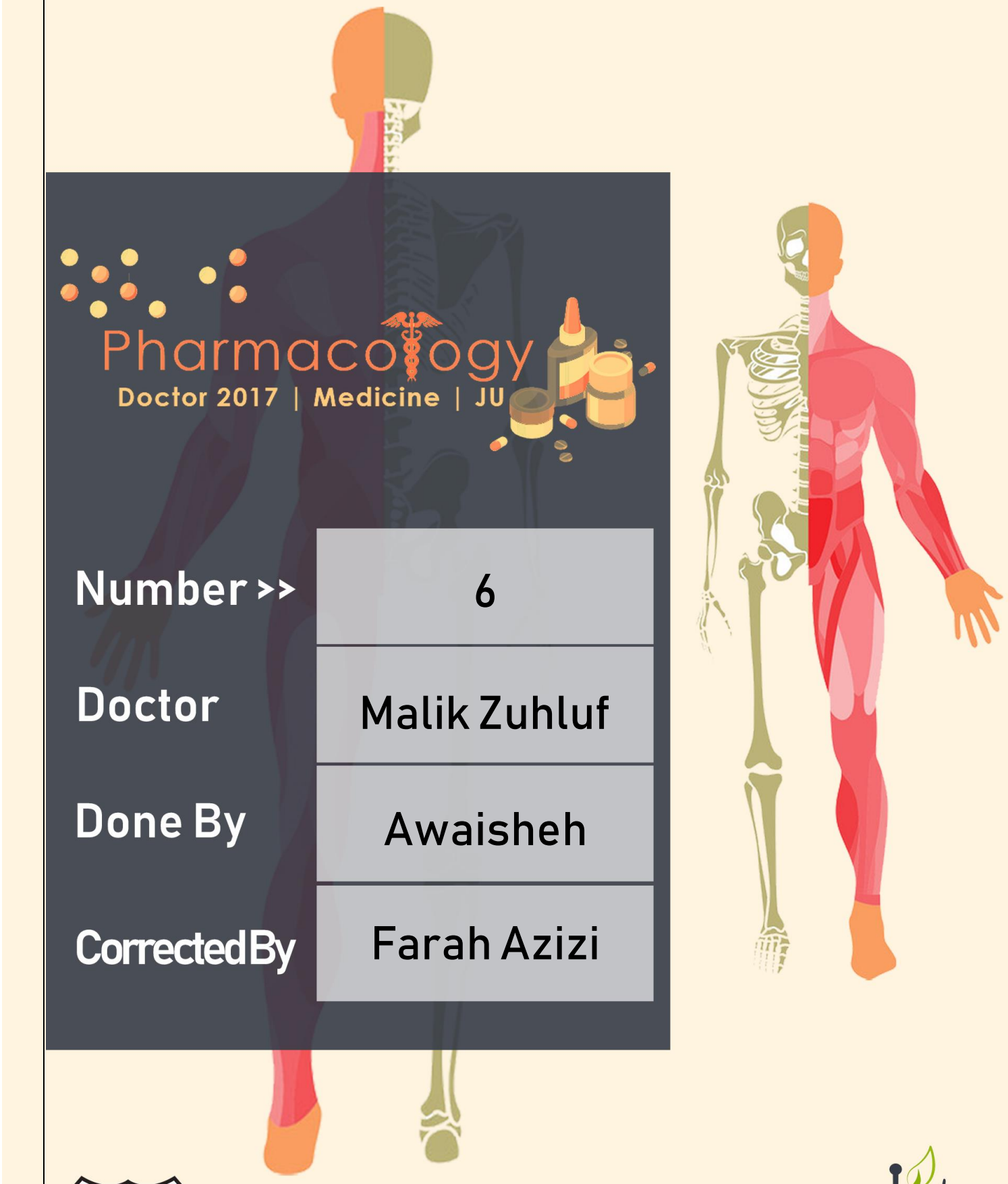

Pharmacology

Doctor 2017 | Medicine | JU

Number >>	6
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1st system - MSS

Muscle Relaxants

Before we start, please quickly recall how nervous signals in the ANS are transmitted, and the role of ACh in signal transmission. The process where signals are sent from the CNS to muscles in the somatic nervous system is very similar, with only a few obvious differences (underlined and blue in the text underlying the role of ACh in muscle activation below):

- Acetylcholine is released from motor neurons in discrete quanta (meaning there is a whole no. of molecules, there is no part of an ACh molecule like $^1/_2$).
- Causes "all-or-none" rapid opening of Na+/K+ channels (duration 1 ms).
- Development of miniature end-plate potentials (mEPP) in the Motor End Plate.
- Generate muscle action potential resulting in muscle contraction.
- ACh is rapidly hydrolyzed by AChE; **no rebinding to the receptor occurs unless an AChE inhibitor is present (**ex. *neostigmine*/*physostigmine*/organophosphates**)**.
- There are no ganglia in the somatic system.

Now that we have refreshed our memories, there are two types of muscle relaxants:

1. Neuro Muscular Junction (NMJ) Blockers.
2. Directly acting muscle relaxants: blockers of signals from the CNS directly.

We'll start with the NMJ blockers.

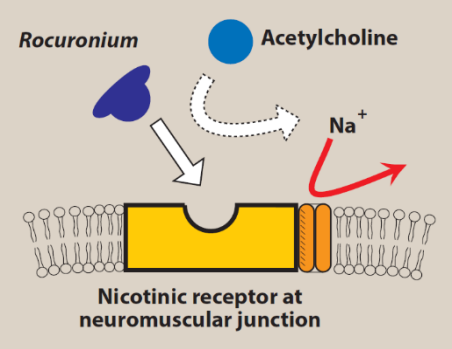
Neuro Muscular Junction Blockers: there are 2 types: *note that they don't enter the CNS*

a) Nondepolarizing (competitive) blockers: cause flaccid paralysis (patient is put under,).

The first drug known to block the skeletal NMJ was *curare*, which some hunters used to paralyze prey. The development of the drug *tubocurarine* (the first prototype) followed, but it has been replaced by other agents with fewer adverse effects (less histamine release, excessive release causes hypotension), such as *Pancuronium.*

The neuromuscular-blocking agents have significantly increased the safety of anaesthesia. Before MRs, only dangerously high doses of anaesthetic produce muscle relaxation, now we can use MRs for muscle relaxation while keeping anaesthetic agents at a low dose, allowing patients to recover quickly and completely after surgery. **The first muscles to be affected are the head & neck muscles, then limb muscles, and finally respiratory muscles; recovery occurs in reverse.** This is the reason why patients are not allowed to drink after general anesthesia as the neck muscles are the last to regain complete function → can lead to choking.

Mechanism of action: *it's pretty straightforward really…*



- At low doses: Nondepolarizing agents **competitively block ACh** (competitive antagonists) 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. Their competitive action can be overcome by administration of cholinesterase inhibitors (at low doses only), such as *neostigmine*, which increase the concentration of ACh in the NMJ.
- **At high doses:** Nondepolarizing agents can block the ion channels of the motor endplate, thereby taking away the ability of cholinesterase inhibitors to reverse the actions of the nondepolarizing blockers.

Classification of Neuromuscular Blockers According to Onset and Duration of Action

	Ultra-Short	Short	Intermediate	Long
	*Succinylcholine**	*Mivacurium*	*Vecuronium*	*Pancuronium*
	Rapacuronium		*Atracurium*	
			Cis-atracurium	
			Rocuronium	
Onset takes:	1 m	5 m	5-10 m	
Duration lasts:	10 m	20 m	30 m	45 m
**Succinylcholine is not a nondepolarizing NMJ blocker, it is depolarizing.*				

Therapeutic uses: We need drugs with different OOA/DOA to suit different medical situations where the patient's muscles will resist the procedure or in surgery to assist in anesthesia and inhibit unconscious reflexes. Ultra-shorts are used in procedures requiring a very short time like relocation of dislocated joints or in intubations. *Pancuronium* is used for long surgeries, it is also very important for surgeries around a lot of muscle like in the abdomen, it relaxes muscles that would otherwise be tense and interfere with the flow of the procedure, plus, it doesn't release histamine, a common side effect of nondepolarizing MRs.

CAUTION: Aminoglycosides and macrolide antibiotics increase the effects of nondepolarizing MRs so never give them to Myasthenia Gravis patients (thought to be because of their binding to nicotinic receptors rendering them dysfunctional).

Summary:

- General clinical uses to muscle relaxants
  - Provide muscle relaxation before major surgeries (help lower the dose of general anesthetic).
  - Provide muscle relaxation before intubation.
  - Prevent fractures and bone dislocation during electroconvulsive therapy.
  - Reduces or controls spasms/tetanus.
- Side effects and drug-drug interactions:
  - ↑ histamine release by mast cells → ↓BP, skin rashes, & bronchospasm.
  - Partial block to sympathetic ganglia (remember they're nicotinic)→ ↓BP.
  - Aminoglycosides and macrolides amplify their effects.
- Most widely used nondepolarizing muscle relaxants:
  - *Pancuronium*: more potent than *curare*, does not release histamine; does not block sympathetic ganglia and has longer OOA & DOA.
  - *Vecuronium*: similar to *Pancuronium*.
  - *Rapacuronium*: Has rapid OOA (1.5 min) and short DOA (20 min), good for short procedures, but releases histamine. The most recent agent of them.

b) Depolarizing agents: (patient can stay awake)

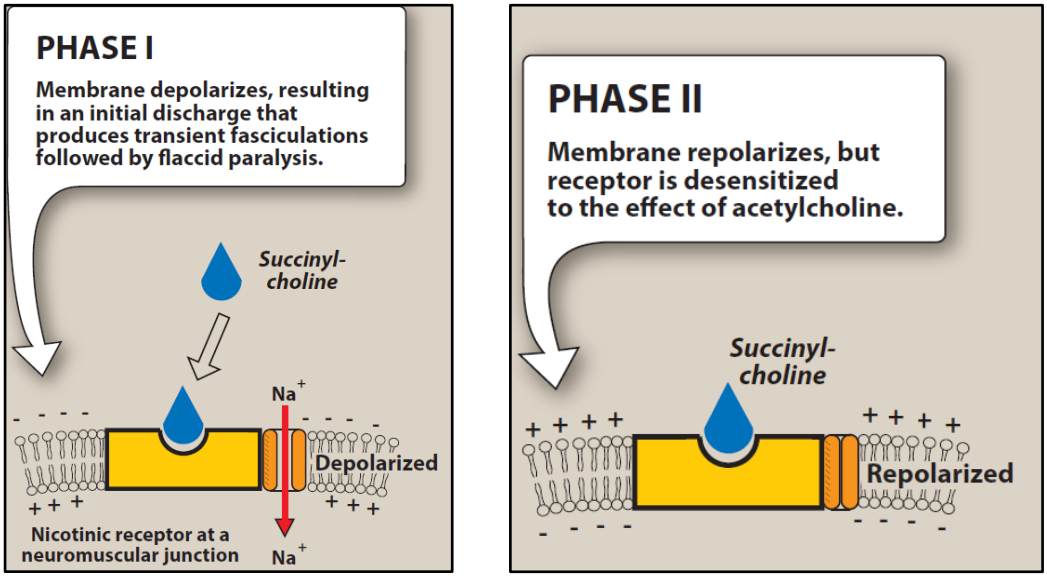
Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fibre, similar to the action of ACh (strong **agonists**). However, these agents are harder to break down by AChE and can thus depolarize the muscle fibres for a longer time. *Succinylcholine* (*Suxamethonium*) is the only depolarizing muscle relaxant in use today; it stays bound to the receptor for 5 mins.

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, *Succinylcholine* remains attached to the receptor for a longer time and provides constant stimulation of the receptor.

The process has **two phases**:

- Phase I or Depolarization block: The depolarizing agent first causes the opening of the sodium channel associated with the ACh receptors, which results in depolarization of the receptor. Since *Succinylcholine* isn't broken by AChE, this leads to a twitching of the muscle (fasciculations). Maintained depolarization leads to Na^+ channel inactivation (they are still open but are inactive) and hence an action potential cannot be generated.

- Phase II or desensitization block: With time, continuous depolarization becomes weaker, and repolarization is restored. Na^+ channels become active again, and membrane excitability is restored.
  But an action potential still cannot be generated due to desensitization of the ACh receptors by *Succinylcholine* (which is not metabolized like ACh, so it continues to occupy the ACh receptors to "desensitize" the end-plate). This causes a resistance to depolarization and **flaccid paralysis**.



Note: Even when the five minutes are over, *Succinylcholine* binds again because of its high concentration in the synaptic cleft (remember this high conc. is due to AChE being unable to hydrolyze it.

The effect is controlled by *neostigmine* (*Physostigmine* isn't used because it enters the CNS).

Normally, the duration of action of *Succinylcholine* is extremely short, due to rapid hydrolysis by plasma *pseudo*cholinesterase (therefore is not in NMJ only plasma). However, redistribution of *Succinylcholine* to plasma is necessary for metabolism (therapeutic benefits last only for about 10 mins).

Therapeutic uses: Because of its rapid onset of action, *Succinylcholine* is useful when rapid endotracheal intubation is required during the induction of anaesthesia. It is also used during electroconvulsive shock treatment.
Why isn't Rapacuronium used instead? Because *Succinylcholine* releases less histamine.

Properties of *Succinylcholine*:

- It is two acetylcholine molecules linked end-to-end.
- IV administration, good for minor procedures because it has a short DOA.
- Metabolized by plasma *pseudo*cholinesterase.
- It has no effects on autonomic ganglia or on muscarinic receptors.
- Does not enter the CNS.
- Releases histamine (but less than *Rapacuronium*).

Side effects:

- **Prolonged apnea** (no breathing): occurs in patients with a polymorphism in their *pseudo*cholinesterase that leads to a reduced concentration or an atypical form of the enzyme, so the drug stays in circulation until it heavily affects the respiratory muscles; patient has to be put on ventilator. Occurs in 1 out of 200 patients.
- **Malignant hyperthermia:** also due to a polymorphism, but in a gene responsible for handling Ca^{+2} in muscle contraction $\rightarrow \uparrow$ conc of Ca^{+2} in the sarcoplasm $\rightarrow \uparrow$ consumption of ATP $\rightarrow \uparrow$ heat production. The increase in temperature can even reach a rate of $+1^{o}C$ per 5 mins! This effect can be fatal in a very short time! Occurs in 1 out of 300 patients.
  Controlled by *dantrolene* (discussed below).
- Hyperkalemia $\rightarrow$ **cardiac arrhythmias**.
  Caused by the long duration of depolarization which allows a lot of K^{+} to leave the cell into the ECF.
- Fasciculation leads to **postoperative pain**.
- Increased intraocular pressure due to contraction of extra ocular muscles.

Directly Acting Muscle Relaxants (spasmolytics):

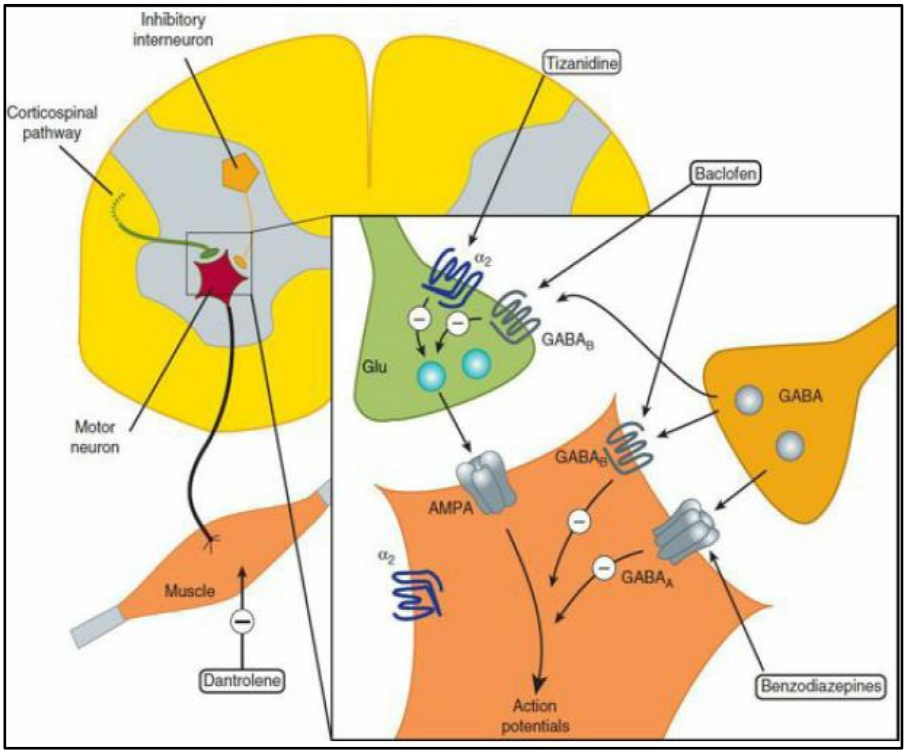
Instead of acting on the NMJ, these drugs **act on the body of the motor neuron in the CNS**. The body of the neuron is supplied by both excitatory and inhibitory neurons, where the excitatory axons release NE and glutamate to excite the motor neuron while the inhibitory axons release GABA. These drugs either work by $\downarrow$ the activity of the excitatory synapses or $\uparrow$ the activity of the inhibitory synapses.

- NE/Glutamate receptors $\rightarrow$ induce the **influx** of Na^{+} to **excite** the neuron.
- $GABA_A$ receptors $\rightarrow$ induces the **influx** of Cl^{-} to **inhibit** the neuron.
- $GABA_B$ receptors $\rightarrow$ induces the **efflux** of K^{+} to **inhibit** the neuron.

This family of drugs are used to deal with spasticity, which is characterized by an increase in basal muscle tone, meaning higher excitability, which to leads to prolonged muscle spasms and muscle weakness. It is often associated with neurological CNS problems such as:

- Spinal injury: where inhibitory neurons are severed → easier excitability → ↑contraction,
- Cerebral palsy,
- Multiple sclerosis,
- and stroke.

1. *Diazepam* (*Valium*): is not really used as a muscle relaxant, because doses required to produce muscle relaxation cannot be reached without causing sedative effects, so it is usually used as an anti-anxiety agent. Only higher doses relief muscle spasms. **Acts at $GABA_A$ receptors in the CNS**.



2. *Baclofen*: orally effective and is the **drug of choice for treating spinal spasticity** and spasticity of multiple sclerosis. **Acts as an agonist at $GABA_B$ receptors**. Activation of these receptors by baclofen results in **<u>hyperpolarization</u>** of the motor neuron body by two distinct actions:
    a) Closure of presynaptic calcium channels.
    b) Postsynaptic K+ efflux.

Baclofen is as effective as diazepam in reducing spasticity and **causes less sedation** (but can cause drowsiness). In addition, baclofen does not reduce overall muscle strength as much as *dantrolene* (will be discussed below) and that is why it is the drug of choice to relieve muscle spasticity.

3. *Tizanidine*: acts as an **agonist on excitatory presynaptic α_2 receptors**, whose activity is inhibiting the release of the excitatory molecules NE and glutamate, therefore it **results in presynaptic inhibition of the motor neuron**.
   It is similar in its mechanism of action to a drug we took in the ANS, *clonidine*. But unlike *clonidine*, *Tizanidine* has approximately $^1/_{10}^{th}$ to $^1/_{15}^{th}$ of the hypotensive effects. *Tizanidine* is:
   - Effective in treating spasms, cramping, and tightness of muscles caused by multiple sclerosis.
   - Given orally.
   - Prescribed for **migraines**, as a sleeping aid, and as an anticonvulsant.
   - **Side Effects**: Low levels of drowsiness (because it ↓ the release of NE which is needed for alertness), hypotension, and dry mouth.
4. *Dantrolene*: is **drug of choice to treat malignant hyperthermia** (mentioned above as a side effect of *Succinylcholine*), because it reduces the release of Ca^{+2} from the SR by acting on the ryanodine receptors in the SR(in cardiac and skeletal muscles); and thus, also blocks contraction. Can be given orally but must be given IV in malignant hyperthermia because it is a medical emergency.
   Uses:
   - Cerebral palsy; reduces spasticity.
   - Multiple sclerosis; reduces spasticity.
   - **Malignant hyperthermia**.

   Side Effects: Muscle weakness, sedation, rare hepatitis.

5. Centrally acting muscle relaxants: have little muscle relaxant activity, they deactivate the motor neuron by an unknown mechanism. They have mild sedative & antianxiety properties and are combined with other analgesics (e.g. Aspirin) and with caffeine. They have no advantage over analgesic anti-inflammatory agents. They are a group of about 10 drugs that as the Dr. said are not commonly used because they're very ineffective, here are a few of them:
   a) *Carisoprodol*: the oldest and least effective of the group:
      - Blocks pain sensations between the nerves and the brain.
      - Depresses spinal polysynaptic reflexes.
      - Effective in muscle spasm associated with injuries.

   b) *Orphenadrine*: myogesic/norgesic (relieves muscle pain) and is combined with either paracetamol or aspirin.

   Side Effects: sedation and confusion**.**

Good luck ☺

Don't forget the 7th lecture online…