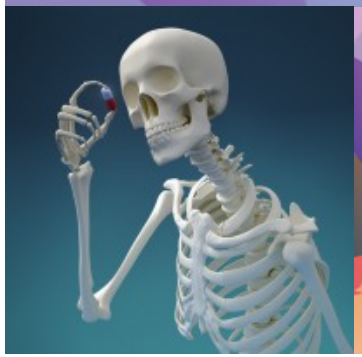
PHARMACOLOGY
433

King Saud University
College of Medicine
1st Year, 2nd Block

Muscle Relaxants 1



Musculoskeletal Block

KEY WORDS

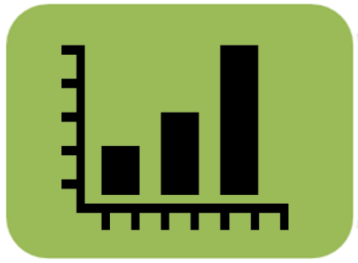
*Direct acting
*Peripherally acting
*Centrally acting
*Non depolarizing
*Depolarizing
*Malignant hyperthermia

Abbreviations :

NMBs = neuromuscular blockers
NMJ= neuromuscular junction
S.C = spinal cord
NE= Norepinephrine
Cvs= Cardiovascular system
SA= sinoatrial
H.R= heart rate
SK muscle: skeletal muscles
BBB=blood brain barrier.

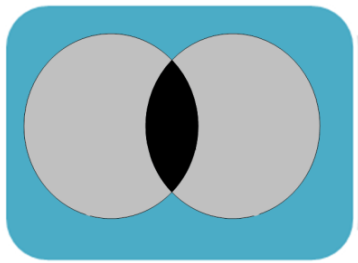
OBJECTIVES

Identify classification of skeletal muscle relaxants

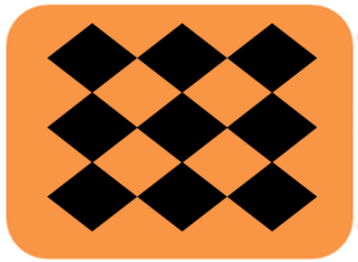


Describe the pharmacokinetics & dynamics of neuromuscular relaxants

Recognize the clinical applications for neuromuscular blockers

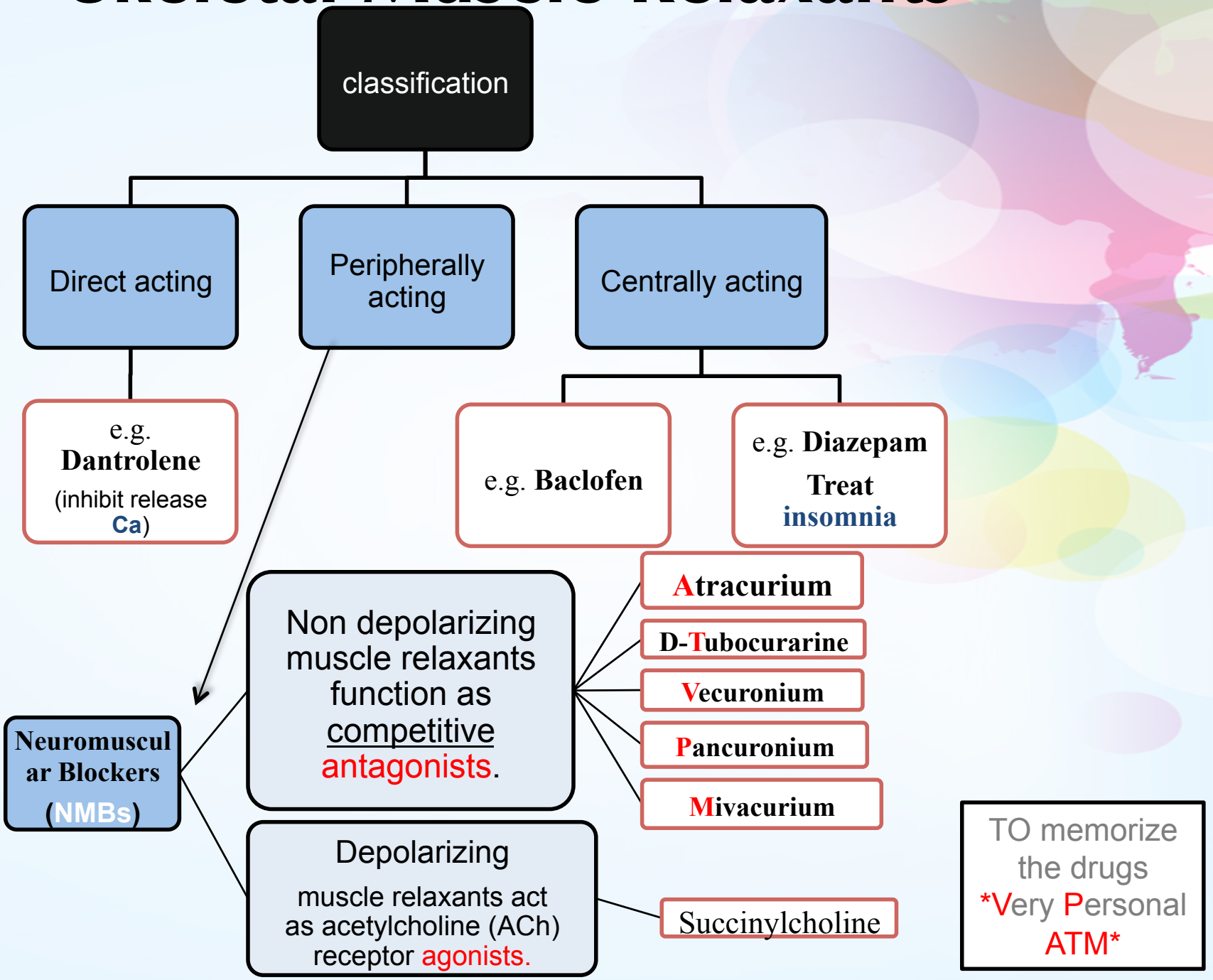


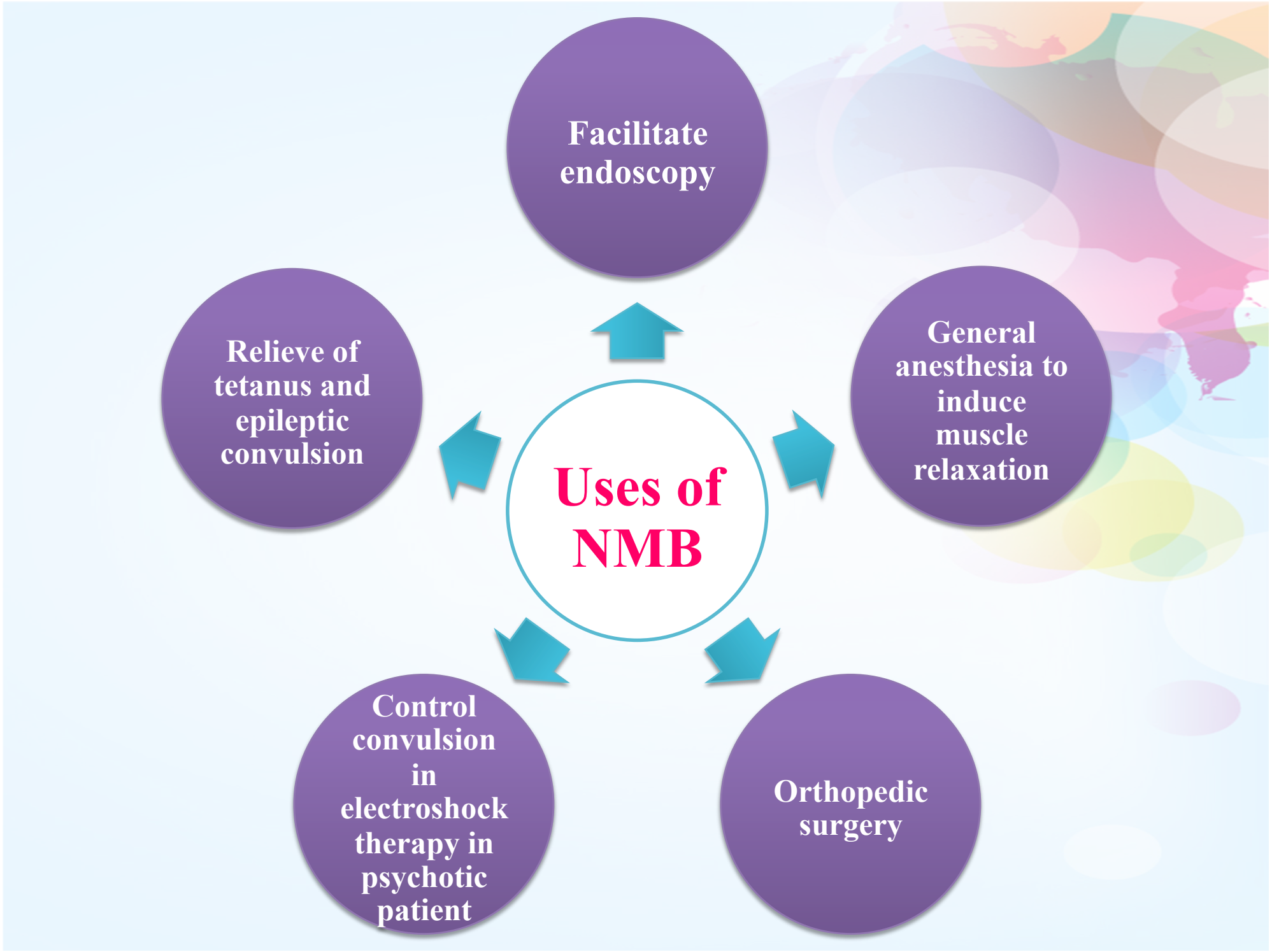
Know the different types of spasmolytics



Describe the pharmacokinetics and dynamics of spasmolytic drugs

Skeletal Muscle Relaxants




Uses of NMB
Facilitate endoscopy
General anesthesia to induce muscle relaxation
Orthopedic surgery
Control convulsion in electroshock therapy in psychotic patient
Relieve of tetanus and epileptic convulsion

Competitive NM blockers

Mechanism of Action:

*Are competitive antagonists for Ach at the nicotinic receptors present in postjunctional membrane of motor end plate.
*No depolarization of postjunctional membrane.
*Cholinesterase inhibitors can reverse blockade (Neostigmine).
*acetycholinesterase inhibitors increase the Ach level in NMJ and displace noncompetitive blockers from nicotinic receptors in NMJ.

Pharmacokinetics:

*They are polar compounds inactive orally & taken parenterally.
*Do not cross placenta, BBB & CNS.
*Elimination depend upon kidney or liver,
Except:
-Mivacurium (degraded by acetylcholinesterase enzyme).
-Atracurium (spontaneous degradation).

Pharmacological actions:

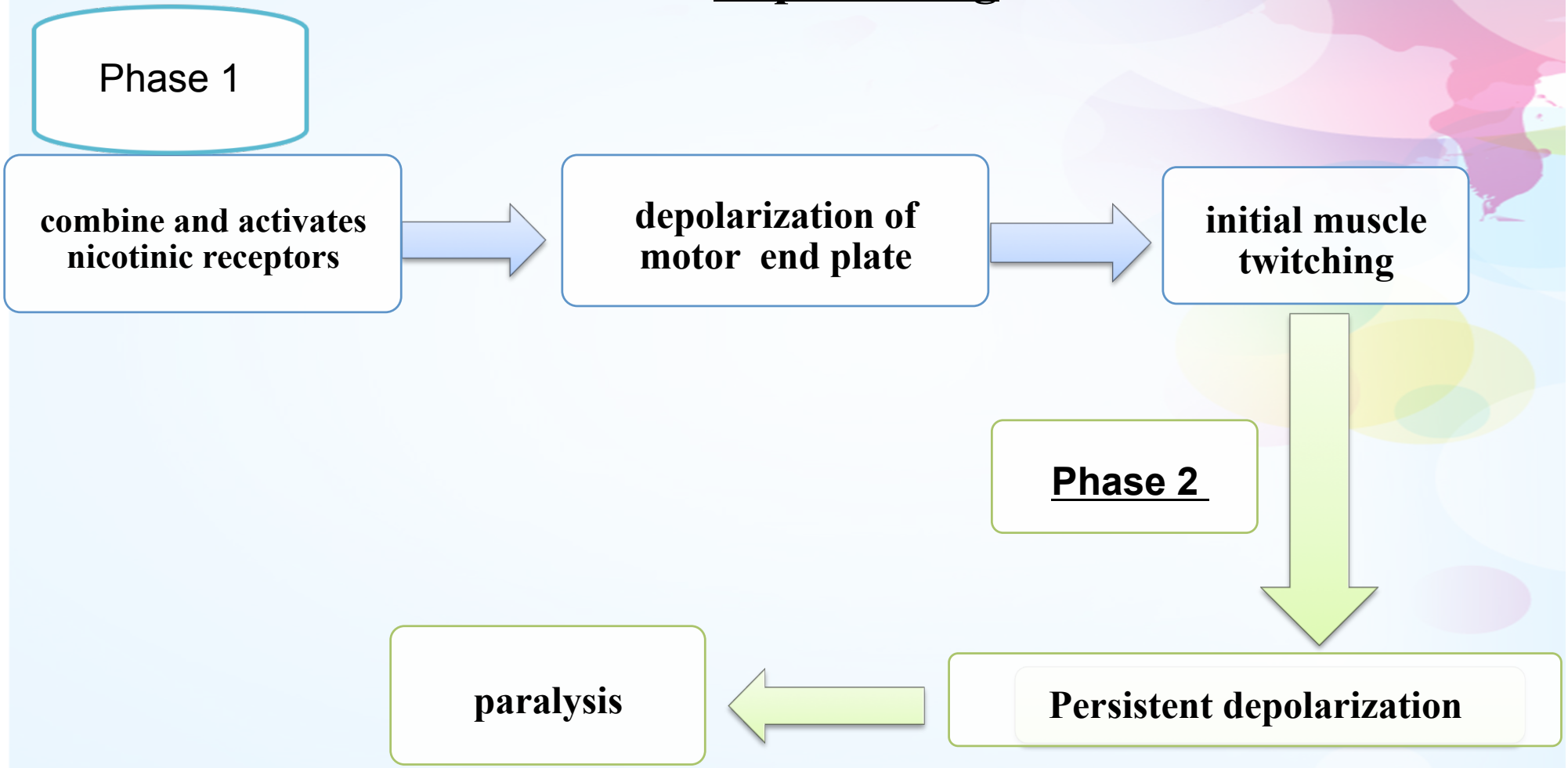
*Skeletal muscle relaxation.
*They produce different effects on CVS.
*Some release histamine and produce hypotension.
-d.Tubocurarine (not used clinically)
-Atracurium
-Mivacurium
*Others produce tachycardia (↑ H.R)
-Pancuronium

	d – Tubocurarine	Atracurium	Mivacurium
Duration	**Long 1-2 h**	**Intermediate 30 min**	**Short 15 min**
Side effects	*Histamine release (Bronchospasm, hypotension) *Blocks autonomic ganglia(nicotinic receptors) (Hypotension) *Tachycardia.	*Liberate histamine (Transient hypotension), Bronchospasm (less than D-tubocurarine) Should be avoided in asthma patient	It releases histamine. similar to atracurium
Notes	*Prototype skeletal muscle relaxant (the first discovered & used clinically). *Not used anymore due to adverse effects. *Eliminated by kidney 60% - liver 40%.	*As potent as curare (1.5). *Eliminated by non enzymatic chemical degradation in plasma (spontaneous hydrolysis at body pH). *used in liver failure & kidney failure (drug of choice). *Giving anti-histamine before it may prevent its side effects. *No effect on muscarinic receptor (ACH receptors found in blood vessels, heart, GIT and eye) nor ganglia.	*Chemically related to atracurium *Fast onset of action *Metabolized by pseudo cholinesterases. *Shortest duration of action of all the nondepolarzing drugs *Longer duration in patient with liver disease or genetic cholinesterase deficiency. *Mivacuriuam induced prolonged muscle paralysis can be reversed by acetycholinesterase inhibitors such as endrophonium. *acetycholinesterase inhibitors increase the Ach level in NMJ and displace Mivacuriam from nicotinic receptors in NMJ.

	Pancuronium	Vecuronium
Duration	**Long 1-2 h**	**Intermediate 40 min**
Side effects	*Tachycardia Caused by: *Anti-muscarinic action (atropine like effects) *Blocks muscarinic receptor in SA node. *↑ NE release from adrenergic nerve endings.	Has few side effects. *No histamine release. *No tachycardia. *No ganglion block. *No antimuscarinic action.
Notes	*More potent than curare (6 times). *80 % metabolized in liver and excretion is renal. *metabolic products have some neuromuscular blocking activities. *should be avoided in a patient with coronary disease	*More potent than tubocurarine (6 times). *Metabolized mainly by liver. *Excretion mainly in bile.

Depolarizing Neuromuscular Blockers

Mechanism **of <u>Depolarizing</u>** action



Phase II clinically resembles non-depolarizing muscle relaxants .

Succinylcholine (suxamethonium)

Pharmacological Actions (due to depolarization of muscle)

SK. muscle	Hyperkalemia (due to sk muscle contraction)	Eye	GIT	CVS
fasciculation → spastic paralysis	Cardiac arrest	↑ intraocular pressure (depolarization and contraction of extraocular muscle).	↑ intragastric pressure → regurgitation of gastric content to esophagus. Difficulty in opening mouth.	arrhythmia

Pharmacokinetics:

*Short onset of action (1 min.).
*Short duration of action (5-10 min.).
*Destroyed by pseudocholinesterase
*Half life is prolonged in:
- -Neonates.
- -Elderly.
- -Pseudcholinesterase deficiency.

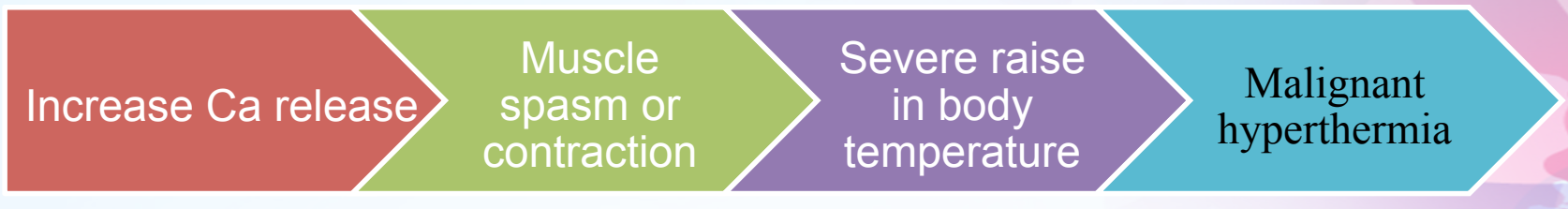
Side Effects:

*Hyperkalemia.
*CVS arrhythmia.
*↑ IOP (not used in case of glaucoma).
*Can produce malignant hyperthermia.
*May cause succinylcholine apnea due to deficiency of pseudocholinesterase by:
- -liver disease.
- -Malnutrition.
- -Organophosphorous poisoning (acetylcholinesterase inhibition).

Malignant hyperthermia

Inability to bind calcium by sarcoplasmic reticulum in some patients due to genetic defect .

*Sensitive to some drugs such as general anesthesia (e.g. halothane) and NMBs (e.g. suxamethonium)



Spasmolytics
(reduce muscle spasm in spastic state)

spastic state produce by:
S.C injury
Stroke
Cerebral Palsy الشلل الدماغي

- Centrally
  - e.g.**Baclofen** GABA agonist Act on S.C
  - e.g.**Diazepam** facilitate GABA action on CNS
- Direct
  - e.g.**Dantrolene** Treat malignant hyperthermia

Notes:
GABA = is neurotransmitter inhibitory in CNS or hyperpolarizing help in muscle relaxation, it works centrally
Ca stored and release from sarcoplasmic reticulum

Dantrolene

Mechanism of action:

- Interferes with the release of calcium from from its stores in skeletal muscles
- It inhibits excitation-contraction coupling in the muscle fiber by block the opening of calcium channel (**Ryanodine receptor (RyR) channel)**

باختصار هو يغلق بوابات الكالسيوم ليمنع حدوث contractions

Uses: Spastic state, malignant hyperthermia, given IV and orally, **(t ½ = 8 - 9 hrs).**

Contraindications of muscle relaxants

myasthenia gravis, Kidney failure & Liver failure: in this diseases there is muscle weakness and Ach is compromised so we never use muscle relaxant.

Parkinsonasim: increasing in muscle rigidity ,using of muscle relaxant has no indication and depolarizing muscle relaxants may worse the condition so we *use **anti-cholinergic drugs**

Drugs and diseases that modify NM blockers effects

- Aminoglycosides antibiotics (e.g streptomycin, gentamycin) enhances the effects of NM blockers.
- General anesthetics
- Cholinesterase inhibitors may enhance the effect of depolarizing relaxants but decrease the effect of nondepolarzing relaxants.
- Magnesium sulphate** may antagonize the effect of muscle relaxants.
- anticonvulsant
- Disease states such as mysthania gravis and parkinson modify the response to muscle relaxants.

anticholinergic drugs

هي الأدوية اللي تسوي بلوك لعمل الاسيتيل كولين،

contraction المغنيسيوم يساعد في عملية ال

Summary

Skeletal muscle relaxants

Acting Neuromuscular blockers:
Peripherally: e.g.
(competitive) ATM, Pancuronium, Vecuronium.
(depolarizing) Succinylcholine .

Acting skeletal muscle relaxants:
Centrally: e.g. Baclofen - Diazepam
Direct: e.g. Dantrolene

- Spasmolytics (reduce muscle spasm)
- Dantrolene (treatment of malignant hyperthermia)
- Streptomycin enhances the effects of NM blockers.
- Cholinesterase inhibitors: ↑ effect of depolarizing relaxants , ↓Non-depolarizing relaxants.
- Mysthania gravis and parkinson diseases that modify the response to muscle relaxants.

NM Blockers	Competitive (non-depolarizing)	Depolarizing
Example	ATM 1) Atracurium 2)d.Tubocurarine 3)Mivacurium 4)Pancuronium 5)Vecuronium	Succinylcholine
Pharmaco -kinetics	➢Polar ➢taken parenterally. ➢Not cross CNS. Elimination: kidney or liver. Exept Mivacurium, Atracurium.	➢Short action & duration. ➢Half live prolonged: •Neonates, Elderly.
Action	Skeletal Muscle Relaxation	Skeletal Muscle fasciculation → spastic paralysis
S/E	▪Effect CVS. ▪ATM release histamine → Hypotension. ▪Pancuronium → Tachycardia	▪Hyperkalemia ▪CVS arrhythmia ▪malignant hyperthermia ▪succinylcholine apnea

M.C.Q.s

1- competitive NM blockers are antagonist for Ach at :

A-Nicotinic receptors.
B-Muscarinic receptors.
C-Insulin receptors.
D-Cytokine receptors.

2- which of the following NM blockers more safe :

A- d.tubocurarine.
B- Atracurium.
C- Pancuronium.
D- Vecuronium.

3- which of the following NM blockers, can't be used for patient with coronary disease :
A- Pancuronium.
B- Atracurium.
C- Vecuronium.
D- d.tubocurarine.

4- All the following NM blockers, depend upon kidney or liver in elimination EXCEPT :

A- d.tubocurarine.
B- Atracurium.
C-Pancuronium.
D- Vecuronium.

5- Drug that cause bronchospasm for asthma patient :

A- Atracurium.
B- Pancuronium.
C- Vencuronium.
D- A and B

1- A 2- D
3- A 4- B
5- A

M.C.Q.s

6- Drug that cause hyperkalemia , CVS arrhythmia and glaucoma :

A- Baclofen
B- Succinylcholine
C- Diazepam
D- Dantrolene

7- Someone has a …… the doctors never give him a muscle relaxants drugs:

A- Myasthenia gravis
B- Malignant hyperthermia
C- Parkinsonasim
D- A and C

8- Which of the following drug used for treatment malignant hyperthermia :

A- Dantrolene
B- Succinylcholine
C- Diazepam
D- Baclofen

9- Drug has direct action on skeletal muscles :

A- Baclofen
B- Dantrolene
C- Diazepam
D- A and C

8- A	9- B
6- B	7- D

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We hope that we made this lecture easier for you

Good Luck !