CHAPTER

61

Dermatologic Pharmacology

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CASE STUDY

A 22-year-old woman presents with a complaint of worsening psoriasis. She has a strong family history of the disease and has had lesions on her scalp and elbows for several years. She recently noted new lesions developing on her knees and the soles of her feet. She has been using topical over-the-counter hydrocortisone cream but admits that this treatment does not seem to help. What therapeutic options are available for the treatment of this chronic disease?

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 (Figure 61–1), human skin is a complex series of diffusion barriers. 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, the 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.

REACTIONS TO DERMATOLOGIC MEDICATIONS

The 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 the solubility of the active agent in the vehicle; the rate of release of the agent from the vehicle; the ability of the vehicle to hydrate the stratum corneum, 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.

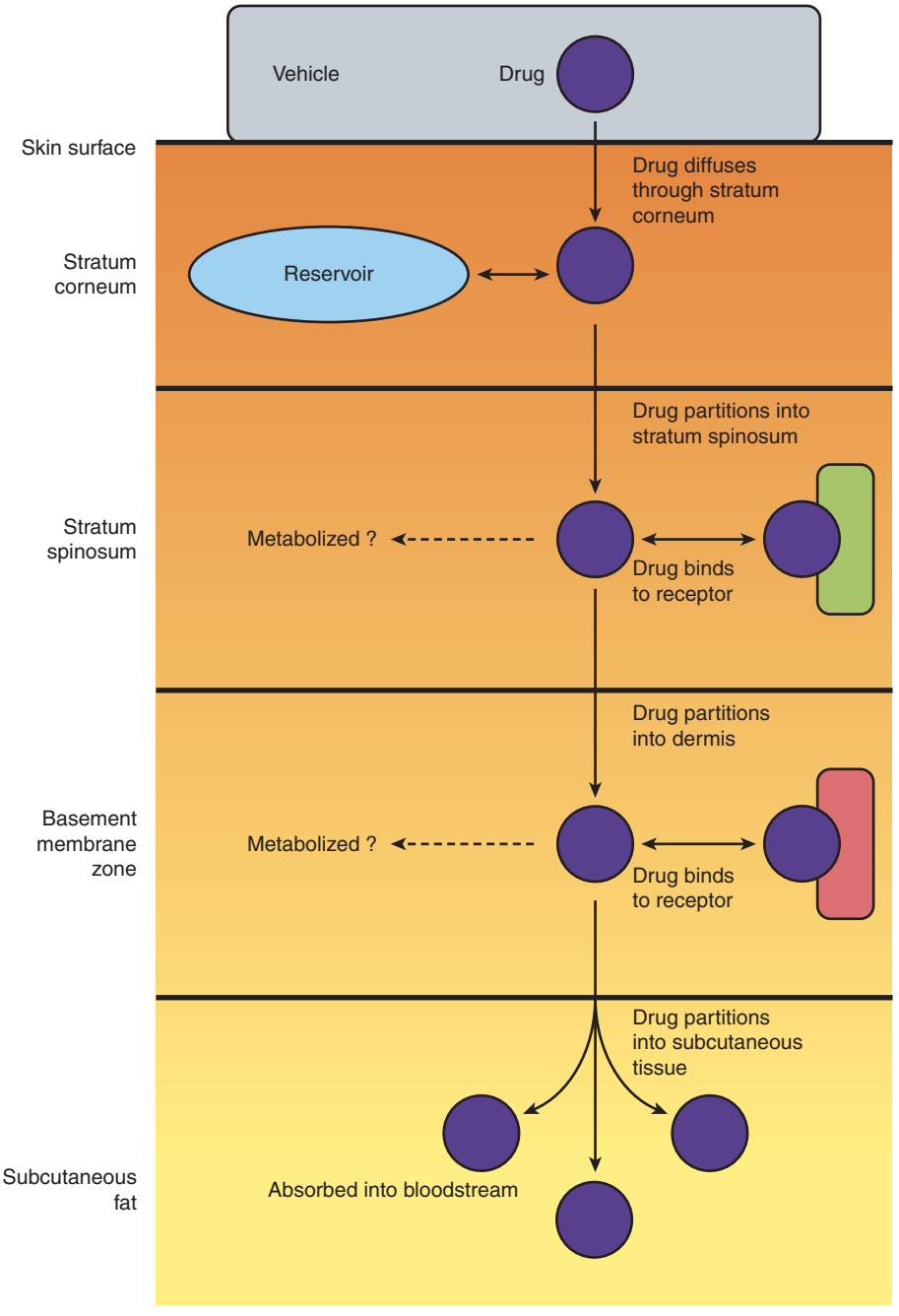


FIGURE 61–1 Schematic diagram of percutaneous absorption. (Redrawn from Orkin M, Maibach HI, Dahl MV: *Dermatology*. Appleton & Lange, 1991.)

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 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.

TABLE 61–1 Local cutaneous reactions to topical medications.

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

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. The 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.

The 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.

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.

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 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. To date only four cases of allergic contact dermatitis have 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 containing polymyxin B are available. 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.

NEOMYCIN & GENTAMICIN

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, both 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

Several systemic antibiotics that have traditionally been used in the treatment of acne vulgaris have been shown to be effective when applied topically. Currently, four antibiotics are so utilized: clindamycin phosphate, erythromycin base, metronidazole, and sulfacetamide. The effectiveness of topical therapy is less than that achieved by systemic administration of the same antibiotic. Therefore, topical therapy is generally suitable only in mild to moderate cases of inflammatory acne.

Clindamycin

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), and with tretinoin (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 of the possible complications 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 the time of application 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 the treatment of rosacea. 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.

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% 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. However, a slight decrease in hemoglobin concentration was noted in patients with G6PD deficiency, suggestive of mild hemolysis. To date, serious adverse reactions associated with oral dapsone use as delineated in Chapter 47 have not been reported with topical use. 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, miconazole, econazole, ketoconazole, oxiconazole, sulconazole, sertaconazole, ciclopirox olamine, naftifine, terbinafine, butenafine, and tolnaftate; or (2) with orally administered agents, ie, griseofulvin, terbinafine, ketoconazole, fluconazole, and itraconazole. Superficial infections caused by candida species may be treated with topical applications of clotrimazole, miconazole, econazole, ketoconazole, oxiconazole, ciclopirox olamine, nystatin, or amphotericin B. Chronic generalized mucocutaneous candidiasis is responsive to long-term therapy with oral ketoconazole.

TOPICAL ANTIFUNGAL PREPARATIONS

TOPICAL AZOLE DERIVATIVES

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

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. 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. 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

Ciclopirox olamine is a synthetic broad-spectrum antimycotic agent with inhibitory activity against dermatophytes, candida species, and *P orbiculare*. This agent appears to inhibit 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) has been approved for the treatment of mild to moderate onychomycosis of fingernails and toenails. Although well tolerated with minimal side effects, the overall cure rates in clinical trials are less than 12%.

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. 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 that is 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.

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 AZOLE DERIVATIVES

Azole derivatives currently available for oral treatment of systemic mycosis include fluconazole (Diflucan), itraconazole (Sporanox), ketoconazole (Nizoral), and others. 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.

Patients with chronic mucocutaneous candidiasis respond well to a once-daily dose of 200 mg of ketoconazole, with a median clearing time of 16 weeks. Most patients require long-term maintenance therapy. Variable results have been reported in treatment of chromomycosis.

Ketoconazole is effective in the therapy of cutaneous infections caused by epidermophyton, microsporum, and trichophyton species. Infections of the glabrous skin often respond within 2–3 weeks to a once-daily oral dose of 200 mg. Palmar-plantar skin is slower to respond, often taking 4–6 weeks at a dosage of 200 mg twice daily. Infections of the hair and nails may take even longer before resolving, with low cure rates noted for tinea capitis. Tinea versicolor is responsive to short courses of a once-daily dose of 200 mg.

Nausea or pruritus occurs in approximately 3% of patients taking ketoconazole. More significant adverse effects include gynecomastia, elevations of hepatic enzyme levels, and hepatitis. Caution is advised when using ketoconazole in patients with a history of hepatitis. Routine evaluation of hepatic function is advisable for patients on prolonged therapy.

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.*

GRISEOFULVIN

Griseofulvin is effective orally against dermatophyte infections caused by epidermophyton, microsporum, and trichophyton. It 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 the oral administration of 1 g of micronized griseofulvin, drug can be detected in the stratum corneum 4–8 hours later. Reducing the particle size of the medication greatly increases

absorption of the drug. Formulations that contain the smallest particle size are labeled "ultramicronized." Ultramicronized griseofulvin achieves bioequivalent plasma levels with half the dose of micronized drug. In addition, solubilizing griseofulvin in polyethylene glycol enhances absorption even further. Micronized griseofulvin is available as 250 mg and 500 mg tablets, and ultramicronized drug is available as 125 mg, 165 mg, 250 mg, and 330 mg tablets and as 250 mg capsules.

The usual adult dosage of the micronized ("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 of griseofulvin. Fingernails may respond to 6 months of therapy, whereas toenails are quite 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.

TERBINAFINE

Terbinafine (described above) is quite 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.

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 usage in the treatment of cutaneous infections are discussed in Chapter 49.

Topical acyclovir (Zovirax) is available as a 5% ointment; 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 basal cell carcinomas on the trunk, neck, and extremities. A lower 3.75% concentration cream (Zyclara) is 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-α 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 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 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 side 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 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 Food and Drug Administration has added 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.

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.

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 (Kwell, etc) is available as a 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 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. California has prohibited the medical use of lindane following evaluation of its toxicologic profile. The risk of adverse systemic reactions to lindane appears to be minimal when it is used properly and according to directions in adult patients. However, 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 of use 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 ovacidal, 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 recent 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 Parasol 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.

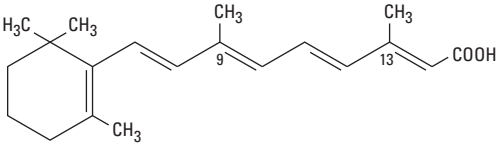
The sun protection factor (SPF) of a given sunscreen is a measure of its effectiveness in absorbing erythrogenic ultraviolet light. It is determined by measuring the minimal erythema dose with and without the sunscreen in a group of normal people. The ratio of the minimal erythema dose with sunscreen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

Recently updated FDA regulations limit the claimed maximum SPF value on sunscreen labels to 50+ because there is not sufficient data to show that products with SPF values higher than 50 provide greater protection for users. These new FDA regulations require that sunscreens labeled as "broad spectrum" sunscreens will have to pass a standard test comparing the amount of UVA radiation protection in relation to the amount of UVB radiation. 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 will only be allowed to claim to 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.

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. 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).

Tazarotene (Tazorac) is an acetylenic retinoid that is available as a 0.1% gel and cream 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, extensively bound to plasma albumin, and has an elimination half-life of 10–20 hours.

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, 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 is an effective topical agent in the treatment of acne vulgaris. It 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), 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 (in the form of Azelex) and acne rosacea (Finacea). 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 or 15% gel 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.

DRUGS FOR PSORIASIS

ACITRETIN

Acitretin (Soriatane), a metabolite of the aromatic retinoid etretinate, is quite 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) is a synthetic vitamin D_3 derivative (available as a 0.005% cream or scalp lotion) that is effective in the treatment of plaque-type psoriasis vulgaris of moderate severity. Improvement of psoriasis was 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 containing calcipotriene and betamethasone dipropionate (Taclonex) is 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 T-cell modulator alefacept, the TNF-α inhibitors etanercept, infliximab, and adalimumab, and the cytokine inhibitor ustekinumab. TNF-α inhibitors are also discussed in Chapters 36 and 55.

ALEFACEPT

Alefacept (Amevive) is an immunosuppressive dimeric fusion protein that consists of the extracellular CD2-binding portion of the human leukocyte function antigen-3 linked to the Fc portion of human IgG_1. Alefacept interferes with lymphocyte activation, which plays a role in the pathophysiology of psoriasis, and causes a reduction in subsets of CD2 T lymphocytes and circulating total CD4 and CD8 T-lymphocyte counts. The recommended dosage is 7.5 mg given once weekly as an intravenous bolus or 15 mg once weekly as an intramuscular injection for a 12-week course of treatment. Patients should have CD4 lymphocyte counts monitored weekly while taking alefacept, and dosing should be withheld if CD4 counts are below 250 cells/μL. The drug should be discontinued if the counts remain below 250 cells/μL for 1 month. Alefacept is an immunosuppressive agent and should not be administered to patients with clinically significant infection. Because of the possibility of an increased risk of malignancy, it should not be administered to patients with a history of systemic malignancy.

TNF INHIBITORS: ETANERCEPT, INFLIXIMAB, & ADALIMUMAB

Etanercept (Enbrel) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG_1. Etanercept binds selectively

to TNF-α and -β and blocks interaction with cell surface TNF receptors that play a role in the inflammatory process of plaque psoriasis. The recommended dosage of etanercept in psoriasis is a 50 mg subcutaneous injection given twice weekly for 3 months followed by a maintenance dose of 50 mg weekly.

Infliximab (Remicade) is a chimeric IgG_1 monoclonal antibody composed of human constant and murine variable regions. Infliximab binds to the soluble and transmembrane forms of TNF-α and inhibits binding of TNF-α with its receptors. The recommended dose of infliximab is 5 mg/kg given as an intravenous infusion followed by similar doses at 2 and 6 weeks after the first infusion and then every 8 weeks thereafter.

Adalimumab (Humira) is a recombinant $1gG_1$ monoclonal antibody that binds specifically to TNF-α and blocks its interaction with cell surface TNF receptors. The recommended dose for adalimumab in psoriasis is an initial dose of 80 mg administered subcutaneously followed by 40 mg given every other week starting 1 week after the initial dose.

Serious life-threatening infections, including sepsis and pneumonia, have been reported with the use of TNF inhibitors. Patients should be evaluated for tuberculosis risk factors and tested for latent tuberculosis infection prior to starting therapy. Concurrent use with other immunosuppressive therapy should be avoided. In clinical trials of all TNF-blocking agents more cases of lymphoma were observed compared with control patients. Patients with a prior history of prolonged phototherapy treatment should be monitored for nonmelanoma skin cancers.

USTEKINUMAB

Ustekinumab (Stelara) is a human $IgG_1κ$ monoclonal antibody that binds with high affinity and specificity to interleukin (IL)-12 and IL-23 cytokines inhibiting TH1 and TH17 cell-mediated responses, which are involved in the pathogenesis of psoriasis. The recommended treatment protocol is 45 mg for patients weighing less than 100 kg and 90 mg for patients weighing more than 100 kg given as a subcutaneous injection initially, followed by the same dose 4 weeks later, and then once every 12 weeks. Serious allergic reactions including angioedema and anaphylaxis have occurred and caution should be exercised in patients receiving allergy immunotherapy. Serious infections, especially from mycobacterial organisms, are possible and patients must be evaluated for tuberculosis prior to initiating therapy. Live vaccines, including Bacillus Calmette-Guérin (BCG), should not be given with ustekinumab. One case of reversible posterior leukoencephalopathy syndrome (RPLS) has been reported.

■ 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.

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 61–2). 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 five-fold. 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.

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 10-fold 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

TABLE 61–2 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.

vehicles are used, as demonstrated by newer formulations of betamethasone dipropionate and diflorasone diacetate.

Table 61–2 groups topical corticosteroid formulations according to approximate relative efficacy. Table 61–3 lists major dermatologic diseases in order of their responsiveness to these drugs. 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 61–3 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

TABLE 61–3 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
Vitiligo
Granuloma annulare
Least responsive: Intralesional injection required
Keloids
Hypertrophic scars
Hypertrophic lichen planus
Alopecia areata
Acne cysts
Prurigo nodularis
Chondrodermatitis nodularis chronica helicis

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, 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.

TAR COMPOUNDS

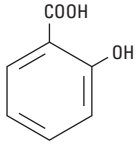
Tar preparations are used mainly in the treatment of psoriasis, dermatitis, and lichen simplex chronicus. The phenolic constituents endow these compounds with antipruritic properties, making them particularly valuable in the treatment of chronic lichenified dermatitis. Acute dermatitis with vesiculation 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%, and 5% concentrations. 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.

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 ACIDS

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 has 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.

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 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 that is available as a 0.03% ophthalmic solution to treat hypotrichosis of the eyelashes. The 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.

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 to be 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

Alitretinoin (Panretin) is a topical formulation of 9-*cis*-retinoic acid which 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) is a member of a subclass of retinoids that selectively binds and activates retinoid X receptor subtypes. It 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.

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.

ANTISEBORRHEA AGENTS

Table 61–4 lists topical formulations for the treatment of seborrheic dermatitis. These are of variable efficacy and may

TABLE 61–4 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

necessitate concomitant treatment with topical corticosteroids for severe cases.

MISCELLANEOUS MEDICATIONS

A number of drugs used primarily for other conditions also find use as oral therapeutic agents for dermatologic conditions. A few such preparations are listed in Table 61–5.

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TABLE 61–5 Miscellaneous medications and the dermatologic conditions in which they are used.

Drug or Group	Conditions	Comment
Alitretinoin	AIDS-related Kaposi's sarcoma	See also Chapter 49.
Antihistamines	Pruritus (any cause), urticaria	See also Chapter 16.
Antimalarials	Lupus erythematosus, photosensitization	See also Chapter 36.
Antimetabolites	Psoriasis, pemphigus, pemphigoid	See also Chapter 54.
Becaplermin	Diabetic neuropathic ulcers	See also Chapter 41.
Bexarotene	Cutaneous T-cell lymphoma	See also Chapter 54.
Corticosteroids	Pemphigus, pemphigoid, lupus erythematosus, allergic contact dermatoses, and certain other dermatoses	See also Chapter 39.
Cyclosporine	Psoriasis	See also Chapter 55.
Dapsone	Dermatitis herpetiformis, erythema elevatum diutinum, pemphigus, pemphigoid, bullous lupus erythematosus	See also Chapter 47.
Denileukin diftitox	Cutaneous T-cell lymphoma	See also Chapter 54.
Drospirenone/ethinyl estradiol	Moderate female acne	See also Chapter 39.
Interferon	Melanoma, viral warts	See also Chapter 55.
Mycophenolate mofetil	Bullous disease	See also Chapter 55.
Romidepsin	Cutaneous T-cell lymphoma	See also Chapter 54.
Thalidomide	Erythema nodosum leprosum	See also Chapters 47 and 55.
Vorinostat	Cutaneous T-cell lymphoma	See also Chapter 54

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CASE STUDY ANSWER

Initial therapy consisting of twice-daily applications of a medium-strength topical corticosteroid combined with once-daily topical calcipotriene or calcitriol should provide adequate control for this patient's localized psoriasis. A coal tar shampoo should be initiated for her scalp psoriasis with nightly application of a corticosteroid solution to recalcitrant plaques.

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CHAPTER

62

Drugs Used in the Treatment of Gastrointestinal Diseases

Kenneth R. McQuaid, MD

CASE STUDY

A 21-year-old woman comes with her parents to discuss therapeutic options for her Crohn's disease. She was diagnosed with Crohn's disease 2 years ago, and it involves her terminal ileum and proximal colon, as confirmed by colonoscopy and small bowel radiography. She was initially treated with mesalamine and budesonide with good response, but over the last 2 months, she has had a relapse of her symptoms. She is experiencing fatigue, cramping, abdominal pains, and nonbloody diarrhea up to 10 times daily, and she has had a 15-lb weight loss.

She has no other significant medical or surgical history. Her current medications are mesalamine 2.4 g/d and budesonide 9 mg/d. She appears thin and tired. Abdominal examination reveals tenderness without guarding in the right lower quadrant; no masses are palpable. On perianal examination, there is no tenderness, fissure, or fistula. Her laboratory data are notable for anemia and elevated C-reactive protein. What are the options for immediate control of her symptoms and disease? What are the long-term management options?

INTRODUCTION

Many of the drug groups discussed elsewhere in this book have important applications in the treatment of diseases of the gastrointestinal tract and other organs. Other groups are used almost exclusively for their effects on the gut; these are discussed in the following text according to their therapeutic uses.

DRUGS USED IN ACID-PEPTIC DISEASES

Acid-peptic diseases include gastroesophageal reflux, peptic ulcer (gastric and duodenal), and stress-related mucosal injury. In all these conditions, mucosal erosions or ulceration arise when the caustic effects of aggressive factors (acid, pepsin, bile) overwhelm the defensive factors of the gastrointestinal mucosa (mucus and bicarbonate secretion, prostaglandins, blood flow, and the processes of restitution and regeneration after cellular injury). Over 90% of peptic ulcers are caused by infection with the bacterium *Helicobacter pylori* or by use of nonsteroidal anti-inflammatory drugs (NSAIDs). Drugs used in the treatment of acid-peptic disorders may be divided into two classes: agents that reduce intragastric acidity and agents that promote mucosal defense.

AGENTS THAT REDUCE INTRAGASTRIC ACIDITY

PHYSIOLOGY OF ACID SECRETION

The parietal cell contains receptors for gastrin (CCK-B), histamine (H_2), and acetylcholine (muscarinic, M_3) (Figure 62–1). When acetylcholine (from vagal postganglionic nerves) or gastrin (released from antral G cells into the blood) bind to the parietal cell receptors, they cause an increase in cytosolic calcium, which in turn stimulates protein kinases that stimulate acid secretion from a H^+/K^+-ATPase (the proton pump) on the canalicular surface.

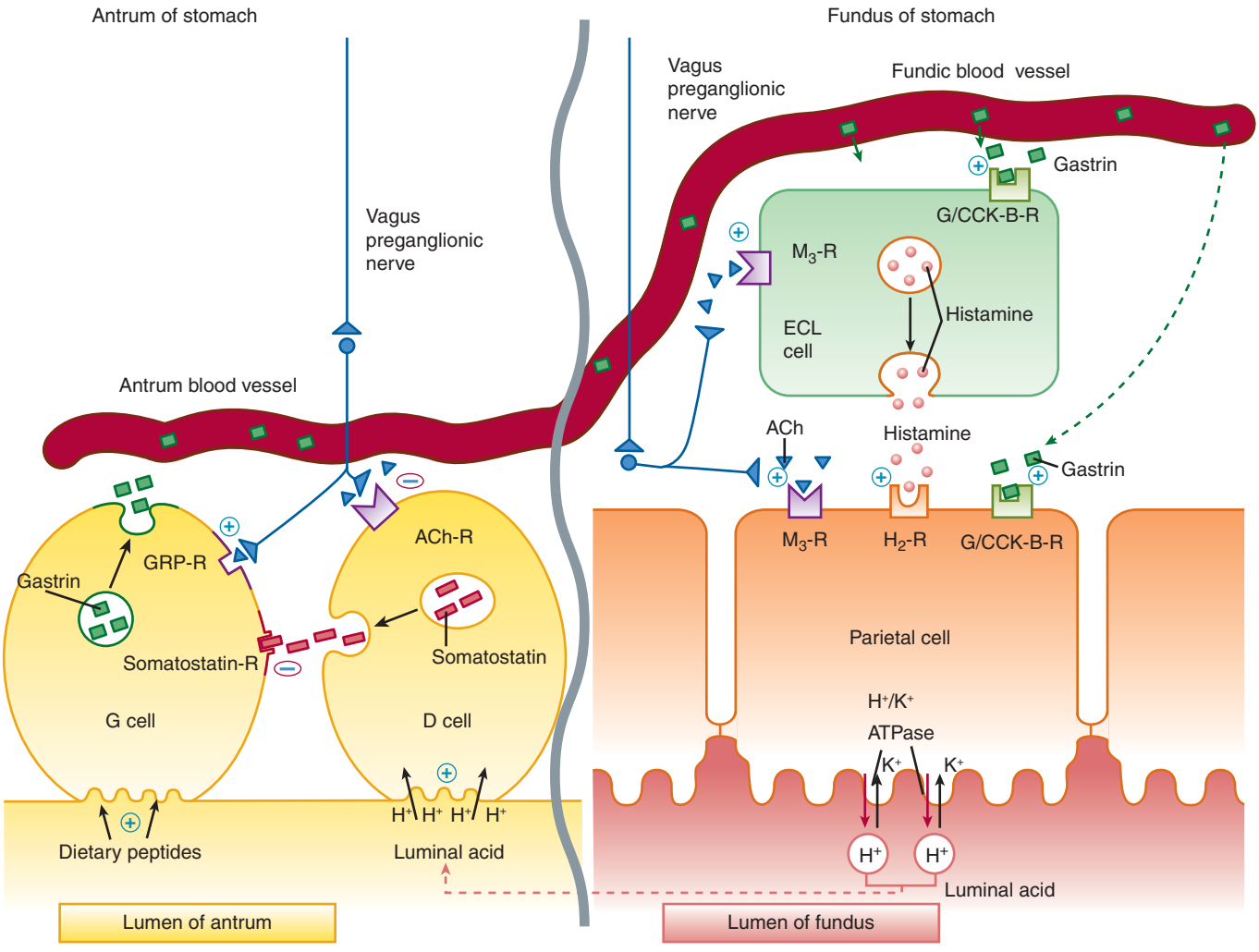


FIGURE 62–1 Schematic model for physiologic control of hydrogen ion (acid) secretion by the parietal cells of the gastric fundic glands. Parietal cells are stimulated to secrete acid (H^+) by gastrin (acting on gastrin/CCK-B receptor), acetylcholine (M_3 receptor), and histamine (H_2 receptor). Acid is secreted across the parietal cell canalicular membrane by the H^+/K^+-ATPase proton pump into the gastric lumen. Gastrin is secreted by antral G cells into blood vessels in response to intraluminal dietary peptides. Within the gastric body, gastrin passes from the blood vessels into the submucosal tissue of the fundic glands, where it binds to gastrin-CCK-B receptors on parietal cells and enterochromaffin-like (ECL) cells. The vagus nerve stimulates postganglionic neurons of the enteric nervous system to release acetylcholine (ACh), which binds to M_3 receptors on parietal cells and ECL cells. Stimulation of ECL cells by gastrin (CCK-B receptor) or acetylcholine (M_3 receptor) stimulates release of histamine. Within the gastric antrum, vagal stimulation of postganglionic enteric neurons enhances gastrin release directly by stimulation of antral G cells (through gastrin-releasing peptide, GRP) and indirectly by inhibition of somatostatin secretion from antral D cells. Acid secretion must eventually be turned off. Antral D cells are stimulated to release somatostatin by the rise in intraluminal H^+ concentration and by CCK that is released into the bloodstream by duodenal I cells in response to proteins and fats (not shown). Binding of somatostatin to receptors on adjacent antral G cells inhibits further gastrin release. ATPase, H^+/K^+-ATPase proton pump; CCK, cholecystokinin; M_3, muscarinic receptors.

In close proximity to the parietal cells are gut endocrine cells called *enterochromaffin-like (ECL) cells*. ECL cells also have receptors for gastrin and acetylcholine, which stimulate histamine release. Histamine binds to the H_2 receptor on the parietal cell, resulting in activation of adenylyl cyclase, which increases intracellular cyclic adenosine monophosphate (cAMP) and activates protein kinases that stimulate acid secretion by the H^+/K^+-ATPase. In humans, it is believed that the major effect of gastrin upon acid secretion is mediated indirectly through the release of histamine from ECL cells rather than through direct parietal cell stimulation. In contrast, acetylcholine provides potent direct parietal cell stimulation.

ANTACIDS

Antacids have been used for centuries in the treatment of patients with dyspepsia and acid-peptic disorders. They were the mainstay of treatment for acid-peptic disorders until the advent of H2–receptor antagonists and proton pump inhibitors. They con-

tinue to be used commonly by patients as nonprescription remedies for the treatment of intermittent heartburn and dyspepsia.

Antacids are weak bases that react with gastric hydrochloric acid to form a salt and water. Their principal mechanism of action is reduction of intragastric acidity. After a meal, approximately 45 mEq/h of hydrochloric acid is secreted. A single dose of 156 mEq of antacid given 1 hour after a meal effectively neutralizes gastric acid for up to 2 hours. However, the acid-neutralization capacity among different proprietary formulations of antacids is highly variable, depending on their rate of dissolution (tablet versus liquid), water solubility, rate of reaction with acid, and rate of gastric emptying.

Sodium bicarbonate (eg, baking soda, Alka Seltzer) reacts rapidly with hydrochloric acid (HCL) to produce carbon dioxide and sodium chloride. Formation of carbon dioxide results in gastric distention and belching. Unreacted alkali is readily absorbed, potentially causing metabolic alkalosis when given in high doses or to patients with renal insufficiency. Sodium chloride absorption may exacerbate fluid retention in patients with heart failure, hypertension, and renal insufficiency. **Calcium carbonate** (eg, Tums, Os-Cal) is less soluble and reacts more slowly than sodium bicarbonate with HCl to form carbon dioxide and calcium chloride ($CaCl_2$). Like sodium bicarbonate, calcium carbonate may cause belching or metabolic alkalosis. Calcium carbonate is used for a number of other indications apart from its antacid properties (see Chapter 42). Excessive doses of either sodium bicarbonate or calcium carbonate with calcium-containing dairy products can lead to hypercalcemia, renal insufficiency, and metabolic alkalosis (milk-alkali syndrome).

Formulations containing **magnesium hydroxide** or **aluminum hydroxide** react slowly with HCl to form magnesium chloride or aluminum chloride and water. Because no gas is generated, belching does not occur. Metabolic alkalosis is also uncommon because of the efficiency of the neutralization reaction. Because unabsorbed magnesium salts may cause an osmotic diarrhea and aluminum salts may cause constipation, these agents are commonly administered together in proprietary formulations (eg, Gelusil, Maalox, Mylanta) to minimize the impact on bowel function. Both magnesium and aluminum are absorbed and excreted by the kidneys. Hence, patients with renal insufficiency should not take these agents long-term.

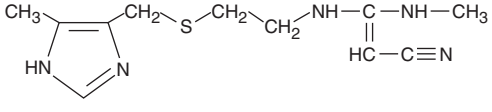
All antacids may affect the absorption of other medications by binding the drug (reducing its absorption) or by increasing intragastric pH so that the drug's dissolution or solubility (especially weakly basic or acidic drugs) is altered. Therefore, antacids should not be given within 2 hours of doses of tetracyclines, fluoroquinolones, itraconazole, and iron.

H_2-RECEPTOR ANTAGONISTS

From their introduction in the 1970s until the early 1990s, H_2-receptor antagonists (commonly referred to as H_2 blockers) were the most commonly prescribed drugs in the world (see Clinical Uses). With the recognition of the role of *H pylori* in ulcer disease (which may be treated with appropriate antibacterial therapy) and the advent of proton pump inhibitors, the use of prescription H_2 blockers has declined markedly.

Chemistry & Pharmacokinetics

Four H_2 antagonists are in clinical use: cimetidine, ranitidine, famotidine, and nizatidine. All four agents are rapidly absorbed from the intestine. Cimetidine, ranitidine, and famotidine undergo first-pass hepatic metabolism resulting in a bioavailability of approximately 50%. Nizatidine has little first-pass metabolism. The serum half-lives of the four agents range from 1.1 to 4 hours; however, duration of action depends on the dose given (Table 62–1). H_2 antagonists are cleared by a combination of hepatic metabolism, glomerular filtration, and renal tubular secretion. Dose reduction is required in patients with moderate to severe renal (and possibly severe hepatic) insufficiency. In the elderly, there is a decline of up to 50% in drug clearance as well as a significant reduction in volume of distribution.



Cimetidine

TABLE 62–1 Clinical comparisons of H_2–receptor blockers.

Drug	Relative Potency	Dose to Achieve > 50% Acid Inhibition for 10 Hours	Usual Dose for Acute Duodenal or Gastric Ulcer	Usual Dose for Gastroesophageal Reflux Disease	Usual Dose for Prevention of Stress–Related Bleeding
Cimetidine	1	400–800 mg	800 mg HS or 400 mg bid	800 mg bid	50 mg/h continuous infusion
Ranitidine	4–10	150 mg	300 mg HS or 150 mg bid	150 mg bid	6.25 mg/h continuous infusion or 50 mg IV every 6–8 h
Nizatidine	4–10	150 mg	300 mg HS or 150 mg bid	150 mg bid	Not available
Famotidine	20–50	20 mg	40 mg HS or 20 mg bid	20 mg bid	20 mg IV every 12 h

BID, twice daily; HS, bedtime.

Pharmacodynamics

The H_2 antagonists exhibit competitive inhibition at the parietal cell H_2 receptor and suppress basal and meal-stimulated acid secretion (Figure 62–2) in a linear, dose-dependent manner. They are highly selective and do not affect H_1 or H_3 receptors (see Chapter 16). The volume of gastric secretion and the concentration of pepsin are also reduced.

H_2 antagonists reduce acid secretion stimulated by histamine as well as by gastrin and cholinomimetic agents through two mechanisms. First, histamine released from ECL cells by gastrin or vagal stimulation is blocked from binding to the parietal cell H_2 receptor. Second, direct stimulation of the parietal cell by gastrin or acetylcholine has a diminished effect on acid secretion in the presence of H_2-receptor blockade.

The potencies of the four H_2-receptor antagonists vary over a 50-fold range (Table 62–1). When given in usual prescription doses however, all inhibit 60–70% of total 24-hour acid secretion. H_2 antagonists are especially effective at inhibiting nocturnal acid secretion (which depends largely on histamine), but they have a modest impact on meal-stimulated acid secretion (which is stimulated by gastrin and acetylcholine as well as histamine). Therefore, nocturnal and fasting intragastric pH is raised to 4–5 but the impact on the daytime, meal-stimulated pH profile is less. Recommended prescription doses maintain greater than 50% acid inhibition for 10 hours; hence, these drugs are commonly given twice daily. At doses available in over-the-counter formulations, the duration of acid inhibition is less than 6 hours.

Clinical Uses

H_2-receptor antagonists continue to be prescribed but proton pump inhibitors (see below) are steadily replacing H_2 antagonists for most clinical indications. However, the over-the-counter preparations of the H_2 antagonists are heavily used by the public.

A. Gastroesophageal Reflux Disease (GERD)

Patients with infrequent heartburn or dyspepsia (fewer than 3 times per week) may take either antacids or intermittent H_2 antagonists. Because antacids provide rapid acid neutralization, they afford faster symptom relief than H_2 antagonists. However, the effect of antacids is short-lived (1–2 hours) compared with H_2 antagonists (6–10 hours). H_2 antagonists may be taken prophylactically before meals in an effort to reduce the likelihood of heartburn. Frequent heartburn is better treated with twice-daily H_2 antagonists (Table 62–1) or proton pump inhibitors. In patients with erosive esophagitis (approximately 50% of patients with GERD), H_2 antagonists afford healing in less than 50% of patients; hence proton pump inhibitors are preferred because of their superior acid inhibition.

B. Peptic Ulcer Disease

Proton pump inhibitors have largely replaced H_2 antagonists in the treatment of acute peptic ulcer disease. Nevertheless, H_2 antagonists are still sometimes used. Nocturnal acid suppression by H_2 antagonists affords effective ulcer healing in most patients

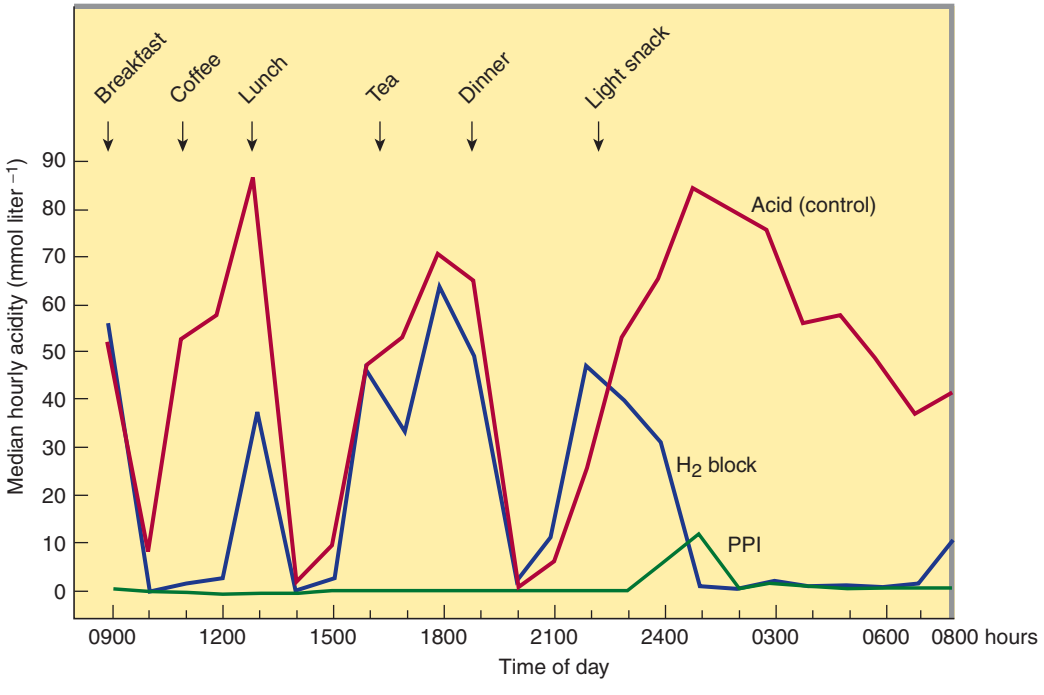


FIGURE 62–2 Twenty-four-hour median intragastric acidity pretreatment (red) and after 1 month of treatment with either ranitidine, 150 mg twice daily (blue, H_2 block), or omeprazole, 20 mg once daily (green, PPI). Note that H_2-receptor antagonists have a marked effect on nocturnal acid secretion but only a modest effect on meal-stimulated secretion. Proton pump inhibitors (PPIs) markedly suppress meal-stimulated and nocturnal acid secretion. (Redrawn from data in Lanzon-Miller S et al: Twenty-four-hour intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidine or omeprazole. Aliment Pharmacol Ther 1987;1:239.)

with uncomplicated gastric and duodenal ulcers. Hence, all the agents may be administered once daily at bedtime, resulting in ulcer healing rates of more than 80–90% after 6–8 weeks of therapy. For patients with ulcers caused by aspirin or other NSAIDs, the NSAID should be discontinued. If the NSAID must be continued for clinical reasons despite active ulceration, a proton pump inhibitor should be given instead of an H_2 antagonist to more reliably promote ulcer healing. For patients with acute peptic ulcers caused by *H pylori,* H_2 antagonists no longer play a significant therapeutic role. *H pylori* should be treated with a 10- to 14-day course of therapy including a proton pump inhibitor and two antibiotics (see below). This regimen achieves ulcer healing and eradication of the infection in more than 90% of patients. For the minority of patients in whom *H pylori* cannot be successfully eradicated, H_2 antagonists may be given daily at bedtime in half of the usual ulcer therapeutic dose to prevent ulcer recurrence (eg, ranitidine, 150 mg; famotidine, 20 mg).

C. Nonulcer Dyspepsia

H_2 antagonists are commonly used as over-the-counter agents and prescription agents for treatment of intermittent dyspepsia not caused by peptic ulcer. However, benefit compared with placebo has never been convincingly demonstrated.

D. Prevention of Bleeding from Stress-Related Gastritis

Clinically important bleeding from upper gastrointestinal erosions or ulcers occurs in 1–5% of critically ill patients as a result of impaired mucosal defense mechanisms caused by poor perfusion. Although most critically ill patients have normal or decreased acid secretion, numerous studies have shown that agents that increase intragastric pH (H_2 antagonists or proton pump inhibitors) reduce the incidence of clinically significant bleeding. However, the optimal agent is uncertain at this time. For patients without a nasoenteric tube or with significant ileus, intravenous H_2 antagonists are preferable over intravenous proton pump inhibitors because of their proven efficacy and lower cost. Continuous infusions of H_2 antagonists are generally preferred to bolus infusions because they achieve more consistent, sustained elevation of intragastric pH.

Adverse Effects

H_2 antagonists are extremely safe drugs. Adverse effects occur in less than 3% of patients and include diarrhea, headache, fatigue, myalgias, and constipation. Some studies suggest that intravenous H_2 antagonists (or proton pump inhibitors) may increase the risk of nosocomial pneumonia in critically ill patients.

Mental status changes (confusion, hallucinations, agitation) may occur with administration of intravenous H_2 antagonists, especially in patients in the intensive care unit who are elderly or who have renal or hepatic dysfunction. These events may be more common with cimetidine. Mental status changes rarely occur in ambulatory patients.

Cimetidine inhibits binding of dihydrotestosterone to androgen receptors, inhibits metabolism of estradiol, and increases serum prolactin levels. When used long-term or in high doses, it may cause gynecomastia or impotence in men and galactorrhea in women. These effects are specific to cimetidine and do not occur with the other H_2 antagonists.

Although there are no known harmful effects on the fetus, H_2 antagonists cross the placenta. Therefore, they should not be administered to pregnant women unless absolutely necessary. The H_2 antagonists are secreted into breast milk and may therefore affect nursing infants.

H_2 antagonists may rarely cause blood dyscrasias. Blockade of cardiac H_2 receptors may cause bradycardia, but this is rarely of clinical significance. Rapid intravenous infusion may cause bradycardia and hypotension through blockade of cardiac H_2 receptors; therefore, intravenous injections should be given over 30 minutes. H_2 antagonists rarely cause reversible abnormalities in liver chemistry.

Drug Interactions

Cimetidine interferes with several important hepatic cytochrome P450 drug metabolism pathways, including those catalyzed by CYP1A2, CYP2C9, CYP2D6, and CYP3A4 (see Chapter 4). Hence, the half-lives of drugs metabolized by these pathways may be prolonged. Ranitidine binds 4–10 times less avidly than cimetidine to cytochrome P450. Negligible interaction occurs with nizatidine and famotidine.

H_2 antagonists compete with creatinine and certain drugs (eg, procainamide) for renal tubular secretion. All of these agents except famotidine inhibit gastric first-pass metabolism of ethanol, especially in women. Although the importance of this is debated, increased bioavailability of ethanol could lead to increased blood ethanol levels.

PROTON PUMP INHIBITORS

Since their introduction in the late 1980s, these efficacious acid inhibitory agents have assumed the major role for the treatment of acid-peptic disorders. Proton pump inhibitors (PPIs) are now among the most widely prescribed drugs worldwide due to their outstanding efficacy and safety.

Chemistry & Pharmacokinetics

Six proton pump inhibitors are available for clinical use: **omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole,** and **pantoprazole.** All are substituted benzimidazoles that resemble H_2 antagonists in structure (Figure 62–3) but have a completely different mechanism of action. Omeprazole and lansoprazole are racemic mixtures of *R*- and *S*-isomers. Esomeprazole is the *S*-isomer of omeprazole and dexlansoprazole the *R*-isomer of lansoprazole. All are available in oral formulations. Esomeprazole and pantoprazole are also available in intravenous formulations (Table 62–2).

Proton pump inhibitors are administered as inactive prodrugs. To protect the acid-labile prodrug from rapid destruction within the gastric lumen, oral products are formulated for delayed release as acid-resistant, enteric-coated capsules or tablets. After passing through the stomach into the alkaline intestinal lumen, the enteric

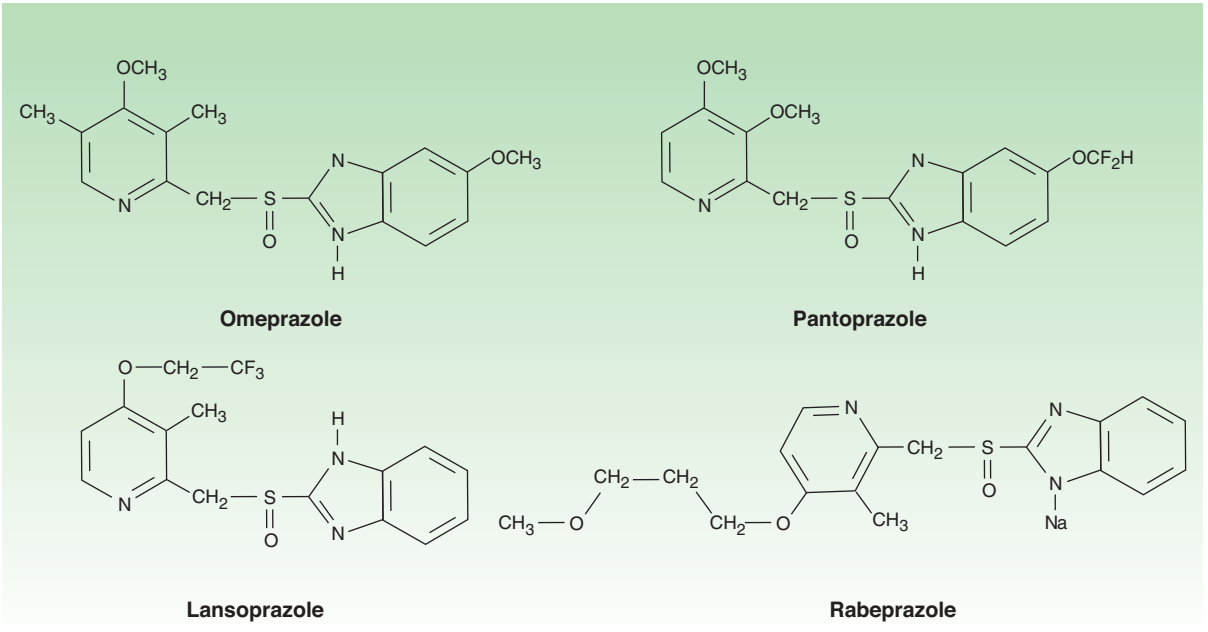


FIGURE 62–3 Molecular structure of the proton pump inhibitors: omeprazole, lansoprazole, pantoprazole, and the sodium salt of rabeprazole. Omeprazole and esomeprazole have the same chemical structure (see text).

coatings dissolve and the prodrug is absorbed. For children or patients with dysphagia or enteral feeding tubes, capsule formulations (but not tablets) may be opened and the microgranules mixed with apple or orange juice or mixed with soft foods (eg, applesauce). Lansoprazole is also available as a tablet formulation that disintegrates in the mouth, or it may be mixed with water and administered via oral syringe or enteral tube. Omeprazole is also available as a powder formulation (capsule or packet) that contains sodium bicarbonate (1100–1680 mg $NaHCO_3$; 304–460 mg of sodium) to protect the naked (non-enteric-coated) drug from acid degradation. When administered on an empty stomach by mouth or enteral tube, this "immediate-release" suspension results in rapid omeprazole absorption (T_{max} < 30 minutes) and onset of acid inhibition.

The proton pump inhibitors are lipophilic weak bases (pK_a 4–5) and after intestinal absorption diffuse readily across lipid membranes into acidified compartments (eg, the parietal cell canaliculus). The prodrug rapidly becomes protonated within the canaliculus and is concentrated more than 1000-fold by Henderson-Hasselbalch trapping (see Chapter 1). There, it rapidly undergoes a molecular conversion to the active form, a reactive thiophilic sulfenamide cation, which forms a covalent disulfide bond with the H^+/K^+-ATPase, irreversibly inactivating the enzyme.

The pharmacokinetics of available proton pump inhibitors are shown in Table 62–2. Immediate-release omeprazole has a faster onset of acid inhibition than other oral formulations. Although differences in pharmacokinetic profiles may affect speed of onset and duration of acid inhibition in the first few days of therapy, they are of little clinical importance with continued daily administration. The bioavailability of all agents is decreased approximately 50% by food; hence, the drugs should be administered on

TABLE 62–2 Pharmacokinetics of proton pump inhibitors.

Drug	pK_a	Bioavailability (%)	$t_{1/2}$ (h)	T_{max} (h)	Usual Dosage for Peptic Ulcer or GERD
Omeprazole	4	40–65	0.5–1.0	1–3	20–40 mg qd
Esomeprazole	4	> 80	1.5	1.6	20–40 mg qd
Lansoprazole	4	> 80	1.0–2.0	1.7	30 mg qd
Dexlansoprazole	4	NA	1.0–2.0	5.0	30–60mg qd
Pantoprazole	3.9	77	1.0–1.9	2.5–4.0	40 mg qd
Rabeprazole	5	52	1.0–2.0	3.1	20 mg qd

GERD, gastroesophageal reflux disease; NA, data not available.

an empty stomach. In a fasting state, only 10% of proton pumps are actively secreting acid and susceptible to inhibition. Proton pump inhibitors should be administered approximately 1 hour before a meal (usually breakfast), so that the peak serum concentration coincides with the maximal activity of proton pump secretion. The drugs have a short serum half-life of about 1.5 hours, but acid inhibition lasts up to 24 hours owing to the irreversible inactivation of the proton pump. At least 18 hours are required for synthesis of new H^+/K^+-ATPase pump molecules. Because not all proton pumps are inactivated with the first dose of medication, up to 3–4 days of daily medication are required before the full acid-inhibiting potential is reached. Similarly, after stopping the drug, it takes 3–4 days for full acid secretion to return.

Proton pump inhibitors undergo rapid first-pass and systemic hepatic metabolism and have negligible renal clearance. Dose reduction is not needed for patients with renal insufficiency or mild to moderate liver disease but should be considered in patients with severe liver impairment. Although other proton pumps exist in the body, the H^+/K^+-ATPase appears to exist only in the parietal cell and is distinct structurally and functionally from other H^+-transporting enzymes.

The intravenous formulations of esomeprazole and pantoprazole have characteristics similar to those of the oral drugs. When given to a fasting patient, they inactivate acid pumps that are actively secreting, but they have no effect on pumps in quiescent, nonsecreting vesicles. Because the half-life of a single injection of the intravenous formulation is short, acid secretion returns several hours later as pumps move from the tubulovesicles to the canalicular surface. Thus, to provide maximal inhibition during the first 24–48 hours of treatment, the intravenous formulations must be given as a continuous infusion or as repeated bolus injections. The optimal dosing of intravenous proton pump inhibitors to achieve maximal blockade in fasting patients is not yet established.

From a pharmacokinetic perspective, proton pump inhibitors are ideal drugs: they have a short serum half-life, they are concentrated and activated near their site of action, and they have a long duration of action.

Pharmacodynamics

In contrast to H_2 antagonists, proton pump inhibitors inhibit both fasting and meal-stimulated secretion because they block the final common pathway of acid secretion, the proton pump. In standard doses, proton pump inhibitors inhibit 90–98% of 24-hour acid secretion (Figure 62–2). When administered at equivalent doses, the different agents show little difference in clinical efficacy. In a crossover study of patients receiving long-term therapy with five proton pump inhibitors, the mean 24-hour intragastric pH varied from 3.3 (pantoprazole, 40 mg) to 4.0 (esomeprazole, 40 mg) and the mean number of hours the pH was higher than 4 varied from 10.1 (pantoprazole, 40 mg) to 14.0 (esomeprazole, 40 mg). Although dexlansoprazole has a delayed-release formulation that results in a longer T_{max} and greater AUC than other proton pump inhibitors, it appears comparable to other agents in the ability to suppress acid secretion. This is because acid suppression is more dependent upon irreversible inactivation of the proton pump than the pharmacokinetics of different agents.

Clinical Uses

A. Gastroesophageal Reflux Disease (GERD)

Proton pump inhibitors are the most effective agents for the treatment of nonerosive and erosive reflux disease, esophageal complications of reflux disease (peptic stricture or Barrett's esophagus), and extraesophageal manifestations of reflux disease. Once-daily dosing provides effective symptom relief and tissue healing in 85–90% of patients; up to 15% of patients require twice-daily dosing.

GERD symptoms recur in over 80% of patients within 6 months after discontinuation of a proton pump inhibitor. For patients with erosive esophagitis or esophageal complications, long-term daily maintenance therapy with a full-dose or half-dose proton pump inhibitor is usually needed. Many patients with nonerosive GERD may be treated successfully with intermittent courses of proton pump inhibitors or H_2 antagonists taken as needed ("on demand") for recurrent symptoms.

In current clinical practice, many patients with symptomatic GERD are treated empirically with medications without prior endoscopy, ie, without knowledge of whether the patient has erosive or nonerosive reflux disease. Empiric treatment with proton pump inhibitors provides sustained symptomatic relief in 70–80% of patients, compared with 50–60% with H_2 antagonists. Because of recent cost reductions, proton pump inhibitors are being used increasingly as first-line therapy for patients with symptomatic GERD.

Sustained acid suppression with twice-daily proton pump inhibitors for at least 3 months is used to treat extraesophageal complications of reflux disease (asthma, chronic cough, laryngitis, and noncardiac chest pain).

B. Peptic Ulcer Disease

Compared with H_2 antagonists, proton pump inhibitors afford more rapid symptom relief and faster ulcer healing for duodenal ulcers and, to a lesser extent, gastric ulcers. All the pump inhibitors heal more than 90% of duodenal ulcers within 4 weeks and a similar percentage of gastric ulcers within 6–8 weeks.

1. H pylori-associated ulcers—For *H pylori*-associated ulcers, there are two therapeutic goals: to heal the ulcer and to eradicate the organism. The most effective regimens for *H pylori* eradication are combinations of two antibiotics and a proton pump inhibitor. Proton pump inhibitors promote eradication of *H pylori* through several mechanisms: direct antimicrobial properties (minor) and—by raising intragastric pH—lowering the minimal inhibitory concentrations of antibiotics against *H pylori*. The best treatment regimen consists of a 14-day regimen of "triple therapy": a proton pump inhibitor twice daily; clarithromycin, 500 mg twice daily; and either amoxicillin, 1 g twice daily, or metronidazole, 500 mg twice daily. After completion of triple therapy, the proton pump inhibitor should be continued once daily for a total of 4–6 weeks to ensure complete ulcer healing. Alternatively, 10 days

of "sequential treatment" consisting on days 1–5 of a proton pump inhibitor twice daily plus amoxicillin, 1 g twice daily, and followed on days 6–10 by five additional days of a proton pump inhibitor twice daily, plus clarithromycin, 500 mg twice daily, and tinidazole, 500 mg twice daily, has been shown to be a highly effective treatment regimen.

2. NSAID-associated ulcers—For patients with ulcers caused by aspirin or other NSAIDs, either H_2 antagonists or proton pump inhibitors provide rapid ulcer healing so long as the NSAID is discontinued; however continued use of the NSAID impairs ulcer healing. In patients with NSAID-induced ulcers who require continued NSAID therapy, treatment with a once- or twice-daily proton pump inhibitor more reliably promotes ulcer healing.

Asymptomatic peptic ulceration develops in 10–20% of people taking frequent NSAIDs, and ulcer-related complications (bleeding, perforation) develop in 1–2% of persons per year. Proton pump inhibitors taken once daily are effective in reducing the incidence of ulcers and ulcer complications in patients taking aspirin or other NSAIDs.

3. Prevention of rebleeding from peptic ulcers—In patients with acute gastrointestinal bleeding due to peptic ulcers, the risk of rebleeding from ulcers that have a visible vessel or adherent clot is increased. Rebleeding of this subset of high-risk ulcers is reduced significantly with proton pump inhibitors administered for 3–5 days either as high-dose oral therapy (eg, omeprazole, 40 mg orally twice daily) or as a continuous intravenous infusion. It is believed that an intragastric pH higher than 6 may enhance coagulation and platelet aggregation. The optimal dose of intravenous proton pump inhibitor needed to achieve and maintain this level of near-complete acid inhibition is unknown; however, initial bolus administration of esomeprazole or pantoprazole (80 mg) followed by constant infusion (8 mg/h) is commonly recommended.

C. Nonulcer Dyspepsia

Proton pump inhibitors have modest efficacy for treatment of nonulcer dyspepsia, benefiting 10–20% more patients than placebo. Despite their use for this indication, superiority to H_2 antagonists (or even placebo) has not been conclusively demonstrated.

D. Prevention of Stress-Related Mucosal Bleeding

As discussed previously (see H_2-Receptor Antagonists) proton pump inhibitors (given orally, by nasogastric tube, or by intravenous infusions) may be administered to reduce the risk of clinically significant stress-related mucosal bleeding in critically ill patients. The only proton pump inhibitor approved by the Food and Drug Administration (FDA) for this indication is an oral immediate-release omeprazole formulation, which is administered by nasogastric tube twice daily on the first day, then once daily. For patients with nasoenteric tubes, immediate-release omeprazole may be preferred to intravenous H_2 antagonists or other proton pump inhibitors because of comparable efficacy, lower cost, and ease of administration.

For patients without a nasoenteric tube or with significant ileus, intravenous H_2 antagonists are preferred to intravenous proton pump inhibitors because of their proven efficacy and lower cost. Although proton pump inhibitors are increasingly used, there are no controlled trials demonstrating efficacy or optimal dosing.

E. Gastrinoma and Other Hypersecretory Conditions

Patients with isolated gastrinomas are best treated with surgical resection. In patients with metastatic or unresectable gastrinomas, massive acid hypersecretion results in peptic ulceration, erosive esophagitis, and malabsorption. Previously, these patients required vagotomy and extraordinarily high doses of H_2 antagonists, which still resulted in suboptimal acid suppression. With proton pump inhibitors, excellent acid suppression can be achieved in all patients. Dosage is titrated to reduce basal acid output to less than 5–10 mEq/h. Typical doses of omeprazole are 60–120 mg/d.

Adverse Effects

A. General

Proton pump inhibitors are extremely safe. Diarrhea, headache, and abdominal pain are reported in 1–5% of patients, although the frequency of these events is only slightly increased compared with placebo. Increasing cases of acute interstitial nephritis have been reported. Proton pump inhibitors do not have teratogenicity in animal models; however, safety during pregnancy has not been established.

B. Nutrition

Acid is important in releasing vitamin B_{12} from food. A minor reduction in oral cyanocobalamin absorption occurs during proton pump inhibition, potentially leading to subnormal B_{12} levels with prolonged therapy. Acid also promotes absorption of food-bound minerals (non-heme iron, insoluble calcium salts, magnesium). Several case-control studies have suggested a modest increase in the risk of hip fracture in patients taking proton pump inhibitors over a long term compared with matched controls. Although a causal relationship is unproven, proton pump inhibitors may reduce calcium absorption or inhibit osteoclast function. Pending further studies, patients who require long-term proton pump inhibitors—especially those with risk factors for osteoporosis—should have monitoring of bone density and should be provided calcium supplements. Cases of severe, life-threatening hypomagnesemia with secondary hypocalcemia due to proton pump inhibitors have been reported; however, the mechanism of action is unknown.

C. Respiratory and Enteric Infections

Gastric acid is an important barrier to colonization and infection of the stomach and intestine from ingested bacteria. Increases in gastric bacterial concentrations are detected in patients taking proton pump inhibitors, which is of unknown clinical significance. Some studies have reported an increased risk of both community-acquired respiratory infections and nosocomial pneumonia among patients taking proton pump inhibitors.

There is a 2- to 3-fold increased risk for hospital- and community-acquired *Clostridium difficile* infection in patients taking proton pump inhibitors. There also is a small increased risk of other enteric infections (eg, *Salmonella, Shigella, E coli, Campylobacter*), which should be considered particularly when traveling in underdeveloped countries.

D. Potential Problems Due to Increased Serum Gastrin

Gastrin levels are regulated by intragastric acidity. Acid suppression alters normal feedback inhibition so that median serum gastrin levels rise 1.5- to 2-fold in patients taking proton pump inhibitors. Although gastrin levels remain within normal limits in most patients, they exceed 500 pg/mL (normal, < 100 pg/mL) in 3%. Upon stopping the drug, the levels normalize within 4 weeks. The rise in serum gastrin levels may stimulate hyperplasia of ECL and parietal cells, which may cause transient rebound acid hypersecretion with increased dyspepsia or heartburn after drug discontinuation, which abate within 2–4 weeks after gastrin and acid secretion normalize. In female rats given proton pump inhibitors for prolonged periods, hypergastrinemia caused gastric carcinoid tumors that developed in areas of ECL hyperplasia. Although humans who take proton pump inhibitors for a long time also may exhibit ECL hyperplasia, carcinoid tumor formation has not been documented. At present, routine monitoring of serum gastrin levels is not recommended in patients receiving prolonged proton pump inhibitor therapy.

E. Other Potential Problems Due to Decreased Gastric Acidity

Among patients infected with *H pylori*, long-term acid suppression leads to increased chronic inflammation in the gastric body and decreased inflammation in the antrum. Concerns have been raised that increased gastric inflammation may accelerate gastric gland atrophy (atrophic gastritis) and intestinal metaplasia—known risk factors for gastric adenocarcinoma. A special FDA Gastrointestinal Advisory Committee concluded that there is no evidence that prolonged proton pump inhibitor therapy produces the kind of atrophic gastritis (multifocal atrophic gastritis) or intestinal metaplasia that is associated with increased risk of adenocarcinoma. Routine testing for *H pylori* is not recommended in patients who require long-term proton pump inhibitor therapy. Long-term proton pump inhibitor therapy is associated with the development of small benign gastric fundic-gland polyps in a small number of patients, which may disappear after stopping the drug and are of uncertain clinical significance.

Drug Interactions

Decreased gastric acidity may alter absorption of drugs for which intragastric acidity affects drug bioavailability, eg, ketoconazole, itraconazole, digoxin, and atazanavir. All proton pump inhibitors are metabolized by hepatic P450 cytochromes, including CYP2C19 and CYP3A4. Because of the short half-lives of proton pump inhibitors, clinically significant drug interactions are rare. Omeprazole may inhibit the metabolism of warfarin, diazepam, and phenytoin. Esomeprazole also may decrease metabolism of diazepam. Lansoprazole may enhance clearance of theophylline. Rabeprazole and pantoprazole have no significant drug interactions.

The FDA has issued a warning about a potentially important adverse interaction between clopidogrel and proton pump inhibitors. Clopidogrel is a prodrug that requires activation by the hepatic P450 CYP2C19 isoenzyme, which also is involved to varying degrees in the metabolism of proton pump inhibitors (especially omeprazole, esomeprazole, lansoprazole, and dexlansoprazole). Thus, proton pump inhibitors could reduce clopidogrel activation (and its antiplatelet action) in some patients. Several large retrospective studies have reported an increased incidence of serious cardiovascular events in patients taking clopidogrel and a proton pump inhibitor. In contrast, three smaller prospective randomized trials have not detected an increased risk. Pending further studies, proton pump inhibitors should be prescribed to patients taking clopidogrel only if they have an increased risk of gastrointestinal bleeding or require them for chronic gastroesophageal reflux or peptic ulcer disease, in which case agents with minimal CYP2C19 inhibition (pantoprazole or rabeprazole) are preferred.

MUCOSAL PROTECTIVE AGENTS

The gastroduodenal mucosa has evolved a number of defense mechanisms to protect itself against the noxious effects of acid and pepsin. Both mucus and epithelial cell-cell tight junctions restrict back diffusion of acid and pepsin. Epithelial bicarbonate secretion establishes a pH gradient within the mucous layer in which the pH ranges from 7 at the mucosal surface to 1–2 in the gastric lumen. Blood flow carries bicarbonate and vital nutrients to surface cells. Areas of injured epithelium are quickly repaired by restitution, a process in which migration of cells from gland neck cells seals small erosions to reestablish intact epithelium. Mucosal prostaglandins appear to be important in stimulating mucus and bicarbonate secretion and mucosal blood flow. A number of agents that potentiate these mucosal defense mechanisms are available for the prevention and treatment of acid-peptic disorders.

SUCRALFATE

Chemistry & Pharmacokinetics

Sucralfate is a salt of sucrose complexed to sulfated aluminum hydroxide. In water or acidic solutions it forms a viscous, tenacious paste that binds selectively to ulcers or erosions for up to 6 hours. Sucralfate has limited solubility, breaking down into sucrose sulfate (strongly negatively charged) and an aluminum salt. Less than 3% of intact drug and aluminum is absorbed from the intestinal tract; the remainder is excreted in the feces.

Pharmacodynamics

A variety of beneficial effects have been attributed to sucralfate, but the precise mechanism of action is unclear. It is believed that the negatively charged sucrose sulfate binds to positively charged

proteins in the base of ulcers or erosion, forming a physical barrier that restricts further caustic damage and stimulates mucosal prostaglandin and bicarbonate secretion.

Clinical Uses

Sucralfate is administered in a dosage of 1 g four times daily on an empty stomach (at least 1 hour before meals). At present, its clinical uses are limited. Sucralfate (administered as a slurry through a nasogastric tube) reduces the incidence of clinically significant upper gastrointestinal bleeding in critically ill patients hospitalized in the intensive care unit, although it is slightly less effective than intravenous H_2 antagonists. Sucralfate is still used by many clinicians for prevention of stress-related bleeding because of concerns that acid inhibitory therapies (antacids, H_2 antagonists, and proton pump inhibitors) may increase the risk of nosocomial pneumonia.

Adverse Effects

Because it is not absorbed, sucralfate is virtually devoid of systemic adverse effects. Constipation occurs in 2% of patients due to the aluminum salt. Because a small amount of aluminum is absorbed, it should not be used for prolonged periods in patients with renal insufficiency.

Drug Interactions

Sucralfate may bind to other medications, impairing their absorption.

PROSTAGLANDIN ANALOGS

Chemistry & Pharmacokinetics

The human gastrointestinal mucosa synthesizes a number of prostaglandins (see Chapter 18); the primary ones are prostaglandins E and F. **Misoprostol,** a methyl analog of PGE_1, has been approved for gastrointestinal conditions. After oral administration, it is rapidly absorbed and metabolized to a metabolically active free acid. The serum half-life is less than 30 minutes; hence, it must be administered 3–4 times daily. It is excreted in the urine; however, dose reduction is not needed in patients with renal insufficiency.

Pharmacodynamics

Misoprostol has both acid inhibitory and mucosal protective properties. It is believed to stimulate mucus and bicarbonate secretion and enhance mucosal blood flow. In addition, it binds to a prostaglandin receptor on parietal cells, reducing histamine-stimulated cAMP production and causing modest acid inhibition. Prostaglandins have a variety of other actions, including stimulation of intestinal electrolyte and fluid secretion, intestinal motility, and uterine contractions.

Clinical Uses

Peptic ulcers develop in approximately 10–20% of patients who receive long-term NSAID therapy (see Proton Pump Inhibitors, above). Misoprostol reduces the incidence of NSAID-induced ulcers to less than 3% and the incidence of ulcer complications by 50%. It is approved for prevention of NSAID-induced ulcers in high-risk patients; however, misoprostol has never achieved widespread use owing to its high adverse-effect profile and need for multiple daily dosing. As discussed, proton pump inhibitors may be as effective as and better tolerated than misoprostol for this indication. Cyclooxygenase-2-selective NSAIDs, which may have less gastrointestinal toxicity (see Chapter 36), offer another option for patients at high risk for NSAID-induced complications.

Adverse Effects & Drug Interactions

Diarrhea and cramping abdominal pain occur in 10–20% of patients. Because misoprostol stimulates uterine contractions (see Chapter 18), it should not be used during pregnancy or in women of childbearing potential unless they have a negative serum pregnancy test and are compliant with effective contraceptive measures. No significant drug interactions are reported.

BISMUTH COMPOUNDS

Chemistry & Pharmacokinetics

Two bismuth compounds are available: **bismuth subsalicylate,** a nonprescription formulation containing bismuth and salicylate, and **bismuth subcitrate potassium.** In the USA, bismuth subcitrate is available only as a combination prescription product that also contains metronidazole and tetracycline for the treatment of *H pylori.* Bismuth subsalicylate undergoes rapid dissociation within the stomach, allowing absorption of salicylate. Over 99% of the bismuth appears in the stool. Although minimal (< 1%), bismuth is absorbed; it is stored in many tissues and has slow renal excretion. Salicylate (like aspirin) is readily absorbed and excreted in the urine.

Pharmacodynamics

The precise mechanisms of action of bismuth are unknown. Bismuth coats ulcers and erosions, creating a protective layer against acid and pepsin. It may also stimulate prostaglandin, mucus, and bicarbonate secretion. Bismuth subsalicylate reduces stool frequency and liquidity in acute infectious diarrhea, due to salicylate inhibition of intestinal prostaglandin and chloride secretion. Bismuth has direct antimicrobial effects and binds enterotoxins, accounting for its benefit in preventing and treating traveler's diarrhea. Bismuth compounds have direct antimicrobial activity against *H pylori.*

Clinical Uses

In spite of the lack of comparative trials, nonprescription bismuth compounds (eg, Pepto-Bismol, Kaopectate) are widely used by patients for the nonspecific treatment of dyspepsia and acute diarrhea. Bismuth subsalicylate also is used for the prevention of traveler's diarrhea (30 mL or 2 tablets four times daily).

Bismuth compounds are used in 4-drug regimens for the eradication of *H pylori* infection. One regimen consists of a proton pump inhibitor twice daily combined with bismuth subsalicylate (2 tablets; 262 mg each), tetracycline (250–500 mg), and metronidazole (500 mg) four times daily for 10–14 days. Another regimen consists of a proton pump inhibitor twice daily combined with three capsules of a combination prescription formulation (each capsule containing bismuth subcitrate 140 mg, metronidazole 125 mg, and tetracycline 125 mg) taken four times daily for 10 days. Although these are effective, standard "triple therapy" regimens (ie, proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole twice daily for 14 days) generally are preferred for first-line therapy because of twice-daily dosing and superior compliance. Bismuth-based quadruple therapies are commonly used as second-line therapies.

Adverse Effects

All bismuth formulations have excellent safety profiles. Bismuth causes harmless blackening of the stool, which may be confused with gastrointestinal bleeding. Liquid formulations may cause harmless darkening of the tongue. Bismuth agents should be used for short periods only and should be avoided in patients with renal insufficiency. Prolonged usage of some bismuth compounds may rarely lead to bismuth toxicity, resulting in encephalopathy (ataxia, headaches, confusion, seizures). However, such toxicity is not reported with bismuth subsalicylate or bismuth citrate. High dosages of bismuth subsalicylate may lead to salicylate toxicity.

DRUGS STIMULATING GASTROINTESTINAL MOTILITY

Drugs that can selectively stimulate gut motor function (**prokinetic** agents) have significant potential clinical usefulness. Agents that increase lower esophageal sphincter pressures may be useful for GERD. Drugs that improve gastric emptying may be helpful for gastroparesis and postsurgical gastric emptying delay. Agents that stimulate the small intestine may be beneficial for postoperative ileus or chronic intestinal pseudo-obstruction. Finally, agents that enhance colonic transit may be useful in the treatment of constipation. Unfortunately, only a limited number of agents in this group are available for clinical use at this time.

PHYSIOLOGY OF THE ENTERIC NERVOUS SYSTEM

The enteric nervous system (see also Chapter 6) is composed of interconnected networks of ganglion cells and nerve fibers mainly located in the submucosa (submucosal plexus) and between the circular and longitudinal muscle layers (myenteric plexus). These networks give rise to nerve fibers that connect with the mucosa and muscle. Although extrinsic sympathetic and parasympathetic nerves project onto the submucosal and myenteric plexuses, the enteric nervous system can independently regulate gastrointestinal motility and secretion. Extrinsic primary afferent neurons project via the dorsal root ganglia or vagus nerve to the central nervous system (Figure 62–4). Release of serotonin (5-HT) from intestinal mucosa enterochromaffin (EC) cells stimulates 5-HT_3 receptors on the extrinsic afferent nerves, stimulating nausea, vomiting, or abdominal pain. Serotonin also stimulates submucosal 5-HT_{1P} receptors of the intrinsic primary afferent nerves (IPANs), which contain calcitonin gene-related peptide (CGRP) and acetylcholine and project to myenteric plexus interneurons. 5-HT_4 receptors on the presynaptic terminals of the IPANs appear to enhance release of CGRP or acetylcholine. The myenteric interneurons are important in controlling the peristaltic reflex, promoting release of excitatory mediators proximally and inhibitory mediators distally. Motilin may stimulate excitatory neurons or muscle cells directly. Dopamine acts as an inhibitory neurotransmitter in the gastrointestinal tract, decreasing the intensity of esophageal and gastric contractions.

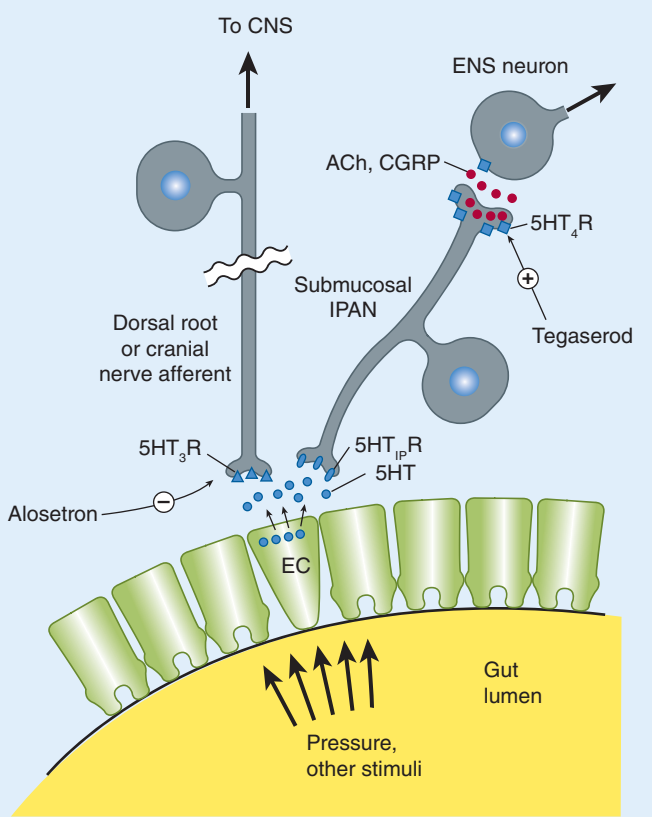


FIGURE 62–4 Release of serotonin (5-HT) by enterochromaffin (EC) cells from gut distention stimulates submucosal intrinsic primary afferent neurons (IPANs) via 5-HT_{1P} receptors and extrinsic primary afferent neurons via 5-HT_3 receptors (5-HT_{1P}R, 5-HT_3R). Submucosal IPANs activate the enteric neurons responsible for peristaltic and secretory reflex activity. Stimulation of 5-HT_4 receptors (5-HT_4R) on presynaptic terminals of IPANs enhances release of acetylcholine (ACh) and calcitonin gene-related peptide (CGRP), promoting reflex activity. CNS, central nervous system; ENS, enteric nervous system. (Redrawn from Gershon MD: Serotonin and its implication for the management of irritable bowel syndrome. Rev Gastroenterol Dis 2003;3[Suppl 2]:S25.)

Although there are at least 14 serotonin receptor subtypes, 5-HT drug development for gastrointestinal applications to date has focused on **5-HT$_3$-receptor antagonists and 5-HT$_4$-receptor agonists.** These agents—which have effects on gastrointestinal motility and visceral afferent sensation—are discussed under Drugs Used for the Treatment of Irritable Bowel Syndrome and Antiemetic Agents. Other drugs acting on 5-HT receptors are discussed in Chapters 16, 29, and 30.

CHOLINOMIMETIC AGENTS

Cholinomimetic agonists such as bethanechol stimulate muscarinic M_3 receptors on muscle cells and at myenteric plexus synapses (see Chapter 7). Bethanechol was used in the past for the treatment of GERD and gastroparesis. Owing to multiple cholinergic effects and the advent of less toxic agents, it is now seldom used. The acetylcholinesterase inhibitor neostigmine can enhance gastric, small intestine, and colonic emptying. Intravenous neostigmine has enjoyed a resurgence in clinical usage for the treatment of hospitalized patients with acute large bowel distention (known as acute colonic pseudo-obstruction or Ogilvie's syndrome). Administration of 2 mg results in prompt colonic evacuation of flatus and feces in the majority of patients. Cholinergic effects include excessive salivation, nausea, vomiting, diarrhea, and bradycardia.

METOCLOPRAMIDE & DOMPERIDONE

Metoclopramide and domperidone are dopamine D_2-receptor antagonists. Within the gastrointestinal tract activation of dopamine receptors inhibits cholinergic smooth muscle stimulation; blockade of this effect is believed to be the primary prokinetic mechanism of action of these agents. These agents increase esophageal peristaltic amplitude, increase lower esophageal sphincter pressure, and enhance gastric emptying but have no effect on small intestine or colonic motility. Metoclopramide and domperidone also block dopamine D_2 receptors in the chemoreceptor trigger zone of the medulla (area postrema), resulting in potent antinausea and antiemetic action.

Clinical Uses

A. Gastroesophageal Reflux Disease

Metoclopramide is available for clinical use in the USA; domperidone is available in many other countries. These agents are sometimes used in the treatment of symptomatic GERD but are not effective in patients with erosive esophagitis. Because of the superior efficacy and safety of antisecretory agents in the treatment of heartburn, prokinetic agents are used mainly in combination with antisecretory agents in patients with regurgitation or refractory heartburn.

B. Impaired Gastric Emptying

These agents are widely used in the treatment of patients with delayed gastric emptying due to postsurgical disorders (vagotomy, antrectomy) and diabetic gastroparesis. Metoclopramide is sometimes administered in hospitalized patients to promote advancement of nasoenteric feeding tubes from the stomach into the duodenum.

C. Nonulcer Dyspepsia

These agents lead to symptomatic improvement in a small number of patients with chronic dyspepsia.

D. Prevention of Vomiting

Because of their potent antiemetic action, metoclopramide and domperidone are used for the prevention and treatment of emesis.

E. Postpartum Lactation Stimulation

Domperidone is sometimes recommended to promote postpartum lactation (see also Adverse Effects).

Adverse Effects

The most common adverse effects of metoclopramide involve the central nervous system. Restlessness, drowsiness, insomnia, anxiety, and agitation occur in 10–20% of patients, especially the elderly. Extrapyramidal effects (dystonias, akathisia, parkinsonian features) due to central dopamine receptor blockade occur acutely in 25% of patients given high doses and in 5% of patients receiving long-term therapy. Tardive dyskinesia, sometimes irreversible, has developed in patients treated for a prolonged period with metoclopramide. For this reason, long-term use should be avoided unless absolutely necessary, especially in the elderly. Elevated prolactin levels (caused by both metoclopramide and domperidone) can cause galactorrhea, gynecomastia, impotence, and menstrual disorders.

Domperidone is extremely well tolerated. Because it does not cross the blood-brain barrier to a significant degree, neuropsychiatric and extrapyramidal effects are rare.

MACROLIDES

Macrolide antibiotics such as **erythromycin** directly stimulate motilin receptors on gastrointestinal smooth muscle and promote the onset of a migrating motor complex. Intravenous erythromycin (3 mg/kg) is beneficial in some patients with gastroparesis; however, tolerance rapidly develops. It may be used in patients with acute upper gastrointestinal hemorrhage to promote gastric emptying of blood before endoscopy.

LAXATIVES

The overwhelming majority of people do not need laxatives; yet they are self-prescribed by a large portion of the population. For most people, intermittent constipation is best prevented with a high-fiber diet, adequate fluid intake, regular exercise, and the heeding of nature's call. Patients not responding to dietary changes or fiber supplements should undergo medical evaluation before initiating long-term laxative treatment. Laxatives may be classified by their major mechanism of action, but many work through more than one mechanism.

BULK-FORMING LAXATIVES

Bulk-forming laxatives are indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis. Common preparations include natural plant products (**psyllium, methylcellulose**) and synthetic fibers **(polycarbophil)**. Bacterial digestion of plant fibers within the colon may lead to increased bloating and flatus.

STOOL SURFACTANT AGENTS (SOFTENERS)

These agents soften stool material, permitting water and lipids to penetrate. They may be administered orally or rectally. Common agents include **docusate** (oral or enema) and **glycerin suppository**. In hospitalized patients, docusate is commonly prescribed to prevent constipation and minimize straining. **Mineral oil** is a clear, viscous oil that lubricates fecal material, retarding water absorption from the stool. It is used to prevent and treat fecal impaction in young children and debilitated adults. It is not palatable but may be mixed with juices. Aspiration can result in a severe lipid pneumonitis. Long-term use can impair absorption of fat-soluble vitamins (A, D, E, K).

OSMOTIC LAXATIVES

The colon can neither concentrate nor dilute fecal fluid: fecal water is isotonic throughout the colon. Osmotic laxatives are soluble but nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.

Nonabsorbable Sugars or Salts

These agents may be used for the treatment of acute constipation or the prevention of chronic constipation. **Magnesium hydroxide (milk of magnesia)** is a commonly used osmotic laxative. It should not be used for prolonged periods in patients with renal insufficiency due to the risk of hypermagnesemia. **Sorbitol** and **lactulose** are nonabsorbable sugars that can be used to prevent or treat chronic constipation. These sugars are metabolized by colonic bacteria, producing severe flatus and cramps.

High doses of osmotically active agents produce prompt bowel evacuation (purgation) within 1–3 hours. The rapid movement of water into the distal small bowel and colon leads to a high volume of liquid stool followed by rapid relief of constipation. The most commonly used purgatives are **magnesium citrate** and **sodium phosphate.** Sodium phosphate is available as a nonprescription liquid formulation and by prescription as a tablet formulation. When taking these agents, it is very important that patients maintain adequate hydration by taking increased oral liquids to compensate for fecal fluid loss. Sodium phosphate frequently causes hyperphosphatemia, hypocalcemia, hypernatremia, and hypokalemia. Although these electrolyte abnormalities are clinically insignificant in most patients, they may lead to cardiac arrhythmias or acute renal failure due to tubular deposition of calcium phosphate (nephrocalcinosis). Sodium phosphate preparations should not be used in patients who are frail or elderly, have renal insufficiency, have significant cardiac disease, or are unable to maintain adequate hydration during bowel preparation.

Balanced Polyethylene Glycol

Lavage solutions containing **polyethylene glycol (PEG)** are used for complete colonic cleansing before gastrointestinal endoscopic procedures. These balanced, isotonic solutions contain an inert, nonabsorbable, osmotically active sugar (PEG) with sodium sulfate, sodium chloride, sodium bicarbonate, and potassium chloride. The solution is designed so that no significant intravascular fluid or electrolyte shifts occur. Therefore, they are safe for all patients. The solution should be ingested rapidly (2–4 L over 2–4 hours) to promote bowel cleansing. For treatment or prevention of chronic constipation, smaller doses of PEG powder may be mixed with water or juices (17 g/8 oz) and ingested daily. In contrast to sorbitol or lactulose, PEG does not produce significant cramps or flatus.

STIMULANT LAXATIVES

Stimulant laxatives (cathartics) induce bowel movements through a number of poorly understood mechanisms. These include direct stimulation of the enteric nervous system and colonic electrolyte and fluid secretion. There has been concern that long-term use of cathartics could lead to dependence and destruction of the myenteric plexus, resulting in colonic atony and dilation. More recent research suggests that long-term use of these agents probably is safe in most patients. Cathartics may be required on a long-term basis, especially in patients who are neurologically impaired and in bed-bound patients in long-term care facilities.

Anthraquinone Derivatives

Aloe, senna, and **cascara** occur naturally in plants. These laxatives are poorly absorbed and after hydrolysis in the colon, produce a bowel movement in 6–12 hours when given orally and within 2 hours when given rectally. Chronic use leads to a characteristic brown pigmentation of the colon known as "melanosis coli." There has been some concern that these agents may be carcinogenic, but epidemiologic studies do not suggest a relation to colorectal cancer.

Diphenylmethane Derivatives

Bisacodyl is available in tablet and suppository formulations for the treatment of acute and chronic constipation. It also is used in conjunction with PEG solutions for colonic cleansing prior to colonoscopy. It induces a bowel movement within 6–10 hours when given orally and 30–60 minutes when taken rectally. It has minimal systemic absorption and appears to be safe for acute and long-term use. Phenolphthalein, another agent in this class, was removed from the market owing to concerns about possible cardiac toxicity.

CHLORIDE CHANNEL ACTIVATOR

Lubiprostone is a prostanoic acid derivative labeled for use in chronic constipation and irritable bowel syndrome (IBS) with predominant constipation. It acts by stimulating the type 2 chloride channel (ClC-2) in the small intestine. This increases chloride-rich fluid secretion into the intestine, which stimulates intestinal motility and shortens intestinal transit time. Over 50% of patients experience a bowel movement within 24 hours of taking one dose. There appears to be no loss of efficacy with long-term therapy. After discontinuation of the drug, constipation may return to its pretreatment severity. Lubiprostone has minimal systemic absorption but is designated category C for pregnancy because of increased fetal loss in guinea pigs. Lubiprostone may cause nausea in up to 30% of patients due to delayed gastric emptying.

OPIOID RECEPTOR ANTAGONISTS

Acute and chronic therapy with opioids may cause constipation by decreasing intestinal motility, which results in prolonged transit time and increased absorption of fecal water (see Chapter 31). Use of opioids after surgery for treatment of pain as well as endogenous opioids also may prolong the duration of postoperative ileus. These effects are mainly mediated through intestinal mu (μ)-opioid receptors. Two selective antagonists of the μ-opioid receptor are commercially available: **methylnaltrexone** bromide and **alvimopan.** Because these agents do not readily cross the blood-brain barrier, they inhibit peripheral μ-opioid receptors without impacting analgesic effects within the central nervous system. Methylnaltrexone is approved for the treatment of opioid-induced constipation in patients receiving palliative care for advanced illness who have had inadequate response to other agents. It is administered as a subcutaneous injection (0.15 mg/kg) every 2 days. Alvimopan is approved for short-term use to shorten the period of postoperative ileus in hospitalized patients who have undergone small or large bowel resection. Alvimopan (12 mg capsule) is administered orally within 5 hours before surgery and twice daily after surgery until bowel function has recovered, but for no more than 7 days. Because of possible cardiovascular toxicity, alvimopan currently is restricted to short-term use in hospitalized patients only.

SEROTONIN 5-HT$_4$-RECEPTOR AGONISTS

Stimulation of 5-HT$_4$ receptors on the presynaptic terminal of submucosal intrinsic primary afferent nerves enhances the release of their neurotransmitters, including calcitonin gene-related peptide, which stimulate second-order enteric neurons to promote the peristaltic reflex (Figure 62–4). These enteric neurons stimulate proximal bowel contraction (via acetylcholine and substance P) and distal bowel relaxation (via nitric oxide and vasoactive intestinal peptide).

Tegaserod is a serotonin 5-HT$_4$ partial agonist that has high affinity for 5-HT$_4$ receptors but no appreciable binding to 5-HT$_3$ or dopamine receptors. Tegaserod was approved for the treatment of patients with chronic constipation and IBS with predominant constipation. Although tegaserod initially appeared to be extremely safe, it was voluntarily removed from the general market in 2007 because of an increased incidence of serious cardiovascular events. These adverse events have been attributed to inhibition of the 5-HT$_{1B}$ receptor. Another partial 5-HT$_4$ agonist, **cisapride,** was also associated with an increased incidence of cardiovascular events that was attributed to inhibition of cardiac hERG (human ether-a-go-go-related gene) K^+ channels, which resulted in QT_c prolongation in some patients.

Prucalopride is a high-affinity 5-HT$_4$ agonist that is available in Europe (but not in the USA) for the treatment of chronic constipation in women. In contrast to cisapride and tegaserod, it does not appear to have significant affinities for either hERG channels or 5-HT$_{1B}$. In three 12-week clinical trials of patients with severe chronic constipation, it resulted in a significant increase in bowel movements compared with placebo. The long-term efficacy and safety of this agent require further study.

GUANYLATE CYCLASE C AGONISTS

Linaclotide is a poorly absorbed 14-amino-acid peptide that binds to the guanylate cylase C receptor on the luminal surface of intestinal enterocytes, activating the cystic fibrosis transmembrane conductance channel and stimulating intestinal fluid secretion. Preliminary results of phase 3 clinical trials confirm its efficacy in patients with chronic constipation. Further studies are anticipated.

ANTIDIARRHEAL AGENTS

Antidiarrheal agents may be used safely in patients with mild to moderate acute diarrhea. However, these agents should not be used in patients with bloody diarrhea, high fever, or systemic toxicity because of the risk of worsening the underlying condition. They should be discontinued in patients whose diarrhea is worsening despite therapy. Antidiarrheals are also used to control chronic diarrhea caused by such conditions as irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD).

OPIOID AGONISTS

As previously noted, opioids have significant constipating effects (see Chapter 31). They increase colonic phasic segmenting activity through inhibition of presynaptic cholinergic nerves in the submucosal and myenteric plexuses and lead to increased colonic transit time and fecal water absorption. They also decrease mass colonic movements and the gastrocolic reflex. Although all opioids have antidiarrheal effects, central nervous system effects and potential for addiction limit the usefulness of most.

Loperamide is a nonprescription opioid agonist that does not cross the blood-brain barrier and has no analgesic properties or potential for addiction. Tolerance to long-term use has not been reported. It is typically administered in doses of 2 mg taken one to four times daily. **Diphenoxylate** is a prescription opioid agonist

that has no analgesic properties in standard doses; however, higher doses have central nervous system effects, and prolonged use can lead to opioid dependence. Commercial preparations commonly contain small amounts of atropine to discourage overdosage (2.5 mg diphenoxylate with 0.025 mg atropine). The anticholinergic properties of atropine may contribute to the antidiarrheal action.

COLLOIDAL BISMUTH COMPOUNDS

See the section under Mucosal Protective Agents in earlier text.

BILE SALT-BINDING RESINS

Conjugated bile salts are normally absorbed in the terminal ileum. Disease of the terminal ileum (eg, Crohn's disease) or surgical resection leads to malabsorption of bile salts, which may cause colonic secretory diarrhea. The bile salt-binding resins **cholestyramine, colestipol,** or **colesevelam,** may decrease diarrhea caused by excess fecal bile acids (see Chapter 35). These products come in a variety of powder and pill formulations that may be taken one to three times daily before meals. Adverse effects include bloating, flatulence, constipation, and fecal impaction. In patients with diminished circulating bile acid pools, further removal of bile acids may lead to an exacerbation of fat malabsorption. Cholestyramine and colestipol bind a number of drugs and reduce their absorption; hence, they should not be given within 2 hours of other drugs. Colesevelam does not appear to have significant effects on absorption of other drugs.

OCTREOTIDE

Somatostatin is a 14-amino-acid peptide that is released in the gastrointestinal tract and pancreas from paracrine cells, D cells, and enteric nerves as well as from the hypothalamus (see Chapter 37). Somatostatin is a key regulatory peptide that has many physiologic effects:

1. It inhibits the secretion of numerous hormones and transmitters, including gastrin, cholecystokinin, glucagon, growth hormone, insulin, secretin, pancreatic polypeptide, vasoactive intestinal peptide, and 5-HT.
2. It reduces intestinal fluid secretion and pancreatic secretion.
3. It slows gastrointestinal motility and inhibits gallbladder contraction.
4. It reduces portal and splanchnic blood flow.
5. It inhibits secretion of some anterior pituitary hormones.

The clinical usefulness of somatostatin is limited by its short half-life in the circulation (3 minutes) when it is administered by intravenous injection. **Octreotide** is a synthetic octapeptide with actions similar to somatostatin. When administered intravenously, it has a serum half-life of 1.5 hours. It also may be administered by subcutaneous injection, resulting in a 6- to 12-hour duration of action. A longer-acting formulation is available for once-monthly depot intramuscular injection.

Clinical Uses

A. Inhibition of Endocrine Tumor Effects

Two gastrointestinal neuroendocrine tumors (carcinoid, VIPoma) cause secretory diarrhea and systemic symptoms such as flushing and wheezing. For patients with advanced symptomatic tumors that cannot be completely removed by surgery, octreotide decreases secretory diarrhea and systemic symptoms through inhibition of hormonal secretion and may slow tumor progression.

B. Other Causes of Diarrhea

Octreotide inhibits intestinal secretion and has dose-related effects on bowel motility. In low doses (50 mcg subcutaneously), it stimulates motility, whereas at higher doses (eg, 100–250 mcg subcutaneously), it inhibits motility. Octreotide is effective in higher doses for the treatment of diarrhea due to vagotomy or dumping syndrome as well as for diarrhea caused by short bowel syndrome or AIDS. Octreotide has been used in low doses (50 mcg subcutaneously) to stimulate small bowel motility in patients with small bowel bacterial overgrowth or intestinal pseudo-obstruction secondary to scleroderma.

C. Other Uses

Because it inhibits pancreatic secretion, octreotide may be of value in patients with pancreatic fistula. The role of octreotide in the treatment of pituitary tumors (eg, acromegaly) is discussed in Chapter 37. Octreotide is sometimes used in gastrointestinal bleeding (see below).

Adverse Effects

Impaired pancreatic secretion may cause steatorrhea, which can lead to fat-soluble vitamin deficiency. Alterations in gastrointestinal motility cause nausea, abdominal pain, flatulence, and diarrhea. Because of inhibition of gallbladder contractility and alterations in fat absorption, long-term use of octreotide can cause formation of sludge or gallstones in over 50% of patients, which rarely results in the development of acute cholecystitis. Because octreotide alters the balance among insulin, glucagon, and growth hormone, hyperglycemia or, less frequently, hypoglycemia (usually mild) can occur. Prolonged treatment with octreotide may result in hypothyroidism. Octreotide also can cause bradycardia.

DRUGS USED IN THE TREATMENT OF IRRITABLE BOWEL SYNDROME

IBS is an idiopathic chronic, relapsing disorder characterized by abdominal discomfort (pain, bloating, distention, or cramps) in association with alterations in bowel habits (diarrhea, constipation, or both). With episodes of abdominal pain or discomfort, patients note a change in the frequency or consistency of their bowel movements.

Pharmacologic therapies for IBS are directed at relieving abdominal pain and discomfort and improving bowel function.

For patients with predominant diarrhea, antidiarrheal agents, especially loperamide, are helpful in reducing stool frequency and fecal urgency. For patients with predominant constipation, fiber supplements may lead to softening of stools and reduced straining; however, increased gas production may exacerbate bloating and abdominal discomfort. Consequently, osmotic laxatives, especially milk of magnesia, are commonly used to soften stools and promote increased stool frequency.

For chronic abdominal pain, low doses of tricyclic antidepressants (eg, amitriptyline or desipramine, 10–50 mg/d) appear to be helpful (see Chapter 30). At these doses, these agents have no effect on mood but may alter central processing of visceral afferent information. The anticholinergic properties of these agents also may have effects on gastrointestinal motility and secretion, reducing stool frequency and liquidity. Finally, tricyclic antidepressants may alter receptors for enteric neurotransmitters such as serotonin, affecting visceral afferent sensation.

Several other agents are available that are specifically intended for the treatment of IBS.

ANTISPASMODICS (ANTICHOLINERGICS)

Some agents are promoted as providing relief of abdominal pain or discomfort through antispasmodic actions. However, small or large bowel spasm has not been found to be an important cause of symptoms in patients with IBS. Antispasmodics work primarily through anticholinergic activities. Commonly used medications in this class include **dicyclomine** and **hyoscyamine** (see Chapter 8). These drugs inhibit muscarinic cholinergic receptors in the enteric plexus and on smooth muscle. The efficacy of antispasmodics for relief of abdominal symptoms has never been convincingly demonstrated. At low doses, they have minimal autonomic effects. However, at higher doses they exhibit significant additional anticholinergic effects, including dry mouth, visual disturbances, urinary retention, and constipation. For these reasons, antispasmodics are infrequently used.

SEROTONIN 5-HT$_3$-RECEPTOR ANTAGONISTS

5-HT$_3$ receptors in the gastrointestinal tract activate visceral afferent pain sensation via extrinsic sensory neurons from the gut to the spinal cord and central nervous system. Inhibition of afferent gastrointestinal 5-HT$_3$ receptors may reduce unpleasant visceral afferent sensation, including nausea, bloating, and pain. Blockade of central 5-HT$_3$ receptors also reduces the central response to visceral afferent stimulation. In addition, 5-HT$_3$-receptor blockade on the terminals of enteric cholinergic neurons inhibits colonic motility, especially in the left colon, increasing total colonic transit time.

Alosetron is a 5-HT$_3$ antagonist that has been approved for the treatment of patients with severe IBS with diarrhea (Figure 62–5). Four other 5-HT$_3$ antagonists (ondansetron, granisetron, dolasetron, and palonosetron) have been approved for the prevention and treatment of nausea and vomiting (see Antiemetics); however, their efficacy in the treatment of IBS has not been determined. The differences between these 5-HT$_3$ antagonists that determine their pharmacodynamic effects have not been well studied.

Pharmacokinetics & Pharmacodynamics

Alosetron is a highly potent and selective antagonist of the 5-HT$_3$ receptor. It is rapidly absorbed from the gastrointestinal tract with a bioavailability of 50–60% and has a plasma half-life of 1.5 hours but a much longer duration of effect. It undergoes extensive hepatic cytochrome P450 metabolism with renal excretion of most metabolites. Alosetron binds with higher affinity and dissociates more slowly from 5-HT$_3$ receptors than other 5-HT$_3$ antagonists, which may account for its long duration of action.

Clinical Uses

Alosetron is approved for the treatment of women with severe IBS in whom diarrhea is the predominant symptom ("diarrhea-predominant IBS"). Its efficacy in men has not been established. In a dosage of 1 mg once or twice daily, it reduces IBS-related lower abdominal pain, cramps, urgency, and diarrhea. Approximately 50–60% of patients report adequate relief of pain and discomfort with alosetron compared with 30–40% of patients treated with placebo. It also leads to a reduction in the mean number of bowel movements per day and improvement in stool consistency. Alosetron has not been evaluated for the treatment of other causes of diarrhea.

Adverse Events

In contrast to the excellent safety profile of other 5-HT$_3$-receptor antagonists, alosetron is associated with rare but serious gastrointestinal toxicity. Constipation occurs in up to 30% of patients with diarrhea-predominant IBS, requiring discontinuation of the drug in 10%. Serious complications of constipation requiring hospitalization or surgery have occurred in 1 of every 1000 patients. Episodes of ischemic colitis—some fatal—have been reported in up to 3 per 1000 patients. Given the seriousness of these adverse events, alosetron is restricted to women with severe diarrhea-predominant IBS who have not responded to conventional therapies and who have been educated about the relative risks and benefits.

Drug Interactions

Despite being metabolized by a number of CYP enzymes, alosetron does not appear to have clinically significant interactions with other drugs.

SEROTONIN 5-HT$_4$-RECEPTOR AGONISTS

The pharmacology of tegaserod was discussed previously under Laxatives. This agent was approved for the short-term treatment of women with IBS who had predominant constipation. Controlled studies demonstrated a modest improvement (approximately 15%)

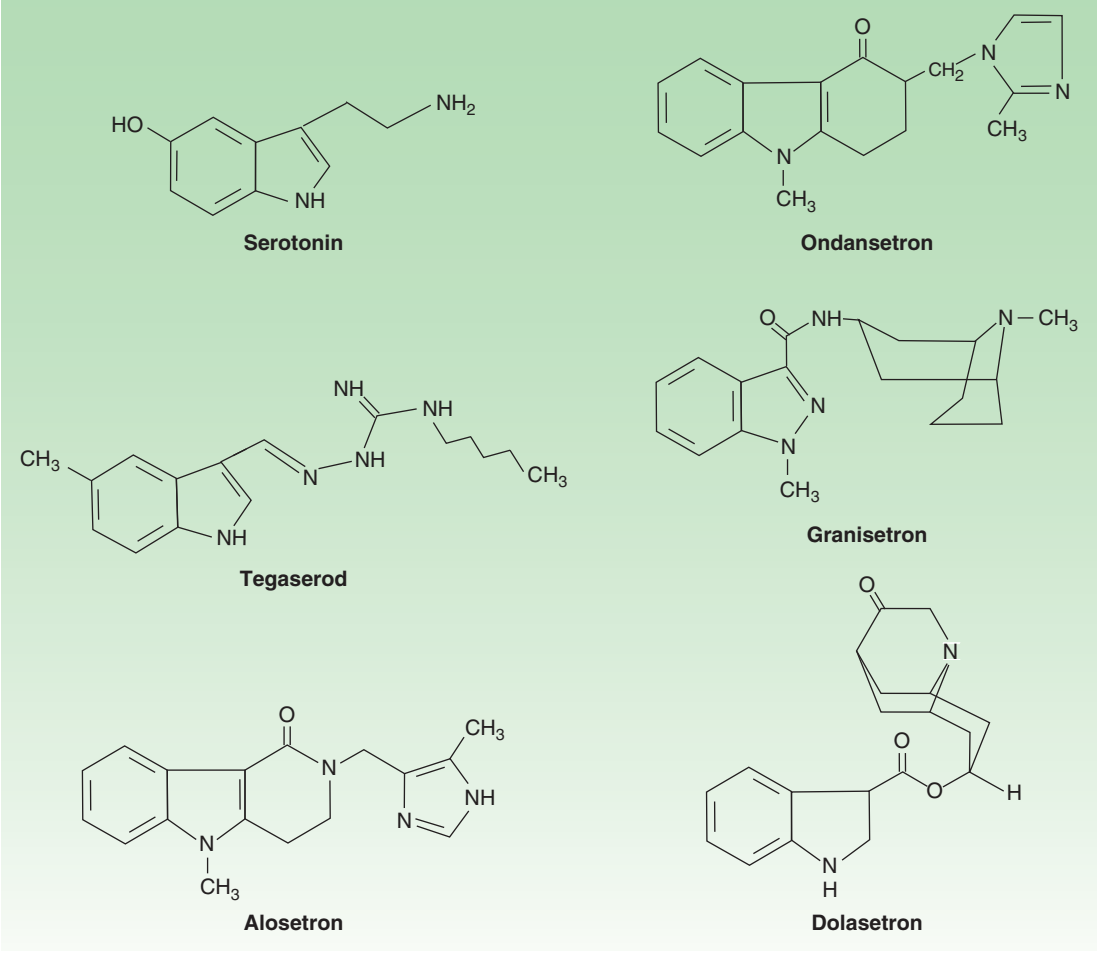


FIGURE 62–5 Chemical structure of serotonin; the 5-HT_3 antagonists ondansetron, granisetron, dolasetron, and alosetron; and the 5-HT_4 partial agonist tegaserod.

in patient global satisfaction and a reduction in severity of pain and bloating in patients treated with tegaserod, 6 mg twice daily, compared with placebo. Owing to an increased number of cardiovascular deaths observed in post-marketing studies in patients taking tegaserod, it was voluntarily removed from the market.

CHLORIDE CHANNEL ACTIVATOR

As discussed previously, lubiprostone is a prostanoic acid derivative that stimulates the type 2 chloride channel (ClC-2) in the small intestine and is used in the treatment of chronic constipation. Lubiprostone recently was approved for the treatment of women with IBS with predominant constipation. Its efficacy for men with IBS is unproven. The approved dose for IBS is 8 mcg twice daily (compared with 24 mcg twice daily for chronic constipation). Lubiprostone has not been compared with other less expensive laxatives (eg, milk of magnesia). Lubiprostone is listed as category C for pregnancy and should be avoided in women of child-bearing age.

■ ANTIEMETIC AGENTS

Nausea and vomiting may be manifestations of a wide variety of conditions, including adverse effects from medications; systemic disorders or infections; pregnancy; vestibular dysfunction; central nervous system infection or increased pressure; peritonitis; hepatobiliary disorders; radiation or chemotherapy; and gastrointestinal obstruction, dysmotility, or infections.

PATHOPHYSIOLOGY

The brainstem "vomiting center" is a loosely organized neuronal region within the lateral medullary reticular formation and coordinates the complex act of vomiting through interactions with cranial nerves VIII and X and neural networks in the nucleus tractus solitarius that control respiratory, salivatory, and vasomotor centers. High concentrations of muscarinic M_1, histamine H_1, neurokinin 1 (NK_1), and serotonin 5-HT_3 receptors have been identified in the vomiting center (Figure 62–6).

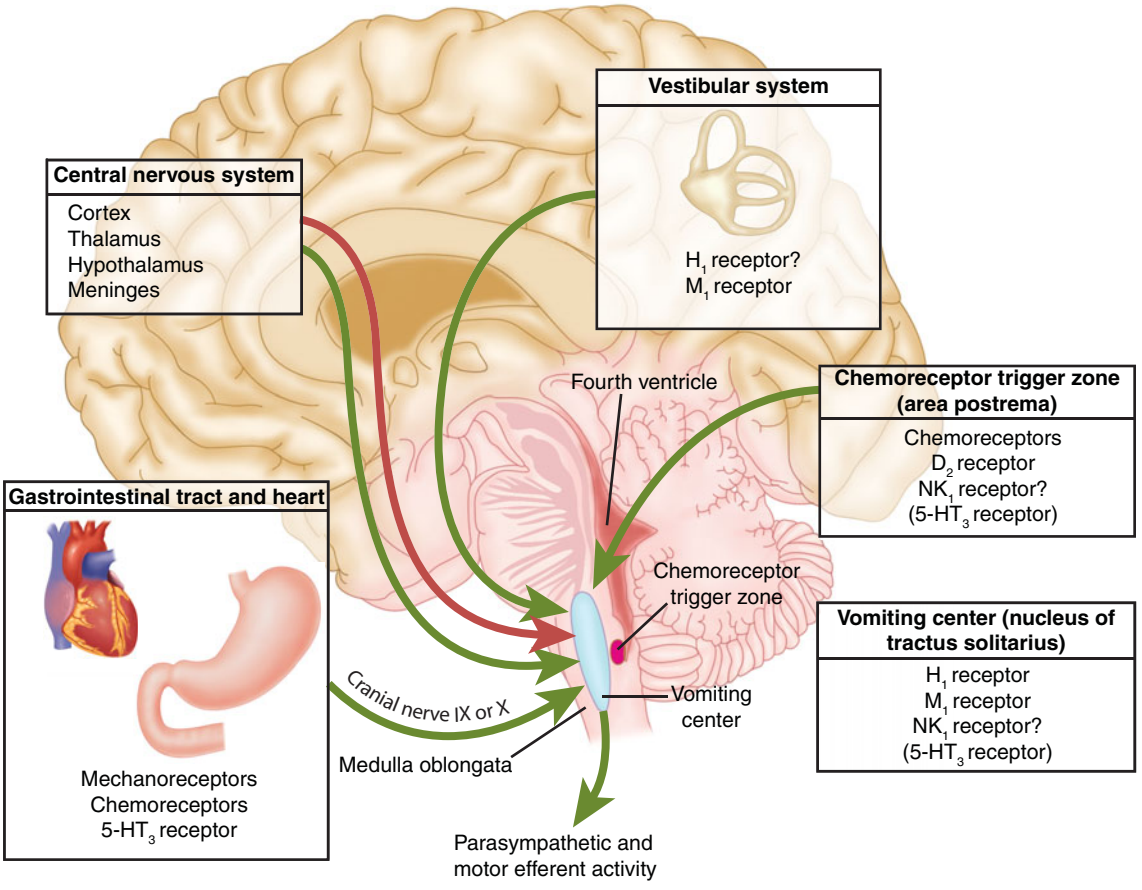


FIGURE 62–6 Neurologic pathways involved in pathogenesis of nausea and vomiting (see text). (Modified and reproduced, with permission, from Krakauer EL et al: Case records of the Massachusetts General Hospital. N Engl J Med 2005;352:817.)

There are four important sources of afferent input to the vomiting center:

1. The "chemoreceptor trigger zone" or area postrema is located at the caudal end of the fourth ventricle. This is outside the blood-brain barrier but is accessible to emetogenic stimuli in the blood or cerebrospinal fluid. The chemoreceptor trigger zone is rich in dopamine D_2 receptors and opioid receptors, and possibly serotonin 5-HT_3 receptors and NK_1 receptors.
2. The vestibular system is important in motion sickness via cranial nerve VIII. It is rich in muscarinic M_1 and histamine H_1 receptors.
3. Vagal and spinal afferent nerves from the gastrointestinal tract are rich in 5-HT_3 receptors. Irritation of the gastrointestinal mucosa by chemotherapy, radiation therapy, distention, or acute infectious gastroenteritis leads to release of mucosal serotonin and activation of these receptors, which stimulate vagal afferent input to the vomiting center and chemoreceptor trigger zone.
4. The central nervous system plays a role in vomiting due to psychiatric disorders, stress, and anticipatory vomiting prior to cancer chemotherapy.

Identification of the different neurotransmitters involved with emesis has allowed development of a diverse group of antiemetic agents that have affinity for various receptors. Combinations of antiemetic agents with different mechanisms of action are often used, especially in patients with vomiting due to chemotherapeutic agents.

SEROTONIN 5-HT_3 ANTAGONISTS

Pharmacokinetics & Pharmacodynamics

Selective 5-HT_3-receptor antagonists have potent antiemetic properties that are mediated in part through central 5-HT_3-receptor blockade in the vomiting center and chemoreceptor trigger zone but mainly through blockade of peripheral 5-HT_3 receptors on extrinsic intestinal vagal and spinal afferent nerves. The antiemetic action of these agents is restricted to emesis attributable to vagal stimulation (eg, postoperative) and chemotherapy; other emetic stimuli such as motion sickness are poorly controlled.

Four agents are available in the USA: **ondansetron, granisetron, dolasetron, and palonosetron.** (Tropisetron is another agent available outside the USA.) The first three agents (ondansetron, granisetron, and dolasetron, Figure 62–5) have a serum half-life of 4–9 hours and may be administered once daily by oral or intravenous routes. All three drugs have comparable efficacy and

tolerability when administered at equipotent doses. Palonosetron is a newer intravenous agent that has greater affinity for the 5-HT_3 receptor and a long serum half-life of 40 hours. All four drugs undergo extensive hepatic metabolism and are eliminated by renal and hepatic excretion. However, dose reduction is not required in geriatric patients or patients with renal insufficiency. For patients with hepatic insufficiency, dose reduction may be required with ondansetron.

5-HT_3-receptor antagonists do not inhibit dopamine or muscarinic receptors. They do not have effects on esophageal or gastric motility but may slow colonic transit.

Clinical Uses

A. Chemotherapy-Induced Nausea and Vomiting

5-HT_3-receptor antagonists are the primary agents for the prevention of acute chemotherapy-induced nausea and emesis. When used alone, these drugs have little or no efficacy for the prevention of delayed nausea and vomiting (ie, occurring > 24 hours after chemotherapy). The drugs are most effective when given as a single dose by intravenous injection 30 minutes prior to administration of chemotherapy in the following doses: ondansetron, 8 mg; granisetron, 1 mg; dolasetron, 100 mg; or palonosetron, 0.25 mg. A single oral dose given 1 hour before chemotherapy may be equally effective in the following regimens: ondansetron 8 mg twice daily or 24 mg once; granisetron, 2 mg; dolasetron, 100 mg. Although 5-HT_3-receptor antagonists are effective as single agents for the prevention of chemotherapy-induced nausea and vomiting, their efficacy is enhanced by combination therapy with a corticosteroid (dexamethasone) and NK_1-receptor antagonist (see below).

B. Postoperative and Postradiation Nausea and Vomiting

5-HT_3-receptor antagonists are used to prevent or treat postoperative nausea and vomiting. Because of adverse effects and increased restrictions on the use of other antiemetic agents, 5-HT_3-receptor antagonists are increasingly used for this indication. They are also effective in the prevention and treatment of nausea and vomiting in patients undergoing radiation therapy to the whole body or abdomen.

Adverse Effects

The 5-HT_3-receptor antagonists are well-tolerated agents with excellent safety profiles. The most commonly reported adverse effects are headache, dizziness, and constipation. All four agents cause a small but statistically significant prolongation of the QT interval, but this is most pronounced with dolasetron. Although cardiac arrhythmias have not been linked to dolasetron, it should not be administered to patients with prolonged QT or in conjunction with other medications that may prolong the QT interval (see Chapter 14).

Drug Interactions

No significant drug interactions have been reported with 5-HT_3-receptor antagonists. All four agents undergo some metabolism by the hepatic cytochrome P450 system but they do not appear to affect the metabolism of other drugs. However, other drugs may reduce hepatic clearance of the 5-HT_3-receptor antagonists, altering their half-life.

CORTICOSTEROIDS

Corticosteroids (dexamethasone, methylprednisolone) have antiemetic properties, but the basis for these effects is unknown. The pharmacology of this class of drugs is discussed in Chapter 39. These agents appear to enhance the efficacy of 5-HT_3-receptor antagonists for prevention of acute and delayed nausea and vomiting in patients receiving moderately to highly emetogenic chemotherapy regimens. Although a number of corticosteroids have been used, dexamethasone, 8–20 mg intravenously before chemotherapy, followed by 8 mg/d orally for 2–4 days, is commonly administered.

NEUROKININ RECEPTOR ANTAGONISTS

Neurokinin 1 (NK_1)-receptor antagonists have antiemetic properties that are mediated through central blockade in the area postrema. **Aprepitant** (an oral formulation) is a highly selective NK_1-receptor antagonist that crosses the blood-brain barrier and occupies brain NK_1 receptors. It has no affinity for serotonin, dopamine, or corticosteroid receptors. **Fosaprepitant** is an intravenous formulation that is converted within 30 minutes after infusion to aprepitant.

Pharmacokinetics

The oral bioavailability of aprepitant is 65%, and the serum half-life is 12 hours. Aprepitant is metabolized by the liver, primarily by the CYP3A4 pathway.

Clinical Uses

Aprepitant is used in combination with 5-HT_3-receptor antagonists and corticosteroids for the prevention of acute and delayed nausea and vomiting from highly emetogenic chemotherapeutic regimens. Combined therapy with aprepitant, a 5-HT_3-receptor antagonist, and dexamethasone prevents acute emesis in 80–90% of patients compared with less than 70% treated without aprepitant. Prevention of delayed emesis occurs in more than 70% of patients receiving combined therapy versus 30–50% treated without aprepitant. NK_1-receptor antagonists may be administered for 3 days as follows: oral aprepitant 125 mg or intravenous fosaprepitant 115 mg given 1 hour before chemotherapy, followed by oral aprepitant 80 mg/d for 2 days after chemotherapy.

Adverse Effects & Drug Interactions

Aprepitant may be associated with fatigue, dizziness, and diarrhea. The drug is metabolized by CYP3A4 and may inhibit the metabolism of other drugs metabolized by the CYP3A4 pathway. Several chemotherapeutic agents are metabolized by CYP3A4, including docetaxel, paclitaxel, etoposide, irinotecan, imatinib, vinblastine, and vincristine. Drugs that inhibit CYP3A4 metabolism may

significantly increase aprepitant plasma levels (eg, ketoconazole, ciprofloxacin, clarithromycin, nefazodone, ritonavir, nelfinavir, verapamil, and quinidine). Aprepitant decreases the international normalized ratio (INR) in patients taking warfarin.

PHENOTHIAZINES & BUTYROPHENONES

Phenothiazines are antipsychotic agents that can be used for their potent antiemetic and sedative properties (see Chapter 29). The antiemetic properties of phenothiazines are mediated through inhibition of dopamine and muscarinic receptors. Sedative properties are due to their antihistamine activity. The agents most commonly used as antiemetics are **prochlorperazine, promethazine,** and **thiethylperazine.**

Antipsychotic butyrophenones also possess antiemetic properties due to their central dopaminergic blockade (see Chapter 29). The main agent used is **droperidol,** which can be given by intramuscular or intravenous injection. In antiemetic doses, droperidol is extremely sedating. Previously, it was used extensively for postoperative nausea and vomiting, in conjunction with opiates and benzodiazepines for sedation for surgical and endoscopic procedures, for neuroleptanalgesia, and for induction and maintenance of general anesthesia. Extrapyramidal effects and hypotension may occur. Droperidol may prolong the QT interval, rarely resulting in fatal episodes of ventricular tachycardia including torsades de pointes. Therefore, droperidol should not be used in patients with QT prolongation and should be used only in patients who have not responded adequately to alternative agents.

SUBSTITUTED BENZAMIDES

Substituted benzamides include **metoclopramide** (discussed previously) and **trimethobenzamide.** Their primary mechanism of antiemetic action is believed to be dopamine-receptor blockade. Trimethobenzamide also has weak antihistaminic activity. For prevention and treatment of nausea and vomiting, metoclopramide may be given in the relatively high dosage of 10–20 mg orally or intravenously every 6 hours. The usual dose of trimethobenzamide is 300 mg orally, or 200 mg by intramuscular injection. The principal adverse effects of these central dopamine antagonists are extrapyramidal: restlessness, dystonias, and parkinsonian symptoms.

H_1 ANTIHISTAMINES & ANTICHOLINERGIC DRUGS

The pharmacology of anticholinergic agents is discussed in Chapter 8 and that of H_1 antihistaminic agents in Chapter 16. As single agents, these drugs have weak antiemetic activity, although they are particularly useful for the prevention or treatment of motion sickness. Their use may be limited by dizziness, sedation, confusion, dry mouth, cycloplegia, and urinary retention. **Diphenhydramine** and one of its salts, **dimenhydrinate,** are first-generation histamine H_1 antagonists that also have significant anticholinergic properties. Because of its sedating properties, diphenhydramine is commonly used in conjunction with other antiemetics for treatment of emesis due to chemotherapy. **Meclizine** is an H_1 antihistaminic agent with minimal anticholinergic properties that also causes less sedation. It is used for the prevention of motion sickness and the treatment of vertigo due to labyrinth dysfunction.

Hyoscine (scopolamine), a prototypic muscarinic receptor antagonist, is one of the best agents for the prevention of motion sickness. However, it has a very high incidence of anticholinergic effects when given orally or parenterally. It is better tolerated as a transdermal patch. Superiority to dimenhydrinate has not been proved.

BENZODIAZEPINES

Benzodiazepines such as lorazepam or diazepam are used before the initiation of chemotherapy to reduce anticipatory vomiting or vomiting caused by anxiety. The pharmacology of these agents is presented in Chapter 22.

CANNABINOIDS

Dronabinol is Δ^9-tetrahydrocannabinol (THC), the major psychoactive chemical in marijuana (see Chapter 32). After oral ingestion, the drug is almost completely absorbed but undergoes significant first-pass hepatic metabolism. Its metabolites are excreted slowly over days to weeks in the feces and urine. Like crude marijuana, dronabinol is a psychoactive agent that is used medically as an appetite stimulant and as an antiemetic, but the mechanisms for these effects are not understood. Because of the availability of more effective agents, dronabinol now is uncommonly used for the prevention of chemotherapy-induced nausea and vomiting. Combination therapy with phenothiazines provides synergistic antiemetic action and appears to attenuate the adverse effects of both agents. Dronabinol is usually administered in a dosage of 5 mg/m^2 just prior to chemotherapy and every 2–4 hours as needed. Adverse effects include euphoria, dysphoria, sedation, hallucinations, dry mouth, and increased appetite. It has some autonomic effects that may result in tachycardia, conjunctival injection, and orthostatic hypotension. Dronabinol has no significant drug-drug interactions but may potentiate the clinical effects of other psychoactive agents.

Nabilone is a closely related THC analog that has been available in other countries and is now approved for use in the USA.

■ DRUGS USED TO TREAT INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) comprises two distinct disorders: ulcerative colitis and Crohn's disease. The etiology and pathogenesis of these disorders remain unknown. For this reason, pharmacologic

treatment of inflammatory bowel disorders often involves drugs that belong to different therapeutic classes and have different but nonspecific mechanisms of anti-inflammatory action. Drugs used in inflammatory bowel disease are chosen on the basis of disease severity, responsiveness, and drug toxicity (Figure 62–7).

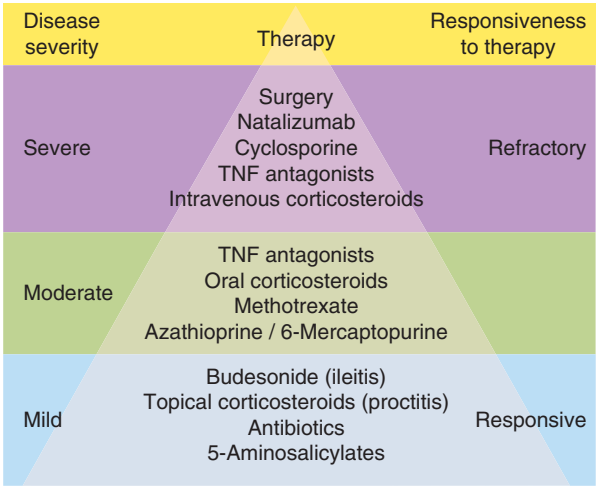


FIGURE 62–7 Therapeutic pyramid approach to inflammatory bowel diseases. Treatment choice is predicated on both the severity of the illness and the responsiveness to therapy. Agents at the bottom of the pyramid are less efficacious but carry a lower risk of serious adverse effects. Drugs may be used alone or in various combinations. Patients with mild disease may be treated with 5-aminosalicylates (with ulcerative colitis or Crohn's colitis), topical corticosteroids (ulcerative colitis), antibiotics (Crohn's colitis or Crohn's perianal disease), or budesonide (Crohn's ileitis). Patients with moderate disease or patients who fail initial therapy for mild disease may be treated with oral corticosteroids to promote disease remission; immunomodulators (azathioprine, mercaptopurine, methotrexate) to promote or maintain disease remission; or anti-TNF antibodies. Patients with moderate disease who fail other therapies or patients with severe disease may require intravenous corticosteroids, anti-TNF antibodies, or surgery. Natalizumab is reserved for patients with severe Crohn's disease who have failed immunomodulators and TNF antagonists. Cyclosporine is used primarily for patients with severe ulcerative colitis who have failed a course of intravenous corticosteroids. TNF, tumor necrosis factor.

AMINOSALICYLATES

Chemistry & Formulations

Drugs that contain **5-aminosalicylic acid (5-ASA)** have been used successfully for decades in the treatment of inflammatory bowel diseases (Figure 62–8). 5-ASA differs from salicylic acid only by the addition of an amino group at the 5 (meta) position. Aminosalicylates are believed to work topically (not systemically) in areas of diseased gastrointestinal mucosa. Up to 80% of unformulated, aqueous 5-ASA is absorbed from the small intestine and does not reach the distal small bowel or colon in appreciable quantities. To overcome the rapid absorption of 5-ASA from the proximal small intestine, a number of formulations have been designed to deliver 5-ASA to various distal segments of the small bowel or the colon. These include **sulfasalazine, olsalazine, balsalazide,** and various forms of **mesalamine.**

A. Azo Compounds

Sulfasalazine, balsalazide, and olsalazine contain 5-ASA bound by an azo (N=N) bond to an inert compound or to another 5-ASA molecule (Figure 62–8). In sulfasalazine, 5-ASA is bound to sulfapyridine; in balsalazide, 5-ASA is bound to 4-aminobenzoyl-β-alanine; and in olsalazine, two 5-ASA molecules are bound together. The azo structure markedly reduces absorption of the parent drug from the small intestine. In the terminal ileum and colon, resident bacteria cleave the azo bond by means of an azoreductase enzyme, releasing the active 5-ASA. Consequently, high

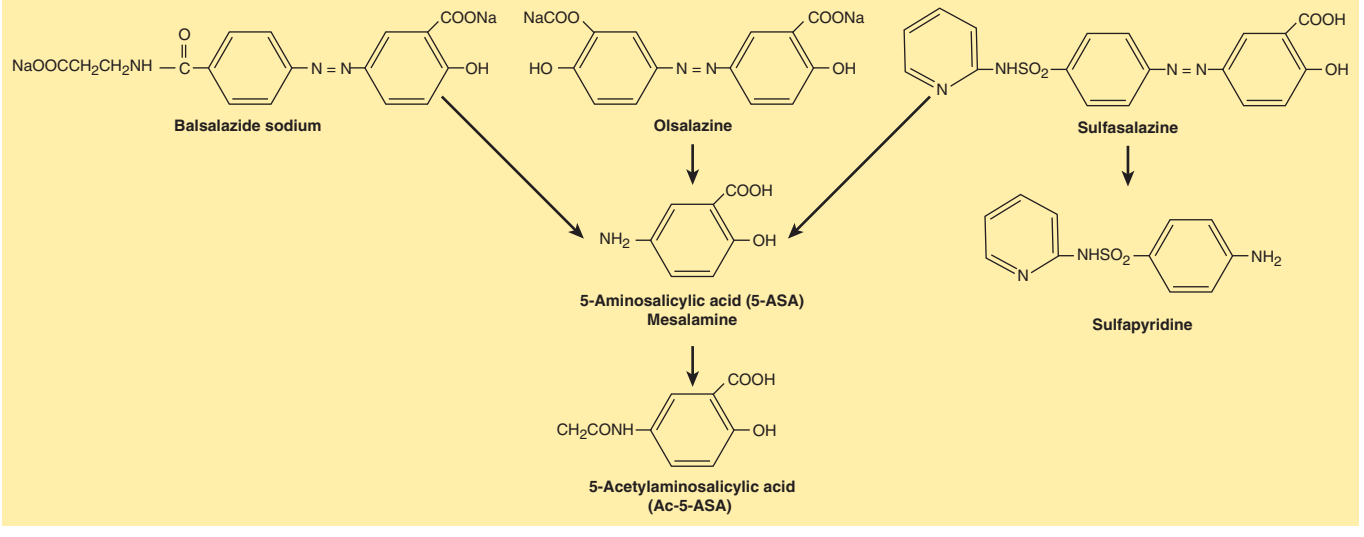


FIGURE 62–8 Chemical structures and metabolism of aminosalicylates. Azo compounds (balsalazide, olsalazine, sulfasalazine) are converted by bacterial azoreductase to 5-aminosalicylic acid (mesalamine), the active therapeutic moiety.

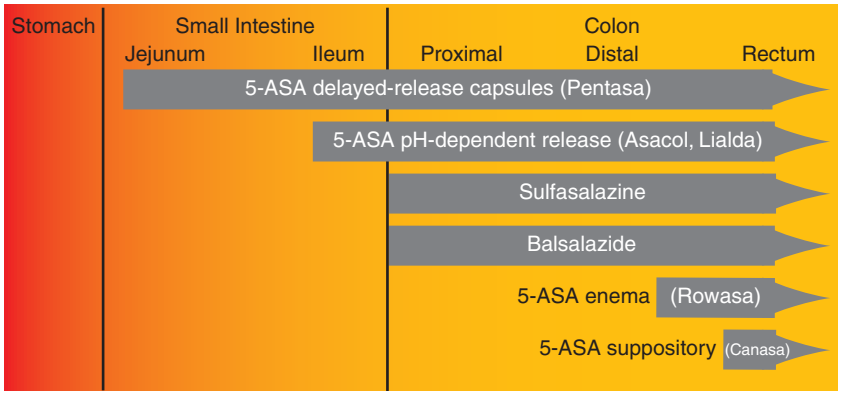


FIGURE 62–9 Sites of 5-aminosalicylic acid (5-ASA) release from different formulations in the small and large intestines.

concentrations of active drug are made available in the terminal ileum or colon.

B. Mesalamine Compounds

Other proprietary formulations have been designed that package 5-ASA itself in various ways to deliver it to different segments of the small or large bowel. These 5-ASA formulations are known generically as **mesalamine. Pentasa** is a mesalamine formulation that contains timed-release microgranules that release 5-ASA throughout the small intestine (Figure 62–9). **Asacol** and **Apriso** have 5-ASA coated in a pH-sensitive resin that dissolves at pH 6-7 (the pH of the distal ileum and proximal colon). **Lialda** also uses a pH-dependent resin that encases a multimatrix core. On dissolution of the pH-sensitive resin in the colon, water slowly penetrates its hydrophilic and lipophilic core, leading to slow release of mesalamine throughout the colon. 5-ASA also may be delivered in high concentrations to the rectum and sigmoid colon by means of enema formulations **(Rowasa)** or suppositories **(Canasa).**

Pharmacokinetics & Pharmacodynamics

Although unformulated 5-ASA is readily absorbed from the small intestine, absorption of 5-ASA from the colon is extremely low. In contrast, approximately 20–30% of 5-ASA from current oral mesalamine formulations is systemically absorbed in the small intestine. Absorbed 5-ASA undergoes *N*-acetylation in the gut epithelium and liver to a metabolite that does not possess significant anti-inflammatory activity. The acetylated metabolite is excreted by the kidneys.

Of the azo compounds, 10% of sulfasalazine and less than 1% of balsalazide are absorbed as native compounds. After azoreductase breakdown of sulfasalazine, over 85% of the carrier molecule sulfapyridine is absorbed from the colon. Sulfapyridine undergoes hepatic metabolism (including acetylation) followed by renal excretion. By contrast, after azoreductase breakdown of balsalazide, over 70% of the carrier peptide is recovered intact in the feces and only a small amount of systemic absorption occurs.

The mechanism of action of 5-ASA is not certain. The primary action of salicylate and other NSAIDs is due to blockade of prostaglandin synthesis by inhibition of cyclooxygenase. However, the aminosalicylates have variable effects on prostaglandin production. It is thought that 5-ASA modulates inflammatory mediators derived from both the cyclooxygenase and lipoxygenase pathways. Other potential mechanisms of action of the 5-ASA drugs relate to their ability to interfere with the production of inflammatory cytokines. 5-ASA inhibits the activity of nuclear factor-κB (NF-κB), an important transcription factor for proinflammatory cytokines. 5-ASA may also inhibit cellular functions of natural killer cells, mucosal lymphocytes, and macrophages, and it may scavenge reactive oxygen metabolites.

Clinical Uses

5-ASA drugs induce and maintain remission in ulcerative colitis and are considered to be the first-line agents for treatment of mild to moderate active ulcerative colitis. Their efficacy in Crohn's disease is unproven, although many clinicians use 5-ASA agents as first-line therapy for mild to moderate disease involving the colon or distal ileum.

The effectiveness of 5-ASA therapy depends in part on achieving high drug concentration at the site of active disease. Thus, 5-ASA suppositories or enemas are useful in patients with ulcerative colitis or Crohn's disease confined to the rectum (proctitis) or distal colon (proctosigmoiditis). In patients with ulcerative colitis or Crohn's colitis that extends to the proximal colon, both the azo compounds and mesalamine formulations are useful. For the treatment of Crohn's disease involving the small bowel, mesalamine compounds, which release 5-ASA in the small intestine, have a theoretic advantage over the azo compounds.

Adverse Effects

Sulfasalazine has a high incidence of adverse effects, most of which are attributable to systemic effects of the sulfapyridine molecule. Slow acetylators of sulfapyridine have more frequent and more severe adverse effects than fast acetylators. Up to 40% of patients cannot tolerate therapeutic doses of sulfasalazine. The most common problems are dose-related and include nausea, gastrointestinal

upset, headaches, arthralgias, myalgias, bone marrow suppression, and malaise. Hypersensitivity to sulfapyridine (or, rarely, 5-ASA) can result in fever, exfoliative dermatitis, pancreatitis, pneumonitis, hemolytic anemia, pericarditis, or hepatitis. Sulfasalazine has also been associated with oligospermia, which reverses upon discontinuation of the drug. Sulfasalazine impairs folate absorption and processing; hence, dietary supplementation with 1 mg/d folic acid is recommended.

In contrast to sulfasalazine, other aminosalicylate formulations are well tolerated. In most clinical trials, the frequency of drug adverse events is similar to that in patients treated with placebo. For unclear reasons, olsalazine may stimulate a secretory diarrhea—which should not be confused with active inflammatory bowel disease—in 10% of patients. Rare hypersensitivity reactions may occur with all aminosalicylates but are much less common than with sulfasalazine. Careful studies have documented subtle changes indicative of renal tubular damage in patients receiving high doses of aminosalicylates. Rare cases of interstitial nephritis are reported, particularly in association with high doses of mesalamine formulations; this may be attributable to the higher serum 5-ASA levels attained with these drugs. Sulfasalazine and other aminosalicylates rarely cause worsening of colitis, which may be misinterpreted as refractory colitis.

GLUCOCORTICOIDS

Pharmacokinetics & Pharmacodynamics

In gastrointestinal practice, prednisone and prednisolone are the most commonly used oral glucocorticoids. These drugs have an intermediate duration of biologic activity allowing once-daily dosing.

Hydrocortisone enemas, foam, or suppositories are used to maximize colonic tissue effects and minimize systemic absorption via topical treatment of active inflammatory bowel disease in the rectum and sigmoid colon. Absorption of hydrocortisone is reduced with rectal administration, although 15–30% of the administered dosage is still absorbed.

Budesonide is a potent synthetic analog of prednisolone that has high affinity for the glucocorticoid receptor but is subject to rapid first-pass hepatic metabolism (in part by CYP3A4), resulting in low oral bioavailability. A controlled-release oral formulation of budesonide (Entocort) is available that releases the drug in the distal ileum and colon, where it is absorbed. The bioavailability of controlled-release budesonide capsules is approximately 10%.

As in other tissues, glucocorticoids inhibit production of inflammatory cytokines (TNF-α, IL-1) and chemokines (IL-8); reduce expression of inflammatory cell adhesion molecules; and inhibit gene transcription of nitric oxide synthase, phospholipase A_2, cyclooxygenase-2, and NF-κB.

Clinical Uses

Glucocorticoids are commonly used in the treatment of patients with moderate to severe active inflammatory bowel disease. Active disease is commonly treated with an initial oral dosage of 40–60 mg/d of prednisone or prednisolone. Higher doses have not been shown to be more efficacious but have significantly greater adverse effects. Once a patient responds to initial therapy (usually within 1–2 weeks), the dosage is tapered to minimize development of adverse effects. In severely ill patients, the drugs are usually administered intravenously.

For the treatment of inflammatory bowel disease involving the rectum or sigmoid colon, rectally administered glucocorticoids are preferred because of their lower systemic absorption.

Oral controlled-release budesonide (9 mg/d) is commonly used in the treatment of mild to moderate Crohn's disease involving the ileum and proximal colon. It appears to be slightly less effective than prednisolone in achieving clinical remission, but has significantly less adverse systemic effects.

Corticosteroids are not useful for maintaining disease remission. Other medications such as aminosalicylates or immunosuppressive agents should be used for this purpose.

Adverse Effects

Adverse effects of glucocorticoids are reviewed in Chapter 39.

PURINE ANALOGS: AZATHIOPRINE & 6-MERCAPTOPURINE

Pharmacokinetics & Pharmacodynamics

Azathioprine and 6-mercaptopurine (6-MP) are purine antimetabolites that have immunosuppressive properties (see Chapters 54 and 55).

The bioavailability of azathioprine (80%) is superior to 6-MP (50%). After absorption azathioprine is rapidly converted by a nonenzymatic process to 6-MP. 6-Mercaptopurine subsequently undergoes a complex biotransformation via competing catabolic enzymes (xanthine oxidase and thiopurine methyltransferase) that produce inactive metabolites and anabolic pathways that produce active thioguanine nucleotides. Azathioprine and 6-MP have a serum half-life of less than 2 hours; however, the active 6-thioguanine nucleotides are concentrated in cells resulting in a prolonged half-life of days. The prolonged kinetics of 6-thioguanine nucleotide results in a median delay of 17 weeks before onset of therapeutic benefit from oral azathioprine or 6-MP is observed in patients with inflammatory bowel disease.

Clinical Uses

Azathioprine and 6-MP are important agents in the induction and maintenance of remission of ulcerative colitis and Crohn's disease. Although the optimal dose is uncertain, most patients with normal thiopurine-*S*-methyltransferase (TPMT) activity (see below) are treated with 6-MP, 1–1.5 mg/kg/d, or azathioprine, 2–2.5 mg/kg/d. After 3–6 months of treatment, 50–60% of patients with active disease achieve remission. These agents help maintain remission in up to 80% of patients. Among patients who depend on long-term glucocorticoid therapy to control active disease, purine analogs allow dose reduction or elimination of steroids in the majority.

Adverse Effects

Dose-related toxicities of azathioprine or 6-MP include nausea, vomiting, bone marrow depression (leading to leukopenia, macrocytosis, anemia, or thrombocytopenia), and hepatic toxicity. Routine laboratory monitoring with complete blood count and liver function tests is required in all patients. Leukopenia or elevations in liver chemistries usually respond to medication dose reduction. Severe leukopenia may predispose to opportunistic infections; leukopenia may respond to therapy with granulocyte stimulating factor. Catabolism of 6-MP by TPMT is low in 11% and absent in 0.3% of the population, leading to increased production of active 6-thioguanine metabolites and increased risk of bone marrow depression. TPMT levels can be measured before initiating therapy. These drugs should not be administered to patients with no TPMT activity and should be initiated at lower doses in patients with intermediate activity. Hypersensitivity reactions to azathioprine or 6-MP occur in 5% of patients. These include fever, rash, pancreatitis, diarrhea, and hepatitis.

As with transplant recipients receiving long-term 6-MP or azathioprine therapy, there appears to be an increased risk of lymphoma among patients with inflammatory bowel disease. These drugs cross the placenta; however, there are many reports of successful pregnancies in women taking these agents, and the risk of teratogenicity appears to be small.

Drug Interactions

Allopurinol markedly reduces xanthine oxide catabolism of the purine analogs, potentially increasing active 6-thioguanine nucleotides that may lead to severe leukopenia. Allopurinol should not be given to patients taking 6-MP or azathioprine except in carefully monitored situations.

METHOTREXATE

Pharmacokinetics & Pharmacodynamics

Methotrexate is another antimetabolite that has beneficial effects in a number of chronic inflammatory diseases, including Crohn's disease and rheumatoid arthritis (see Chapter 36), and in cancer (see Chapter 54). Methotrexate may be given orally, subcutaneously, or intramuscularly. Reported oral bioavailability is 50–90% at doses used in chronic inflammatory diseases. Intramuscular and subcutaneous methotrexate exhibit nearly complete bioavailability.

The principal mechanism of action is inhibition of dihydrofolate reductase, an enzyme important in the production of thymidine and purines. At the high doses used for chemotherapy, methotrexate inhibits cellular proliferation. However, at the low doses used in the treatment of inflammatory bowel disease (12–25 mg/wk), the antiproliferative effects may not be evident. Methotrexate may interfere with the inflammatory actions of interleukin-1. It may also stimulate increased release of adenosine, an endogenous anti-inflammatory autacoid. Methotrexate may also stimulate apoptosis and death of activated T lymphocytes.

Clinical Uses

Methotrexate is used to induce and maintain remission in patients with Crohn's disease. Its efficacy in ulcerative colitis is uncertain. To induce remission, patients are treated with 15–25 mg of methotrexate once weekly by subcutaneous injection. If a satisfactory response is achieved within 8–12 weeks, the dose is reduced to 15 mg/wk.

Adverse Effects

At higher dosage, methotrexate may cause bone marrow depression, megaloblastic anemia, alopecia, and mucositis. At the doses used in the treatment of inflammatory bowel disease, these events are uncommon but warrant dose reduction if they do occur. Folate supplementation reduces the risk of these events without impairing the anti-inflammatory action.

In patients with psoriasis treated with methotrexate, hepatic damage is common; however, among patients with inflammatory bowel disease and rheumatoid arthritis, the risk is significantly lower. Renal insufficiency may increase risk of hepatic accumulation and toxicity.

ANTI-TUMOR NECROSIS FACTOR THERAPY

Pharmacokinetics & Pharmacodynamics

A dysregulation of the helper T cell type 1 (TH1) response and regulatory T cells (Tregs) is present in inflammatory bowel disease, especially Crohn's disease. One of the key proinflammatory cytokines in inflammatory bowel disease is tumor necrosis factor (TNF). TNF is produced by the innate immune system (eg, dendritic cells, macrophages), the adaptive immune system (especially TH1 cells), and nonimmune cells (fibroblasts, smooth muscle cells). TNF exists in two biologically active forms: soluble TNF and membrane-bound TNF. The biologic activity of soluble and membrane-bound TNF is mediated by binding to TNF receptors (TNFR) that are present on some cells (especially TH1 cells, innate immune cells, and fibroblasts). Binding of TNF to TNFR initially activates components including NF-κB that stimulate transcription, growth, and expansion. Biologic actions ascribed to TNFR activation include release of proinflammatory cytokines from macrophages, T-cell activation and proliferation, fibroblast collagen production, up-regulation of endothelial adhesion molecules responsible for leukocyte migration, and stimulation of hepatic acute phase reactants. Activation of TNFR may later lead to apoptosis (programmed cell death) of activated cells.

Three monoclonal antibodies to human TNF are approved for the treatment of inflammatory bowel disease: infliximab, adalimumab, and certolizumab (Table 62–3). Infliximab and adalimumab are antibodies of the IgG_1 subclass. Certolizumab is a recombinant antibody that contains an Fab fragment that is conjugated to polyethylene glycol (PEG) but lacks an Fc portion. The Fab portions of infliximab and certolizumab are chimeric mouse-human antibodies but adalimumab is fully humanized. Infliximab

TABLE 62–3 Anti-TNF antibodies used in inflammatory bowel disease.

	Infliximab	Adalimumab	Certolizumab
Class	Monoclonal antibody	Monoclonal antibody	Monoclonal antibody
% Human	75%	100%	95%
Structure	IgG_1	IgG_1	Fab fragment attached to PEG (lacks Fc portion)
Route of administration	Intravenous	Subcutaneous	Subcutaneous
Half–life	8–10 days	10–20 days	14 days
Neutralizes soluble TNF	Yes	Yes	Yes
Neutralizes membrane-bound TNF	Yes	Yes	Yes
Induces apoptosis of cells expressing membrane-bound TNF	Yes	Yes	No
Complement-mediated cytotoxicity of cells expressing membrane–bound TNF	Yes	Yes	No
Induction dose	5 mg/kg at 0, 2, and 6 weeks	160 mg, 80 mg, and 40 mg at 0, 2, and 4 weeks	400 mg at 0, 2, and 4 weeks
Maintenance dose	5 mg/kg every 8 weeks	40 mg every 2 weeks	400 mg every 4 weeks

TNF, tumor necrosis factor.

is administered as an intravenous infusion. At therapeutic doses of 5–10 mg/kg, the half-life of infliximab is approximately 8–10 days, resulting in plasma disappearance of antibodies over 8–12 weeks. Adalimumab and certolizumab are administered by subcutaneous injection. The half-life for both is approximately 2 weeks.

All three agents bind to soluble and membrane-bound TNF with high affinity, preventing the cytokine from binding to its receptors. Binding of all three antibodies to membrane-bound TNF also causes reverse signaling that suppresses cytokine release. When infliximab or adalimumab bind to membrane-bound TNF, the Fc portion of the human IgG_1 region promotes antibody-mediated apoptosis, complement activation, and cellular cytotoxicity of activated T lymphocytes and macrophages. Certolizumab, without an Fc portion, lacks these properties.

Clinical Uses

All three agents are approved for the acute and chronic treatment of patients with moderate to severe Crohn's disease who have had an inadequate response to conventional therapies. Infliximab also is approved for the acute and chronic treatment of moderate to severe ulcerative colitis. With induction therapy, all three agents lead to symptomatic improvement in 60% and disease remission in 30% of patients with moderate to severe Crohn's disease, including patients who have been dependent on glucocorticoids or who have not responded to 6-MP or methotrexate. The median time to clinical response is 2 weeks. Induction therapy is generally given as follows: infliximab 5 mg/kg intravenous infusion at 0, 2, and 6 weeks; adalimumab 160 mg (in divided doses) initially and 80 mg subcutaneous injection at 2 weeks; and certolizumab 400 mg subcutaneous injection at 0, 2, and 4 weeks. Patients who respond may be treated with chronic maintenance therapy, as follows: infliximab 5 mg/kg intravenous infusion every 8 weeks; adalimumab 40 mg subcutaneous injection every 2 weeks; certolizumab 400 mg subcutaneous injection every 4 weeks. With chronic, regularly scheduled therapy, clinical response is maintained in more than 60% of patients and disease remission in 40%. However, one-third of patients eventually lose response despite higher doses or more frequent injections. Loss of response in many patients may be due to the development of antibodies to the TNF antibody or to other mechanisms.

Infliximab is approved for the treatment of patients with moderate to severe ulcerative colitis who have had inadequate response to mesalamine or corticosteroids. After induction therapy of 5–10 mg/wk at 0, 2, and 6 weeks, 70% of patients have a clinical response and one third achieve a clinical remission. With continued maintenance infusions every 8 weeks, approximately 50% of patients have continued clinical response.

Adverse Effects

Serious adverse events occur in up to 6% of patients with anti-TNF therapy. The most important adverse effect of these drugs is infection due to suppression of the TH1 inflammatory response. This may lead to serious infections such as bacterial sepsis, tuberculosis, invasive fungal organisms, reactivation of hepatitis B, listeriosis, and other opportunistic infections. Reactivation of latent tuberculosis, with dissemination, has occurred. Before administering anti-TNF therapy, all patients must undergo testing with tuberculin skin tests or interferon gamma release assays. Prophylactic therapy for tuberculosis is warranted for patients with positive test results before beginning anti-TNF therapy.

More common but usually less serious infections include upper respiratory infections (sinusitis, bronchitis, and pneumonia) and cellulitis. The risk of serious infections is increased markedly in patients taking concomitant corticosteroids.

Antibodies to the antibody (ATA) may develop with all three agents. These antibodies may attenuate or eliminate the clinical response and increase the likelihood of developing acute or delayed infusion or injection reactions. Antibody formation is much more likely in patients given episodic anti-TNF therapy than regular scheduled injections. In patients on chronic maintenance therapy, the prevalence of ATA with infliximab is 10%, certolizumab 8%, and adalimumab 3%. Antibody development also is less likely in patients who receive concomitant therapy with immunomodulators (ie, 6-MP or methotrexate). Concomitant treatment with anti-TNF agents and immunomodulators may increase the risk of lymphoma.

Infliximab intravenous infusions result in acute adverse infusion reactions in up to 10% of patients, but discontinuation of the infusion for severe reactions is required in less than 2%. Infusion reactions are more common with the second or subsequent infusions than with the first. Early mild reactions include fever, headache, dizziness, urticaria, or mild cardiopulmonary symptoms that include chest pain, dyspnea, or hemodynamic instability. Reactions to subsequent infusions may be reduced with prophylactic administration of acetaminophen, diphenhydramine, or corticosteroids. Severe acute reactions include significant hypotension, shortness of breath, muscle spasms, and chest discomfort; such reactions may require treatment with oxygen, epinephrine, and corticosteroids.

A delayed serum sickness-like reaction may occur 1–2 weeks after anti-TNF therapy in 1% of patients. These reactions consist of myalgia, arthralgia, jaw tightness, fever, rash, urticaria, and edema and usually require discontinuation of that agent. Positive antinuclear antibodies and anti-double-stranded DNA develop in a small number of patients. Development of a lupus-like syndrome is rare and resolves after discontinuation of the drug.

Rare but serious adverse effects of all anti-TNF agents also include severe hepatic reactions leading to acute hepatic failure, demyelinating disorders, hematologic reactions, and new or worsened congestive heart failure in patients with underlying heart disease. Anti-TNF agents may cause a variety of psoriatic skin rashes, which usually resolve after drug discontinuation.

Lymphoma appears to be increased in patients with untreated inflammatory bowel disease. Anti-TNF agents may further increase the risk of lymphoma in this population, although the relative risk is uncertain. An increased number of cases of hepatosplenic T-cell lymphoma, a rare but usually fatal disease, have been noted in children and young adults, virtually all of whom have been on combined therapy with immunomodulators, anti-TNF agents, or corticosteroids.

ANTI-INTEGRIN THERAPY

Integrins are a family of adhesion molecules on the surface of leukocytes that may interact with another class of adhesion molecules on the surface of the vascular endothelium known as selectins, allowing circulating leukocytes to adhere to the vascular endothelium and subsequently move through the vessel wall into the tissue. Integrins consist of heterodimers that contain two subunits, alpha and beta. **Natalizumab** is a humanized IgG_4 monoclonal antibody targeted against the $\alpha 4$ subunit, and thereby blocks several integrins on circulating inflammatory cells and thus prevents binding to the vascular adhesion molecules and subsequent migration into surrounding tissues.

Natalizumab has shown significant efficacy for a subset of patients with moderate to severe Crohn's disease. Unfortunately, in initial clinical trials of patients with Crohn's disease and multiple sclerosis, 3 of 3100 patients treated with natalizumab developed progressive multifocal leukoencephalopathy due to reactivation of a human polyomavirus (JC virus), which is present in latent form in over 80% of adults. All three patients were receiving concomitant therapy with other immunomodulators. After voluntary withdrawal and review of the drug by the manufacturer in 2005, it was approved by the FDA in 2008 for patients with moderate to severe Crohn's disease who have failed other therapies through a carefully restricted program. The approved dosage is 300 mg every 4 weeks by intravenous infusion, and patients should not be on other immune suppressant agents. Approximately 50% of patients respond to initial therapy with natalizumab. Of patients with an initial response, long-term response is maintained in 60% and remission in over 40%. Other adverse effects include acute infusion reactions and a small risk of opportunistic infections.

PANCREATIC ENZYME SUPPLEMENTS

Exocrine pancreatic insufficiency is most commonly caused by cystic fibrosis, chronic pancreatitis, or pancreatic resection. When secretion of pancreatic enzymes falls below 10% of normal, fat and protein digestion is impaired and can lead to steatorrhea, azotorrhea, vitamin malabsorption, and weight loss. Pancreatic enzyme supplements, which contain a mixture of amylase, lipase, and proteases, are the mainstay of treatment for pancreatic enzyme insufficiency. Two major types of preparations in use are **pancreatin** and **pancrelipase.** Pancreatin is an alcohol-derived extract of hog pancreas with relatively low concentrations of lipase and proteolytic enzymes, whereas pancrelipase is an enriched preparation. On a per-weight basis, pancrelipase has approximately 12 times the lipolytic activity and more than 4 times the proteolytic activity of pancreatin. Consequently, pancreatin is no longer in common clinical use. Only pancrelipase is discussed here.

Pancrelipase is available worldwide in both non-enteric-coated and enteric-coated preparations. Formulations are available in sizes containing varying amounts of lipase, amylase, and protease. However, manufacturers' listings of enzyme content do not always reflect true enzymatic activity. Pancrelipase enzymes are rapidly and permanently inactivated by gastric acids. Therefore, non-enteric-coated preparations (eg, Viokase tablets or powder) should be given concomitantly with acid suppression therapy (proton

pump inhibitor or H_2 antagonist) to reduce acid-mediated destruction within the stomach. Enteric-coated formulations are more commonly used because they do not require concomitant acid suppression therapy. In 2006, the FDA announced that all products must undergo an approval process to demonstrate product quality, safety, and efficacy. At present, three formulations (all enteric-coated capsules) are approved for use (Creon, Pancreaze, Zenpep).

Pancrelipase preparations are administered with each meal and snack. Enzyme activity may be listed in international units (IU) or USP units. One IU is equal to 2–3 USP units. Dosing should be individualized according to the age and weight of the patient, the degree of pancreatic insufficiency, and the amount of dietary fat intake. Therapy is initiated at a dose that provides 60,000–90,000 USP units (20–30,000 IU) of lipase activity in the prandial and postprandial period—a level that is sufficient to reduce steatorrhea to a clinically insignificant level in most cases. Suboptimal response to enteric-coated formulations may be due to poor mixing of granules with food or slow dissolution and release of enzymes. Gradual increase of dose, change to a different formulation, or addition of acid suppression therapy may improve response. For patients with feeding tubes, microspheres may be mixed with enteral feeding prior to administration.

Pancreatic enzyme supplements are well tolerated. The capsules should be swallowed, not chewed, because pancreatic enzymes may cause oropharyngeal mucositis. Excessive doses may cause diarrhea and abdominal pain. The high purine content of pancreas extracts may lead to hyperuricosuria and renal stones. Several cases of colonic strictures were reported in patients with cystic fibrosis who received high doses of pancrelipase with high lipase activity. These high-dose formulations have since been removed from the market.

■ BILE ACID THERAPY FOR GALLSTONES

Ursodiol (ursodeoxycholic acid) is a naturally occurring bile acid that makes up less than 5% of the circulating bile salt pool in humans and a much higher percentage in bears. After oral administration, it is absorbed, conjugated in the liver with glycine or taurine, and excreted in the bile. Conjugated ursodiol undergoes extensive enterohepatic recirculation. The serum half-life is approximately 100 hours. With long-term daily administration, ursodiol constitutes 30–50% of the circulating bile acid pool. A small amount of unabsorbed conjugated or unconjugated ursodiol passes into the colon, where it is either excreted or undergoes dehydroxylation by colonic bacteria to lithocholic acid, a substance with potential hepatic toxicity.

Pharmacodynamics

The solubility of cholesterol in bile is determined by the relative proportions of bile acids, lecithin, and cholesterol. Although prolonged ursodiol therapy expands the bile acid pool, this does not appear to be the principal mechanism of action for dissolution of gallstones. Ursodiol decreases the cholesterol content of bile by reducing hepatic cholesterol secretion. Ursodiol also appears to stabilize hepatocyte canalicular membranes, possibly through a reduction in the concentration of other endogenous bile acids or through inhibition of immune-mediated hepatocyte destruction.

Clinical Use

Ursodiol is used for dissolution of small cholesterol gallstones in patients with symptomatic gallbladder disease who refuse cholecystectomy or who are poor surgical candidates. At a dosage of 10 mg/kg/d for 12–24 months, dissolution occurs in up to 50% of patients with small (< 5–10 mm) noncalcified gallstones. It is also effective for the prevention of gallstones in obese patients undergoing rapid weight loss therapy. Several trials demonstrate that ursodiol 13–15 mg/kg/d is helpful for patients with early-stage primary biliary cirrhosis, reducing liver function abnormalities and improving liver histology.

Adverse Effects

Ursodiol is practically free of serious adverse effects. Bile salt-induced diarrhea is uncommon. Unlike its predecessor, chenodeoxycholate, ursodiol has not been associated with hepatotoxicity.

■ DRUGS USED TO TREAT VARICEAL HEMORRHAGE

Portal hypertension most commonly occurs as a consequence of chronic liver disease. Portal hypertension is caused by increased blood flow within the portal venous system and increased resistance to portal flow within the liver. Splanchnic blood flow is increased in patients with cirrhosis due to low arteriolar resistance that is mediated by increased circulating vasodilators and decreased vascular sensitivity to vasoconstrictors. Intrahepatic vascular resistance is increased in cirrhosis due to fixed fibrosis within the spaces of Disse and hepatic veins as well as reversible vasoconstriction of hepatic sinusoids and venules. Among the consequences of portal hypertension are ascites, hepatic encephalopathy, and the development of portosystemic collaterals—especially gastric or esophageal varices. Varices can rupture, leading to massive upper gastrointestinal bleeding.

Several drugs are available that reduce portal pressures. These may be used in the short term for the treatment of active variceal hemorrhage or long term to reduce the risk of hemorrhage.

SOMATOSTATIN & OCTREOTIDE

The pharmacology of octreotide is discussed above under Antidiarrheal Agents. In patients with cirrhosis and portal hypertension, intravenous somatostatin (250 mcg/h) or octreotide (50 mcg/h) reduces portal blood flow and variceal pressures; however, the mechanism by which they do so is poorly understood. They do

not appear to induce direct contraction of vascular smooth muscle. Their activity may be mediated through inhibition of release of glucagon and other gut peptides that alter mesenteric blood flow. Although data from clinical trials are conflicting, these agents are probably effective in promoting initial hemostasis from bleeding esophageal varices. They are generally administered for 3–5 days.

VASOPRESSIN & TERLIPRESSIN

Vasopressin (antidiuretic hormone) is a polypeptide hormone secreted by the hypothalamus and stored in the posterior pituitary. Its pharmacology is discussed in Chapters 17 and 37. Although its primary physiologic role is to maintain serum osmolality, it is also a potent arterial vasoconstrictor. When administered intravenously by continuous infusion, vasopressin causes splanchnic arterial vasoconstriction that leads to reduced splanchnic perfusion and lowered portal venous pressures. Before the advent of octreotide, vasopressin was commonly used to treat acute variceal hemorrhage. However, because of its high adverse-effect profile, it is no longer used for this purpose. In contrast, for patients with acute gastrointestinal bleeding from small bowel or large bowel vascular ectasias or diverticulosis, vasopressin may be infused—to promote vasospasm—into one of the branches of the superior or inferior mesenteric artery through an angiographically placed catheter. Adverse effects with systemic vasopressin are common. Systemic and peripheral vasoconstriction can lead to hypertension, myocardial ischemia or infarction, or mesenteric infarction. These effects may be reduced by coadministration of nitroglycerin, which may further reduce portal venous pressures (by reducing portohepatic vascular resistance) and may also reduce the coronary and peripheral vascular vasospasm caused by vasopressin. Other common adverse effects are nausea, abdominal cramps, and diarrhea (due to intestinal hyperactivity). Furthermore, the antidiuretic effects of vasopressin promote retention of free water, which can lead to hyponatremia, fluid retention, and pulmonary edema.

Terlipressin is a vasopressin analog that appears to have similar efficacy to vasopressin with fewer adverse effects. Although this agent is available in other countries, it has never been approved for use in the USA.

BETA-RECEPTOR-BLOCKING DRUGS

The pharmacology of β-receptor-blocking agents is discussed in Chapter 10. Beta-receptor antagonists reduce portal venous pressures via a decrease in portal venous inflow. This decrease is due to a decrease in cardiac output (β_1 blockade) and to splanchnic vasoconstriction (β_2 blockade) caused by the unopposed effect of systemic catecholamines on α receptors. Thus, nonselective β blockers such as propranolol and nadolol are more effective than selective β_1 blockers in reducing portal pressures. Among patients with cirrhosis and esophageal varices who have not previously had an episode of variceal hemorrhage, the incidence of bleeding among patients treated with nonselective β blockers is 15% compared with 25% in control groups. Among patients with a history of variceal hemorrhage, the likelihood of recurrent hemorrhage is 80% within 2 years. Nonselective β blockers significantly reduce the rate of recurrent bleeding, although a reduction in mortality is unproved.

SUMMARY Drugs Used Primarily for Gastrointestinal Conditions

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DRUGS USED IN ACID-PEPTIC DISEASES				
• Proton pump inhibitors (PPIs), eg, omeprazole, lanso prazole	Irreversible blockade of H^+, K^+-ATPase pump in active parietal cells of stomach	Long-lasting reduction of stimulated and nocturnal acid secretion	Peptic ulcer, gastroesophageal reflux disease, erosive gastritis	Half-lives much shorter than duration of action • low toxicity • reduction of stomach acid may reduce absorption of some drugs and increase that of others
• *H_2-receptor blockers, eg, cimetidine: Effective reduction of nocturnal acid but less effective against stimulated secretion; very safe, available over the counter (OTC). Cimetidine, but not other H_2 blockers, is a weak antiandrogenic agent and a potent CYP enzyme inhibitor*				
• *Sucralfate: Polymerizes at site of tissue damage (ulcer bed) and protects against further damage; very insoluble with no systemic effects; must be given four times daily*				
• *Antacids: Popular OTC medication for symptomatic relief of heartburn; not as useful as PPI and H_2 blockers in peptic diseases*				
DRUGS STIMULATING MOTILITY				
• Metoclopramide	D_2-receptor blocker • removes inhibition of acetylcholine neurons in enteric nervous system	Increases gastric emptying and intestinal motility	Gastric paresis (eg, in diabetes) • antiemetic (see below)	Parkinsonian symptoms due to block of central nervous system (CNS) D_2 receptors
• *Domperidone: Like metoclopramide, but less CNS effect; not available in USA*				
• *Cholinomimetics: Neostigmine often used for colonic pseudo-obstruction in hospitalized patients*				
• *Macrolides: Erythromycin useful in diabetic gastroparesis but tolerance develops*				
LAXATIVES				
• Magnesium hydrox ide, other nonabsorb able salts and sugars	Osmotic agents increase water content of stool	Usually causes evacuation within 4–6 h, sooner in large doses	Simple constipation; bowel prep for endoscopy (especially PEG solutions)	Magnesium may be absorbed and cause toxicity in renal impairment
• *Bulk-forming laxatives: Methylcellulose, psyllium, etc: increase volume of colon, stimulate evacuation*				
• *Stimulants: senna, cascara; stimulate activity; may cause cramping*				
• *Stool surfactants: Docusate, mineral oil; lubricate stool, ease passage*				
• *Chloride channel activator: Lubiprostone, prostanoic acid derivative, stimulates chloride secretion into intestine, increasing fluid content*				
• *Opioid receptor antagonists: Alvimopan, methylnaltrexone; block intestinal μ-opioid receptors but do not enter CNS, so analgesia is maintained*				
• *5-HT_4 agonists: Tegaserod; activates enteric 5-HT_4 receptors and increases intestinal motility*				
ANTIDIARRHEAL DRUGS				
• Loperamide	Activates μ-opioid receptors in enteric nervous system	Slows motility in gut with negligible CNS effects	Nonspecific, noninfectious diarrhea	Mild cramping but little or no CNS toxicity
• *Diphenoxylate: Similar to loperamide, but high doses can cause CNS opioid effects and toxicity*				
• *Colloidal bismuth compounds: Subsalicylate and citrate salts available. OTC preparations popular and have some value in travelers' diarrhea due to adsorption of toxins*				
• *Kaolin + pectin: Adsorbent compounds available OTC in some countries*				
DRUGS FOR IRRITABLE BOWEL SYNDROME (IBS)				
• Alosetron	5-HT_3 antagonist of high potency and duration of binding	Reduces smooth muscle activity in gut	Approved for severe diarrhea-predominant IBS in women	Rare but serious constipation • ischemic colitis • infarction
• *Anticholinergics: Nonselective action on gut activity, usually associated with typical antimuscarinic toxicity*				
• *Chloride channel activator: Lubiprostone (see above); useful in constipation-predominant IBS in women*				

(*continued*)

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
ANTIEMETIC DRUGS				
• Ondansetron, other 5-HT_3 antagonists	5-HT_3 blockade in gut and CNS with shorter duration of binding than alosetron	Extremely effective in preventing chemotherapy-induced and postoperative nausea and vomiting	First-line agents in cancer chemotherapy; also useful for postop emesis	Usually given IV but orally active in prophylaxis • 4–9 h duration of action • very low toxicity but may slow colonic transit
• Aprepitant	NK_1-receptor blocker in CNS	Interferes with vomiting reflex • no effect on 5-HT, dopamine, or steroid receptors	Effective in reducing both early and delayed emesis in cancer chemotherapy	Given orally • IV fosaprepitant available • fatigue, dizziness, diarrhea • CYP interactions
• *Corticosteroids: Mechanism not known but useful in antiemetic IV cocktails*				
• *Antimuscarinics (scopolamine): Effective in emesis due to motion sickness; not other types*				
• *Antihistaminics: Moderate efficacy in motion sickness and chemotherapy-induced emesis*				
• *Phenothiazines: Act primarily through block of D_2 and muscarinic receptors*				
• *Cannabinoids: Dronabinol is available for use in chemotherapy-induced nausea and vomiting, but is associated with CNS marijuana effects*				
DRUGS USED IN INFLAMMATORY BOWEL DISEASE (IBD)				
• 5-Aminosalicylates, eg, mesalamine in many formulations • Sulfasalazine	Mechanism uncertain • may be inhibition of eicosanoid inflammatory mediators	Topical therapeutic action • systemic absorption may cause toxicity	Mild to moderately severe Crohn's disease and ulcerative colitis	Sulfasalazine causes sulfonamide toxicity and may cause GI upset, myalgias, arthralgias, myelosuppression • other aminosalicylates much less toxic
• Purine analogs and antimetabolites, eg, 6-mercaptopurine, methotrexate	Mechanism uncertain • may promote apoptosis of immune cells • Methotrexate blocks dihydrofolate reductase	Generalized suppression of immune processes	Moderately severe to severe Crohn's disease and ulcerative colitis	GI upset, mucositis • myelosuppression • purine analogs may cause hepatotoxicity, but rare with methotrexate at the low doses used
• Anti-TNF antibodies, eg, infliximab, others	Bind tumor necrosis factor and prevent it from binding to its receptors	Suppression of several aspects of immune function, especially T_H1 lymphocytes	Infliximab: Moderately severe to severe Crohn's disease and ulcerative colitis • others approved in Crohn's disease	Infusion reactions • reactivation of latent tuberculosis • increased risk of dangerous systemic fungal and bacterial infections
• *Corticosteroids: Generalized anti-inflammatory effect; see Chapter 39*				
PANCREATIC SUPPLEMENTS				
• Pancrelipase	Replacement enzymes from animal pancreatic extracts	Improves digestion of dietary fat, protein, and carbohydrate	Pancreatic insufficiency due to cystic fibrosis, pancreatitis, pancreatectomy	Taken with every meal • may increase incidence of gout
• *Pancreatin: Similar pancreatic extracts but much lower potency; rarely used*				
BILE ACID THERAPY FOR GALLSTONES				
• Ursodiol	Reduces cholesterol secretion into bile	Dissolves gallstones	Gallstones in patients refusing or not eligible for surgery	May cause diarrhea
DRUGS USED TO TREAT VARICEAL HEMORRHAGE				
• Octreotide	Somatostatin analog • mechanism not certain	May alter portal blood flow and variceal pressures	Patients with bleeding varices or at high risk of repeat bleeding	Reduced endocrine and exocrine pancreatic activity • other endocrine abnormalities • GI upset
• *β Blockers: Reduce cardiac output and splanchnic blood flow; see Chapter 10*				

PREPARATIONS AVAILABLE

ANTACIDS

Aluminum hydroxide gel* (AlternaGEL, others)
Oral: 300, 500, 600 mg tablets; 400, 500 mg capsules; 320, 450, 675 mg/5 mL suspension

Calcium carbonate* (Tums, others)
Oral: 350, 420, 500, 600, 650, 750, 1000, 1250 mg chewable tablets; 1250 mg/5 mL suspension

Combination aluminum hydroxide and magnesium hydroxide preparations* (Maalox, Mylanta, Gaviscon, Gelusil, others)
Oral: 400 to 800 mg combined hydroxides per tablet, capsule, or 5 mL suspension

H_2 HISTAMINE RECEPTOR BLOCKERS

Cimetidine (generic, Tagamet, Tagamet HB*)
Oral: 200,* 300, 400, 800 mg tablets; 300 mg/5 mL liquid
Parenteral: 300 mg/2 mL, 300 mg/50 mL for injection

Famotidine (generic, Pepcid, Pepcid AC,* Pepcid Complete*)
Oral: 10, 20 mg tablets,* gelcaps*; powder to reconstitute for 40 mg/5 mL suspension
Parenteral: 10 mg/mL for injection

Nizatidine (generic, Axid, Axid AR*)
Oral: 75 mg tablets*; 150, 300 mg capsules

Ranitidine (generic, Zantac, Zantac 75*)
Oral: 75,* 150, 300 mg tablets
Parenteral: 1, 25 mg/mL for injection

SELECTED ANTICHOLINERGIC DRUGS

Atropine (generic)
Oral: 0.4 mg tablets
Parenteral: 0.05, 0.1, 0.3, 0.4, 0.5, 0.8, 1 mg/mL for injection

Belladonna alkaloids tincture (generic)
Oral: 0.27–0.33 mg/mL liquid

Dicyclomine (generic, Bentyl, others)
Oral: 10, 20 mg capsules; 20 mg tablets; 10 mg/5 mL syrup
Parenteral: 10 mg/mL for injection

Glycopyrrolate (generic, Robinul)
Oral: 1, 2 mg tablets
Parenteral: 0.2 mg/mL for injection

Hyoscyamine (Anaspaz, Levsin, others)
Oral: 0.125, 0.15 mg tablets; 0.375 mg timed-release capsules; 0.125 mg/5 mL oral elixir and solution
Parenteral: 0.5 mg/mL for injection

Scopolamine (generic, Transderm Scop)
Oral: 0.4 mg tablets
Transdermal patch: 1.5 mg/2.5 cm^2
Parenteral: 0.4, 1 mg/mL for injection

PROTON PUMP INHIBITORS

Esomeprazole (Nexium)
Oral: 20, 40 mg delayed-release capsules
Parenteral: 20, 40 mg vial powder for IV injection

Omeprazole (Prilosec, Prilosec OTC,* Zegerid)
Oral: 10, 20, 40 mg delayed-release capsules; 20 mg delayed-release tablet*

Lansoprazole (Prevacid)
Oral: 15, 30 mg delayed-release capsules; 15, 30 mg orally disintegrating tablet containing delayed-release granules; 15, 30 mg delayed-release granules for oral suspension
Parenteral: 30 mg powder for injection

Dexlansoprazole (Dexilant)
Oral: 30, 60 mg delayed-release capsules

Pantoprazole (Protonix)
Oral: 20, 40 mg delayed-release tablets; 40 mg delayed-release granules for oral suspension
Parenteral: 40 mg/vial powder for IV injection

Rabeprazole (Aciphex)
Oral: 20 mg delayed-release tablets

MUCOSAL PROTECTIVE AGENTS

Misoprostol (Cytotec)
Oral: 100, 200 mcg tablets

Sucralfate (generic, Carafate)
Oral: 1 g tablets; 1 g/10 mL suspension

DIGESTIVE ENZYMES

Pancrelipase (Creon, Pancrease, Zenpep)
Oral: Delayed-release capsules containing varying amounts of lipase, protease, and amylase activity. See manufacturers' literature for details.

DRUGS FOR MOTILITY DISORDERS & SELECTED ANTIEMETICS

5-HT_3-RECEPTOR ANTAGONISTS

Alosetron (Lotronex)
Oral: 0.5, 1 mg tablets

Dolasetron (Anzemet)
Oral: 50, 100 mg tablets
Parenteral: 20 mg/mL for injection

Granisetron (generic, Kytril)
Oral: 1 mg tablets; 2 mg/10 mL oral solution
Parenteral: 0.1, 1 mg/mL for injection

Ondansetron (generic, Zofran)
Oral: 4, 8, 16, 24 mg tablets; 4, 8 mg orally disintegrating tablets; 4 mg/5 mL oral solution
Parenteral: 2 mg/mL, 32 mg/50 mL for IV injection

Palonosetron (Aloxi)
Oral: 0.5 mg capsules
Parenteral: 0.05 mg/mL for injection

OTHER MOTILITY AND ANTIEMETIC AGENTS

Aprepitant (Emend)
Oral: 80, 125 mg capsules

Dronabinol (Marinol)
Oral: 2.5, 5, 10 mg capsules

Fosaprepitant (Emend)
Parenteral: 115 mg/10 mL for IV injection

Metoclopramide (generic, Reglan, others)
Oral: 5, 10 mg tablets; 5 mg/5 mL syrup, 10 mg/mL concentrated solution
Parenteral: 5 mg/mL for injection

Nabilone (Cesamet)
Oral: 1 mg tablets

Prochlorperazine (Compazine)
Oral: 5, 10, 25 mg tablets; 10, 15, 30 mg capsules; 1 mg/mL solution
Rectal: 2.5, 5, 25 mg suppositories
Parenteral: 5 mg/mL for injection

Promethazine (generic, Phenergan, others)
Oral: 10, 13.2, 25, 50 mg tablets; 5, 6.25, 10 mg/5 mL syrup
Rectal: 10, 12.5, 25, 50 mg suppositories
Parenteral: 25, 50 mg/mL for IM or IV injection

Scopolamine (Transderm Scop)
Transdermal patch: 1.5 mg/2.5 cm^2

Tegaserod (Zelnorm)
Oral: 2, 6 mg tablets

Trimethobenzamide (generic, Tigan, others)
Oral: 250, 300 mg capsules
Parenteral: 100 mg/mL for injection

SELECTED ANTI–INFLAMMATORY DRUGS USED IN GASTROINTESTINAL DISEASE (SEE ALSO CHAPTER 55)

Adalimumab (Humira)
Parenteral: 40 mg/0.8 mL for subcutaneous injection by syringe or auto-pen

Balsalazide (Colazal)
Oral: 750 mg capsules

Budesonide (Entocort)
Oral: 3 mg capsules

Certolizumab (Cimzia)
Parenteral: 200 mg powder (reconstituted with 1 mL) for subcutaneous injection

Hydrocortisone (Cortenema, Cortifoam, Proctofoam–HC)
Rectal: 100 mg/60 mL unit retention enema; 90 mg/applicatorful intrarectal foam
Anal: 1% hydrocortisone/1% pramoxine as aerosol application

Infliximab (Remicade)
Parenteral: 100 mg powder for intravenous injection

Mesalamine (5–ASA)
Oral: Asacol: 400 mg, 800 mg delayed-release tablets; Pentasa: 250 mg controlled-release capsules; Lialda: 1.2 g delayed-release tablets; Apriso: 375 mg delayed-release capsules
Rectal: Rowasa: 4 g/60 mL suspension
Canasa: 1000 mg suppositories

Methylprednisolone (Medrol Enpack)
Rectal: 40 mg/bottle retention enema

Olsalazine (Dipentum)
Oral: 250 mg capsules

Sulfasalazine (generic, Azulfidine)
Oral: 500 mg tablets and delayed-release enteric-coated tablets

SELECTED ANTIDIARRHEAL DRUGS

Bismuth subsalicylate* (Pepto–Bismol, others)
Oral: 262 mg caplets, chewable tablets; 130, 262, 524 mg/15 mL suspension

Difenoxin (Motofen)
Oral: 1 mg (with 0.025 mg atropine sulfate) tablets

Diphenoxylate (generic, Lomotil, others)
Oral: 2.5 mg (with 0.025 mg atropine sulfate) tablets and liquid

Loperamide* (generic, Imodium)
Oral: 2 mg tablets, capsules; 1 mg/5 mL liquid

BULK-FORMING LAXATIVES*

Methylcellulose (generic, Citrucel)
Oral: bulk powder, capsules

Psyllium (generic, Serutan, Metamucil, others)
Oral: granules, bulk powder, wafer

OTHER SELECTED LAXATIVE DRUGS

Alvimopan (Entereg)
Oral: 12 mg capsules

Bisacodyl* (generic, Dulcolax, others)
Oral: 5 mg enteric-coated tablets
Rectal: 5 mg, 10 mg suppositories

Cascara sagrada* (generic)
Oral: 325 mg tablets; 5 mL per dose fluid extract (approximately 18% alcohol)

Docusate* (generic, Colace, others)
Oral: 50, 100, 250 mg capsules; 100 mg tablets; 20, 50, 60, 150 mg/15 mL syrup

Lactulose (Chronulac, Cephulac)
Oral: 10 g/15 mL syrup

Lubiprostone (Amitiza)
Oral: 8, 24 mcg capsules

Magnesium hydroxide [milk of magnesia, Epsom Salt]* (generic)
Oral: 400, 800 mg/5 mL aqueous suspension

Methylnaltrexone bromide (Relistor)
Parenteral: 12 mg/0.6 mL

Polycarbophil* (Equalactin, Mitrolan, FiberCon, Fiber–Lax)
Oral: 500, 625 mg tablets; 500 mg chewable tablets

Polyethylene glycol electrolyte solution (Co–Lyte, GoLYTELY, HalfLytely, Moviprep, others)
Oral: Powder for oral solution, makes 2L or 4L

Senna* (Senokot, ExoLax, others)
Oral: 8.6, 15, 17, 25 mg tablets; 8.8, 15 mg/mL liquid

Sodium Phosphate (Fleets Phospho-soda, OsmoPrep, Visicol)
Oral: 1.5 g tablets; 10 g/15 mL liquid

DRUGS THAT DISSOLVE GALLSTONES

Ursodiol (generic, Actigall, URSO)
Oral: 250, 500 mg tablets; 300 mg capsules

*Over-the-counter formulations.

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CASE STUDY ANSWER

The immediate goals of therapy are to improve this young woman's symptoms of abdominal pain, diarrhea, weight loss, and fatigue. Equally important goals are to reduce the intestinal inflammation in hopes of preventing progression to intestinal stenosis, fistulization, and need for surgery. One option now is to "step up" her therapy by giving her a slow, tapering course of systemic corticosteroids (eg, prednisone) for 8–12 weeks in order to quickly bring her symptoms and inflammation under control while also initiating therapy with an immunomodulator (eg, azathioprine or mercaptopurine) in hopes of achieving long-term disease remission. If satisfactory disease control is not achieved within 3–6 months, therapy with an anti-TNF agent then would be recommended. Alternatively, patients with moderate-to-severe Crohn's disease who have failed mesalamine may be treated upfront with *both* an anti-TNF agent and immunomodulators, which achieves higher remission rates than either agent alone and may improve long-term outcomes.

CHAPTER 63

Therapeutic & Toxic Potential of Over-the-Counter Agents

Robin L. Corelli, PharmD

CASE STUDY

A 66-year-old man presents to his primary care provider for worsening shortness of breath, chest congestion, and symptoms of a severe cold (cough, rhinorrhea, nasal congestion, drowsiness) over the past week. His past medical history is significant for heart failure, hypertension, and hyperlipidemia. His current medications include lisinopril 20 mg daily, simvastatin 40 mg daily, furosemide 40 mg daily, and potassium chloride 20 mEq daily. The patient reports sporadic compliance with his prescribed medications but admits to taking several over-the-counter (OTC) medications over the past 5 days for his recent cold symptoms, including Alka-Seltzer Plus Cold Formula (2 tablets every 4 hours during the day), Sudafed (60 mg every 6 hours), and Advil PM (2 tablets at bedtime). His social history is significant for alcohol use (3–4 beers/night). His vital signs include the following: afebrile, blood pressure 172/94 mm Hg, pulse 84 bpm, respiratory rate 16/min. On physical examination an S_3 gallop is heard; 3+ pitting edema is noted in his lower extremities, and a chest examination reveals inspiratory rales bilaterally. What drugs do OTC "cold" preparations typically contain? Which of the OTC medications might have contributed to the patient's current hypertension? Are any of these preparations implicated in the signs of heart failure?

In the USA, drugs are divided by law into two classes: those restricted to sale by prescription only and those for which directions for safe use by the public can be written. The latter category constitutes the nonprescription or over-the-counter (OTC) drugs. In 2010, the American public spent approximately $17 billion on over 100,000 OTC products to medicate themselves for ailments ranging from acne to warts. These products contain approximately 1000 active ingredients in various forms and combinations.

It is apparent that many OTC drugs are no more than "me too" products advertised to the public in ways that suggest significant differences between them. For example, there are over 100 different systemic analgesic products, almost all of which contain aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or a combination of these agents as primary ingredients. They are made different from one another by the addition of questionable ingredients such as caffeine or antihistamines; by brand names chosen to suggest a specific use or strength ("women's," "migraine," "arthritis," "maximum"); or by special dosage formulations (enteric-coated tablets, geltabs, liquids, orally disintegrating strips and tablets, sustained-release products, powders, seltzers). There is a price attached to all of these features, and in most cases a less expensive generic product can be equally effective. It is probably safe to assume that the public is generally overwhelmed and confused by the wide array of products presented and will probably use those that are most heavily advertised.

Over the past four decades the Food and Drug Administration (FDA) has been engaged in a methodical review of OTC ingredients for both safety and efficacy. There have been two major outcomes of this review: (1) Ingredients designated as ineffective or unsafe for their claimed therapeutic use are being eliminated from OTC product formulations (eg, antimuscarinic agents have been eliminated from OTC sleep aids, attapulgite and polycarbophil can no longer be marketed as OTC antidiarrheal products); and (2) agents previously available by prescription only have been made available for OTC use because they were judged by the review panel to be generally safe and effective for consumer use without medical supervision (Table 63–1). The prescription-to-OTC

TABLE 63–1 Selected agents switched from prescription to OTC status by the Food and Drug Administration.

Ingredient	Indication	Year Ingredient First Switched	Single-Ingredient Product Examples
Systemic agents			
Cetirizine	Antihistamine	2007	Zyrtec
Cimetidine	Acid reducer (H_2 blocker)	1995	Tagamet HB
Clemastine	Antihistamine	1992	Tavist Allergy
Famotidine	Acid reducer (H_2 blocker)	1995	Pepcid AC
Fexofenadine	Antihistamine	2011	Allegra 12 Hour, Allegra 24 Hour
Ibuprofen	Analgesic, antipyretic (NSAID)	1984	Advil, Motrin IB
Lansoprazole	Acid reducer (proton pump inhibitor)	2009	Prevacid 24 HR
Levonorgestrel	Emergency contraceptive	2006	Plan B One-Step
Loratadine	Antihistamine	2002	Claritin, Alavert
Naproxen sodium	Analgesic, antipyretic (NSAID)	1994	Aleve
Nicotine transdermal system	Smoking cessation	1996	Nicoderm CQ
Nicotine polacrilex gum	Smoking cessation	1996	Nicorette
Nizatidine	Acid reducer (H_2 blocker)	1996	Axid AR
Omeprazole	Acid reducer (proton pump inhibitor)	2003	Prilosec OTC, Zegerid OTC
Orlistat	Weight loss aid	2007	Alli
Polyethylene glycol	Laxative	2006	MiraLax
Ranitidine	Acid reducer (H_2 blocker)	1995	Zantac 75, Zantac 150
Topical agents			
Butenafine	Antifungal (topical)	2001	Lotrimin Ultra
Butoconazole	Antifungal (vaginal)	1995	Femstat-3
Clotrimazole	Antifungal (vaginal)	1990	Gyne-Lotrimin-7, Gyne-Lotrimin-3
Cromolyn	Nasal antiallergy	1997	Nasalcrom
Ketoconazole	Dandruff shampoo	1997	Nizoral A-D
Ketotifen fumarate	Ophthalmic antihistamine	2006	Alaway, Zaditor
Miconazole	Antifungal (vaginal)	1991	Monistat-7, Monistat-3
Minoxidil	Hair growth stimulant	1996	Rogaine Regular and Extra Strength For Men, Rogaine For Women
Naphazoline/Pheniramine	Ophthalmic decongestant antihistamine	1994	Naphcon A, Opcon A, Visine-A
Terbinafine	Antifungal (topical)	1999	Lamisil AT
Tioconazole	Antifungal (vaginal)	1997	Monistat-1, Vagistat-1

switch process has significantly enhanced and expanded self-care options for US consumers. Indeed, more than 700 OTC products contain ingredients and dosages that were available only by prescription less than 30 years ago. Some agents such as docosanol and the nicotine polacrilex lozenge have bypassed the prescription route altogether and have been released directly to the OTC market. Other OTC ingredients previously available in low doses only are now available in higher-strength or original prescription strength formulations. Examples of other prescription drugs with the potential for future OTC reclassification include nicotine replacement therapy (oral inhaler, nasal spray) for smoking cessation, proton-pump inhibitors (pantoprazole) for heartburn, and second-generation nonsedating antihistamines (desloratadine, fexofenadine, levocetirizine) for relief of allergy and cold symptoms. The frequency of prescription-to-OTC switches, while commonplace in the mid-1990s, has largely declined over the past decade. The prescription-to-OTC reclassification process is both costly and rigorous and fewer prescription medications are appropriate candidates for a switch (eg, a consumer can self-diagnose and safely treat the condition). For example, the cholesterol-lowering agents cholestyramine, lovastatin, and pravastatin were denied OTC status on the basis that these agents could not be used safely and effectively in an OTC setting. The nonprescription drug advisory committee believed that diagnosis and ongoing management by a health care professional was necessary for the management of hyperlipidemia, a chronic, asymptomatic

condition with potentially life-threatening consequences. In a similar recommendation, oral acyclovir for OTC use in the treatment of recurrent genital herpes was not approved because of concerns about misdiagnosis and inappropriate use leading to increased viral resistance.

There are three reasons why it is essential for clinicians to be familiar with the OTC class of products. First, many OTC medications are effective in treating common ailments, and it is important to be able to help the patient select a safe, effective product. Because managed-care practices encourage clinicians to limit the cost of drugs they prescribe, many will recommend effective OTC treatments to their patients, since these drugs are rarely paid for by the insurance plan (Table 63–2). Second, many of the active ingredients contained in OTC drugs may worsen existing medical conditions or interact with prescription medications. (See Chapter 66, Important Drug Interactions & Their Mechanisms.) Finally, the misuse or abuse of OTC products may actually produce significant medical complications. Phenylpropanolamine, for example, a sympathomimetic previously found in many cold, allergy, and weight control products, was withdrawn from the United States market by the FDA based on reports that the drug increased the risk of hemorrhagic stroke. Dextromethorphan, an antitussive found in many cough and cold preparations, has been increasingly abused in high doses (eg, > 5–10 times the recommended antitussive dose) by adolescents as a hallucinogen. Although severe complications associated with dextromethorphan as a single agent in overdose are uncommon, many dextromethorphan-containing products are formulated with other ingredients (acetaminophen, antihistamines, and sympathomimetics) that can be fatal in overdose. Additionally, pseudoephedrine, a decongestant contained in numerous OTC cold preparations, has been used in the illicit manufacture of methamphetamine. A general awareness of these products and their formulations will enable clinicians to more fully appreciate the potential for OTC drug-related problems in their patients.

Table 63–2 lists examples of OTC products that may be used effectively to treat common medical problems. The selection of one ingredient over another may be important in patients with certain medical conditions or in patients taking other medications. These are discussed in detail in other chapters. The recommendations listed in Table 63–2 are based on the efficacy of the ingredients and on the principles set forth in the following paragraphs.

1. Select the product that is simplest in formulation with regard to ingredients and dosage form. In general, single-ingredient products are preferred. Although some combination products contain effective doses of all ingredients, others contain therapeutic doses of some ingredients and subtherapeutic doses of others. Furthermore, there may be differing durations of action among the ingredients, and there is always a possibility that the clinician or patient is unaware of the presence of certain active ingredients in the product. Acetaminophen, for example, is in many cough and cold preparations; a patient unaware of this may take separate doses of analgesic in addition to that contained in the cold preparation, potentially leading to hepatotoxicity.
2. Select a product that contains a therapeutically effective dose.
3. Consumers and providers should carefully read the "Drug Facts" label to determine which ingredients are appropriate based on the patient's symptoms, underlying health conditions, and whatever is known about the medications the patient is already taking. This is critical because many products with the same brand name contain different ingredients that are labeled for different uses. For example, multiple laxative products (with different active ingredients) carry the Dulcolax name including Dulcolax Balance (polyethylene glycol), Dulcolax Laxative (bisacodyl), and Dulcolax Stool Softener (docusate sodium). This marketing practice of "extending a brand name" across product lines, while legal, is confusing and can lead to medication errors.
4. Recommend a generic product if one is available.
5. Be wary of "gimmicks" or advertising claims of specific superiority over similar products.
6. For children, the dose, dosage form, and palatability of the product are prime considerations.

Certain ingredients in OTC products should be avoided or used with caution in selected patients because they may exacerbate existing medical problems or interact with other medications the patient is taking. Many of the more potent OTC ingredients are hidden in products where their presence would not ordinarily be expected (Table 63–3). Although OTC medications have standardized label formatting and content requirements that specify the indications for use, dosage, warnings, and active and inactive ingredients contained in the product, many consumers do not carefully read or comprehend this information. Lack of awareness of the ingredients in OTC products and the belief by many providers that OTC products are ineffective and harmless may cause diagnostic confusion and perhaps interfere with therapy. For example, innumerable OTC products, including analgesics and allergy, cough, and cold preparations, contain sympathomimetics. These agents should be avoided or used cautiously by type 1 diabetics and patients with hypertension, angina, or hyperthyroidism. Aspirin should not be used in children and adolescents for viral infections (with or without fever) because of an increased risk of Reye's syndrome. Aspirin and other NSAIDs should be avoided by individuals with active peptic ulcer disease, certain platelet disorders, and patients taking oral anticoagulants. Cimetidine, an H_2-receptor antagonist, is a well-known inhibitor of hepatic drug metabolism and can increase the blood levels and toxicity of drugs such as phenytoin, theophylline, and warfarin.

Overuse or misuse of OTC products may induce significant medical problems. A prime example is rebound congestion from the regular use of decongestant nasal sprays for more than 3 days. The improper and long-term use of some antacids (eg, aluminum hydroxide) may cause constipation and even impaction in elderly people, as well as hypophosphatemia. Laxative abuse can result in abdominal cramping and fluid and electrolyte disturbances. Insomnia, nervousness, and restlessness can result from the use of sympathomimetics or caffeine hidden in many OTC products (Table 63–3). The long-term use of some analgesics containing large amounts of caffeine may produce rebound headaches, and long-term use of analgesics has been associated with interstitial nephritis. OTC products containing aspirin, other salicylates, acetaminophen, ibuprofen, or naproxen may increase the risk of hepatotoxicity and gastrointestinal hemorrhage in individuals who consume three or more alcoholic drinks daily. Recent evidence

TABLE 63–2 Ingredients of known efficacy for selected OTC classes.

OTC Category	Ingredient and Usual Adult Dosage	Product Examples	Comments
Acid reducers (H_2 antagonists)	Cimetidine, 200 mg once or twice daily	Tagamet HB, various generic	These products have been approved for the relief of "heartburn associated with acid indigestion, and sour stomach." They should not be taken for longer than 2 weeks and are not recommended for children < 12 years of age.
	Famotidine, 10–20 mg once or twice daily	Pepcid AC, Maximum Strength Pepcid AC, various generic	
	Nizatidine, 75 mg once or twice daily	Axid AR	
	Ranitidine, 75–150 mg once or twice daily	Zantac 75, Zantac 150, various generic	
Acid reducers (proton pump inhibitors)	Lansoprazole, 15 mg once daily for 14 days	Prevacid 24 HR	Proton pump inhibitors are approved for the treatment of frequent heartburn in adults (≥ 18 years of age) with symptoms of heartburn 2 or more days per week. These products are not intended for immediate relief of heartburn, as they may take 1–4 days for full effect. They should not be taken for more than 14 days or more often than every 4 months unless directed by a physician. Omeprazole magnesium 20.6 mg is equivalent to 20 mg of omeprazole (prescription strength).
	Omeprazole magnesium, 20.6 mg once daily for 14 days	Prilosec OTC, various generic	
	Omeprazole (20 mg) with sodium bicarbonate (1100 mg), once daily for 14 days	Zegerid OTC	
Acne preparations	Benzoyl peroxide, 5%, 10%	Clearasil, Oxy-10, various generic	One of the most effective acne preparations. Apply sparingly once or twice daily. Decrease concentration or frequency if excessive skin irritation occurs.
Allergy and "cold" preparations	Chlorpheniramine, 4 mg every 4–6 hours; 8 mg (extended-release) every 8–12 hours; 12 mg (extended-release) every 12 hours	Chlor-Trimeton Allergy, various generic	Antihistamines alone relieve most symptoms associated with allergic rhinitis or hay fever. Chlorpheniramine, brompheniramine, and clemastine may cause less drowsiness than diphenhydramine. Cetirizine, fexofenadine and loratadine (second generation antihistamines), are therapeutically comparable to first-generation agents; these agents have minimal anti-cholinergic effects and are therefore associated with a lower incidence of sedation. Occasionally, symptoms unrelieved by the antihistamine respond to the addition of a sympathomimetic decongestant. OTC sale of products containing pseudoephedrine is restricted (see comments under Decongestants, systemic).
	Clemastine, 1.34 mg every 12 hours	Tavist Allergy	
	Cetirizine, 10 mg every 24 hours	Zyrtec, various generic	
	Diphenhydramine, 25–50 mg every 4–6 hours	Benadryl Allergy, various generic	
	Fexofenadine 60 mg every 12 hours; 180 mg every 24 hours	Allegra 12 Hour, Allegra 24 Hour	
	Loratadine, 10 mg every 24 hours	Alavert, Claritin, various generic	
	Brompheniramine (4 mg) with phenylephrine (10 mg) every 4 hours	Dimetapp Cold & Allergy, various generic	
	Cetirizine (5 mg) with pseudoephedrine (120 mg) every 12 hours	Zyrtec-D	
	Chlorpheniramine (4 mg) with phenylephrine (10 mg) every 4 hours	Allerest PE, Sudafed PE Sinus & Allergy, various generic	
	Fexofenadine 60 mg every 12 hours; 180 mg every 24 hours	Allegra-D 12 Hour	
	Loratadine (5 mg) with pseudoephedrine (120 mg) every 12 hours	Claritin-D 12 Hour	
	Loratadine (10 mg) with pseudoephedrine (240 mg) every 24 hours	Claritin-D 24 Hour	
	Triprolidine (2.5 mg) with phenylephrine (10 mg) every 4 hours	Actifed Cold & Allergy, various generic	

(*continued*)

TABLE 63–2 Ingredients of known efficacy for selected OTC classes. (Continued)

OTC Category	Ingredient and Usual Adult Dosage	Product Examples	Comments
Analgesics and antipyretics	Acetaminophen, 325–650 mg every 4–6 hours; 650–1300 mg (extended-release) every 8 hours	Panadol, Tylenol, Extra Strength Tylenol, Tylenol 8-Hour, various generic	Acetaminophen lacks anti-inflammatory activity but is available as a liquid; this dosage form is used primarily for infants and children who cannot chew or swallow tablets. Use of products containing acetaminophen may increase the risk of severe liver damage in individuals who ingest more than 4 g in 24 hours, take with other drugs containing acetaminophen, or consume ≥ three alcoholic drinks daily. In January 2011, the FDA announced that manufacturers of prescription acetaminophen combination products must limit the maximum amount of acetaminophen in these formulations to 325 mg per dosage unit to reduce the risk of severe liver injury from acetaminophen overdosing. There are numerous product modifications, including the addition of antacids and caffeine; enteric-coated tablets and seltzers; long-acting or extra-strength formulations; and various mixtures of analgesics. None has any substantial advantage over a single-ingredient product. Aspirin should be used cautiously in certain individuals (see text). Use of products containing aspirin may increase the risk of severe gastrointestinal hemorrhage in individuals who consume ≥ 3 alcoholic drinks daily. Use of products containing NSAIDs may increase the risk of severe gastrointestinal hemorrhage in individuals who are age 60 or older, have had stomach ulcers or bleeding problems, take anticoagulant or steroid drugs, take other drugs containing prescription or nonprescription NSAIDs, consume 3 or more alcoholic drinks daily or take more or for a longer time than directed. Long-term continuous use of NSAIDs may increase the risk of heart attack or stroke.
	Aspirin, 325–650 mg every 4–6 hours	Bayer Aspirin, Ecotrin, Bufferin, various generic	
	Ibuprofen, 200–400 mg every 4–6 hours (not to exceed 1200 mg in a 24-hour period)	Advil, Motrin IB, various generic	
	Naproxen sodium, 220 mg every 8–12 hours (not to exceed 660 mg in a 24-hour period)	Aleve, various generic	
Antacids	Magnesium hydroxide and aluminum hydroxide alone or in combination; calcium carbonate, dosage varies; consult product labeling	Alternagel, Maalox, Milk of Magnesia, Mylanta, Tums, various generic	Combinations of magnesium and aluminum hydroxide are less likely to cause constipation or diarrhea and offer high neutralizing capacity. Some preparations include simethicone, an antiflatulent to relieve symptoms of bloating and pressure.
Antihelminthics (pinworm infection)	Pyrantel pamoate, 11 mg/kg (maximum: 1 g)	Pin-X, Reese's Pinworm	Treat all members of the household. Consult physician for children < 2 years of age or < 25 lb. Undergarments, pajamas, and linens should be washed daily until the infection is resolved. If symptoms persist beyond 2 weeks, contact a physician to determine if a repeat dose is indicated.
Antidiarrheal agents	Bismuth subsalicylate, 524 mg every 30–60 minutes as needed up to 8 doses daily	Kaopectate, Pepto-Bismol, various generics	Antidiarrheals should not be used if diarrhea is accompanied by fever > 101°F or if blood or mucus is present in stool. Bismuth salts can cause dark discoloration of the tongue and/or stools. Salicylates are absorbed and can cause tinnitus if coadministered with aspirin.
	Loperamide, 4 mg initially, then 2 mg after each loose stool, not to exceed 8 mg in 24 hours	Imodium A-D, various generic	Loperamide, a synthetic opioid, acts on intestinal smooth muscle to decrease motility allowing for absorption of water and electrolytes. Poorly penetrates the CNS and has a lower risk of side effects compared with diphenoxylate or opiates. Not considered a controlled substance.

(*continued*)

TABLE 63–2 Ingredients of known efficacy for selected OTC classes. (Continued)

OTC Category	Ingredient and Usual Adult Dosage	Product Examples	Comments
Antifungal topical preparations	Butenafine, 1% (cream) apply to affected areas once daily	Lotrimin Ultra	Effective for the treatment of tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm). Clotrimazole and miconazole also effective against *Candida albicans*. Clinicians should be aware that products carrying the same brand name do not necessarily contain the same active ingredient.
	Clotrimazole, 1% (cream, powder, solution), apply to affected areas twice daily (morning and evening)	Lotrimin AF (various formulations), various generic	
	Miconazole, 2% (cream, powder, solution), apply to affected areas twice daily (morning and night)	Cruex, Desenex, Lotrimin AF (powder, spray), Zeasorb-AF	
	Terbinafine, 1% (cream, gel, solution), apply to affected areas once daily (ringworm/jock itch) or twice daily (athlete's foot)	Lamisil AT	
	Tolnaftate, 1% (cream, powder, spray, solution), apply to affected areas twice daily (morning and night)	Lamisil AF Defense (powder), Tinactin, Ting cream, various generic	
	Undecylenic acid, 12–25% (powder, solution) apply to affected areas twice daily	Blis-To-Sol, Elon Dual Defense Anti-Fungal	
Antifungal vaginal preparations	Clotrimazole (1%, 2% vaginal cream, 100 mg, 200 mg tablet); see comments for dosage	Gyne-Lotrimin-7, Gyne-Lotrimin-3, various generic	Topical vaginal antifungals should only be used for treatment of recurrent vulvovaginal candidiasis in otherwise healthy, nonpregnant women previously diagnosed by a clinician. Insert one applicatorful (1%) or one tablet (100 mg) intravaginally at bedtime for 7 consecutive days. Alternatively: Insert one applicatorful (2%) or one tablet (200 mg) intravaginally at bedtime for 3 consecutive days.
	Miconazole (2%, 4% vaginal cream; 100 mg, 200 mg, 1200 mg vaginal suppositories); see comments for dosage	Monistat-7, Monistat-3, Vagistat-3, various generic	Insert one applicatorful intravaginally at bedtime for 3 consecutive days (4%) or 7 consecutive days (2%). Alternatively: Insert one suppository intravaginally at bedtime for 1 day (1200 mg), 3 consecutive days (200 mg), or 7 consecutive days (100 mg).
	Tioconazole, 6.5% vaginal ointment, one applicatorful intravaginally at bedtime (single dose)	Monistat-1, Vagistat-1, various generic	
Anti-inflammatory topical preparations	Hydrocortisone, 0.5% (cream, ointment, lotion), 1% (cream, gel, ointment, lotion, spray)	Cortaid, Cortizone-10, Preparation H, Hydrocortisone, various generic	Used to temporarily relieve itching and inflammation associated with minor rashes due to contact or allergic dermatitides, insect bites, and hemorrhoids. Apply sparingly to affected areas two to four times daily.
Antiseborrheal agents	Coal tar, 0.5-5% shampoo, dosage varies; consult product labeling	Denorex Therapeutic, Ionil T Plus, various generic	Tar derivatives inhibit epidermal proliferation and may possess antipruritic and antimicrobial activity.
	Ketoconazole, 1% shampoo, apply every 3–4 days	Nizoral A-D	Synthetic azole antifungal agent with activity versus *Pityrosporum ovale*, a fungus that may cause seborrhea and dandruff. Massage over entire scalp for 3 minutes. Rinse thoroughly and repeat application.
	Pyrithione zinc, 1–2% shampoo, apply once or twice weekly	Head & Shoulders, Selsun Blue Salon, various generic	Both selenium sulfide and zinc pyrithione are cytostatic agents that decrease epidermal turnover rates. Massage into wet scalp for 2–3 minutes. Rinse thoroughly and repeat application. Selenium sulfide can be irritating to the eyes and skin.
	Selenium sulfide, 1% shampoo, apply once or twice weekly	Head & Shoulders Intensive Treatment, Selsun Blue Medicated, various generic	

(*continued*)

TABLE 63–2 Ingredients of known efficacy for selected OTC classes. (Continued)

OTC Category	Ingredient and Usual Adult Dosage	Product Examples	Comments
Antitussives	Codeine, 10–20 mg every 4–6 hours, not to exceed 120 mg in 24 hours (with guaifenesin)	Guiatuss AC, Mytussin AC, various generic	Acts centrally to increase the cough threshold. In doses required for cough suppression, the addiction liability associated with codeine is low. Codeine-containing antitussive combinations are schedule V narcotics, and OTC sale is restricted in some states.
	Dextromethorphan, 10–20 mg every 4 hours or 30 mg every 6–8 hours; 60 mg (extended-release suspension) every 12 hours	Delsym 12-Hour Cough, Hold DM, Robitussin Cough, Vicks 44 Dry Cough, various generic	Dextromethorphan is a nonopioid congener of levorphanol without analgesic or addictive properties. Often is used with antihistamines, decongestants, and expectorants in combination products. In high dosages (> 2 mg/kg) dextromethorphan can induce phencyclidine-like hallucinogenic effects.
Decongestants, topical	Oxymetazoline, 0.05% nasal solution, 2–3 sprays per nostril not more often than every 10–12 hours Phenylephrine (0.5%, 1%), nasal solution, 2–3 sprays per nostril no more often than every 4 hours	Afrin, Dristan, Neo-Synephrine Nighttime 12 Hour, Sudafed OM, Vicks Sinex, various generic Neo-Synephrine, various generic	Topical sympathomimetics are effective for the temporary acute management of rhinorrhea associated with common colds and allergies. Long-acting agents (oxymetazoline-containing products) are generally preferred, although phenylephrine is equally effective. Topical decongestants should not be used for longer than 3 days to prevent rebound nasal congestion.
Decongestants, systemic	Phenylephrine, 10 mg every 4 hours Pseudoephedrine, 60 mg every 4–6 hours or 120 mg (extended-release) every 12 hours, or 240 mg (extended-release) every 24 hours	Sudafed PE, various generic combination products Sudafed, various generic	Oral decongestants have a prolonged duration of action but may cause more systemic effects, including nervousness, excitability, restlessness, and insomnia. Also available in antihistamine, antitussive, expectorant, and analgesic combination products. Federal regulations established to discourage the illicit manufacture of methamphetamine specify that all drug products containing pseudoephedrine must be stored in locked cabinets or behind the pharmacy counter and can only be sold in limited quantities to consumers after they provide photo identification and sign a logbook.
Emergency contraceptive	Levonorgestrel, 1.5 mg tablet taken as soon as possible within 72 hours after unprotected intercourse	Plan B One-Step	Levonorgestrel prevents ovulation and may inhibit fertilization or implantation. Reduces the chance of pregnancy by up to 89% when taken as directed within 72 hours after unprotected intercourse. Plan B is available behind the counter at pharmacies and sold under the supervision of a licensed pharmacist. A prescription is needed for women ≤ 17 years of age.
Expectorants	Guaifenesin, 200–400 mg every 4 hours; 600–1200 mg (extended-release) every 12 hours	Mucinex, Robitussin, various generic	The only OTC expectorant recognized as safe and effective by the FDA. Often used with antihistamines, decongestants, and antitussives in combination products.
Hair growth stimulants	Minoxidil, 2% solution (for women), 5% foam, solution (for men), apply 1/2 capful (foam) or 1 mL (solution) to affected areas of scalp twice daily	Rogaine for Men, Rogaine for Women, Rogaine Extra Strength for Men	Minoxidil appears to directly stimulate hair follicles resulting in increased hair thickness and reduced hair loss. Treatment for 4 months or longer may be necessary to achieve visible results. If new hair growth is observed, continued treatment is necessary as hair density returns to pretreatment levels within months following drug discontinuation.

(*continued*)

TABLE 63–2 Ingredients of known efficacy for selected OTC classes. (Continued)

OTC Category	Ingredient and Usual Adult Dosage	Product Examples	Comments
Laxatives	Bulk formers: Polycarbophil, psyllium, and methylcellulose preparations. Dosage varies; consult product labeling	Citrucel, Fibercon, Konsyl, Metamucil, various generic	The safest laxatives for chronic use include the bulk formers and stool softeners. Saline laxatives and stimulants may be used acutely but not chronically (see text). Bulk formers hold water and expand in stool, promoting peristalsis.
	Hyperosmotics: Glycerin, 2–3 g suppository per rectum daily. Polyethylene glycol 3350 (powder), 17 g dissolved in 4–8 oz of beverage daily	Fleet Glycerin Suppository, various generic; Dulcolax Balance, MiraLax	Glycerin induces a local irritant effect in combination with an osmotic effect. Polyethylene glycol formulations are large, poorly absorbed molecules that induce an osmotic effect causing distention and catharsis.
	Stool softeners: Docusate sodium, 50–500 mg daily. Docusate calcium, 240 mg daily	Colace, Dulcolax, Surfak, various generic	Softens fecal material via detergent action that allows water to penetrate stool.
	Stimulant laxatives: Bisacodyl, 5–15 mg daily. Senna, dosage varies, consult product labeling	Dulcolax, Ex-Lax, Senokot, various generic	Stimulant laxative actions include direct irritation of intestinal mucosa or stimulation of the myenteric plexus, resulting in peristalsis. These agents may also cause alteration of fluid and electrolyte absorption, resulting in luminal fluid accumulation and bowel evacuation.
Pediculicides (head lice)	Permethrin 1% Pyrethrins (0.3%) combined with piperonyl butoxide (3–4%)	Nix A-200, RID	Instructions for use vary; consult product labeling. Avoid contact with eyes. Comb out nits. Linens, pajamas, combs, and brushes should be washed daily until the infestation is eliminated. For pyrethrin products, retreat in 7–10 days to kill any newly hatched nits. Permethrin products have residual effects for up to 10 days; therefore, reapplication is not required unless live nits are visible 7 days or more after the initial treatment.
Sleep aids	Diphenhydramine, 25–50 mg at bedtime Doxylamine, 25 mg 30 minutes before bedtime	Nytol, Simply Sleep, Sominex, various generic Unisom, various generic	Diphenhydramine and doxylamine are antihistamines with well-documented CNS depressant effects. Because insomnia may be indicative of a serious underlying condition requiring medical attention, patients should consult a physician if insomnia persists continuously for longer than 2 weeks.
Smoking cessation aids	Nicotine polacrilex gum; dosage varies; consult product labeling Nicotine polacrilex lozenge, dosage varies, consult product labeling Nicotine (transdermal system), dosage varies; consult product labeling	Nicorette, various generic Nicorette, various generic Nicoderm CQ, various generic	Nicotine replacement products in combination with behavioral support approximately double long-term cessation rates compared with placebo. Review directions for use carefully, since product strengths vary and self-titration and tapering may be necessary.
Weight loss aids	Orlistat, 60 mg with each meal containing fat (not to exceed 180 mg/d)	Alli	Approved for weight loss in overweight adults ≥ 18 years of age when used in combination with a reduced-calorie, low-fat diet and exercise program. Orlistat is a nonsystemically absorbed inhibitor of gastrointestinal lipase that blocks the absorption of dietary fat. OTC formulation is a half-strength version of the prescription product (Xenical).

TABLE 63–3 Hidden ingredients in OTC products.

Hidden Drug or Drug Class	OTC Class Containing Drug	Product Examples
Alcohol (percent ethanol)	Cough syrups, cold preparations	Theraflu Nighttime (10%); Vicks NyQuil Cold & Flu Liquid (10%); Vicks NyQuil Cough (10%)
	Mouthwashes	Listerine (27%); Scope (15%); Cepacol (14%)
Antihistamines	Analgesics	Advil PM; Alka-Seltzer PM; Excedrin PM; Bayer PM; Extra Strength Doan's PM; Goody's PM Pain Relief Powder; Tylenol PM
	Menstrual products	Midol Menstrual Complete; Pamprin Multi-Symptom
	Sleep aids	Nytol; Simply Sleep; Sominex; Unisom
Aspirin and other salicylates	Antidiarrheals	Pepto-Bismol (bismuth subsalicylate); Kaopectate (bismuth subsalicylate)
	Cold/allergy preparations	Alka-Seltzer Plus Flu
Caffeine (mg/tablets or as stated)	Analgesics	Anacin (32); Anacin Maximum Strength (32); Arthritis Strength BC (65/pre-measured packet); BC Powder (65/pre-measured packet); Excedrin Extra Strength (65); Excedrin Migraine (65); Excedrin Tension Headache (65); Goody's Extra Strength Headache Powder (33/pre-measured packet); Goody's Cool Orange (65/pre-measured packet)
	Menstrual products	Excedrin Menstrual Complete (65); Midol Menstrual Complete (60); Pamprin Max (65)
	Stimulants	NoDoz (200); Vivarin (200)
Local anesthetics (usually benzocaine)	Antitussives/lozenges	Cepacol Sore Throat Lozenges; Chloraseptic Sore Throat; Sucrets Sore Throat; Sucrets Complete
	Dermatologic preparations	Americaine; Bactine; Dermoplast; Lanacane; Solarcaine
	Hemorrhoidal products	Americaine Ointment; Nupercainal; Tronolane; Tucks Ointment
	Toothache, cold sore, and teething products	Anbesol; Kank-A; Orajel; Zilactin-B
Sodium (mg/tablet or as stated)	Analgesics	Alka-Seltzer Original Effervescent Tablet (567); Alka-Seltzer Extra Strength Effervescent Tablet (588); Bromo-Seltzer Granules (959/pre-measured packet)
	Antacids	Alka-Seltzer Original Effervescent Tablet (567); Alka-Seltzer Extra Strength Effervescent Tablet (588); Alka-Seltzer Gold (309); Alka-Seltzer Heartburn Relief (575); Brioschi (500/6 g dose); Bromo-Seltzer Granules (959/pre-measured packet)
	Cold/cough preparations	Alka-Seltzer Plus Formulations: Day Cold (416); Cold & Cough (415); Flu (387); Night Cold (474)
	Laxatives	Fleets Enema (4,439 mg, of which 275-400 mg/enema is absorbed)
Sympathomimetics	Analgesics	Excedrin Sinus Headache; Sine-Off; Sinutab; Tylenol Congestion & Pain; Tylenol Sinus Severe Congestion
	Asthma products	Bronkaid Dual Action; Primatene Mist; Primatene Tablets
	Cold/cough/allergy preparations	Advil Cold & Sinus; Alka-Seltzer Plus (many); Comtrex Severe Cold & Sinus; Congestac; Contac Cold+Flu; Dimetapp (many); Dristan Cold; PediaCare (many); Robitussin Cough, Cold & Flu; Robitussin Cough & Cold CF; Sudafed PE Cold & Cough; Theraflu (many); Triaminic (many); Tylenol Cold (many); Tylenol Sinus (many); Tylenol Allergy (many); Vicks (many)
	Hemorrhoidal products	Hemorid; Preparation H (cream, ointment, suppository)

suggests the long-term use of certain NSAIDs may increase the risk of heart attack or stroke. Furthermore, acute ingestion of large amounts of acetaminophen by adults or children can cause serious, and often fatal, hepatotoxicity. Antihistamines may cause sedation or drowsiness, especially when taken concurrently with sedative-hypnotics, tranquilizers, alcohol, or other central nervous system depressants. Antihistamines and other substances contained in OTC topical and vaginal products may induce allergic reactions.

Finally, use of OTC cough and cold preparations in the pediatric population has been under scrutiny by the FDA based on a lack of efficacy data in children less than 12 years of age and reports of serious toxicity in children. In 2008, the FDA issued an advisory alert recommending that OTC cough and cold agents (eg, products containing antitussives, expectorants, decongestants, and antihistamines) not be used in infants and children less than 2 years of age because of the potential for serious and possibly life-threatening adverse events. More recently, in October 2008, leading pharmaceutical manufacturers voluntarily modified product labels on OTC cough and cold preparations to state, "do not use" in children under 4 years of age. Further safety reviews by the FDA regarding the use of these agents in children between the ages of 2 and 11 are ongoing.

There are three major drug information sources for OTC products. *Handbook of Nonprescription Drugs* is the most comprehensive resource for OTC medications; it evaluates ingredients contained in major OTC drug classes and lists the ingredients included in many OTC products. *Nonprescription Drug* Therapy is an online reference that is updated monthly; it provides detailed OTC product information and patient counseling instructions. *Physicians' Desk Reference for Nonprescription Drugs, Dietary Supplements and Herbs*, a compendium of manufacturers' information regarding OTC products, is published annually but is somewhat incomplete with regard to the number of products included. Any health care provider who seeks more specific information regarding OTC products may find useful the references listed below.

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CASE STUDY ANSWER

OTC cold medications typically contain antihistamines (eg, brompheniramine, chlorpheniramine, diphenhydramine), antitussives (eg, dextromethorphan), expectorants (eg, guaifenesin), and nasal decongestants (eg, phenylephrine, pseudoephedrine). Systemic nasal decongestants (contained in Alka-Seltzer and Sudafed) stimulate α_1-adrenoceptors and may raise blood pressure through direct vasoconstrictor effects. Additionally, NSAIDs (contained in Advil PM) increase blood pressure and may reduce the effectiveness of antihypertensive agents. NSAIDs may also exacerbate heart failure through increased fluid retention and elevated blood pressure. Alka-Seltzer cold preparations should be avoided in patients with heart failure due to the high sodium content, which can lead to fluid retention. The sodium content in one dose of Alka-Seltzer Plus cold medicine (948 mg/dose) provides approximately half of the maximum recommended sodium allowance for patients with heart failure.

CHAPTER

64

Dietary Supplements & Herbal Medications*

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CASE STUDY

A 65-year-old man with a history of coronary artery disease, high cholesterol, type 2 diabetes, and hypertension presents with a question about a dietary supplement. He is in good health, exercises regularly, and eats a low-fat, low-salt diet. His most recent laboratory values show that his low-density lipoprotein (LDL) cholesterol is still slightly above goal at 120 mg/dL (goal < 100 mg/dL) and his hemoglobin A_{1C} is well controlled at 6%. His blood pressure is also well controlled. His medications include simvastatin, metformin, benazepril, and aspirin. He also regularly takes a vitamin B complex supplement and coenzyme Q10. He asks you if taking a garlic supplement could help to bring his LDL cholesterol down to less than 100 mg/dL. What are two rationales for why he might be using a coenzyme Q10 supplement? Are there any supplements that could increase bleeding risk if taken with aspirin?

The medical use of plants in their natural and unprocessed form undoubtedly began when the first intelligent animals noticed that certain food plants altered particular body functions. While there is a great deal of historical information about the use of plant-based supplements, there is also much unreliable information from poorly designed clinical studies that do not account for randomization errors, confounders, and—most importantly—a placebo effect that can contribute 30–50% of the observed response. Since the literature surrounding dietary supplements is evolving and much of it is not peer-reviewed, it is recommended that reputable evidence-based resources be used to help guide treatment decisions. An unbiased and regularly updated compendium of basic and clinical reports regarding botanicals is *Pharmacists Letter/Prescribers Letter Natural Medicines Comprehensive Database* (see references). Another evidence-based resource is *Natural Standard*, which includes an international, multidisciplinary collaborative website, http://www.naturalstandard.com. Unfortunately, the evidence available to these objective and unbiased evaluators is rarely adequate to permit clear conclusions. As a result, all statements regarding positive benefits should be regarded as preliminary and even conclusions regarding safety should be considered tentative at this time.

For legal purposes, "dietary supplements" are distinguished from "prescription drugs" derived from plants (morphine, digitalis, atropine, etc) by virtue of being available without a prescription and, unlike "over-the-counter medications," are legally considered dietary supplements rather than drugs. This distinction eliminates the need for proof of efficacy and safety prior to marketing and also places the burden of proof on the Food and Drug Administration (FDA) to prove that a supplement is harmful before its use can be restricted or removed from the market. Although manufacturers are prohibited from marketing unsafe or ineffective products, the FDA has met significant challenges from the supplement industry largely due to the strong lobbying effort by supplement manufacturers and the variability in interpretation of the Dietary Supplement Health and Education Act (DSHEA). DSHEA defines dietary supplements as vitamins, minerals, herbs or other botanicals, amino acids or dietary supplements used to supplement the diet by increasing dietary intake, or concentrates, metabolites, constituents, extracts, or any combination of these ingredients. For the purposes of this chapter, plant-based substances and synthetic purified

*The industry marketing these materials is replacing the terms "herbal medication" and "botanical medication" with the term "dietary supplement" in order to avoid legal liability and added governmental regulation. For the purposes of this chapter, they are identical.

chemicals will be referred to as dietary supplements. Among the purified chemicals, glucosamine, coenzyme Q10, and melatonin are of significant pharmacologic interest.

This chapter provides some historical perspective and describes the evidence provided by randomized, double-blind, placebo-controlled trials, meta-analyses, and systematic reviews involving several of the most commonly used agents in this class. Ephedrine, the active principle in Ma-huang, is discussed in Chapter 9.

HISTORICAL & REGULATORY FACTORS

Under the DSHEA, dietary supplements are not considered over-the-counter drugs in the USA but rather food supplements used for health maintenance. Although dietary supplements are regulated as food, consumers may use them in the same fashion as drugs and even use them in place of drugs or in combination with drugs.

In 1994, the United States Congress, influenced by growing "consumerism" as well as strong manufacturer lobbying efforts, passed the DSHEA. DSHEA required the establishment of Good Manufacturing Practice (GMP) standards for the supplement industry; however, it was not until 2007 that the FDA issued a final rule on the proposed GMP standards. This 13-year delay allowed supplement manufacturers to self-regulate the manufacturing process and resulted in many instances of adulteration, misbranding, and contamination. Therefore, much of the criticism regarding the dietary supplement industry involves a lack of product purity and variations in potency. Under the new GMP standards, large and small dietary supplement manufacturers should now be in compliance with this legislation. The FDA, however, has limited resources to adequately investigate and oversee compliance with manufacturing standards, particularly since many ingredient suppliers are based overseas. Furthermore, the dietary supplement ingredient supply chain is complex and federal regulators are not able to adequately inspect manufacturing facilities in a timely or efficient matter.

Because of the problems that resulted from self-regulation, another law, the Dietary Supplement and Non-Prescription Drug Consumer Protection Act, was approved in 2006. This law requires manufacturers, packers, or distributors of supplements to submit reports of serious adverse events to the FDA. Serious adverse events are defined as death, a life-threatening event, hospitalization, a persistent or significant disability or incapacity, congenital anomaly or birth defect, or an adverse event that requires medical or surgical intervention to prevent such outcomes based on reasonable medical judgment. These reports are intended to identify trends in adverse effects and would help to alert the public to safety issues.

CLINICAL ASPECTS OF THE USE OF BOTANICALS

Many United States consumers have embraced the use of dietary supplements as a "natural" approach to their health care. Unfortunately, misconceptions regarding safety and efficacy of the agents are common, and the fact that a substance can be called "natural" does not of course guarantee its safety. In fact, these products may be inherently inert, toxic, or may have been adulterated, misbranded, or contaminated either intentionally or unintentionally in a variety of ways.

Adverse effects have been documented for a variety of dietary supplements; however, under-reporting of adverse effects is likely since consumers do not routinely report, and do not know how to report an adverse effect if they suspect that the event was caused by consumption of a supplement. Furthermore, chemical analysis is rarely performed on the products involved, including those products that are described in the literature as being linked to an adverse event. This leads to confusion about whether the primary ingredient or an adulterant caused the adverse effect. In some cases, the chemical constituents of the herb can clearly lead to toxicity. Some of the herbs that should be used cautiously or not at all are listed in Table 64–1.

An important risk factor in the use of dietary supplements is the lack of adequate testing for drug interactions. Since botanicals may contain hundreds of active and inactive ingredients, it is very difficult and costly to study potential drug interactions when they are combined with other medications. This may present significant risks to patients.

BOTANICAL SUBSTANCES

ECHINACEA (*ECHINACEA PURPUREA*)

Chemistry

The three most widely used species of *Echinacea* are *Echinacea purpurea, E pallida,* and *E angustifolia.* The chemical constituents include flavonoids, lipophilic constituents (eg, alkamides, polyacetylenes), water-soluble polysaccharides, and water-soluble caffeoyl conjugates (eg, echinacoside, cichoric acid, caffeic acid). Within any marketed echinacea formulation, the relative amounts of these components are dependent upon the species used, the method of manufacture, and the plant parts used. *E purpurea* has been the most widely studied in clinical trials. Although the active constituents of echinacea are not completely known, cichoric acid from *E purpurea* and echinacoside from *E pallida and E angustifolia,* as well as alkamides and polysaccharides, are most often noted as having immune-modulating properties. Most commercial formulations, however, are not standardized for any particular constituent.

Pharmacologic Effects

A. Immune Modulation

The effect of echinacea on the immune system is controversial. In vivo human studies using commercially marketed formulations of *E purpurea* have shown increased phagocytosis, total circulating white blood cells, monocytes, neutrophils, and natural killer cells but not immunostimulation. In vitro, *E purpurea* juice increased production of interleukins-1, -6, and -10, and tumor necrosis factor-α by human macrophages. Enhanced natural killer cell activity and antibody-dependent cellular toxicity was also observed

TABLE 64–1 Various supplements and some associated risks.

Commercial Name, Scientific Name, Plant Parts	Intended Use	Toxic Agents, Effects	Comments
Aconite *Aconitum* species	Analgesic	Alkaloid, cardiac and central nervous system effects	Avoid
Aristolochic acid *Aristolochia* species	Traditional Chinese medicine; various uses	Carcinogen, nephrotoxicity	Avoid
Black cohosh *Cimicifuga racemosa*	Menopausal symptoms	Hepatotoxicity	Avoid[1]
Borage *Borago officinalis* Tops, leaves	Anti-inflammatory; diuretic	Pyrrolizidine alkaloids, hepatotoxicity	Avoid
Chaparral *Larrea tridentata* Twigs, leaves	Anti-infective; antioxidant; anticancer	Hepatotoxicity	Avoid
Coltsfoot *Tussilago farfara* Leaves, flower	Upper respiratory tract infections	Pyrrolizidine alkaloids, hepatotoxicity	Avoid ingestion of any parts of plant; leaves may be used topically for anti-inflammatory effects for up to 4–6 weeks
Comfrey *Symphytum* species Leaves and roots	Internal digestive aid; topical for wound healing	Pyrrolizidine alkaloids, hepatotoxicity	Avoid ingestion; topical use should be limited to 4–6 weeks
Ephedra, Ma-huang *Ephedra* species	Diet aid; stimulant; bronchodilator	Central nervous system toxicity, cardiac toxicity	Avoid in patients at risk for stroke, myocardial infarction, uncontrolled blood pressure, seizures, general anxiety disorder
Germander *Teucrium chamaedrys* Leaves, tops	Diet aid	Hepatotoxicity	Avoid
Gland-derived extracts (thymus, adrenal, thyroid)	Hormone replacement	Risk of bacterial, viral, or prion transmission; variable hormone content	Avoid
Human placenta derivatives	Antirheumatic; anti-inflammatory	Risk of bacterial, viral, or prion transmission	Avoid
Jin Bu Huan	Analgesic; sedative	Hepatotoxicity	Avoid
Kava-kava	Anxiety	Hepatotoxicity	Avoid
Pennyroyal *Mentha pulegium* or *Hedeoma pulegioides* Extract	Digestive aid; induction of menstrual flow; abortifacient	Pulegone and pulegone metabolite, liver failure, renal failure	Avoid
Poke root *Phytolacca americana*	Antirheumatic	Hemorrhagic gastritis	Avoid
Royal jelly *Apis mellifera* (honeybee)	Tonic	Bronchospasm, anaphylaxis	Avoid in patients with chronic allergies or respiratory diseases; asthma, chronic obstructive pulmonary disease, emphysema, atopy
Sassafras *Sassafras albidum* Root bark	Blood thinner	Safrole oil, hepatocarcinogen in animals	Avoid

[1]Cases of hepatotoxicity have occurred; these cases are rare given the widespread use of black cohosh

with *E purpurea* extract in cell lines from both healthy and immunocompromised patients. Studies using the isolated purified polysaccharides from *E purpurea* have also shown cytokine activation. Polysaccharides by themselves, however, are unlikely to accurately reproduce the activity of the entire extract.

B. Anti-Inflammatory Effects

Certain echinacea constituents have demonstrated anti-inflammatory properties in vitro. Inhibition of cyclooxygenase, 5-lipoxygenase, and hyaluronidase may be involved. In animals, application of *E purpurea* prior to application of a topical irritant reduced

both paw and ear edema. Despite these laboratory findings, randomized, controlled clinical trials involving echinacea for wound healing have not been performed in humans.

C. Antibacterial, Antifungal, Antiviral, and Antioxidant Effects

In vitro studies have reported some antibacterial, anti-fungal, antiviral, and antioxidant activity with echinacea constituents. In vitro, a standardized extract of the aerial parts of *E purpurea* demonstrated potent virucidal (MIC_{100} < 1 μg/mL) against influenza and herpes simplex viruses and potent bactericidal activity against *Streptococcus pyogenes*, *Haemophilus influenzae,* and *Legionella pneumophila* in human bronchial cells. The pro-inflammatory cytokine release caused by these viruses and bacteria were also reversed by echinacea.

Clinical Trials

Echinacea is most often used to enhance immune function in individuals who have colds and other respiratory tract infections.

Two recent reviews have assessed the efficacy of echinacea for this primary indication. A review by the Cochrane Collaboration involved 16 randomized trials with 22 comparisons. Trials were included if they involved monopreparations of echinacea for cold treatment or prevention. Prevention trials involving rhinovirus inoculation versus natural cold development were excluded. Overall, the review concluded that there was some evidence of efficacy for the aerial (above-ground) parts of *E purpurea* plants in the early treatment of colds but that efficacy for prevention and for other species of echinacea was not clearly shown. Among the placebo-controlled comparisons for cold treatment, echinacea was superior in nine trials, showed a positive trend in one trial, and was insignificant in six trials.

A separate meta-analysis involving 14 randomized, placebo-controlled trials of echinacea for cold treatment or prevention was published in *Lancet*. In this review, echinacea decreased the odds of developing clear signs and symptoms of a cold by 58% and decreased symptom duration by 1.25 days. This review, however, was confounded by the inclusion of four clinical trials involving multi-ingredient echinacea preparations, as well as three studies using rhinovirus inoculation versus natural cold development.

Echinacea has been used investigationally to enhance hematologic recovery following chemotherapy. It has also been used as an adjunct in the treatment of urinary tract and vaginal fungal infections. These indications require further research before they can be accepted in clinical practice. *E purpurea* is ineffective in treating recurrent genital herpes.

Adverse Effects

Flu-like symptoms (eg, fever, shivering, headache, vomiting) have been reported following the intravenous use of echinacea extracts. Adverse effects with oral commercial formulations are minimal and most often include unpleasant taste, gastrointestinal upset, or rash. In one large clinical trial, pediatric patients using an oral echinacea product were significantly more likely to develop a rash (~ 5%) than those taking placebo.

Drug Interactions & Precautions

Until the role of echinacea in immune modulation is better defined, this agent should be avoided in patients with immune deficiency disorders (eg, AIDS, cancer), autoimmune disorders (eg, multiple sclerosis, rheumatoid arthritis), and patients with tuberculosis. While there are no reported drug interactions for echinacea, some preparations have a high alcohol content and should not be used with medications known to cause a disulfiram-like reaction. In theory, echinacea should also be avoided in persons taking immunosuppressant medications (eg, organ transplant recipients).

Dosage

It is recommended to follow the dosing on the package label, as there may be slight variations in dose based on the product manufacturer. Standardized preparations made from the above-ground parts of *E purpurea* (Echinaforce, Echinaguard) as an alcoholic extract or fresh pressed juice have some clinical support and may be taken within the first 24 hours of cold symptoms. It should not be used as a preventative agent or for longer than 10–14 days.

GARLIC (*ALLIUM SATIVUM*)

Chemistry

The pharmacologic activity of garlic involves a variety of organosulfur compounds. Dried and powdered formulations contain many of the organosulfur compounds found in raw garlic and will likely be standardized to allicin or alliin content. Allicin is responsible for the characteristic odor of garlic, and alliin is its chemical precursor. Dried powdered formulations are often enteric-coated to protect the enzyme allinase (the enzyme that converts alliin to allicin) from degradation by stomach acid. Aged garlic extract has also been studied in clinical trials, but to a lesser degree than dried, powdered garlic. Aged garlic extract contains no alliin or allicin and is odor-free. Its primary constituents are water-soluble organosulfur compounds, and packages may carry a standardization to the compound *S*-allylcysteine.

Pharmacologic Effects

A. Cardiovascular Effects

In vitro, allicin and related compounds inhibit HMG-CoA reductase, which is involved in cholesterol biosynthesis (see Chapter 35), and exhibit antioxidant properties. Several clinical trials have investigated the lipid-lowering potential of garlic. The most recent meta-analysis involved 29 randomized, double-blind, placebo-controlled trials and found a small but significant reduction in both total cholesterol (–0.19 mmol/L) and triglycerides (–0.011 mmol/L), but no effect on low- or high-density lipoproteins. These results echoed another review in patients with baseline hypercholesterolemia (total cholesterol > 200 mg/dL) that found a significant reduction in total cholesterol of 5.8% using garlic for

2–6 months. The effect of garlic became insignificant, however, when dietary controls were in place. Results of a study by the National Center of Complementary and Alternative Medicine (NCCAM) evaluating three different sources of garlic (fresh, powdered, and aged garlic extract) in adults with moderately elevated cholesterol contradicted the findings of these reviews and found no effect of any formulation of garlic versus placebo on LDL cholesterol. Cumulatively, these data indicate that garlic is unlikely to be effective in reducing cholesterol to a clinically significant extent. Clinical trials report antiplatelet effects (possibly through inhibition of thromboxane synthesis or stimulation of nitric oxide synthesis) following garlic ingestion. A majority of human studies also suggest enhancement of fibrinolytic activity. These effects in combination with antioxidant effects (eg, increased resistance to low-density lipoprotein oxidation) and reductions in total cholesterol might be beneficial in patients with atherosclerosis. A randomized, controlled trial among persons with advanced coronary artery disease who consumed dried powdered garlic for 4 years showed significant reductions in secondary markers (plaque accumulation in the carotid and femoral arteries) as compared with placebo, but primary endpoints (death, stroke, myocardial infarction) were not assessed.

Garlic constituents may affect blood vessel elasticity and blood pressure. A variety of mechanisms have been proposed. There have been a limited number of randomized, controlled trials in humans for this indication. Ten trials were included in a systematic review and meta-analysis that found no effect on systolic or diastolic pressure in patients without elevated systolic blood pressure but a significant reduction in systolic and diastolic pressure among the three trials involving patients with elevated systolic blood pressure.

B. Endocrine Effects

The effect of garlic on glucose homeostasis does not appear to be significant in persons with diabetes. Certain organosulfur constituents in garlic, however, have demonstrated hypoglycemic effects in nondiabetic animal models.

C. Antimicrobial Effects

The antimicrobial effect of garlic has not been extensively studied in clinical trials. Allicin has been reported to have in vitro activity against some gram-positive and gram-negative bacteria as well as fungi (*Candida albicans*), protozoa (*Entamoeba histolytica*), and certain viruses. The primary mechanism involves the inhibition of thiol-containing enzymes needed by these microbes. Given the availability of safe and effective prescription antimicrobials, the usefulness of garlic in this area appears limited.

D. Antineoplastic Effects

In rodent studies, garlic inhibits procarcinogens for colon, esophageal, lung, breast, and stomach cancer, possibly by detoxification of carcinogens and reduced carcinogen activation. Several epidemiologic case-control studies demonstrate a reduced incidence of stomach, esophageal, and colorectal cancers in persons with high dietary garlic consumption.

Adverse Effects

Following oral ingestion, adverse effects may include nausea (6%), hypotension (1.3%), allergy (1.1%), and bleeding (rare). Breath and body odor have been reported with an incidence of 20–40% at recommended doses using enteric-coated powdered garlic formulations. Contact dermatitis may occur with the handling of raw garlic.

Drug Interactions & Precautions

Because of reported antiplatelet effects, patients using anticlotting medications (eg, warfarin, aspirin, ibuprofen) should use garlic cautiously. Additional monitoring of blood pressure and signs and symptoms of bleeding is warranted. Garlic may reduce the bioavailability of saquinavir, an antiviral protease inhibitor, but it does not appear to affect the bioavailability of ritonavir.

Dosage

Dried, powdered garlic products should be standardized to contain 1.3% alliin (the allicin precursor) or have an allicin-generating potential of 0.6%. Enteric-coated formulations are recommended to minimize degradation of the active substances. A daily dose of 600–900 mg/d of powdered garlic is most common. This is equivalent to one clove of raw garlic (2–4 g) per day.

GINKGO (*GINKGO BILOBA*)

Chemistry

Ginkgo biloba extract is prepared from the leaves of the ginkgo tree. The most common formulation is prepared by concentrating 50 parts of the crude leaf to prepare one part of extract. The active constituents in ginkgo are flavone glycosides and terpenoids (ie, ginkgolides A, B, C, J, and bilobalide).

Pharmacologic Effects

A. Cardiovascular Effects

In animal models and some human studies, ginkgo has been shown to increase blood flow, reduce blood viscosity, and promote vasodilation, thus enhancing tissue perfusion. Enhancement of endogenous nitric oxide (see Chapter 19) and antagonism of platelet-activating factor have been observed in animal models.

Ginkgo biloba has been studied for its effects on mild to moderate occlusive peripheral arterial disease. Among 11 randomized, placebo-controlled studies involving 477 participants using standardized ginkgo leaf extract (EGb761) for up to 6 months, a nonsignificant trend toward improvements in pain-free walking distance (increase of 64.5 meters) was observed ($p = .06$).

The Ginkgo Evaluation of Memory (GEM) study evaluated cardiovascular outcomes associated with the long-term use of ginkgo for 6 years in 3069 patients over 75 years of age. Daily use of 240 mg/d EGb761 did not affect the incidence of hypertension or reduce blood pressure among persons with hypertension or prehypertension. No significant effects in cardiovascular disease

mortality or events or hemorrhagic stroke were observed. There was, however, a significant reduction in peripheral vascular disease events in the ginkgo arm versus the placebo arm.

B. Metabolic Effects

Antioxidant and radical-scavenging properties have been observed for the flavonoid fraction of ginkgo as well as some of the terpene constituents. In vitro, ginkgo has been reported to have superoxide dismutase-like activity and superoxide anion- and hydroxyl radical-scavenging properties. The flavonoid fraction has also been observed to have anti-apoptotic properties. In some studies, it has also demonstrated a protective effect in limiting free radical formation in animal models of ischemic injury and in reducing markers of oxidative stress in patients undergoing coronary artery bypass surgery.

C. Central Nervous System Effects

In aged animal models, chronic administration of ginkgo for 3–4 weeks led to modifications in central nervous system receptors and neurotransmitters. Receptor densities increased for muscarinic, α_2, and 5-HT_{1a} receptors and decreased for β adrenoceptors. Increased serum levels of acetylcholine and norepinephrine and enhanced synaptosomal reuptake of serotonin have also been reported. Additional effects include reduced corticosterone synthesis and inhibition of amyloid-beta fibril formation.

Ginkgo has been used to treat cerebral insufficiency and dementia of the Alzheimer type. The term *cerebral insufficiency*, however, includes a variety of manifestations ranging from poor concentration and confusion to anxiety and depression as well as physical complaints such as hearing loss and headache. For this reason, studies evaluating cerebral insufficiency tend to be more inclusive and difficult to assess than trials evaluating dementia. An updated meta-analysis of ginkgo for cognitive impairment or dementia was performed by the Cochrane Collaboration. They reviewed 36 randomized, double-blind, placebo-controlled trials ranging in length from 3 to 52 weeks. Significant improvements in cognition and activities of daily living were observed at 12 but not 24 weeks. Significant improvements in clinical global improvement, however, were observed at 24 but not 12 weeks. The authors concluded that the effects of ginkgo in the treatment of cognitive impairment and dementia were unpredictable and unlikely to be clinically relevant. In the GEM study, the effects of gingko as a prophylactic agent to prevent progression to dementia were assessed. No benefit was observed with 6 years of ginkgo treatment. To date, there is no known therapy that prevents progression to dementia.

D. Miscellaneous Effects

Ginkgo has been studied for its effects in allergic and asthmatic bronchoconstriction, short-term memory in healthy, non-demented adults, erectile dysfunction, tinnitus and hearing loss, and macular degeneration. For each of these conditions, there is insufficient evidence to warrant clinical use.

Adverse Effects

Adverse effects have been reported with a frequency comparable to that of placebo. These include nausea, headache, stomach upset, diarrhea, allergy, anxiety, and insomnia. A few case reports noted bleeding complications in patients using ginkgo. In a few of these cases, the patients were also using either aspirin or warfarin.

Drug Interactions & Precautions

Ginkgo may have antiplatelet properties and should not be used in combination with antiplatelet or anticoagulant medications. One case of an enhanced sedative effect was reported when ginkgo was combined with trazodone. Seizures have been reported as a toxic effect of ginkgo, most likely related to seed contamination in the leaf formulations. Uncooked ginkgo seeds are epileptogenic due to the presence of ginkgotoxin. Ginkgo formulations should be avoided in individuals with preexisting seizure disorders.

Dosage

Ginkgo biloba dried leaf extract is usually standardized to contain 24% flavone glycosides and 6% terpene lactones. The daily dose ranges from 120 to 240 mg of the dried extract in two or three divided doses.

GINSENG

Chemistry

Ginseng may be derived from any of several species of the genus *Panax.* Of these, crude preparations or extracts of *Panax ginseng*, the Chinese or Korean variety, and *P quinquefolium*, the American variety, are most often available to consumers in the United States. The active principles appear to be the triterpenoid saponin glycosides called ginsenosides or panaxosides, of which there are approximately 30 different types. It is recommended that commercial *P ginseng* formulations be standardized to contain 4–10% ginsenosides.

Other plant materials are commonly sold under the name ginseng but are not from *Panax* species. These include Siberian ginseng (*Eleutherococcus senticosus*) and Brazilian ginseng (*Pfaffia paniculata*). Of these, Siberian ginseng is more widely available in the USA. Siberian ginseng contains eleutherosides but no ginsenosides. Currently, there is no recommended standardization for eleutheroside content in Siberian ginseng products.

Pharmacology

An extensive literature exists on the potential pharmacologic effects of ginsenosides. Unfortunately, the studies differ widely in the species of *Panax* used, the ginsenosides studied, the degree of purification applied to the extracts, the animal species studied, and the measurements used to evaluate the responses. A remarkable list of reported beneficial pharmacologic effects include modulation of immune function (induced mRNA expression for interleukins-2 and -1α, interferon-γ, and granulocyte-macrophage colony-stimulating factor; activated B and T cells, natural killer cells, and macrophages); central nervous system effects (increased proliferating ability of neural progenitors; increased central levels of acetylcholine, serotonin, norepinephrine, and dopamine in the

cerebral cortex); antioxidant activity; anti-inflammatory effects (inhibition of TNF-α, interleukin-1β, and vascular and intracellular cell adhesion molecules); antistress activity (ie, stimulation of pituitary-adreno-cortical system, agonist at glucocorticoid receptor); analgesia (inhibition of substance P); vasoregulatory effects (increased endothelial nitric oxide and inhibition of prostacyclin production); cardioprotective activity (reduced ventricular remodeling and cardiac hypertrophy in animal models of myocardial ischemia); antiplatelet activity; improved glucose homeostasis (increased insulin release, number of insulin receptors, and insulin sensitivity); and anticancer properties (reduced tumor angiogenesis, increased tumor cell apoptosis).

Clinical Trials

Ginseng is most often claimed to help improve physical and mental performance or to function as an "adaptogen," an agent that helps the body to return to normal when exposed to stressful or noxious stimuli. Unfortunately, the clinical trials evaluating ginseng for these indications have shown few if any benefits. Some randomized controlled trials evaluating "quality of life" have claimed significant benefits in some subscale measures of quality of life but rarely in overall composite scores using *P ginseng*. Better results have been observed with *P quinquefolium* and *P ginseng* in lowering postprandial glucose indices in subjects with and without diabetes. This was the subject of a recent systematic review in which 15 studies (13 randomized and 2 nonrandomized) were evaluated. Nine of the studies reported significant reductions in blood glucose. Newer randomized, placebo-controlled trials have reported some immunomodulating benefits of *P quinquefolium* (four trials) and *P ginseng* (one trial) in preventing upper respiratory tract infections. Use of ginseng for 2–4 months in healthy seniors may reduce the incidence of acquiring the common cold as well as the duration of symptoms. Because of heterogeneity in these trials, however, these findings are insufficient to warrant recommending the use of ginseng for this indication at this time. Two case-control studies, a cohort study and one randomized, double-blind, placebo-controlled study, also suggest a non-organ-specific cancer preventative effect with long-term administration of *P ginseng*. In summary, the strongest support for use of *P ginseng* or *P quinquefolium* currently relates to its effects in cold prevention, lowering postprandial glucose, and nonspecific cancer prevention.

Adverse Effects

Vaginal bleeding and mastalgia have been described in case reports. Central nervous system stimulation (eg, insomnia, nervousness) and hypertension have been reported in patients using high doses (more than 3 g/d) of *P ginseng*. Methylxanthines found in the ginseng plant may contribute to this effect. Vasoregulatory effects of ginseng are unlikely to be clinically significant.

Drug Interactions & Precautions

Irritability, sleeplessness, and manic behavior have been reported in psychiatric patients using ginseng in combination with other medications (phenelzine, lithium, neuroleptics). Ginseng should be used cautiously in patients taking any psychiatric, estrogenic, or hypoglycemic medications. Ginseng has antiplatelet properties and should not be used in combination with warfarin. Cytokine stimulation has been claimed for both *P ginseng* and *P quinquefolium* in vitro and in animal models. In a randomized, double-blind, placebo-controlled study, *P ginseng* significantly increased natural killer cell activity versus placebo with 8 and 12 weeks of use. Immunocompromised individuals, those taking immune stimulants, and those with autoimmune disorders should use ginseng products with caution.

Dosing

One to two grams of the crude *P ginseng* root or its equivalent is considered standard dosing. Two hundred milligrams of standardized *P ginseng* extract is equivalent to 1 g of the crude root. Ginsana has been used as a standardized extract in some clinical trials and is available in the USA.

MILK THISTLE (*SILYBUM MARIANUM*)

Chemistry

The fruit and seeds of the milk thistle plant contain a lipophilic mixture of flavonolignans known as silymarin. Silymarin comprises 2–3% of the dried herb and is composed of three primary isomers, silybin (also known as silybinin or silibinin), silychristin (silichristin), and silydianin (silidianin). Silybin is the most prevalent and potent of the three isomers and accounts for about 50% of the silymarin complex. Products should be standardized to contain 70–80% silymarin.

Pharmacologic Effects

A. Liver Disease

In animal models, milk thistle purportedly limits hepatic injury associated with a variety of toxins, including *Amanita* mushrooms, galactosamine, carbon tetrachloride, acetaminophen, radiation, cold ischemia, and ethanol. In vitro studies and some in vivo studies demonstrate that silymarin reduces lipid peroxidation, scavenges free radicals, and enhances glutathione and superoxide dismutase levels. This may contribute to membrane stabilization and reduce toxin entry.

Milk thistle appears to have anti-inflammatory properties. In vitro, silybin strongly and noncompetitively inhibits lipoxygenase activity and reduces leukotriene formation. Inhibition of leukocyte migration has been observed in vivo and may be a factor when acute inflammation is present. Silymarin also inhibits tumor necrosis factor-α-mediated activation of nuclear factor kappa B (NF-κB), which promotes inflammatory responses. One of the most unusual mechanisms claimed for milk thistle involves an increase in RNA polymerase I activity in nonmalignant hepatocytes but not in hepatoma or other malignant cell lines. By increasing this enzyme's activity, enhanced protein synthesis and cellular regeneration may occur in healthy but not malignant cells.

In an animal model of cirrhosis, it reduced collagen accumulation, and in an in vitro model it reduced expression of the fibrogenic cytokine transforming growth factor-β. If confirmed, milk thistle may have a role in the treatment of hepatic fibrosis.

In animal models, silymarin has a dose-dependent stimulatory effect on bile flow that could be beneficial in cases of cholestasis. To date, however, there is insufficient evidence to warrant the use of milk thistle for these indications.

B. Chemotherapeutic Effects

Preliminary in vitro and animal studies of the effects of silymarin and silybinin have been carried out with several cancer cell lines. In murine models of skin cancer, silybinin and silymarin were said to reduce tumor initiation and promotion. Induction of apoptosis has also been reported using silymarin in a variety of malignant human cell lines (eg, melanoma, prostate, leukemia cells, bladder transitional-cell papilloma cells, and hepatoma cells). Inhibition of cell growth and proliferation by inducing a G_1 cell cycle arrest has also been claimed in cultured human breast and prostate cancer cell lines. The use of milk thistle in the clinical treatment of cancer has not yet been adequately studied but preliminary trials are under way.

C. Lactation

Historically, milk thistle has been used by herbalists and midwives to induce lactation in pregnant or postpartum women. In female rats, milk thistle increases prolactin production. As such, it is possible that it could have an effect on human breast milk production. Clinical trial data are lacking, however, for this indication, as are safety data on nursing mothers and infants. Until further data become available, milk thistle should not be used for this indication.

Clinical Trials

Milk thistle has been used to treat acute and chronic viral hepatitis, alcoholic liver disease, and toxin-induced liver injury in human patients. A systematic review of 13 randomized trials involving 915 patients with alcoholic liver disease or hepatitis B or C found no significant reductions in all-cause mortality, liver histopathology, or complications of liver disease with 6 months of use. A significant reduction in liver-related mortality was claimed using the data from all the surveyed trials, but not when the data were limited to trials of better design and controls. It was concluded that the effects of milk thistle in improving liver function or mortality from liver disease are currently poorly substantiated. Until additional well-designed clinical trials (possibly exploring higher doses) can be performed, a clinical effect can be neither supported nor ruled out.

Although milk thistle has not been confirmed as an antidote following acute exposure to liver toxins in humans, parenteral silybin is nevertheless marketed and used in Europe as an antidote in *Amanita phalloides* mushroom poisoning. This use is based on favorable outcomes reported in case-control studies.

Adverse Effects

Milk thistle has rarely been reported to cause adverse effects when used at recommended doses. In clinical trials, the incidence of adverse effects (eg, gastrointestinal upset, dermatologic, headaches) was comparable to that of placebo. At high doses (> 1500 mg), it can have a laxative effect caused by stimulation of bile flow and secretion.

DRUG INTERACTIONS, PRECAUTIONS, & DOSING

There are no reported drug-drug interactions or precautions for milk thistle. Recommended dosage is 280–420 mg/d, calculated as silybin, in three divided doses.

ST. JOHN'S WORT (*HYPERICUM PERFORATUM*)

Chemistry

St. John's wort, also known as hypericum, contains a variety of constituents that might contribute to its claimed pharmacologic activity in the treatment of depression. Hypericin, a marker of standardization for currently marketed products, was thought to be the primary antidepressant constituent. Recent attention has focused on hyperforin, but a combination of several compounds is probably involved. Commercial formulations are usually prepared by soaking the dried chopped flowers in methanol to create a hydroalcoholic extract that is then dried.

Pharmacologic Effects

A. Antidepressant Action

The hypericin fraction was initially reported to have MAO-A and -B inhibitor properties. Later studies found that the concentration required for this inhibition was higher than that achieved with recommended dosages. In vitro studies using the commercially formulated hydroalcoholic extract have shown inhibition of nerve terminal reuptake of serotonin, norepinephrine, and dopamine. While the hypericin constituent did not show reuptake inhibition for any of these systems, the hyperforin constituent did. Chronic administration of the commercial extract has also been reported to significantly down-regulate the expression of cortical β adrenoceptors and up-regulate the expression of serotonin receptors ($5\text{-}HT_2$) in a rodent model.

Other effects observed in vitro include sigma receptor binding using the hypericin fraction and GABA receptor binding using the commercial extract. Interleukin-6 production is also reduced in the presence of the extract.

1. Clinical trials for depression—The most recent systematic review and meta-analysis involved 29 randomized, double-blind, controlled trials (18 compared St. John's wort to placebo, 5 to tricyclic antidepressants, and 12 to selective serotonin reuptake inhibitors [SSRIs]). Only studies meeting defined classification criteria for major depression were included. St. John's wort was reported to be more efficacious than placebo and equivalent to prescription reference treatments including the SSRIs for mild to

moderate depression but with fewer side effects. Most trials used 900 mg/d of St. John's wort for 4–12 weeks. Depression severity was mild to moderate in 19 trials, moderate to severe in 9 trials, and not stated in one trial. These data support a role for St. John's wort in relieving symptoms of major depression.

St. John's wort has been studied for several other indications related to mood, including premenstrual dysphoric disorder, climacteric complaints, somatoform disorders, and anxiety. These studies are too few in number, however, to draw any firm conclusions regarding efficacy.

B. Antiviral and Anticarcinogenic Effects

The hypericin constituent of St. John's wort is photolabile and can be activated by exposure to certain wavelengths of visible or ultraviolet A light. Parenteral formulations of hypericin (photoactivated just before administration) have been used investigationally to treat HIV infection (given intravenously) and basal and squamous cell carcinoma (given by intralesional injection). In vitro, photoactivated hypericin inhibits a variety of enveloped and non-enveloped viruses as well as the growth of cells in some neoplastic tissues. Inhibition of protein kinase C and inhibition of singlet oxygen radical generation have been proposed as possible mechanisms. The latter could inhibit cell growth or cause cell apoptosis. These studies were carried out using the isolated hypericin constituent of St. John's wort; the usual hydroalcoholic extract of St. John's wort has not been studied for these indications and should not be recommended for patients with viral illness or cancer.

Adverse Effects

Photosensitization is related to the hypericin and pseudohypericin constituents in St. John's wort. Consumers should be instructed to wear sunscreen and eye protection while using this product when exposed to the sun. Hypomania, mania, and autonomic arousal have also been reported in patients using St. John's wort.

Drug Interactions & Precautions

Inhibition of reuptake of various amine transmitters has been highlighted as a potential mechanism of action for St. John's wort. Drugs with similar mechanisms (ie, antidepressants, stimulants) should be used cautiously or avoided in patients using St. John's wort due to the risk of serotonin syndrome (see Chapters 16 and 30). This herb may induce hepatic CYP enzymes (3A4, 2C9, 1A2) and the P-glycoprotein drug transporter. This has led to case reports of subtherapeutic levels of numerous drugs, including digoxin, birth control drugs (and subsequent pregnancy), cyclosporine, HIV protease and nonnucleoside reverse transcriptase inhibitors, warfarin, irinotecan, theophylline, and anticonvulsants.

Dosage

The most common commercial formulation of St. John's wort is the dried hydroalcoholic extract. Products should be standardized to 2–5% hyperforin, although most still bear the older standardized marker of 0.3% hypericin. The recommended dosing for mild to moderate depression is 900 mg of the dried extract per day in three divided doses. Onset of effect may take 2–4 weeks. Long-term benefits beyond 12 weeks have not been sufficiently studied.

SAW PALMETTO (*SERENOA REPENS OR SABAL SERRULATA*)

Chemistry

The active constituents in saw palmetto berries are not well defined. Phytosterols (eg, β-sitosterol), aliphatic alcohols, polyprenic compounds, and flavonoids are all present. Marketed preparations are dried lipophilic extracts that are generally standardized to contain 85–95% fatty acids and sterols.

Pharmacologic Effects

Saw palmetto is most often promoted for the treatment of benign prostatic hyperplasia (BPH). Enzymatic conversion of testosterone to dihydrotestosterone (DHT) by 5α-reductase is inhibited by saw palmetto in vitro. Specifically, saw palmetto shows a noncompetitive inhibition of both isoforms (I and II) of this enzyme, thereby reducing DHT production. In vitro, saw palmetto also inhibits the binding of DHT to androgen receptors. Additional effects that have been observed in vitro include inhibition of prostatic growth factors, blockade of α_1 adrenoceptors, and inhibition of inflammatory mediators produced by the 5-lipoxygenase pathway.

The clinical pharmacology of saw palmetto in humans is not well defined. One week of treatment in healthy volunteers failed to influence 5α-reductase activity, DHT concentration, or testosterone concentration. Six months of treatment in patients with BPH also failed to affect prostate-specific antigen (PSA) levels, a marker that is typically reduced by enzymatic inhibition of 5α-reductase. In contrast, other researchers have reported a reduction in epidermal growth factor, DHT levels, and antagonist activity at the nuclear estrogen receptor in the prostate after 3 months of treatment with saw palmetto in patients with BPH.

Clinical Trials

The most recent review involved 30 randomized controlled trials in men with symptoms consistent with BPH. Fourteen trials used saw palmetto monotherapy compared to placebo and found no significant improvement in most urologic symptoms (eg, international prostate symptom scores, peak flow, prostate size). Although nocturia was significantly improved with saw palmetto compared to placebo, when studies were limited to those of higher quality and larger sample size, this significance was lost. In contrast, saw palmetto, 320 mg/d, was shown to have comparable efficacy to 5 mg/d of finasteride (a prescription 5α-reductase inhibitor) and 0.4 mg/d of tamsulosin (a prescription α blocker) in one randomized, double-blind, clinical trial each, lasting 6 months and 1 year, respectively. These two trials lacked placebo controls.

Adverse Effects

Adverse effects are reported with an incidence of 1–3%. The most common include abdominal pain, nausea, diarrhea, fatigue, headache, decreased libido, and rhinitis. Saw palmetto has been associated with a few rare case reports of pancreatitis, liver damage, and increased bleeding risk, but due to confounding factors, causality remains inconclusive. In comparison to tamsulosin and finasteride, saw palmetto was claimed to be less likely to affect sexual function (eg, ejaculation).

Drug Interactions, Precautions, & Dosing

No drug-drug interactions have been reported for saw palmetto. Because saw palmetto has no effect on the PSA marker, it will not interfere with prostate cancer screening using this test. Recommended dosing of a standardized dried extract (containing 85–95% fatty acids and sterols) is 160 mg orally twice daily. Patients should be instructed that it may take 4–6 weeks for onset of clinical effects.

■ PURIFIED NUTRITIONAL SUPPLEMENTS

COENZYME Q10

Coenzyme Q10, also known as CoQ, CoQ10, and ubiquinone, is found in the mitochondria of many organs, including the heart, kidney, liver, and skeletal muscle. After ingestion, the reduced form of coenzyme Q10, ubiquinol, predominates in the systemic circulation. Coenzyme Q10 is a potent antioxidant and may have a role in maintaining healthy muscle function, although the clinical significance of this effect is unknown. Reduced serum levels have been reported in Parkinson's disease.

Clinical Uses

A. Hypertension

In early clinical trials, small but significant reductions in systolic and diastolic blood pressure were reported after 8–10 weeks of coenzyme Q10 supplementation. The exact mechanism is unknown but, if correct, might be related to the antioxidant and vasodilating properties of coenzyme Q10. In three well-designed randomized, placebo-controlled trials, coenzyme Q10 was reported to significantly lower systolic blood pressure and diastolic blood pressure by 11 mm Hg and 7 mm Hg, respectively, as compared with no change in the placebo groups. Whether coenzyme Q10 can be used to lower blood pressure remains unclear. Since all three clinical trials have shown a benefit, it is possible that publication bias may be present. Furthermore, an exaggerated treatment effect may occur as adequate randomization, blinding, and concealment of allocation have been questioned for these studies.

B. Heart Failure

Low endogenous coenzyme Q10 levels have been associated with worse heart failure outcomes, but this association is likely because low levels are a marker for more advanced heart failure, rather than a predictor of disease. Despite these findings, coenzyme Q10 is often advocated to improve heart muscle function in patients with heart failure. According to the most recent meta-analysis, coenzyme Q10 was shown to improve ejection fraction by 3.7% with a more significant effect being observed in patients not receiving angiotensin-converting enzyme inhibitors. It is unclear whether the improvements in ejection fraction are applicable to all patients with heart failure, as more research is required to assess the role of coenzyme Q10 in heart failure and its impact on disease severity.

C. Ischemic Heart Disease

The effects of coenzyme Q10 on coronary artery disease and chronic stable angina are modest but appear promising. A theoretical basis for such benefit could be metabolic protection of the ischemic myocardium. Double-blind, placebo-controlled trials have demonstrated that coenzyme Q10 supplementation improved a number of clinical measures in patients with a history of acute myocardial infarction (AMI). Improvements have been observed in lipoprotein a, high-density lipoprotein cholesterol, exercise tolerance, and time to development of ischemic changes on the electrocardiogram during stress tests. In addition, very small reductions in cardiac deaths and rate of reinfarction in patients with previous AMI have been reported (absolute risk reduction 1.5%).

D. Prevention of Statin-Induced Myopathy

Statins reduce cholesterol by inhibiting the HMG-CoA reductase enzyme (see Chapter 35). This enzyme is also required for synthesis of coenzyme Q10. Initiating statin therapy has been shown to reduce endogenous coenzyme Q10 levels, which may block steps in muscle cell energy generation, possibly leading to statin-related myopathy. It is unknown whether a reduction in intramuscular coenzyme Q10 levels leads to statin myopathy or if the myopathy causes cellular damage that reduces intramuscular coenzyme Q10 levels. In one of the largest studies, when rosuvastatin was used in patients with heart failure, there was no association between statin-induced low coenzyme Q10 levels and a worse heart failure outcome. Furthermore, the study found no observable difference in the incidence of statin-induced myopathy regardless of endogenous coenzyme Q10 levels. More information is needed to determine which patients with statin-related myopathy might benefit most from coenzyme Q10 especially as it relates to the specific statin, the dose, and the duration of therapy.

Adverse Effects

Coenzyme Q10 is well tolerated, rarely leading to any adverse effects at doses as high as 3000 mg/d. In clinical trials, gastrointestinal upset, including diarrhea, nausea, heartburn, and anorexia, has been reported with an incidence of less than 1%. Cases of

maculopapular rash and thrombocytopenia have very rarely been observed. Other rare adverse effects include irritability, dizziness, and headache.

Drug Interactions

Coenzyme Q10 shares a structural similarity with vitamin K, and an interaction has been observed between coenzyme Q10 and warfarin. Coenzyme Q10 supplements may decrease the effects of warfarin therapy. This combination should be avoided or very carefully monitored.

Dosage

As a dietary supplement, 30 mg of coenzyme Q10 is adequate to replace low endogenous levels. For cardiac effects, typical dosages are 100–600 mg/d given in two or three divided doses. These doses increase endogenous levels to 2–3 mcg/mL (normal for healthy adults, 0.7–1 mcg/mL).

GLUCOSAMINE

Glucosamine is found in human tissue, is a substrate for the production of articular cartilage, and serves as a cartilage nutrient. Glucosamine is commercially derived from crabs and other crustaceans. As a dietary supplement, glucosamine is primarily used for pain associated with knee osteoarthritis. Sulfate and hydrochloride forms are available, but recent research has shown the hydrochloride form to be ineffective.

Pharmacologic Effects & Clinical Uses

Endogenous glucosamine is used for the production of glycosaminoglycans and other proteoglycans in articular cartilage. In osteoarthritis, the rate of production of new cartilage is exceeded by the rate of degradation of existing cartilage. Supplementation with glucosamine is thought to increase the supply of the necessary glycosaminoglycan building blocks, leading to better maintenance and strengthening of existing cartilage.

Many clinical trials have been conducted on the effects of both oral and intra-articular administration of glucosamine. Early studies reported significant improvements in overall mobility, range of motion, and strength in patients with osteoarthritis. More recent studies have reported mixed results, with both positive and negative outcomes. One of the largest and well-designed clinical trials, which compared glucosamine, chondroitin sulfate, the combination, celecoxib, and placebo, found no benefit for glucosamine therapy in mild to moderate disease. Unfortunately the investigators studied the glucosamine hydrochloride formulation, which has been shown to be inferior to the sulfate formulation. The formulation of glucosamine appears to play an important role with regard to efficacy. More research is needed to better define the specific patient populations that stand to benefit from glucosamine sulfate.

Adverse Effects

Glucosamine sulfate is very well tolerated. In clinical trials, mild diarrhea and nausea were occasionally reported. Cross allergenicity in people with shellfish allergies is a potential concern; however, this is unlikely if the formulation has been properly manufactured and purified.

Drug Interactions & Precautions

Glucosamine sulfate may increase the international normalized ratio (INR) in patients taking warfarin, increasing the risk for bruising and bleeding. The mechanism is not well understood and may be dose-related as increases in INR have occurred when the glucosamine dose was increased. Until more is known, the combination should be avoided or very carefully monitored.

Dosage

The dosage used most often in clinical trials is 500 mg three times daily or 1500 mg once daily. Glucosamine does not have direct analgesic effects, and improvements in function, if any, may not be observed for 1–2 months.

MELATONIN

Melatonin, a serotonin derivative produced by the pineal gland and some other tissues (see also Chapter 16), is believed to be responsible for regulating sleep-wake cycles. Release coincides with darkness; it typically begins around 9 PM and lasts until about 4 AM. Melatonin release is suppressed by daylight. Melatonin has also been studied for a number of other functions, including contraception, protection against endogenous oxidants, prevention of aging, treatment of depression, HIV infection, and a variety of cancers. Currently, melatonin is most often used to prevent jet lag and to induce sleep.

Pharmacologic Effects & Clinical Uses

A. Jet Lag

Jet lag, a disturbance of the sleep-wake cycle, occurs when there is a disparity between the external time and the traveler's endogenous circadian clock (internal time). The internal time regulates not only daily sleep rhythms but also body temperature and many metabolic systems. The synchronization of the circadian clock relies on light as the most potent "zeitgeber" (time giver).

Jet lag is especially common among frequent travelers and airplane cabin crews. Typical symptoms of jet lag may include daytime drowsiness, insomnia, frequent awakenings, and gastrointestinal upset. Clinical studies with administration of melatonin have reported subjective reduction in daytime fatigue, improved mood, and a quicker recovery time (return to normal sleep patterns, energy, and alertness). Although taking melatonin has not been shown to adjust circadian patterns of melatonin release,

it may have a role in helping people fall asleep once they arrive at their new destination. When traveling across five or more time zones, jet lag symptoms are reduced when taking melatonin close to the target bedtime (10 PM to midnight) at the new destination. The benefit of melatonin is thought to be greater as more time zones are crossed. In addition, melatonin appears more effective for eastbound travel than for westward travel. Finally, maximizing exposure to daylight on arrival at the new destination can also aid in resetting the internal clock.

B. Insomnia

Melatonin has been studied in the treatment of various sleep disorders, including insomnia and delayed sleep-phase syndrome. It has been reported to improve sleep onset, duration, and quality when administered to healthy volunteers, suggesting a pharmacologic hypnotic effect. Melatonin has also been shown to increase rapid-eye-movement (REM) sleep. These observations have been applied to the development of ramelteon, a prescription hypnotic, which is an agonist at melatonin receptors (see Chapter 22).

Clinical studies in patients with primary insomnia have shown that oral melatonin supplementation may alter sleep architecture. Subjective improvements in sleep quality and improvements in sleep onset and sleep duration have been reported. Specifically, melatonin taken at the desired bedtime, with bedroom lights off, has been shown to improve morning alertness and quality of sleep as compared to placebo. These effects have been observed in both young and older adults (18–80 years of age). Interestingly, baseline endogenous melatonin levels were not predictive of exogenous melatonin efficacy.

C. Female Reproductive Function

Melatonin receptors have been identified in granulosa cell membranes, and significant amounts of melatonin have been detected in ovarian follicular fluid. Melatonin has been associated with midcycle suppression of luteinizing hormone surge and secretion. This may result in partial inhibition of ovulation. Nightly doses of melatonin (75–300 mg) given with a progestin through days 1–21 of the menstrual cycle resulted in lower mean luteinizing hormone levels. Therefore, melatonin should not be used by women who are pregnant or attempting to conceive. Furthermore, melatonin supplementation may decrease prolactin release in women and therefore should be used cautiously or not at all while nursing.

D. Male Reproductive Function

In healthy men, chronic melatonin administration (≥ 6 months) decreased sperm quality, possibly by aromatase inhibition in the testes. However, when endogenous melatonin levels were measured in healthy men, high endogenous melatonin concentrations were associated with enhanced sperm quality and short-term in vitro exposure to melatonin improved sperm motility. Until more is known, melatonin should not be used by couples who are actively trying to conceive.

Adverse Effects

Melatonin appears to be well tolerated and is often used in preference to over-the-counter "sleep-aid" drugs. Although melatonin is associated with few adverse effects, some next-day drowsiness has been reported as well as fatigue, dizziness, headache, and irritability. Melatonin may affect blood pressure as both increases and decreases in blood pressure have been observed. Careful monitoring is recommended, particularly in patients initiating melatonin therapy while taking antihypertensive medications.

Drug Interactions

Melatonin drug interactions have not been formally studied. Various studies, however, suggest that melatonin concentrations are altered by a variety of drugs, including nonsteroidal anti-inflammatory drugs, antidepressants, β-adrenoceptor agonists and antagonists, scopolamine, and sodium valproate. The relevance of these effects is unknown. Melatonin is metabolized by CYP450 1A2 and may interact with other drugs that either inhibit or induce the 1A2 isoenzyme, including fluvoxamine. Melatonin may decrease prothrombin time and may theoretically decrease the effects of warfarin therapy. A dose-response relationship between the plasma concentration of melatonin and coagulation activity has been suggested according to one in vitro analysis. If combination therapy is desired, careful monitoring is recommended especially if melatonin is being used on a short-term basis. Melatonin may interact with nifedipine, possibly leading to an increased blood pressure and heart rate. The exact mechanism is unknown.

Dosage

A. Jet Lag

Daily doses of 0.5–5 mg appear to be equally effective for jet lag; however, the 5-mg dose resulted in a faster onset of sleep and better sleep quality than lower doses. The immediate-release formulation is preferred and should be given at the desired sleep time (10 PM–midnight) upon arrival at the new destination and for 1–3 nights after arrival. The value of extended-release formulations remains unknown, as evidence suggests the short-acting, high-peak effect of the immediate-release formulation to be more effective. Exposure to daylight at the new time zone is also important to regulate the sleep-wake cycle.

B. Insomnia

Doses of 0.3–10 mg of the immediate-release formulation orally given once nightly have been tried. The lowest effective dose should be used first and may be repeated in 30 minutes up to a maximum of 10–20 mg. Sustained-release formulations are effective and may be used but currently do not appear to offer any advantages over the immediate-release formulations. Sustained-release formulations are also more costly.

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CASE STUDY ANSWER

Garlic has not been shown to significantly lower LDL cholesterol. It has been shown to have a small but significant lowering effect on total cholesterol, but only when dietary controls were not in place. There is limited evidence to suggest that garlic may lower plaque burden in patients with coronary artery disease (CAD). It is advisable to monitor blood pressure for 2 weeks after initiating a garlic supplement since he is on prescription medications for hypertension. This patient might be using coenzyme Q10 for CAD or hypertension, or because he takes simvastatin. Current literature does not support a reduced risk of statin-related myopathy. The data supporting benefits of coenzyme Q10 in patients with CAD are preliminary and limited to studies in persons with a previous myocardial infarction. Several of the dietary supplements reviewed in this chapter (garlic, ginkgo, and ginseng) have antiplatelet effects that could be additive with aspirin. If this patient were also taking warfarin, additional interactions could occur with coenzyme Q10 (vitamin K-like structure), St. John's wort (cytochrome P450 1A2, 2C9, 3A4 inducer), and melatonin (in vitro decreased prothrombin time), leading to a decreased warfarin effect, or with glucosamine (increased international normalized ratio), leading to an increased warfarin effect.

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CHAPTER

65

Rational Prescribing & Prescription Writing

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Once a patient with a clinical problem has been evaluated and a diagnosis has been reached, the practitioner can often select from a variety of therapeutic approaches. Medication, surgery, psychiatric treatment, radiation, physical therapy, health education, counseling, further consultation, and no therapy are some of the options available. Of these options, drug therapy is by far the one most frequently chosen. In most cases, this requires the writing of a prescription. A written prescription is the prescriber's order to prepare or dispense a specific treatment—usually medication—for a specific patient. When a patient comes for an office visit, the physician or other authorized health professional prescribes medications 67% of the time, and an average of one prescription per office visit is written because more than one prescription may be written at a single visit.

In this chapter, a plan for prescribing is presented. The physical form of the prescription, common prescribing errors, and legal requirements that govern various features of the prescribing process are then discussed. Finally, some of the social and economic factors involved in prescribing and drug use are described.

RATIONAL PRESCRIBING

Like any other process in health care, writing a prescription should be based on a series of rational steps.

1. **Make a specific diagnosis:** Prescriptions based merely on a desire to satisfy the patient's psychological need for some type of therapy are often unsatisfactory and may result in adverse effects. A specific diagnosis, even if it is tentative, is required to move to the next step. For example, in a patient with a probable diagnosis of rheumatoid arthritis, the diagnosis and the reasoning underlying it should be clear and should be shared with the patient.
2. **Consider the pathophysiologic implications of the diagnosis:** If the disorder is well understood, the prescriber is in a much better position to offer effective therapy. For example, increasing knowledge about the mediators of inflammation makes possible more effective use of nonsteroidal anti-inflammatory drugs (NSAIDs) and other agents used in rheumatoid arthritis. The patient should be provided with the appropriate level and amount of information about the pathophysiology. Many pharmacies, websites, and disease-oriented public and private agencies (eg, American Heart Association, American Cancer Society, Arthritis Foundation) provide information sheets suitable for patients.
3. **Select a specific therapeutic objective:** A therapeutic objective should be chosen for each of the pathophysiologic processes defined in the preceding step. In a patient with rheumatoid arthritis, relief of pain by reduction of the inflammatory process is one of the major therapeutic goals that identifies the drug groups that will be considered. Arresting the course of the disease process in rheumatoid arthritis is a different therapeutic goal, which might lead to consideration of other drug groups and prescriptions.
4. **Select a drug of choice:** One or more drug groups will be suggested by each of the therapeutic goals specified in the preceding step. Selection of a drug of choice from among these groups follows from a consideration of the specific characteristics of the patient and the clinical presentation. For certain drugs, characteristics such as age, other diseases, and other drugs being taken are extremely important in determining the most suitable drug for management of the present complaint. In the example of the patient with probable rheumatoid arthritis, it would be important to know whether the patient has a history of aspirin intolerance or ulcer disease, whether the cost of medication is an especially important factor and the nature of the patient's insurance coverage, and whether there is a need for once-daily dosing. Based on this information, a drug would probably be selected from the NSAID group. If the patient is intolerant of aspirin and does not have ulcer disease but does have a need for low-cost treatment, ibuprofen or naproxen would be a rational choice.
5. **Determine the appropriate dosing regimen:** The dosing regimen is determined primarily by the pharmacokinetics of the drug in that patient. If the patient is known to have disease of the organs required for elimination of the drug selected, adjustment of the average regimen is needed. For a drug such as ibuprofen, which is eliminated mainly by the kidneys, renal function should be assessed. If renal function is normal, the

half-life of ibuprofen (about 2 hours) requires administration three or four times daily. The dose suggested in this book, drug handbooks, and the manufacturer's literature is 400–800 mg four times daily.

6. **Devise a plan for monitoring the drug's action and determine an end point for therapy:** The prescriber should be able to describe to the patient the kinds of drug effects that will be monitored and in what way, including laboratory tests (if necessary) and signs and symptoms that the patient should report. For conditions that call for a limited course of therapy (eg, most infections), the duration of therapy should be made clear so that the patient does not stop taking the drug prematurely and understands why the prescription probably need not be renewed. For the patient with rheumatoid arthritis, the need for prolonged—perhaps indefinite—therapy should be explained. The prescriber should also specify any changes in the patient's condition that would call for changes in therapy. For example, in the patient with rheumatoid arthritis, development of gastrointestinal bleeding would require an immediate change in drug therapy and a prompt workup of the bleeding. Major toxicities that require immediate attention should be explained clearly to the patient.
7. **Plan a program of patient education:** The prescriber and other members of the health team should be prepared to repeat, extend, and reinforce the information transmitted to the patient as often as necessary. The more toxic the drug prescribed, the greater the importance of this educational program. The importance of informing and involving the patient in each of the above steps must be recognized, as shown by experience with teratogenic drugs (see Chapter 59). Many pharmacies routinely provide this type of information with each prescription filled, but the prescriber must not assume that this will occur.

THE PRESCRIPTION

Although a prescription can be written on any piece of paper (as long as all of the legal elements are present), it usually takes a specific form. A typical printed prescription form for outpatients is shown in Figure 65–1.

In the hospital setting, drugs are prescribed on a particular page of the patient's hospital chart called the **physician's order sheet (POS)** or **chart order.** The contents of that prescription are specified in the medical staff rules by the hospital's Pharmacy and Therapeutics Committee. The patient's name is typed or written on the form; therefore, the orders consist of the name and strength of the medication, the dose, the route and frequency of administration, the date, other pertinent information, and the signature of the prescriber. If the duration of therapy or the number of doses is not specified (which is often the case), the medication is continued until the prescriber discontinues the order or until it is terminated as a matter of policy routine, eg, a stop-order policy.

A typical chart order might be as follows:

11/15/08

10:30 a.m.

(1) Ampicillin 500 mg IV q6h × 5 days

(2) Aspirin 0.6 g per rectum q6h prn temp over 101

[Signed] Janet B. Doe, MD

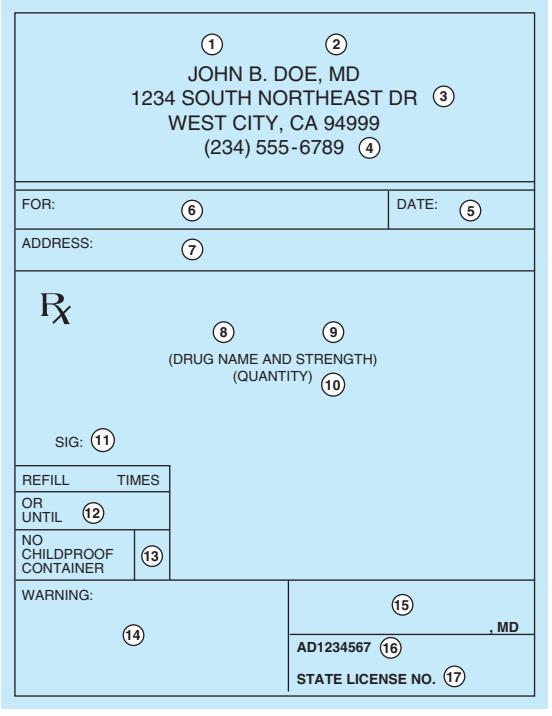

FIGURE 65–1 Common form of outpatient prescription. Circled numbers are explained in the text.

Thus, the elements of the hospital chart order are equivalent to the central elements (5, 8–11, 15) of the outpatient prescription.

Elements of the Prescription

The first four elements (see circled numerals in Figure 65–1) of the outpatient prescription establish the identity of the prescriber: name, license classification (ie, professional degree), address, and office telephone number. Before dispensing a prescription, the pharmacist must establish the prescriber's bona fides and should be able to contact the prescriber by telephone if any questions arise. Element [5] is the date on which the prescription was written. It should be near the top of the prescription form or at the beginning (left margin) of the chart order. Since the order has legal significance and usually has some temporal relationship to the date of the patient-prescriber interview, a pharmacist should refuse to fill a prescription without verification by telephone if too much time has elapsed since its writing.

Elements [6] and [7] identify the patient by name and address. The patient's name and full address should be clearly spelled out.

The body of the prescription contains the elements [8] to [11] that specify the medication, the strength and quantity to be dispensed, the dosage, and complete directions for use. When writing the drug name (element [8]), either the brand name (proprietary name) or the generic name (nonproprietary name) may be used. Reasons for using one or the other are discussed below. The strength of the medication [9] should be written in metric units. However, the prescriber should be familiar with both

systems now in use: metric and apothecary. For practical purposes, the following approximate conversions are useful:

1 grain (gr) = 0.065 grams (g), often rounded to 60 milligrams (mg)

15 gr = 1 g

1 ounce (oz) by volume = 30 milliliters (mL)

1 teaspoonful (tsp) = 5 mL

1 tablespoonful (tbsp) = 15 mL

1 quart (qt) = 1000 mL

1 minim = 1 drop (gtt)

20 drops = 1 mL

2.2 pounds (lb) = 1 kilogram (kg)

The strength of a solution is usually expressed as the quantity of solute in sufficient solvent to make 100 mL; for instance, 20% potassium chloride solution is 20 grams of KCl per deciliter (g/dL) of final solution. Both the concentration and the volume should be explicitly written out.

The quantity of medication prescribed should reflect the anticipated duration of therapy, the cost, the need for continued contact with the clinic or physician, the potential for abuse, and the potential for toxicity or overdose. Consideration should be given also to the standard sizes in which the product is available and whether this is the initial prescription of the drug or a repeat prescription or refill. If 10 days of therapy are required to effectively cure a streptococcal infection, an appropriate quantity for the full course should be prescribed. Birth control pills are often prescribed for 1 year or until the next examination is due; however, some patients may not be able to afford a year's supply at one time; therefore, a 3-month supply might be ordered, with refill instructions to renew three times or for 1 year (element [12]). Some third-party (insurance) plans limit the amount of medicine that can be dispensed—often to only a month's supply. Finally, when first prescribing medications that are to be used for the treatment of a chronic disease, the initial quantity should be small, with refills for larger quantities. The purpose of beginning treatment with a small quantity of drug is to reduce the cost if the patient cannot tolerate it. Once it is determined that intolerance is not a problem, a larger quantity purchased less frequently is sometimes less expensive.

The directions for use (element [11]) must be both drug-specific and patient-specific. The simpler the directions, the better; and the fewer the number of doses (and drugs) per day, the better. Patient noncompliance (also known as nonadherence, failure to adhere to the drug regimen) is a major cause of treatment failure. To help patients remember to take their medications, prescribers often give an instruction that medications be taken at or around mealtimes and at bedtime. However, it is important to inquire about the patient's eating habits and other lifestyle patterns, because many patients do not eat three regularly spaced meals a day.

The instructions on how and when to take medications, the duration of therapy, and the purpose of the medication must be explained to each patient both by the prescriber and by the pharmacist. (Neither should assume that the other will do it.) Furthermore, the drug name, the purpose for which it is given, and the duration of therapy should be written on each label so that the drug may be identified easily in case of overdose. An instruction to "take as directed" may save the time it takes to write the orders out but often leads to noncompliance, patient confusion, and medication error. The directions for use must be clear and concise to prevent toxicity and to obtain the greatest benefits from therapy.

Although directions for use are no longer written in Latin, many Latin apothecary abbreviations (and some others included below) are still in use. Knowledge of these abbreviations is essential for the dispensing pharmacist and often useful for the prescriber. Some of the abbreviations still used are listed in Table 65–1.

Note: It is always safer to write out the direction without abbreviating.

Elements [12] to [14] of the prescription include refill information, waiver of the requirement for childproof containers, and additional labeling instructions (eg, warnings such as "may cause drowsiness," "do not drink alcohol"). Pharmacists put the name of the medication on the label unless directed otherwise by the prescriber, and some medications have the name of the drug stamped or imprinted on the tablet or capsule. Pharmacists must place the expiration date for the drug on the label. If the patient or prescriber does not request waiver of childproof containers, the pharmacist or dispenser must place the medication in such a container. Pharmacists may not refill a prescription medication without authorization from the prescriber. Prescribers may grant authorization to renew prescriptions at the time of writing the prescription or over the telephone. Elements [15] to [17] are the prescriber's signature and other identification data.

PRESCRIBING ERRORS

All prescription orders should be legible, unambiguous, dated (and timed in the case of a chart order), and signed clearly for optimal communication between prescriber, pharmacist, and nurse. Furthermore, a good prescription or chart order should contain sufficient information to permit the pharmacist or nurse to discover possible errors before the drug is dispensed or administered.

Several types of prescribing errors are particularly common. These include errors involving omission of needed information; poor writing perhaps leading to errors of drug dose or timing; and prescription of drugs that are inappropriate for the specific situation.

Omission of Information

Errors of omission are common in hospital orders and may include instructions to "resume pre-op meds," which assumes that a full and accurate record of the "pre-op meds" is available; "continue present IV fluids," which fails to state exactly what fluids are to be given, in what volume, and over what time period; or "continue eye drops," which omits mention of which eye is to be treated as well as the drug, concentration, and frequency of administration. Chart orders may also fail to discontinue a prior medication when a new

TABLE 65–1 Abbreviations used in prescriptions and chart orders.

Abbreviation	Explanation	Abbreviation	Explanation
a̅	before	PO	by mouth
ac	before meals	PR	per rectum
agit	shake, stir	prn	when needed
Aq	water	q	every
Aq dest	distilled water	qam, om	every morning
bid	twice a day	qd (do not use)	every day (write "daily")
c̅	with	qh, q1h	every hour
cap	capsule	q2h, q3h, etc	every 2 hours, every 3 hours, etc
D5W, D_5W	dextrose 5% in water	qhs	every night at bedtime
dil	dissolve dilute	qid	four times a day
disp, dis	dispense	qod (do not use)	every other day
elix	elixir	qs	sufficient quantity
ext	extract	rept, repet	may be repeated
g	gram	Rx	take
gr	grain	s̅	without
gtt	drops	SC, SQ	subcutaneous
h	hour	sid (veterinary)	once a day
hs	at bedtime	Sig, S	label
IA	intra-arterial	sos	if needed
IM	intramuscular	s̅s̅, ss	one-half
IV	intravenous	stat	at once
IVPB	IV piggyback	sup, supp	suppository
kg	kilogram	susp	suspension
mcg, µg (do not use)	microgram (always write out "microgram")	tab	tablet
mEq, meq	milliequivalent	tbsp, T (do not use)	tablespoon (always write out "15 mL")
mg	milligram	tid	three times a day
no	number	Tr, tinct	tincture
non rep	do not repeat	tsp (do not use)	teaspoon (always write out "5 mL")
OD	right eye	U (do not use)	units (always write out "units")
OS, OL	left eye	vag	vaginal
OTC	over-the-counter	i, ii, iii, iv, etc	one, two, three, four, etc
OU	both eyes	℥ (do not use)	dram (in fluid measure 3.7 mL)
p̅	after	℥̿ (do not use)	ounce (in fluid measure 29.6 mL)
pc	after meals		

one is begun; may fail to state whether a regular or long-acting form is to be used; may fail to specify a strength or notation for long-acting forms; or may authorize "as needed" (prn) use that fails to state what conditions will justify the need.

Poor Prescription Writing

Poor prescription writing is traditionally exemplified by illegible handwriting. However, other types of poor writing are common and often more dangerous. One of the most important is the misplaced or ambiguous decimal point. Thus ".1" is easily misread as "1," a tenfold overdose, if the decimal point is not unmistakably clear. This danger is easily avoided by always preceding the decimal point with a zero. On the other hand, appending an unnecessary zero after a decimal point increases the risk of a tenfold overdose, because "1.0 mg" is easily misread as "10 mg," whereas "1 mg" is not. The slash or virgule ("/") was traditionally used as a substitute for a decimal point. This should be abandoned

because it is too easily misread as the numeral "1." Similarly, the abbreviation "U" for units should never be used because "10U" is easily misread as "100"; the word "units" should *always* be written out. Doses in micrograms should always have this unit written out because the abbreviated form ("μg") is very easily misread as "mg," a 1000-fold overdose! Orders for drugs specifying only the number of dosage units and not the total dose required should not be filled if more than one size dosage unit exists for that drug. For example, ordering "one ampule of furosemide" is unacceptable because furosemide is available in ampules that contain 20, 40, or 100 mg of the drug. The abbreviation "OD" should be used (if at all) only to mean "the right eye"; it has been used for "every day" and has caused inappropriate administration of drugs into the eye. Similarly, "Q.D." or "QD" should not be used because it is often read as "QID," resulting in four daily doses instead of one. Acronyms and abbreviations such as "ASA" (aspirin), "5-ASA" (5-aminosalicylic acid), "6MP" (6-mercaptopurine), etc, should not be used; drug names should be written out. Unclear handwriting can be lethal when drugs with similar names but very different effects are available, eg, acetazolamide and acetohexamide, methotrexate and metolazone. In this situation, errors are best avoided by noting the indication for the drug in the body of the prescription, eg, "acetazolamide, for glaucoma."

Inappropriate Drug Prescriptions

Prescribing an inappropriate drug for a particular patient results from failure to recognize contraindications imposed by other diseases the patient may have, failure to obtain information about other drugs the patient is taking (including over-the-counter drugs), or failure to recognize possible physicochemical incompatibilities between drugs that may react with each other. Contraindications to drugs in the presence of other diseases or pharmacokinetic characteristics are listed in the discussions of the drugs described in this book. The manufacturer's package insert usually contains similar information. Some of the important drug interactions are listed in Chapter 66 of this book as well as in package inserts.

Physicochemical incompatibilities are of particular concern when parenteral administration is planned. For example, certain insulin preparations should not be mixed. Similarly, the simultaneous administration of antacids or products high in metal content may compromise the absorption of many drugs in the intestine, eg, tetracyclines. The package insert and the *Handbook on Injectable Drugs* (see References) are good sources for this information.

E-PRESCRIBING

Electronic prescribing of prescriptions is gaining momentum in the USA. Congress has passed legislation to support this health care initiative. Essentially e-prescribing provides an electronic flow of information between the prescriber, intermediary, pharmacy, and health plan. The health plan can provide information on patient eligibility, formulary, benefits, costs, and sometimes, a medication history. The prescriber selects the medication, strength, dosage form, quantity, and directions for use and the prescription is transmitted to the pharmacy where the appropriate data fields are populated. The pharmacist reviews the order and, if appropriate, dispenses the prescription. The electronic system must be Health Insurance Portability and Accountability Act (HIPAA)-compliant, and there needs to be a business association agreement between the parties involved.

Prescribers can obtain decision support information such as disease-drug and drug-drug interaction information or cost information prior to prescribing as part of the health plan information. Prescriptions can be clear in their writing, but pull-down drug lists can create new errors. Prescription renewals can be processed electronically and drug misuse or abuse may be identifiable. Theoretically, time to process prescription orders should be reduced and patients would have their medication ready when they arrive at the pharmacy.

The Drug Enforcement Administration has begun to issue tentative rules for e-prescribing of controlled substances. Currently, only registered prescribers can e-prescribe, and there will be several independent identification proofing sources required: a unique pin number, or retinal scan, or a finger print. The objective is to prevent drug diversion. Pharmacies currently can order controlled drugs via computer using a specific form once they are certified.

COMPLIANCE

Compliance (sometimes called adherence) is the extent to which patients follow treatment instructions. There are four types of noncompliance leading to medication errors.

1. The patient fails to obtain the medication. Some studies suggest that one third of patients never have their prescriptions filled. Some patients leave the hospital without obtaining their discharge medications, whereas others leave the hospital without having their prehospitalization medications resumed. Some patients cannot afford the medications prescribed.
2. The patient fails to take the medication as prescribed. Examples include wrong dosage, wrong frequency of administration, improper timing or sequencing of administration, wrong route or technique of administration, or taking medication for the wrong purpose. This usually results from inadequate communication between the patient and the prescriber and the pharmacist.
3. The patient prematurely discontinues the medication. This can occur, for instance, if the patient incorrectly assumes that the medication is no longer needed because the bottle is empty or symptomatic improvement has occurred.
4. The patient (or another person) takes medication inappropriately. For example, the patient may share a medication with others for any of several reasons.

Several factors encourage noncompliance. Some diseases cause no symptoms (eg, hypertension); patients with these diseases therefore have no symptoms to remind them to take their medications. Patients with painful conditions such as arthritis may continually change medications in the hope of finding a better one.

Characteristics of the therapy itself can limit the degree of compliance; patients taking a drug once a day are much more likely to be compliant than those taking a drug four times a day. Various patient factors also play a role in compliance. Patients living alone are much less likely to be compliant than married patients of the same age. Packaging may also be a deterrent to compliance—elderly arthritic patients often have difficulty opening their medication containers. Lack of transportation as well as various social or personal beliefs about medications are likewise barriers to compliance.

Strategies for improving compliance include enhanced communication between the patient and health care team members; assessment of personal, social, and economic conditions (often reflected in the patient's lifestyle); development of a routine for taking medications (eg, at mealtimes if the patient has regular meals); provision of systems to assist taking medications (ie, containers that separate drug doses by day of the week, or medication alarm clocks that remind patients to take their medications); and mailing of refill reminders by the pharmacist to patients taking drugs chronically. The patient who is likely to discontinue a medication because of a perceived drug-related problem should receive instruction about how to monitor and understand the effects of the medication. Compliance can often be improved by enlisting the patient's active participation in the treatment.

LEGAL FACTORS (USA)

The United States government recognizes two classes of drugs: (1) over-the-counter (OTC) drugs and (2) those that require a prescription from a licensed prescriber (Rx Only). OTC drugs are those that can be safely self-administered by the layman for self-limiting conditions and for which appropriate labels can be written for lay comprehension (see Chapter 63). Half of all drug doses consumed by the American public are OTC drugs.

Physicians, dentists, podiatrists, and veterinarians—and, in some states, specialized pharmacists, nurses, physician's assistants, and optometrists—are granted authority to prescribe dangerous drugs (those bearing the federal legend statement, "Rx Only") on the basis of their training in diagnosis and treatment (see Box: Who May Prescribe?). Pharmacists are authorized to dispense prescriptions pursuant to a prescriber's order provided that the medication order is appropriate and rational for the patient. Nurses are authorized to administer medications to patients subject to a prescriber's order (Table 65–2).

Because of the multiplicity of third-party payers (health insurers) and Medicare and Medicaid claimants, the concept of electronic processing of prescriptions ("e-prescribing") has become urgent. (Further information about e-prescribing may be found at

TABLE 65–2 Prescribing authority of certain allied health professionals in selected states.

State	Pharmacists	Nurse Practitioners	Physician's Assistants	Optometrists
California	Yes, under protocol[1]; must be trained in clinical practice	Yes[2]	Yes, under protocol[1]	Yes; limited to certain drug classes
Florida	Yes, according to state formulary; protocol not required	Yes[2]	Yes[2]	Yes; limited to certain drug classes
Michigan	Yes, under protocol; must be specially qualified by education, training, or experience	Yes; do not need physician supervision	Yes[2]	Yes; limited to certain drug classes
Mississippi	Yes, under protocol in an institutional setting	Yes,[2] under narrowly specified conditions	No	Yes; limited to certain drug classes
Nevada	Yes, under protocol, within a licensed medical facility	Yes[2]	Yes[2]	Yes; limited to certain drug classes
New Mexico	Yes, under protocol, must be "pharmacist clinician"	Yes; do not need physician supervision	Yes[2]	Yes; limited to certain drug classes
North Dakota	Yes, under protocol in an institutional setting	Yes; do not need physician supervision	Yes	Yes; limited to certain drug classes
Oregon	Yes, under guidelines set by the state board	Yes; do not need physician supervision	Yes[2]	Yes; limited to certain drug classes
Texas	Yes, under protocol set for a particular patient in an institutional setting	Yes; do not need physician supervision	Yes	Yes; limited to certain drug classes
Washington	Yes, under guidelines set by the state board	Yes; do not need physician supervision	Yes[2]	Yes; limited to certain drug classes

[1]Under protocol; see Box: Who May Prescribe?

[2]In collaboration with or under the supervision of a physician.

Who May Prescribe?

The right to prescribe drugs has traditionally been the responsibility of the physician, dentist, podiatrist, or veterinarian. Prescribing now includes—in a number of states and in varying degrees—pharmacists, nurse practitioners, nurse midwives, physician's assistants, and optometrists (see Table 65–2). In the future, physical therapists may be licensed to prescribe drugs relevant to their practice. The development of large health maintenance organizations has greatly strengthened this expansion of prescribing rights because it offers these extremely powerful economic bodies a way to reduce their expenses.

The primary organizations controlling the privilege of prescribing in the USA are the state boards, under the powers delegated to them by the state legislatures. As indicated in Table 65–2, many state boards have attempted to reserve some measure of the primary responsibility for prescribing to physicians by requiring that the ancillary professional work with or under a physician according to a specific protocol. In the state of California, this protocol must include a statement of the training, supervision, and documentation requirements of the arrangement and must specify referral requirements, limitations to the list of drugs that may be prescribed (ie, a formulary), and a method of evaluation by the supervising physician. The protocol must be in writing and must be periodically updated (see reference: An Explanation of the Scope of RN Practice, 1994).

http://www.cms.hhs.gov/eprescribing/.) To further standardize electronic prescription transmission and billing, the Centers for Medicare and Medicaid (CMS) issued regulations effective in 2008 requiring all US health care providers to obtain a National Provider Identification (NPI) number. This 10-digit identifier is issued by the National Plan and Provider Enumeration System (NPPES) at https://NPPES.cms.hhs.gov. The purpose of the NPI is to identify all health care transactions (and associated costs) incurred by a particular practitioner with a single number.

In addition to a health care provider's unique identification number, some states require that prescriptions for controlled substances be written on tamper-resistant security prescription forms. The purpose of this legislation is to prevent forgeries and to tighten the control of prescription order forms.

The concept of a "secure" prescription form was expanded by the federal government in 2008 to all prescriptions written for Medicaid patients. Any prescription for a Medicaid patient must be written on a security form if the pharmacist is to be compensated for the prescription service. In turn, the use of "triplicate" prescription forms was eliminated and replaced with an online electronic transmission system whereby orders for Schedule II and Schedule III prescriptions are transmitted to a company that acts as a repository for these transactions. In California, it is called the CURES program (Controlled Substances Utilization Review and Evaluation System). Additional information about CURES may be found at http://ag.ca.gov/bne/trips.php.

Prescription drugs are controlled by the United States Food and Drug Administration as described in Chapter 5. The federal legend statement as well as the package insert is part of the packaging requirements for all prescription drugs. The package insert is the official brochure setting forth the indications, contraindications, warnings, and dosing for the drug.

The prescriber, by writing and signing a prescription order, controls who may obtain prescription drugs. The pharmacist may purchase these drugs, but they may be dispensed only on the order of a legally qualified prescriber. Thus, a **prescription** is actually three things: the **physician's order in the patient's chart,** the **written order to which the pharmacist refers** when dispensing, and the patient's **medication container with a label affixed.**

Whereas the federal government controls the drugs and their labeling and distribution, the state legislatures control who may prescribe drugs through their licensing boards, eg, the Board of Medical Examiners. Prescribers must pass examinations, pay fees, and—in the case of some states and some professions—meet other requirements for relicensure such as continuing education. If these requirements are met, the prescriber is licensed to order dispensing of drugs.

The federal government and the states further impose special restrictions on drugs according to their perceived potential for abuse (Table 65–3). Such drugs include opioids, hallucinogens, stimulants, depressants, and anabolic steroids. Special requirements

TABLE 65–3 Classification of controlled substances. (See Inside Front Cover for examples.)

Schedule	Potential for Abuse	Other Comments
I	High	No accepted medical use; lack of accepted safety as drug.
II	High	Current accepted medical use. Abuse may lead to psychological or physical dependence.
III	Less than I or II	Current accepted medical use. Moderate or low potential for physical dependence and high potential for psychological dependence.
IV	Less than III	Current accepted medical use. Limited potential for dependence.
V	Less than IV	Current accepted medical use. Limited dependence possible.

must be met when these drugs are to be prescribed. The Controlled Drug Act requires prescribers and dispensers to register with the Drug Enforcement Agency (DEA), pay a fee, receive a personal registration number, and keep records of all controlled drugs prescribed or dispensed. Every time a controlled drug is prescribed, a valid DEA number must appear on the prescription blank.

Prescriptions for substances with a high potential for abuse (Schedule II drugs) cannot be refilled. However, multiple prescriptions for the same drug may be written with instructions not to dispense before a certain date and up to a total of 90 days. Prescriptions for Schedules III, IV, and V can be refilled if ordered, but there is a five-refill maximum, and in no case may the prescription be refilled after 6 months from the date of writing. Schedule II drug orders may not be transmitted over the telephone, and some states require a tamper-resistant security prescription blank to reduce the chances for drug diversion.

These restrictive prescribing laws are intended to limit the amount of drugs of abuse that are made available to the public.

Unfortunately, the inconvenience occasioned by these laws—and an unwarranted fear by medical professionals themselves regarding the risk of patient tolerance and addiction—continues to hamper adequate treatment of patients with terminal conditions. This has been shown to be particularly true in children and elderly patients with cancer. *There is no excuse for inadequate treatment of pain in a terminal patient; not only is addiction irrelevant in such a patient, it is actually uncommon in patients who are being treated for pain* (see Chapter 31).

Some states have recognized the underutilization of pain medications in the treatment of pain associated with chronic and terminal conditions. California, for example, has enacted an "intractable pain treatment" act that reduces the difficulty of renewing prescriptions for opioids. Under the provisions of this act, upon receipt of a copy of the order from the prescriber, eg, by fax, a pharmacist may write a prescription for a Schedule II substance for a patient under hospice care or living in a skilled nursing facility or in cases in which the patient is expected to live less than 6 months, provided that the prescriber countersigns the order (by fax); the word "exemption" with regulatory code number is written on a typical prescription, thus providing easier access for the terminally ill.

Medication Therapy Management

The Medicare Modernization Act of 2003 established the requirement that Medicare Part D plan sponsors offer a Medication Therapy Management (MTM) program to their beneficiaries. The MTM program is targeted for patients who have at least two chronic diseases and have used multiple drugs at significant expense (initially a $4000 annual drug expense and now lowered to $3000/yr). The pharmacist collects the patient's drug information and analyzes the drug history and drug utilization information with the objective to optimize drug therapy, lower costs, improve drug safety, and improve the patients' understanding of their medications. Pharmacists collaborate with physicians to address the drug therapy challenges in these high-use groups.

Labeled & Off-Labeled Uses of Drugs

In the USA, the FDA approves a drug only for the specific uses proposed and documented by the manufacturer in its New Drug Application (see Chapter 5). These approved (labeled) uses or indications are set forth in the package insert that accompanies the drug. For a variety of reasons, these labeled indications may not include all the conditions in which the drug might be useful. Therefore, a clinician may wish to prescribe the agent for some other, unapproved (off-label), clinical condition, often on the basis of adequate or even compelling scientific evidence. Federal laws governing FDA regulations and drug use place no restrictions on such unapproved use.*

Even if the patient suffers injury from the drug, its use for an unlabeled purpose does not in itself constitute "malpractice." However, the courts may consider the package insert labeling as a complete listing of the indications for which the drug is considered safe unless the clinician can show that other use is considered safe by competent expert testimony.

Drug Safety Surveillance

Governmental drug-regulating agencies have responsibility for monitoring drug safety. In the USA, the FDA-sponsored Med Watch program collects data on safety and adverse drug effects (ADEs) through mandatory reporting by drug manufacturers and voluntary reporting by health care practitioners. Practitioners may submit reports on any suspected adverse drug (or medical device) effect using a simple form obtainable from http://www.fda.gov/medwatch/index.html. The FDA is expected to use these data to establish an adverse effect rate. It is not clear that the FDA has sufficient resources at present to carry out this mandate, but they are empowered to take further regulatory actions if deemed necessary. A similar vaccine reporting program is in place to monitor vaccine safety.

The FDA has also increased requirements for labeling on drugs that carry special risks. Dispensers of medications are required to distribute "Med Guides" to patients when these medications are dispensed. These guides are provided by the manufacturers of the medications. In addition, pharmacists often provide patient educational materials that describe the drug, its

*"Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in the approved labeling. Such 'unapproved' or, more precisely, 'unlabeled' uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature."—FDA Drug Bull 1982;12:4.

use, adverse effects, storage requirements, methods of administration, what to do when a dose is missed, and the potential need for ongoing therapy.

SOCIOECONOMIC FACTORS

Generic Prescribing

Prescribing by generic name offers the pharmacist flexibility in selecting the particular drug product to fill the order and offers the patient a potential savings when there is price competition. For example, the brand name of a popular sedative is *Valium*, manufactured by Hoffmann-LaRoche. The generic (public nonproprietary) name of the same chemical substance adopted by United States Adopted Names (USAN) and approved by the FDA is *diazepam*. All diazepam drug products in the USA meet the pharmaceutical standards expressed in the *United States Pharmacopeia (USP)*. However, there are several manufacturers, and prices vary greatly. For drugs in common use, the difference in cost between the trade-named product and generic products varies from less than twofold to more than 100-fold.

In most states and in most hospitals, pharmacists have the option of supplying a generically equivalent drug product even if a proprietary name has been specified in the order. If the prescriber wants a particular brand of drug product dispensed, handwritten instructions to "dispense as written" or words of similar meaning are required. Some government-subsidized health care programs and many third-party insurance payers *require* that pharmacists dispense the cheapest generically equivalent product in the inventory (generic substitution). However, the principles of drug product selection by private pharmacists do not permit substituting one therapeutic agent for another (therapeutic substitution); that is, dispensing trichlormethiazide for hydrochlorothiazide would not be permitted without the prescriber's permission even though these two diuretics may be considered pharmacodynamically equivalent. Pharmacists within managed care organizations may follow different policies; see below.

It cannot be assumed that every generic drug product is as satisfactory as the trade-named product, although examples of unsatisfactory generics are rare. Bioavailability—the effective absorption of the drug product—varies between manufacturers and sometimes between different lots of a drug produced by the same manufacturer. In spite of the evidence, many practitioners avoid generic prescribing, thereby increasing medical costs. In the case of a very small number of drugs, which usually have a low therapeutic index, poor solubility, or a high ratio of inert ingredients to active drug content, a specific manufacturer's product may give more consistent results. In the case of life-threatening diseases, the advantages of generic substitution may be outweighed by the clinical urgency so that the prescription should be filled as written.

In an effort to codify bioequivalence information, the FDA publishes *Approved Drug Products with Therapeutic Equivalence Evaluations*, with monthly supplements, commonly called "the Orange Book." The book contains listings of multi-source products in one of two categories: Products given a code beginning with the letter "A" are considered bioequivalent to a reference standard formulation of the same drug and to all other versions of that product with a similar "A" coding. Products not considered bioequivalent are coded "B." Of the approximately 8000 products listed, 90% are coded "A." Additional code letters and numerals are appended to the initial "A" or "B" and indicate the approved route of administration and other variables.

Mandatory drug product selection on the basis of price is common practice in the USA because third-party payers (insurance companies, health maintenance organizations, etc) enforce money-saving regulations. If outside a managed care organization, the prescriber can sometimes override these controls by writing "dispense as written" on a prescription that calls for a brand-named product. However, in such cases, the patient may have to pay the difference between the dispensed product and the cheaper one.

Within most managed care organizations, formulary controls have been put in place that force the selection of less expensive medications whenever they are available. In a managed care environment, the prescriber often selects the drug group rather than a specific agent, and the pharmacist dispenses the formulary drug from that group. For example, if a prescriber in such an organization decides that a patient needs a thiazide diuretic, the pharmacist automatically dispenses the single thiazide diuretic carried on the organization's formulary. As noted below, the choice of drugs for the organization's formulary may change from time to time, depending on negotiation of prices and rebates with different manufacturers.

Other Cost Factors

The private pharmacy bases its charges on the cost of the drug plus a fee for providing a professional service. Each time a prescription is dispensed, there is a fee. The prescriber controls the frequency of filling prescriptions by authorizing refills and specifying the quantity to be dispensed. However, for medications used for chronic illnesses, the quantity covered by insurance may be limited to the amount used in 1 month. Thus, the prescriber can save the patient money by prescribing standard sizes (so that drugs do not have to be repackaged) and, when chronic treatment is involved, by ordering the largest quantity consistent with safety, expense, and third-party plan. Optimal prescribing for cost savings often involves consultation between the prescriber and the pharmacist. Because of continuing increases in the wholesale prices of drugs in the USA, prescription costs have risen dramatically over the past 3 decades; and from 1999 to 2009, the number of prescriptions purchased has increased 39% while the population grew 9% (see Box: The Cost of Prescriptions).

The Cost of Prescriptions

The cost of prescriptions has risen dramatically in the last several decades. The average price for a single prescription in the USA in 2004 was $55. By 2006, this average cost had risen to $75. In the California Medicaid Sector, the average charge was over $80, with generic products being under $40 per prescription and brand-name products over $140. This rise is occasioned by new technology, marketing costs, and stockholder expectations. The pharmaceutical industry typically posts profits of 10-15% annually, whereas the retail business sector shows a 3% profit. The cost to the patient for many new drugs such as statins exceeds $1000 per year. The cost of some therapeutic antibody products (eg, MABs) is more than $10,000 per year. Pharmaceuticals tend to be the highest out-of-pocket health-related cost because other health care services are covered by health insurance, whereas prescriptions often are not, although this is changing.

Because of public and political pressure resulting from this problem, the US Congress enacted the Medicare Modernization Act in 2003 establishing the Medicare Part D plan. This voluntary prescription plan provides for partial payment by private medical insurance companies for some prescriptions for patients who are Medicare-eligible. Unfortunately, the complexity of the legislation and the resulting confusing insurance plans with gaps in coverage, formulary and quantity limits, and the favored economic treatment given the pharmaceutical industry, prevent this plan from solving the high drug cost problem.

High drug costs have caused payers and consumers alike to do without or seek alternative sources. Because most other governments, eg, Canada, have done a better job in controlling drug prices, the prices for the same drug are usually less in other countries than those in the United States. This fact has caused a number of US citizens to purchase their drugs "off-shore" in a variety of countries for "personal use" in quantities up to a 3-month supply—at substantial savings, often as much as 50%. However, there is no assurance that these drugs are always what they are purported to be, or that they will be delivered in a timely manner, or that there is a traditional doctor-pharmacist-patient relationship and the safeguards that such a relationship offers.

Without a true universal health care program, the cost of drugs in the USA will continue to be subject to the negotiating power (or lack thereof) of the purchasing group-insurance company, hospital consortium, HMO, small retail pharmacy, etc, and will be driven primarily by the economic policies of the large manufacturers. In most companies, these policies favor executive compensation and stockholder dividends above the interests of consumers or employees. Thus far, only the US Veterans Administration system, the larger HMOs, and a few "big box" stores have proved strong enough to control costs through bulk purchases of drugs and serious negotiation of prices with manufacturers. Until new legislation gives other organizations the same power to negotiate, or pricing policies are made more equitable, no real solution to the drug cost problem can be expected.

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CHAPTER

66

Important Drug Interactions & Their Mechanisms

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One of the factors that can alter the response to drugs is the concurrent administration of other drugs. There are several mechanisms by which drugs may interact, but most can be categorized as pharmacokinetic (absorption, distribution, metabolism, excretion), pharmacodynamic (additive, synergistic, or antagonistic effects), or combined interactions. The general principles of pharmacokinetics are discussed in Chapters 3 and 4; the general principles of pharmacodynamics in Chapter 2.

Botanical medications ("herbals") may interact with each other or with conventional drugs. Unfortunately, botanicals are much less well studied than other drugs, so information about their interactions is scanty. Pharmacodynamic interactions are described in Chapter 64. Pharmacokinetic interactions that have been documented (eg, St. John's wort) are listed in Table 66–1.

Knowledge of the mechanism by which a given drug interaction occurs is often clinically useful, since the mechanism may influence both the time course and the methods of circumventing the interaction. Some important drug interactions occur as a result of two or more mechanisms.

PREDICTABILITY OF DRUG INTERACTIONS

The designations listed in Table 66–1 are used here to *estimate* the predictability of the drug interactions. These estimates are intended to indicate simply whether or not the interaction will occur, and they do not always mean that the interaction is likely to produce an adverse effect. Whether or not the interaction occurs (precipitant drug produces a measurable change in the object drug) and produces an adverse effect depends on both patient- and drug-specific factors. Patient factors can include intrinsic drug clearance, genetics, gender, concurrent diseases, and diet. Drug-specific factors include dose, route of administration, drug formulation, and the sequence of drug administration. The most important factor that can mitigate the risk of patient harm is recognition by the prescriber of a potential interaction followed by appropriate action.

Pharmacokinetic Mechanisms

The gastrointestinal **absorption** of drugs may be affected by concurrent use of other agents that (1) have a large surface area upon which the drug can be adsorbed, (2) bind or chelate, (3) alter gastric pH, (4) alter gastrointestinal motility, or (5) affect transport proteins such as P-glycoprotein and organic anion transporters. One must distinguish between effects on absorption *rate* and effects on *extent* of absorption. A reduction in only the absorption rate of a drug is seldom clinically important, whereas a reduction in the extent of absorption is clinically important if it results in subtherapeutic serum concentrations.

The mechanisms by which drug interactions alter drug **distribution** include (1) competition for plasma protein binding, (2) displacement from tissue binding sites, and (3) alterations in local tissue barriers, eg, P-glycoprotein inhibition in the blood-brain barrier. Although competition for plasma protein binding can increase the free concentration (and thus the effect) of the displaced drug in plasma, the increase will be transient owing to a compensatory increase in drug disposition. The clinical importance of protein binding displacement has been overemphasized; current evidence suggests that such interactions are unlikely to result in adverse effects. Displacement from tissue binding sites would tend to transiently increase the blood concentration of the displaced drug.

The **metabolism** of drugs can be stimulated or inhibited by concurrent therapy, and the importance of the effect varies from negligible to dramatic. Drug metabolism primarily occurs in the liver and the wall of the small intestine, but other sites include plasma, lung, and kidney. Induction (stimulation) of cytochrome P450 isozymes in the liver and small intestine can be caused by drugs such as barbiturates, bosentan, carbamazepine, efavirenz, nevirapine, phenytoin, primidone, rifampin,

rifabutin, and St. John's wort. Enzyme inducers can also increase the activity of phase II metabolism such as glucuronidation. Enzyme induction does not take place quickly; maximal effects usually occur after 7–10 days and require an equal or longer time to dissipate after the enzyme inducer is stopped. Rifampin, however, may produce enzyme induction after only a few doses. Inhibition of metabolism generally takes place more quickly than enzyme induction and may begin as soon as sufficient tissue concentration of the inhibitor is achieved. However, if the half-life of the affected (object) drug is long, it may take a week or more (three to four half-lives) to reach a new steady-state serum concentration. Drugs that may inhibit the cytochrome P450 metabolism of other drugs include amiodarone, androgens, atazanavir, chloramphenicol, cimetidine, ciprofloxacin, clarithromycin, cyclosporine, delavirdine, diltiazem, diphenhydramine, disulfiram, enoxacin, erythromycin, fluconazole, fluoxetine, fluvoxamine, furanocoumarins (substances in grapefruit juice), indinavir, isoniazid, itraconazole, ketoconazole, metronidazole, mexiletine, miconazole, nefazodone, omeprazole, paroxetine, propoxyphene, quinidine, ritonavir, sulfamethizole, verapamil, voriconazole, zafirlukast, and zileuton.

The **renal excretion** of active drug can also be affected by concurrent drug therapy. The renal excretion of certain drugs that are weak acids or weak bases may be influenced by other drugs that affect urinary pH. This is due to changes in ionization of the drug, as described in Chapter 1 under Ionization of Weak Acids and Weak Bases; the Henderson-Hasselbalch equation. For some drugs, active secretion into the renal tubules is an important elimination pathway. P-glycoprotein, organic anion transporters, and organic cation transporters are involved in active tubular secretion of some drugs, and inhibition of these transporters can inhibit renal elimination with attendant increase in serum drug concentrations.

Pharmacodynamic Mechanisms

When drugs with similar pharmacologic effects are administered concurrently, an additive or synergistic response is usually seen. The two drugs may or may not act on the same receptor to produce such effects. In theory, drugs acting on the same receptor or process are usually additive, eg, benzodiazepines plus barbiturates. Drugs acting on different receptors or sequential processes may be synergistic, eg, nitrates plus sildenafil or sulfonamides plus trimethoprim. Conversely, drugs with opposing pharmacologic effects may reduce the response to one or both drugs. Pharmacodynamic drug interactions are relatively common in clinical practice, but adverse effects can usually be minimized if one understands the pharmacology of the drugs involved. In this way, the interactions can be anticipated and appropriate countermeasures taken.

Combined Toxicity

The combined use of two or more drugs, each of which has toxic effects on the same organ, can greatly increase the likelihood of organ damage. For example, concurrent administration of two nephrotoxic drugs can produce kidney damage, even though the dose of either drug alone may have been insufficient to produce toxicity. Furthermore, some drugs can enhance the organ toxicity of another drug, even though the enhancing drug has no intrinsic toxic effect on that organ.

TABLE 66–1 Important drug interactions.

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Alcohol	Chronic alcoholism results in enzyme induction. Acute alcoholic intoxication tends to inhibit drug metabolism (whether person is alcoholic or not). Severe alcohol-induced hepatic dysfunction may inhibit ability to metabolize drugs. Disulfiram-like reaction in the presence of certain drugs. Additive central nervous system depression with other central nervous system depressants.	**Acetaminophen:** [NE] Increased formation of hepatotoxic acetaminophen metabolites (in chronic alcoholics). **Acitretin:** [P] Increased conversion of acitretin to etretinate (teratogenic). **Anticoagulants, oral:** [NE] Increased hypoprothrombinemic effect with acute alcohol intoxication. **Central nervous system depressants:** [HP] Additive or synergistic central nervous system depression. **Insulin:** [NE] Acute alcohol intake may increase hypoglycemic effect of insulin (especially in fasting patients). *Drugs that may produce a disulfiram-like reaction:* **Cephalosporins:** [NP] Disulfiram-like reactions are noted with cefamandole, cefoperazone, cefotetan, and moxalactam. **Chloral hydrate:** [NP] Mechanism not established. **Disulfiram:** [HP] Inhibited aldehyde dehydrogenase. **Metronidazole:** [NP] Mechanism not established. **Sulfonylureas:** [NE] Chlorpropamide is most likely to produce a disulfiram-like reaction; acute alcohol intake may increase hypoglycemic effect (especially in fasting patients).

HP, Highly predictable. Interaction occurs in almost all patients receiving the interacting combination; P, Predictable. Interaction occurs in most patients receiving the combination; NP, Not predictable. Interaction occurs only in some patients receiving the combination; NE, Not established. Insufficient data available on which to base estimate of predictability.

(*continued*)

TABLE 66–1 Important drug interactions. (Continued)

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Allopurinol	Inhibits hepatic drug-metabolizing enzymes. Febuxostat (another drug used in gout) will also inhibit the metabolism of azathioprine and mercaptopurine.	**Anticoagulants, oral:** [NP] Increased hypoprothrombinemic effect. **Azathioprine:** [P] Decreased azathioprine detoxification resulting in increased azathioprine toxicity. **Mercaptopurine:** [P] Decreased mercaptopurine metabolism resulting in increased mercaptopurine toxicity.
Antacids	Antacids may adsorb drugs in gastrointestinal tract, thus reducing absorption. Antacids tend to speed gastric emptying, thus delivering drugs to absorbing sites in the intestine more quickly. Some antacids (eg, magnesium hydroxide with aluminum hydroxide) alkalinize the urine somewhat, thus altering excretion of drugs sensitive to urinary pH.	**Atazanavir:** [NP] Decreased absorption of atazanavir (requires acid for absorption). **Digoxin:** [NP] Decreased gastrointestinal absorption of digoxin. **Indinavir:** [NP] Decreased absorption of indinavir (requires acid for absorption). **Iron:** [P] Decreased gastrointestinal absorption of iron with calcium-containing antacids. **Itraconazole:** [P] Reduced gastrointestinal absorption of itraconazole due to increased pH (itraconazole requires acid for dissolution). **Ketoconazole:** [P] Reduced gastrointestinal absorption of ketoconazole due to increased pH (ketoconazole requires acid for dissolution). **Quinolones:** [HP] Decreased gastrointestinal absorption of ciprofloxacin, norfloxacin, and enoxacin (and probably other quinolones). **Salicylates:** [P] Increased renal clearance of salicylates due to increased urine pH; occurs only with large doses of salicylates. **Sodium polystyrene sulfonate:** [NE] Binds antacid cation in gut, resulting in metabolic alkalosis. **Tetracyclines:** [HP] Decreased gastrointestinal absorption of tetracyclines. **Thyroxine:** [NP] Reduced gastrointestinal absorption of thyroxine.
Anticoagulants, oral	Metabolism inducible. Susceptible to inhibition of CYP2C9-mediated metabolism. Highly bound to plasma proteins. Anticoagulation response altered by drugs that affect clotting factor synthesis or catabolism.	*Drugs that may increase anticoagulant effect:* **Acetaminophen:** [NE] Impaired synthesis of clotting factors. **Amiodarone:** [P] Inhibited anticoagulant metabolism. **Anabolic steroids:** [P] Altered clotting factor disposition? **Chloramphenicol:** [NE] Decreased dicumarol metabolism (probably also warfarin). **Cimetidine:** [HP] Decreased warfarin metabolism. **Clofibrate:** [P] Mechanism not established. **Clopidogrel:** [NP] Decreased warfarin metabolism and inhibits platelet function. **Danazol:** [NE] Impaired synthesis of clotting factors? **Dextrothyroxine:** [P] Enhanced clotting factor catabolism? **Disulfiram:** [P] Decreased warfarin metabolism. **Erythromycin:** [NP] Probably inhibits anticoagulant metabolism. **Fluconazole:** [P] Decreased warfarin metabolism. **Fluoxetine:** [P] Decreased warfarin metabolism. **Gemfibrozil:** [NE] Mechanism not established. **Lovastatin:** [NP] Decreased warfarin metabolism. **Metronidazole:** [P] Decreased warfarin metabolism. **Miconazole:** [NE] Decreased warfarin metabolism.

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(*continued*)

TABLE 66–1 Important drug interactions. (Continued)

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Anticoagulants, oral (*cont.*)		**Nonsteroidal anti-inflammatory drugs:** [P] Inhibition of platelet function, gastric erosions; some agents increase hypoprothrombinemic response (unlikely with diclofenac, ibuprofen, or naproxen). **Propafenone:** [NE] Probably decreases anticoagulant metabolism. **Quinidine:** [NP] Additive hypoprothrombinemia. **Salicylates:** [HP] Platelet inhibition with aspirin but not with other salicylates; [P] large doses have hypoprothrombinemic effect. **Simvastatin:** [NP] Decreased warfarin metabolism. **Sulfinpyrazone:** [NE] Inhibited warfarin metabolism. **Sulfonamides:** [NE] Inhibited warfarin metabolism. **Thyroid hormones:** [P] Enhanced clotting factor catabolism. **Trimethoprim-sulfamethoxazole:** [P] Inhibited warfarin metabolism; displaces from protein binding. **Voriconazole:** [NP] Decreased warfarin metabolism. *See also* Alcohol; Allopurinol. *Drugs that may decrease anticoagulant effect:* **Aminoglutethimide:** [P] Enzyme induction. **Barbiturates:** [P] Enzyme induction. **Bosentan:** [P] Enzyme induction. **Carbamazepine:** [P] Enzyme induction. **Cholestyramine:** [P] Reduced absorption of anticoagulant. **Glutethimide:** [P] Enzyme induction. **Nafcillin:** [NE] Enzyme induction. **Phenytoin:** [NE] Enzyme induction; anticoagulant effect may increase transiently at start of phenytoin therapy due to protein-binding displacement. **Primidone:** [P] Enzyme induction. **Rifabutin:** [P] Enzyme induction. **Rifampin:** [P] Enzyme induction. **St. John's wort:** [NE] Enzyme induction. *Effects of anticoagulants on other drugs:* **Hypoglycemics, oral:** [P] Dicumarol inhibits hepatic metabolism of tolbutamide and chlorpropamide. **Phenytoin:** [P] Dicumarol inhibits metabolism of phenytoin.
Antidepressants, tricyclic and heterocyclic	Inhibition of amine uptake into postganglionic adrenergic neuron. Antimuscarinic effects may be additive with other antimuscarinic drugs. Metabolism inducible. Susceptible to inhibition of metabolism via CYP2D6, CYP3A4, and other CYP450 enzymes.	**Amiodarone:** [P] Decreased antidepressant metabolism. **Barbiturates:** [P] Increased antidepressant metabolism. **Bupropion:** [NE] Decreased antidepressant metabolism. **Carbamazepine:** [NE] Enhanced metabolism of antidepressants. **Cimetidine:** [P] Decreased antidepressant metabolism. **Clonidine:** [P] Decreased clonidine antihypertensive effect. **Guanadrel:** [P] Decreased uptake of guanadrel into sites of action. **Guanethidine:** [P] Decreased uptake of guanethidine into sites of action. **Haloperidol:** [P] Decreased antidepressant metabolism. **Monoamine oxidase inhibitors:** [NP] Some cases of excitation, hyperpyrexia, mania, and convulsions, especially with serotonergic antidepressants such as clomipramine and imipramine, but many patients have received combination without ill effects.

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TABLE 66–1 Important drug interactions. (Continued)

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Antidepressants, tricyclic and heterocyclic (*cont.*)		**Quinidine:** [NE] Decreased antidepressant metabolism. **Rifampin:** [P] Increased antidepressant metabolism. **Selective serotonin reuptake inhibitors (SSRIs):** [P] Fluoxetine and paroxetine inhibit CYP2D6 and decrease metabolism of antidepressants metabolized by this enzyme (eg, desipramine). Citalopram, sertraline, and fluvoxamine are only weak inhibitors of CYP2D6, but fluvoxamine inhibits CYP1A2 and CYP3A4 and thus can inhibit the metabolism of antidepressants metabolized by these enzymes. **Sympathomimetics:** [P] Increased pressor response to norepinephrine, epinephrine, and phenylephrine. **Terbinafine:** [P] Decreased antidepressant metabolism.
Azole antifungals	Inhibition of CYP3A4 (itraconazole = ketoconazole > posaconazole > voriconazole > fluconazole). Inhibition of CYP2C9 (fluconazole, voriconazole). Susceptible to enzyme inducers (itraconazole, ketoconazole, voriconazole). Gastrointestinal absorption pH-dependent (itraconazole, ketoconazole, posaconazole). Inhibition of P-glycoprotein (itraconazole, ketoconazole, posaconazole).	**Barbiturates:** [P] Increased metabolism of itraconazole, ketoconazole, voriconazole. **Calcium channel blockers:** [P] Decreased calcium channel blocker metabolism. **Carbamazepine:** [P] Decreased carbamazepine metabolism. Potential increased metabolism of azole antifungal. **Cisapride:** [NP] Decreased metabolism of cisapride; possible ventricular arrhythmias. **Colchicine:** [P] Decreased metabolism and transport of colchicine. **Cyclosporine:** [P] Decreased metabolism of cyclosporine. **Digoxin:** [NE] Increased plasma concentrations of digoxin with itraconazole, posaconazole, and ketoconazole. **H_2-receptor antagonists:** [NE] Decreased absorption of itraconazole, ketoconazole, and posaconazole. **HMG-CoA reductase inhibitors:** [HP] Decreased metabolism of lovastatin, simvastatin, and, to a lesser extent, atorvastatin. **Phenytoin:** [P] Decreased metabolism of phenytoin with fluconazole and probably voriconazole. **Pimozide:** [NE] Decreased pimozide metabolism. **Proton pump inhibitors:** [P] Decreased absorption of itraconazole, ketoconazole, and posaconazole. **Rifabutin:** [P] Decreased rifabutin metabolism. Increased metabolism of itraconazole, ketoconazole, and voriconazole. **Rifampin:** [P] Increased metabolism of itraconazole, ketoconazole, and voriconazole. *See also* Antacids; Anticoagulants, oral.
Barbiturates	Induction of hepatic microsomal drug metabolizing enzymes. Additive central nervous system depression with other central nervous system depressants.	**Beta-adrenoceptor blockers:** [P] Increased β-blocker metabolism. **Calcium channel blockers:** [P] Increased calcium channel blocker metabolism. **Central nervous system depressants:** [HP] Additive central nervous system depression. **Corticosteroids:** [P] Increased corticosteroid metabolism. **Cyclosporine:** [NE] Increased cyclosporine metabolism. **Delavirdine:** [P] Increased delavirdine metabolism. **Doxycycline:** [P] Increased doxycycline metabolism. **Estrogens:** [P] Increased estrogen metabolism. **Methadone:** [NE] Increased methadone metabolism. **Phenothiazine:** [P] Increased phenothiazine metabolism. **Protease inhibitors:** [NE] Increased protease inhibitor metabolism. **Quinidine:** [P] Increased quinidine metabolism. **Sirolimus:** [NE] Increased sirolimus metabolism.

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TABLE 66–1 Important drug interactions. (Continued)

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Barbiturates (*cont.*)		**Tacrolimus:** [NE] Increased tacrolimus metabolism. **Theophylline:** [NE] Increased theophylline metabolism; reduced theophylline effect. **Valproic acid:** [P] Decreased phenobarbital metabolism. *See also* Anticoagulants, oral; Antidepressants, tricyclic.
Beta-adrenoceptor blockers	Beta-blockade (especially with nonselective agents such as propranolol) alters response to sympathomimetics with β-agonist activity (eg, epinephrine). Beta blockers that undergo extensive first-pass metabolism may be affected by drugs capable of altering this process. Beta blockers may reduce hepatic blood flow.	*Drugs that may increase β-blocker effect:* **Cimetidine:** [P] Decreased metabolism of β blockers that are cleared primarily by the liver, eg, propranolol. Less effect (if any) on those cleared by the kidneys, eg, atenolol, nadolol. **Selective serotonin reuptake inhibitors (SSRIs):** [P] Fluoxetine and paroxetine inhibit CYP2D6 and increase concentrations of timolol, propranolol, metoprolol, carvedilol, and labetalol. *Drugs that may decrease β-blocker effect:* **Enzyme inducers:** [P] Barbiturates, phenytoin, and rifampin may enhance β-blocker metabolism; other enzyme inducers may produce similar effects. **Nonsteroidal anti-inflammatory drugs:** [P] Indomethacin reduces antihypertensive response; other prostaglandin inhibitors probably also interact. *Effects of β blockers on other drugs:* **Clonidine:** [NE] Hypertensive reaction if clonidine is withdrawn while patient is taking propranolol. **Insulin:** [P] Inhibition of glucose recovery from hypoglycemia; inhibition of symptoms of hypoglycemia (except sweating); increased blood pressure during hypoglycemia. **Prazosin:** [P] Increased hypotensive response to first dose of prazosin. **Sympathomimetics:** [P] Increased pressor response to epinephrine (and possibly other sympathomimetics); this is more likely to occur with nonselective β blockers. *See also* Barbiturates; Theophylline.
Bile acid–binding resins	Resins may bind with orally administered drugs in gastrointestinal tract. Resins may bind in gastrointestinal tract with drugs that undergo enterohepatic circulation, even if the latter are given parenterally.	**Acetaminophen:** [NE] Decreased gastrointestinal absorption of acetaminophen. **Digitalis glycosides:** [NE] Decreased gastrointestinal absorption of digitoxin (possibly also digoxin). **Furosemide:** [P] Decreased gastrointestinal absorption of furosemide. **Methotrexate:** [NE] Reduced gastrointestinal absorption of methotrexate. **Mycophenolate:** [P] Reduced gastrointestinal absorption of mycophenolate. **Thiazide diuretics:** [P] Reduced gastrointestinal absorption of thiazides. **Thyroid hormones:** [P] Reduced thyroid absorption. *See also* Anticoagulants, oral.
Calcium channel blockers	Verapamil, diltiazem, and perhaps nicardipine (but not nifedipine) inhibit hepatic drug-metabolizing enzymes. Metabolism (via CYP3A4) of diltiazem, felodipine, nicardipine, nifedipine, verapamil, and probably other calcium channel blockers subject to induction and inhibition.	**Atazanavir:** [NE] Decreased metabolism of calcium channel blockers. **Carbamazepine:** [P] Decreased carbamazepine metabolism with diltiazem and verapamil; possible increase in calcium channel blocker metabolism. **Cimetidine:** [NP] Decreased metabolism of calcium channel blockers. **Clarithromycin:** [P] Decreased metabolism of calcium channel blockers. **Colchicine:** Decreased colchicine metabolism and transport with diltiazem and verapamil. **Conivaptan:** [NE] Decreased metabolism of calcium channel blockers.

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(*continued*)

TABLE 66–1 Important drug interactions. (Continued)

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Calcium channel blockers (*cont.*)		**Cyclosporine:** [P] Decreased cyclosporine metabolism with diltiazem, nicardipine, verapamil. **Erythromycin:** [P] Decreased metabolism of calcium channel blockers. **Phenytoin:** [NE] Increased metabolism of calcium channel blockers. **Rifampin:** [P] Increased metabolism of calcium channel blockers. **Sirolimus:** [P] Decreased sirolimus metabolism with diltiazem, nicardipine, verapamil. **Tacrolimus:** [P] Decreased tacrolimus metabolism with diltiazem, nicardipine, verapamil. *See also* Azole antifungals; Barbiturates; Theophylline; Digitalis glycosides.
Carbamazepine	Induction of hepatic microsomal drug-metabolizing enzymes. Susceptible to inhibition of metabolism, primarily by CYP3A4.	**Atazanavir:** [NE] Decreased metabolism of carbamazepine. **Cimetidine:** [P] Decreased carbamazepine metabolism. **Clarithromycin:** [P] Decreased carbamazepine metabolism. **Corticosteroids:** [P] Increased corticosteroid metabolism. **Cyclosporine:** [P] Increased cyclosporine metabolism and possible decreased carbamazepine metabolism. **Danazol:** [P] Decreased carbamazepine metabolism. **Doxycycline:** [P] Increased doxycycline metabolism. **Erythromycin:** [NE] Decreased carbamazepine metabolism. **Fluvoxamine:** [NE] Decreased carbamazepine metabolism. **Estrogens:** [P] Increased estrogen metabolism. **Haloperidol:** [P] Increased haloperidol metabolism. **Isoniazid:** [P] Decreased carbamazepine metabolism. **Nefazodone:** [NE] Decreased carbamazepine metabolism. **Propoxyphene:** [HP] Decreased carbamazepine metabolism and possible increased propoxyphene metabolism. **Rifampin:** [P] Increased carbamazepine metabolism. **Selective serotonin reuptake inhibitors (SSRIs):** [NE] Fluoxetine and fluvoxamine decrease carbamazepine metabolism. **Sirolimus:** [P] Increased sirolimus metabolism. **St. John's wort:** [P] Increased carbamazepine metabolism. **Tacrolimus:** [P] Increased tacrolimus metabolism. **Theophylline:** [NE] Increased theophylline metabolism. *See also* Anticoagulants, oral; Antidepressants, tricyclic; Azole antifungals; Calcium channel blockers.
Chloramphenicol	Inhibits hepatic drug-metabolizing enzymes.	**Phenytoin:** [P] Decreased phenytoin metabolism. **Sulfonylurea hypoglycemics:** [P] Decreased sulfonylurea metabolism. *See also* Anticoagulants, oral.

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(*continued*)

TABLE 66–1 Important drug interactions. (Continued)

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Cimetidine	Inhibits hepatic microsomal drug-metabolizing enzymes. (Ranitidine, famotidine, and nizatidine do not.) May inhibit the renal tubular secretion of weak bases.	**Atazanavir:** [NP] Decreased absorption of atazanavir (requires acid for absorption; other H_2 blockers and proton pump inhibitors would be expected to have the same effect). **Benzodiazepines:** [P] Decreased metabolism of alprazolam, chlordiazepoxide, diazepam, halazepam, prazepam, and clorazepate but not oxazepam, lorazepam, or temazepam. **Carmustine:** [NE] Increased bone marrow suppression. **Indinavir:** [NP] Decreased absorption of indinavir (requires acid for absorption; other H_2 blockers and proton pump inhibitors would be expected to have the same effect). **Lidocaine:** [P] Decreased metabolism of lidocaine; increased serum lidocaine concentrations. **Phenytoin:** [NE] Decreased phenytoin metabolism; increased serum phenytoin concentrations. **Procainamide:** [P] Decreased renal excretion of procainamide; increased serum procainamide concentrations. **Quinidine:** [P] Decreased metabolism of quinidine; increased serum quinidine concentrations. **Theophylline:** [P] Decreased theophylline metabolism; increased plasma theophylline concentrations. *See also* Anticoagulants, oral; Antidepressants, tricyclic; Azole antifungals; Beta-adrenoceptor blockers; Calcium channel blockers; Carbamazepine.
Cisapride	Susceptible to inhibition of metabolism by CYP3A4 inhibitors. High cisapride serum concentrations can result in ventricular arrhythmias.	**Atazanavir:** [NE] Decreased metabolism of cisapride; possible ventricular arrhythmia. **Clarithromycin:** [NP] Decreased metabolism of cisapride; possible ventricular arrhythmia. **Cyclosporine:** [NE] Decreased metabolism of cisapride; possible ventricular arrhythmia. **Erythromycin:** [NP] Decreased metabolism of cisapride; possible ventricular arrhythmia. **Nefazodone:** [NP] Possibly decreased metabolism of cisapride by CYP3A4; possible ventricular arrhythmia. **Ritonavir:** [NE] Decreased metabolism of cisapride; possible ventricular arrhythmia. **Selective serotonin reuptake inhibitors (SSRIs):** [NP] Fluvoxamine inhibits CYP3A4 and probably decreases cisapride metabolism; possible ventricular arrhythmia. *See also* Azole antifungals.
Colchicine	Susceptible to inhibition of CYP3A4 metabolism and P-glycoprotein transport.	**Amiodarone:** [NP] Decreased colchicine metabolism and transport. **Amprenavir:** [P] Decreased colchicine metabolism. **Carbamazepine:** [P] Increased metabolism of colchicine. **Clarithromycin:** [P] Decreased colchicine metabolism and transport. **Cyclosporine:** [P] Decreased colchicine metabolism and transport. **Dronedarone:** [NE] Decreased colchicine transport. **Erythromycin:** [P] Decreased colchicine metabolism and transport. **Nefazodone:** [NE] Decreased colchicine metabolism. **Rifampin:** [P] Increased colchicine metabolism. **Ritonavir:** [P] Decreased colchicine metabolism. *See also* Azole antifungals, Calcium channel blockers.

HP, Highly predictable. Interaction occurs in almost all patients receiving the interacting combination; P, Predictable. Interaction occurs in most patients receiving the combination; NP, Not predictable. Interaction occurs only in some patients receiving the combination; NE, Not established. Insufficient data available on which to base estimate of predictability.

(*continued*)

TABLE 66–1 Important drug interactions. (Continued)

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Cyclosporine	Metabolism inducible. Susceptible to inhibition of metabolism by CYP3A4. (Tacrolimus and sirolimus appear to have similar interactions.)	**Aminoglycosides:** [NE] Possible additive nephrotoxicity. **Amphotericin B:** [NE] Possible additive nephrotoxicity. **Amprenavir:** [P] Increased cyclosporine metabolism. **Androgens:** [NE] Increased serum cyclosporine. **Atazanavir:** [NE] Decreased metabolism of cyclosporine. **Barbiturates:** [P] Increased cyclosporine metabolism. **Carbamazepine:** [P] Increased cyclosporine metabolism. **Clarithromycin:** [P] Decreased cyclosporine metabolism. **Erythromycin:** [NP] Decreased cyclosporine metabolism. **Lovastatin:** [NP] Decreased metabolism of lovastatin. Myopathy and rhabdomyolysis noted in patients taking lovastatin and cyclosporine. **Nefazodone:** [P] Decreased cyclosporine metabolism. **Phenytoin:** [NE] Increased cyclosporine metabolism. **Pimozide:** [NE] Decreased pimozide metabolism. **Quinupristin:** [P] Increased cyclosporine metabolism. **Rifampin:** [P] Increased cyclosporine metabolism. **Ritonavir:** [P] Decreased cyclosporine metabolism. **Simvastatin:** [NP] Decreased metabolism of simvastatin. Myopathy and rhabdomyolysis noted in patients taking simvastatin and cyclosporine. **St. John's wort:** [NP] Increased cyclosporine metabolism. *See also* Azole antifungals; Barbiturates; Calcium channel blockers.
Digitalis glycosides	Digoxin susceptible to alteration of gastrointestinal absorption. Digitalis toxicity may be increased by drug-induced electrolyte imbalance (eg, hypokalemia). Digitoxin metabolism inducible. Renal and nonrenal excretion of digoxin susceptible to inhibition.	*Drugs that may increase digitalis effect:* **Amiodarone:** [P] Increased plasma digoxin concentrations. **Azithromycin:** [NP] Increased plasma concentration of digoxin. **Clarithromycin:** [P] Increased plasma concentration of digoxin. **Diltiazem:** [P] Increased plasma digoxin and additive AV conduction effects. **Erythromycin:** [NP] Increased plasma concentration of digoxin. **Potassium-depleting drugs:** [P] Increases likelihood of digitalis toxicity. **Propafenone:** [P] Increases plasma digoxin levels. **Quinidine:** [HP] Increased digoxin plasma concentrations; displaces digoxin from tissue binding sites. **Spironolactone:** [NE] Decreased renal digoxin excretion and interferes with some serum digoxin assays. **Verapamil:** [P] Increased plasma digoxin levels and additive AV conduction effects. *See also* Azole antifungals. *Drugs that may decrease digitalis effect:* **Kaolin-pectin:** [P] Decreased gastrointestinal digoxin absorption. **Rifampin:** [NE] Increased metabolism of digitoxin and elimination digoxin. **Sulfasalazine:** [NE] Decreased gastrointestinal digoxin absorption. *See also* Antacids; Bile acid–binding resins.

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(*continued*)

TABLE 66–1 Important drug interactions. (Continued)

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Disulfiram	Inhibits hepatic microsomal drug-metabolizing enzymes. Inhibits aldehyde dehydrogenase.	**Benzodiazepines:** [P] Decreased metabolism of chlordiazepoxide and diazepam but not lorazepam and oxazepam. **Metronidazole:** [NE] Confusion and psychoses reported in patients receiving this combination; mechanisms unknown. **Phenytoin:** [P] Decreased phenytoin metabolism. *See also* Alcohol; Anticoagulants, oral.
Estrogens	Metabolism inducible. Enterohepatic circulation of estrogen may be interrupted by alteration in bowel flora (eg, due to antibiotics).	**Ampicillin:** [NP] Interruption of enterohepatic circulation of estrogen; possible reduction in oral contraceptive efficacy. Some other oral antibiotics may have a similar effect. **Bosentan:** [NP] Enzyme induction leading to reduced estrogen effect. **Corticosteroids:** [P] Decreased metabolism of corticosteroids leading to increased corticosteroid effect. **Griseofulvin:** [NE] Possible inhibition of oral contraceptive efficacy; mechanism unknown. **Phenytoin:** [NP] Increased estrogen metabolism; possible reduction in oral contraceptive efficacy. **Primidone:** [NP] Increased estrogen metabolism; possible reduction in oral contraceptive efficacy. **Rifabutin:** [NP] Increased estrogen metabolism; possible reduction in oral contraceptive efficacy. **Rifampin:** [NP] Increased estrogen metabolism; possible reduction in oral contraceptive efficacy. **St. John's wort:** [NE] Increased estrogen metabolism; possible reduction in oral contraceptive efficacy. *See also* Barbiturates; Carbamazepine.
HMG-CoA reductase inhibitors	Lovastatin, simvastatin, and, to a lesser extent, atorvastatin are susceptible to CYP3A4 inhibitors; lovastatin, simvastatin, and, to a lesser extent, atorvastatin are susceptible to CYP3A4 inducers; increased risk of additive myopathy risk with other drugs that can cause myopathy.	**Amiodarone:** [NP] Decreased statin metabolism. **Atazanavir:** [NP] Decreased statin metabolism. **Carbamazepine:** [P] Increased statin metabolism. **Clarithromycin:** [P] Decreased statin metabolism. **Clofibrate:** [NP] Increased risk of myopathy. **Cyclosporine:** [P] Decreased statin metabolism. **Diltiazem:** [NE] Decreased statin metabolism. **Erythromycin:** [P] Decreased statin metabolism. **Gemfibrozil:** [NP] Increased plasma lovastatin and simvastatin and increase the risk of myopathy. **Indinavir:** [NE] Decreased statin metabolism. **Nefazodone:** [NE] Decreased statin metabolism. **Rifampin:** [P] Increased statin metabolism. **Ritonavir:** [NE] Decreased statin metabolism. **St. John's wort:** [NP] Increased statin metabolism. **Verapamil:** [NE] Decreased statin metabolism. *See also* Azole antifungals; Cyclosporine.
Iron	Binds with drugs in gastrointestinal tract, reducing absorption.	**Methyldopa:** [NE] Decreased methyldopa absorption. **Mycophenolate:** [P] Decreased absorption of mycophenolate. **Quinolones:** [P] Decreased absorption of ciprofloxacin and other quinolones. **Tetracyclines:** [P] Decreased absorption of tetracyclines; decreased efficacy of iron. **Thyroid hormones:** [P] Decreased thyroxine absorption. *See also* Antacids.

HP, Highly predictable. Interaction occurs in almost all patients receiving the interacting combination; P, Predictable. Interaction occurs in most patients receiving the combination; NP, Not predictable. Interaction occurs only in some patients receiving the combination; NE, Not established. Insufficient data available on which to base estimate of predictability.

(*continued*)

TABLE 66–1 Important drug interactions. (Continued)

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Levodopa	Levodopa degraded in gut prior to reaching sites of absorption. Agents that alter gastrointestinal motility may alter degree of intraluminal degradation. Anti-parkinsonism effect of levodopa susceptible to inhibition by other drugs.	**Clonidine:** [NE] Inhibited antiparkinsonism effect. **Monoamine oxidase inhibitors:** [P] Hypertensive reaction (carbidopa prevents the interaction). **Papaverine:** [NE] Inhibited antiparkinsonism effect. **Phenothiazines:** [P] Inhibited antiparkinsonism effect. **Phenytoin:** [NE] Inhibited antiparkinsonism effect. **Pyridoxine:** [P] Inhibited antiparkinsonism effect (carbidopa prevents the interaction). *See also* Antimuscarinics.
Lithium	Renal lithium excretion sensitive to changes in sodium balance. (Sodium depletion tends to cause lithium retention.) Susceptible to drugs enhancing central nervous system lithium toxicity.	**ACE inhibitors:** [NE] Probably reduce renal clearance of lithium; increase lithium effect. **Angiotensin II receptor blockers:** [NE] Probably reduce renal clearance of lithium; increase lithium effect. **Diuretics (especially thiazides):** [P] Decreased excretion of lithium; furosemide may be less likely to produce this effect than thiazide diuretics. **Haloperidol:** [NP] Occasional cases of neurotoxicity in manic patients, especially with large doses of one or both drugs. **Methyldopa:** [NE] Increased likelihood of central nervous system lithium toxicity. **Nonsteroidal anti-inflammatory drugs:** [NE] Reduced renal lithium excretion (except sulindac and salicylates). **Theophylline:** [P] Increased renal excretion of lithium; reduced lithium effect.
Macrolides	The macrolides clarithromycin and erythromycin are known to inhibit CYP3A4 and P-glycoprotein. Azithromycin does not appear to inhibit CYP3A4 but is a modest inhibitor of P-glycoprotein.	**Pimozide:** [NE] Increased pimozide concentrations. **Quinidine:** [P] Increased serum quinidine concentrations. **Theophylline:** [P] Decreased metabolism of theophylline. *See also* Anticoagulants, oral; Calcium channel blockers; Carbamazepine; Cisapride; Colchicine; Cyclosporine; Digitalis glycosides; HMG-CoA reductase inhibitors.
Monoamine oxidase inhibitors (MAOIs)	Increased norepinephrine stored in adrenergic neuron. Displacement of these stores by other drugs may produce acute hypertensive response. MAOIs have intrinsic hypoglycemic activity.	**Anorexiants:** [P] Hypertensive episodes due to release of stored norepinephrine (benzphetamine, diethylpropion, mazindol, phendimetrazine, phentermine). **Antidiabetic agents:** [P] Additive hypoglycemic effect. **Buspirone:** [NE] Possible serotonin syndrome; *avoid* concurrent use. **Dextromethorphan:** [NE] Severe reactions (hyperpyrexia, coma, death) have been reported. **Guanethidine:** [P] Reversal of the hypotensive action of guanethidine. **Mirtazapine:** [NE] Possible serotonin syndrome; *avoid* concurrent use. **Narcotic analgesics:** [NP] Some patients develop hypertension, rigidity, excitation; meperidine may be more likely to interact than morphine. **Nefazodone:** [NE] Possible serotonin syndrome; *avoid* concurrent use. **Phenylephrine:** [P] Hypertensive episode, since phenylephrine is metabolized by monoamine oxidase. **Selective serotonin reuptake inhibitors (SSRIs):** [P] Fatalities have occurred due to serotonin syndrome; contraindicated in patients taking MAOIs. **Sibutramine:** [NE] Possible serotonin syndrome; *avoid* concurrent use.

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(*continued*)

TABLE 66–1 Important drug interactions. (Continued)

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Monoamine oxidase inhibitors (MAOIs) (*cont.*)		**Sympathomimetics (indirect-acting):** [HP] Hypertensive episode due to release of stored norepinephrine (amphetamines, ephedrine, isometheptene, phenylpropanolamine, pseudoephedrine). **Tramadol:** [NE] Possible serotonin syndrome; *avoid* concurrent use. **Venlafaxine:** [NE] Possible serotonin syndrome; *avoid* concurrent use. *See also* Antidepressants, tricyclic and heterocyclic; Levodopa.
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Prostaglandin inhibition may result in reduced renal sodium excretion, impaired resistance to hypertensive stimuli, and reduced renal lithium excretion. Most NSAIDs inhibit platelet function; may increase likelihood of bleeding due to other drugs that impair hemostasis.	**ACE inhibitors:** [P] Decreased antihypertensive response. **Angiotensin II receptor blockers:** [P] Decreased antihypertensive response. **Furosemide:** [P] Decreased diuretic, natriuretic, and antihypertensive response to furosemide. **Hydralazine:** [NE] Decreased antihypertensive response to hydralazine. **Methotrexate:** [NE] Possibly increased methotrexate toxicity (especially with anticancer doses of methotrexate). **Selective serotonin reuptake inhibitors (SSRIs):** Increased risk of bleeding due to platelet inhibition. **Thiazide diuretics:** [P] Decreased diuretic, natriuretic, and antihypertensive response. **Triamterene:** [NE] Decreased renal function noted with triamterene plus indomethacin in both healthy subjects and patients. *See also* Anticoagulants, oral; Beta-adrenoceptor blockers; Lithium.
Phenytoin	Induces hepatic microsomal drug metabolism. Susceptible to inhibition of metabolism by CYP2C9 and, to a lesser extent, CYP2C19.	*Drugs whose metabolism is stimulated by phenytoin:* **Corticosteroids:** [P] Decreased serum corticosteroid levels. **Doxycycline:** [P] Decreased serum doxycycline levels. **Methadone:** [P] Decreased serum methadone levels; watch for withdrawal symptoms. **Mexiletine:** [NE] Decreased serum mexiletine levels. **Quinidine:** [P] Decreased serum quinidine levels. **Theophylline:** [NE] Decreased serum theophylline levels. *See also* Calcium channel blockers; Cyclosporine; Estrogens. *Drugs that inhibit phenytoin metabolism:* **Amiodarone:** [P] Increased serum phenytoin; possible reduction in serum amiodarone. **Capecitabine:** [NE] Increased serum phenytoin. **Chloramphenicol:** [P] Increased serum phenytoin. **Felbamate:** [P] Increased serum phenytoin. **Fluorouracil:** [NE] Increased serum phenytoin. **Fluvoxamine:** [NE] Increased serum phenytoin. **Isoniazid:** [NP] Increased serum phenytoin; problem primarily with slow acetylators of isoniazid. **Metronidazole:** [NP] Increased serum phenytoin. **Ticlopidine:** [NP] Increased serum phenytoin. *See also* Azole antifungals; Cimetidine; Disulfiram. *Drugs that enhance phenytoin metabolism:* **Carbamazepine:** [P] Decreased serum phenytoin levels. **Rifampin:** [P] Decreased serum phenytoin levels.

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(*continued*)

TABLE 66–1 Important drug interactions.

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Pimozide	Susceptible to CYP3A4 inhibitors; may exhibit additive effects with other agents that prolong QT_c interval.	**Nefazodone:** [NE] Decreased pimozide metabolism. *See also* Azole antifungals; Cyclosporine; Macrolides.
Potassium-sparing diuretics (amiloride, eplerenone, spironolactone, triamterene)	Additive effects with other agents increasing serum potassium concentration. May alter renal excretion of substances other than potassium (eg, digoxin, hydrogen ions).	**ACE inhibitors:** [NP] Additive hyperkalemic effect. **Angiotensin II receptor blockers:** [NP] Additive hyperkalemic effect. **Potassium-sparing diuretics:** [P] Additive hyperkalemic effect. **Potassium supplements:** [P] Additive hyperkalemic effect; especially a problem in presence of renal impairment. *See also* Digitalis glycosides; Nonsteroidal anti-inflammatory drugs.
Probenecid	Interference with renal excretion of drugs that undergo active tubular secretion, especially weak acids. Inhibition of glucuronide conjugation of other drugs.	**Clofibrate:** [P] Reduced glucuronide conjugation of clofibric acid. **Methotrexate:** [P] Decreased renal methotrexate excretion; possible methotrexate toxicity. **Palatrexate:** [P] Decreased renal palatrexate excretion; possible palatrexate toxicity. **Penicillin:** [P] Decreased renal penicillin excretion. **Salicylates:** [P] Decreased uricosuric effect of probenecid (interaction unlikely with less than 1.5 g of salicylate daily).
Quinidine	Substrate of CYP3A4. Inhibits CYP2D6. Renal excretion susceptible to changes in urine pH. Additive effects with other agents that prolong the QT_c interval.	**Acetazolamide:** [P] Decreased renal quinidine excretion due to increased urinary pH; elevated serum quinidine. **Amiodarone:** [NP] Increased serum quinidine levels. **Kaolin-pectin:** [NE] Decreased gastrointestinal absorption of quinidine. **Rifampin:** [P] Increased hepatic quinidine metabolism. **Thioridazine:** [NE] Decreased thioridazine metabolism; additive prolongation of QT_c interval. *See also* Anticoagulants, oral; Antidepressants, tricyclic; Barbiturates; Cimetidine; Digitalis glycosides; Macrolides; Phenytoin.
Quinolone antibiotics	Susceptible to inhibition of gastrointestinal absorption. Some quinolones inhibit CYP1A2.	**Caffeine:** [P] Ciprofloxacin, enoxacin, pipedemic acid, and, to a lesser extent, norfloxacin inhibit caffeine metabolism. **Sucralfate:** [HP] Reduced gastrointestinal absorption of ciprofloxacin, norfloxacin, and probably other quinolones. **Theophylline:** [P] Ciprofloxacin, enoxacin, and, to a lesser extent, norfloxacin inhibit theophylline metabolism; gatifloxacin, levofloxacin, lomefloxacin, ofloxacin, and sparfloxacin appear to have little effect. *See also* Antacids; Anticoagulants, oral; Iron.
Rifampin	Inducer (strong) of hepatic microsomal drug-metabolizing enzymes.	**Corticosteroids:** [P] Increased corticosteroid hepatic metabolism; reduced corticosteroid effect. **Mexiletine:** [NE] Increased mexiletine metabolism; reduced mexiletine effect. **Sulfonylurea hypoglycemics:** [P] Increased hepatic metabolism of tolbutamide and probably other sulfonylureas metabolized by the liver (including chlorpropamide). **Theophylline:** [P] Increased theophylline metabolism; reduced theophylline effect. *See also* Anticoagulants, oral; Azole antifungals; Beta-adrenoceptor blockers; Calcium channel blockers; Cyclosporine; Digitalis glycosides; Estrogens.

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(*continued*)

TABLE 66–1 Important drug interactions.

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Salicylates	Interference with renal excretion of drugs that undergo active tubular secretion. Salicylate renal excretion dependent on urinary pH when large doses of salicylate used. Aspirin (but not other salicylates) interferes with platelet function. Large doses of salicylates have intrinsic hypoglycemic activity.	**Carbonic anhydrase inhibitors:** [NE] Increased acetazolamide serum concentrations; increase salicylate toxicity due to decreased blood pH. **Corticosteroids:** [P] Increased salicylate elimination; possible additive toxic effect on gastric mucosa. **Heparin:** [NE] Increased bleeding tendency with aspirin, but probably not with other salicylates. **Methotrexate:** [P] Decreased renal methotrexate clearance; increases methotrexate toxicity (primarily at anticancer doses). **Sulfinpyrazone:** [HP] Decreased uricosuric effect of sulfinpyrazone (interaction unlikely with less than 1.5 g of salicylate daily). *See also* Antacids; Anticoagulants, oral; Probenecid.
Selective serotonin reuptake inhibitors	Selective serotonin reuptake inhibitors (SSRIs) can lead to excessive serotonin response when administered with other serotonergic drugs (eg, MAOIs). Some SSRIs inhibit various cytochrome P450s including CYP2D6, CYP1A2, CYP3A4, and CYP2C19.	**Theophylline:** [P] Decreased metabolism by fluvoxamine-induced inhibition of CYP. *See also* Anticoagulants, oral; Antidepressants, tricyclic and heterocyclic; Beta-adrenoceptor blockers; Carbamazepine; Cisapride; Colchicine; Cyclosporine; HMG-CoA reductase inhibitors; Monoamine oxidase inhibitors; Nonsteroidal anti-inflammatory drugs; Phenytoin; Pimozide.
Theophylline	Susceptible to inhibition of hepatic metabolism by CYP1A2. Metabolism inducible.	**Benzodiazepines:** [NE] Inhibition of benzodiazepine sedation. **Beta-adrenoceptor blockers:** [NP] Decreased theophylline bronchodilation especially with nonselective β blockers. **Diltiazem:** [NP] Decreased theophylline metabolism. **Smoking:** [HP] Increased theophylline metabolism. **Tacrine:** [NP] Decreased theophylline metabolism. **Ticlopidine:** [NE] Decreased theophylline metabolism. **Verapamil:** [NP] Decreased theophylline metabolism. **Zileuton:** [NP] Decreased theophylline metabolism. *See also* Barbiturates; Carbamazepine; Cimetidine; Lithium; Macrolides; Phenytoin; Quinolones; Rifampin.

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