the ganglionic blockers, show a preference for the nicotinic receptors of the sympathetic and parasympathetic ganglia.

Clinically, they are the least important of the anticholinergic drugs.

A third family of compounds, the neuromuscular blocking agents, interfere with transmission of efferent impulses to skeletal muscles.

These agent are used as adjuvants in anesthesia during surgery.


AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
Preganglionic neuron
Ganglionic transmitter
Acetylcholine
Acetylcholine
Acetylcholine
No ganglia
Sites of action of ganglionic blockers
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Neuroeffector transmitter
Epinephrine released into the blood
Norepinephrine
Acetylcholine
Site of action of neuro-muscular blockers
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Site of action of antimuscarinic drugs
Effector organs
Striated muscle


CHOLINERGIC ANTAGONISTS
ANTIMUSCARINIC AGENTS
Atropine
Cyclopentolate
Ipratropium
Scopolamine
Tropicamide
GANGLIONIC BLOCKERS
Mecamylamine
Nicotine
NEUROMUSCULAR BLOCKERS
Atracurium
Cisatracurium
Doxacurium
Metocurine
Mivacurium
Pancuronium
Rocuronium
Succinylcholine
Tubocurarine
Vecuronium

# Antimuscarinic Agents

Commonly known as antimuscarinics, these agents (for example, *atropine* and *scopolamine*) block muscarinic receptors, causing inhibition of all muscarinic functions.

In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating salivary and sweat glands.

In contrast to the cholinergic agonists, which have limited usefulness therapeutically, the cholinergic blockers are beneficial in a variety of clinical situations.

Because they do not block nicotinic receptors, the antimuscarinic drugs have little or no action at skeletal neuromuscular junctions or autonomic ganglia.

# *A. Atropine*

A tertiary amine belladonna alkaloid, has a high affinity for muscarinic receptors, where it binds competitively, preventing acetylcholine from binding to those sites.

*Atropine* acts both centrally and peripherally.

Its general actions last about 4 hours except when placed topically in the eye, where the action may last for days.

# 1. Actions

Eye: *Atropin*e blocks all cholinergic activity on the eye, resulting in persistent mydriasis (dilation of the pupil), unresponsiveness to light, and cycloplegia (inability to focus for near vision).

In patients with narrow-angle glaucoma, intraocular pressure may rise dangerously.

Shorter-acting agents, such as the antimuscarinic *tropicamide*, or an α-adrenergic drug, like *phenylephrine*, are generally favored for producing mydriasis in ophthalmic examinations.

Gastrointestinal (GI): *Atropine* can be used as an antispasmodic to reduce activity of the GI tract.

*Atropine* and *scopolamine* are probably the most potent drugs available that produce this effect.

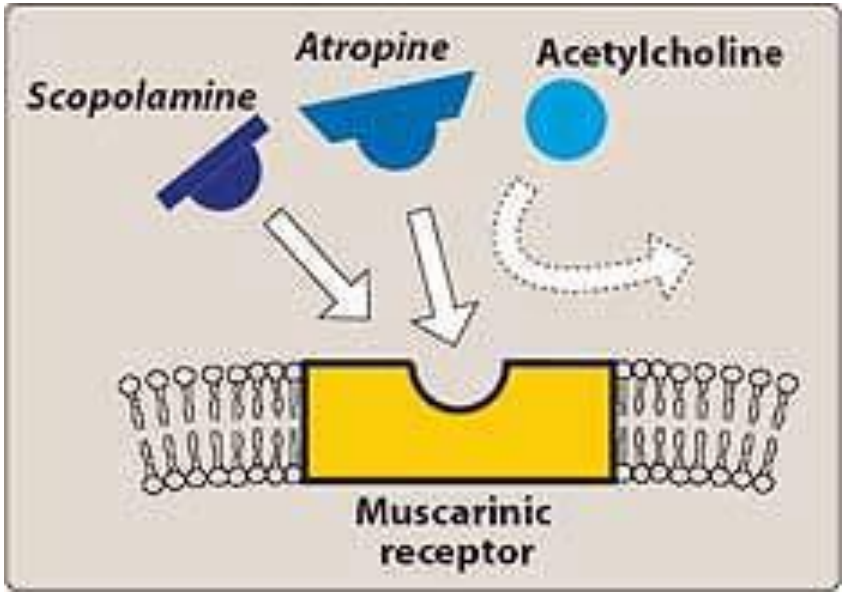
Although gastric motility is reduced, hydrochloric acid production is not significantly affected.

Thus, the drug is not effective in promoting healing of peptic ulcer.

*Pirenzepine*, an $M_1$-muscarinic antagonist, does reduce gastric acid secretion at doses that do not antagonize other systems.

Urinary system: *Atropine* is also employed to reduce hypermotility states of the urinary bladder.

It is still occasionally used in enuresis (involuntary voiding of urine) among children, but α-adrenergic agonists with fewer side effects may be more effective.



Cardiovascular: *Atropine* produces divergent effects on the cardiovascular system, depending on the dose.

At low doses, the predominant effect is a decreased cardiac rate (bradycardia).

The effect is known to result from blockade of the $M_1$ receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased acetylcholine release.

With higher doses of *atropin*e, the $M_2$ receptors on the sinoatrial node are blocked, and the cardiac rate increases.

This generally requires at least 1 mg of *atropine*, which is a higher dose than ordinarily given.

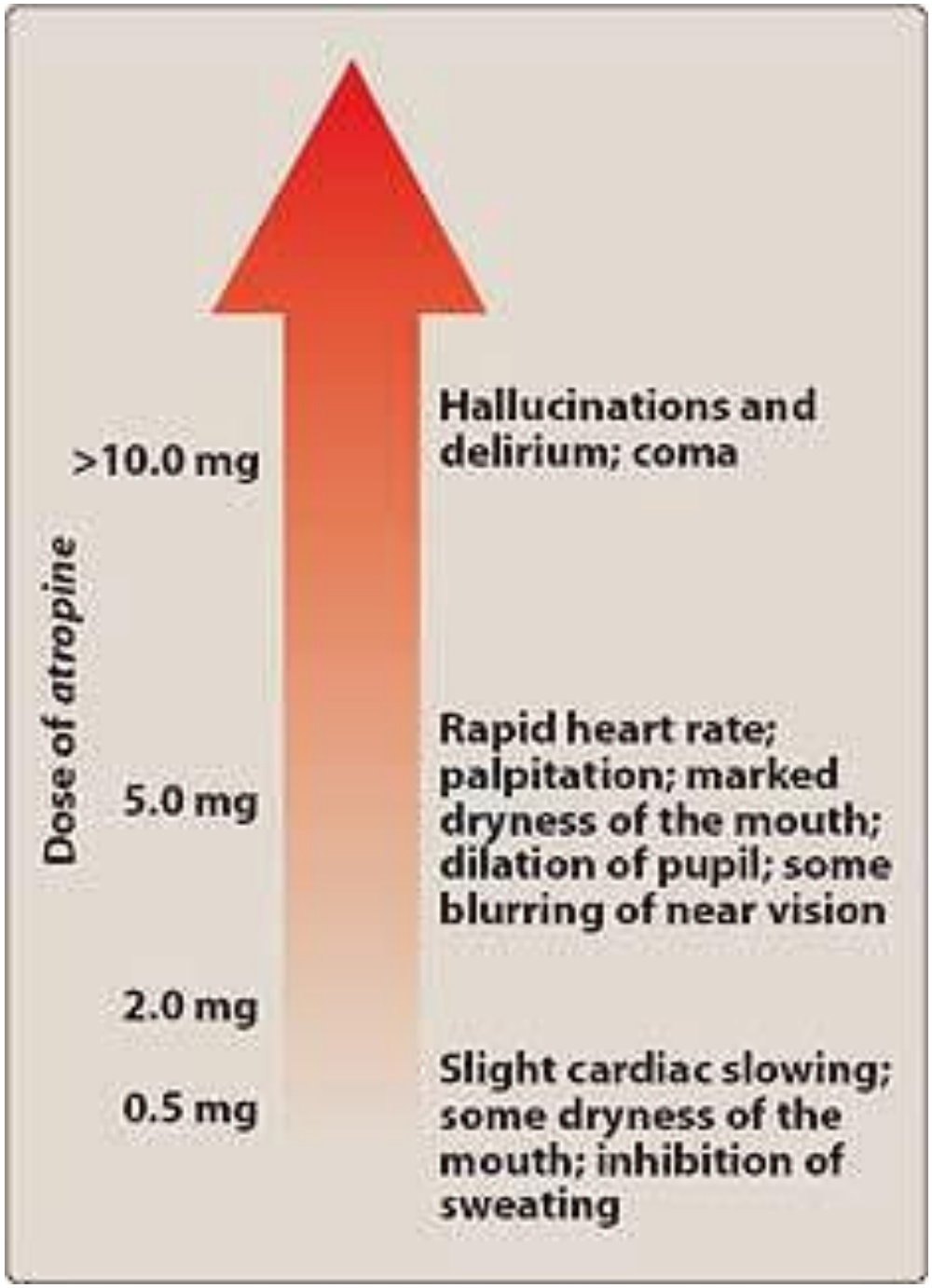
Arterial blood pressure is unaffected, but at toxic levels, *atropine* will dilate the cutaneous vasculature.

Secretions: *Atropine* blocks the salivary glands, producing a drying effect on the oral mucous membranes (xerostomia).

The salivary glands are exquisitely sensitive to *atropine*.

Sweat and lacrimal glands are also affected.

Inhibition of secretions by sweat glands can cause elevated body temperature.


Dose of atropine
>10.0 mg
5.0 mg
2.0 mg
0.5 mg
Hallucinations and delirium; coma
Rapid heart rate; palpitation; marked dryness of the mouth; dilation of pupil; some blurring of near vision
Slight cardiac slowing; some dryness of the mouth; inhibition of sweating

## 2. Therapeutic uses

Ophthalmic: In the eye, topical *atropine* exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors without interference by the capacity of the eye.

Note: *Phenylephrine* or similar α-adrenergic drugs are preferred for pupillary dilation if cycloplegia is not required.

Shorter-acting antimuscarinics, *cyclopentolate* and *tropicamide*, have largely replaced *atropine* due to prolonged mydriasis observed with *atropine*.

*Atropine* may induce an acute attack of eye pain due to sudden increases in eye pressure in individuals with narrow-angle glaucoma.

Antispasmodic: *Atropine* is used as an antispasmodic agent to relax the GI tract and bladder.

Antidote for cholinergic agonists: *Atropine* is used for the treatment of overdoses of cholinesterase inhibitor insecticides and some types of mushroom poisoning.

Massive doses of the antagonist may be required over a long period of time to counteract the poisons.

The ability of *atropine* to enter the CNS is of particular importance.

The drug also blocks the effects of excess acetylcholine resulting from acetylcholinesterase inhibitors, such as *physostigmine*.

Antisecretory: The drug is sometimes used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery.

## 3. Pharmacokinetics

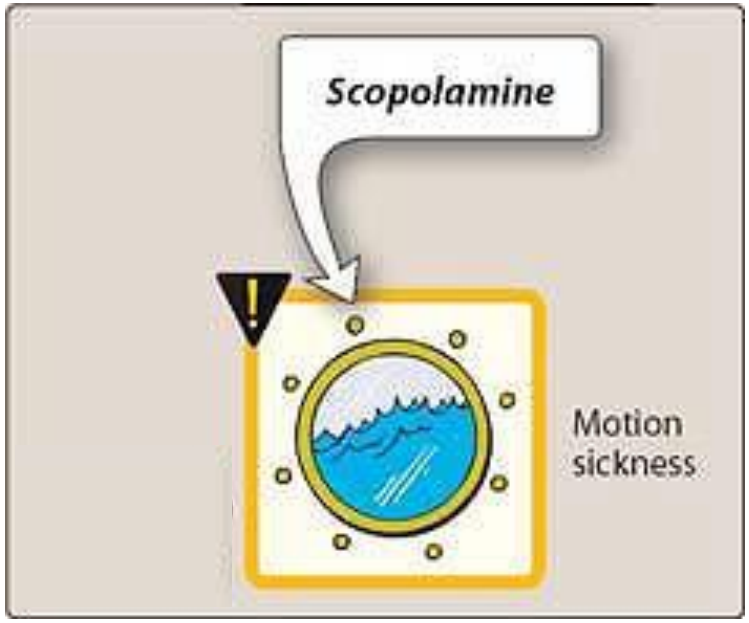
*Atropine* is readily absorbed, partially metabolized by the liver, and eliminated primarily in the urine. It has a half-life of about 4 hours.

## 4. Adverse effects

Depending on the dose, *atropine* may cause dry mouth, blurred vision, sandy eyes, tachycardia, and constipation. Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death. Low doses of cholinesterase inhibitors such as *physostigmine* may be used to overcome *atropine* toxicity. In older individuals, the use of *atropine* to induce mydriasis and cycloplegia is considered to be too risky, because it may exacerbate an attack of glaucoma in someone with a latent condition. In other older individuals, *atropine* may induce urinary retention that is troublesome. Children are sensitive to effects of *atropine* in particular, the rapid increases in body temperature that it may elicit.

# *B. Scopolamine*

*Scopolamine*, another tertiary amine belladonna alkaloid, produces peripheral effects similar to those of *atropine*. However, *scopolamin*e has greater action on the CNS (unlike with *atropine*, CNS effects are observed at therapeutic doses) and a longer duration of action in comparison to those of *atropine*.



**Actions:** *Scopolamine* is one of the most effective anti motion sickness drugs available. In contrast to *atropine, scopolamine* produces sedation, but at higher doses it can produce excitement instead. *Scopolamine* may produce euphoria and is subject to abuse.

**Therapeutic uses:** Although similar to *atropine*, therapeutic use of *scopolamine* is limited to prevention of motion sickness (for which it is particularly effective). As with all such drugs used for motion sickness, it is much more effective prophylactically than for treating motion sickness once it occurs. The amnesic action of *scopolamine* makes it an important adjunct drug in anesthetic procedures.

**Pharmacokinetics and adverse effects:** These aspects are similar to those of *atropine*.

## *C. Ipratropium*

Inhaled *ipratropium*, a quaternary derivative of *atropine*, is useful in treating asthma in patients who are unable to take adrenergic agonists.

*Ipratropium* is also beneficial in the management of chronic obstructive pulmonary disease.

Because of its positive charge, it does not enter the systemic circulation or the CNS, isolating its effects to the pulmonary system.

## *D. Tropicamide and cyclopentolate*

These agents are used as ophthalmic solutions for similar conditions as *atropine* (mydriasis and cycloplegia), but their duration of action is shorter than that of *atropine*, *tropicamide* produces mydriasis for 6 hours and *cyclopentolate* for 24 hours.

# Ganglionic Blockers

Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia.

Some also block the ion channels of the autonomic ganglia.

These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists.

Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor.

The responses observed are complex and unpredictable, making it impossible to achieve selective actions.

Therefore, ganglionic blockade is rarely used therapeutically.

However, ganglionic blockers often serve as tools in experimental pharmacology.

# *A. Nicotine*

A component of cigarette smoke, nicotine is a poison with many undesirable actions.

It is without therapeutic benefit and is deleterious to health.

Nicotine is available as patches, lozenges, gums, and other forms. The drug is absorbed and is effective in reducing the craving for nicotine in people who wish to stop smoking.

Depending on the dose, nicotine depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia.

The stimulatory effects are complex due to effects on both sympathetic and parasympathetic ganglia.

The effects include increased blood pressure and cardiac rate (due to release of transmitter from adrenergic terminals and from the adrenal medulla) and increased peristalsis and secretions.

At higher doses, the blood pressure falls because of ganglionic blockade, and activity both in the GI tract and bladder musculature ceases.

## *B. Mecamylamine*

*Mecamylamine* produces a competitive nicotinic blockade of the ganglia. The duration of action is about 10 hours after a single administration. The uptake of the drug via oral absorption is good. It is primarily used to lower blood pressure in emergency situations.

# Neuromuscular Blocking Drugs

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the neuromuscular end plate of skeletal muscle.

These neuromuscular blockers are structural analogs of acetylcholine, and they act either as antagonists (nondepolarizing type) or agonists (depolarizing type) at the receptors on the end plate of the neuromuscular junction.

Neuromuscular blockers are clinically useful during surgery for producing complete muscle relaxation, without having to employ higher anesthetic doses to achieve comparable muscular relaxation.

Agents are also useful in facilitating intubation as well.

A second group of muscle relaxants, the central muscle relaxants, are used to control spastic muscle tone.

These drugs include *diazepam*, which binds at GABA receptors; *dantrolen*e, which acts directly on muscles by interfering with the release of calcium from the sarcoplasmic reticulum; and *baclofen*, which probably acts at GABA receptors in the CNS.

## *A. Nondepolarizing (competitive) blockers*

The first drug that was found to be capable of blocking the skeletal neuromuscular junction was curare, which the native hunters of the Amazon in South America used to paralyze game.

The drug *tubocurarine* was ultimately purified and introduced into clinical practice in the early 1940s.

Although *tubocurarine* is considered to be the prototype agent in this class, it has been largely replaced by other agents due to side effects.

The neuromuscular blocking agents have significantly increased the safety of anesthesia, because less anesthetic is required to produce muscle relaxation, allowing patients to recover quickly and completely after surgery.

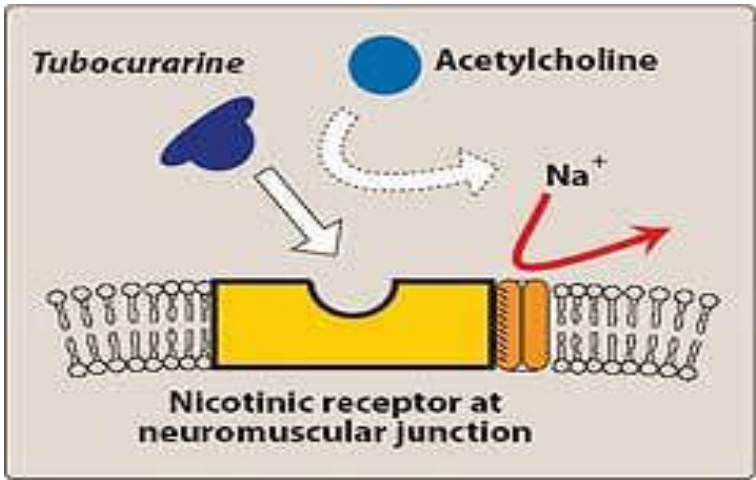
Higher doses of anesthesia may produce respiratory paralysis and cardiac depression, increasing recovery time after surgery.

# 1. Mechanism of action:

At low doses: Nondepolarizing neuromuscular blocking drugs interact with the nicotinic receptors to prevent the binding of acetylcholine.

These drugs thus prevent depolarization of the muscle cell membrane and inhibit muscular contraction.

Because these agents compete with acetylcholine at the receptor without stimulating the receptor, they are called competitive blockers.



Their action can be overcome by increasing the concentration of acetylcholine in the synaptic gap for example, by administration of cholinesterase inhibitors, such as *neostigmine, pyridostigmine*, or *edrophonium*.

Anesthesiologists often employ this strategy to shorten the duration of the neuromuscular blockade.

At high doses: Nondepolarizing blockers can block the ion channels of the end plate.

This leads to further weakening of neuromuscular transmission, and it reduces the ability of acetylcholinesterase inhibitors to reverse the actions of nondepolarizing muscle relaxants.

**Actions:** Not all muscles are equally sensitive to blockade by competitive blockers. Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers. Thereafter, the limbs, neck, and trunk muscles are paralyzed. Then the intercostal muscles are affected, and lastly, the diaphragm muscles are paralyzed. Those agents (for example, *tubocurarine, mivacurium*, and *atracurium*), which release histamine, can produce a fall in blood pressure, flushing, and bronchoconstriction.

**Therapeutic uses:** These blockers are used therapeutically as adjuvant drugs in anesthesia during surgery to relax skeletal muscle. These agents are also used to facilitate intubation as well as during orthopedic surgery.

**Pharmacokinetics:** All neuromuscular blocking agents are injected intravenously, because their uptake via oral absorption is minimal.

These agents possess two or more quaternary amines in their bulky ring structure, making them orally ineffective.

They penetrate membranes very poorly and do not enter cells or cross the blood-brain barrier.

Many of the drugs are not metabolized; their actions are terminated by redistribution.

For example, *tubocurarine, pancuronium, mivacurium, metocurin*e, and *doxacurium* are excreted in the urine unchanged.

*Atracurium* is degraded spontaneously in the plasma and by ester hydrolysis. *Atracurium* has been replaced by its isomer, *cisatracurium.*

*Atracurium* releases histamine and is metabolized to laudanosine, which can provoke seizures.

*Cisatracurium*, which has the same pharmacokinetic properties as *atracurium,* is less likely to have these effects.

The aminosteroid drugs (*vecuronium* and *rocuronium*) are deacetylated in the liver, and their clearance may be prolonged in patients with hepatic disease.

These drugs are also excreted unchanged in the bile.

The choice of an agent will depend on how quickly muscle relaxation is needed and on the duration of the muscle relaxation.

**Adverse effects:** In general, agents are safe with minimal side effects.

## Drug interactions:

Cholinesterase inhibitors: Drugs such as *neostigmine, physostigmine, pyridostigmine*, and *edrophonium* can overcome the action of nondepolarizing neuromuscular blockers, but with increased dosage, cholinesterase inhibitors can cause a depolarizing block as a result of elevated acetylcholine concentrations at the end-plate membrane. If the neuromuscular blocker has entered the ion channel, cholinesterase inhibitors are not as effective in overcoming blockade.

Halogenated hydrocarbon anesthetics: Drugs such as *halothane* act to enhance neuromuscular blockade by exerting a stabilizing action at the neuromuscular junction. These agents sensitize the neuromuscular junction to the effects of neuromuscular blockers.

Aminoglycoside antibiotics: Drugs such as *gentamicin* or *tobramycin* inhibit acetylcholine release from cholinergic nerves by competing with calcium ions. They synergize with *tubocurarine* and other competitive blockers, enhancing the blockade.

Calcium-channel blockers: These agents may increase the neuromuscular block of *tubocurarine* and other competitive blockers as well as depolarizing blockers.

## *B. Depolarizing agents*

**Mechanism of action:** The depolarizing neuromuscular blocking drug *succinylcholine* attaches to the nicotinic receptor and acts like acetylcholine to depolarize the junction.

Unlike acetylcholine, which is instantly destroyed by acetylcholinesterase, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively longer time and providing a constant stimulation of the receptor.

The depolarizing agent first causes the opening of the sodium channel associated with the nicotinic receptors, which results in depolarization of the receptor (Phase I).

This leads to a transient twitching of the muscle (fasciculations).

Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked.

This causes a resistance to depolarization (Phase II) and a flaccid paralysis.

**Actions:** The sequence of paralysis may be slightly different, but as with the competitive blockers, the respiratory muscles are paralyzed last. *Succinylcholine* initially produces short-lasting muscle fasciculations, followed within a few minutes by paralysis. The drug does not produce a ganglionic block except at high doses, but it does have weak histamine-releasing action. Normally, the duration of action of *succinylcholine* is extremely short, because this drug is rapidly broken down by plasma cholinesterase. However, *succinylcholine* that gets to the neuromusclular junction is not metabolized by acetylcholinesterase, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes). Genetic variants in which plasma cholinesterase levels are low or absent leads to prolonged neuromuscular paralysis.

**Therapeutic uses:** Because of its rapid onset and short duration of action, *succinylcholine* is useful when rapid endotracheal intubation is required during the induction of anesthesia (a rapid action is essential if aspiration of gastric contents is to be avoided during intubation). It is also employed during electroconvulsive shock treatment.

**Pharmacokinetics:** *Succinylcholine* is injected intravenously. Its brief duration of action (several minutes) results from redistribution and rapid hydrolysis by plasma cholinesterase. It therefore is usually given by continuous infusion.

**Adverse effects:** Hyperthermia: When *halothane* is used as an anesthetic, administration of *succinylcholine* has occasionally caused malignant hyperthermia (with muscular rigidity and hyperpyrexia) in genetically susceptible people. This is treated by rapidly cooling the patient and by administration of *dantrolene*, which blocks release of $Ca^{2+}$ from the sarcoplasmic reticulum of muscle cells, thus reducing heat production and relaxing muscle tone. Apnea: Administration of *succinylcholine* to a patient who is genetically deficient in plasma cholinesterase or has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm. Hyperkalemia: *Succinylcholine* increases potassium release from intracellular stores. This may be particularly dangerous in burn patients or patients with massive tissue damage in which potassium is been rapidly lost from within cells.