DRUGS THAT ACT IN THE CNS

Cholinergic Antagonists
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Cholinergic Antagonists

Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.

The most clinically useful of these agents are selective blockers of **muscarinic** receptors (**anticholinergic, antimuscarinic**).

A second group of drugs, the **ganglionic blockers**, shows a reference for the **nicotinic receptors** of the sympathetic and parasympathetic ganglia.

A third family of compounds, the **neuromuscular-blocking agents** (mostly **nicotinic antagonists**), interfere with transmission of efferent impulses to skeletal muscles.

ANTIMUSCARINIC AGENTS

Atropine ISOPTO ATROPINE,
Benztropine COGENTIN
Cyclopentolate AK-PENTOLATE, CYCLOGYL
Darifenacin ENABLEX
Fesoterodine TOVIAZ
Ipratropium ATROVENT
Oxybutynin DITROPAN, GELNIQUE, OXYTROL
Scopolamine ISOPTO HYOSCINE, SCOPACE, TRANSDERM SCŌP
Solifenacin VESICARE
Tiotropium SPIRIVA HANDIHALER
Tolterodine DETROL
Trihexyphenidyl ARTANE
Tropicamide MYDRIACYL, TROPICACYL
Trospium chloride SANCTURA

GANGLIONIC BLOCKERS

Mecamylamine NOT AVAILABLE
Nicotine COMMIT, NICODERM, NICORETTE, NICOTROL INHALER

NEUROMUSCULAR BLOCKERS

Atracurium ONLY GENERIC
Cisatracurium NIMBEX
Pancuronium PAVULON
Rocuronium ZEMURON
Succinylcholine ANECTINE, QUELICIN
Vecuronium ONLY GENERIC

ANTIMUSCARINIC AGENTS

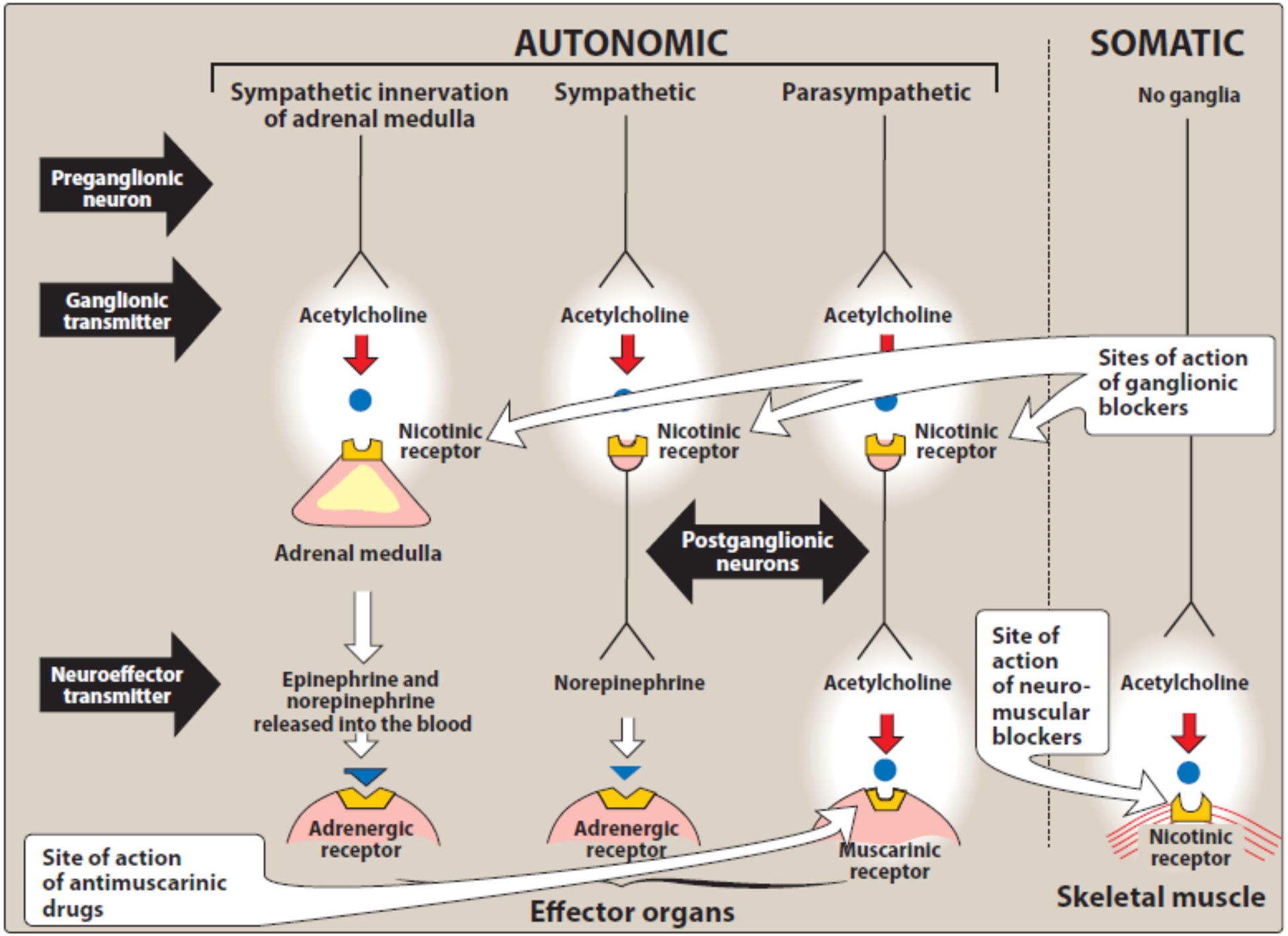
Known as anticholinergic drugs, these agents (for example, **atropine and scopolamine**)

Block muscarinic receptors cause inhibition of muscarinic functions.

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

The anticholinergic drugs are beneficial in a variety of clinical situations.

A number of antihistamines and antidepressants (mainly tricyclic antidepressants) also have antimuscarinic activity.



Sites of actions of cholinergic antagonists.

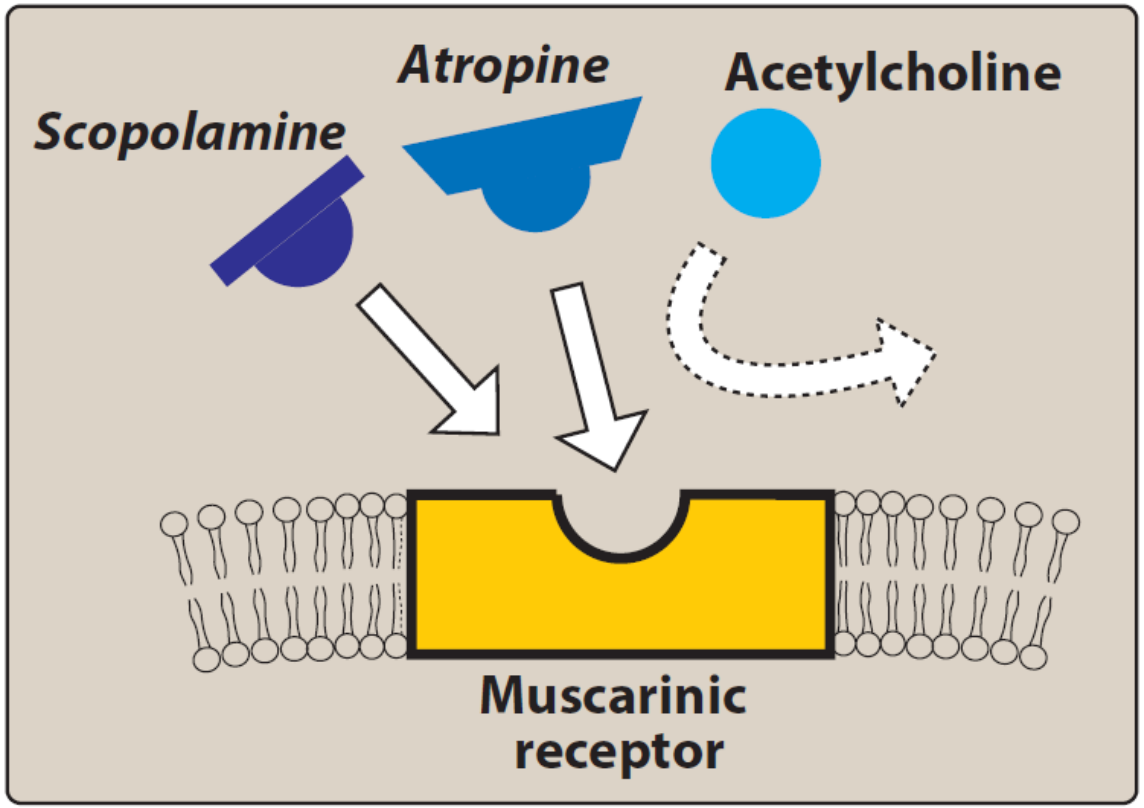
ANTIMUSCARINIC AGENTS/ A. Atropine

Atropine is a **tertiary amine** belladonna alkaloid with a high affinity for muscarinic receptors. It binds competitively and prevents ACh 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.

Neuroeffector organs have varying sensitivity to atropine.

The greatest inhibitory effects are on **bronchial** tissue and the secretion of **sweat and saliva**.



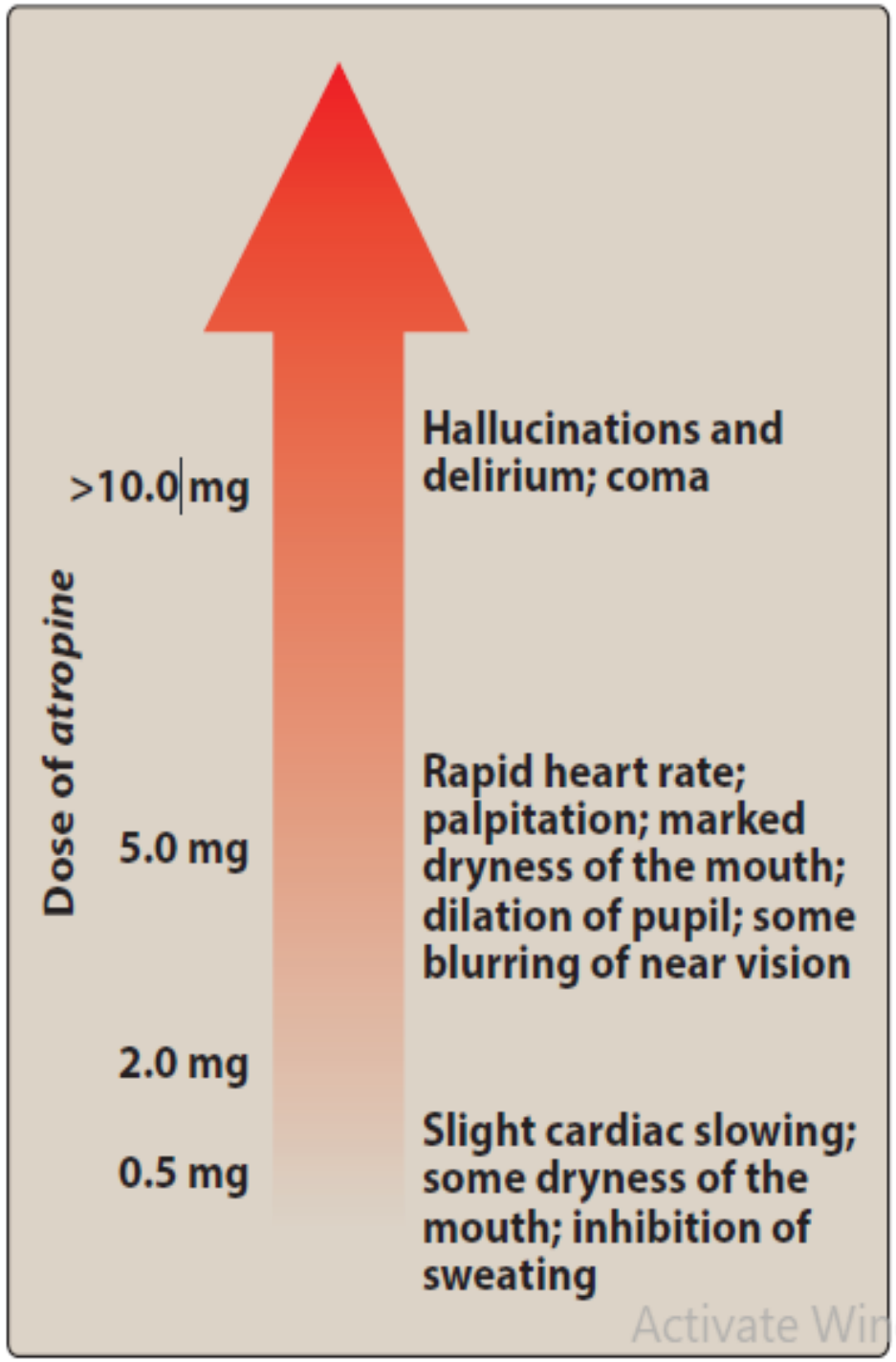
ANTIMUSCARINIC AGENTS/ A. Atropine/1. Actions:

a. Eye: Atropine blocks muscarinic activity in the eye, resulting in **mydriasis** (dilation of the pupil), unresponsiveness to light, and **cycloplegia** (inability to focus for near vision).

b. Gastrointestinal (GI): Atropine (as the active isomer, l-hyoscyamine) can be used as an antispasmodic to reduce activity of the GI tract.

Atropine and scopolamine are probably the most potent antispasmodic drugs available.

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



ANTIMUSCARINIC AGENTS/ A. Atropine/1. Actions:

c. Cardiovascular: Atropine produces divergent effects on the cardiovascular system, depending on the dose (see the above figure).

At low doses, the predominant effect is a slight **decrease in heart rate**. This effect results from blockade of the **M1** receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release.

Higher doses of atropine cause a progressive **increase in heart rate** by blocking the **M2** receptors on the sinoatrial node.

d. Secretions: Atropine blocks muscarinic receptors in the salivary glands, producing dryness of the mouth (xerostomia). The salivary glands are exquisitely sensitive to atropine. Sweat and lacrimal glands are similarly affected.

ANTIMUSCARINIC AGENTS/ A. Atropine/ 2. Therapeutic uses:

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

Shorter-acting antimuscarinics (**cyclopentolate and tropicamide**) have largely replaced atropine due to prolonged mydriasis observed with atropine (7 to 14 days vs. 6 to 24 hours with other agents). **[Note: Phenylephrine or similar α-adrenergic drugs are preferred for pupillary dilation if cycloplegia is not required.]**

b. Antispasmodic: Atropine is used as an antispasmodic agent to relax the GI tract.

c. Cardiovascular: The drug is used to treat bradycardia of varying etiologies.

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

ANTIMUSCARINIC AGENTS/ A. Atropine/ 2. Therapeutic uses:

e. Antidote for cholinergic agonists: Atropine is used for the treatment of organophosphate (insecticides, nerve gases) poisoning, of overdose of clinically used anticholinesterases such as physostigmine, and in some types of mushroom poisoning (certain mushrooms contain cholinergic substances that block cholinesterases).

The ability of atropine to enter the central nervous system (CNS) is of particular importance in treating central toxic effects of anticholinesterases.

ANTIMUSCARINIC AGENTS/ A. Atropine/ 3. Adverse effects:

Depending on the dose, atropine may cause dry mouth, blurred vision, “sandy eyes,” tachycardia, urinary retention, 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.

ANTIMUSCARINIC AGENTS/ B. Scopolamine

Scopolamine, another **tertiary amine** plant alkaloid, produces peripheral effects similar to those of atropine.

However, scopolamine has greater action on the CNS (unlike atropine, CNS effects are observed at therapeutic doses) and a longer duration of action as compared to atropine. It has some special actions as indicated below.

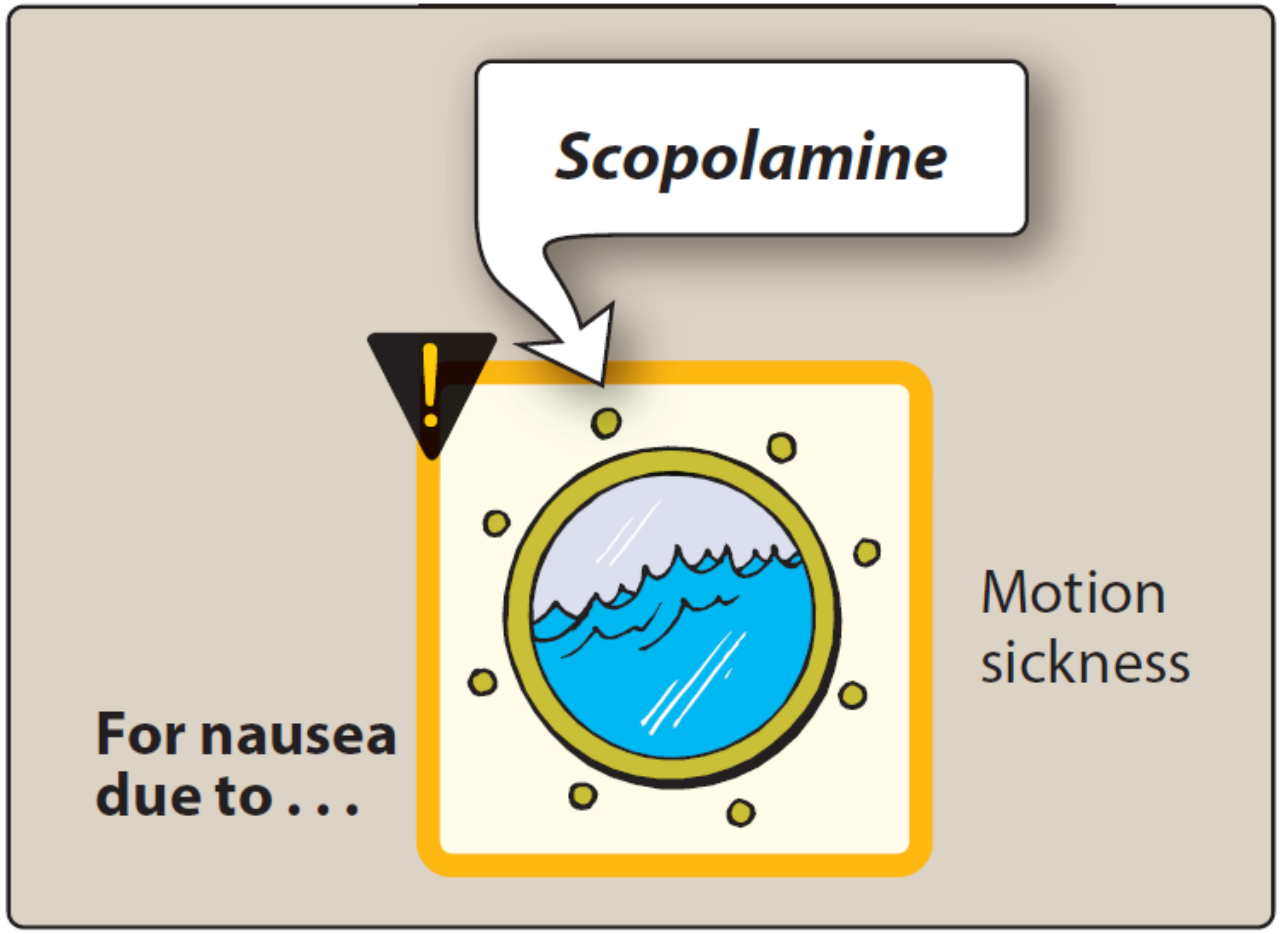
ANTIMUSCARINIC AGENTS/ B. Scopolamine/ 1. Actions:

Scopolamine is one of the most effective **anti–motion sickness** drugs available.

It also has the unusual effect of blocking short-term memory.

In contrast to atropine, Scopolamine produces **sedation**, but at higher doses, it can produce **excitement**.

Scopolamine may produce **euphoria** and is susceptible to abuse.



ANTIMUSCARINIC AGENTS/ B. Scopolamine/ 2. Therapeutic uses:

The therapeutic use of scopolamine is limited to prevention of **motion sickness** and postoperative nausea and vomiting.

[Note: As with all drugs used for motion sickness, it is much more effective **prophylactically** than for treating motion sickness once it occurs.]

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

ANTIMUSCARINIC AGENTS/ C. Ipratropium and tiotropium

Ipratropium and tiotropium are **quaternary derivatives** of atropine. These agents are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (**COPD**).

Ipratropium is also used in the acute management of bronchospasm in **asthma**. Both agents are delivered via inhalation.

Because of their positive charges, these drugs do not enter the systemic circulation or the CNS, isolating their effects to the pulmonary system.

Tiotropium is administered once daily, a major advantage over ipratropium, which requires dosing up to four times daily.

ANTIMUSCARINIC AGENTS/ D. Tropicamide and cyclopentolate

These agents are used as ophthalmic solutions for **mydriasis and cycloplegia.**

Their duration of action is shorter than that of atropine.

Tropicamide produces mydriasis for 6 hours and cyclopentolate for 24 hours.

Drug	Therapeutic uses
Muscarinic blockers	
Trihexyphenidyl *Benztropine*	● Treatment of Parkinson's disease
Darifenacin *Fesoterodine* *Oxybutynin* *Solifenacin* *Tolterodine* *Trospium*	● Treatment of overactive urinary bladder
Cyclopentolate *Tropicamide* *Atropine**	● In ophthalmology, to produce mydriasis and cycloplegia prior to refraction
*Atropine**	● To treat spastic disorders of the GI tract ● To treat organophosphate poisoning ● To suppress respiratory secretions prior to surgery ● To treat bradycardia
Scopolamine	● To prevent motion sickness
Ipratropium *Tiotropium*	● Treatment of COPD
Ganglionic blockers	
Nicotine	● Smoking cessation

Summary of cholinergic antagonists. *Contraindicated in angle-closure glaucoma. GI = gastrointestinal; COPD = chronic obstructive pulmonary disease

ANTIMUSCARINIC AGENTS/ E. Benztropine and trihexyphenidyl

Benztropine and trihexyphenidyl are useful as adjuncts with other antiparkinsonian agents to treat **Parkinson's disease** and other types of parkinsonian syndromes, including antipsychotic induced extrapyramidal symptoms.

ANTIMUSCARINIC AGENTS/ F. Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium chloride

These synthetic atropine-like drugs are used to treat **overactive bladder**.

By blocking muscarinic receptors in the bladder, intravesical pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced.

Side effects include dry mouth, constipation, and blurred vision, which limit tolerability of these agents if used continually.

The overall efficacies of these antimuscarinic drugs are similar.

III. 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.

Except for nicotine, the other drugs mentioned in this category are nondepolarizing, competitive antagonists.

III. GANGLIONIC BLOCKERS/ 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.

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

The stimulatory effects are complex and result from increased release of neurotransmitters, due to effects on both sympathetic and parasympathetic ganglia.

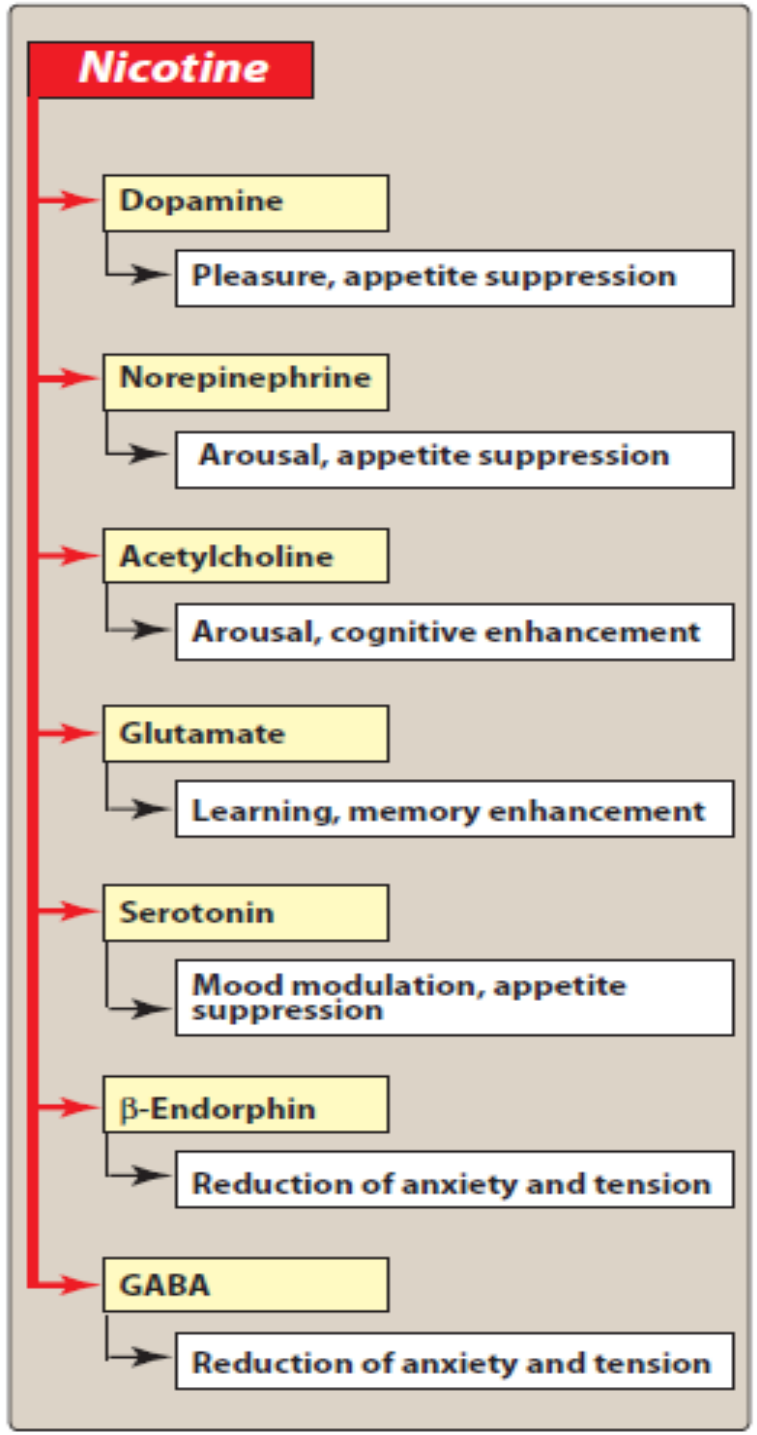
The overall response of a physiologic system is a summation of the stimulatory and inhibitory effects of nicotine.

III. GANGLIONIC BLOCKERS/ A. Nicotine

These 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 and activity in both the GI tract and bladder musculature ceases.

III. GANGLIONIC BLOCKERS



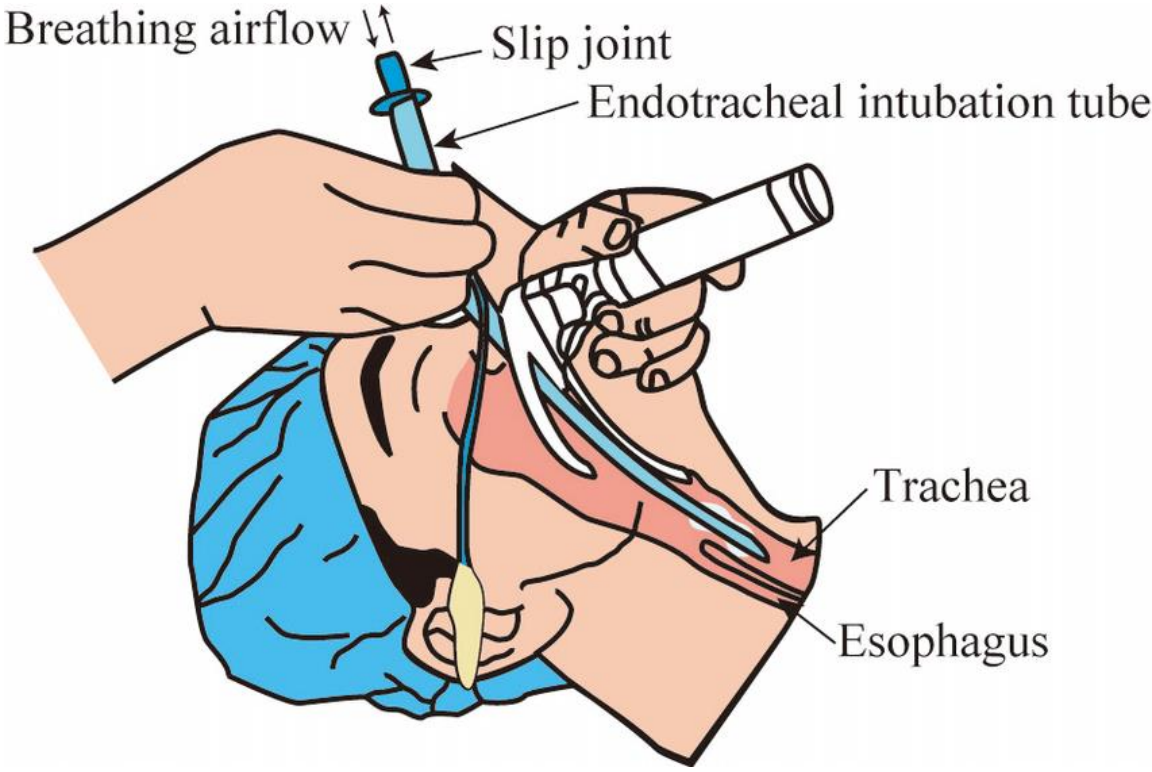
Neurochemical effects of nicotine.
GABA = γ-aminobutyric acid.

IV. NEUROMUSCULAR-BLOCKING AGENTS

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on **the skeletal muscle**.

They possess some chemical similarities to ACh, and they act either as **antagonists (nondepolarizing type) or as agonists (depolarizing type)** at the receptors on the endplate of the NMJ.

Neuromuscular blockers are clinically useful **during surgery** to facilitate **tracheal intubation** and provide complete muscle relaxation at lower anesthetic doses, allowing for more rapid recovery from anesthesia and reducing postoperative respiratory depression.



IV. NEUROMUSCULAR-BLOCKING AGENTS/ A. Nondepolarizing (competitive) blockers

The first drug known to block the skeletal NMJ was **curare**, which native South American hunters of the Amazon region used to paralyze prey.

The development of the drug **tubocurarine** followed, but it has been replaced by other agents with fewer adverse effects, such as **cisatracurium, pancuronium, rocuronium, and vecuronium**.

The neuromuscular-blocking agents have significantly increased the safety of anesthesia.

Neuromuscular blockers should not be used to substitute for inadequate depth of anesthesia.

IV. NEUROMUSCULAR-BLOCKING AGENTS/ A. Nondepolarizing (competitive) blockers/ 1. Mechanism of action:

a. At low doses: Nondepolarizing agents competitively block ACh at the nicotinic receptors.

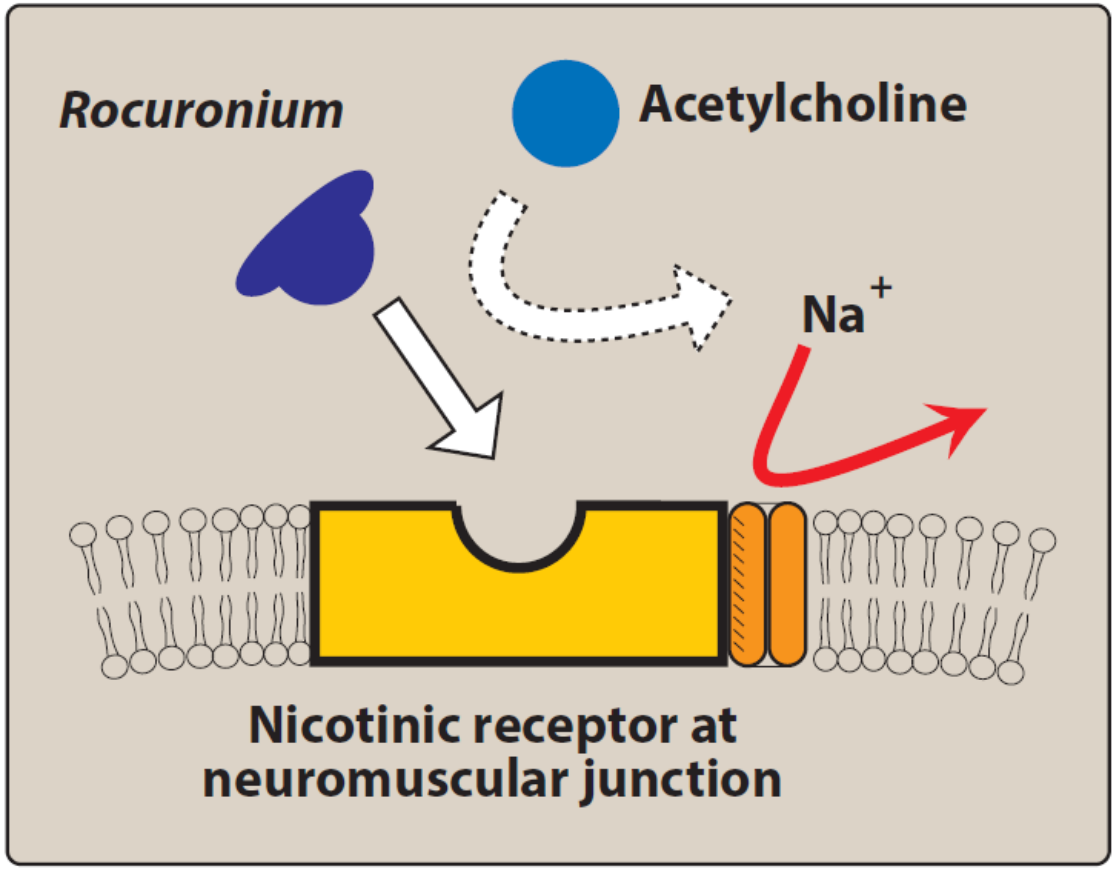
That is, they compete with ACh at the receptor without stimulating it. Thus, these drugs prevent depolarization of the muscle cell membrane and inhibit muscular contraction.

In addition, at low doses the muscle will respond to direct electrical stimulation from a peripheral nerve stimulator to varying degrees, allowing for monitoring of the extent of neuromuscular blockade.

IV. NEUROMUSCULAR-BLOCKING AGENTS/ A. Nondepolarizing (competitive) blockers/ 1. Mechanism of action:

b. At high doses: Nondepolarizing agents can block the ion channels of the motor endplate.

With complete blockade, the muscle does not respond to direct electrical stimulation.



IV. NEUROMUSCULAR-BLOCKING AGENTS/ A. Nondepolarizing (competitive) blockers/ 2. Actions:

Not all muscles are equally sensitive to blockade by competitive agents.

Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers, limbs, neck, and trunk muscles.

Next, the intercostal muscles are affected and, lastly, **the diaphragm**. The muscles recover in the reverse manner.

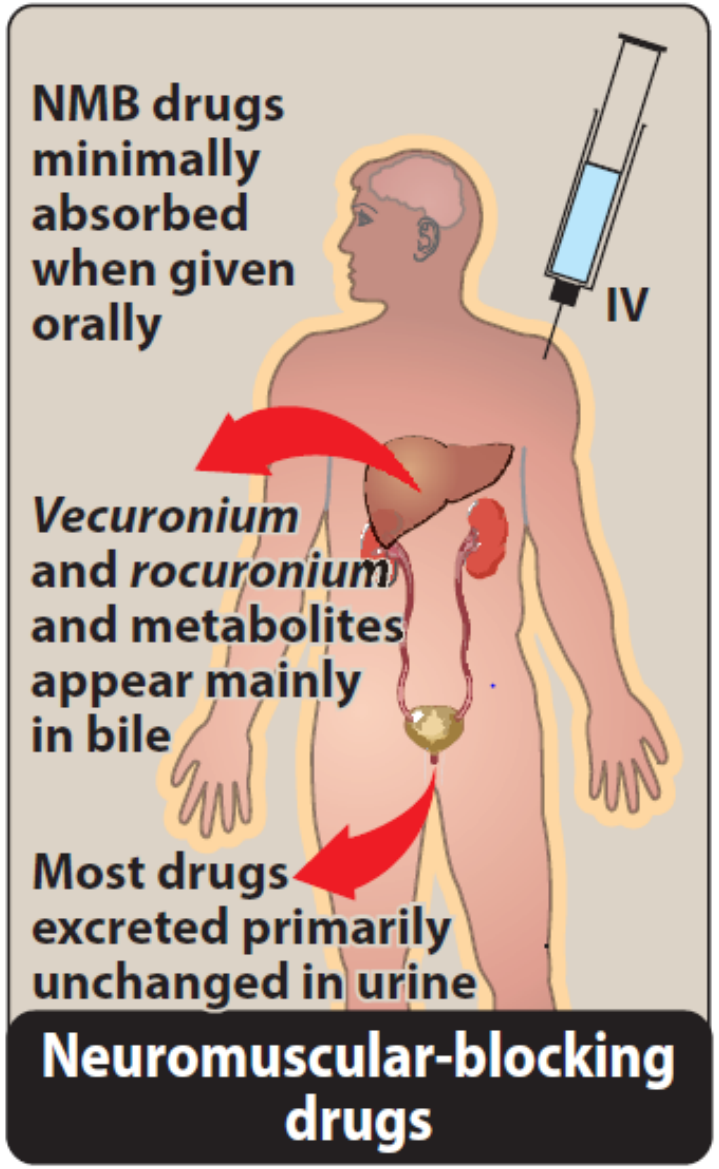
IV. NEUROMUSCULAR-BLOCKING AGENTS/ A. Nondepolarizing (competitive) blockers/ 3. Pharmacokinetics:

All neuromuscular-blocking agents are injected **intravenously** or occasionally intramuscularly since they are not effective orally.

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

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

For example, pancuronium is excreted unchanged in urine. Cisatracurium is degraded spontaneously in plasma and by ester hydrolysis.



IV. NEUROMUSCULAR-BLOCKING AGENTS/ A. Nondepolarizing (competitive) blockers/ 3. Pharmacokinetics:

[Note: 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 amino steroid drugs vecuronium and rocuronium are deacetylated in the liver, and their clearance may be prolonged in patients with hepatic disease.

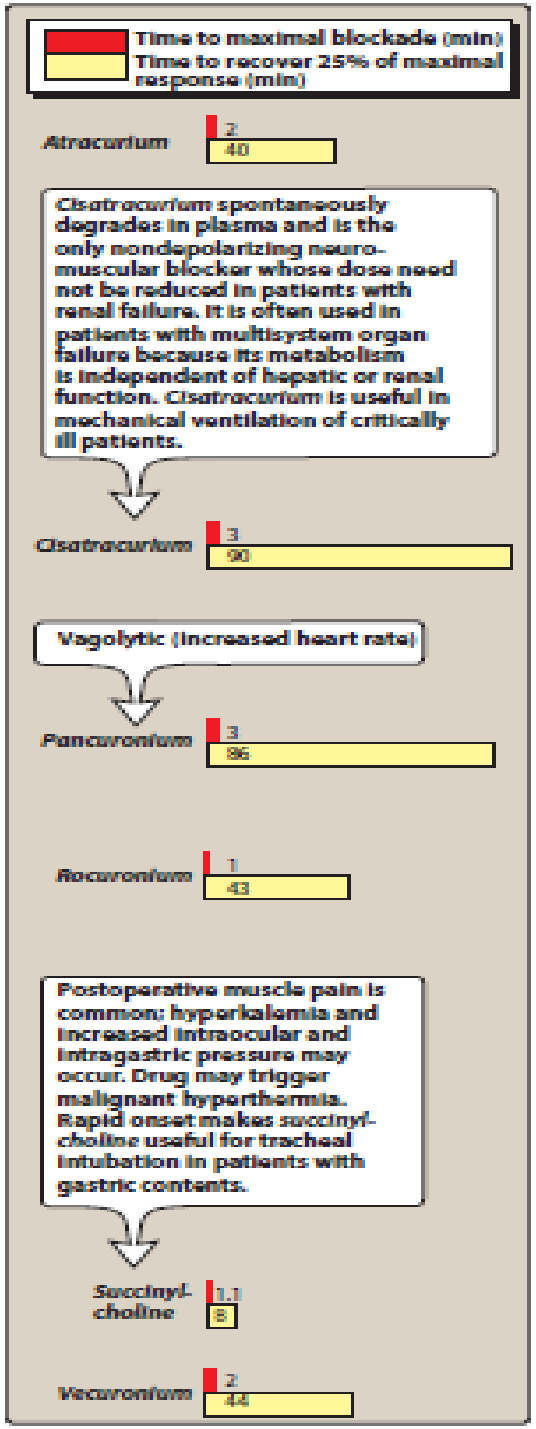
These drugs are also excreted unchanged in bile.

The choice of an agent depends on the desired onset and duration of the muscle relaxation.

IV. NEUROMUSCULAR-BLOCKING AGENTS/ A. Nondepolarizing (competitive) blockers/

4. Adverse effects:

In general, these agents are safe with minimal side effects.



IV. NEUROMUSCULAR-BLOCKING AGENTS/ A. Nondepolarizing (competitive) blockers/ 5. Drug interactions:

a. Cholinesterase inhibitors: Drugs such as neostigmine, physostigmine, pyridostigmine, and edrophonium can **overcome** the action of nondepolarizing neuromuscular blockers.

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

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

d. Calcium channel blockers: These agents may increase the neuromuscular blockade of competitive blockers.

NEUROMUSCULAR-BLOCKING AGENTS/ B. Depolarizing agents

Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh.

However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can thus more persistently depolarize the muscle fibers.

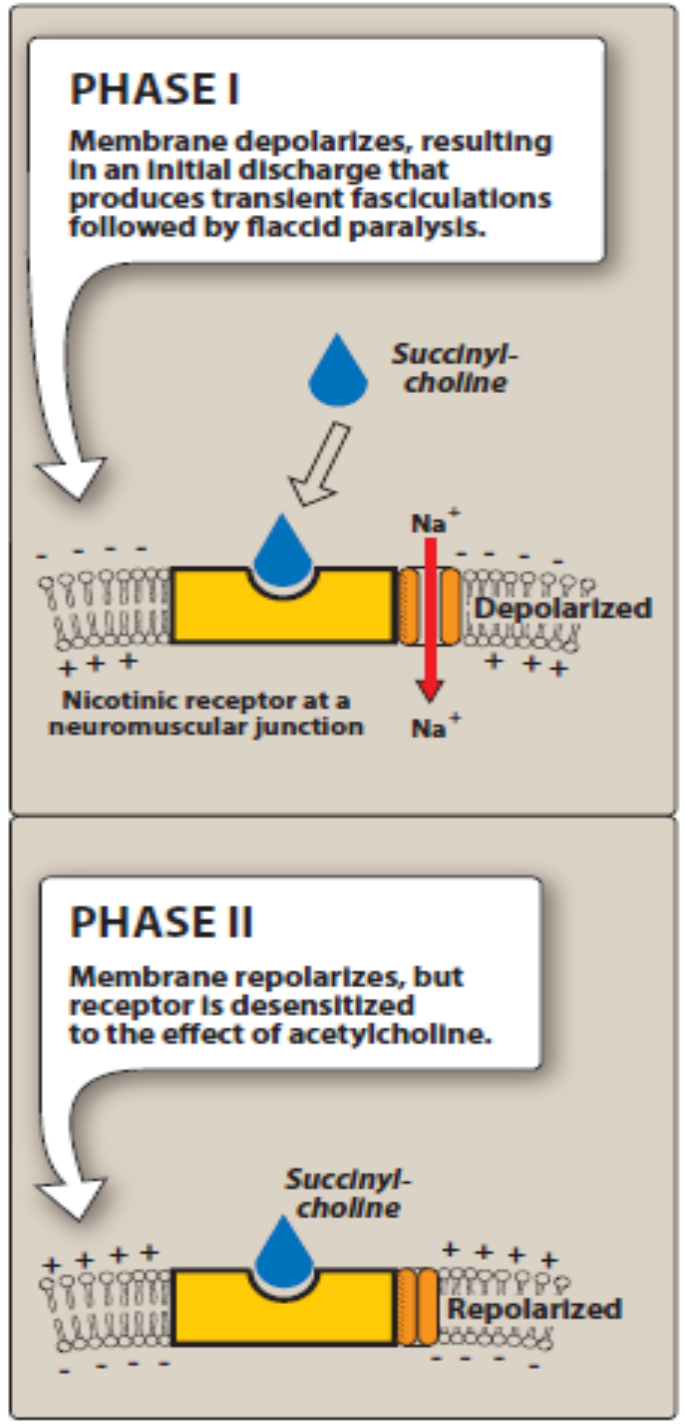
Succinylcholine is the only depolarizing muscle relaxant in use today.

NEUROMUSCULAR-BLOCKING AGENTS/ B. Depolarizing agents/

1. Mechanism of action:

Succinylcholine attaches to the nicotinic receptor and acts like ACh to depolarize the junction.

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



NEUROMUSCULAR-BLOCKING AGENTS/ B. Depolarizing agents/ 1. Mechanism of action:

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 flaccid **paralysis**.

NEUROMUSCULAR-BLOCKING AGENTS/ B. Depolarizing agents/ 2. Actions:

As with the competitive blockers, the respiratory muscles are paralyzed last.

Succinylcholine initially produces brief muscle fasciculations that cause muscle soreness.

This may be prevented by administering a small dose of nondepolarizing neuromuscular blocker prior to succinylcholine.

Normally, the duration of action of succinylcholine is extremely short, due to rapid hydrolysis by plasma **pseudocholinesterase**.

However, succinylcholine that gets to the NMJ is not metabolized by AChE, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes).

NEUROMUSCULAR-BLOCKING AGENTS/ B. Depolarizing agents/ 3. Therapeutic uses:

Because of its rapid onset 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 used during electroconvulsive shock treatment.

NEUROMUSCULAR-BLOCKING AGENTS/ B. Depolarizing agents/ 4. Pharmacokinetics:

Succinylcholine is injected intravenously. Its brief duration of action results from redistribution and rapid hydrolysis by plasma pseudocholinesterase.

Therefore, it is sometimes given by continuous infusion to maintain a longer duration of effect.

Drug effects rapidly disappear upon discontinuation.

NEUROMUSCULAR-BLOCKING AGENTS/ B. Depolarizing agents/ 5. Adverse effects:

a. Hyperthermia: Succinylcholine can potentially induce malignant hyperthermia in susceptible patients.

b. Apnea: Administration of succinylcholine to a patient who is deficient in plasma cholinesterase or who has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm.

c. Hyperkalemia: Succinylcholine increases potassium release from intracellular stores. This may be particularly dangerous in burn patients and patients with massive tissue damage in which potassium has been rapidly lost from within cells.