Skin Pharmacology

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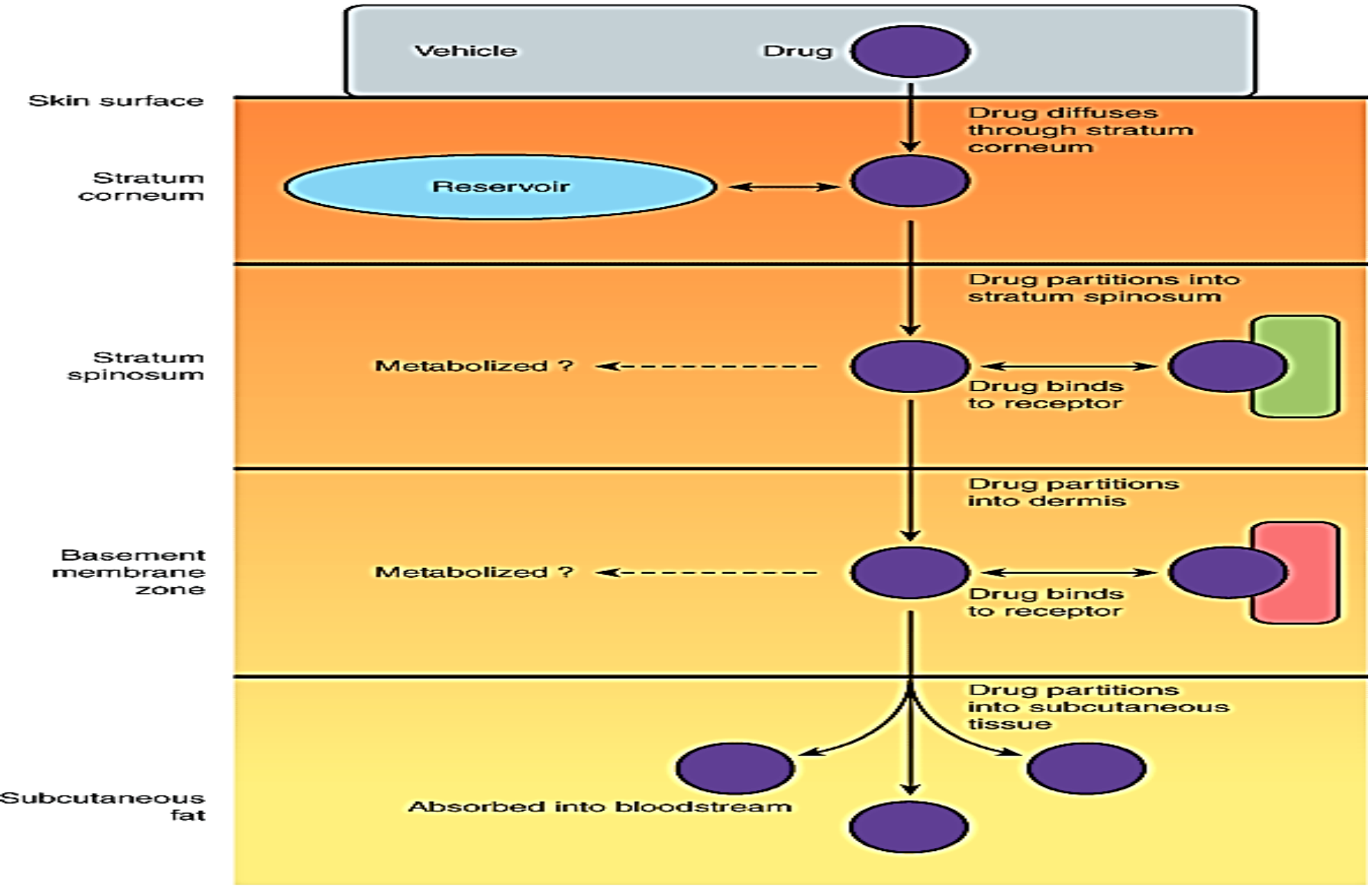
Dermatologic Pharmacology

Variables affecting Pharmacologic Response:

- **Regional variation in drug penetration.**
- **Concentration gradient.**
- **Dosing schedule.**
- **Vehicles and occlusion.**

Percutaneous Absorption.



Dermatologic Formulations

- **Tinctures.**
- **Wet dressings.**
- **Lotions.**
- **Gels.**
- **Powders.**
- **Pastes.**
- **Creams.**
- **Ointments.**

Adverse Effects of Dermatologic Preparations

- **Burning or stinging sensation.**
- **Drying and irritation**
- **Pruritus.**
- **Erythema.**
- **Sensitization.**
- **Staining**
- **Superficial erosion.**

TABLE 61–1
Local cutaneous reactions to topical medications.

Reaction type	Mechanism	Comment
Irritation	Non-allergic	Most common local reaction
Photoirritation	Non-allergic	Phototoxicity; usually requires UVA exposure
Allergic contact dermatitis	Allergic	Type IV delayed hypersensitivity
Photoallergic contact dermatitis	Allergic	Type IV delayed hypersensitivity; usually requires UVA exposure
Immunologic contact urticaria	Allergic	IgE-mediated type I immediate hypersensitivity; may result in anaphylaxis
Non-immunologic contact urticaria	Non-allergic	Most common contact urticaria; occurs without prior sensitization

Topical Antibacterial Agents

- **Gram-positive bacteria**
  - **Bacitracin**
  - **Gramicidin**
- **Gram-negative bacteria**
  - **Polymyxin B Sulfate**
  - **Neomycin**
  - **Genatamicin**

BACITRACIN

- **Active against streptococci, pneumococci, and staphylococci**
- **Also , most anaerobic cocci, neisseriae, tetanus bacilli, and diphtheria bacilli are sensitive.**
- **MOA???**

- **Side effects: Toxicity ???**

Allergic contact dermatitis occurs frequently, and immunologic allergic contact urticaria rarely. Bacitracin is poorly absorbed through the skin, so systemic toxicity is rare.

- Frequently used in combination with other agents (polymyxin B and neomycin)
- Form: creams, ointments, and aerosol preparations
- Usually Antiinflammatory agents added
  - (Hydrocortisone)

GRAMICIDIN

- **Only for topical use, in combination with other antibiotics such as neomycin, polymyxin, bacitracin, and nystatin**
- **MOA??**

- **Hemolysis**

POLYMYXIN B SULFATE

- **gram-negative :Pseudomonas aeruginosa, Escherichia coli, enterobacter, and klebsiella.**
- **Proteus and serratia are resistant, as are all gram-positive organisms.**
- **Side effects: total daily dose applied to denuded skin or open wounds should not exceed 200 mg in order to reduce the likelihood of toxicity "neurotoxicity and nephrotoxicity"**
  - **Allergic contact dermatitis NOT common.**

NEOMYCIN & GENTAMICIN

Neomycin

- **Aminoglycoside antibiotics**
- **gram-negative :E coli, proteus, klebsiella, and enterobacter.**
- **SE: allergic contact dermatitis**

- **Gentamicin generally shows greater activity against P aeruginosa than neomycin.**
- **Gentamicin more active against staphylococci and group A β-hemolytic streptococci.**
- **Be careful with systemic toxicity : esp in renal failure**
- **Hospital acquired resistant**

Topical Antibacterials in Acne

- **Clindamycin.**
- **Erythromycin.**
- **Metronidazole: rosacea**
- **Sodium sulfacetamide.**
- **Dapsone**

Clindamycin

- **10% absorbed, so, possibility of *Pseudomembranous colitis***
- The hydroalcoholic vehicle and foam formulation (Evoclin) ……may cause drying and irritation of the skin, with complaints of burning and stinging.
- The water-based gel and lotion formulations….. well tolerated and less likely to cause irritation. *Allergic contact dermatitis is uncommon.*
- Clindamycin is also available in fixed-combination topical gels with benzoyl peroxide (Acanya, BenzaClin, Duac), and with tretinoin (Ziana).

Metronidazole

- Effective in the treatment of rosacea.
- The mechanism of action is unknown, but it may relate to the inhibitory effects of metronidazole on *Demodex brevis*; This drug may act as an anti-inflammatory agent by direct effect on neutrophil cellular function
- Adverse local effects include dryness, burning, and stinging.
- Less drying formulations may be better tolerated (MetroCream, MetroLotion, and Noritate cream).
- Caution should be exercised when applying metronidazole near the eyes to avoid excessive tearing.

Erythromycin

- In topical preparations, erythromycin base rather than a salt is used to facilitate penetration
- One of the possible complications of topical therapy is the development of antibiotic-resistant strains of organisms, including staphylococci
- Adverse local reactions to erythromycin solution may include a burning sensation at the time of application and drying and irritation of the skin
- Erythromycin is also available in a fixed combination preparation with benzoyl peroxide (Benzamycin) for topical treatment of acne vulgaris.

Topical Antifungal Agents

- **Azole Derivatives:**
  - **Clotrimazole**
  - **Econazole.**
  - **Ketoconazole.**
  - **Miconazole.**
  - **Oxiconazole.**
  - **Sulconazole.**
    - **Activity against dermatophytes (*epidermophyton, microsporum, and trichophton*) and yeasts, including *Candida albicans and Pityrosporum orbiculare.***

Topical Antifungal Agents

- **Ciclopirox Olamine.**
- **Naftifine and Terbinafine.**
- **Tolnaftate.**
- **Nystatin and Amphotericin B:**
  - **Only for *Candida albicans.***
  - **Available *as* topical preparations, oral suspension, or vaginal tablets**


Tinea Versicolor

Oral Antifungal Agents

- **Azole Derivatives:**
  - **Fluconazole.**
  - **Itraconazole.**
  - **Ketoconazole.**
    - **Affect the permeability of fungal cell membrane through alteration of sterol synthesis.**
    - **Effective in systemic mycosis, mucocutaneous candidiasis, and other cutaneous infections.**
    - **Might have systemic side effects: hepatitis and liver enzyme elevations, and interactions.**

Oral Antifungal Agents

- **Azole Derivatives.**
- **Griseofulvin:**
  - **Effective against *epidermophyton, microsporum, and trichophton.***
  - **Requires prolonged treatment:**
    - **4-6 weeks for the scalp.**
    - **6 months for fingernails.**
    - **8-18 months for toenails.**
    - **Has many side effects.**
- **Terbinafine:**
  - **Recommended for *onchomycosis.***
    - **6 weeks for fingernails.**
    - **12 weeks for toenails.**

NYSTATIN & AMPHOTERICIN B

- **Topical therapy of C albicans infections but ineffective against dermatophytes.**
- **Cutanuoes and mucosal candida infections**

- **Amphotericin B : broader antifungal**

intravenously in the treatment of many systemic mycoses and to a lesser extent in the treatment of cutaneous candida infections.

- **Toxicity with systemic administration**

Topical Antiviral Agents

- **Acyclovir.**
- **Valacyclovir.**
- **Penciclovir.**
- **Famciclovir.**
  - **Synthetic guanine analogs with inhibitory activity against herpes viruses.**
  - **Ointments and creams are useful for recurrent orolabial herpes simplex infection**

Immunomodulators

- **Imiquimod:**
- **Stimulates peripheral mononuclear cells to release interferon- ά and to stimulate macrophages to produce interleukins-1,-6, and -8 and tumor necrosis factor-ά.**
- **Uses:**
  - **For external genital and perianal warts.**
  - **Actinic keratosis on the face and scalp.**
  - **Primary basal cell carcinoma.**
- **Tacrolimus.**
- **Pimecrolimus.**
  - **Useful for atopic dermatitis.**
  - **Inhibit T-lymphocyte activation and prevent release of inflammatory cytokines and mast cell mediators**
  - **(Black box warning)**

Ectoparasiticides

- **Permethrin:**
  - **Toxic to P*ediculus humanus, Pthirus pubis, and Sarcoptes scabiei***
  - **Pediculosis:cream applied for 10 minutes and then rinsed off with warm water.**
  - **Scabies: cream applied for the whole body for 8-14 hours.**
- **Lindane(Hexachlorocyclohexane):**
  - **10% absorbed and concentrated in fatty tissues.**
  - **Can cause neurotoxicity and hematoxicity**
- **Crotamiton.**
- **Sulfur.**
- **Malathion.**

Agents affecting Pigmentation

- **Hydroquinone.**
- **Monobenzone.**
- **Monobenzone may be toxic to melanocytes resulting in permanent depigmentation.**
- **Mequinol**
  - **Reduce hyperpigmentation of skin by inhibiting the enzyme tyrosinase which will interfere with biosynthesis of melanin.**

Agents affecting Pigmentation

- **Trioxsalen.**
- **Methoxsalen.**
  - **Are psoralens used for the repigmentation of depigmented macules of vitiligo.**
  - **Must be photoactivated by long-wave-length ultraviolet light (320-400nm) to produce a beneficial effect.**
  - **They intercalate with DNA.**
  - **Can cause cataract and skin cancer.**

Sunscreens and Sunshades

- **Sunscreens absorb UV light.**
  - **Examples are para amino benzoic acid (PABA) and its esters.**
- **Sunshades are opaque materials that reflect light, like titanium dioxide.**
- **Useful in polymorphous light eruption, lupus erythematosus, and drug –induced photosensitivity.**

Acne Preparations

- **Retinoic Acid and Derivatives:**
  - **Retinoic Acid.**
  - **Adapalene.**
  - **Tazarotene.**

Acne Preparations

- **Retinoic Acid and Derivatives:**
  - **Retinoic Acid(Tretinoin): is the acid form of Vitamin A. Stabilizes lysosomes, increases RNA polymerase activity, increases PGE_2, cAMP, and cGMP levels, and increases the incorporation of thymidine into DNA.**
  - **Decreases cohesion between epidermal cells and increases epidermal cell turnover. This will result in expulsion of open comedones and the transformation of closed comedones into open ones.**
  - **Also, promotes dermal collagen synthesis, new blood vessel formation, and thickening of the epidermis, which helps diminish fine lines and wrinkles.**
  - **Can cause erythema and dryness.**
  - **Tumerogenic in animals**

Acne Preparations

- **Isotretinoin(Accutane):**
  - **Restricted for severe cystic acne resistant to standard treatment.**
  - **Inhibits sebaceous gland size and function.**
  - **Given orally.**
  - **Toxic: dryness, itching, headache, corneal opacities, pseudotumor cerebri, inflammatory bowel disease, anorexia, alopecia, and muscle and joint pains. Also lipid abnormalities.**
  - **Teratogenicity**

Acne Preparations

- **Benzoyl Peroxide:**
  - **Penetrates the stratum corneum or follicular openings and converted to benzoic acid within the epidermis and dermis.**
  - **Has antimicrobial activity against *P. acnes* and peeling and comedolytic effects.**
  - **Can be combined with erythromycin or clindamycin.**
  - **Potent contact sensitizer.**
  - **Can cause bleaching of hair or colored fabrics.**
- **Azelaic Acid:**
  - **Has antimicrobial activity and inhibits conversion of testosterone to dihydrotetosterone.**

Drugs for Psoriasis

- **Acitretin:**
  - **Related to isotretinoin.**
  - **Given orally.**
  - **Hepatotoxic and teratogenic.**
  - **Patients should not become pregnant for 3 years after stopping treatment, and also should not donate blood.**

Drugs for Psoriasis

- **Tazarotene:**
  - **Topical.**
  - **Anti-inflammatory and antiproliferative actions.**
  - **Teratogenic. Also, can cause burning, stinging, peeling, erythema, and localized edema of skin.**
- **Calcipotiene:**
  - **Synthetic vitamin D_3 derivative**

Drugs for Psoriasis

- **Biologic Agents:**
  - **Alefacept:**
    - **Immunosuppressive dimer fusion protein of CD2 linked to the Fc portion of human IgG_1.**
  - **Efalizumab:**
    - **Recombinant humanized IgG_1 monoclonal antibody.**
    - **Withdrawn :progressive multifocal leukoencephalopathy (PML),**
    - **Can cause thrombocytopenia.**
  - **Etanercept:**
    - **Dimeric fusion protein of TNF receptor linked to the Fc portion of human IgG_1.**

Anti-inflammatory Agents

- **Topical Corticosteroids:**
  - **Hydrocortisone.**
  - **Prednisolone and Methylprednisolone.**
  - **Dexamethasone and Betamethasone.**
  - **Triamcinolone.**
  - **Fluocinonide.**

Anti-inflammatory Agents

- **Topical Corticosteroids:**
  - **Absorption:**
    - **1% of hydrocortisone applied to the ventral forearm.**
    - **0.14 times of hydrocortisone applied to the plantar foot.**
    - **0.83 times of hydrocortisone applied to the palm.**
    - **3.5 times of hydrocortisone applied to the scalp.**
    - **6 times of hydrocortisone applied to the forehead.**
    - **9 times of hydrocortisone applied to the vulvar skin.**

Anti-inflammatory Agents

- **Topical Corticosteroids:**
  - **Absorption:**
    - **Absorption increased with inflammation.**
    - **Increasing the concentration does not proportionally increase the absorption.**
    - **Can be given by intralesional injection.**

Anti-inflammatory Agents

- **Topical Cortcosteroids:**
  - **Dermatologic disorders very responsive to steroids:**
    - **Atopic dermatitis.**
    - **Seborrheic dermatitis.**
    - **Lichen simplex chronicus.**
    - **Pruritus ani.**
    - **Allergic contact dermatitis.**
    - **Eczematous dermatitis.**
    - **Psoriasis**

Anti-inflammatory Agents

- **Topical Cortcosteroids:**
  - **Adverse Effects:**
    - **Suppression of pituitary-adrenal axis.**
    - **Systemic effects.**
    - **Skin atrophy.**
    - **Erythema.**
    - **Pustules.**
    - **Acne.**
    - **Infections.**
    - **Hypopigmentation.**
    - **Allergic contact dermatitis.**

Anti-inflammatory Agents

- **Topical Cortcosteroids.**
- **Tar compounds:**
  - **Mainly for psoriasis, dermatitis, and lichen simplex chronicus**
  - **Can cause irritant folliculitis, phototoxicity, and allergic contact dermatitis.**

Keratolytic and Destructive Agents

- **Salicylic acid:**
  - **Solubilizes cell surface proteins resulting in desquamation of keratotic debris.**
  - **Keratolytic in 3-6% concentration, but destructive in higher concentrations.**
  - **Can result in salicylism due to systemic absorption.**
  - **Locally, can cause urticaria, anaphylactic and erythema multiforme reactions, irritation, inflammation, and ulceration.**

Keratolytic and Destructive Agents

- **Salicylic acid:**
- **Propylene Glycole:**
  - **Usually used as a vehicle for organic compounds.**
  - **Used alone as a keratolytic agent in concentrations of 40%- 70%, with plastic occlusion, or in gel with 6% salicylic acid.**
  - **Minimally absorbed, oxidized in liver to lactic acid and pyruvic acid.**
  - **Develops an osmotic gradient through the stratum corneum, thereby increasing hydration of the outer layers of skin.**

Keratolytic and Destructive Agents

- **Salicylic acid.**
- **Propylene Glycole.**
- **Urea:**
  - **Has a humectant activity, i.e. softening and moisturizing effect on the stratum corneum.**
  - **Increases water content as a result of its hygroscopic characteristics.**
  - **Decreases the unpleasant oily feel of dermatologic preparations.**
  - **When absorbed, it is excreted in urine.**

Keratolytic and Destructive Agents

- **Salicylic acid.**
- **Propylene Glycole.**
- **Urea:**
- **Podophyllum Resin and Podofilox:**
  - **An alcoholic extract of P*odophyllum peltatum*(Mandrake root or May apple).**
  - **Used in the treatment of condyloma acuminatum and other verrucae.**
  - **Cytotoxic activity with specific affinity for the microtubule protein of the mitotic spindle.**
  - **Can cause N, V, muscle weakness, neuropathy, coma, and even death.**

Keratolytic and Destructive Agents

- **Salicylic acid.**
- **Propylene Glycole.**
- **Urea:**
- **Podophyllum Resin and Podofilox.**
- **Flurouracil:**
  - **Antimetabolite that resembles uracil and inhibits thymidylate synthetase, thus interferes with DNA and may be RNA synthesis.**
  - **Used in multiple actinic keratosis.**

Keratolytic and Destructive Agents

- **Salicylic acid.**
- **Propylene Glycole.**
- **Urea:**
- **Podophyllum Resin and Podofilox.**
- **Flurouracil.**
- **Nonsteroidal Anti-inflammatory Drugs:**
  - **3% gel formulation diclofenac.**

Keratolytic and Destructive Agents

- **Salicylic acid.**
- **Propylene Glycole.**
- **Urea:**
- **Podophyllum Resin and Podofilox.**
- **Flurouracil.**
- **Nonsteroidal Anti-inflammatory Drugs.**
- **Aminolevulinic Acid:**
  - **Used in actinic keratosis.**
  - **After topical application(20%) and exposure to light, produces a cytotoxic superoxide and hydroxyl radicals.**

Antipruritic Agents

- **Doxepine:**
  - **Potent H_1 and H_2 _ receptor antagonist.**
  - **Can cause drowsiness and anticholinergic effects.**
- **Pramoxine:**
  - **Is a topical local anesthetic agent.**

Trichogenic and Antitrichogenic Agents

- **Minoxidil (Rogaine):**
  - **Designed as an antihypertensive agent.**
  - **Effective in reversing the progressive miniaturization of terminal scalp hairs associated with androgenic alopecia.**
  - **Vertex balding is more responsive than frontal balding.**

Trichogenic and Antitrichogenic Agents

- **Minoxidil.**
- **Finasteride (Propecia):**
  - **5ά-reductase inhibitor which blocks the conversion of testosterone to dihydrotestosterne.**
  - **Oral tablets.**
  - **Can cause decreased libido, ejaculation disorders, and erectile dysfunction.**

Trichogenic and Antitrichogenic Agents

- **Minoxidil.**
- **Finasteride.**
- **Eflornithine:**
  - **Is an irreversible inhibitor of ornithine decarboxylase, therefore, inhibits polyamine synthesis. Polyamines are important in cell division and hair growth.**
  - **Effective in reducing facial hair growth in 30% of women when used for 6 months.**

Drugs for Leishmania

Caused by three *Leishmania species:*

***L.tropica* causes: Cutaneous leishmaniasis or oriental sore.**

***L. brazeliensis* causes: Mucocutaneous leishmaniasis.**

***L. Donovani* causes: Visceral leishmaniasis**

Sodium Stibogluconate

Pentravalent antimonial

Binds to SH groups on proteins.

Typical preparations contain 30% to 34% pentavalent antimony by weight as well as *m*-chlorocresol added as a preservative.

Also, inhibits phosphofructokinase

Local, IM or slow IV, irritant.

Given for 20-28 days.

Drug of choice for all forms of leishmaniasis.

Resistance is increasing, especially in India.

Cough, V, D, myalgia, arthralgia, ECG changes, Rash, Pruritus.

Amphotericin

- **Antifungal agent, difficult to use, and toxic.**
- **Alternative therapy for visceral leishmaniasis, especially in areas with high resistance.**

Miltefosine

- **For visceral leishmaniasis.**
- **Given orally, for 28 days.**
- **Causes V & D, hepatotoxicity, nephrotoxicity, and it is teratogenic.**

Pentamidine

- **Inhibits DNA replication.**
- **Also, DHF reductase inhibitor**

- **Given IM or IV injection and Inhalation**
- **Binds avidly to tissues, not the CNS.**

Pentamidine

Leishmaniasis:

Alternative to Na stibogluconate

Pneumocystis jiroveci:

Treatment and prophylaxis of patients who cannot tolerate or fail other drugs.

Trypanosomiasis:

For early hemolymphatic stage.

Pentamidine

- **<u>Adverse Effects:</u>**
- **Rapid Infusion: Hypotension, tachycardia, dizziness.**
- **Pain at the injection site.**
- **Others: Pancreatic, Renal, and Hepatic toxicity.**

Antilepromatous Drugs

- **Dapsone and Sulphones:**
  - **Related to sulphonamides.**
  - **Inhibit folate synthesis.**
  - **Resistance develops.**
  - **Combined with Rifampin and Clofazimine.**
  - **Also used for *Pn. Jeroveci* in AIDS patients.**
  - **Well absorbed and distributed.**
  - **Retained in the skin, muscle, liver and kidney.**

Antilepromatous Drugs

- **<u>Dapsone and Sulphones:</u>**
  - **Hemolysis, particularly in G-6-PD deficiency.**
  - **GIT intolerance**
  - **Fever, Pruritus, Rashes.**
  - **Erythema Nodosum Leprosum:**

    suppressed by steroids or thalidomide.

Antilepromatous Drugs

- **Rifampin:**
  - **Discussed with antituberculous drugs.**
- **Clofazimine:**
  - **Binds to DNA.**
  - **Stored widely in RES and skin.**
  - **Released slowly from storage sites, $t_{1/2}$ = 2 months.**
  - **Given for sulphone- resistant or intolerant cases.**
  - **Causes skin discoloration (red-brown to black) and GIT intolerance.**