Chapter 7
The Antifungal Drugs Used in Skin Disease

Bárður Sigurgeirsson and Roderick J. Hay

7.1 Introduction

The medical treatment of fungal infections affecting the skin has changed considerably over the past 200 years from the application of crude astringent or emollient dressings to the current use of active and specific antifungal agents. Indeed in the early part of the nineteenth century, there was still a debate over the need to treat fungal infections, such as favus, at all, some arguing that the infection "exerted a salutary influence on the constitution" and therefore required no treatment, whereas others believed that it always interfered with "the moral and intellectual faculties" of children affected by it [1] and should be treated. There were a wide variety of different options although popular choices including bathing affected areas in sulfurous or alkaline waters. The later treatments devised were equally controversial. For instance, in the *Dermatophyte* infection, favus, the use of depilatory plasters was much advocated [1]. The plaster might contain, among other ingredients, copper bicarbonate and pitch (tar), both of which are now recognized to have antifungal properties. The plaster was applied to the affected scalp and left in place for 2–3 days before being rapidly removed and then replaced by another such plaster; such treatment was widely practiced although acknowledged to be very distressing to the patient. A more humane approach used a depilatory ointment containing astringents such as potassium bicarbonate in hog's lard applied every 10–15 min to the scalp for varying periods. This resulted in inflammation and subsequent shedding of the affected hairs without the trauma of physical removal.

B. Sigurgeirsson, MD, PhD
Department of Dermatology, Faculty of Medicine, University of Iceland, Reykjavík, Iceland

R.J. Hay, DM, FRCP (✉)
Department of Dermatology, Kings College London and Kings College Hospital NHS Trust, London, UK
e-mail: roderick.hay@ifd.org

© Springer International Publishing Switzerland 2016

J.H. Ólafsson, R.J. Hay (eds.), *Antibiotic and Antifungal Therapies in Dermatology*, DOI 10.1007/978-3-319-39424-4_7

The introduction of early precursors of the modern approach to the development of antibiotics through the work of the new chemical and dyeing industries in the late nineteenth century provided a number of different chemicals, some of which had an antifungal effect. They included gentian violet, brilliant green, and magenta. With the passage of time, some of these became viable additions to a list of antifungal treatments available. These included brilliant green [2], gentian violet [3], and magenta paint, the last of which, when combined with resorcinol, was known as Castellani's paint after Aldo Castellani [4]. Gentian violet, while less effective in *Dermatophyte* infections, had a therapeutic effect in *Candida* infections.

A further advance was the combination of salicylic acid with benzoic acid, the former providing a means of descaling fungal infected skin and the other in inhibiting growth of the organisms. Benzoic acid compound was introduced as an antifungal treatment for superficial mycoses and is known as Whitfield's ointment. It is still available for use today [5]. It contains a mixture of 3 % salicylic acid and 6 % benzoic acid. After 1945 developments in treatment focused on antifungals with specific antifungal activity. The first of these, mainly used for superficial infections, were derivatives of undecylenic acid [6] such as zinc undecenoate which inhibits the growth of *Dermatophytes* or thiocarbamates, tolnaftate [7], and tolciclate [8] which were the first inhibitors of squalene epoxidase which plays a key role in the biosynthesis of ergosterol in the fungal cell membrane. Another early specific antifungal was haloprogin, an acetylenic compound, which was thought to inhibit oxygen uptake; haloprogin had a broader spectrum of activity, affecting yeasts as well as *Dermatophyte* fungi. With the discovery of the antifungal activity of a novel antibiotic, nystatin, [9] in 1950, a new family of antifungal agents, the polyenes, also derived from microorganisms, *Streptomyces* species, such as *S. nodosus*, evolved. These include the topically active compounds nystatin and natamycin [10] as well as amphotericin B [11] which when stabilized with bile salts lasts provided an intravenous means of treatment. Other polyene drugs, such as hamycin, were not developed further for human use. Nystatin is still used in the treatment of superficial mycoses, and amphotericin B, although usually nowadays given in a lipid-associated form, remains a first-line drug in the management of systemic mycoses. In 1958 griseofulvin, a compound synthesized of the mold fungus *Penicillium griseofulvum*, was found to be active orally in the treatment of dermatophytosis in humans [12], and its rapid development led to the rapid elimination of tinea capitis in much of Europe and the United States. It was only active orally although many attempts have been made to produce a topically active version; yet none have been commercially viable. The drug works through inhibition of the formation of microtubules in the fungal cell.

The early 1970s saw the introduction of the first azole antifungals whose mode of action was on the formation of the fungal cell membrane at the step of inhibition of 14 α demethylase. The first products miconazole [13] and econazole [14] have been followed by other imidazoles and then by a subbranch of this group called triazoles. Ketoconazole was the first of these compounds to be found to have activity after oral absorption [15] although early formulations of clotrimazole in the

form of troches produced low serum levels. Ketoconazole was succeeded by fluconazole and then by newer triazoles such as itraconazole [16], posaconazole [17], and voriconazole [18], all of which are absorbed after oral administration. Another family of antifungal agents, the allylamines, was developed which had both topical, terbinafine, butenafine, and naftifine, and oral activities, terbinafine [19]. These are all potent inhibitors of squalene epoxidase. Ciclopirox olamine, a hydroxypyridone antifungal which disrupts the cell membrane structure [20], and the morpholine derivatives amorolfine which inhibits two stages of the formation of ergosterol, Δ14 reductase and Δ7-D8 isomerase activity, were to later additions.

Other recent developments have been the introduction of the echinocandins such as caspofungin, anidulafungin, and micafungin, all available as intravenous compounds used in the treatment of *Candida* and other systemic infections [21]. They act by inhibition of the formation of the fungal cell wall through interaction with 1,3 β-glucan synthase. They are not used in dermatology. The triazole antifungals have also expanded, although at the time of writing no new drugs have been licensed: albaconazole, isavuconazole, ravuconazole, terconazole, and pramiconazole [22–24]. A further topical thiazole agent, abafungin [25], has also been assessed in clinical trials, mainly against *Dermatophyte*s, but has not yet been licensed.

Much work has also been performed to try to alter the way in which antifungals are absorbed, penetrate, or achieve optimal bioactivity. These include the formulation of amphotericin B with lipids such as liposomes (AmBisome) or lipid microstrands (Abelcet), as a means of reducing toxicity [26]. The reformulation of azoles such as itraconazole to overcome variations in absorption, e.g., Lozanoc [27], has also been attempted. In the case of the topical agents for treatment of cutaneous mycoses, there has been considerable interest in developing other methods of treatment that improve nail penetration. Some of these compounds are available such as amorolfine [28] nail lacquer which is one of the first agents to be presented in the form of a Transungual Delivery System, or TUDS, designed to enhance penetration, in this case by allowing the drugs to concentrate in a stable base before penetration through the nail plate; others such as oxaborole and some of the terbinafine penetration enhancers (see Chapter 10) are in development.

Under specific sections, other approaches to therapy including lasers and photodynamic therapy will be discussed.

In the current day, the treatment of fungal infections is now comparatively straightforward, and in uncomplicated infections, cure rates are around 80 % [29]. The treatment results are less satisfactory in certain forms of superficial fungal infection, namely, onychomycosis, mycoses in the presence of immunodeficiency, infection due to uncommon organisms such as *Fusarium* or *Neoscytalidium* species, and very widespread infections such as extensive tinea corporis. There is now a wide selection of antifungal agents which can be used in both topical and oral formulations [30–33]. All these are effective in a substantial majority of patients, provided they are used regularly and as instructed.

7.2 Topical Applications

A great variety of topical applications have been used for the treatment of ringworm infections [32]. Allergic contact dermatitis is rare. Irritant effects may occur with any of them, especially on raw skin and in fissures between the toes. However benzoic acid compound ointment (Whitfield's ointment), full strength, is particularly an irritant and is not used on tender skin sites, such as the scrotum or the groins. Magenta paint (Castellani's paint) is still used in some cases of inflammatory tinea pedis, particularly when bacterial infection coexists, although potassium permanganate followed by a topical antifungal is preferred. Other cream or powder preparations that can be purchased without prescription include tolnaftate or zinc undecenoate.

Imidazole preparations for topical use, such as clotrimazole, econazole, and ketoconazole, are now well established as effective treatments in ringworm infections with an extremely low incidence of adverse reactions; other drugs in this group, miconazole, isoconazole, tioconazole, and sulconazole, are equally effective. Newer preparations such as sertaconazole, luliconazole [34], and isoconazole [35] are available in some countries. Generally they are used in cream, solution, or spray formulations at a concentration of 1 %. Most are used twice daily for 2–4 weeks although bifonazole is licensed for once-daily use.

The major topical alternative is the topical formulation of terbinafine. Terbinafine applied topically has been shown to produce responses in some *Dermatophyte* infections in very short periods of application, e.g., 1–7 days. There is also a topical formulation of terbinafine which is designed for use in infections of the sole of the foot.

Ciclopirox, amorolfine, and bifonazole are available as topical treatments in some but not all countries. The first two agents are available as specially formulated topical nail treatments and the latter as both a cream formulation and as combined treatment in a urea based for nail ablation.

The most recent Cochrane review of topical treatments for foot infections indicates little difference in efficacy between these different azole compounds and alternatives.

7.3 Oral Antifungals

7.3.1 Griseofulvin

This is a metabolic product derived from several species of *Penicillium*, which was first isolated from *P. griseofulvum*. Its activity, which is fungistatic, is largely restricted to *Dermatophyte* infections. It has little activity against yeasts and other mold fungi. The mode of action appears to be in part, through inhibition of the formation of intracellular microtubules; as a result it inhibits nucleic acid synthesis,

arresting cell division and inhibiting fungal cell wall synthesis [36–38]. Resistance to griseofulvin among *Dermatophytes* is rare. The smaller particle size microcrystalline preparations of griseofulvin are better absorbed than those with larger particles, and the micronized form is now the standard preparation. Unlike itraconazole, griseofulvin is not firmly bound to keratin.

The usual human regimen is 10 mg/kg/day (1,000–2,000 mg daily) given in tablet form, or solution form for children; the latter is no longer available in many countries. Treatment duration varies between 2 and 4 weeks for tinea corporis to over 1 year for onychomycosis of toenails. In tinea capitis, a single dose of 1–2 g griseofulvin has been reported to be effective in some patients with tinea capitis. Drug interaction with phenobarbital and coumarin anticoagulants occurs. Headaches and nausea are common complaints with griseofulvin; however, serious side effects have been extremely rare. There are a few reports of apparent precipitation or exacerbation of systemic lupus erythematosus (SLE) and porphyrias by griseofulvin. Occasionally, urticarial rashes are seen, and light-sensitivity eruptions (distinct from lupus erythematosus and porphyria) have occasionally been reported.

The use of griseofulvin has largely been superseded in many countries by terbinafine or itraconazole, except in tinea capitis.

7.3.2 Terbinafine

Discovered in 1983, it is closely related to naftifine [19, 39]. Terbinafine was licensed in Europe in 1991 and in 1996 in the United States. It is an allylamine that inhibits the enzyme squalene epoxidase (Fig. 7.1) and thus depletes the fungal cell wall of ergosterol, a key sterol component in the plasma membrane of the fungal cell [40, 41]. A deficiency of ergosterol results in a fungistatic effect similar to that seen with the azole antifungal compounds. Since the biosynthetic pathway of ergosterol is disrupted, squalene accumulates in the intracellular space, which is believed to exert a further toxic effect on susceptible fungal cells, thereby exerting fungicidal activity [42].

The two main antifungal allylamine compounds in clinical use are naftifine and terbinafine. Both are active in vitro against *Dermatophytes* in addition to other fungi. Terbinafine is a broad-spectrum antimycotic drug that exhibits the best activity against *Dermatophytes*, reasonable activity against most *Aspergillus* species and *Scopulariopsis brevicaulis*, but poorer response against yeasts including most *Candida* species [43–46]. It is both fungicidal and fungistatic (Fig. 7.1). Terbinafine is quickly absorbed after oral intake, is 99 % bound to plasma proteins, and accumulates in the skin and adipose tissue, from where it is slowly released [47].

Terbinafine can be given topically or orally. When given orally, it is rapidly laid down in the stratum corneum, and it persists in the nails at high concentrations for several months. These may exceed the minimum inhibitory concentration 80 days after the end of therapy. Terbinafine is given orally in a dosage of 250 mg/day. It has

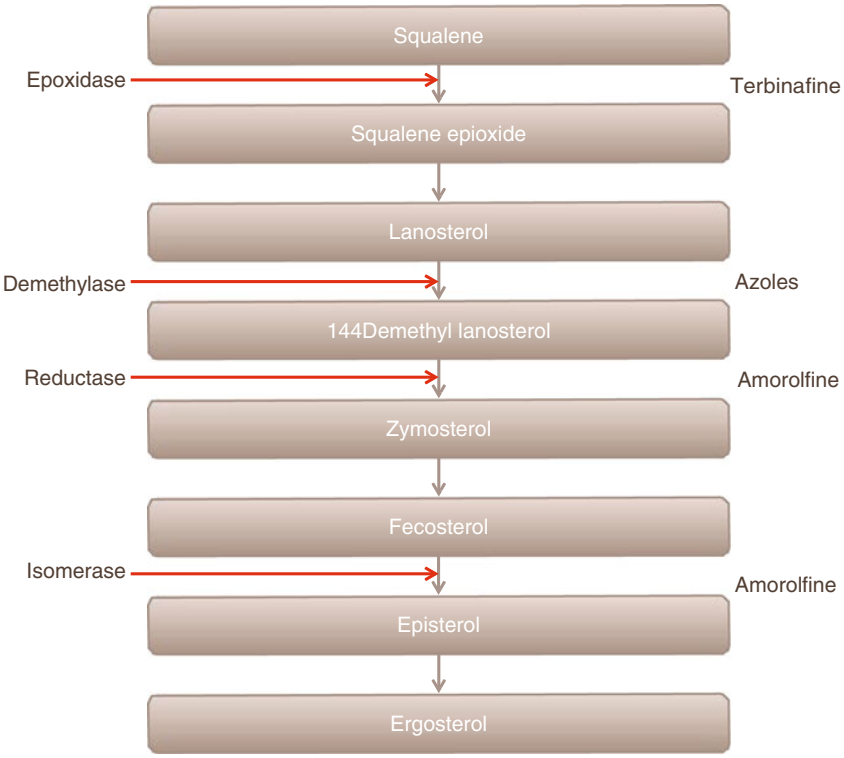

Fig. 7.1 Mechanism of action of antifungal drugs. *Red arrows* indicate the enzyme that is blocked by the corresponding drug

produced rapid and long-lasting remissions in both nail disease and persistent tinea pedis as well as tinea corporis. A smaller tablet form of 125 mg is available in some countries for treatment of children.

Safety Terbinafine is an unusual cause of significant drug-to-drug interactions [39], probably because terbinafine does not interact with the mammalian cytochrome P-450 enzyme system. In vitro studies have shown that terbinafine inhibits the CYP2D6 liver enzyme and may be of importance for patients taking tricyclic antidepressants, SSRI antidepressants, MAO inhibitors, and beta-blockers. Terbinafine can increase serum levels of imipramine and nortriptyline [48, 49].

The need for monitoring of liver function tests in patients taking terbinafine has been debated. In the US clinical trials, asymptomatic liver enzyme abnormalities have occurred in 3.3 % of patients receiving terbinafine versus 1.4 % of patients receiving placebo [50]. Signs of hepatobiliary dysfunction were seen in 1:45,000 patients [50]. The SPC (Summary of Product Characteristics) now recommends monitoring in patients with and without preexisting liver disease (pretreatment and after 4–6 weeks of treatment) [48] since hepatitis can occur without preexisting liver disease.

Terbinafine is generally well tolerated, but that does not mean that adverse events do not occur [51]. In a large uncontrolled post marketing surveillance study of 25,884 patients, adverse events were reported in 10.4 %, mainly from the gastrointestinal system (4.9 %) and skin (2.3 %) [51]. The most common reactions in the skin are eczema, pruritus, urticaria, and rash [51]. Serious adverse events (SAEs) occur, but are rare [52]. In a register-based study (the National Adverse Reaction Database) from Denmark, SAEs during a 10-year period were studied [53].

Terbinafine use as measured by DDD rose steadily in the period studied, from 929,000 DDD in 1998 to 3,132,000 DDD in 2007. During this period 263 patients reportedly experienced an adverse event due to terbinafine. One third of the reports noted skin reactions, subacute cutaneous lupus erythematosus ($n=4$), erythema multiforme ($n=8$), exfoliative dermatitis ($n=8$), Stevens-Johnson syndrome ($n=2$), and toxic epidermal necrolysis (TEN) ($n=2$) [53]. Taste disturbances were seen in ten patients. Hepatobiliary disorders ($n=7$) and increases in liver enzymes ($n=22$) together accounted for 15 % of the reports. Gastrointestinal disorders ($n=17$) and general disorders ($n=17$) each accounted for 9 % [53]. One case of death was reported during the period studied: an 86-year-old man died of pancytopenia on receiving treatment for fungal skin infection [53].

One study estimated the frequency of erythema multiforme to be 15 per 110,000 patients treated with terbinafine [54]. So it must be remembered that although terbinafine is perceived as a relatively safe medication, serious adverse events occur although they are rare.

7.3.3 Itraconazole

This is an orally absorbed triazole. It has similar activity to the imidazole and ketoconazole, but with less risk of hepatotoxicity. Its mode of action is through the inhibition of the cytochrome P-450-dependent demethylation stage in the formation of ergosterol on the fungal cell membrane (Fig. 7.1) [55]. It is active in vitro as a fungistatic drug against all the main superficial fungal pathogens including *Candida albicans*, as well as a wide range of fungi that cause deep infections such as *Histoplasma capsulatum*. Itraconazole is well absorbed orally, and because of its highly lipophilic character, it is accumulated in the tissue at a higher level than in the plasma [56]. Itraconazole rapidly penetrates to the outer stratum corneum and is also found in sebum. It is strongly bound to keratin-containing tissues and, in the nail, for instance, may persist long after cessation of therapy.

It has been shown that after 3 months of 200 mg/day itraconazole, levels in the toenail persist for up to 6 months [57]. This feature allows a range of different dose regimens. These have evolved so that the initial treatments first described involving 100 mg/day itraconazole have been superseded by higher or intermittent (pulsed) therapy. It is active against a wide range of *Dermatophytes* and is effective in regimens of 100 mg for 15 days in tinea cruris and tinea corporis or 30 days in tinea pedis. The currently preferred regimen uses 400 mg/day, given as two daily doses of

200 mg. In tinea corporis, 1 week of therapy is sufficient and in tinea pedis, 2 weeks. For onychomycosis, a regimen of 400 mg/day for 1 week every month for 3 months is usually given. Occasionally, longer periods of treatment are needed. Although it is not licensed yet in many countries for the treatment of tinea capitis in children, it is effective in this indication.

The bioavailability of the drug is increased if it is taken with a fatty meal, but can be decreased in patients taking drugs that impair gastric acidity, such as histamine-2 blockers and antacids [58].

Safety Itraconazole is embryotoxic and teratogenic in rats [31] and should not be used during pregnancy [59]. Women of childbearing potential taking itraconazole should use contraceptives. A very small amount of itraconazole is excreted in human milk [59], and therefore itraconazole should not be given to breastfeeding women.

Itraconazole is generally well tolerated. The incidence of side effects is 7 % with short-term treatment, but rises to 12.5 % with longer duration of therapy [31, 60, 61]. The most common side effects are headache and gastrointestinal symptoms such as nausea, dyspepsia, abdominal pain, diarrhea, and flatulence [52]. Dermatological symptoms such as rash, pruritus, and urticaria and acute generalized exanthematous pustulosis and toxic epidermal necrolysis are less common [52].

Elevated liver function tests have been described in 0.3–5 % of cases [31, 59]. Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have been described [59]. Liver function monitoring is recommended in patients receiving treatment with itraconazole of over one month duration [59]. Itraconazole may be associated with congestive heart failure [62, 63]. High-dose itraconazole (400 mg/day) causes a significant decrease in serum LDL-cholesterol and a significant increase in HDL-cholesterol [64].

Absorption of itraconazole from capsules is impaired when gastric acidity is reduced in patients with reduced gastric acidity; it is advisable to administer the drug with an acidic beverage and/or a high-fat meal [59].

Itraconazole is metabolized in the liver by CYP3A4 enzyme system and therefore has a long list of potential drug interactions (Table 7.1). The interacting drugs are categorized as follows: *contraindicated* (2 weeks washout), *not recommended* (2 weeks washout), or *use with caution* (careful monitoring required) (see Table 7.2).

7.3.4 Ketoconazole

This orally active imidazole is a broad-spectrum antifungal agent. It was the first broad-spectrum oral antifungal drug. In ringworm infections requiring systemic treatment, it offers an alternative agent and is given in a 200–400 mg/day regimen with food (for adults). It works well on *Dermatophytes* and *Candida*, but the effect on molds is poor [15]. Hepatitis is a proven complication, occurring in 1 in 10,000 patients. Because of this, ketoconazole is not used in Europe and the United States for superficial infections. At high doses, ketoconazole may also inhibit androgen biosynthesis.

Table 7.1 Drug interactions

Type of drug interaction	Terbinafine	Itraconazole	Fluconazole
Decreased absorption of antifungal drug (mainly itraconazole capsules)		Antacids	
		H2-receptor antagonists	
		Proton pump inhibitors	
		Didanosine	
Antifungal drug	Rifampin	Rifampin	Rifampin
Decreased		Rifabutin	
		Phenytoin	
		Isoniazid	
		Carbamazepine	
		Nevirapine	
	Phenobarbital	Phenobarbital	
		Statins	
Increased concentration of coadministered drug	Warfarin	Warfarin	Warfarin
		Phenytoin	Phenytoin
	Nortriptyline		Nortriptyline
	Imipramine	H1 antagonist	H1 antagonist
	Nicotinamide		
	Desipramine	Cyclosporine	Cyclosporine
		Tacrolimus	Tacrolimus
		Sulfonylureas	Sulfonylureas
		Terfenadine	Terfenadine
		Astemizole	Astemizole
		Rifabutin	Rifabutin
		Midazolam	Midazolam
		Triazolam	Triazolam
		Alprazolam	Alprazolam
		Calcium channel antagonists	Calcium channel antagonists
		Quinidine	Quinidine Statins Zidovudine Theophylline
		Statins Zidovudine Pimozide Digoxin	Diazepam Amitriptyline Losartan Irbesartan
		Fluoxetine Corticosteroids	Cyclophosphamide Methadone Sulfamethoxazole
		Vinca alkaloids Indinavir Saquinavir Buspirone Busulfan Sildenafil Dofetilide Cisapride Protease inhibitors	

(continued)

Table 7.1 (continued)

Type of drug interaction	Terbinafine	Itraconazole	Fluconazole
Drugs increasing level of antimycotic	Cimetidine		Hydrochlorothiazide and possibly other thiazide diuretics
Drugs that may be decreased in activity		Oral contraceptives Antipyrine	Oral contraceptives

Drug interactions of antifungal drugs. Adapted from Brodell, Dismukes [76] Lamisil SPC [48], Sporanox SPC [59]. This list may not be complete. Readers are advised to check the manufacturers' prescribing information to see whether additional contraindications for drug use have been introduced

Table 7.2 Itraconazole drug interactions

Drug class	Contraindicated	Not recommended	Use with caution
Alpha-blockers		Tamsulosin	
Analgesics	Levacetylmethadol (levomethadyl), methadone	Fentanyl	Alfentanil, buprenorphine IV and sublingual, oxycodone
Antiarrhythmics	Disopyramide, dofetilide, dronedarone, quinidine		Digoxin
Antibacterials		Rifabutin	
Anticoagulants and antiplatelet drugs		Rivaroxaban	Coumarins, cilostazol, dabigatran
Anticonvulsants		Carbamazepine	
Antidiabetics			Repaglinide, saxagliptin
Anthelmintics and antiprotozoals	Halofantrine		Praziquantel
Antihistamines	Astemizole, mizolastine, terfenadine		Ebastine
Antimigraine drugs	Ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)		Eletriptan
Antineoplastics	Irinotecan	Dasatinib, nilotinib, trabectedin	Bortezomib, busulfan, docetaxel, erlotinib, ixabepilone, lapatinib, trimetrexate, vinca alkaloids
Antipsychotics, anxiolytics, and hypnotics	Lurasidone, oral midazolam, pimozide, sertindole, triazolam		Alprazolam, aripiprazole, brotizolam, buspirone, haloperidol, midazolam IV, perospirone, quetiapine, ramelteon, risperidone

Table 7.2 (continued)

Drug class	Contraindicated	Not recommended	Use with caution
Antivirals			Maraviroc, indinavir, ritonavir[b], saquinavir
Beta-blockers			Nadolol
Calcium channel blockers	Bepridil, felodipine, lercanidipine, nisoldipine		Other dihydropyridines, including verapamil
Cardiovascular drugs, miscellaneous	Ivabradine, ranolazine	Aliskiren	
Diuretics	Eplerenone		
Gastrointestinal drugs	Cisapride		Aprepitant, domperidone
Immunosuppressants		Everolimus	Budesonide, ciclesonide, cyclosporine, dexamethasone, fluticasone, methylprednisolone, rapamycin (also known as sirolimus), tacrolimus, temsirolimus
Lipid regulating drugs	Lovastatin, simvastatin		Atorvastatin
Respiratory drugs		Salmeterol	
SSRIs, tricyclics, and related antidepressants			Reboxetine
Urological drugs		Vardenafil	Fesoterodine, imidafenacin, sildenafil, solifenacin, tadalafil, tolterodine
Others	Colchicine, in subjects with renal or hepatic impairment	Colchicine	Alitretinoin (oral formulation), cinacalcet, mozavaptan, tolvaptan

Drugs that may have their plasma concentrations increased by itraconazole presented by drug class with advice regarding coadministration with itraconazole. Based on SPC for itraconazole [59]. This list may not be complete. Readers are advised to check the manufacturers' prescribing information to see whether additional contraindications for drug use have been introduced

7.3.5 Fluconazole

Fluconazole is an orally active bis-triazole antifungal used for the treatment of *Dermatophyte* and *Candida* infections as well as systemic mycoses. Being an azole it inhibits the same step as other azoles in the ergosterol biosynthesis (Fig. 7.1) [65].

This leads to ergosterol depletion and fungistatic action [66]. This antifungal is dependent on the CYP450 system. Fluconazole interacts with the cytochrome system

more weakly than itraconazole, but despite this there is potential for drug-drug interactions (Table 7.1) [67]. Although the MIC for fluconazole is high, it works well against most fungi that cause dermatomycoses [68]; in vitro drug sensitivities are a poorer predictor of antifungal efficacy with this drug. In contrast with many other azoles and terbinafine, fluconazole does not bind strongly to the plasma proteins. It is mostly eliminated unchanged and has a long half-life, which allows once weekly dosing. It is metabolically stable and excreted in urine (91 %) and feces (2 %) [69].

Because of this the dose needs to be adjusted depending on creatinine clearance [70]. It is given either as a continuous regimen of 100–200 mg daily or intermittently at 150 mg/week for 2–3 weeks for tinea corporis and tinea cruris and somewhat longer for dry-type tinea pedis. It is also reported to be effective given in weekly doses in onychomycosis. There are fewer interactions than with itraconazole, but, like the latter, side effects are rare and mainly confined to gastrointestinal discomfort.

However, drug resistance in *Candida* species, particularly *C. krusei* and *C. glabrata*, has been described. There is *C. albicans* resistance in patients particularly in those with HIV/AIDS.

Safety Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor, and these concomitant drugs that are metabolized through these enzymes should be avoided or closely monitored (Table 7.1). It should not be coadministered with oral hypoglycemic agents, phenytoin, cyclosporine, rifampin, theophylline, or terfenadine (Table 7.1).

Fluconazole is well tolerated in general. Adverse drug reactions reported include mostly mild gastrointestinal disturbances, skin rashes, headache, and diarrhea [68, 71, 72]. In a meta-analysis, pooled risks for discontinuation of treatment due to any adverse event were 1.98 % (95 % CI, 0.05–3.92) with fluconazole 150 mg/week and 5.76 % (95 % CI, 2.42–9.10) for fluconazole 300–450 mg/week [73]. The risk for discontinuation because of elevated liver function tests was 0.4–0.9 %, depending on the dose [73]. Due to limited data and long treatment period, liver function test monitoring may be indicated, but this matter is controversial [74].

7.3.6 Other Antifungal Drugs

There is little data at present on the use of posaconazole, although this is active in onychomycosis, and voriconazole in dermatophytosis. Both drugs have a similar mode of action to itraconazole and voriconazole and are mainly used for the treatment or prophylaxis of systemic mycoses. Voriconazole has a slightly higher incidence rate of reported liver adverse reactions than posaconazole and is also associated with the development of photosensitivity and rapidly growing skin cancers, mainly nonmelanoma but melanomas have been reported. Other newer azole antifungal agents such as ravuconazole, albaconazole, and pramiconazole are not marketed for the treatment of superficial mycoses at the time of writing.

The echinocandins have not been used in superficial or mucosal fungal infections apart from *Candida* esophagitis. All are given intravenously. Renovate (VT-1161) is a potent and selective orally available inhibitor of fungal CYP51. It blocks the production of ergosterol. It has been demonstrated to be effective against *Candida* and *Dermatophytes* and is currently in phase II trial [75].

References

1. Rayer P. A treatise on the diseases of the skin (translated by Dickinson WB). London: Bailliere; 1835.
2. Narat JK. Brilliant green: a clinical study of its value as a local antiseptic. Ann Surg. 1931;94:1007–12.
3. Maley AM, Arbiser JL. Gentian violet: a 19th century drug re –emerges in the 21st century. Exp Dermatol. 2013;22:775–80.
4. Castellani A. Carbolfuchsin paints in the treatment of certain cases of epidermophytosis. Amer Med. 1928;34:351–6.
5. Gooskens V, Pönnighaus JM, Clayton Y, Mkandawire P, Sterne JA. Treatment of superficial mycoses in the tropics: Whitfield's ointment versus clotrimazole. Int J Dermatol. 1994;33:738–42.
6. Muskatblit E. Clinical evaluation of undecylenic acid as a fungicide. Arch Derm Syphilol. 1947;56:256–63.
7. Robinson HM, Raskin J. Tolnaftate, a potent topical antifungal agent. Arch Dermatol. 1965;91:372–6.
8. Bianchi A, Monti G, de Carneri I. Tolciclate: further antimycotic studies. Antimicrob Agents Chemother. 1977;12:429–30.
9. Sloane MB. A new antifungal antibiotic, mycostatin (nystatin), for the treatment of moniliasis: a preliminary report. J Invest Dermatol. 1955;24:569–71.
10. Fegeler F, Biess B, Nolting S. Pimaricin: a new broad-spectrum mycostatic antibiotic. Ger Med Mon. 1966;11:155–8.
11. Oura M, Sternberg TH, Wright ET. A new antifungal antibiotic, amphotericin B. Antibiot Annu. 1955;3:566–73.
12. Williams DI, Marten RH, Sarkany I. Oral treatment of ringworm with griseofulvin. Lancet. 1958;2:1212–3.
13. Brugmans JP, Van Cutsem JM, Thienpont DC. Treatment of long-term tinea pedis with miconazole. Double-blind clinical evaluation. Arch Dermatol. 1970;102:428–32.
14. Hempel M. [Clinical experiences in the local treatment of dermatomycoses with Econazole lotion]. Mykosen. 1975;18:213–9.
15. Botter AA, Dethier F, Mertens RL, Morias J, Peremans W. Skin and nail mycoses: treatment with ketoconazole, a new oral antimycotic agent. Mykosen. 1979;22:274–8.
16. Stevens DA. Advances in systemic antifungal therapy. Clin Dermatol. 2012;30:657–61.
17. Katragkou A, Tsikopoulou F, Roilides E, Zaoutis TE. Posaconazole: when and how? The clinician's view. Mycoses. 2012;55:110–22.
18. Mikulska M, Novelli A, Aversa F, Cesaro S, de Rosa FG, Girmenia C, et al. Voriconazole in clinical practice. J Chemother. 2012;24:311–27.
19. Petranyi G, Ryder NS, Stütz A. Allylamine derivatives: new class of synthetic antifungal agents inhibiting fungal squalene epoxidase. Science. 1984;224:1239–41.
20. Sehgal VN. Ciclopirox: a new topical pyrodonium antimycotic agent. A double-blind study in superficial dermatomycoses. Br J Dermatol. 1976;95:83–8.
21. Denning DW. Echinocandins and pneumocandins – a new antifungal class with a novel mode of action. J Antimicrob Chemother. 1997;40:611–4.

22. Gupta AK, Leonardi C, Stoltz RR, Pierce PF, Conetta B. Ravuconazole onychomycosis group. A phase I/II randomized, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy, safety and pharmacokinetics of ravuconazole in the treatment of onychomycosis. J Eur Acad Dermatol Venereol. 2005;19:437–43.
23. Geria AN, Scheinfeld NS. Pramiconazole, a triazole compound for the treatment of fungal infections. IDrugs. 2008;11:661–70.
24. Sigurgeirsson B, van Rossem K, Malahias S, Raterink K. A phase II, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study to investigate the efficacy and safety of 4 dose regimens of oral albaconazole in patients with distal subungual onychomycosis. J Am Acad Dermatol. 2013;69:416–25.
25. Borelli C, Schaller M, Niewerth M, Nocker K, Baasner B, Berg D, et al. Modes of action of the new arylguanidine abafungin beyond interference with ergosterol biosynthesis and in vitro activity against medically important fungi. Chemotherapy. 2008;54:245–59.
26. Hay RJ. Lipid amphotericin B combinations; 'la crème de la crème'? J Infect. 1999;39:16–20.
27. Lozanoc 50 mg hard capsules (itraconazole) – UK/H/4345/001/DC; PL 37190/0001.
28. Polak A. Mode of action of morpholine derivatives. Ann N Y Acad Sci. 1988;544:221–8.
29. Sigurgeirsson B, Billstein S, Rantanen T, Ruzicka T, di Fonzo E, Vermeer BJ, et al. L.I.ON. Study: efficacy and tolerability of continuous terbinafine (Lamisil) compared to intermittent itraconazole in the treatment of toenail onychomycosis. Lamisil vs. Itraconazole in Onychomycosis. Br J Dermatol. 1999;141 Suppl 56:5–14.
30. Gupta AK, Sauder DN, Shear NH. Antifungal agents: an overview. Part I. J Am Acad Dermatol. 1994;30:677–98; quiz 698–700.
31. Gupta AK, Sauder DN, Shear NH. Antifungal agents: an overview. Part II. J Am Acad Dermatol. 1994;30:911–33; quiz 934–6.
32. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. Cochrane Database Syst Rev. 2007:CD001434.
33. Rotta I, Ziegelmann PK, Otuki MF, Riveros BS, Bernardo NL, Correr CJ. Efficacy of topical antifungals in the treatment of dermatophytosis: a mixed-treatment comparison meta-analysis involving 14 treatments. JAMA Dermatol. 2013;149:341–9.
34. Jerajani H, Janaki C, Kumar S, Phiske M. Comparative assessment of the efficacy and safety of sertaconazole (2%) cream versus terbinafine cream (1%) versus luliconazole (1%) cream in patients with dermatophytoses: a pilot study. Indian J Dermatol. 2013;58:34–8.
35. Veraldi S, Persico MC, Schianchi R. Isoconazole nitrate vs isoconazole nitrate and diflucortolone valerate in the treatment of tinea inguinalis: results of a multicenter retrospective study. J Drugs Dermatol. 2012;11:e70–3.
36. Wehland J, Herzog W, Weber K. Interaction of griseofulvin with microtubules, microtubule protein and tubulin. J Mol Biol. 1977;111:329–42.
37. Roobol A, Gull K, Pogson I. Evidence that griseofulvin binds to a microtubule associated protein. FEBS Lett. 1977;75:149–53.
38. Roobol A, Gull K, Pogson CI. Griseofulvin-induced aggregation of microtubule protein. Biochem J. 1977;167:39–43.
39. Balfour JA, Faulds D. Terbinafine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial mycoses. Drugs. 1992;43:259–84.
40. Ryder NS. Specific inhibition of fungal sterol biosynthesis by SF 86–327, a new allylamine antimycotic agent. Antimicrob Agents Chemother. 1985;27:252–6.
41. Ryder NS, Dupont MC. Inhibition of squalene epoxidase by allylamine antimycotic compounds. A comparative study of the fungal and mammalian enzymes. Biochem J. 1985;230:765–70.
42. Ryder NS. Terbinafine: mode of action and properties of the squalene epoxidase inhibition. Br J Dermatol. 1992;126 Suppl 39:2–7.
43. Ryder NS, Favre B. Antifungal activity and mechanism of action of terbinafine. Rev Contemp Pharmacother. 1997;8:275–88.

44. Petranyi G, Meingassner JG, Mieth H. Antifungal activity of the allylamine derivative terbinafine in vitro. Antimicrob Agents Chemother. 1987;31:1365–8.
45. Rinaldi MG. In vitro susceptibility of dermatophytes to antifungal drugs. Int J Dermatol. 1993;32:502–3.
46. Chiritescu MM, Chiritescu ME, Scher RK. Newer systemic antifungal drugs for the treatment of onychomycosis. Clin Podiatr Med Surg. 1996;13:741–58.
47. Shear NH, Gupta AK. Terbinafine for the treatment of pedal onychomycosis. A foot closer to the promised land of cured nails? Arch Dermatol. 1995;131:937–42.
48. Novartis pharma. Lamisil – Summary of Product Characteristics (last revision 21.05.2013). 2013.
49. Katz HI, Gupta AK. Oral antifungal drug interactions. Dermatol Clin. 1997;15:535–44.
50. Baran R, Hay RJ, Garduno JI. Review of antifungal therapy and the severity index for assessing onychomycosis: part I. J Dermatolog Treat. 2008;19:72–81.
51. Hall M, Monka C, Krupp P, O'Sullivan D. Safety of oral terbinafine: results of a postmarketing surveillance study in 25,884 patients. Arch Dermatol. 1997;133:1213–9.
52. Elewski B, Tavakkol A. Safety and tolerability of oral antifungal agents in the treatment of fungal nail disease: a proven reality. Ther Clin Risk Manag. 2005;1:299–306.
53. Bangsgaard N, Saunte DM, Folkenberg M, Zachariae C. Serious adverse events reporting on systemic terbinafine: a Danish register-based study. Acta Derm Venereol. 2011;91:358–9.
54. McGregor JM, Rustin MH. Terbinafine and erythema multiforme. Br J Dermatol. 1994;131:587–8.
55. Fromtling RA. Overview of medically important antifungal azole derivatives. Clin Microbiol Rev. 1988;1:187–217.
56. Heykants J, Van Peer A, Van de Velde V, Van Rooy P, Meuldermans W, Lavrijsen K, et al. The clinical pharmacokinetics of itraconazole: an overview. Mycoses. 1989;32 Suppl 1:67–87.
57. Willemsen M, De Doncker P, Willems J, Woestenborghs R, Van de Velde V, Heykants J, et al. Posttreatment itraconazole levels in the nail. New implications for treatment in onychomycosis. J Am Acad Dermatol. 1992;26:731–5.
58. Debruyne D, Coquerel A. Pharmacokinetics of antifungal agents in onychomycoses. Clin Pharmacokinet. 2001;40:441–72.
59. Janssen-Cilag. Sporanox – Summary of Product Characteristics (last revision 23/04/2013). 2013.
60. Cleary JD, Taylor JW, Chapman SW. Itraconazole in antifungal therapy. Ann Pharmacother. 1992;26:502–9.
61. Grant SM, Clissold SP. Itraconazole. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. Drugs. 1989;37:310–44.
62. Okuyan H, Altın C. Heart failure induced by itraconazole. Indian J Pharmacol. 2013;45:524–5.
63. Gelfand MS, Cleveland KO. Acute congestive heart failure and death secondary to itraconazole therapy. AIDS. 2012;26:1848–50.
64. Schneider B, Gerdsen R, Plat J, Dullens S, Björkhem I, Diczfalusy U, et al. Effects of high-dose itraconazole treatment on lipoproteins in men. Int J Clin Pharmacol Ther. 2007;45:377–84.
65. Hazen KC. Fungicidal versus fungistatic activity of terbinafine and itraconazole: an in vitro comparison. J Am Acad Dermatol. 1998;38:S37–41.
66. Elewski BE. Mechanisms of action of systemic antifungal agents. J Am Acad Dermatol. 1993;28:S28–34.
67. Niwa T, Shiraga T, Takagi A. Effect of antifungal drugs on cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4 activities in human liver microsomes. Biol Pharm Bull. 2005;28:1805–8.
68. Scher RK, Breneman D, Rich P, Savin RC, Feingold DS, Konnikov N, et al. Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. J Am Acad Dermatol. 1998;38:S77–86.
69. Welsh O, Vera-Cabrera L, Welsh E. Onychomycosis. Clin Dermatol. 2010;28:151–9.

70. Elewski BE. Onychomycosis: pathogenesis, diagnosis, and management. Clin Microbiol Rev. 1998;11:415–29.
71. Ling MR, Swinyer LJ, Jarratt MT, Falo L, Monroe EW, Tharp M, et al. Once-weekly fluconazole (450 mg) for 4, 6, or 9 months of treatment for distal subungual onychomycosis of the toenail. J Am Acad Dermatol. 1998;38:S95–102.
72. Drake L, Babel D, Stewart DM, Rich P, Ling MR, Breneman D, et al. Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungual onychomycosis of the fingernail. J Am Acad Dermatol. 1998;38:S87–94.
73. Chang CH, Young-Xu Y, Kurth T, Orav JE, Chan AK. The safety of oral antifungal treatments for superficial dermatophytosis and onychomycosis: a meta-analysis. Am J Med. 2007;120:791–8.
74. Scher R, Daniel R, editors. Nails diagnosis, therapy, surgery. Oxford: Elsevier Saunders; 2005.
75. Warrilow AG, Hull CM, Parker JE, Garvey EP, Hoekstra WJ, Moore WR, et al. The clinical candidate VT-1161 is a highly potent inhibitor of *Candida albicans* CYP51 but fails to bind the human enzyme. Antimicrob Agents Chemother. 2014;58:7121–7.
76. Brodell RT, Elewski BE. Clinical pearl: systemic antifungal drugs and drug interactions. J Am Acad Dermatol. 1995;33:259–60