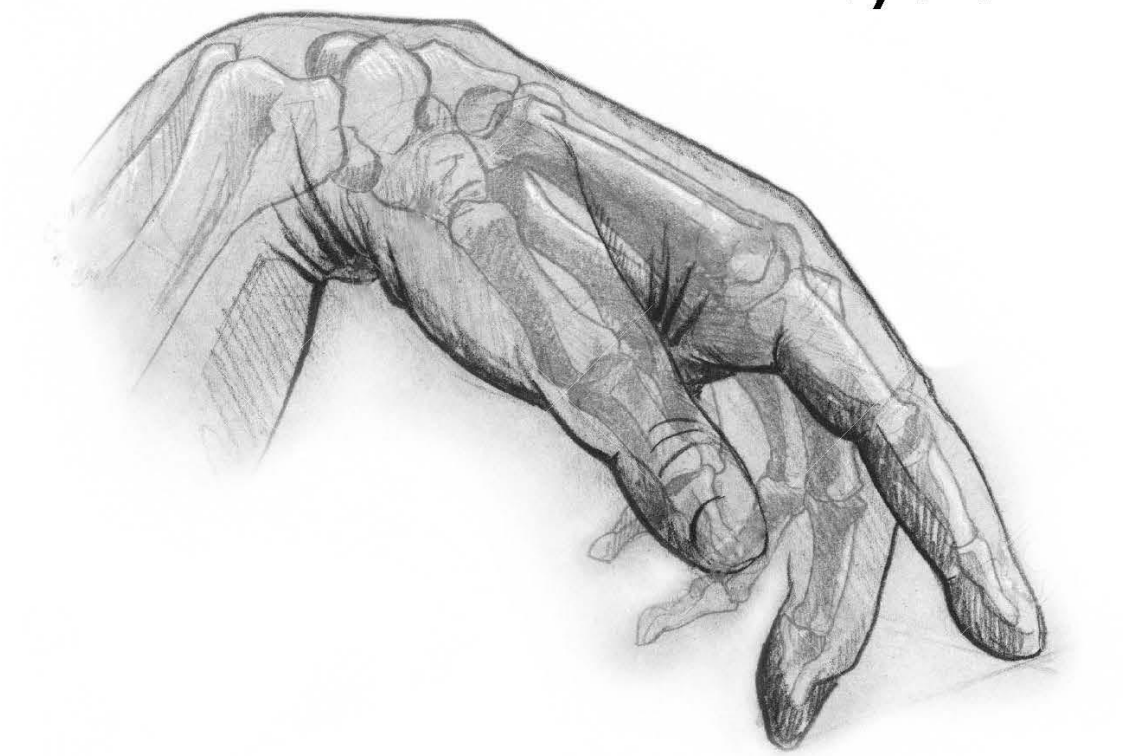
The

Musculoskeletal

System



Pharmacology

☑ Sheet ☐ Slide ☐ Handout

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Oral Anti-Fungal Drugs

In the previous lecture we talked about antifungal agents which are mainly related to the Azole family. These antifungal drugs can be given orally and topically to treat fungal infections.

The oral group of the antifungal drugs contain 3 main drugs:

1- Fluconazole

2- Itraconazole

3- Ketoconazole

Mechanism of action:

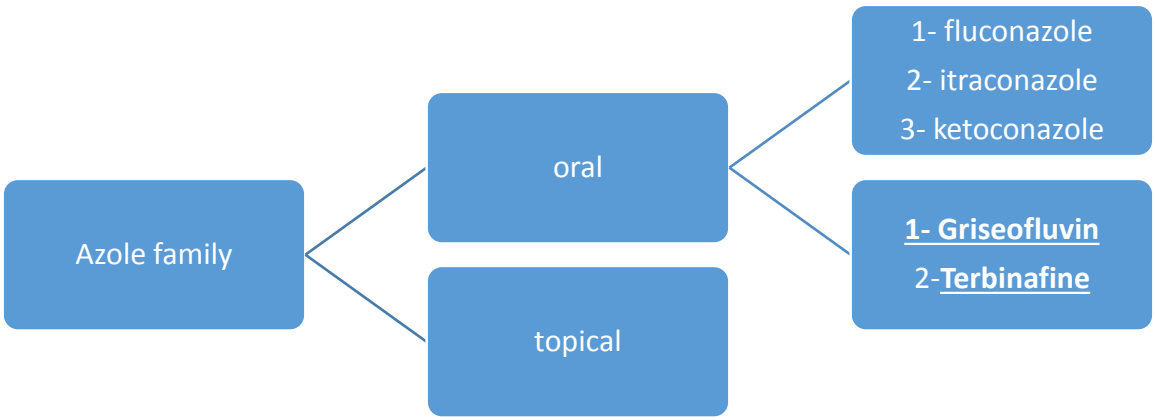
These drugs work mainly by inhibiting steroid synthesis, which is a main component of the fungal cell membrane (Ergosterol) so they alter the permeability of the membrane by inhibiting the syntheses of theses steroids.

Uses:

These drugs are mainly used to treat **systemic mycosis, mucocutaneous candidiasis, and other cutaneous infections.**

Side effects:

Their side effects are mainly related to to the liver so they can cause hepatitis and liver enzyme dysfunction, in addition to interaction with other agents in the body**.**



Other anti fungal drugs that are also part of the azole family are Griseofluvin and Terbinafine

They are used mainly to treat dermatophyte. Both drugs are given orally and for long period of time (long treatment period).

So they are used to treat fungal infections of the skin, hair, and nails.

The treatment of the scalp usually takes 46 weeks , and finger nails needs up to 6 months of taking oral drug from these agents .

Side effects:

Mainly related to liver enzyme function.

NYSTATIN & AMPHOTERICIN B

These drugs are used mainly to treat candida infections.

Candida infections usually cause inversion to certain areas in the body which can be the Oral cavity or the Vagina.

They can be used topically but in certain cases they need to be given orally.

Nystatin:

Is given as oral suspension to treat oral fungal infections and thrush in infants , its given usually as 2 ml in the infants mouth .

Side effect:

this drug is highly toxic , but in infants this side effect seems to be neglected because the drug is not well absorbed from his GI tract so the drug stays in the mouth or the GI system where it need to work v that's why it used to treat oral cavity and GI tract infection .

Amphotricin B:

Used to:

This drug is used to treat cutaneous candida infection which is a systemic disease caused by candida in immunocompromised patients like AIDS and cancer patients.

Toxicity:

The main toxicity of Amphoticin B is Nephrotoxicity.

Antiviral Drugs

We have different antiviral drugs but we are going to focus on Acyclovir.

Acyclovir:

This is an antiviral drug that can be used topically in the form of cream or lotion to treat viral infection like herpes labialis .

Herpes labialis is a disease caused by herpes simplex virus that occurs during childhood usually but even after you cure from the disease the virus stays in your body as it escapes to the dorsal root ganglia in the vertebra and stays in the inactive form, once the virus find suitable environment to get activated again it goes through the nerves and its expressed in the Abdomen, oral cavity , or on the face forming ulceration on the skin and mucous membrane.

The virus get activated only under certain conditions like:

1- Getting cold

2- under stress and during stressful situation (during exams)

Mechanism of action:

Acyclovir is a prodrug so it needs to be activated, it's activated by several steps:

1- Acyclovir is converted to **acyclovir mono phosphate** by a viral enzyme called **thymidine kinase**.

2- Then acyclovir mono phosphate is converted to **acyclovir tri phosphate** by host cell enzyme

Then the drug integrate with the viral replication process and block it and prevent transcription and translation of the viral DNA.

Ectoparasiticides

We have several types of parasite but we will be focusing on lice mainly .

Lice mainly infect the scalp and the genital areas , different types of lice are found mainly they are : **P*ediculus humanus, Pthirus pubis, and Sarcoptes scabiei.***

ectoparasiticide is a big family that contain several drugs the main ectoparasiticides are:

- **Permethrin**

- **Lindane (Hexachlorocyclohexane)**

- **Crotamiton**

- **Sulfur**

- **Malathion**

They are usually found as lotions or shampoos**.**

Scabies: الجرب

Treated by a cream that's applied for long period of time about 8-14 hours a day for several months , sometimes collusion is used to keep the cream in its place .

Pigmentation:

Agents affecting pigmentation can be divided into :

1- Agents causing Depigmentation. (remove the color)

2- Agents causing Repigmentation.

Depigmenting agent:

- **Hydroquinone.**
- **Monobenzone.**
- **Mequinol**

These drugs causes depigmentation of the skin by inhibiting an enzyme called tyrosinase.

This enzyme is found in melanocytes and its responsible for the production of melanin once its inhibited this will result in depigmentation of the skin .

*please note that monobenzone can be toxic to melanocytes and can result in permanent depigmentation of the skin.

Repigmenting agents:

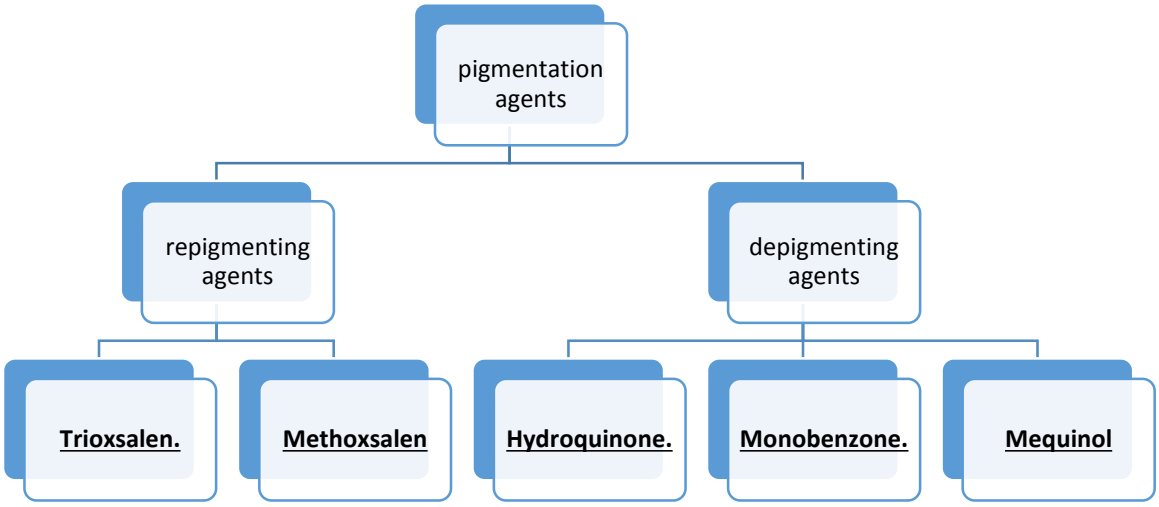
- **Trioxsalen.**
- **Methoxsalen.**

Those drugs are used when a patient has a problem with pigmentation like vitiligo patients

This disease is characterized by the presence of white patches on certain areas on the skin due to depigmentation of these areas, these white patches need to be repigmented again using these agents.

Mechanism of action:

These drugs interfere intercalate with the DNA,, because the affect the DNA these drugs increase the chance of getting skin cancer and make them more sensitive to this disease .



Sunscreens and sunshades

Sunscreens:

Present to absorb UV light to get rid of its damaging effect to the skin

Example: (PABA) **para amino benzoic acid**

Sunshades:

They are opaque substances they prevent the passage of the light into the skin.

Usually sunshades are minerals like **titanium dioxide**

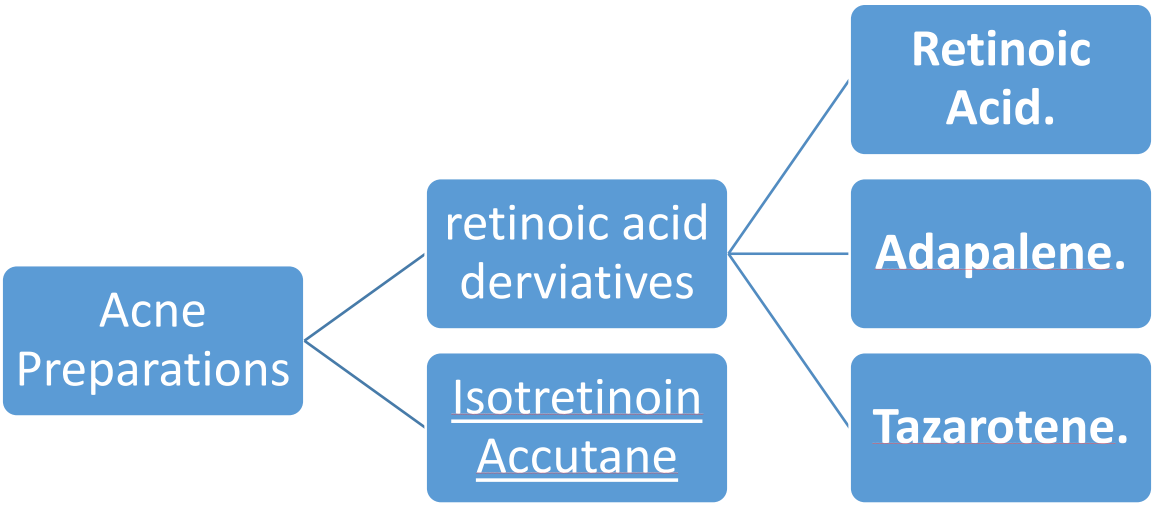
Uses:

It's usually used in photosensitive patients,, those patients will have skin eruption when they are subjected to light so they are advised to use high degree on these sunscreens and sunshades therapeutically to prevent these sun induced skin eruptions .

Drugs to treat acne

Several antibiotics can be used to treat acne topically but there are special group of antibiotics that is used specifically for the treatment of acne most of them are **Retinoic Acid Derivatives (vitamin A derivatives)**

Acne drugs can be divided into:



Retinoic Acid and Derivatives:

These drugs results in the opening of acne temples and formation of comedone to get rid of all its content and all the pus that's found in it.

So the help to get rid of the existing open comedones and opening of the closed ones.

These drugs are used for long period of time usually 4-6 months.

The dose and the duration depends on :

1- Condition of the patient

2- Weight of the patient

in which the drug must reach the effective concentration in the patients' blood in order to get rid of the infection .

How they work ?

On the molecular level these drugs Stabilizes lysosomes, increases RNA polymerase activity, increases PGE2, cAMP, and cGMP levels, and increases the incorporation of thymidine into DNA

Physiologically these drugs decrease the attachment between skin cells and it Decreases cohesion between epidermal cells and increases epidermal cell turnover. This will result in shedding of skin layers over and over

Side effects:

These drugs have many side effects that can be summarized in these few points:

1- Interfere with liver enzymes and cause liver damage.

2- Interfere with LDL level and cause increase to the LDL level in the body.

For this particular reason liver test and LDL level must be measured every month and even before starting the treatment to make sure of that the LDL is not elevated and the liver enzymes are functioning properly.

3- Initiate collagen synthesis which results in diminishing fine lines and wrinkles so the patient will have a tighten face.

4- These drugs are teratogenic. That's why these drugs must not be used during pregnancy at all.

The drug must be stopped at least before 3 - 6 months before getting pregnant because its concentration in the blood stays high even after stopping the drug (depending on the half-life of the drug).

5- Dryness. These drugs cause dryness to all mucous membrane in the body this will result in dry lips and oral cavity.
Furthermore patients taking these drugs are very sensitive to the sun so they must use high degree of sun protections and sun blocks and they must keep their skin moist.

6- Depression. Some cases has been reported but this side effect is not common.

7- Tumorigenic in animals

Isotretinoin (Accunate)

Is used for sever cystic acne that is resistant to normal treatment.
Usually the treatment should starts with tetracycline (doxycyclins most of the time) if the patient doesn't respond to them isotretinoin is used.

Side effects:

1- Pseudotumor cerebri.
This drug causes elevation of blood pressure in the cranial cavity just like the effect of tumor in the cranial cavity.

2- Dryness. Mainly eye dryness (corneal opacities)

3- It also can cause inflammatory bowel disease, anorexia, alopecia, and muscle and joint pains.

4- Lipid abnormality

5- Teratogenic (very important to know it)

6- Tumorigenic in animals. It has been found the mice that are injected by this drug has higher tendency to get cancer but this doesn't occur in human.

Benzoyl peroxide:

This drug is used topically in the treatment of acne .

Mechanism of action:

This drug is very similar to hydrogen peroxide (H_2O_2). That's why it works by producing free radicals.
Which helps in getting rid of the anaerobic microbes that lives in the sebaceous glands.
So benzoyl peroxide has antimicrobial activity against the microbes.

Note that
Benzoyl peroxide is usually combined with erythromycin and clindamycin for topical treatment of acne.

The bad thing about benzoyl peroxide is that it causes bleaching for the clothes or for the hair, so patients are usually advised to wear white clothes while sleeping.

Azeliac acid:

This is a topical applied drug that has antimicrobial activity as well as preventing the conversion of testosterone into dihydrotestosterone.

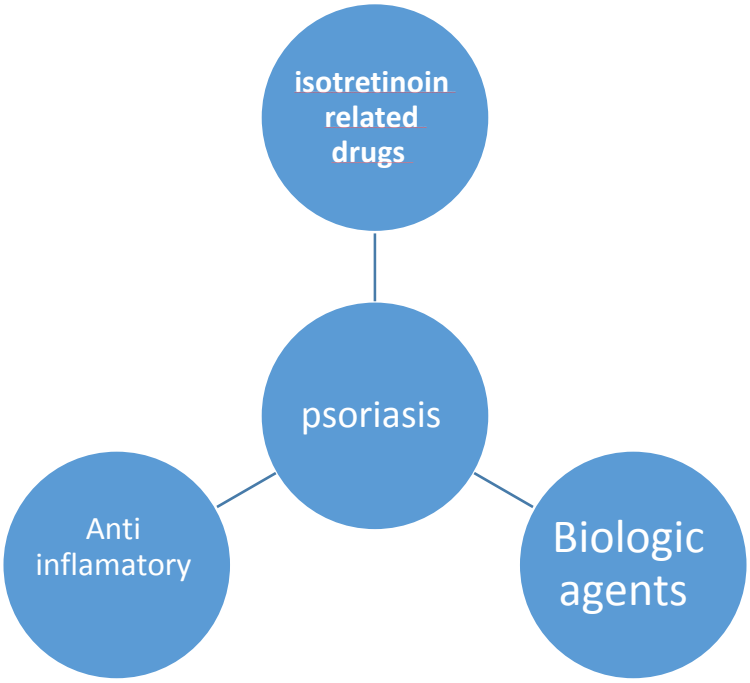
In other words this drug can be used to treat acne due to its activity for testosterone conversion into dihydrotestosterone because acne formation is usually formed due to the imbalance in these hormones.

Drugs for psoriasis

What is psoriasis?

Psoriasis is an autoimmune inflammatory reaction that usually occurs by itself and can be sometimes induced by some drugs, however it’s usually produced due to the hyperactivity of the body toward its own skin cells resulting in red or pinky patches of the skin.
It sometimes occurs in the scalp this stops the growth of hair in this area which may lead to hair loss in these areas.

Drugs used to treat psoriasis:



Acitretin :

Acitretin is a drug that is related to tretinoin family and it has very similar structure to isotretinoin. It's usually given orally.

Side effects:

1- hepatotoxic and cause damage to the liver just like isotretinoin

2- - teratogenic

3- It stays in the body for longer time than isotretinoin, so female patient should not get pregnant for at least 3 years after stopping the drug.

Anti inflammatory drugs

Tazorotein :

This drug is used topically and it works by inhibiting inflammation.
Tazorotein also has antiproliferative effect so it helps in preventing the production of the unwanted skin layers.

Side effects:

This drug is Teratogenic. Also, it can cause burning, stinging, peeling, erythema, and localized edema of skin.

Calcipotein

Is a vitamin D derivative that is used to treat psoriasis.

Please note that psoriasis is very resistant to treatment so sometimes we need to prescribe drugs orally to inhibit this immune response.

Biologic Agents

These agents are related to antibodies in which their structures are highly related to the structure of IgG antibodies. (These agents can be used to treat other autoimmune diseases such as rheumatoid arthritis).

These biologic agents are humanized antibodies i.e. they are produced according to a certain human gene sequences for the FC portion so the body don't reject this drug and don't consider it as foreign material.
So again.. these agents are produced according to the FC portion gene of the IgG antibodies.

Example:

1- Alefacept
2- Efalizumab
3- Etanercept

Alefacept :

This drug is Immunosuppressive dimer fusion protein of CD2
And it has FC portion similar to IgG antibody.

Efalizumab

Is a Recombinant humanized IgG1 monoclonal antibody.

This drug has been withdrawn from the market because it causes progressive multifocal leukoencephalopathy (PML).

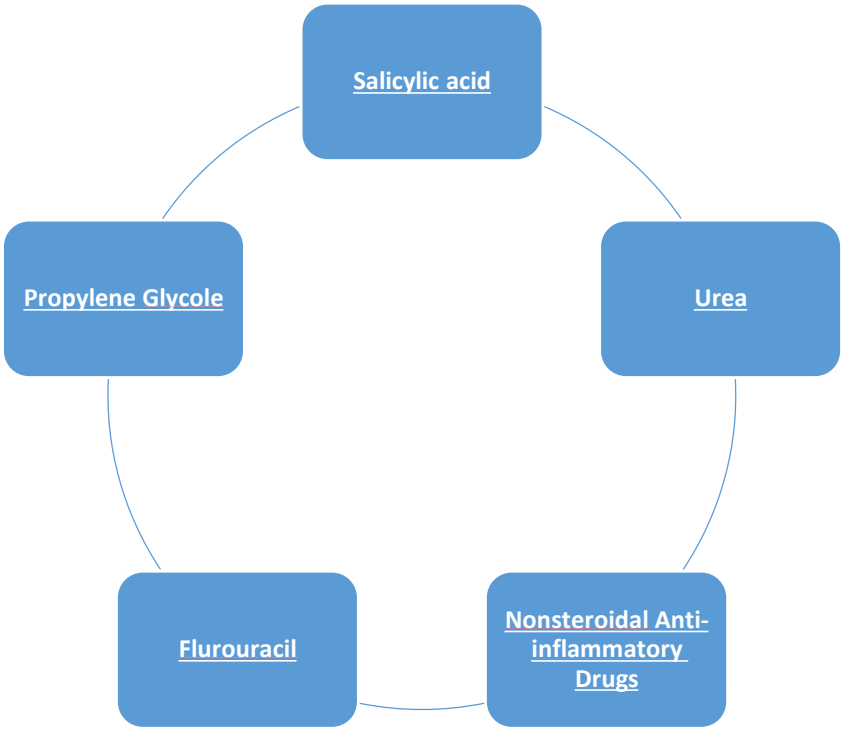
It also can cause thrombocytopenia

Etanercept

This drug has very similar structure to our antibody, so we don't have many side effects associated with it.
Mechanism of action:
This drug targets and inhibit TNF alpha that is elevated during inflammation so it is used to treat chromatin arthritis.

Slides 31-36 (Anti-inflammatory Agents) are not required.

Keratolytic and Destructive Agents



1-Salicylic acid

Salicylic acid its nothing but aspirin that's used to reduce pain.
Salicylic acid is a keratolytic and destructive agent.

Uses:

It's used topically to inhibit keratinization if the skin
The drug also solubilize the skin proteins and cause desquamation of these keratotic debris.

It's used to treat foot corn (مسمار اللحم).

Side effect:

Part of it can be absorbed to the systemic circulation causing side effects related to salicylic acid (**salicylism**)
The toxicity is associated with aspirin and salicylic acid derivative and since many people has allergy to salicylic acid derivative we should be aware from anaphylactic shock

Propylene Glycole:

This drug is used as vehicle to dissolve many creams, lotions, and topical applied drugs so it helps dissolving organic drugs.

However, the drug by itself has keratolytic activity so used as keratolyte.
Sometimes it's mixed with salicylic acid to get synergistic effect of the 2 drugs together.

Urea :

Is a natural substance that is produced in the body.

Urea act as moisture to the skin as it helps the skin to absorb more water and keep it moist.
Urea has humectants activity i.e. softening and moisturizing effect on the stratum corneum.

Please note that urea has **hygroscopic characteristic** i.e it increases the attraction of water thus keeping the skin moist.

We don't care about its toxicity because its excreted with the urine in the body.

Remember: nh3 ..... urea cycle.... urea ..... excreted with the urine

Flurouracil :

Is antimetabolite that resemble the structure of uracil so it interfere with DNA synthesis.

Uses:

1-Used to treat certain cases of keratosis.

2-Its used in chemotherapy in skin cancer treatment such as basal cell carcinoma. Because it inhibits DNA replication by interfering with DNA structure.

Nonsteriodal anti-inflamatory drugs :

Example: ***dicolfanic sodium*** which can be used in certain formulation as keratolytic agent but it has very minimal keratolytic activity .

Antipuratic agent

Antipuratic agents Drugs that inhibit itching feeling of the skin.

We have 2 main drugs in this family:

Doxepine
Pramoxine

Dexopin: Is histamine antagonist.

Histamine is secreted by mast cells as a way to respond to antigen. It increases the permeability of blood vessels and cause them to vasodilator resulting in redness, and swelling.

Important to know :
In our body we have 33 types of histamine receptors H1 .. H2 .. H3 .

Dexopine acts by inhibiting H1 AND H2 receptors of histamine,, by inhibiting these receptors we are inhibiting the action of histamine ... and so we are inhibiting the production of cytokines which causes the itching feeling of the skin .

As we said before we have 3 types of histamine receptors

H1 receptor.. is found all over the body and the histamine antagonists that target H1 receptor are usually used to treat allergy like **(Allerfin)**

While H2 receptors are found mainly in the gastric mucosa.

H1 antagonist are classified into:

1st generation histamine antagonist

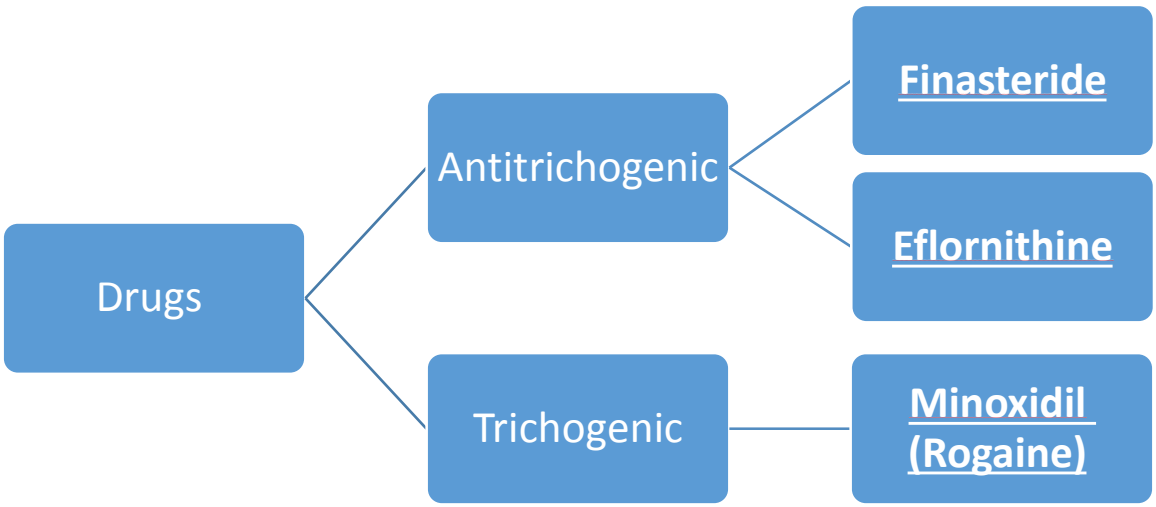
2nd generation histamine antagonist

1st generation drugs like **Allerfin** has a structure that can cross the blood brain barrier so they can penetrate to the CNS causing sedation, and sleepiness

- However , the 2nd generation drugs like **Loratadine** and **Claritin** can't cross the blood brain barrier that's why they don't cause these side effects .

Pramoxine .. its a local atheistic agent so it blocks nerve impulses to the brain thus the patient don't feel pain nor itching feeling .

Trichogenic and Antitrichogenic Agents



Mildoxin

It is a trichogenic agent that increase hair growth.

This drug was designed as antihypertensive drug but it was absorbed that it inhibits a condition known as androgenic alopecia. (a condition that cause hair loss) .
So the drug is used in treating male pattern baldness

Finsteriod :

Is 5 alpha reductase inhibitor

.

5 alpha reductase is an enzyme that convert testosterone into dihydrotestosterone

.

Dihydrotestosterone is responsible for secondary make characteristics,, one of them is hair growth .

So by blocking this enzyme… less formation of dihydrotestosterone... less hair growth

Side effects:

Can cause decreased libido, ejaculation disorders, and erectile dysfunction

Eflornithine

This drug inhibits **ornithine decarboxylase** enzyme.

This enzyme converts ornithine amino acid into polyamines

Polyamines is associated with proliferation, cell division and hair growth.

Thus by inhibiting this enzyme… inhibit polyamines formation… less proliferation... less hair growth.

This drug reduce facial growth if hair by 30%.

The drug must be used for at least 6 months.