

Skin Pharmacology

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Dermatologic Pharmacology

Variables affecting Pharmacologic Response:

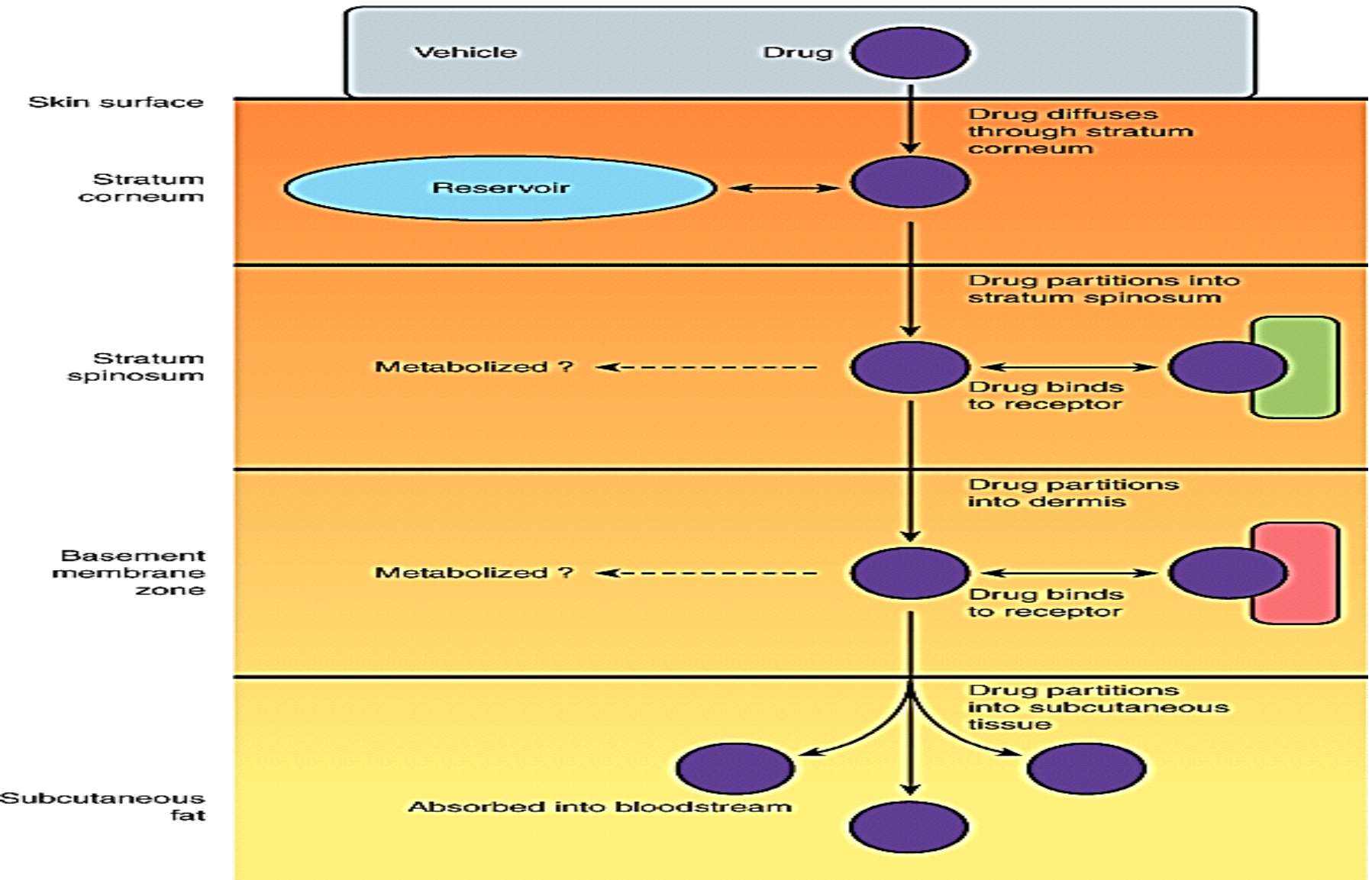
Regional variation in drug penetration.

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
 - Fusidic acid

- **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)

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.

Fusidic acid

- acts as a bacterial protein synthesis inhibitor
- Staphylococcus species, Streptococcus species, and Corynebacterium species.
- often used topically in creams and eyedrops



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

Acne treatment

- ✚ **One of the most common skin diseases presenting to family physicians**
- ✚ **Considerable psychological impact on the quality of life**
- ✚ **Four main factors cause acne:**
 - **Excess oil (sebum) production.**
 - **Hair follicles clogged by oil and dead skin cells.**
 - **Bacteria.**
 - **Inflammation**
- ✚ **The anaerobic bacterium *Cutibacterium acnes* (*Propionibacterium acnes*) is believed to play an important role in the pathophysiology of the common skin disease acne vulgaris.**

Comedonal Lesions



Inflammatory Lesions



Nodulocystic Lesions







Scarring



Topical Therapy (Indications)

-  **comedonal acne**
-  **mild to moderate inflammatory acne**

Topical Therapy (Treatment Vehicle)

-  **cream → sensitive or dry skin**
-  **lotion → any skin type**
-  **gel → oily skin**
-  **solution → oily skin**

Topical Therapy (Anti Comedonal Agents)

 **Topical Retinoids 0.025% - 0.5%**

 **Azelaic acid**

 **Salicylic acid**

Topical Retinoids (Adapalene, Differin)

Topical Retinoids 0.025% - 0.5%

- apply at night
- always apply test dose
- start at low concentrations
- avoid in pregnancy


Side Effects:

- pustular flare
- photosensitivity
- skin irritation and erythema
- dryness and peeling

Avoid in Pregnancy



Azelaic Acid 20%





 **competitive inhibitor of mitochondrial oxidoreductases and of 5 alpha-reductase, inhibiting the conversion of testosterone to 5-dehydrotestosterone. It also possesses bacteriostatic activity to both aerobic and anaerobic bacteria including Propionibacterium acnes**

 **applied twice daily**

 **Side Effects**

- **erythema and irritation**
- **decrease in pigmentation**

Salicylic Acid 0.5 - 2%

-  **keratolytic. It belongs to the same class of drugs as aspirin (salicylates)**
-  **Can reduce swelling and redness and unplugging blocked skin pores to allow pimples to shrink**
-  **applied twice daily**
-  **skin dryness and irritation**

Topical Therapy (Anti Inflammatory Agents)

 **Benzoyl Peroxide 2.5 - 10%**

**exhibits bactericidal effects against *Cutibacterium*
acnes**

 **apply once to twice daily**

 **always apply test dose**

 **avoid use at night**

 **dryness of skin**

Topical Therapy (Anti Inflammatory Agents)

 **Clindamycin.**

 **Erythromycin.**

- **apply twice daily**
- **skin dryness**

Combination therapy

 **5% Benzoyl Peroxide and 3% Erythromycin**

 **5% Benzoyl Peroxide and 1% Clindamycin**

 **Topical antibiotics and Azelaic acid or Tretinoin**

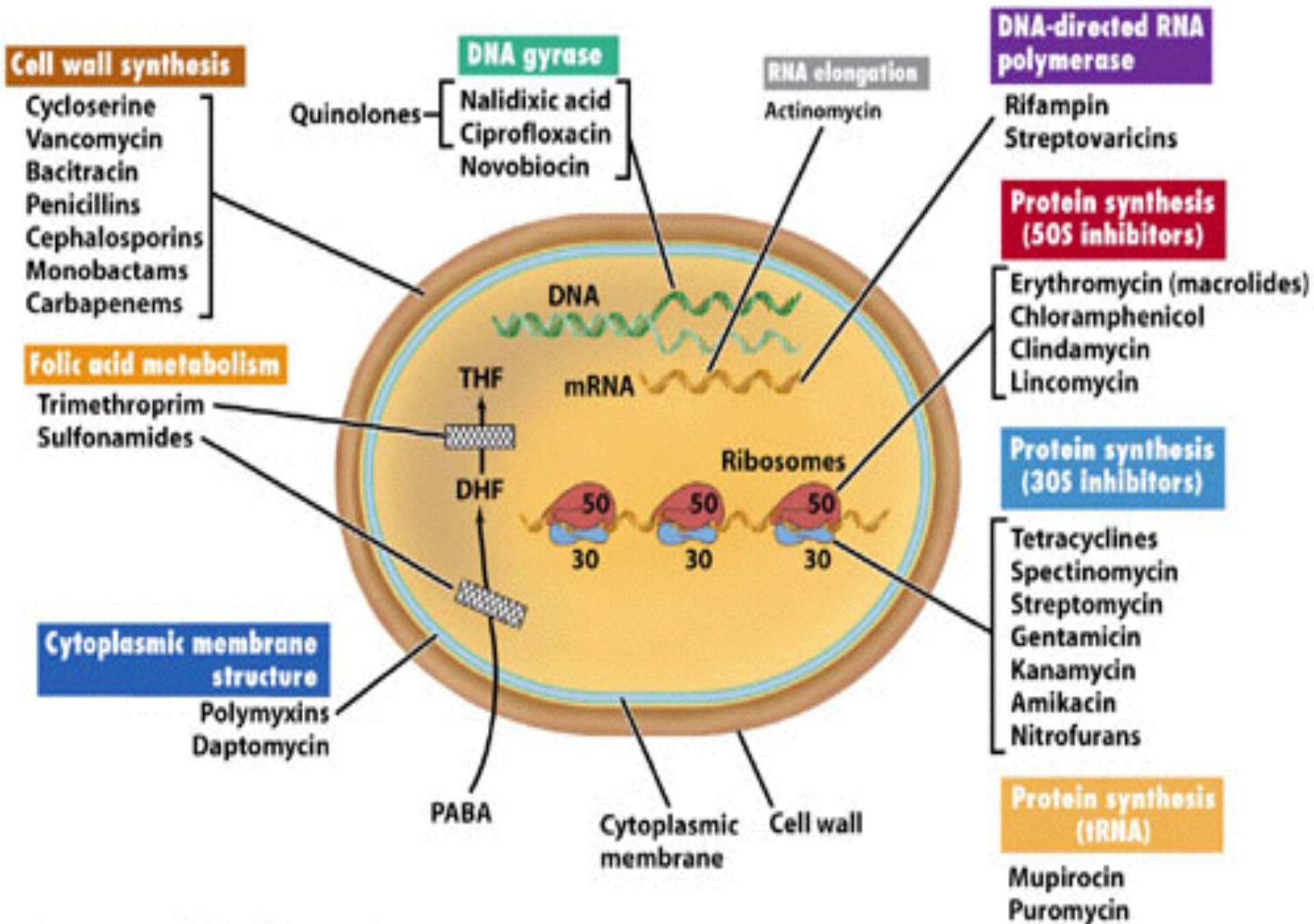


Figure 20-14 Brock Biology of Microorganisms 11/e
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Clindamycin

- 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).

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
- 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.
- Rosacea: common skin condition that causes blushing or flushing and visible blood vessels in your face. It may also produce small, pus-filled bumps. These signs and symptoms may flare up for weeks to months and then go away for a while



Metronidazole

- 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.
 - ✚ Caution should be exercised when applying metronidazole near the eyes to avoid excessive tearing.

Systemic therapy

Indications:

- **Moderate inflammatory acne non-responsive to topical therapy**
- **nodulocystic acne**

Systemic therapy

 **Oral Antibiotics**

 **Isotretinoin**

 **Hormonal Therapy**

Oral Antibiotics (used for 3-6 months)

 **Tetracycline 500mg X BD**




 **Doxycycline 100mg X BD**

 **Minocycline 100mg X OD**







 **Erythromycin 500mg X BD**


 **combined with topical therapy**

Isotretinoin (Accutane) indicated in




-  **severe nodulocystic acne**
-  **non responsive acne**
-  **severe psychological distress**

Isotretinoin (RoAccutane) side effects

-  **teratogenic**
-  **mucosal dryness**
-  **photosensitivity**
-  **arthralgias**
-  **alteration of liver enzymes**
-  **hypertriglyceridemia and hypercholesterolemia**

-  **Tumerogenic in animals**

Isotretinoin (RoAccutane)

-  **Retinoic Acid(Tretinoin):** is the acid form of Vitamin A. Stabilizes lysosomes, increases RNA polymerase activity, increases PGE₂, 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.**

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 D₃ derivative

New Drugs for Psoriasis

Apremilast(Otezla)

- psoriasis and psoriatic arthritis.
- It may also be useful for other immune system-related inflammatory diseases.
- The drug acts as a selective inhibitor of the enzyme phosphodiesterase 4 (PDE4) and inhibits spontaneous production of TNF-alpha from human rheumatoid synovial cells.

Side Effects

- diarrhea
 - nausea.
 - stomach pain.
 - vomiting.
 - headache.
 - sore throat, cough, and fever.
 - sneezing, runny nose, and nasal congestion.
- e-to-severe psoriasis demonstrating superior efficacy to apremilast

New Drugs for Psoriasis

Deucravacitinib (Sotyktu)

- A new oral treatment option for adults with plaque psoriasis.
- moderate-to-severe plaque psoriasis
- It is a once-daily oral medication with its clinical trials in moderate-to-severe psoriasis demonstrating superior efficacy to apremilast
- MOA: Allosteric inhibitor of TYK2
- Side effects: runny nose, congestion, or sore throat, sore on mouth, lips, gums, tongue or roof of mouth, acne.

New Drugs for Psoriasis

Roflumilast (Zorvye) cream

selective, long-acting inhibitor of the enzyme phosphodiesterase-4 (PDE-4). It has anti-inflammatory effects

- chronic plaque psoriasis
- an effective topical therapy for use on all psoriasis-affected areas including body, face, and intertriginous areas

Tapinarof (Vtama) is a topical (on the skin) medication used to treat plaque psoriasis in adults.

- MOA: immune modulation, skin-barrier normalization, and antioxidant activity.
- It's convenient to use because it's only applied once daily

Drugs for Psoriasis

- **Biologic Agents:**

- **Alefacept:**

- Immunosuppressive dimer fusion protein of CD2 linked to the Fc portion of human IgG₁.

- **Efalizumab:**

- Recombinant humanized IgG₁ monoclonal antibody.
 - Withdrawn :progressive multifocal leukoencephalopathy (PML),
 - Can cause thrombocytopenia.

- **Etanercept:**

- Dimeric fusion protein of TNF receptor linked to the Fc portion of human IgG₁.

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.

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.

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):
 - 5 α -reductase inhibitor which blocks the conversion of testosterone to dihydrotestosterone.
 - 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.