Pharmacology team 436

MEDICINE 436 KING SAUD UNIVERSITY

Skeletal muscle relaxants

Objectives:

- Identify classification of skeletal muscle relaxants.
- Describe the pharmacokinetics and dynamics of neuromuscular relaxants.
- Recognize the clinical application for neuromuscular blockers
- Know the different types of spasmolytic.
- Describe the pharmacokinetics and dynamics of spasmolytic drugs.
- Recognize the clinical application for spasmolytic drugs.

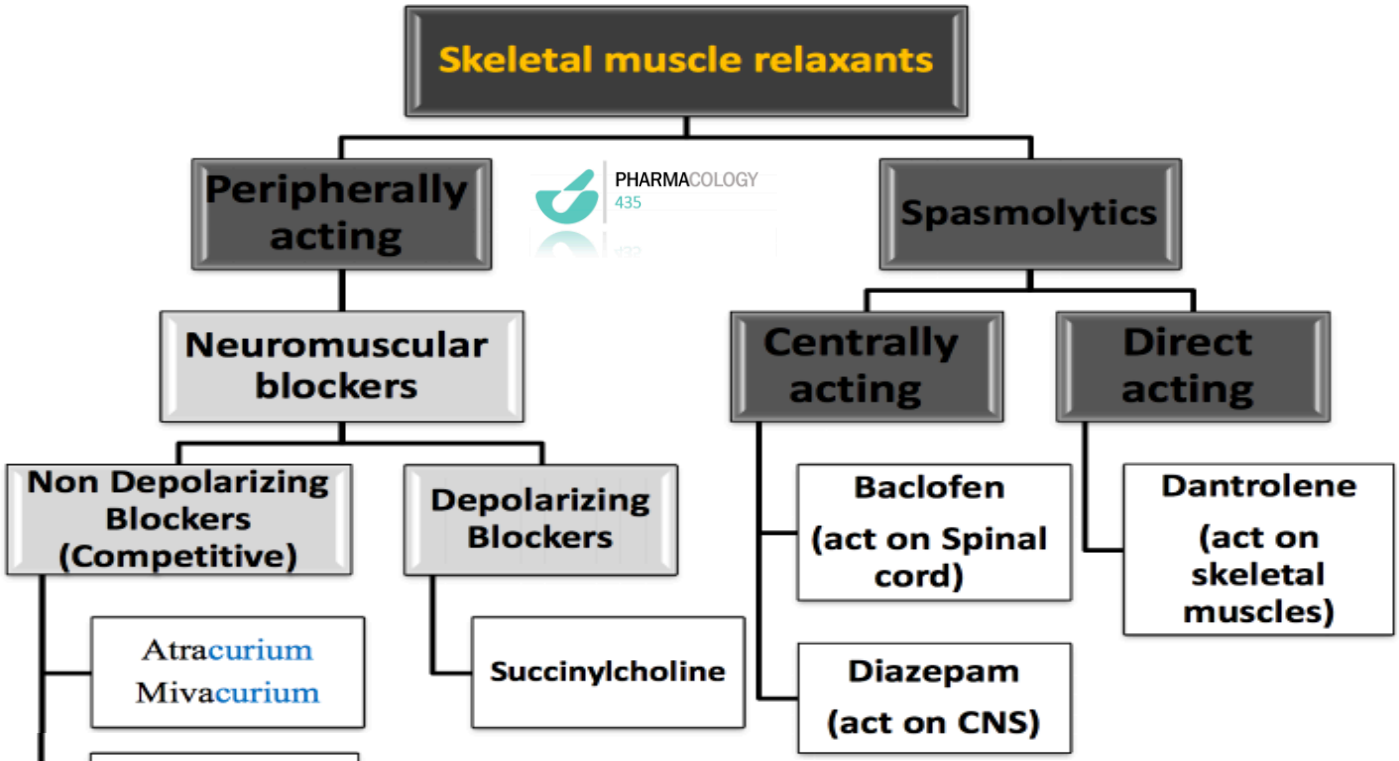
- We recommend you to study NEUROMUSCLAR JUNCTION Lecture in physiology.

"إجعلوا أحلامكم كحمام الحرم محرم قتلها."

- Titles
- Very important
- Extra information
- Terms

Skeletal muscle relaxants

- Are drugs used to induce skeletal muscle relaxation



Danatrolene

دا (Da) هوا (natrilene) اللي تدور عليه يله (Act dirctly) ايش تنتظر

Diazepam

نقسم اسم الدرق قسمين الأول (Diaze) يشبه كلمة dizzy والدوار يصير بالرأس معناته هالدواء يشتغل على (CNS) والقسم الثاني (zepam) يشبه spasm والتشنج له علاقة بالعضلات ,فلما نجمعهم مع بعض نتذكر ان هالدواء يشتغل على الجهاز العصبي المركزي ويعالج العضلات المتشنجة

Baclofen

البكله (Baclo) فين (fen) براسك يعني(CNS acting) وينها بالضبط طيب رابطة شعرك(Act on spinal cord) "تخيلوا المخ راسها والحبل الشوكي شعرها ف البكله وين؟ اكيد بالشعر يعني تشتغل على الحبل الشوكي"

Over all view

Peripherally acting skeletal muscle relaxants (Neuromuscular blockers):

They act by blocking neuromuscular junction or motor end plate leading to skeletal muscle relaxation.

1- Competitive neuromuscular blockers.

(Non-Depolarizing neuromuscular blockers)

2- Depolarizing neuromuscular blockers.

Long acting

1- **d-tubocurarine (prototype drug)**

2- Pancuronium

Intermediate acting

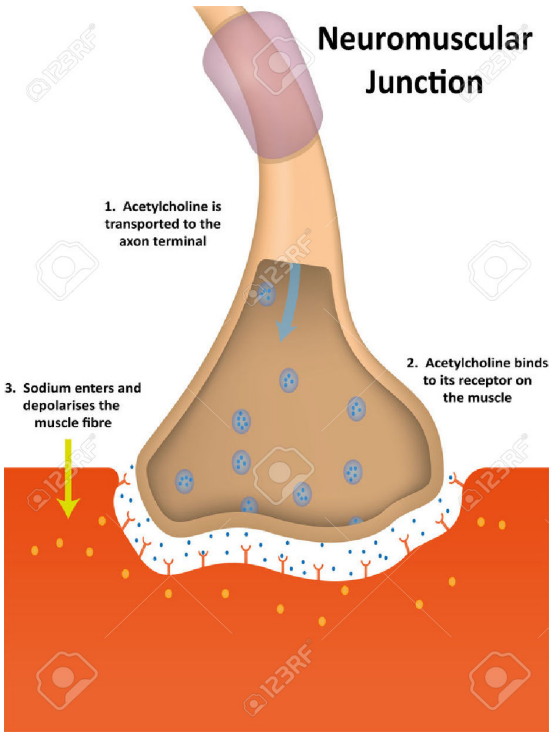
1- Atracurium

2- Vecuronium

Short acting

E.g. Mivacurium

Succinylcholine (suxamethonium)



Normally in the neuromuscular junction, the acetylcholine will attach with the acetyl choline receptors (in skeletal muscle the receptors are nicotinic receptors type 1 after that a lot of changes will happen and then the muscle will contract. The Neuromuscular blockers basically will block the nicotinic receptors so the acetyl choline can not bind with the receptors and produce its action (muscle contraction) and if the muscle will not contract it will relax ☺.

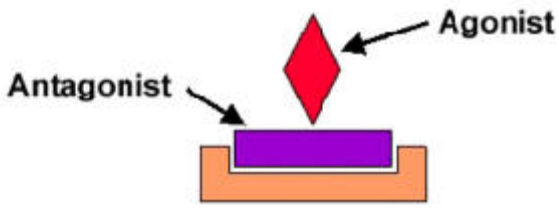
Mechanism of action:

- Compete with Ach for the nicotinic receptors present in post-junctional membrane of neuromuscular junction or motor end plate. (the competition will be regarding to the concentration, who has more concentration will bind with the receptors, so if the acetyl choline has more concentration it will bind with the receptors, if the drug has more concentration it will bind with the receptors and blocks them
- No depolarization of post-junctional membrane (non depolarizing). (they do not produce depolarization to relax the muscle, they just block the receptors)

❑ Because they are competitive drugs we call them *antagonist*.

The suffix of the competitive neuromuscular blockers:

curium or curonium (so whenever you see this suffix in any drug you immediately realize that this drug is competitive neuromuscular blocker)



Antagonists bind to receptors but do not lead to receptor activation

Classification of competitive neuromuscular blockers according to their duration of action:

Long acting

1- d-tubocuranine (prototype drug) not use clinically.

2- pancuronium

generally, the long acting drugs are metabolized and execrated by the kidneys.

توبه(Tubo) استخدم هال (curanine) مره ثانية مره يطول تأثيره بالجسم مع انه أصلي(prototype) بس خلاص اذة رض من السمة.

Interm ediate acting

1- atracurium

2- vecuronium

they are metabolized and execrated by the liver.

Short acting

1- mivacurium

Execrated by pseudo-cholinesterase enzyme in the blood.

جربت كريم (curium) نيفيا (miva) = nivea كذابين (pseudo-cholinesterase) مره موزين ما يطول بالجسم بسرعه يروح أثره (the shotest one)

Pharmacokinetics of competitive neuromuscular blockers:

- They are polar compounds. (Inactive orally & taken parentally)
- Inactive orally & taken parentally (they are polar so they have low distribution, so if I give them orally they will not distribute to the blood, so I give the drug IV to go to the blood immediately).
- Do not cross Blood Brain Barrier (BBB) (no central action). Because they are polar as mentioned before.
- Do not cross placenta. So no effect on the fetus.
- There Metabolism depends mainly upon kidneys and liver. So if there is a disease modifying the liver or the kidney you should give it carefully.

Except: Mivacurium (degraded by acetyl pseudo-cholinesterase).
Atracurium (spontaneous degradation in blood).

قطرة (Atra) وحده من الدم (in blood) على هال (curium) كافية انها تخليه يتحلل من نفسه

Atracurium	(Spontaneous degradation)

Pharmacological actions of competitive Neuromuscular blockers:

- Skeletal muscle relaxation. Wanted use
- They produce different effects on Cardiovascular system

which cause by:

- ❖ Some release histamine and produce hypotension. The meaning here is the competitive NMBs have the ability to release histamine from the mast cell, and as you now histamine will cause vasodilatation which will cause hypotension

The drugs can release histamine:

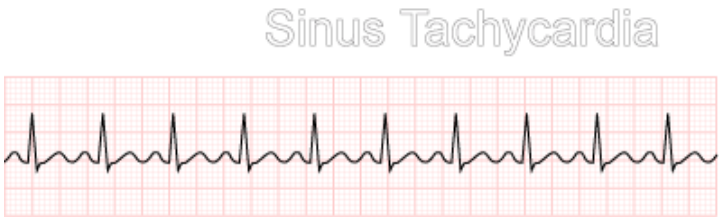
1. d-Tubocurarine*. (Strong histamine releaser).
2. Atracurium. (Intermediate histamine releaser).
3. Mivacurium. (Weak histamine releaser).

كيف اعرف ترتيبهم من هالناحية ، واحد يسأل رتبت اللي قلت لك ويرد الثاني تم (TAM)

- ❖ Others produce tachycardia (Heart Rate ↑) by the drug Pancuronium.

Pancuronium

كيف اربط ان هالدواء له علاقة بمعدل ضربات القلب ، بنك(Panc) الدم بالجسم هو القلب(increase heart rate).



يعني باختصار عندنا تأثيرين أساسيين لهذول الأدوية:
١- تأثير نبغاه اللي هو انبساط العضلات.
٢- تأثر ما نبغاه على الجهاز القلبي من خلال طريقتين:
-يا إنها تقلل الضغط عشانها تسبب إفراز هيستامين.
-أو إنها تزيد معدل ضربات القلب (على حسب الدوا اللي استعمله).

*Remember that d-tubocuurrarine is a prototype and not used clinically due to its side effects.

Drugs	d – Tubocurarine	Atracurium	Mivacurium	Pancuronium	Vecuronium
Duration of action	Long (1- 2 hours)	Intermediate (30 min)	The shortest (15 min) with Fast onset of action	Long (1-2 hours)	Intermediate (40 min.)
Metabolism and execration	Eliminated by kidney 60% - liver 40%.	Eliminated by non-enzymatic chemical degradation in plasma (spontaneous hydrolysis at body pH). So that, it's the Drug of choice in renal and kidney failure.	pseudo-cholinesterase It's enzyme in the blood which breaks down the Ach or any drugs like Ach or any other Easter	Excreted by the kidney (80 %).	Metabolized mainly by liver and excreted in bile.
Side effect	It is histamine releaser which leading to: Bronchospasm Hypotension Tachycardia Because of adverse effect , it is not used clinically but we use more safer derivatives	Liberate histamine (Transient hypotension). يعني هو يسبب إفراز الهيستامين بس بكمية قليلة و هالشي يعني فيه انخفاض ضغط لكن برضو مو انخافض كبير. also it may cause bronchospasm which is chemically related to the histamkne.	Transient hypotension (due to histamine release).	Hypertension, tachycardia (due to): ↑norepinephrine release from adrenergic nerve Endings. Anti-muscarinic action (block parasympathetic action).	few side effects : No histamine release. That's why it has low side effect. No tachycardia.
Contraindications (should be avoid in)	---------	asthmatic patients. Because they already have bronchospasm.	1- liver disease 2- Genetic cholinesterase deficiency 3- malnutrition (in any of this disease the duration of action will increase)	patient with coronary diseases	---------
Potency	A type of curare drugs.	As potent as curare.		6 times more potent than curare.	

More explanation for the information in the previous table:

- Atracurium is a drug injected inside the blood circulation and after 30 minutes it degrades by itself (without the involvement of any enzyme), it degrades because the ph of this drug differs from the ph of the blood which makes the drug unstable, which leads to drug degradation.
- ❖ So the we can use Atracurium in liver and kidney failure because it can be metabolized by itself.
- The liver disease can make the duration of action of Mivacurium longer, because the liver is responsible for the synthesis of the enzyme (pseudo-cholinesterase), which the mivacrurium metabolized by.
- Also malnutrition can cause longer duration because if there is no amino acid, which is the main source for protein synthesis while the enzyme is a form of proteins.
- The Pancuronium act by the stimulation of sympathetic nervous system by increase releasing of norepinephrine. By the same time the drug inhibit parasympathetic nervous system by blocking muscarinic receptors (parasympathetic receptors), however, sympathetic is stimulated which leads to hypertension and increasing of the heart rate while the parasympathetic is sleeping. So, no revers action.
- Anti-histamine pretreatment may prevent side effect that is related to histamine.

- ➢ Liver diseases will increase the duration of action of the drugs metabolized or excreted by the liver.
- ➢ As well as kidney diseases

Depolarizing Neuromuscular Blockers

Mechanism of action:

in post- junctional membrane of neuromuscular junction

Persistent depolarization leading to paralysis.
The muscle fibers will not repolarize, therefore the cell is not ready to bind with Ach.
They are agonist drugs

Example: Succinylcholine (suxamethonium)

	Action	Side effect	Contra-indications	Duration of action	Metabolism
Succinylcholine (suxamethonium)	Skeletal muscles: twitching relaxation	*Hyperkalemia which lead to Cardiac arrest. *CVS: arrhythmia. *Eye: ↑ intraocular pressure (due to contraction of extra-ocular muscle). *Produce malignant hyperthermia. *succinylcholine apnea due to deficiency of pseudo-cholinesterase. *GIT: increased intra-gastric pressure leads to regurgitation of gastric content to esophagus and difficulty in opening mouth. regurgitate: bring swallowed food up again to the mouth.	*Glaucoma *Patient with cardiac diseases.	Fast onset (1 min) with short duration of action (5-10 min). Half-life is prolonged in: 1. Neonates. 2. Elderly. 3. Pseudo-cholinesterase deficiency due to: A. *Liver disease. B. *Malnutrition. C. *Genetic cholinesterase deficiency.	Metabolized by pseudo-cholinesterase in plasma.

Malignant hyperthermia

Definition: the rare bizarre inherited condition of having a body temperature greatly above normal.

Occurs upon administration of drugs as:

- general anesthesia e.g. halothane
- neuromuscular blockers e.g. succinylcholine

Mechanism of the disease:

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

2- ↑ Ca release

3- intense muscle spasm

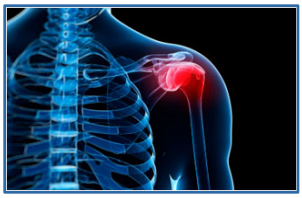
4- Hyperthermia

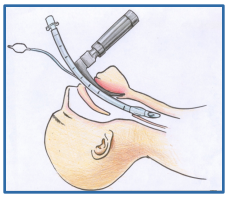
Treatment : Dantrolene

Uses of neuromuscular blockers

- control convulsion → electroshock therapy in psychotic patients (before we give electrical shock, we need to relax the muscle, so we use neuromuscular blockers. If we don't use NMB and give the electrical shock that may cause bone fracture)

- Relieve of tetanus and epileptic convulsion.
- As adjuvant in general anesthesia to induce muscle relaxation (surgeon use muscle relaxant with the anesthesia to relax the muscle so they can operate easily)
- Facilitate endotracheal intubation
- Orthopedic surgery.





Drugs and diseases that modify effects of neuromuscular blockers

- **Myasthenia gravis: increase** the response to muscle relaxants.
- **Drugs** as aminoglycosides* (e.g. strepto**mycin**).
- Magnesium sulphate. general anesthetics can potentiate or **enhance** the effect of neuromuscular blockers.

*Aminoglycosides
Are Group of antibiotics.

Spasmolytics

Reduce muscle spasm in spastic states

Centrally acting

Example: Baclofen

GABA (gama-amino butyric acid 'GABA')* agonist – acts on spinal cord.

Example: Diazepam (Benzodiazepines):

facilitate GABA* action on CNS

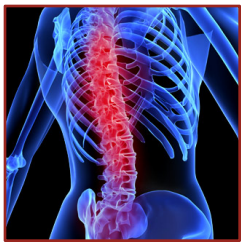
direct action on skeletal muscles

Example: Dantrolene

Uses of spamolytics:

They reduce muscle spasm in spastic static state produced by neurological disorders such as:

- spinal cord injury
- Cerebral stroke
- Cerebral palsy



*GABA: γ-Aminobutyric acid is the chief inhibitory neurotransmitter in the mammalian CNS. It plays the principal role in reducing neuronal excitability throughout the nervous system, thus reducing contraction.

Example of Spasmolytic:

	Mechanism of action	Rout of administration	uses
Dantrolene	1. It interferes with the release of calcium from its stores in skeletal muscles (sarcoplasmic reticulum). 2. It inhibits excitation-contraction coupling in the muscle fiber (Acts directly on skeletal muscles)	• Orally • IV (t $^{1}/_{2}$ = 8-9 hours)	For treatment of: • Spastic state • Malignant hyperthermia (actually the disease happen because of blocking of the Ca in the sarcoplasmic reticulum and dantrolene releases the Ca from sarcoplasmic reticulum)

		Drugs	Duration	Mechanism	Metabolism	Side effect
Peripherally acting (Neuromuscular blockers)	Competitive (non depolarized)	D-tubocurarine	Long (1-2 h)	Compete with **Ach** for the **nicotinic receptors** present in postjunctional membrane of neuromuscular junction or motor end plate ANTAGONIST	60% liver, 40% kidney	Bronchospasm Hypotension Tachycardia
		Atracurium	Intermediat (30 min)		spontaneous hydrolysis	Transient hypotension bronchospasm
		Mivacurium	The shortest (15 min)		by pseudo-cholinesterase (enzyme)	Transient hypotension
		Pancuronium	Long		By kidney	*Hypertension tachycardia * ↑ norepinephrine *Antimuscarinic action
		Vecuronium	Intermediate		Metabolized by liver and excreted in bile	A Few No histamine release. No tachycardia.
	Depolarizing	Succinylcholine (suxamethonium)	Short (5-10 min)	combine with nicotinic receptors → initial depolarization → muscle twitching → persistent depolarization → Skeletal muscle relaxation	by pseudo-cholinesterase in plasma	• Cardiac arrest • Arrhythmia • ↑ intraocular pressure • malignant hyperthermia • succinylcholine apnea
Spasmolytics	central	Baclofen	-	GABA inhibitor agonist on CNS	-	**Uses**
		Diazepam (Benzodiazepines)		facilitate GABA on CNS		reduce muscle spasm in spastic states
	Direct	Dantrolene	$t^{1}/_{2}$ $(half-life)$ = 8 - 9 h	1. interferes with the release of calcium from its stores in skeletal muscles 2. inhibits excitation-contraction coupling in the muscle fiber.	-	Treatment of: • Spastic states • Malignant hyperthermia

SAQ

42 pregnant women in her 11th week come with sudden hypotension. After taking her history, we found that one month ago she had suffered from muscular spasm and the doctor prescribed MIVACURINURN as relaxant drug.

Q1: What is the underlying cause for hypotension in this case ?

Mivacurinurn act as Histamine releaser, which leading to dilatation in the blood vessle and decrease the blood pressure (Hypotension).

Q2: Which classification of skeletal muscle relaxants this drug belong to ?

Peripherally acting → Competitive neuromuscular blockers

Q3:How is it metabolized and Where ?

Metabolized by pseudo-cholinesterase in plasma.

Q4: Is there any risk for her baby if she decide to continue taking this drug during her pregnancy and why/why not ?

No there is not, because it is polar drug so can not cross placenta.

Q5: Later, The investigations show that she had liver disease, Do we expect any change in the duration of action of this drug and why/why not ?

Yes, it will be longer, Because it is metabolized by pseudo-cholinesterase in plasma which is produce mainly by the liver so any disease in the liver , it will lead to decrease the concentration of this enzyme therefore the drug will not metabolized and has longer duration.

Q6: from previous question, list two drugs of choice in this case :

Atracurium / Vecuronium

SAQ

59 male has Glaucoma . 2 weeks ago, he had an abdominal surgery and during operation the surgeon used a relaxant drug. After 9 days, the same patient come again with live-threating condition which is known as malignant hyperthermia and also increasing in the Intraocular pressure. His past medical history includes no kidney or liver disease.

Q1: Which drug do you think was used in his surgery ?

May be Succinylcholine (suxamethonium).

Q2: Which classification of skeletal muscle relaxants this drug belong to ?

Peripherally acting → Depolarizing Neuromuscular Blockers

Q3:How is it metabolized and Where ?

Metabolized by pseudo-cholinesterase in plasma.

Q4: What is its mechanism ?

Combines with nicotinic receptors and activates depolarization of motor end plate
initial stimulation → initial muscle twitching → persistent depolarization → SKM relaxation

Q5: Is it act as Agonist or antagonist drug, and prove your answer :

Succinylcholine act as agonist drug, because it has affanty and prduce action (efficacy)

Q6:list two undesirable Pharmacological Actions of this drug other than increasing in the Intraocular pressure :

Hyperkalemia → Cardiac arrest. / CVS → arrhythmia.

Q7:list two contraindications of this drug other than patient with glaucoma :

Patient with CVS disease / Patient with liver disease

Q8:What is the malignant hyperthermia and its underlying mechanism ?

- It is a rare bizarre inherited condition of having a body temperature greatly above normal.
- Occurs upon administration of some drugs such as Succinylcholine.

ryanodine receptor

1. Inability to bind calcium by sarcoplasmic reticulum in some patients due to mutation of the (RYR1).
2. Opened RYR1 leads to increased intracellular Ca release which causes intense muscle spasm.
3. Severe rise in body temperature (hyperthermia)

Q9:Which drug of choice to treat malignant hyperthermia ?

Dantrolene

SAQ

Q1: simply explain the mechanism of action of Dantrolene:

Acts directly on skeletal muscles, as it interferes with the release of calcium from its stores in skeletal muscles.

Q2: mention a route to give the Dantrolene :

Orally
IV

Q3: Dantrolene could be used in the treatment of ?

Spastic states
Malignant hyperthermia

Q4: simply explain the mechanism of action of Spasmolytic:

They reduce muscle spasm in spastic states

Q5:spasmolytics could be used in reducing muscle spasm in spastic states produced by neurological disorders such as:

Spinal cord injury
Cerebral stroke
Cerebral palsy

QUIZ


Boys	Girls
عبدالرحمن ذكري	اللولو الصليهم
عبدالعزيز رضوان	روان سعد القحطاني
مؤيد أحمد	أثير الرشيد
فيصل العباد	سما الحربي
فارس النفيسة	نوره الشبيب
خالد العيسى	وتين الحمود
معاذ الفرحان	أمل القرني
عبدالرحمن الجريان	ابتسام المطيري
محمد خوجة	انوار العجمي
عمر التركستاني	رنا باراسين

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