CHAPTER

61 Dermatologic Pharmacology

Dirk B. Robertson, MD &
Howard I. Maibach, MD

السلام عليكم..
لاحظنا إنه الدكتورة بتقرأ حرفي من الكتاب فآثرنا إنه نحط الصفحات مع تظليل الكلام
اللي بتحكيه الدكتورة تمامًا
-الصفحات ملينة بس المحدد مش كتير
المحاضرة الأولى أول صفحات ونص مع تحيات

CASE STUDY

A 43-year-old woman presents with a complaint of worsening rosacea. She initially responded to once-daily topical metronidazole 0.75% gel with excellent clearing of the papulopustular component of her acne rosacea. Recently, she has noted increasing persistent facial erythema. What therapeutic options are available?

شامل حكي الدكتورة + السلايدات

Diseases of the skin offer special opportunities to the clinician. In particular, the topical administration route is especially appropriate for skin diseases, although some dermatologic diseases respond as well or better to drugs administered systemically.

The general pharmacokinetic principles governing the use of drugs applied to the skin are the same as those involved in other routes of administration (see Chapters 1 and 3). Although often depicted as a simple three-layered structure, human skin is a complex series of diffusion barriers (Figure 61–1). Quantitation of the flux of drugs and drug vehicles through these barriers is the basis for pharmacokinetic analysis of dermatologic therapy, and techniques for making such measurements are rapidly increasing in number and sensitivity.

Major variables that determine pharmacologic response to drugs applied to the skin include the following:

1. **Regional variation in drug penetration:** For example, the scrotum, face, axilla, and scalp are far more permeable than the forearm and may require less drug for equivalent effect.
2. **Concentration gradient:** Increasing the concentration gradient increases the mass of drug transferred per unit time, just as in the case of diffusion across other barriers (see Chapter 1). Thus, resistance to topical corticosteroids can sometimes be overcome by use of higher concentrations of drug.
3. **Dosing schedule:** Because of its physical properties, skin acts as a reservoir for many drugs. As a result, the "local half-life" may be long enough to permit once-daily application of drugs with short systemic half-lives. For example, once-daily application of corticosteroids appears to be just as effective as multiple applications in many conditions.
4. **Vehicles and occlusion:** An appropriate vehicle maximizes the ability of the drug to penetrate the outer layers of the skin. In addition, through their physical properties (moistening or drying effects), vehicles may themselves have important therapeutic effects. Occlusion (application of a plastic wrap to hold the drug and its vehicle in close contact with the skin) is extremely effective in maximizing efficacy.

   something(like a plastic wrap) that we add to the drug to keep it in place

   vehicle = carrier

   eg: alcohol causes dryness of the skin,
   creams and oilments cause its moisturization

REACTIONS TO DERMATOLOGIC MEDICATIONS

Skin reacts to many systemic medications with a variety of symptom-generating responses. In addition, some dermatologic medications themselves cause skin reactions. The major types of reactions are summarized in Table 61–1.

DERMATOLOGIC VEHICLES

Topical medications usually consist of active ingredients incorporated in a vehicle that facilitates cutaneous application. Important considerations in vehicle selection include solubility of the active

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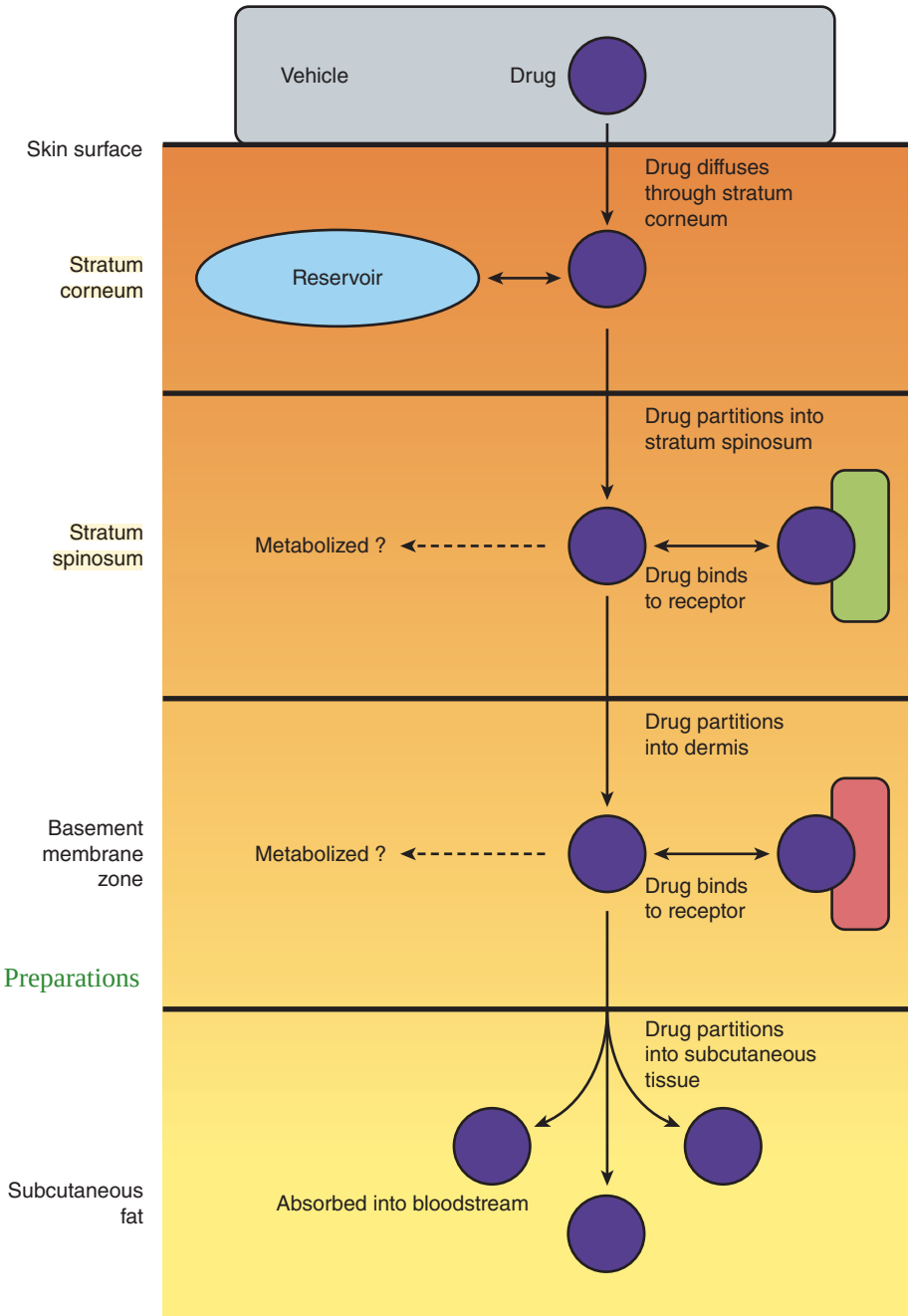

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Adverse Effects of Dermatologic Preparations
- Burning or stinging sensation.
- Drying and irritation
- Pruritus.ةكح
- Erythema. رارمحا
- Sensitization.
- Staining
- Superficial erosion.

FIGURE 61–1 Schematic diagram of percutaneous absorption. (Redrawn from Orkin M, Maibach HI, Dahl MV: *Dermatology*. Appleton & Lange, 1991.)

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agent in the vehicle; the rate of release of the agent from the 3 vehicle; the ability of the vehicle to hydrate the stratum corneum, 4 thus enhancing penetration; the stability of the therapeutic agent in the vehicle; and interactions, chemical and physical, of the vehicle, stratum corneum, and active agent.

Depending upon the vehicle, dermatologic formulations may be classified as tinctures, wet dressings, lotions, gels, aerosols, powders, pastes, creams, foams, and ointments. The ability of the vehicle to retard evaporation from the surface of the skin increases in this series, being least in tinctures and wet dressings and greatest in ointments. In general, acute inflammation with oozing, vesiculation, and crusting is best treated with drying preparations such as tinctures, wet dressings, and lotions, whereas chronic inflammation with xerosis, scaling, and lichenification is best treated with more lubricating preparations such as creams and ointments. Tinctures, lotions, gels, foams, and aerosols are convenient for application to the scalp and hairy areas. Emulsified vanishing-type creams may be used in intertriginous areas without causing maceration.

Emulsifying agents provide homogeneous, stable preparations when mixtures of immiscible liquids such as oil-in-water creams

These are agents that help keep a mixture of immiscible liquid together

TABLE 61–1 Local cutaneous reactions to topical medications.

Reaction Type	Mechanism	Comment
Irritation	Nonallergic	Most common local reaction
Photoirritation	Nonallergic	Phototoxicity; usually requires UVA exposure (sun light)
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
Nonimmunologic contact urticaria	Nonallergic	Most common contact urticaria; occurs without prior sensitization

Contact = touch
Urticaria = rxn that happens within 10-15 min of contact, usually resorb very quickly
↳ happens because of a previous contact.
↳ happens without a previous contact with the thing that causes the condition

are compounded. Some patients develop irritation from these agents. Substituting a preparation that does not contain them or using one containing a lower concentration may resolve the problem.

ANTIBACTERIAL AGENTS

TOPICAL ANTIBACTERIAL PREPARATIONS

Topical antibacterial agents may be useful in preventing infections in clean wounds, in the early treatment of infected dermatoses and wounds, in reducing colonization of the nares by staphylococci, in axillary deodorization, and in the management of acne vulgaris. Efficacy of antibiotics in these topical applications is not uniform. The general pharmacology of the antimicrobial drugs is discussed in Chapters 43–51.

Some topical anti-infectives contain corticosteroids in addition to antibiotics. There is no convincing evidence that topical corticosteroids inhibit the antibacterial effect of antibiotics when the two are incorporated in the same preparation. In the treatment of secondarily infected dermatoses, which are usually colonized with streptococci, staphylococci, or both, combination therapy may prove superior to corticosteroid therapy alone. Antibiotic-corticosteroid combinations may be useful in treating diaper dermatitis, otitis externa, and impetiginized eczema.

Selection of a particular antibiotic depends upon the diagnosis and, when appropriate, in vitro culture and sensitivity studies of clinical samples. The pathogens isolated from most infected dermatoses are group A β-hemolytic streptococci, *Staphylococcus aureus,* or both. The pathogens present in surgical wounds will be those resident in the environment. Information about regional patterns of drug resistance is therefore important in selecting a therapeutic agent. Prepackaged topical antibacterial preparations that contain multiple antibiotics are available in fixed dosages well above the therapeutic threshold. These formulations offer the advantages of efficacy in mixed infections, broader coverage for infections due to undetermined pathogens, and delayed microbial resistance to any single component antibiotic.

BACITRACIN & GRAMICIDIN

Bacitracin and gramicidin are peptide antibiotics, active against Gram-positive organisms such as streptococci, pneumococci, and staphylococci. In addition, most anaerobic cocci, neisseriae, tetanus bacilli, and diphtheria bacilli are sensitive. Bacitracin is compounded in an ointment base alone or in combination with neomycin, polymyxin B, or both. The use of bacitracin in the anterior nares may temporarily decrease colonization by pathogenic staphylococci. Microbial resistance may develop following prolonged use. Bacitracin-induced contact urticaria syndrome, including anaphylaxis, occurs rarely. Allergic contact dermatitis occurs frequently, and immunologic allergic contact urticaria rarely. Bacitracin is poorly absorbed through the skin, so systemic toxicity is rare.

Side effects

Usually Antiinflammatory agents is added, like (Hydrocortisone)

Gramicidin is available only for topical use, in combination with other antibiotics such as neomycin, polymyxin, bacitracin, and nystatin. Systemic toxicity limits this drug to topical use. The incidence of sensitization following topical application is exceedingly low in therapeutic concentrations. (Rare systemic side effects because the applied concentration is low).

Hemolysis is one of its rare side effects

MUPIROCIN

Mupirocin (pseudomonic acid A) is structurally unrelated to other currently available topical antibacterial agents. Most Gram-positive aerobic bacteria, including methicillin-resistant *S aureus* (MRSA), are sensitive to mupirocin (see Chapter 50). It is effective in the treatment of impetigo caused by *S aureus* and group A β-hemolytic streptococci.

Intranasal mupirocin ointment for eliminating nasal carriage of *S aureus* may be associated with irritation of mucous membranes caused by the polyethylene glycol vehicle. Mupirocin is not appreciably absorbed systemically after topical application to intact skin.

RETAPAMULIN

Retapamulin (Altabax) is a semisynthetic pleromutilin derivative effective in the treatment of uncomplicated superficial skin infection caused by group A β-hemolytic streptococci and *S aureus*, excluding MRSA. Topical retapamulin 1% ointment is indicated for use in adult and pediatric patients, 9 months or older, for the treatment of impetigo. Recommended treatment regimen is twice-daily application for 5 days. Retapamulin is well tolerated with only occasional local irritation of the treatment site. Although uncommon, allergic contact dermatitis has been reported.

POLYMYXIN B SULFATE

Polymyxin B is a peptide antibiotic effective against Gram-negative organisms, including *Pseudomonas aeruginosa, Escherichia coli, Enterobacter,* and *Klebsiella*. Most strains of *Proteus* and *Serratia*

are resistant, as are all Gram-positive organisms. Topical preparations may be compounded in either a solution or ointment base. Numerous prepackaged antibiotic combinations contain polymyxin B. Detectable serum concentrations are difficult to achieve from topical application, but the total daily dose applied to denuded skin or open wounds should not exceed 200 mg in order to reduce the likelihood of neurotoxicity and nephrotoxicity. Allergic contact dermatitis to topically applied polymyxin B sulfate is uncommon.

Side effects

NEOMYCIN & GENTAMICIN

Be careful with systemic toxicity : especially in renal failure.
• Hospital acquired resistant patients.

Neomycin and gentamicin are aminoglycoside antibiotics active against Gram-negative organisms, including *E coli, Proteus, Klebsiella,* and *Enterobacter*. Gentamicin generally shows greater activity against *P aeruginosa* than neomycin. Gentamicin is also more active against staphylococci and group A β-hemolytic streptococci. Widespread topical use of gentamicin, especially in a hospital environment, should be avoided to slow the appearance of gentamicin-resistant organisms.

Neomycin is available in numerous topical formulations, alone and in combination with polymyxin, bacitracin, and other antibiotics. It is also available as a sterile powder for topical use. Gentamicin is available as an ointment or cream.

Topical application of neomycin rarely results in detectable serum concentrations. However, in the case of gentamicin, serum concentrations of 1–18 mcg/mL are possible if the drug is applied in a water-miscible preparation to large areas of denuded skin, as in burned patients. Both drugs are water-soluble and are excreted primarily in the urine. Renal failure may permit the accumulation of these antibiotics, with possible nephrotoxicity, neurotoxicity, and ototoxicity.

Neomycin frequently causes allergic contact dermatitis, particularly if applied to eczematous dermatoses or if compounded in an ointment vehicle. When sensitization occurs, cross-sensitivity to streptomycin, kanamycin, paromomycin, and gentamicin is possible.

TOPICAL ANTIBIOTICS IN ACNE

Systemic antibiotics traditionally used in the treatment of acne vulgaris have been shown effective when applied topically. Currently, two antibiotics are used topically for this indication: clindamycin phosphate and erythromycin base. Effectiveness of topical therapy is less than that achieved by its oral administration. Therefore, topical therapy is generally suitable only in mild to moderate cases of inflammatory acne.

Topical Antibacterials in Acne
• Clindamycin.
• Erythromycin.
• Metronidazole: rosacea
• Sodium sulfacetamide.
• Dapsone

Clindamycin

Binds to the 50s Ribosomal subunit

Clindamycin has in vitro activity against *Propionibacterium acnes;* this has been postulated as the mechanism of its beneficial effect in acne therapy. Approximately 10% of an applied dose is absorbed, and rare cases of bloody diarrhea and pseudomembranous colitis have been reported following topical application. 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 are 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, Onexton) and with tretinoin (Velitin, Ziana).

Erythromycin

In topical preparations, erythromycin base rather than a salt is used to facilitate penetration. The mechanism of action of topical erythromycin in inflammatory acne vulgaris is unknown but is presumed to be due to its inhibitory effects on *P acnes*. One complication of topical therapy is the development of antibiotic-resistant strains of organisms, including staphylococci. If this occurs in association with a clinical infection, topical erythromycin should be discontinued and appropriate systemic antibiotic therapy started. Adverse local reactions to erythromycin solution may include a burning sensation at application time and drying and irritation of the skin. The topical water-based gel is less drying and may be better tolerated. Allergic contact dermatitis is uncommon. Erythromycin is also available in a fixed combination preparation with benzoyl peroxide (Benzamycin) for topical treatment of acne vulgaris.

Metronidazole

Topical metronidazole is effective in rosacea treatment. The mechanism of action is unknown, but it may relate to the inhibitory effects of metronidazole on *Demodex brevis;* alternatively, the drug may act as an anti-inflammatory agent by direct effect on neutrophil cellular function. Oral metronidazole has been shown to be a carcinogen in susceptible rodent species, and topical use during pregnancy and by nursing mothers and children is therefore not recommended.

Adverse local effects of the water-based gel formulation (MetroGel) 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.

a side effect of this drug if applied close to the eye

Ivermectin

Topical ivermectin is available as a 1% cream (Soolantra) for the treatment of inflammatory lesions of rosacea. The mechanism of action is unknown. Oral ivermectin has antiparasitic activity against *Demodex* mites and possibly an anti-inflammatory effect. Topical application is well tolerated with occasional complaints of burning and irritation.

Sodium Sulfacetamide

Topical sulfacetamide is available alone as a 10% lotion (Klaron) and as a 10% wash (Ovace), and in several preparations in combination with sulfur for the treatment of acne vulgaris and acne rosacea. The mechanism of action is thought to be inhibition of

P acnes by competitive inhibition of *p*-aminobenzoic acid utilization. Approximately 4% of topically applied sulfacetamide is absorbed percutaneously, and its use is therefore contraindicated in patients having a known hypersensitivity to sulfonamides.

Dapsone

Topical dapsone is available as a 5% and 7.5% gel (Aczone) for the treatment of acne vulgaris. The mechanism of action is unknown. Topical use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency has not been shown to cause clinically relevant hemolysis or anemia, but a slight decrease in hemoglobin concentration was noted in patients with G6PD deficiency, suggestive of mild hemolysis. Cases of methemoglobinemia have been reported in association with topical dapsone gel, and its use should be avoided in patients with congenital or idiopathic methemoglobinemia. Adverse local side effects include mild dryness, redness, oiliness, and skin peeling. Application of dapsone gel followed by benzoyl peroxide may result in a temporary yellow discoloration of the skin and hair.

ANTIFUNGAL AGENTS

The treatment of superficial fungal infections caused by dermatophytic fungi may be accomplished (1) with topical antifungal agents, eg, clotrimazole, efinaconazole, econazole, ketoconazole, luliconazole, miconazole, oxiconazole, sertaconazole, sulconazole, ciclopirox olamine, naftifine, terbinafine, butenafine, and tolnaftate; or (2) with orally administered agents, ie, griseofulvin, terbinafine, fluconazole, and itraconazole. Their mechanisms of action are described in Chapter 48. Superficial infections caused by *Candida* species may be treated with topical applications of clotrimazole, miconazole, econazole, ketoconazole, oxiconazole, ciclopirox olamine, nystatin, or amphotericin B.

TOPICAL ANTIFUNGAL PREPARATIONS

TOPICAL AZOLE DERIVATIVES

The topical imidazoles, which include clotrimazole, econazole, ketoconazole, luliconazole, miconazole, oxiconazole, sertaconazole, and sulconazole, have a wide range of activity against dermatophytes (*Epidermophyton*, *Microsporum*, and *Trichophyton*) and yeasts, including *Candida albicans* and *Pityrosporum orbiculare* (see Chapter 48).

43:51 دقيقة بالعربي

Miconazole (Monistat, Micatin) is available for topical application as a cream or lotion and as vaginal cream or suppositories for use in vulvovaginal candidiasis. Clotrimazole (Lotrimin, Mycelex) is available for topical application to the skin as a cream or lotion and as vaginal cream and tablets for use in vulvovaginal candidiasis.

Efinaconazole (Jublia) is available as a 10% solution for the treatment of onychomycosis of the toenails. Daily application to affected toenails should be continued for 48 weeks. Complete cure rates in clinical trials are between 15% and 18%. Econazole (Spectazole) is available as a cream for topical application. Oxiconazole (Oxistat) is available as a cream and lotion for topical use. Ketoconazole (Nizoral) is available as a cream for topical treatment of dermatophytosis and candidiasis and as a shampoo or foam for the treatment of seborrheic dermatitis. Luliconazole (Luzu) is available as a cream. Sulconazole (Exelderm) is available as a cream or solution. Sertaconazole (Ertaczo) is available as a cream. Topical antifungal-corticosteroid fixed combinations have been introduced on the basis of providing more rapid symptomatic improvement than an antifungal agent alone. Clotrimazole-betamethasone dipropionate cream (Lotrisone) is one such combination.

Once- or twice-daily application to the affected area will generally result in clearing of superficial dermatophyte infections in 2–3 weeks, although the medication should be continued until eradication of the organism is confirmed. Paronychial and intertriginous candidiasis can be treated effectively by any of these agents when applied three or four times daily. Seborrheic dermatitis should be treated with twice-daily applications of ketoconazole until clinical clearing is obtained.

Adverse local reactions to the imidazoles may include stinging, pruritus, erythema, and local irritation. Allergic contact dermatitis is uncommon.

CICLOPIROX OLAMINE

44:55 دقيقة

Ciclopirox olamine is a synthetic broad-spectrum antimycotic agent with inhibitory activity against dermatophytes, *Candida* species, and *P orbiculare*. This agent inhibits the uptake of precursors of macromolecular synthesis; the site of action is probably the fungal cell membrane.

Pharmacokinetic studies indicate that 1–2% of the dose is absorbed when applied as a solution on the back under an occlusive dressing. Ciclopirox olamine is available as a 1% cream and lotion (Loprox) for the topical treatment of dermatomycosis, candidiasis, and tinea versicolor. The incidence of adverse reactions has been low. Pruritus and worsening of clinical disease have been reported. The potential for allergic contact dermatitis is small.

Topical 8% ciclopirox olamine (Penlac nail lacquer) is approved for the treatment of mild to moderate onychomycosis of fingernails and toenails. Although well tolerated with minimal side effects, the complete cure rates in clinical trials are between 5.5% and 8.5%.

TAVABOROLE

Tavaborole is the first oxaborole antifungal drug approved for the treatment of toenail onychomycosis. Tavaborole blocks fungal protein synthesis by inhibiting aminoacyl-transfer ribonucleic acid synthetase. Tavaborole is available as a 5% solution (Kerydin) that should be applied to the affected toenails once daily for 48 weeks. Complete cure rates in clinical trials are between 6.5% and 9.1%.

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 (continued)
• Ciclopirox Olamine.
• Naftifine and Terbinafine.
• Tolnaftate.
• Nystatin and Amphotericin B:
– Only for Candida albicans.
– Available as topical preparations, oral suspension, or vaginal tablets

ALLYLAMINES: NAFTIFINE & TERBINAFINE

Naftifine hydrochloride and terbinafine (Lamisil) are allylamines that are highly active against dermatophytes but less active against yeasts. The antifungal activity derives from selective inhibition of squalene epoxidase, a key enzyme for the synthesis of ergosterol (see Figure 48–1).

They are available as 1% creams and other forms for the topical treatment of dermatophytosis, to be applied on a twice-daily dosing schedule for 1–2 weeks. Adverse reactions include local irritation, burning sensation, and erythema. Contact with mucous membranes should be avoided.

BUTENAFINE

Butenafine hydrochloride (Mentax) is a benzylamine that is structurally related to the allylamines. As with the allylamines, butenafine inhibits the epoxidation of squalene, thus blocking the synthesis of ergosterol, an essential component of fungal cell membranes. Butenafine is available as a 1% cream to be applied once daily for the treatment of superficial dermatophytosis.

TOLNAFTATE

Tolnaftate is a synthetic antifungal compound effective topically against dermatophyte infections caused by *Epidermophyton*, *Microsporum*, and *Trichophyton*. It is also active against *P orbiculare* but not against *Candida*.

Tolnaftate (Aftate, Tinactin) is available as a cream, solution, powder, or powder aerosol for application twice daily to infected areas. Recurrences following cessation of therapy are common, and infections of the palms, soles, and nails are usually unresponsive to tolnaftate alone. The powder or powder aerosol may be used chronically following initial treatment in patients susceptible to tinea infections. Tolnaftate is generally well tolerated and rarely causes irritation or allergic contact dermatitis.

used for only serious fungal infections and sometimes for leishmania , also in asperilloges, mycoses, and cryptocoses

NYSTATIN & AMPHOTERICIN B

Nystatin and amphotericin B are useful in the topical therapy of *C albicans* infections but ineffective against dermatophytes. Nystatin is limited to topical treatment of cutaneous and mucosal candida infections because of its narrow spectrum and negligible absorption from the gastrointestinal tract following oral administration. Amphotericin B has a broader antifungal spectrum and is used intravenously in the treatment of many systemic mycoses (see Chapter 48) and to a lesser extent in the treatment of cutaneous *Candida* infections.

The recommended dosage for topical preparations of nystatin in treating paronychial and intertriginous candidiasis is application two or three times a day. Oral candidiasis (thrush) is treated by holding 5 mL (infants, 2 mL) of nystatin oral suspension in the mouth for several minutes four times daily before swallowing. An alternative therapy for thrush is to retain a vaginal tablet in the mouth until dissolved four times daily. Recurrent or recalcitrant perianal, vaginal, vulvar, and diaper area candidiasis may respond to oral nystatin, 0.5–1 million units in adults (100,000 units in children) four times daily, in addition to local therapy. Vulvovaginal candidiasis may be treated by insertion of 1 vaginal tablet twice daily for 14 days, then nightly for an additional 14–21 days.

Amphotericin B (Fungizone) is available for topical use in cream and lotion form. The recommended dosage in the treatment of paronychial and intertriginous candidiasis is application two to four times daily to the affected area.

Adverse effects associated with oral administration of nystatin include mild nausea, diarrhea, and occasional vomiting. Topical application is nonirritating, and allergic contact hypersensitivity is exceedingly uncommon. Topical amphotericin B is well tolerated and only occasionally locally irritating. The drug may cause a temporary yellow staining of the skin, especially when the cream vehicle is used.

ORAL ANTIFUNGAL AGENTS

Oral Antifungal Agents
• Azole Derivatives:
– Fluconazole.
– Itraconazole.
– Ketoconazole.

ORAL AZOLE DERIVATIVES

Azole derivatives currently available for oral treatment of candida and dermatophyte infections include fluconazole (Diflucan) and itraconazole (Sporanox). As discussed in Chapter 48, imidazole derivatives act by affecting the permeability of the cell membrane of sensitive cells through alterations of the biosynthesis of lipids, especially sterols, in the fungal cell.

Fluconazole and itraconazole are effective in the therapy of cutaneous infections caused by *Epidermophyton*, *Microsporum*, and *Trichophyton* species as well as *Candida*. Tinea versicolor is responsive to short courses of oral azoles.

Fluconazole is well absorbed following oral administration, with a plasma half-life of 30 hours. In view of this long half-life, daily doses of 100 mg are sufficient to treat mucocutaneous candidiasis; alternate-day doses are sufficient for dermatophyte infections. The plasma half-life of itraconazole is similar to that of fluconazole, and detectable therapeutic concentrations remain in the stratum corneum for up to 28 days following termination of therapy. Itraconazole is effective for the treatment of onychomycosis in a dosage of 200 mg daily taken with food to ensure maximum absorption for 3 consecutive months. Recent reports of heart failure in patients receiving itraconazole for onychomycosis have resulted in recommendations that it not be given for treatment of onychomycosis in patients with ventricular dysfunction. Additionally, routine evaluation of hepatic function is recommended for patients receiving itraconazole for onychomycosis.

Administration of oral azoles with midazolam or triazolam has resulted in elevated plasma concentrations and may potentiate and prolong hypnotic and sedative effects of these agents. Administration with HMG-CoA reductase inhibitors has been shown to cause a significant risk of rhabdomyolysis. *Therefore, administration of the oral azoles with midazolam, triazolam, or HMG-CoA inhibitors is contraindicated.*

• Affect the permeability of fungal cell membrane through alteration of sterol synthesis.
• Effective in systemic mycosis, mucocutaneous candidiasis, and other cutaneous infectio
• Might have systemic side effects: hepatitis and liver enzyme elevations, and interactions

available as 100% cream, its adverse effect are irritation, burning sensation, erythema

TERBINAFINE

active against dermatophytes but less active against yeast

Terbinafine (described above) is effective given orally for the treatment of onychomycosis. Recommended oral dosage is 250 mg daily for 6 weeks for fingernail infections and 12 weeks for toenail infections. Patients receiving terbinafine for onychomycosis should be monitored closely with periodic laboratory evaluations for possible hepatic dysfunction. Rare cases of liver failure have occurred with the use of oral terbinafine; therefore, its use is not recommended in patients with chronic or active liver disease.

GRISEOFULVIN

– Requires prolonged treatment:
- 4-6 weeks for the scalp infection.
- 6 months for fingernails infection.
- 8-18 months for toenails infectiin.

Griseofulvin, effective orally against dermatophyte infections caused by *Epidermophyton*, *Microsporum*, and *Trichophyton*, is ineffective against *Candida* and *P orbiculare*. Griseofulvin's mechanism of antifungal action is not fully understood, but it is active only against growing cells.

Following oral administration of 1 g of microsize griseofulvin, drug can be detected in the stratum corneum 4–8 hours later. Reducing the particle size of the medication greatly increases drug absorption. Formulations that contain the smallest particle size are labeled "ultramicrosize." Ultramicrosize griseofulvin achieves bioequivalent plasma levels with half the dose of microsize drug. In addition, solubilizing griseofulvin in polyethylene glycol enhances absorption even further. Microsized griseofulvin is available as 250 mg and 500 mg tablets, and ultramicrosized drug as 125 mg, 165 mg, 250 mg, and 330 mg tablets and as 250 mg capsules.

The usual adult dosage of the microsize form of the drug is 500 mg daily in single or divided doses with meals; occasionally, 1 g/d is indicated in the treatment of recalcitrant infections. The pediatric dosage is 10 mg/kg of body weight daily in single or divided doses with meals. An oral suspension is available for use in children.

Griseofulvin is most effective in treating tinea infections of the scalp and glabrous (nonhairy) skin. In general, infections of the scalp respond to treatment in 4–6 weeks, and infections of glabrous skin will respond in 3–4 weeks. Dermatophyte infections of the nails respond only to prolonged administration. Fingernails may respond to 6 months of therapy, whereas toenails are recalcitrant to treatment and may require 8–18 months of therapy; relapse almost invariably occurs.

Adverse effects seen with griseofulvin therapy include headaches, nausea, vomiting, diarrhea, photosensitivity, peripheral neuritis, and occasionally mental confusion. Griseofulvin is derived from a *Penicillium* mold, and cross-sensitivity with penicillin may occur. It is contraindicated in patients with porphyria or hepatic failure or those who have had hypersensitivity reactions to it in the past. Its safety in pregnant patients has not been established. Leukopenia and proteinuria have occasionally been reported. Therefore, in patients undergoing prolonged therapy, routine evaluation of the hepatic, renal, and hematopoietic systems is advisable. Coumarin anticoagulant activity may be altered by griseofulvin, and anticoagulant dosage may require adjustment.

People that have allergy against penicillin may also have allergy against Griseofulvin

TOPICAL ANTIVIRAL AGENTS

ACYCLOVIR, VALACYCLOVIR, PENCICLOVIR, & FAMCICLOVIR

Acyclovir, valacyclovir, penciclovir, and famciclovir are synthetic guanine analogs with inhibitory activity against members of the herpesvirus family, including herpes simplex types 1 and 2. Their mechanism of action, indications, and oral use in the treatment of cutaneous infections are discussed in Chapter 49.

Topical acyclovir (Zovirax) is available as a 5% ointment and 50 mg buccal tablet; topical penciclovir (Denavir), as a 1% cream for the treatment of recurrent orolabial herpes simplex virus infection in immunocompetent adults. Adverse local reactions to acyclovir and penciclovir may include pruritus and mild pain with transient stinging or burning.

IMMUNOMODULATORS

IMIQUIMOD

Imiquimod is available as 5% cream (Aldara) for the treatment of external genital and perianal warts in adults, actinic keratoses on the face and scalp, and biopsy-proven primary superficial basal cell carcinomas on the trunk, neck, and extremities. Creams with lower concentrations of 2.5% and 3.75% (Zyclara) are available for the treatment of face and scalp actinic keratoses. The mechanism of its action is thought to be related to imiquimod's ability to stimulate peripheral mononuclear cells to release interferon alpha and to stimulate macrophages to produce interleukins-1, -6, and -8, and tumor necrosis factor-α (TNF-α).

Imiquimod should be applied to the wart tissue three times per week and left on the skin for 6–10 hours prior to washing off with mild soap and water. Treatment should be continued until eradication of the warts is accomplished, but not for more than a total of 16 weeks. Recommended treatment of actinic keratoses consists of twice-weekly applications of the 5% cream on the contiguous area of involvement or nightly applications of the 2.5% or 3.75% cream. The cream is removed after approximately 8 hours with mild soap and water. Treatment of superficial basal cell carcinoma consists of five-times-per-week application of 5% cream to the tumor, including a 1 cm margin of surrounding skin, for a 6-week course of therapy.

Percutaneous absorption is minimal, with less than 0.9% absorbed following a single-dose application. Adverse effects consist of local inflammatory reactions, including pruritus, erythema, and superficial erosion.

TACROLIMUS & PIMECROLIMUS

Tacrolimus (Protopic) and pimecrolimus (Elidel) are macrolide immunosuppressants that have been shown to be of significant benefit in the treatment of atopic dermatitis. Both agents inhibit T-lymphocyte activation and prevent the release of inflammatory

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cytokines and mediators from mast cells in vitro after stimulation by antigen-IgE complexes. Tacrolimus is available as 0.03% and 0.1% ointments, and pimecrolimus is available as a 1% cream. Both are indicated for short-term and intermittent long-term therapy for mild to moderate atopic dermatitis. Tacrolimus 0.03% ointment and pimecrolimus 1% cream are approved for use in children older than 2 years of age, although all strengths are approved for adult use. Recommended dosing of both agents is twice-daily application to affected skin until clearing is noted. Neither medication should be used with occlusive dressings. The most common side effect of both drugs is a burning sensation in the applied area that improves with continued use. The US Food and Drug Administration (FDA) mandates a black box warning regarding the long-term safety of topical tacrolimus and pimecrolimus because of animal tumorigenicity data.

ECTOPARASITICIDES

PERMETHRIN

Permethrin is toxic to *Pediculus humanus, Pthirus pubis*, and *Sarcoptes scabiei*. Less than 2% of an applied dose is absorbed percutaneously. Residual drug persists up to 10 days following application. Resistance to permethrin is becoming more widespread.

It is recommended that permethrin 1% cream rinse (Nix) be applied undiluted to affected areas of pediculosis for 10 minutes and then rinsed off with warm water. For the treatment of scabies, a single application of 5% cream (Elimite, Acticin) is applied to the body from the neck down, left on for 8–14 hours, and then washed off. Adverse reactions to permethrin include transient burning, stinging, and pruritus. Cross-sensitization to pyrethrins or chrysanthemums has been alleged but inadequately documented.

SPINOSAD

Spinosad (Natroba) suspension is approved for the topical treatment of head lice in patients 4 years of age and older. Spinosad is derived from the fermentation of a soil *Actinomyces* bacterium and is toxic to *P humanus* with no appreciable absorption from topical application. It is recommended that the 0.9% suspension be applied to the hair and scalp for 10 minutes and then rinsed out. A repeat treatment may be applied 1 week later if live lice are present.

IVERMECTIN

Ivermectin (Sklice) 0.5% lotion is approved for head lice treatment in patients 6 months of age and older. Ivermectin is toxic to *P humanus,* resulting in paralysis and death of the parasite. The pharmacology of ivermectin is discussed in Chapter 53. The lotion should be applied to the hair and scalp and rinsed out after 10 minutes. Ivermectin is for single use only and should not be repeated without health care provider recommendation.

LINDANE (HEXACHLOROCYCLOHEXANE)

The gamma isomer of hexachlorocyclohexane was commonly called gamma benzene hexachloride, a misnomer, since no benzene ring is present in this compound. Percutaneous absorption studies using a solution of lindane in acetone have shown that almost 10% of a dose applied to the forearm is absorbed, to be subsequently excreted in the urine over a 5-day period. After absorption, lindane is concentrated in fatty tissues, including the brain.

Lindane is available as a 1% shampoo or lotion. For pediculosis capitis or pubis, 30 mL of shampoo is applied to dry hair on the scalp or genital area for 4 minutes and then rinsed off. No additional application is indicated unless living lice are present 1 week after treatment. Then reapplication may be required.

Recent concerns about the toxicity of lindane have altered treatment guidelines for its use in scabies; the current recommendation calls for a single 60 mL application to the entire body from the neck down, left on for 8–12 hours, and then washed off. Patients should be retreated only if active mites can be demonstrated, and never within 1 week of initial treatment.

Concerns about neurotoxicity and hematotoxicity have resulted in warnings that lindane should be used with caution in infants, children, and pregnant women. The current USA package insert recommends that it not be used as a scabicide in premature infants and in patients with known seizure disorders. Local irritation may occur, and contact with the eyes and mucous membranes should be avoided.

CROTAMITON

Crotamiton, *N*-ethyl-*o*-crotonotoluidide, is a scabicide with some antipruritic properties; its mechanism of action is not known. Studies on percutaneous absorption have revealed detectable levels of crotamiton in the urine following a single application on the forearm.

Crotamiton (Eurax) is available as a 10% cream or lotion. Suggested guidelines for scabies treatment call for two applications to the entire body from the chin down at 24-hour intervals, with a cleansing bath 48 hours after the last application. Crotamiton is an effective agent that can be used as an alternative to lindane. Allergic contact dermatitis and primary irritation may occur, necessitating discontinuance of therapy. Application to acutely inflamed skin or to the eyes or mucous membranes should be avoided.

SULFUR

Sulfur has a long history as a scabicide. Although it is nonirritating, it has an unpleasant odor, is staining, and is thus disagreeable to use. It has been replaced by more aesthetic and effective scabicides in recent years, but it remains a possible alternative drug for use in infants and pregnant women. The usual formulation is 5% precipitated sulfur in petrolatum.

MALATHION

Malathion is an organophosphate cholinesterase inhibitor that is hydrolyzed and inactivated by plasma carboxylesterases much faster in humans than in insects, thereby providing a therapeutic advantage in treating pediculosis (see Chapter 7). Malathion is available as a 0.5% lotion (Ovide) that should be applied to the hair when dry; 4–6 hours later, the hair is combed to remove nits and lice.

BENZYL ALCOHOL

Benzyl alcohol (Ulesfia) is available as a 5% lotion for the treatment of head lice in patients older than 6 months. The lotion is applied to dry hair and left on for 10 minutes prior to rinsing off with water. Because the drug is not ovicidal, the treatment must be repeated after 7 days. Eye irritation and allergic contact dermatitis have been reported.

AGENTS AFFECTING PIGMENTATION

HYDROQUINONE, MONOBENZONE, & MEQUINOL

Hydroquinone, monobenzone (Benoquin, the monobenzyl ether of hydroquinone), and mequinol (the monomethyl ether of hydroquinone) are used to reduce hyperpigmentation of the skin. Topical hydroquinone and mequinol usually result in temporary lightening, whereas monobenzone causes irreversible depigmentation.

The mechanism of action of these compounds appears to involve inhibition of the enzyme tyrosinase, thus interfering with the biosynthesis of melanin. In addition, monobenzone may be toxic to melanocytes, resulting in permanent loss of these cells. Some percutaneous absorption of these compounds takes place, because monobenzone may cause hypopigmentation at sites distant from the area of application. Both hydroquinone and monobenzone may cause local irritation. Allergic contact dermatitis to these compounds can occur. Prescription combinations of hydroquinone, fluocinolone acetonide, and retinoic acid (Tri-Luma) and mequinol and retinoic acid (Solagé) are more effective than their individual components.

TRIOXSALEN & METHOXSALEN

Trioxsalen and methoxsalen are psoralens used for the repigmentation of depigmented macules of vitiligo. With the development of high-intensity long-wave ultraviolet fluorescent lamps, photochemotherapy with oral methoxsalen for psoriasis and with oral trioxsalen for vitiligo has been under intensive investigation.

Psoralens must be photoactivated by long-wavelength ultraviolet light in the range of 320–400 nm (ultraviolet A [UVA]) to produce a beneficial effect. Psoralens intercalate with DNA, and with subsequent UVA irradiation, cyclobutane adducts are formed with pyrimidine bases. Both monofunctional and bifunctional adducts may be formed, the latter causing interstrand cross-links. These DNA photoproducts may inhibit DNA synthesis. The major long-term risks of psoralen photochemotherapy are cataracts and skin cancer.

SUNSCREENS

Topical medications useful in protecting against sunlight contain either chemical compounds that absorb ultraviolet light, called sunscreens, or opaque materials such as titanium dioxide that reflect light, called sunshades. The three classes of chemical compounds most commonly used in sunscreens are *p*-aminobenzoic acid (PABA) and its esters, the benzophenones, and the dibenzoylmethanes.

Most sunscreen preparations are designed to absorb ultraviolet light in the ultraviolet B (UVB) wavelength range from 280 to 320 nm, which is the range responsible for most of the erythema and sunburn associated with sun exposure and tanning. Chronic exposure to light in this range induces aging of the skin and photocarcinogenesis. Para-aminobenzoic acid and its esters are the most effective available absorbers in the B region. Ultraviolet in the longer UVA range, 320–400 nm, is also associated with skin aging and cancer.

The benzophenones include oxybenzone, dioxybenzone, and sulisobenzone. These compounds provide a broader spectrum of absorption from 250 to 360 nm, but their effectiveness in the UVB erythema range is less than that of PABA. The dibenzoylmethanes include Parsol and Eusolex. These compounds absorb wavelengths throughout the longer UVA range, with maximum absorption at 360 nm. Patients particularly sensitive to UVA wavelengths include individuals with polymorphous light eruption, cutaneous lupus erythematosus, and drug-induced photosensitivity. In these patients, dibenzoylmethane-containing sunscreen may provide improved photoprotection. Ecamsule (Mexoryl) appears to provide greater UVA protection than the dibenzoylmethanes and is less prone to photodegradation.

The sun protection factor (SPF) of a given sunscreen, a measure of its effectiveness in absorbing erythrogenic ultraviolet light, is determined by measuring the minimal erythema dose with and without the sunscreen in a group of normal people. The ratio of the minimal erythema dose with sunscreen to the minimal erythema dose without sunscreen is the SPF.

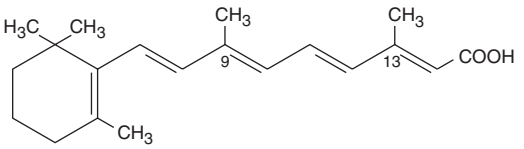
FDA regulations limit the claimed maximum SPF value on sunscreen labels to 50+ because data are insufficient to show that products with SPF values higher than 50 provide greater protection for users. These regulations require that sunscreens labeled "broad spectrum" pass a standard test comparing the amount of UVA radiation protection in relation to the amount of UVB protection. Broad spectrum sunscreens with SPF values of 15 or higher help protect against not only sunburn, but also skin cancer and early skin aging when used as directed. Sunscreens with an SPF value between 2 and 14 can only claim that they help prevent sunburn.

In addition, products claiming to be water resistant must indicate whether they remain effective for 40 minutes or 80 minutes while swimming or sweating, based on standard testing. These regulations are poorly enforced.

ACNE PREPARATIONS

RETINOIC ACID & DERIVATIVES

Retinoic acid, also known as *tretinoin* or all-*trans*-retinoic acid, is the acid form of vitamin A. It is an effective topical treatment for acne vulgaris. Several analogs of vitamin A, eg, 13-*cis*-retinoic acid (isotretinoin), have been shown to be effective in various dermatologic diseases when given orally. Vitamin A alcohol is the physiologic form of vitamin A. The topical therapeutic agent, **retinoic acid,** is formed by the oxidation of the alcohol group, with all four double bonds in the side chain in the *trans* configuration as shown.



Retinoic acid

Retinoic acid is insoluble in water but soluble in many organic solvents. Topically applied retinoic acid remains chiefly in the epidermis, with less than 10% absorption into the circulation. The small quantities of retinoic acid absorbed following topical application are metabolized by the liver and excreted in bile and urine.

Retinoic acid has several effects on epithelial tissues. It stabilizes lysosomes, increases ribonucleic acid polymerase activity, increases prostaglandin E_2, cAMP, and cGMP levels, and increases the incorporation of thymidine into DNA. Its action in acne has been attributed to decreased cohesion between epidermal cells and increased epidermal cell turnover. This is thought to result in the expulsion of open comedones and the transformation of closed comedones into open ones.

Topical retinoic acid is applied initially in a concentration sufficient to induce slight erythema with mild peeling. The concentration or frequency of application may be decreased if too much irritation occurs. Topical retinoic acid should be applied to dry skin only, and care should be taken to avoid contact with the corners of the nose, eyes, mouth, and mucous membranes. During the first 4–6 weeks of therapy, comedones not previously evident may appear and give the impression that the acne has been aggravated by the retinoic acid. However, with continued therapy, the lesions will clear, and in 8–12 weeks optimal clinical improvement should occur. A timed-release formulation of tretinoin containing microspheres (Retin-A Micro) delivers the medication over time and may be less irritating for sensitive patients.

The effects of tretinoin on keratinization and desquamation offer benefits for patients with photo-damaged skin. Prolonged use of tretinoin promotes dermal collagen synthesis, new blood vessel formation, and thickening of the epidermis, which helps diminish fine lines and wrinkles. Specially formulated moisturizing 0.05% cream (Renova, Refissa) is marketed for this purpose.

The most common adverse effects of topical retinoic acid are erythema and dryness that occur in the first few weeks of use, but these can be expected to resolve with continued therapy. Animal studies suggest that this drug may increase the tumorigenic potential of ultraviolet radiation. In light of this, patients using retinoic acid should be advised to avoid or minimize sun exposure and use a protective sunscreen. Allergic contact dermatitis to topical retinoic acid is rare.

Adapalene (Differin) is a derivative of naphthoic acid that resembles retinoic acid in structure and effects. It is available for daily application as a 0.1% gel, cream, or lotion and a 0.3% gel. The 0.1% gel has recently been approved by the FDA for over-the-counter sale. Unlike tretinoin, adapalene is photochemically stable and shows little decrease in efficacy when used in combination with benzoyl peroxide. Adapalene is less irritating than tretinoin and is most effective in patients with mild to moderate acne vulgaris. Adapalene is also available in a fixed-dose combination gel with benzoyl peroxide (Epiduo, Epiduo Forte).

Tazarotene (Tazorac, Fabior) is an acetylenic retinoid available as a 0.1% gel, cream, and foam for the treatment of mild to moderately severe facial acne. Topical tazarotene should be used by women of childbearing age only after contraceptive counseling. It is recommended that tazarotene should not be used by pregnant women.

ISOTRETINOIN

Isotretinoin is a synthetic retinoid currently restricted to the oral treatment of severe cystic acne that is recalcitrant to standard therapies. The precise mechanism of action of isotretinoin in cystic acne is not known, although it appears to act by inhibiting sebaceous gland size and function. The drug is well absorbed, is extensively bound to plasma albumin, and has an elimination half-life of 10–20 hours. A lipid solubilized formulation, CIP-isotretinoin (Absorica), has been approved that provides more consistent absorption and can be taken with or without food.

Most patients with cystic acne respond to 1–2 mg/kg, given in two divided doses daily for 4–5 months. If severe cystic acne persists following this initial treatment, after a period of 2 months, a second course of therapy may be initiated. Common adverse effects resemble hypervitaminosis A and include dryness and itching of the skin and mucous membranes. Less common side effects are headache, corneal opacities, pseudotumor cerebri, inflammatory bowel disease, anorexia, alopecia, and muscle and joint pains. These effects are all reversible on discontinuance of therapy. Skeletal hyperostosis has been observed in patients receiving isotretinoin with premature closure of epiphyses noted in children treated with this medication. Lipid abnormalities (triglycerides, high-density lipoproteins) are frequent; their clinical relevance is unknown at present.

Teratogenicity is a significant risk in patients taking isotretinoin; therefore, the FDA mandates that women of childbearing potential *must* use an effective form of contraception for at least 1 month before, throughout isotretinoin therapy, and for one or more menstrual cycles following discontinuance of treatment.

A negative serum pregnancy test *must* be obtained within 2 weeks before starting therapy in these patients, and therapy should be initiated only on the second or third day of the next normal menstrual period. In the USA, health care professionals, pharmacists, and patients must utilize the mandatory iPLEDGE registration and follow-up system.

BENZOYL PEROXIDE

Benzoyl peroxide, an effective topical agent in acne vulgaris treatment, penetrates the stratum corneum or follicular openings unchanged and is converted metabolically to benzoic acid within the epidermis and dermis. Less than 5% of an applied dose is absorbed from the skin in an 8-hour period. It has been postulated that the mechanism of action of benzoyl peroxide in acne is related to its antimicrobial activity against *P acnes* and to its peeling and comedolytic effects.

To decrease the likelihood of irritation, application should be limited to a low concentration (2.5%) once daily for the first week of therapy and increased in frequency and strength if the preparation is well tolerated. Fixed-combination formulations of 5% benzoyl peroxide with 3% erythromycin base (Benzamycin) or 1% clindamycin (BenzaClin, Duac); 3.75% benzoyl peroxide with 1.2% clindamycin (Onexton); and 2.5% benzoyl peroxide with 1.2% clindamycin (Acanya) or 0.1% adapalene (Epiduo) appear to be more effective than individual agents alone.

Benzoyl peroxide is a potent contact sensitizer in experimental studies, and this adverse effect may occur in up to 1% of acne patients. Care should be taken to avoid contact with the eyes and mucous membranes. Benzoyl peroxide is an oxidant and may rarely cause bleaching of the hair or colored fabrics.

AZELAIC ACID

Azelaic acid is a straight-chain saturated dicarboxylic acid that is effective in the treatment of acne vulgaris (Azelex) and acne rosacea (Finacea, Finacea foam). Its mechanism of action has not been fully determined, but preliminary studies demonstrate antimicrobial activity against *P acnes* as well as in vitro inhibitory effects on the conversion of testosterone to dihydrotestosterone. Initial therapy is begun with once-daily applications of the 20% cream, 15% gel, or 15% foam to the affected areas for 1 week and twice-daily applications thereafter. Most patients experience mild irritation with redness and dryness of the skin during the first week of treatment. Clinical improvement is noted in 6–8 weeks of continuous therapy.

BRIMONIDINE

Brimonidine (Mirvaso) is an α_2-adrenergic agonist indicated for the topical treatment of persistent facial erythema of rosacea in adults 18 years of age or older. Daily topical application of brimonidine 0.33% gel may reduce erythema through direct vasoconstriction. Exacerbation of facial erythema and flushing may occur, ranging from 30 minutes to several hours after application. Alpha$_2$ agonists can lower blood pressure (see Chapter 11); therefore, brimonidine should be used with caution in patients with severe, unstable, or uncontrolled cardiovascular disease.

DRUGS FOR PSORIASIS

ACITRETIN

Acitretin (Soriatane), a metabolite of the aromatic retinoid etretinate, is effective in the treatment of psoriasis, especially pustular forms. It is given orally at a dosage of 25–50 mg/d. Adverse effects attributable to acitretin therapy are similar to those seen with isotretinoin and resemble hypervitaminosis A. Elevations in cholesterol and triglycerides may be noted with acitretin, and hepatotoxicity with liver enzyme elevations has been reported. Acitretin is more teratogenic than isotretinoin in the animal species studied to date, which is of special concern in view of the drug's prolonged elimination time (more than 3 months) after chronic administration. In cases where etretinate is formed by concomitant administration of acitretin and ethanol, etretinate may be found in plasma and subcutaneous fat for many years.

Acitretin must not be used by women who are pregnant or may become pregnant while undergoing treatment or at any time for at least 3 years after treatment is discontinued. Ethanol must be strictly avoided during treatment with acitretin and for 2 months after discontinuing therapy. Patients must not donate blood during treatment and for 3 years after acitretin is stopped.

TAZAROTENE

Tazarotene (Tazorac) is a topical acetylenic retinoid prodrug that is hydrolyzed to its active form by an esterase. The active metabolite, tazarotenic acid, binds to retinoic acid receptors, resulting in modified gene expression. The precise mechanism of action in psoriasis is unknown but may relate to both anti-inflammatory and antiproliferative actions. Tazarotene is absorbed percutaneously, and teratogenic systemic concentrations may be achieved if applied to more than 20% of total body surface area. Women of childbearing potential must therefore be advised of the risk prior to initiating therapy, and adequate birth control measures must be utilized while on therapy.

Treatment of psoriasis should be limited to once-daily application of either 0.05% or 0.1% gel not to exceed 20% of total body surface area. Adverse local effects include a burning or stinging sensation (sensory irritation) and peeling, erythema, and localized edema of the skin (irritant dermatitis). Potentiation of photosensitizing medication may occur, and patients should be cautioned to minimize sunlight exposure and to use sunscreens and protective clothing.

CALCIPOTRIENE & CALCITRIOL

Calcipotriene (Dovonex, Sorilux) is a synthetic vitamin D_3 derivative (available as a 0.005% cream, scalp lotion, and foam) that is effective in the treatment of plaque-type psoriasis vulgaris of

TABLE 61–2 Biologic agents for psoriasis.

Biologic Agent	Usual Adult Dosage
Adalimumab—*Humira*	80 mg SC × 1, then 40 mg q2 weeks
Etanercept—*Enbrel*	50 mg SC twice/week × 12 weeks, then once/week
Infliximab—*Remicade*	5 mg/kg IV at 0, 2, and 6 weeks, then q8 weeks
Ixekizumab—*Taltz*	160 mg at 0 weeks and 80 mg at 2, 4, 6, 8, 10, and 12 weeks, then q4 weeks
Secukinumab—*Cosentyx*	300 mg SC at 0, 1, 2, 3, and 4 weeks, then q4 weeks
Ustekinumab—*Stelara*	Either 45 mg or 90 mg SC at 0 and 4 weeks, then q12 weeks (dose for psoriasis is 45 mg for patients weighing ≤100 kg and 90 mg for those weighing ≥100 kg)

moderate severity. Improvement of psoriasis is generally noted following 2 weeks of therapy, with continued improvement for up to 8 weeks of treatment. However, fewer than 10% of patients demonstrate total clearing while on calcipotriene as single-agent therapy. Adverse effects include burning, itching, and mild irritation, with dryness and erythema of the treatment area. Care should be taken to avoid facial contact, which may cause ocular irritation. A once-daily two-compound ointment (Taclonex) or foam (Enstilar) containing calcipotriene and betamethasone dipropionate are available. This combination is more effective than its individual ingredients and is well tolerated, with a safety profile similar to betamethasone dipropionate.

Calcitriol (Vectical) contains 1,25-dihydroxycholecalciferol, the hormonally active form of vitamin D_3. Calcitriol 3 mcg/g ointment is similar in efficacy to calcipotriene 0.005% ointment for the treatment of plaque-type psoriasis on the body and is better tolerated in intertriginous and sensitive areas of the skin. Clinical studies show comparable safety data regarding adverse cutaneous and systemic reactions between topical calcitriol and calcipotriene ointment.

BIOLOGIC AGENTS

Biologic agents useful in treating adult patients with moderate to severe chronic plaque psoriasis include the TNF-α inhibitors adalimumab, etanercept, and infliximab, and the cytokine inhibitors ixekizumab, secukinumab, and ustekinumab (Table 61–2). The pharmacology of these agents is discussed in Chapters 36 and 55.

APREMILAST

Apremilast (Otezla) is an oral phosphodiesterase 4 (PDE4) inhibitor that is effective in treating moderate to severe plaque psoriasis. Selective inhibition of PDE4 specific for cyclic adenosine monophosphate (cAMP) results in increased intracellular cAMP levels. The specific mechanism by which apremilast exerts its therapeutic effect in psoriasis is not known. Initial dosage titration from day 1 to day 5, intended to reduce the gastrointestinal symptoms associated with starting therapy, is shown in Table 61–3. Following the 5-day titration, a maintenance dose of 30 mg twice daily is started on day 6.

Treatment with apremilast is associated with an increased incidence of depression. Patients should have their weight monitored regularly due to possible weight loss associated with therapy. Use of cytochrome P450 enzyme inducers (see chapter 4) may result in a loss of efficacy and is not recommended. Apremilast is generally well tolerated with mild gastrointestinal complaints occurring early in the course of treatment that resolve with time.

FUMARIC ACID ESTERS

Fumaric acid esters (Fumaderm) are licensed in Germany for the oral treatment of psoriasis. They are considered homeopathic treatment in the USA and are not approved or regulated by the FDA for the treatment of psoriasis. Dimethyl fumarate (Tecfidera) has recently been approved by the FDA for treatment of multiple sclerosis. The mechanism of action of dimethyl fumarate in psoriasis may be due to immunomodulatory effects on lymphocytes and keratinocytes, resulting in a shift away from a psoriatic cytokine profile. Note that four cases of progressive multifocal leukoencephalopathy have been reported in psoriasis patients treated with fumaric acid esters.

■ ANTI-INFLAMMATORY AGENTS

TOPICAL CORTICOSTEROIDS

The remarkable efficacy of topical corticosteroids in the treatment of inflammatory dermatoses was noted soon after the introduction of hydrocortisone in 1952. Numerous analogs are now available that offer extensive choices of potencies, concentrations, and vehicles. The therapeutic effectiveness of topical corticosteroids is based primarily on their anti-inflammatory activity. Definitive explanations of the effects of corticosteroids on endogenous mediators of inflammation await further experimental clarification. The antimitotic effects of corticosteroids on human epidermis may account for an additional mechanism of action in psoriasis and other dermatologic diseases associated with increased cell turnover. The general pharmacology of these endocrine agents is discussed in Chapter 39.

TABLE 61–3 Apremilast dosage titration schedule.

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & Thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

Chemistry & Pharmacokinetics

The original topical glucocorticosteroid was hydrocortisone, the natural glucocorticosteroid of the adrenal cortex. The 9α-fluoro derivative of hydrocortisone was active topically, but its salt-retaining properties made it undesirable even for topical use. Prednisolone and methylprednisolone are as active topically as hydrocortisone (Table 61–4). The 9α-fluorinated steroids dexamethasone and betamethasone did not have any advantage over hydrocortisone. However, triamcinolone and fluocinolone, the acetonide derivatives of the fluorinated steroids, do have a distinct efficacy advantage in topical therapy. Similarly, betamethasone is not very active topically, but attaching a 5-carbon valerate chain to the 17-hydroxyl position results in a compound over 300 times as active as hydrocortisone for topical use. Fluocinonide is the 21-acetate derivative of fluocinolone acetonide; the addition of the 21-acetate enhances the topical activity about fivefold. Fluorination of the corticoid is not required for high potency.

Corticosteroids are only minimally absorbed following application to normal skin; for example, approximately 1% of a dose of hydrocortisone solution applied to the ventral forearm is absorbed. Long-term occlusion with an impermeable film such as plastic wrap is an effective method of enhancing penetration, yielding a tenfold increase in absorption. There is a marked regional anatomic variation in corticosteroid penetration. Compared with the absorption from the forearm, hydrocortisone is absorbed 0.14 times as well through the plantar foot arch, 0.83 times as well through the palm, 3.5 times as well through the scalp, 6 times as well through the forehead, 9 times as well through vulvar skin, and 42 times as well through scrotal skin. Penetration is increased severalfold in the inflamed skin of atopic dermatitis; and in severe exfoliative diseases, such as erythrodermic psoriasis, there appears to be little barrier to penetration.

TABLE 61–4 Relative efficacy of some topical corticosteroids in various formulations.

Concentration in Commonly Used Preparations	Drug
Lowest efficacy	
0.25–2.5%	Hydrocortisone
0.25%	Methylprednisolone acetate (Medrol)
0.1%	Dexamethasone[1] (Decaderm)
1.0%	Methylprednisolone acetate (Medrol)
0.5%	Prednisolone (MetiDerm)
0.2%	Betamethasone[1] (Celestone)
Low efficacy	
0.01%	Fluocinolone acetonide[1] (Fluonid, Synalar)
0.01%	Betamethasone valerate[1] (Valisone)
0.025%	Fluorometholone[1] (Oxylone)
0.05%	Alclometasone dipropionate (Aclovate)
0.025%	Triamcinolone acetonide[1] (Aristocort, Kenalog, Triacet)
0.1%	Clocortolone pivalate[1] (Cloderm)
0.03%	Flumethasone pivalate[1] (Locorten)
Intermediate efficacy	
0.2%	Hydrocortisone valerate (Westcort)
0.1%	Mometasone furoate (Elocon)
0.1%	Hydrocortisone butyrate (Locoid)
0.1%	Hydrocortisone probutate (Pandel)
0.025%	Betamethasone benzoate[1] (Uticort)
0.025%	Flurandrenolide[1] (Cordran)
0.1%	Betamethasone valerate[1] (Valisone)
0.1%	Prednicarbate (Dermatop)
Intermediate efficacy (*continued*)	
0.05%	Fluticasone propionate (Cutivate)
0.05%	Desonide (Desowen)
0.025%	Halcinonide[1] (Halog)
0.05%	Desoximetasone[1] (Topicort L.P.)
0.05%	Flurandrenolide[1] (Cordran)
0.1%	Triamcinolone acetonide[1]
0.025%	Fluocinolone acetonide[1]
High efficacy	
0.05%	Fluocinonide[1] (Lidex)
0.05%	Betamethasone dipropionate[1] (Diprosone, Maxivate)
0.1%	Amcinonide[1] (Cyclocort)
0.25%	Desoximetasone[1] (Topicort)
0.5%	Triamcinolone acetonide[1]
0.2%	Fluocinolone acetonide[1] (Synalar-HP)
0.05%	Diflorasone diacetate[1] (Florone, Maxiflor)
0.1%	Halcinonide[1] (Halog)
Highest efficacy	
0.05%	Betamethasone dipropionate in optimized vehicle (Diprolene)[1]
0.05%	Diflorasone diacetate[1] in optimized vehicle (Psorcon)
0.05%	Halobetasol propionate[1] (Ultravate)
0.05%	Clobetasol propionate[1] (Temovate)

[1]Fluorinated steroids.

Experimental studies on the percutaneous absorption of hydrocortisone fail to reveal a significant increase in absorption when applied on a repetitive basis and a single daily application may be effective in most conditions. Ointment bases tend to give better activity to the corticosteroid than do cream or lotion vehicles. Increasing the concentration of a corticosteroid increases the penetration but not proportionately. For example, approximately 1% of a 0.25% hydrocortisone solution is absorbed from the forearm. A tenfold increase in concentration causes only a fourfold increase in absorption. Solubility of the corticosteroid in the vehicle is a significant determinant of the percutaneous absorption of a topical steroid. Marked increases in efficacy are noted when optimized vehicles are used, as demonstrated by newer formulations of betamethasone dipropionate and diflorasone diacetate.

Table 61–4 groups topical corticosteroid formulations according to approximate relative efficacy. Table 61–5 lists major dermatologic diseases in order of their responsiveness to these drugs.

TABLE 61–5 Dermatologic disorders responsive to topical corticosteroids ranked in order of sensitivity.

Very responsive
Atopic dermatitis
Seborrheic dermatitis
Lichen simplex chronicus
Pruritus ani
Later phase of allergic contact dermatitis
Later phase of irritant dermatitis
Nummular eczematous dermatitis
Stasis dermatitis
Psoriasis, especially of genitalia and face
Less responsive
Discoid lupus erythematosus
Psoriasis of palms and soles
Necrobiosis lipoidica diabeticorum
Sarcoidosis
Lichen striatus
Pemphigus
Familial benign pemphigus
Pemphigoid
Vitiligo
Granuloma annulare
Least responsive: Intralesional injection required
Keloids
Hypertrophic scars
Hypertrophic lichen planus
Alopecia areata
Acne cysts
Prurigo nodularis
Chondrodermatitis nodularis chronica helicis

In the first group of diseases, low- to medium-efficacy corticosteroid preparations often produce clinical remission. In the second group, it is often necessary to use high-efficacy preparations, occlusion therapy, or both. Once a remission has been achieved, every effort should be made to maintain the improvement with a low-efficacy corticosteroid.

The limited penetration of topical corticosteroids can be overcome in certain clinical circumstances by the intralesional injection of relatively insoluble corticosteroids, eg, triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide, and betamethasone acetate-phosphate. When these agents are injected into the lesion, measurable amounts remain in place and are gradually released for 3–4 weeks. This form of therapy is often effective for the lesions listed in Table 61–5 that are generally unresponsive to topical corticosteroids. The dosage of the triamcinolone salts should be limited to 1 mg per treatment site, ie, 0.1 mL of 10 mg/mL suspension, to decrease the incidence of local atrophy (see below).

Adverse Effects

All absorbable topical corticosteroids possess the potential to suppress the pituitary-adrenal axis (see Chapter 39). Although most patients with pituitary-adrenal axis suppression demonstrate only a laboratory test abnormality, cases of severely impaired stress response can occur. Iatrogenic Cushing's syndrome may occur as a result of protracted use of topical corticosteroids in large quantities. Applying potent corticosteroids to extensive areas of the body for prolonged periods, with or without occlusion, increases the likelihood of systemic effects. Fewer of these factors are required to produce adverse systemic effects in children, and growth retardation is of particular concern in the pediatric age group.

Adverse local effects of topical corticosteroids include the following: atrophy, which may present as depressed, shiny, often wrinkled "cigarette paper"-appearing skin with prominent telangiectases and a tendency to develop purpura and ecchymosis; corticoid rosacea, with persistent erythema, telangiectatic vessels, pustules, and papules in central facial distribution; perioral dermatitis, steroid acne, alterations of cutaneous infections, hypopigmentation, and hypertrichosis; increased intraocular pressure; and allergic contact dermatitis. The latter may be confirmed by patch testing with high concentrations of corticosteroids, ie, 1% in petrolatum, because topical corticosteroids are not irritating. Screening for allergic contact dermatitis potential is performed with tixocortol pivalate, budesonide, and hydrocortisone valerate or butyrate. Topical corticosteroids are contraindicated in individuals who demonstrate hypersensitivity to them. Some sensitized subjects develop a generalized flare when dosed with adrenocorticotropic hormone or oral prednisone. Systemic corticosteroid use is discussed in Chapter 39.

CRISABOROLE

Crisaborole (Eucrisa) is a benzoxaborole, nonsteroidal, topical, anti-inflammatory PDE4 inhibitor approved as a 2% ointment for the treatment of mild-to-moderate atopic dermatitis

in patients 2 years of age and older. The most frequent adverse effect is burning or stinging at the site of application. The specific mechanism of action in atopic dermatitis is unknown. Long-term safety in clinical application remains to be determined.

TAR COMPOUNDS

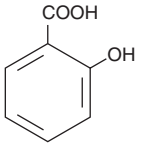
Tar preparations are used mainly in the treatment of psoriasis, dermatitis, and lichen simplex chronicus. The phenolic constituents endow these compounds with antipruritic properties, making them particularly valuable in the treatment of chronic lichenified dermatitis. Acute dermatitis with vesiculation and oozing may be irritated by even weak tar preparations, which should be avoided. However, in the subacute and chronic stages of dermatitis and psoriasis, these preparations are quite useful and offer an alternative to the use of topical corticosteroids.

The most common adverse reaction to coal tar compounds is an irritant folliculitis, necessitating discontinuance of therapy to the affected areas for a period of 3–5 days. Photoirritation and allergic contact dermatitis may also occur. Tar preparations should be avoided in patients who have previously exhibited sensitivity to them.

■ KERATOLYTIC & DESTRUCTIVE AGENTS

SALICYLIC ACID

Salicylic acid has been extensively used in dermatologic therapy as a keratolytic agent. The mechanism by which it produces its keratolytic and other therapeutic effects is poorly understood. The drug may solubilize cell surface proteins that keep the stratum corneum intact, thereby resulting in desquamation of keratotic debris. Salicylic acid is keratolytic in concentrations of 3–6%. In concentrations greater than 6%, it can be destructive to tissues.



Salicylic acid

Salicylism and death have occurred following topical application. In an adult, 1 g of a topically applied 6% salicylic acid preparation will raise the serum salicylate level not more than 0.5 mg/dL of plasma; the threshold for toxicity is 30–50 mg/dL. Higher serum levels are possible in children, who are therefore at a greater risk for salicylism. In cases of severe intoxication, hemodialysis is the treatment of choice (see Chapter 58). It is advisable to limit both the total amount of salicylic acid applied and the frequency of application. Urticarial, anaphylactic, and erythema multiforme reactions may occur in patients who are allergic to salicylates. Topical use may be associated with local irritation, acute inflammation, and even ulceration with the use of high concentrations of salicylic acid. Particular care must be exercised when using the drug on the extremities of patients with diabetes or peripheral vascular disease.

PROPYLENE GLYCOL

Propylene glycol is used extensively in topical preparations because it is an excellent vehicle for organic compounds. It has been used alone as a keratolytic agent in 40–70% concentrations, with plastic occlusion, or in gel with 6% salicylic acid.

Only minimal amounts of a topically applied dose are absorbed through normal stratum corneum. Percutaneously absorbed propylene glycol is oxidized by the liver to lactic acid and pyruvic acid, with subsequent utilization in general body metabolism. Approximately 12–45% of the absorbed agent is excreted unchanged in the urine.

Propylene glycol is an effective keratolytic agent for the removal of hyperkeratotic debris. It is also an effective humectant and increases the water content of the stratum corneum. The hygroscopic characteristics of propylene glycol may help it to develop an osmotic gradient through the stratum corneum, thereby increasing hydration of the outermost layers by drawing water out from the inner layers of the skin.

Propylene glycol is used under polyethylene occlusion or with 6% salicylic acid for the treatment of ichthyosis, palmar and plantar keratodermas, psoriasis, pityriasis rubra pilaris, keratosis pilaris, and hypertrophic lichen planus.

In concentrations greater than 10%, propylene glycol may act as an irritant in some patients; those with eczematous dermatitis may be more sensitive. Allergic contact dermatitis occurs with propylene glycol, and a 4% aqueous propylene glycol solution is recommended for the purpose of patch testing.

UREA

Urea in a compatible cream vehicle or ointment base has a softening and moisturizing effect on the stratum corneum. It has the ability to make creams and lotions feel less greasy, and this has been utilized in dermatologic preparations to decrease the oily feel of a preparation that otherwise might feel unpleasant. It is a white crystalline powder with a slight ammonia odor when moist.

Urea is absorbed percutaneously, although the amount absorbed is minimal. It is distributed predominantly in the extracellular space and excreted in urine. Urea is a natural product of metabolism, and systemic toxicities with topical application do not occur.

Urea increases the water content of the stratum corneum, presumably as a result of the hygroscopic characteristics of this naturally occurring molecule. Urea is also keratolytic. The mechanism of action appears to involve alterations in prekeratin and keratin, leading to increased solubilization. In addition, urea may break hydrogen bonds that keep the stratum corneum intact.

As a humectant, urea is used in concentrations of 2–20% in creams and lotions. As a keratolytic agent, it is used in 20% concentration in diseases such as ichthyosis vulgaris, hyperkeratosis of palms and soles, xerosis, and keratosis pilaris. Concentrations of 30–50% applied to the nail plate have been useful in softening the nail prior to avulsion.

PODOPHYLLUM RESIN & PODOFILOX

Podophyllum resin, an alcoholic extract of *Podophyllum peltatum,* commonly known as mandrake root or May apple, is used in the treatment of condyloma acuminatum and other verrucae. It is a mixture of podophyllotoxin, α and β peltatin, desoxypodophyllotoxin, dehydropodophyllotoxin, and other compounds. It is soluble in alcohol, ether, chloroform, and compound tincture of benzoin.

Percutaneous absorption of podophyllum resin occurs, particularly in intertriginous areas and from applications to large moist condylomas. It is soluble in lipids and therefore is distributed widely throughout the body, including the central nervous system.

The major use of podophyllum resin is in the treatment of condyloma acuminatum. Podophyllotoxin and its derivatives are active cytotoxic agents with specific affinity for the microtubule protein of the mitotic spindle. Normal assembly of the spindle is prevented, and epidermal mitoses are arrested in metaphase. A 25% concentration of podophyllum resin in compound tincture of benzoin is recommended for the treatment of condyloma acuminatum. Application should be restricted to wart tissue only, to limit the total amount of medication used and to prevent severe erosive changes in adjacent tissue. In treating cases of large condylomas, it is advisable to limit application to sections of the affected area to minimize systemic absorption. The patient is instructed to wash off the preparation 2–3 hours after the initial application, because the irritant reaction is variable. Depending on the individual patient's reaction, this period can be extended to 6–8 hours on subsequent applications. If three to five applications have not resulted in significant resolution, other methods of treatment should be considered.

Toxic symptoms associated with excessively large applications include nausea, vomiting, alterations in sensorium, muscle weakness, neuropathy with diminished tendon reflexes, coma, and even death. Local irritation is common, and inadvertent contact with the eye may cause severe conjunctivitis. Use during pregnancy is contraindicated in view of possible cytotoxic effects on the fetus.

Pure podophyllotoxin (podofilox) is approved for use as either a 0.5% solution or gel (Condylox) for application by the patient in the treatment of genital condylomas. The low concentration of podofilox significantly reduces the potential for systemic toxicity. Most men with penile warts may be treated with less than 70 μL per application. At this dose, podofilox is not routinely detected in the serum. Treatment is self-administered in treatment cycles of twice-daily application for 3 consecutive days followed by a 4-day drug-free period. Local adverse effects include inflammation, erosions, burning pain, and itching.

SINECATECHINS

Sinecatechins 15% ointment (Veregen) is a prescription botanical drug product of a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis* containing a mixture of catechins. Sinecatechins ointment is indicated for the topical treatment of external genital and perianal warts in immunocompetent patients 18 years and older. The mechanism of action is unknown. Sinecatechins ointment should be applied three times daily to the warts until complete clearance, not to exceed 16 weeks of therapy.

FLUOROURACIL

Fluorouracil is a fluorinated pyrimidine antimetabolite that resembles uracil, with a fluorine atom substituted for the 5-methyl group. Its systemic pharmacology is described in Chapter 54. Fluorouracil is used topically for the treatment of multiple actinic keratoses.

Approximately 6% of a topically applied dose is absorbed—an amount insufficient to produce adverse systemic effects. Most of the absorbed drug is metabolized and excreted as carbon dioxide, urea, and α-fluoro-β-alanine. A small percentage is eliminated unchanged in the urine. Fluorouracil inhibits thymidylate synthetase activity, interfering with the synthesis of DNA and, to a lesser extent, RNA. These effects are most marked in atypical, rapidly proliferating cells.

Fluorouracil is available in multiple formulations containing 0.5%, 1%, 2%, 4%, and 5% concentrations (Carac, Efudex, Fluoroplex, Tolak). The response to treatment begins with erythema and progresses through vesiculation, erosion, superficial ulceration, necrosis, and finally reepithelialization. Fluorouracil should be continued until the inflammatory reaction reaches the stage of ulceration and necrosis, usually in 3–4 weeks, at which time treatment should be terminated. The healing process may continue for 1–2 months after therapy is discontinued. Local adverse reactions may include pain, pruritus, a burning sensation, tenderness, and residual postinflammatory hyperpigmentation. Excessive exposure to sunlight during treatment may increase the intensity of the reaction and should be avoided. Allergic contact dermatitis to fluorouracil has been reported, and its use is contraindicated in patients with known hypersensitivity.

INGENOL MEBUTATE

Ingenol mebutate (Picato) is derived from the sap of the *Euphorbia peplus* plant and has recently been approved for the topical treatment of actinic keratoses. The mechanism by which ingenol mebutate induces keratinocyte cell death is unknown. For the treatment of actinic keratoses on the face and scalp, the 0.015% gel should be applied once daily for 3 consecutive days. For actinic keratoses on the trunk and extremities, the 0.05% gel should be applied to the

affected area daily for 2 consecutive days. Local skin reactions are to be expected with crusting, swelling, vesiculation, and possible ulceration. Caution must be taken to prevent eye exposure. Patients must wash their hands well after applying the gel and avoid transfer of the drug to the periocular area during and after application.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

A topical 3% gel formulation of the nonsteroidal anti-inflammatory drug diclofenac (Solaraze) has shown moderate effectiveness in the treatment of actinic keratoses. The mechanism of action is unknown. As with other NSAIDs, anaphylactoid reactions may occur with diclofenac, and it should be given with caution to patients with known aspirin hypersensitivity (see Chapter 36).

AMINOLEVULINIC ACID

Aminolevulinic acid (ALA) is an endogenous precursor of photosensitizing porphyrin metabolites. When exogenous ALA is provided to the cell through topical applications, protoporphyrin IX (PpIX) accumulates in the cell. When exposed to light of appropriate wavelength and energy, the accumulated PpIX produces a photodynamic reaction resulting in the formation of cytotoxic superoxide and hydroxyl radicals. Photosensitization of actinic keratoses using ALA (Levulan Kerastick) and illumination with a blue light photodynamic therapy illuminator (BLU-U) is the basis for ALA photodynamic therapy.

Treatment consists of applying ALA 20% topical solution to individual actinic keratoses followed by blue light photodynamic illumination 14–18 hours later. Transient stinging or burning at the treatment site occurs during the period of light exposure. Patients *must* avoid exposure to sunlight or bright indoor lights for at least 40 hours after ALA application. Redness, swelling, and crusting of the actinic keratoses will occur and gradually resolve over a 3- to 4-week time course. Allergic contact dermatitis to methyl ester may occur.

ANTIPRURITIC AGENTS

DOXEPIN

Topical doxepin hydrochloride 5% cream (Zonalon) may provide significant antipruritic activity when utilized in the treatment of pruritus associated with atopic dermatitis or lichen simplex chronicus. The precise mechanism of action is unknown but may relate to the potent H_1- and H_2-receptor antagonist properties of dibenzoxepin tricyclic compounds. Percutaneous absorption is variable and may result in significant drowsiness in some patients. In view of the anticholinergic effect of doxepin, topical use is contraindicated in patients with untreated narrow-angle glaucoma or a tendency to urinary retention.

Plasma levels of doxepin similar to those achieved during oral therapy may be obtained with topical application; the usual drug interactions associated with tricyclic antidepressants may occur. Therefore, monoamine oxidase inhibitors must be discontinued at least 2 weeks prior to the initiation of doxepin cream. Topical application of the cream should be performed four times daily for up to 8 days of therapy. The safety and efficacy of chronic dosing have not been established. Adverse local effects include marked burning and stinging of the treatment site, which may necessitate discontinuation of the cream in some patients. Allergic contact dermatitis appears to be frequent, and patients should be monitored for symptoms of hypersensitivity.

PRAMOXINE

Pramoxine hydrochloride is a topical anesthetic that can provide temporary relief from pruritus associated with mild eczematous dermatoses. Pramoxine is available as a 1% cream, lotion, or gel and in combination with hydrocortisone acetate. Application to the affected area two to four times daily may provide short-term relief of pruritus. Local adverse effects include transient burning and stinging. Care should be exercised to avoid contact with the eyes.

ANTISEBORRHEA AGENTS

Table 61–6 lists topical formulations for the treatment of seborrheic dermatitis. These are of variable efficacy and may necessitate concomitant treatment with topical corticosteroids for severe cases.

TRICHOGENIC & ANTITRICHOGENIC AGENTS

MINOXIDIL

Topical minoxidil (Rogaine) is effective in reversing the progressive miniaturization of terminal scalp hairs associated with androgenic alopecia. Vertex balding is more responsive

TABLE 61–6 Antiseborrhea agents.

Active Ingredient	Typical Trade Name
Betamethasone valerate foam	Luxiq
Chloroxine shampoo	Capitrol
Coal tar shampoo	Ionil-T, Pentrax, Theraplex-T, T-Gel
Fluocinolone acetonide shampoo	FS Shampoo
Ketoconazole shampoo and gel	Nizoral, Xolegel
Selenium sulfide shampoo	Selsun, Exsel
Zinc pyrithione shampoo	DHS-Zinc, Theraplex-Z

to therapy than frontal balding. The mechanism of action of minoxidil on hair follicles is unknown. Chronic dosing studies have demonstrated that the effect of minoxidil is not permanent, and cessation of treatment will lead to hair loss in 4–6 months. Percutaneous absorption of minoxidil in normal scalp is minimal, but possible systemic effects on blood pressure (see Chapter 11) should be monitored in patients with cardiac disease.

FINASTERIDE

Finasteride (Propecia) is a 5α-reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone (see Chapter 40), the androgen responsible for androgenic alopecia in genetically predisposed men. Oral finasteride, 1 mg/d, promotes hair growth and prevents further hair loss in a significant proportion of men with androgenic alopecia. Treatment for at least 3–6 months is necessary to see increased hair growth or prevent further hair loss. Continued treatment with finasteride is necessary to sustain benefit. Reported adverse effects include decreased libido, ejaculation disorders, and erectile dysfunction, which resolve in most men who remain on therapy and in all men who discontinue finasteride.

There are no data to support the use of finasteride in women with androgenic alopecia. Pregnant women should not be exposed to finasteride either by use or by handling crushed tablets because of the risk of hypospadias developing in a male fetus.

BIMATOPROST

Bimatoprost (Latisse) is a prostaglandin analog available as a 0.03% ophthalmic solution to treat hypotrichosis of the eyelashes. Mechanism of action is unknown. Treatment consists of nightly application to the skin of the upper eyelid margins at the base of the eyelashes using a separate disposable applicator for each eyelid. Contact lenses should be removed prior to bimatoprost application. Side effects include pruritus, conjunctival hyperemia, skin pigmentation, and erythema of the eyelids. Although iris darkening has not been reported with applications confined to the upper eyelid skin, increased brown iris pigmentation, which is likely to be permanent, has occurred when bimatoprost ophthalmic solution was instilled onto the eye for glaucoma.

EFLORNITHINE

Eflornithine (Vaniqa) is an irreversible inhibitor of ornithine decarboxylase, which catalyzes the rate-limiting step in the biosynthesis of polyamines. Polyamines are required for cell division and differentiation, and inhibition of ornithine decarboxylase affects the rate of hair growth. Topical eflornithine has been shown effective in reducing facial hair growth in approximately 30% of women when applied twice daily for 6 months of therapy. Hair growth was observed to return to pretreatment levels 8 weeks after discontinuation. Local adverse effects include stinging, burning, and folliculitis.

■ ANTINEOPLASTIC AGENTS

The treatment of melanoma is discussed in Chapter 54.

Alitretinoin (Panretin) is a topical formulation of 9-*cis*-retinoic acid that is approved for the treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma. Localized reactions may include intense erythema, edema, and vesiculation necessitating discontinuation of therapy. Patients who are applying alitretinoin should not concurrently use products containing DEET, a common component of insect repellant products.

Bexarotene (Targretin), a member of a subclass of retinoids that selectively binds and activates retinoid X receptor subtypes, is available both in an oral formulation and as a topical gel for the treatment of cutaneous T-cell lymphoma. Teratogenicity is a significant risk for both systemic and topical treatment with bexarotene, and women of childbearing potential must avoid becoming pregnant throughout therapy and for at least 1 month following discontinuation of the drug. Bexarotene may increase levels of triglycerides and cholesterol; therefore, lipid levels must be monitored during treatment.

Vismodegib (Erivedge) and **sonidegib** (Odomzo) are oral hedgehog pathway inhibitors for the treatment of metastatic basal cell carcinoma or locally advanced basal cell carcinoma in adults who are not candidates for surgery or radiation. They are highly effective in patients with basal cell nevus syndrome. The recommended dosage of vismodegib is 150 mg daily and sonidegib is 200 mg daily. The most common adverse effects include dysgeusia and ageusia, alopecia, fatigue, and muscle spasms.

Baseline serum creatine kinase and creatinine levels prior to initiating therapy and during treatment may be indicated for significant musculoskeletal symptoms.

Hedgehog pathway inhibitors are embryotoxic, fetotoxic, and teratogenic in animals. Pregnancy status of females of reproductive potential must be verified within 7 days prior to initiating therapy. Exposure may occur through seminal fluid.

Vorinostat (Zolinza) and **romidepsin** (Istodax) are histone deacetylase inhibitors that are approved for the treatment of cutaneous T-cell lymphoma in patients with progressive, persistent, or recurrent disease after prior systemic therapy. Adverse effects include thrombocytopenia, anemia, and gastrointestinal disturbances. Pulmonary embolism, which has occurred with vorinostat, has not been reported to date with romidepsin.

■ MISCELLANEOUS MEDICATIONS

Drugs used primarily for other conditions may also find use as oral therapeutic agents for dermatologic conditions. A few such preparations are listed in Table 61–7.

TABLE 61–7 Miscellaneous medications and the dermatologic conditions in which they are used.

Drug or Group	Conditions	For More Details, See:
Antihistamines	Pruritus (any cause), urticarial	Chapter 16
Antimalarials	Lupus erythematosus, photosensitization	Chapters 36, 52
Antimetabolites	Pemphigus, pemphigoid	Chapter 54
Becaplermin	Diabetic neuropathic ulcers	Chapter 41
Belimumab	Systemic lupus erythematosus	Chapters 36, 54
Capsaicin	Postherpetic neuralgia	Chapter 31
Corticosteroids	Pemphigus, pemphigoid, lupus erythematosus, allergic contact dermatoses, and certain other dermatoses	Chapter 39
Cyclosporine	Psoriasis	Chapter 55
Dapsone	Dermatitis herpetiformis, erythema elevatum diutinum, pemphigus, pemphigoid, bullous lupus erythematosus	Chapter 47
Denileukin diftitox	Cutaneous T-cell lymphomas	Chapters 54, 55
Drospirenone/ethinyl estradiol	Moderate female acne	Chapter 39
Mechlorethamine gel	Cutaneous T-cell lymphoma	Chapter 54
Methotrexate	Psoriasis	Chapter 54
Mycophenolate mofetil	Bullous disease	Chapters 54, 55
Thalidomide	Erythema nodosum leprosum	Chapters 54, 55

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CASE STUDY ANSWER

Initiation of oral doxycycline therapy was discussed with the patient. She expressed concerns regarding possible adverse effects of prolonged systemic therapy. In light of this, daily morning application of brimonidine 0.33% gel was added to her treatment regimen. The patient noted prompt response with significant improvement of her facial redness.