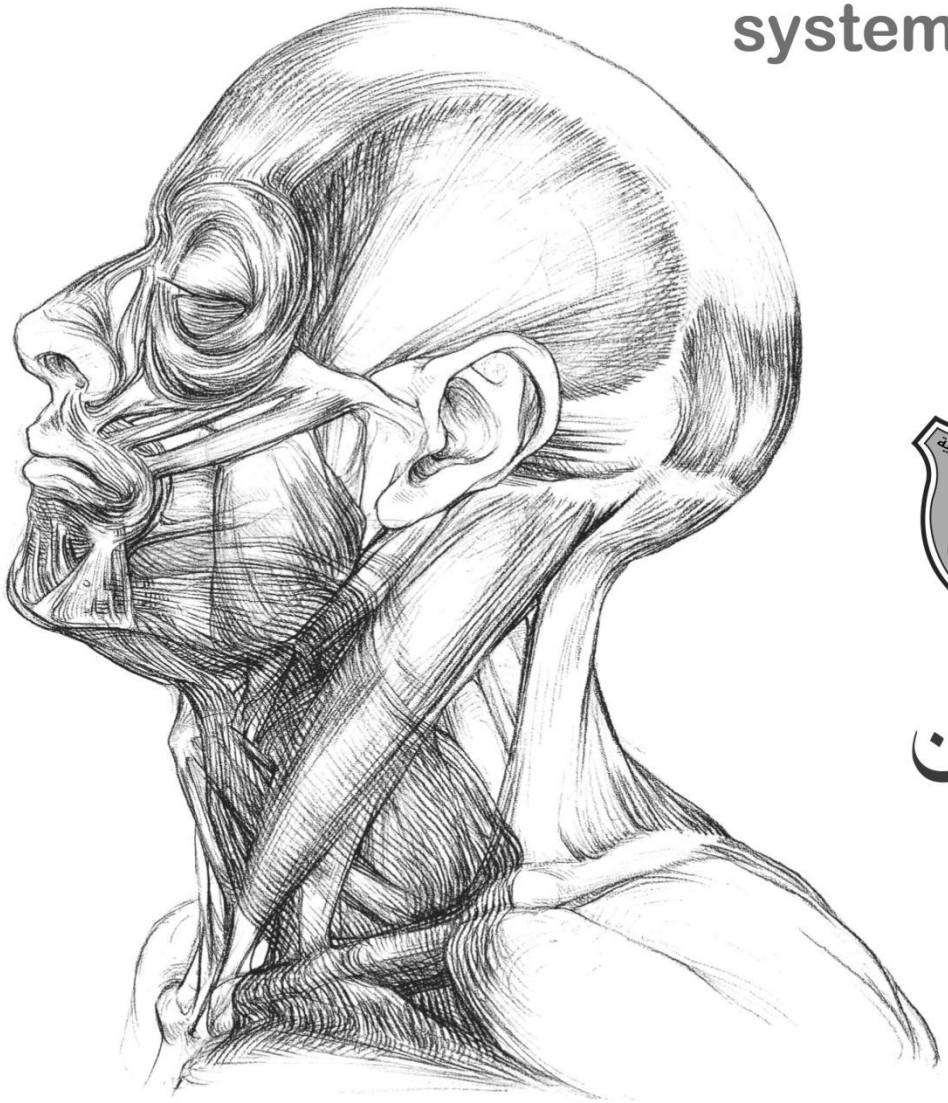
# The skin & Muscloskeletal system



# PHARMACOLOGY

SLIDES ☐
SHEET ■
LECTURE # 7

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يعطيكم العافية دفعة شفاء ^_^ ... اخر الشيت في ملخص عشان اي واحد مو ملحق يدرس عليه *-*

-Anything written in italic font was mentioned in the slides only

-Any point with 3 stars next to it was repeated a lot by the doctor ***

In the last lecture we talked about skeletal muscle relaxants , we talked about neuromuscular blockers which we use in general anaesthesia to relax muscles during surgical procedures , ease up during endotracheal intubtion and *maintain controlled ventilation.*

We can also use these drugs in certain conditions ( spasmic conditions ) :
(from this group some are centrally acting and some are peripherally acting , the majority are centrally acting )

- Generalized ( Chronic neurologic diseases ) like : Multiple Sclerosis
- Acute Injury : Spinal cord damage, muscle inflammation , muscles spasm because of excessive exercise or any traumatic injury to muscles.

**Goal of therapy: Reduce spasticity and pain, while retaining function*

## Spasmolytic Drugs

### 1-Diazepam ( Valium )

Acts on GABAa receptors in the CNS ( remember that GABA receptors are the inhibitory receptors in the brain ) , so there'll be a decrease in the tone for the fibers that supplies the muscles , so it decreases muscles spasticity, its *sedative* .

### 2- Baclofen

Acts on GABAb receptors, resulting in hyperpolarization and presynaptic inhibition through reducing calcium influx , so decreasing muscles spasticity *, can also reduce spasticity by inhibiting release of substance P in the spinal cord , it's less sedative but can cause drowsiness , can be given intrathecally , can reduce craving in alcoholics and migraine.*

### 3-Tizanidine

It is an α2-Adrenoceptor agonist ,causes presynaptic and postsynaptic inhibition of reflex motor output , similar to clonidine ,how ?

Remember that clonidine is an anti-hypertensive agent ( alpha1 receptors are found on blood vessels, binding to them causes vasoconstriction and elevation in blood pressure , it also works on alpha2 receptors presynaptically , binding to them causes negative feed back mechanism, so the neuron will not release Cathecolamines or NE centrally anymore , so it inhibits the activation of the sympathetic nervous systems so it <u>decreases the BP</u> ).

*alpha 1 receptors agonists increase BP ( cause hypertension )

*alpha 2 receptors agonists decrease the BP

That's why clonidine is used as anti-hypertensive agent but it can cause hypertension initially because there is no such thing as complete selectivity so it also has SOME affinity for alpha 1 receptors .

☆ Tizanidine causes relaxation of skeletal muscles but how ? It mainly inhibits certain impulses in the brain ( we don't know them :/ ) leading to skeletal muscle relaxation.

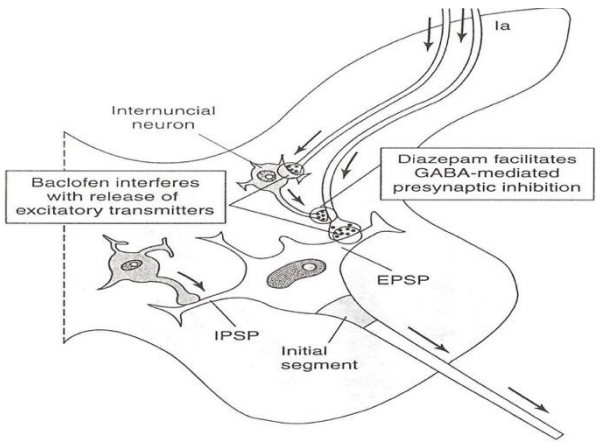
☆ Side effects / toxicities :

- Sedation; as it acts on the CNS
- Hypotension ; as it's related to alpha 2 receptors, so you should be careful about giving it to patients who have history of orthostatic hypotension (also known as postural hypotension : patients tend to have low BP and get dizzy when they wake up or change posture )
- Weakness

*Indications : spasm due to multiple sclerosis , stroke , amyotrophic lateral sclerosis*

*Pharmakokinetics : renal and hepatic elimination , duration 3-6 h .*

**<u>4- Gabapentin</u>** : antiepileptic *Glycine* ,we will talk about it in CNS , we use it when we have muscle pain that doesn't respond to different skeletal muscle relaxants ,but it causes a lot of side effects, so it is used as a last choice.



## 5- Dantrolene

Related to phenytoin (both are antiepileptic) , Dantrolene works by interfering in the contraction of the muscles directly ( *a directly acting drug* )

☆ It is useful in treatment of **malignant hyperthermia**

Malignant hyperthermia : a rare heritable disorder triggered by a variety of stimuli including neuromuscular blockers and as an adverse effect of general anesthesia (when we use isoflorane or halothane "halogenated hydrocarbons" or when we use succinylcoline )

In this condition there is an ***__elevation in the body temperature__** of the pateint to excessive levels because of the elevation in metabolism ( in the beginning we have a lot of ATP then the body can no longer do normal respiration so ***__lactic acidosis__** ocurrs ) , another thing that happens is ***__continuous muscle contractions__** , this all happens because of the increase in the inracellular calcium levels due to the sudden and prolonged release of calcium from the sacroplasmic reticulum which can't sequester calcium as a result of activation of a receptor called "ryanodine receptor (RyR) of the sarcoplasmic reticulum"which is found in muscles and nerves when we use isoflorane or halothane "halogenated hydrocarbons" or when we use succinylcholine on people that have a mutation in this receptor .

*In this condition we will have lactic acidosis as a result of continuous contraction.

*Treatment : *by cooling ,correcting acidosis* and Dantrolene.

-We use Dantrolene in this case because it 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 ( it's the antidote ).

-We can also use dantrolin to relax muscles in spastic conditions ( because it decreases intracellular levels of Ca++ ).

**6-Botulinum Toxin ( Botox )**

A toxin produced by Botulinum bacteria Inhibits acetylcholine release from the presynaptic end neuron so there'll be no acetlcholine release and no muscle contraction.

*Food poisoning caused by this bacteria can result within 12-36 hours, in diplopia,dysphagia, dysarthria and dyspena.*

Therapeutically it is used for :

**1-opthalmic purposes** ( diseases resulting in spasm in some muscles of the eye which leads to squinting so I use it as an ophthalmic solution )

***2-local muscle spasms***

**3-cosmetic treatment of facial wrincles** around the eyes and mouth but it's temproray in this case because it will block irreversibly but the body will get rid off it after some time ( about 3 months ).

***4- for generalized spastic disorders like cerebral palsy.***

**Other agents (work centrally ):**

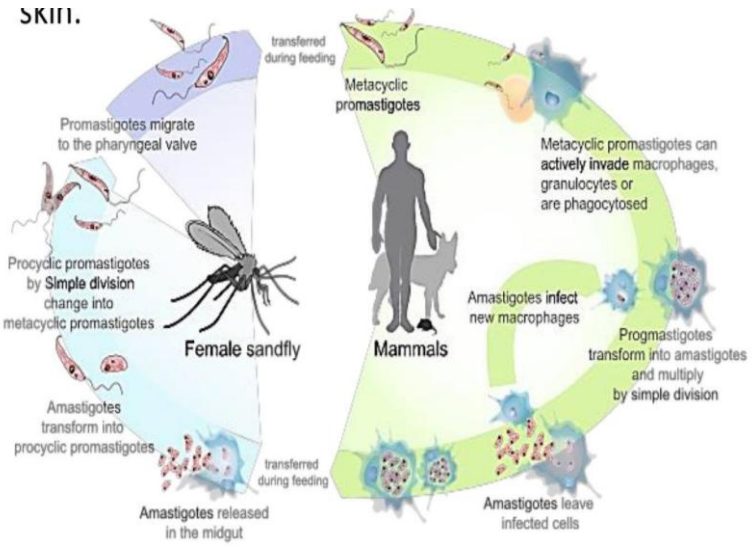
**1-Tolperisone**

**2-Orphenadrine** ( given as Myogesic which consists of Orphenadrine and Paracetamol , inhibits certain impulses in the brain , causes sedation as an adverse effect )

**The table at the end of slide 4 is not required** , but the doctor suggested that we use it review what we are required to know.

## Drugs For Leishmaniasis

Leishmaniasis is caused by leismania , there are different types of leismania according to geographical area ; L.tropica , L.



Brazeliensis , and L.donovani.

☆ Leishmania has two phases : promastigote which has phlagella to move and mastigote phase .

☆ We have different types of leishmaniasis with different leishmania species :

• L.tropica causes: Cutaneous leishmaniasis or oriental sore

• L. brazeliensis causes: Mucocutaneous leishmaniasis

• L. Donovani causes: Visceral leishmaniasis can be lethal because it causes problems in major organs like the liver and spleen causing splenomegaly or hepatomegaly .

☆ leishmania is transmitted from animals to humans by the bite of infected sand fly ( found in areas of hot weather , a lot of breakouts in India,Africa and South America )

**Diagnosed by the presence of parasite in biopsy from skin.*

☆ Cutaneous leishmania if it is not healed early on it will leave a scar that is hard to treat .

**1-Sodium Stibogluconate (Pentostam)**

It is from a group of drugs called " Pentavalent antimonial " ( moni is a parasite )

**☆ Drug of choice for all forms of leishmaniasis**

**☆ MOA : works by binding to SH group of proteins .** The mechanism of action is not well known but it is believed that it causes production of oxygen free radicals / ROS / hydroxyl ion / superoxide , these free radicals like to bind to reactive groups like OH and SH , when they bind to these reactive groups they alter the structure of the protein and DNA .

☆ Not absorbed orally so we give it IV /IM for **long period of time** depending on the type of leishmaniasis : *mostly IV , the way it's given might depend on the formula found in the country

- 20 days for cutaneous leishmaniasis

- 28 days for visceral and mucocutaneous disease ( longer )

*the dose in the slide is not for memorization

**typical preparations contain 30-40% pentavalent antimony by weight.*

☆ Problems with this drug :

☆ Resistance increases in breakout conditions , especially in India.

☆ Given IV or IM for long periods which isn't always easy or convenient

☆ Side effects:

• GIT upset

• Fever, headache , arthralgia , rash.

• local pain , irritation & sterile abscess : after IM injection

• cardiac toxicity like " QT prolongation " results with increase in refractory period for the contraction of the ventricle causing cardiac arrhythmia .

•Hemolytic anaemia (not common)

●Points weren't mentioned in the record

• *Distributed in extravascular compartment, Partially metabolized, Excreted in urine.*

**2-Amphotericin**

It is an anti-fungal and a drug that can be used to treat leishmaniasis

*** It is the alternative drug for visceral leichmaniasis when there is resistance to Sodium Stibogluconate .

☆ we give it IV because it isn't absorbed in GIT .

☆ Side effects :

- Fever, chills, and tachypnea commonly occur shortly after the initial intravenous doses of amphotericin B , all of these will get better after a period of time. ( side effects related to the infusion )
- Anaemia, hypokalaemia , disruption of the bone marrow (so they may cause thrombocytopenia ) , and anaphylatic reactions
- Has many toxicities but the ***Main toxicity of Amphotericin B is nephrotoxicity** ( most common and serious long term toxicity ) as 80% of patients get reduction in kidney function when they use it *but it generally recovers after treatment* , so i can't give this drug to a patient who has problems in kidney functions.
- If given in a short period it will be very toxic

**3-Miltefosine**

New drug ,it was developed to treat leukemia, it showed positive results in inhibiting leukaemic cell proliferation but it didn't reach the clinic because it was a very toxic drug in animals ,but later on they found that it has very good benefit in treating visceral and resistant leishmaniasis.

It is used at much lower dose than it was intended to be used in cancer chemotherapy , so it is not as toxic as the chemotherapy but it is still toxic .

☆ The exact way it works is unknown but it is An alkylphosphocholine analog

( its structure is similar to the structure of phospholipids ) so it interferes with the phospholipid structure of the membrane of microorganisms,results in kiling the microorganism.

☆ ***given orally for 28 days** (only drug given orally , given for a long time)

☆ side effects :

- V & D : Vomiting and diarrhea
- hepatotoxicity, nephrotoxicity
- teratogenic ( because of its structure , shouldn’t be used during pregnancy )

4-**Pentamidine**

☆ Inhibits DNA replication, and a DHF (dihydrofolate) reductase inhibitor

☆ Not absorbed orally , so it is given IV/ IM

☆ it has a very long half life so it is an **Accumulative drug & eliminated slowly in urine (elimination half-life 12 days)*****

☆ Can be inhaled as a nebulized powder ( aerosols ) to make it easier for the patient to take.

**doesn't effectively cross blood brain barrier .*

☆ this drug is given to treat the following cases :

**-Leishmaniasis**: Alternative to sodium stibogluconate for visceral leishmaniasis

**-Pneumocystis jiroveci** in aids patients : Treatment and prophylaxis of patients who cannot tolerate or fail other drugs.

- **Trypanosomiasis :** Systemic infection with trypanosome , *for early hemolymphatic stage .*

*Side effects :*

*1-Rapid infusion : hypotension, tachycardia , dizziness.*

*2-Pain at the injection site.*

*3-Others : pancreatic , renal and hepatic toxicity .*

## Trichogenic and Antitrichogenic Agents

¤ trichogenic means it increases the proliferation of hair.

1) **Minoxidil (Rogaine)**

This drug was **designed as an antihypertensive agent**; it acts on the K channels that are responsible for the repolarization of the smooth muscle cells of the blood vessels, ( remember if there is a contraction in these muscles there will be vasoconstriction and elevation in blood pressure ) so there will be hyperpolarization of these muscles because the channels are still open ,and no more contraction will happen , so the muscle will be relaxed >> dilation in blood vessels >> decrease the blood pressure.

They found that it increases the proliferation of the hair somehow when the patient uses this drug , **so instead of using this drug for hypertension they use it in topical or injectable form to treat male pattern baldness [androgenic alopecia] ( baldness associated with androgenic problems ) . So it is effective in reversing the progressive miniaturization of terminal scalp hair.**

**Vertex balding is more responsive than frontal balding.*

2) **Finasteride (Propecia)**

Orally administered drug used to stop the hair growth, this drug works by inhibiting 5 alpha-reductase (which converts testosterone to dihydrotestosterone " dihydrotestosterone is the form of testosterone which is responsible for the secondary sex characteristics like hair growth " ) so by inhibiting 5 alpha-reductase >> less dihydrotestosterone >> less hair growth.

**Oral tablets*

☆ Side effects (related to decrease in dihydrotestosterone ) : cause decreased libido, ejaculation disorders, and erectile dysfunction. (sexual problems for males )

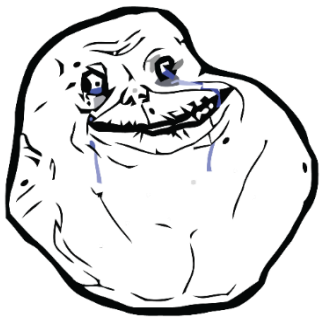
**3) Eflornithine**

Another drug used to inhibit the hair growth.

Eflornithine is an irreversible inhibitor for ornithine decarboxylase (ODC )which converts ornithine to polyamines , polyamines are important in cell division and hair growth .

Block ornithine decarboxylase >> no polyamines formation >> no hair growth.

**effective in reducing facial hair growth in 30% of women when used for 6 months .*



**Leprosy is for your own knowledge only :D**

و هيك بتكون خلصت الفارما *-*

## Summary :

## Spasmolytic Drugs

**1+2) diazepam + baclofen** : both act on GABA receptor in CNS so they decrease muscles spasticity

**3) Tizanidine** it is an α2-Adrenoceptor agonist that causes relaxation of skeletal muscles

- **S.E: 1-**Sedation; as it acts on the CNS 2-Hypotension 3-Weakness

4) **Gabapentin** we use it when we have muscle pain not responding to different skeletal muscle relaxants ,but it causes a lot of side effects, so it is used as a last choice.

**5) Dantrolene** It is useful in treatment of malignant hyperthermia ; We use dantrolin in this case because it inhibits ryanodine receptor (RyR) of the sarcoplasmic reticulum thus we inhibit the excessive release of Ca++ and the continuous contractions . We can also use dantrolin to relax muscles in spastic conditions .

**6) Botulinum Toxin** A toxin produced by Botulinum bacteria Inhibits acetylcholine release from the presynaptic end neuron so there'll be no acetlcholine release and no muscle contraction . used for opthalmic purposes and as a treatment for facial wrincles

7) Other agents (works centrally ): Tolperisone, Orphenadrine

## Drugs For Leishmaniasis

1) **Sodium Stibogluconate (Pentostam)** from a group of drugs called " Pentavalent antimonial " ( moni is a parasite ) ☆ **Drug of choice for all forms of leishmaniasis , works by producing oxygen free radicals that bind to SH group of proteins and alter their structure .**

Used IM/IV : 20 days for cutaneous leishmaniasis and 28 days for visceral and mucocutaneous leishmaniasis . Resistance is increasing in breakout conditions

S.E : GIT upset , Fever, headache / local pain , irritation & sterile abscess : after IM injection / cardiac toxicity like " QT prolongation " results with increase in refractory period for the contraction of the ventricle.

**2) Amphotericin** Is an anti fungal and alternative drug for visceral leichmaniasis when there is resistance to Sodium Stibogluconate .

☆ S.E : 1- fever, chills, and tachypnea occur shortly after the initial intravenous doses of amphotericin B , If given in short period it will be very toxic

- anaemia, hypokalaemia , disruption of the bone marrow (so they may cause thrombocytopenia ) , and anaphylatic reactions
- **Main toxicity of Amphotericin is renal toxicity *****

3) **Miltefosine** Has very good benefit in treating visceral and resistant leishmaniasis. it is an alkylphosphocholine analog

☆ **given orally for 28 days*****

☆ S.E : Vomiting and diarrhea ;hepatotoxicity, nephrotoxicity .

-teratogenic ( because of its structure )

4) **Pentamidine** Inhibits DNA replication, and a DHF (dihydrofolat) reductase inhibitor , given IV/ IM or can be inhaled as a nebulized powder

**☆ Accumulative drug & eliminated slowly in urine (elimination half-life 12 days)*****

this drug is given to treat the following cases :**Leishmaniasis**: Alternative to sodium stibogluconate for visceral leishmaniasis, **Pneumocystis jiroveci** ,and **Trypanosomiasis.**

## Trichogenic and Antitrichogenic Agents

1) **Minoxidil (Rogaine) :** effective in reversing the progressive miniaturization of terminal scalp hair( treat male pattern baldness [androgenic alopecia])
2) **Finasteride (Propecia): inhibits 5 alpha-reductase***** >> no dihydrotestosterone >> no hair growth
   S.E : cause decreased libido, ejaculation disorders, and erectile dysfunction

3) **Eflornithine: irreversible inhibitor for ornithine decarboxylase >> no polyamines formation >> no hair growth .*****

**End of summary**