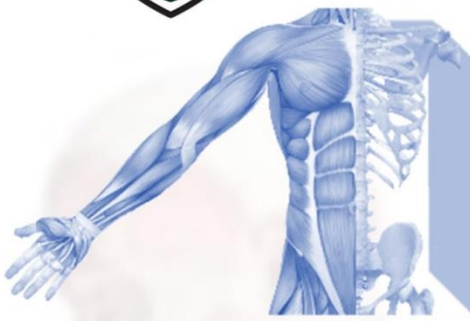

MSS

Musculoskeletal System

Doctor 2019 | Medicine | JU

3 Pharmacology

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Scientific correction:

Grammatical correction:

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Skeletal Muscle Relaxants

A muscle relaxant is a drug that affects skeletal muscle function and decreases muscle tone which can be used to alleviate muscles spasm and pain.

There are different kinds of skeletal muscle relaxant:

1. neuromuscular blockers
2. spasmolytics
3. directly acting drugs

Neuromuscular Blockers

Neuromuscular blockers are medicines that block the interaction between acetylcholine and nicotinic receptor thus, they act as muscle relaxant drugs that can be used during **surgical procedures** to reduce muscle tone so it will be easier to dissect through the muscles and perform the surgery or to ease up the intubation process during anesthesia or artificial ventilation in the **intensive care unit**. Neuromuscular blockers have significantly increased the safety of anesthesia because less anesthetic is required to produce muscle relaxation.

The **chemical structure** of neuromuscular blockers is **one or two quaternary nitrogen's** thus, they are poorly lipid-soluble or highly polar compounds that can't be absorbed through the GI system, instead, they are given parenterally, most likely by intravenous injection. In addition to that, there is a **double acetylcholine molecule** linked into the ends forming a concealed bulky semi-rigid ring system.

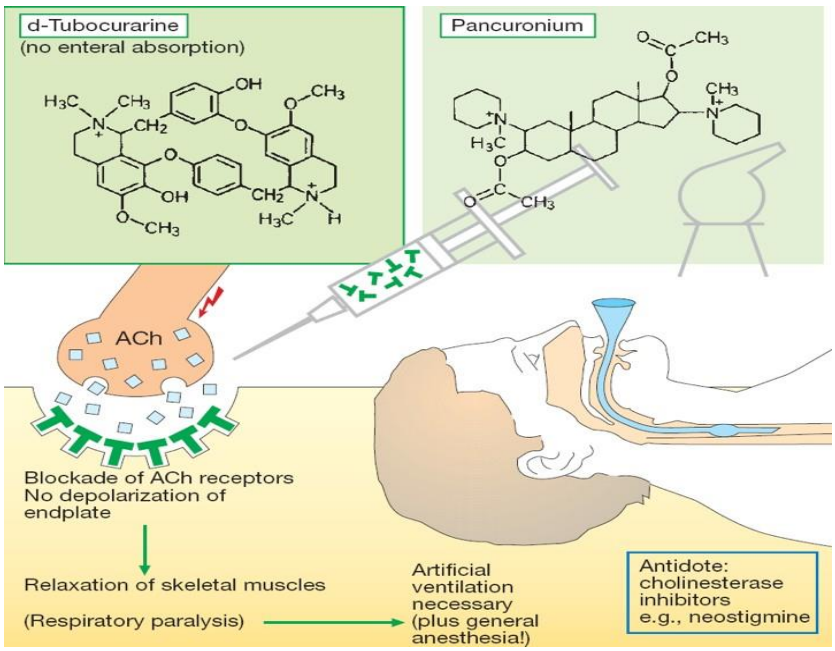
Neuromuscular blockers are classified into **depolarizing drugs** and **non-depolarizing drugs (competitive)**, We will study each type under the concept of Pharmacokinetics and mechanism of the action.

Mechanism of Action

Non-depolarizing drugs

They are **competitive** inhibitors with acetylcholine for the nicotinic receptor sites at the neutral muscular junction.

At high doses, they can enter the pore of the ion channel and cause a more intense blockade thus, they would prevent the binding of acetylcholine to the nicotinic receptor at the muscle and plate, thus prevent the action of acetylcholine on those muscles which stimulate contraction. In addition to that, they can also block pre-junctional sodium channels to interfere with the mobilization of acetylcholine at the nerve endings.



As you see in the figure, these drugs such as **Tubocurarine** or **Pancuronium**, once they are injected into the patient they can compete with acetylcholine for the binding sites on the nicotinic receptor, thus preventing acetylcholine from binding and inducing the contraction of the skeletal muscle.

An example of these skeletal muscles at which we see this effect is the **respiratory muscles,** this inhibition of contraction will lead to the relaxation of the respiratory muscles which as we said can ease the artificial ventilation necessity in the general anesthesia processes.

Depolarizing agents

depolarizing agents work at different phases and we will take **succinylcholine** as an example of these agents to talk about:

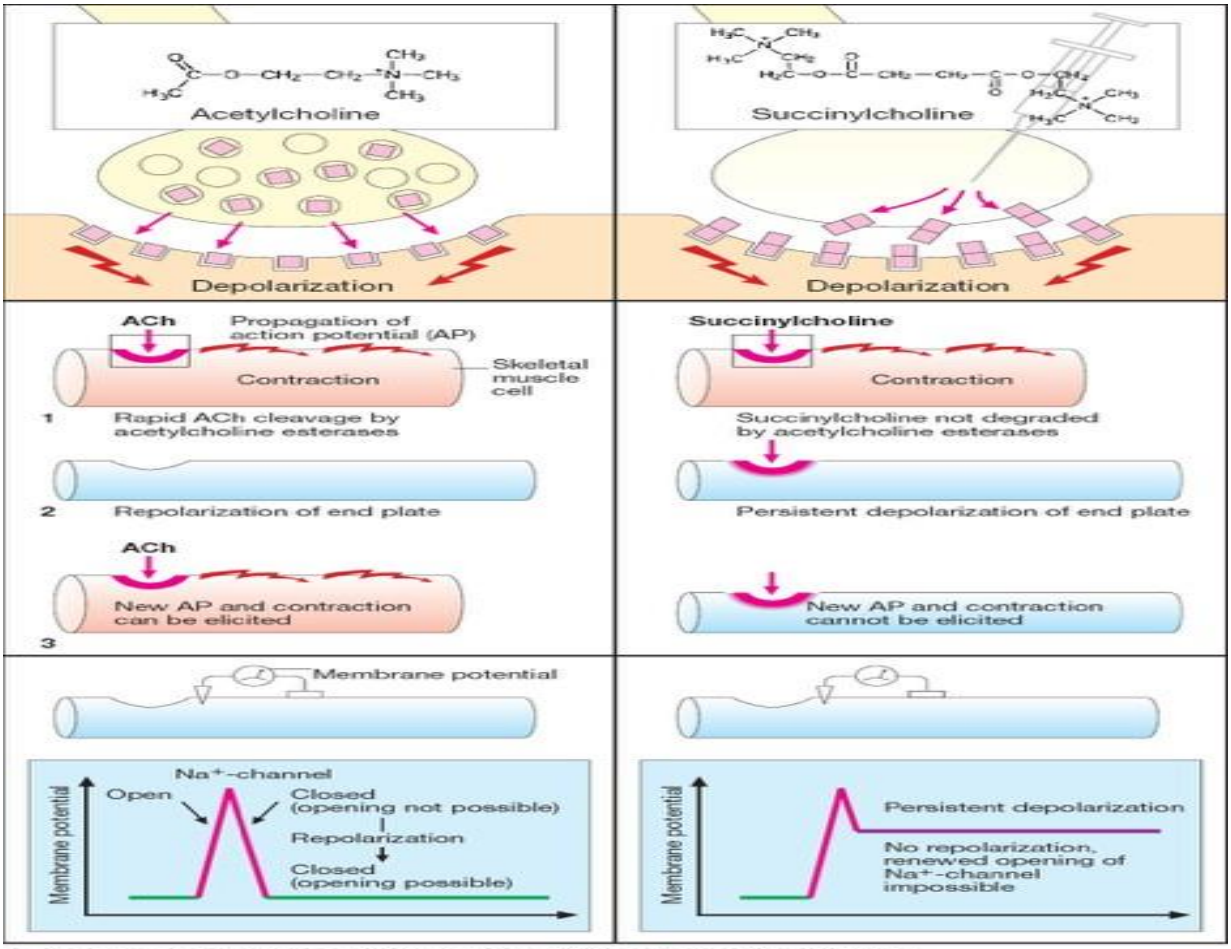
Remember: succinylcholine has a very similar structure to acetylcholine where it is composed of two acetylcholine bound edge to edge.

- ✓ **phase | blocking or the (depolarizing):**

succinylcholine reacts with nicotinic receptors to open the channels and cause depolarization of the motor endplate which will spread to adjacent membranes and cause contraction of the muscle motor units, this can lead to a prolonged "flickering" of the ion conductance. The depolarized membranes remain depolarized and unresponsive to subsequent impulses causing flaccid paralysis which is augmented by cholinesterase inhibitors.

- ✓ **phase || block or the (desensitization):**

with continued exposure, the depolarization decreases, and the membrane becomes more repolarized which cannot be depolarized again because it is desensitized. this can lead to blockage of the ion channel which might be important for the action of these agonists at the receptor so the channels will behave as they are in a prolonged closed state. this phase is reversed by acetylcholinesterase inhibitors.



A. Action of the depolarizing muscle relaxant succinylcholine

In this figure, we can see the difference between acetylcholine and succinylcholine:

- Both of them cause initial depolarization of the muscle.
- **Acetylcholine** (left) will show relaxation after a period of time which allows the muscle to repolarize, meaning that we can perform activation or contraction again.
- **Succinylcholine** (right) will have persistent depolarization with no repolarization meaning that the renewed opening of the sodium channel becomes impossible.

Table 27–2. Comparison of a typical nondepolarizing muscle relaxant (rocuronium) and a depolarizing muscle relaxant (succinylcholine).

		Succinylcholine	
	Rocuronium	Phase I	Phase II
Administration of tubocurarine	Additive	Antagonistic	Augmented[1]
Administration of succinylcholine	Antagonistic	Additive	Augmented[1]
Effect of neostigmine	Antagonistic	Augmented[1]	Antagonistic
Initial excitatory effect on skeletal muscle	None	Fasciculations	None
Response to a tetanic stimulus	Unsustained (fade)	Sustained[2] (no fade)	Unsustained (fade)
Posttetanic facilitation	Yes	No	Yes
Rate of recovery	30–60 min[3]	4–8 min	> 20 min[3]

[1]It is not known whether this interaction is additive or synergistic (superadditive).
[2]The amplitude is decreased, but the response is sustained.
[3]The rate depends on the dose and on the completeness of neuromuscular blockade.

In this table, we have a comparison between a typical non-depolarizing muscle relaxant such as **Rocuronium** and a depolarizing muscle relaxant **succinylcholine**.

Pharmacokinetics of neuromuscular blockers

Non-depolarizing drugs

are excreted in the kidneys and metabolized by the liver.

Ex.

- **Mivacurium** is metabolized by cholinesterase, this rendered the drug has a very short half-life.
- **Atracurium** is spontaneously broken down by a reaction called **Hofmann elimination** this drug also will have a short half-life compared to drugs that are metabolized in the liver.

Depolarizing drugs

have an extremely short duration (5-7 minutes), they get metabolized by cholinesterase in the plasma and liver, and only a small percentage reaches the neural muscular junction where they diffuse away to the extracellular fluid.

We will have variation in the **plasma levels** and the **half-lives** of these drugs, because **some patients have a genetically abnormal variant of plasma cholinesterase** so, one measure to estimate the ability of a patient to metabolize succinylcholine or depolarizing agent is called the **dibucaine number**.

this table shows some of the properties of neuromuscular blocking agents:

Table 27–1. Some properties of neuromuscular blocking drugs.

Drug	Elimination	Clearance (mL/kg/min)	Approximate Duration of Action (minutes)	Approximate Potency Relative to Tubocurarine
Isoquinoline derivatives				
Atracurium	Spontaneous[1]	6.6	20–35	1.5
Cisatracurium	Mostly spontaneous	5–6	25–44	1.5
Doxacurium	Kidney	2.7	> 35	6
Metocurine	Kidney (40%)	1.2	> 35	4
Mivacurium	Plasma ChE[2]	70–95	10–20	4
Tubocurarine	Kidney (40%)	2.3–2.4	> 35	1
Steroid derivatives				
Pancuronium	Kidney (80%)	1.7–1.8	> 35	6
Pipecuronium	Kidney (60%) and liver	2.5–3.0	> 35	6
Rocuronium	Liver (75–90%) and kidney	2.9	20–35	0.8
Vecuronium	Liver (75–90%) and kidney	3–5.3	20–35	6
Depolarizing agent				
Succinylcholine	Plasma ChE[2] (100%)	>100	< 8	0.4

[1]Nonenzymatic and enzymatic hydrolysis of ester bonds.
[2]Butyrylcholinesterase (pseudocholinesterase).

we can notice here:

1. The Elimination is mostly through the kidney while some of these agents get metabolized in the plasma cholinesterase.
2. There are differences in the **half-lives** of these agents which can be measured by the clearance.
3. There are differences in the duration of action and the potencies of these agents compared to **Tubocurarine** which is the prototype of these agents.

Actions of Neuromuscular Blockers

1. Skeletal Muscle Paralysis

This table shows the difference between non-depolarizing and depolarizing neuromuscular blockers on skeletal muscle paralysis.

Non-depolarizing Drugs	Depolarizing Drugs
- The onset of effect is very rapid. - The motor weakness followed by flaccidity. - Starts with small muscles, large muscles are more resistant to blockade and recover more rapidly. Diaphragm is last to be paralyzed. - Effects last for 45-60 minutes.	- Action stars by transient muscle fasciculations over the chest and abdomen within 30 seconds. - Paralysis develops rapidly (within 90 seconds), the arm, neck, and leg muscles followed by the respiratory muscles. - Blockade lasts less than 10 minutes

The neuromuscular blocker's main effect is in muscle paralysis or relaxation, but it also has other effects on other systems which considered as **side effects**:

2. the cardiovascular system

the cardiovascular system effects are usually mediated by the autonomic nervous system or by histamine receptor release. Both sympathetic and parasympathetic ganglia and muscarinic receptors in the heart can be stimulated by these agents this usually leads to hypotension which can be attenuated by antihistamines.

3. hyperkalemia

In patients with burns, nerve damage, or neuromuscular diseases, head injury, and other trauma because this can result in cardiac arrest.

4. Increased Intraocular Pressure

Due to tonic contraction of myofibrils or transient dilation of ocular choroidal blood vessels.

5. Increased Intragastric Pressure

In obese, heavily muscled, diabetics, traumatic patients, fasciculations of succinylcholine can cause regurgitation and aspiration of gastric contents.

6. Muscle Pain

Due to unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis.

Drug Interactions of Neuromuscular Blockers

1. Anesthetics

These agents are used in general anesthesia procedures. we have an important drug interaction especially with halogenated anesthetics such as **isoflurane** and less of that with **nitrous oxide**. This can be happening due to a central action of increased muscle blood flow, as well they can cause a condition called **malignant hyperthermia.**

For example, when **halothane** (which is used as an anesthetic) is administered with succinylcholine, we have occasionally malignant hyperthermia which is associated with muscle rigidity and hyperoxia, **this happens especially in genetically susceptible people**.

One important treatment for this condition is the administration of a directly acting muscle-relaxing called **dantrolene** which blocks the release of calcium from the sarcoplasmic reticulum of the muscle cells thus reducing the heat production and relaxing the muscle tone.

2. Antibiotics

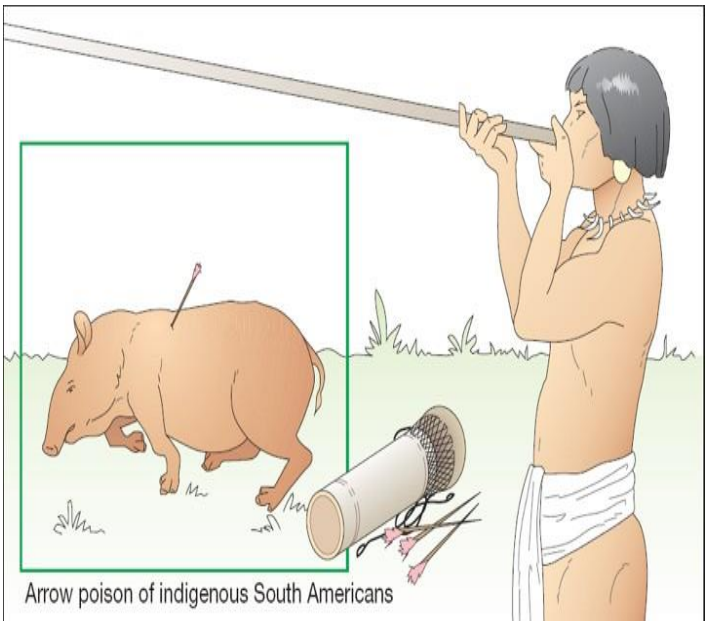
certain antibiotics can interact with neuromuscular blockers, so they decrease or depress the release of acetylcholine due to blocking of certain or specific kinds of P-type calcium channels.

Additionally, **aminoglycoside antibiotics** such as gentamicin or tobramycin can inhibit the acetylcholine released from cholinergic nerves by competing with calcium ions which synergize with tubercular and other competitor blocker enhancing the blockers.

3. Local anesthetics and antiarrhythmic Drugs

4. Other Neuromuscular Blockers.

Curare or **Tubocurarine** which are **Non-depolarizing drugs** were used by native hunters of the amazons in South America as hunting poison for hunting animals, as we said because this poison does not get absorbed through the GI tract it wouldn't harm the individual after they ingest the poisoned meat. while this drug was used a very long time ago as a hunting poison, the clinical practice of these dresses started in the early 1940s.


Arrow poison of indigenous South Americans

Curare is a common name for various plant extract alkaloid arrow poisons originating from indigenous peoples in Central and South America. Used as a paralyzing agent for hunting and therapeutic purposes. Wikipedia

Spasmolytic Drugs

Another group of agents that are used in skeletal muscle relaxant or treatment of spasticity, example:

1. Diazepam

Benzodiazepine spasmolytic drug acts on the $GABA_A$ synapses in the central nervous system and facilitates its action in reducing the spasticity at least partly mediated in the spinal cord since it is effective in patients with cord transection.

Although diazepam can be used in patients with muscle spasms of almost any origin (including local muscle trauma), it also produces sedation at the doses required to reduce muscle tone.

one important **side effect** associated with these agents is that they cause **sedation** and the **tendency for tolerance and dependence**, so we have to be careful about that.

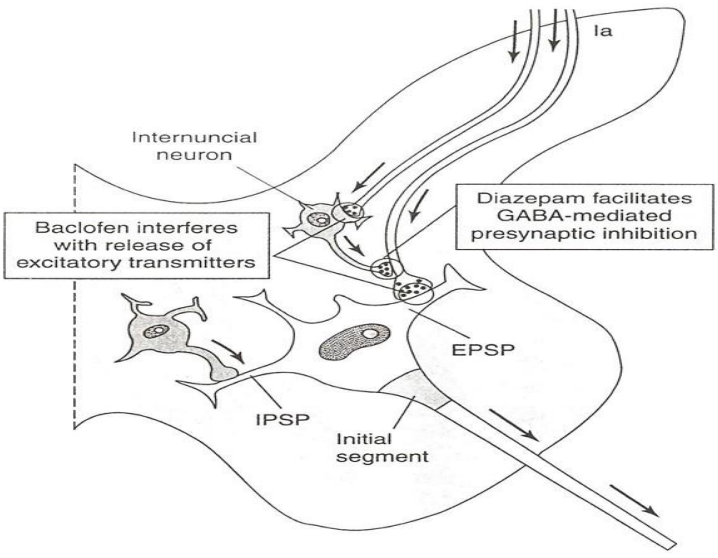
2. Midazolam

Other benzodiazepines spasmolytic drug has been used as spasmolytic agents but the clinical experience with them is very limited.

3. Baclofen

baclofen mainly works at the $GABA_B$ receptor, it causes hyperpolarization and presynaptic inhibition through reducing calcium influx, also it can reduce spasticity by inhibiting the release of **substance P** in the spinal cord, it is less sedative than benzodiazepines, but can cause drowsiness. it Can be given intrathecally. and can reduce craving in alcoholics and migraines.

This picture shows the sites of action of **diazepam** facilitating the GABA-mediated pre-synaptic inhibition while on the other hand **baclofen** interferes with the release of excitatory transmitters in the central nervous system (in the spinal cord here).



4. Tizanidine

Tizanidine related to clonidine

Remember :clonidine work as alpha-2 agonists

Tizanidine is used to treat muscle spasticity, especially due to spinal cord injury or multiple sclerosis.

Since clonidine is an alpha-2 agonist, we use them as an antihypertensive agent (a blood pressure-lowering drug) though, the effect of tizanidine in lowering pressure is much less effective than that of clonidine (about 1:10 or 1:15).

It does have Side effects related to the central nervous system such as **dizziness**, **weakness**, **depression**, **hallucinations,** and **sedation**. it can also cause **dry mouth** and some patients experience **constipation** while other experience **diarrhea** with the use of this agent.

5. Gabapentin

gabapentin is an anti-epileptic glycine use for the treatment of **epilepsy** or **seizure**; we'll talk about it next year in the CNS lecs.

Directly Acting Drugs

Another group of agents that are used in skeletal muscle, example:

Dantrolene

Dantrolene is related to phenytoin, which is an antiepileptic agent. Dantrolene Interferes with excitation-contraction coupling in the muscle fibers by interfering with the release of activator calcium by binding with the ryanodine receptor (RyR) channel of the sarcoplasmic reticulum, thus enhancing the further release of calcium inside the sarcoplasmic from the sarcoplasmic reticulum in the muscle cell, this is why dantrolene is used as an **antidote** for patients exhibiting malignant hyperthermia that induced by the combination of succinylcholine with anesthetic agents such as halothane. we said there is a genetic mutation occurring in patients who exhibit this side effect, and this genetic mutation is related to the **ryanodine receptor**.

Dantrolene can cause weakness, sedation, and hepatitis.

Malignant Hyperthermia

Rare heritable disorder is triggered by a variety of stimuli, including general anesthetics and neuromuscular blockers. For patients who have a hereditary impairment of the sarcoplasmic reticulum to sequester calcium, this can trigger or causes a sudden and prolonged release of calcium, with massive contraction, leading to lactic acidosis, and increased body temperature. Treatment is by cooling, correcting acidosis, and dantrolene to reduce calcium release.

Botulinum Toxin

Produced by Botulinum bacteria.

used as a muscle relaxant by inhibiting acetylcholine release.

Food poisoning caused by this bacterium can result, within 12-36 hours, in diplopia, dysphagia, dysarthria, and dyspnea.

The toxin is used for ophthalmic purposes, local muscle spasms, and in the cosmetic treatment of facial wrinkles around the eyes and mouth, as well as for generalized spastic disorders like cerebral palsy.

To sum the drugs mentioned in this sheet:

• Tubocurarine • Pancuronium • Mivacurium • Atracurium • Rocuronium	**Non-Depolarizing Drug**	• Diazepam • midazolam • Baclofen • Tizanidine • Gabapentin	**Spasmolytic Drugs**
• Succinylcholine	**Depolarizing Drug**	• Dantrolene	**Directly Acting Drug**
• Isoflurane • Halothane	**Anesthetics**	• gentamicin • tobramycin	**Aminoglycoside antibiotics**

Sorry for errors, if there was

Good luck ♥