CHAPTER **31**

ONYCHOMYCOSIS: There is a Cure

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Onychomycosis is the cause of 50% of all nail disturbances, with toenails being affected approximately 4 times as often as fingernails.[1] Onychomycosis represents approximately one-third of all mycotic infections of the integument. More than 48% of patients who are 70 years of age and older, and 32% of 60 to 70-year-old patients are affected by the condition.[2] The overall incidence in the population is not known, but it is reported to be approximately 2 to 13%.[3]

The incidence of onychomycosis is on the rise today due to many factors. A growing proportion of the population is elderly. With the advent of more advanced and broader antibiotics which kill bacteria more effectively, fungi have proliferated. There is an increased use of antineoplastic immunosuppressive drugs for organ transplants and AIDS patients. There is an increased propensity for communal bathing places, recreational facilities, health clubs etc., which provide an ideal setting for fungal infections. In addition, occlusive footwear is more popular in the work place.[4]

Many factors will predispose a patient to onychomycosis. People in the following categories are more susceptible:[5,6]

1. Patients with chronic Tinea pedis or other foot infections.
2. Patients with advanced age who have slower growth of the nail and decreased circulation.
3. Athletes where trauma to the nail weakens the seal between the nail plate and nail bed allowing fungal organisms to penetrate the nail unit. They also sweat profusely. Runners are particularly prone to onychomycosis.
4. Exogenous heat/moisture which worsens the condition as well as hyperhidrosis, as seen in anyone who wears shoes or boots every day for 12 or more hours at a time. People who wear sandals are less vulnerable to fungi as their feet are exposed to the air.
5. The immunosuppressed patient, where the body's ability to combat the infection is compromised.
6. Postmenopausal women are affected, as estrogen appears to exert a protective effect in younger women. Onychomycosis seems to manifest itself in patients in their 40s and 50s.

When comparing the stratum corneum of the epidermis (skin) to the nail, one finds distinct keratins, with the presence of a high sulfur matrix component in the nail plate. The fat content in nails is 0.1% to 1% compared to 10% in the stratum corneum. The water content in nail is 7% to 12%, which is less than the corresponding value of 15-25% for the stratum corneum. There are no sebaceous or eccrine glands in nails.[7,8]

Onychomycosis is caused by dermatophytes (90%), yeasts (6%) and non-dermatophyte molds (4%).[4] Tinea unguium is clinically defined as a dermatophyte infection of the nail plate. Of the dermatophytes, Trichophyton rubrum (T. rubrum) is the offender in 90% of the cases. Other dermatophytes causing onychomycosis include T. mentagrophytes, Microsporum gypseum or nanum, and Epidermophyton floccosum or canis. Candida albicans accounts for 50-83% of the Candida species causing nail infections, although C. parapsilosis is emerging now as a main pathogen in various centers. Other species include C. lypolytica, C. fumata, and C. rugosa.[9] Yeasts are fungi that reproduce by budding.[10] Several non-dermatophyte molds have been identified such as Scopulariopsis brevicaulis, Aspergillus spp, Fusarium oxysportum, Hendersonula toruloidea (Scytalidium dimidiatum), Scytalidium hyalinum, Acremonium tenuis, and Cephalosporium,[3,11] with Scopulariopsis and Scytalidium being the most prevalent.

Onychomycosis can be classified into 4 different types: distal subungual onychomycosis, superficial white onychomycosis, proximal subungual onychomycosis, and candidal onychomycosis.[10,12-14] Distal Subungual Onychomycosis

(DSO) is the most common variety and accounts for 90% of onychomycosis. The disease begins with an initial fungal penetration of the stratum corneum from the hyponychial area, or from the lateral nail fold. Characteristics include a yellow-brown discoloration of the nail plate, onycholysis, and subungual hyperkeratosis without thickening of the actual nail plate. The predominant organism is T. rubrum. There may be a genetic predisposition with an autosomal dominant pattern.

Superficial White Onychomycosis (SWO) is the second most common type, and occurs in approximately 10% of cases of onychomycosis. In this type, fungi directly invade the nail plate and create a white crumbly appearance to the surface. The initial lesions may be randomly dispersed over the nail, but with time these will eventually coalesce to encompass the entire surface of the nail. T. mentagrophytes is the predominating organism. Treatment consists of mechanical debridement as well as topical anti-fungals. The differential diagnosis includes leukonychia, which whitens the nail plate, but cannot be scraped off.

Proximal Subungual Onychomycosis (PSO) is the least common type and accounts for less than 1% of onychomycosis. The infection penetrates the proximal portion of the nail, resulting in hyperkeratosis and onycholysis. This type is usually associated with AIDS and is caused by T. rubrum. A recent study by Elewski et al.[10] showed that 87.1% of 62 patients with AIDS had PSO. Non-HIV infected patients typically have DSO. Presentations of PSO, especially in all ten fingernails should increase one's suspicion of AIDS. Treatment with zidovudine for HIV is not affected during concomitant administration of itraconazole [3]

Candidal Onychomycosis, primarily caused by Candida albicans, occurs in less than 1% of onychomycosis and presents as three recognized forms. The first is a candidal paronychia that results in swelling and erythema of the proximal and lateral nail folds, with secondary involvement of the nail plate. The second is the typical distal and lateral onychomycosis (DSO) occurring when there is separation of the nail plate from the nail bed with erosion of the nail plate. The third is chronic mucocutaneous candidiasis (CMC), where the organism directly invades the nail plate, and the proximal and lateral nail folds become increasingly thick, until the nail becomes totally dystrophic.

There are several conditions that often mimic onychomycosis.[6,13] Included in the differential diagnosis are:

1. Psoriasis, which causes a pitting of the nail plate surface in the fingernails as well as the toenails.
2. Leukonychia, which is a white spot or band that appears proximally and grows out with the nail, which is usually caused by trauma. These spots cannot be burred-off as in SWO.
3. Lichen planus, which is an inflammatory skin disease that involves the nails in 10% of affected patients. Both hands and feet have onychorrhexis (exaggerated longitudinal ridging) and "angel wing deformity" (the central portion of the nail is raised, and the lateral portion is depressed).
4. Yellow-nail syndrome is a condition that exists in conjunction with primary lymphedema and chronic obstructive pulmonary disease. It presents with an absence of cuticles, yellow pigmentation, an excessive curve in the nail, with cessation of nail growth.[15]

Mycological testing includes the use of a Potassium Hydroxide Slide Mount (KOH) as well as a culture. The KOH technique involves applying 15% to 30% potassium hydroxide, either in water or dimethyl sulfoxide, to the test media and viewing the results under a microscope. Heat can be applied during preparation. The incorporation of chlorazol black or Parkers blue/black ink, mixed in equal volumes with KOH, will highlight nail fungi. Phase contrast microscopy or dark field illumination will also highlight nail fungi.[16]

Fungal cultures include the use of Sabouraud's and/or mycosel media. Dermatophyte test medium (DTM) includes an antifungal/antibiotic cycloheximide that inhibits the growth of bacterial and saprophytic fungi. It contains phenol red as a pH indicator, and only dermatophytes will turn the test medium from yellow to red.[17] False positive and negative results are common.

Cultures require an adequate specimen. This involves clipping the full thickness nail together with debris from the underside of the nail, and/or scraping the debris from the nail bed. In the case of SWO, one can scrape the surface of the nail.

Some traditional antifungal agents used to treat dermatophyte infections include the following.[5]

1. Azoles (ketoconazole, clotrimazole, miconazole, sulconazole, oxiconazole, econazole),with or without urea.
2. Whitfield's ointment
3. Potassium permanganate
4. Ciclopirox Olamine
5. Amorolfine
6. Allylamines (naftifine, terbinafine)
7. Organic acids (salicylic, undecylenic)
8. Thiocarbamate derivatives (tolnaftate)
9. Polyenes (nystatin)-not effective against dermatophytes

At the present time there are five oral anti-fungal medications which may be used to treat onychomycosis. The ideal drug would diffuse through the nail bed and be readily incorporated into the nail matrix, would present with a high clinical cure rate as well as a high mycologic cure rate, would provide a low incidence of relapse, would be effective when used for short-term therapy, would have a low incidence of side effects and few drug interactions, and would be cost effective. Table 1 presents details concerning the five available drugs.[3,5-7,13,18-24] Griseofulvin is safe but not highly effective. Ketoconazole is also not highly effective, and has a potential for serious liver toxicity. Itraconazole is very effective and very safe, but does have some serious drug interactions due to its affinity for the cytochrome P-450 enzyme system. Terbinafine is very effective and very safe and has limited drug interactions. Fluconazole is very effective and very safe, but is also limited due to its drug interactions due to the cytochrome P-450 enzyme system. It is not currently FDA approved for the treatment of onychomycosis in the United States.

A review of various drug studies done in many different countries was performed. The statistics are recorded in Table 2.[1,3,6-7,9,11,19,25-42] The reported data reflect studies done in more recent years, therefore, there are limited statistics on the older drugs, griseofulvin and ketoconazole. Most of the studies target itraconazole and terbinafine. Fewer studies have been done on fluconazole in the treatment of onychomycosis.

The overall success rate for terbinafine appears to be better with continuous use for three months, rather than pulse dosing. The reverse is true for itraconazole, with the pulse dosing being superior over continuous therapy, and four pulses seems to have a slightly better result than three. Doubling the dose of itraconazole from 100 to 200mg/day results in a 10-fold increase in nail drug levels.[35] Overall, terbinafine appears to be the drug of choice in the treatment of dermatophyte infections. Terbinafine can be used in immuno-compromised patients, including those with AIDS, in the treatment of dermatophytosis. Increasing the dose to 500mg/day will bring cure rates up to the level of those in otherwise healthy patients.[16] Itraconazole is more effective against Candida albicans and some non-dermatophyte molds than terbinafine, and should be used where indicated based on culture results.[11,18,22] Itraconazole should be used for CMC and should be continued until complete recovery.[16] The concentration of fluconazole found in nails is much higher than that found in the case of terbinafine and itraconazole, indicating that fluconazole should be at least as effective as these drugs in the treatment of onychomycosis.[43] Fluconazole is currently used in the treatment of onychomycosis as an off-label indication, as clinical trials are still needed prior to FDA approval, which is planned for the future. The primary indication for griseofulvin is the treatment of dermatophytosis in children.[16] Ketoconazole, due to its hepatoxicity, is given for short courses rather than long courses, negating its use in the treatment of onychomycosis.

Itraconazole studies indicate that it has fewer side effects than terbinafine, but caution should be exercised when patients are taking a drug which is metabolized by the cytochrome P-450 enzyme system, as drug interactions with itraconazole or fluconazole are possible. A large post-marketing surveillance study of oral terbinafine in the United Kingdom,[21] involving 9879 patients, revealed a 14.5% "medical event" during or after the use of oral terbinafine. Half of these may have been related to terbinafine use. Of these patients, 0.7% (74 patients) were classified as "serious," and only five were assessed as possibly or probably related to terbinafine. Of these patients, 48.6% were using concomitant medications for an array of medical problems.

Short-term use of the oral anti-fungals has proven to be successful in the treatment of topical Tinea pedis. Ninety-three percent of patients treated with one pulse of itraconazole were

clinically cured and 84% were mycologically cured.[26] Another study comparing two-weeks of oral terbinafine (250mg/day) with itraconazole (100mg/day) reported a clinical success rate of 94% and 72%, respectively.[44] The mycology was negative in 86% and 55%, respectively. Possibly increasing the itraconazole dose to 200mg/day would have produced identical results to terbinafine.

A pharmacokinetic evaluation of treatment practices in 13 countries,[45,46] not including the United States, has shown that oral terbinafine is more cost-effective than griseofulvin, ketoconazole, or itraconazole in the treatment of onychomycosis. Again, sufficient data to evaluate fluconazole was not available. The cost of treatment included the cost of the drug, the medical management including laboratory testing, and the management of adverse drug reaction costs. Terbinafine had the lowest cost per mycologic cure after one treatment regimen.

Obviously, the newer drugs have proven to be effective in the treatment of onychomycosis, but like all medication, success is not 100%. Reasons for treatment failures may include the following. In some patients, only some of the affected nails were cleared, or only parts of a nail were cleared and others were not. Fungi may persist along narrow linear streaks that apparently follow the longitudinal oriented nail bed epidermal ridges. This could possibly reflect poor distribution of the drug in some areas of the nail that remained infected during treatment, and become a source of reinfection a few months after treatment is stopped. Secondly, cases where no clinical improvement was noted may be due to poor penetration of the drug into the nail. Peripheral vascular disease with distal occlusion will prevent delivery of the antifungal agent to the nail matrix and bed, resulting in failure. Thirdly, the patient, though clinically clear, may still have latent fungi or be reinfected and the infection will recur.[42] Patients whose nails do not grow or grow excessively slowly, do not generally respond well to oral treatment.[16] Some studies suggest that longer treatment times may eliminate remissions and relapses, bringing the success rate closer to 100%.[34]

A prospective study involving 60 patients who completed three months of terbinafine with a minimum one-year follow-up, as well as 24 patients who completed a trial of fluconazole, will be presented. The results are truly exciting.

The newer oral anti-fungal agents, itraconazole, terbinafine and fluconazole, appear to be more effective than the older agents, griseofulvin and ketoconazole. A variety of effective oral antifungal drugs are now available for use, and the decision to use one drug or another may depend on several factors such as dosage schedule, adverse effects profile, sensitivity to drug or organism(s) isolated, concomitant medical conditions or concurrent drugs, and cost-effectiveness. The new drugs have an increased cure rate, shortened period of treatment time, and increased safety. The newer drugs, although appearing to be more expensive, may actually decrease costs due to shorter treatment times, decreased side effects, and increased efficacy. We now have a cure for onychomycosis.

TABLE I ORAL ANTI-FUNGAL MEDICATIONS

DRUG	GRISEOFULVIN (Gris-peg, Fulvicin, Grisfulvin, Grisatin) Variable strengths, white tablets	Ketoconazole (Nizoral) 200mg white tablets	Itraconazole (Sporonox) 100mg blue/pink capsules	Terbinafine (Lamisil) 250mg white tablets	Fluconazole (Diflucan) 50, 100, 150, 300mg pink tablets oral suspension and IV
CHEMICAL TYPE FORMULA	Penicillium species derivative	Imidazole Cis-1-acetyl-4-[4-[[2-(2,4-dichorophenyl)-2-(1H-imidazole-1-ylmethyl)-1,3-dioxolan-4-yl)methoxyl]phenyl]piperazine	Triazole (+/-)-cis-4-[4-[4-[4-[2-(2,4-dichlorophenyl)-2,(1H-1,24-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methony]phenyl[-1-piperazinylphenyl]2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one)	Allylamine (E)-N-(6,6-dimethyl-2-hepten-4-inyl)-N-methyl-1-naphthaline-methenamine-hydrochoride	Triazol [2-(2,4,-difluorophenyl)1,3-bis(1H-1,2,4-triazole-1-yl)-2propanol]
FDA APPROVED	1958	Early 1980's	September 1995	May 1996	Not FDA approved for onychomycosis at the present time.
Hydro/Lipophilicity	Lipophilic		Lipophilic	Lipophilic	Borderline hydrophobic/hydrophilic
LABORATORY TESTING	Periodic monitoring of renal, hepatic and hematopoietic systems.	CBC & LFT baseline and monthly.	Baseline and periodic LFT's for continuous therapy > 1 month.	LFT recommended if >6 weeks continuous therapy. CBC recommended if >6 weeks if immunodeficiency is suspected.	CBC, platelets and LFT every 2 months (25).
DOSAGE	500-1000mg/day or 330mg ultramicrosized qd-tid for 10-18 months until cured	200mg/day pc for 10-18 months	250mg/day for 3 months Pulse: 200mg bid pc X7 days every fourth week for 3-4 pulses	200mg/day pc for 3 months	150-200mg weekly, 6-12 months
COST	330mg ultramicrosized BID for 12 months = $400	$1000 for 12 months	$900-1000 for continuous 3 months; $500 for 3 pulses; $640 for 4 pulses	$500 for continuous 3 months	$260-520 for 6-12 months
ACTION	Reaches the nail plate through the nail matrix and grows outward with the nail acting as an anti-fungal barrier	Little data available on how it enters the nail, although it has been measured in therapeutic concentrations in nail keratin	Penetrates the nail by diffusion through the nail matrix and nail bed	Penetrates the nail by diffusion through the nail matrix and nail bed	Penetrates the nail by diffusion through the nail matrix and nail bed
MODE OF ACTION	Fungistatic; inhibits formation of intracellular microtubules, probably via a direct effect on the structural protein tubulin; disrupts the mitotic spindle and arrests fungal cell replication.	Fungistatic; blocks fungal and human cytochrome P-450 dependent demethylation in the formation of lanosterol, thus blocking formation of ergosterol needed in fungal cell membrane biosynthesis.	Fungistatic; It competes for oxygen at the catalytic heme iron atom of cytochrome P450 sites. The synthesis of ergosterol in the fungal cell membrane is impaired because of the inhibition of the enzyme 14-alpha-demethylase, which is cytochrome P450 dependent. This manifests as a defective cell membrane with altered permeability and function. The triazoles have a high affinity for fungal cytochrome P450 enzymes and bind only weakly to the mammalian cytochrome P450 enzyme system.	Fungicidal to dermatophytes and C. parapsilosis; fungistatic to other yeasts and molds; It inhibits squalene epoxidase, a key enzyme in ergosterol synthesis. This leads to deficient membrane sterol production and intrafungal accumulation of squalene, which is assumed to lead to fungal cell death. This is believed to be the essential mechanism by which terbinafine exerts its primary fungicidal activity, i.e. its ability to kill fungi at minimal inhibitory concentrations.	Fungistatic; At low azole concentrations there is inhibition of the enzyme 14 alpha-demethylase and ergosterol synthesis, with an elevation in the lanosterol/ergosterol ratio. At higher concentrations there is fungicidal activity with rapid fungal cell membrane damage, not dependent on the lanosterol/ergosterol ratio. Fluconazole demonstrates a 10,000 fold selectivity for the fungal enzyme over the mammalian enzyme.
ABSORPTION	Limited absorption through the GI tract; absorption is increased with ultramicrosize (27-72%) particle form and with food.	Well absorbed with normal gastric acidity; take with meals.	Increased absorption with food.	70-80% is absorbed from GI tract; bioavailability unchanged with or without food.	90% absorbed after ingestion; Absorption is not dependent on food intake.

DRUG	GRISEOFULVIN	KETOCONAZOLE	ITRACONAZOLE	TERBINAFINE	FLUCONAZOLE
DISTRIBUTION	Peak serum levels occur about 4 hours after administration.	Peak plasma levels within 1-2 hours following oral administration.	Rapidly absorbed and peak plasma concentration is reached in approximately 4 hours. Steady state concentration after 10-14 days of therapy. 99.8% of the drug is bound to plasma proteins. Highly lipophilic and the highest concentration occurs in adipose tissue, omentum, skin/nails, endometium and cervical/vaginal mucus. In contrast to nails, plasma levels decrease to an almost undetectable value within 7 days.	Maximum plasma concentration is reached within 2 hours. Terbinafine strongly binds to plasma proteins. Steady state levels are reached within 10-14 days of therapy. The drug is detected in the stratum corneum as early as 24 hours after initiation of treatment. It diffuses from the deepest layers of the stratum corneum to the superficial layers, binding to lipophilic keratinocytes. There is preferential uptake into tissues, especially fat and skin, resulting in low plasma levels. High concentrations are found in the stratum corneum, sebum and hair.	Peak plasma levels occur 1-2 hours after oral administration; steady state levels in 6-10 days; 11% is bound to serum proteins. Balance is in free form. Reaches the nail plate via both the nail bed and nail matrix.
METABOLISM/ EXCRETION	Metabolized by hepatic microsomal enzymes; about 50% of an oral dose is detected in the urine in 5 hours and 36% can be detected in the feces.	Mainly metabolized by the liver and excreted through the bile into the intestinal tract; 13% excreted in urine; 2-4% excreted unchanged. Plasma half-life is biphasic with a 2 hour half-life during the first 10 hours and 8 hours thereafter.	Extensive hepatic metabolism. 35.2% excreted in the urine and 54.1% in the feces; terminal half-life of 20-60 hours.	80% is excreted in metabolized form in the urine and 20% in the feces. Metabolism in the liver results in 15 metabolites that lack antifungal activity. Liver dysfunction leads to decreased plasma clearance of the drug and renal disease impairs elimination. The effective half-life is 36 hours.	80% excreted unchanged by the kidney, 11% in the form of metabolites. Therefore, care needs to be taken when prescribing it to elderly patients with altered renal function. Long plasma half-life of approximately 30 hours. This would result in an accumulation of drug in the serum with multiple dosing. The half-life in the stratum corneum is 60-90 hours, which is 2-3 times slower than elimination from the plasma.
Pharmakokinetics	It is delivered to the nail by the matrix; it is deposited in the keratin precursor cells and has a greater affinity for diseased tissue. The drug is highly bound to new keratin which becomes highly resistant to fungal invasion. It appears at the distal nail 6 months following initiation of therapy and persists no more than 2 weeks after treatment is discontinued. Prolonged administration is required.	Does not persist after stopping therapy; prolonged administration is needed.	Present at the distal end of the nail shortly after therapy is started. Persists in the nail plate 6-12 months after therapy is completed; longer in toenails than finger nails due to slower growth.	Present at the distal end of the nail shortly after therapy started; therapeutic levels persist in the nail for 3-6 months after therapy is discontinued.	Has been detected in the skin within 3 hours and in the nails within 2 weeks after administration of therapy; some studies state it persists in the nail for up to 5 months after therapy is discontinued[7]; others say that it does not persist in the nail after discontinuing treatment due to its hydrophilicity and therefore needs prolonged administration.
PREGNANCY: No drug is safe!!!	Category C; rare cases of conjoined twins have been reported in patients taking griseofulvin during the first trimester of pregnancy.	Category C; dose-dependent maternal toxicity and embryo toxicity in rats.	Category C; dose-dependent maternal toxicity, embryotoxicity and teratogenicity in rats. Itraconazole is excreted in breast milk and is not recommended in nursing mothers.	Category B; no embryonic or fetal toxicity or teratogenicity has been demonstrated in rats. Terbinafine is excreted in breast milk and is not recommended in nursing mothers.	Category C; not embryotoxic, teratogenic or mutagenic except at extremely high doses in rats. Fluconazole is excreted in breast milk and is not recommended in nursing mothers.
CHILDREN	Griseofulvin is approved for use in children. Consult the package inset for the age dependent dose for each brand.	The safety and efficacy has not been established in pediatric patients younger than 2 years of age. A single dose has been used in children over 2 years of age.	The safety and efficacy has not been established in pediatric patients.	The safely and efficacy has not been established in pediatric patients.	Fluconazole is approved for pediatric use for cryptococcal meningitis and Candida and has a high safety profile in children 1 day to 17 years. The efficacy has not been established in infants less 6 months of age.

DRUG	GRISEOFULVIN	KETOCONAZOLE	ITRACONAZOLE	TERBINAFINE	FLUCONAZOLE
SIDE EFFECTS	20%; mostly headache and nausea. Less common are other GI disturbances: vomiting, diarrhea; dermatologic reactions photosensitivity, pruritus, urtiaria, exaerbation's of SLE; hematologic effects: neutropenia, monocytosis, granulocytopenia; and other reactions: photosensitivity, fever, fatigue hepatotoxicity, menstrual irregularity, decreased efficiency of BCP. Griseofulvin tends to enhance the effect of alcohol; 5-7% allergic reactions. Griseofulvin is derived from species of penicillin; the possibility of cross sensitivity exists.	12%; Headache, dizziness, somnolence, fever & chills; GI disturbances: abdominal pain (1.2%), diarrhea, nausea & vomiting (3%); gynecomastia impotence; blood changes: thrombocytopenia, leukopenia, anemia; cutaneous side effects include pruitus (1.5%), photophobia, urticccaria and allergic reacctions; hepatotoxicity varies from 1/2000 to 1/70,000...increase risk with increase of prolonged use (>6 months), with patients over 40 years of age, female sex, with preexisting liver disease, alcoholism and previous treatment with griseofulvin; 2-10% have abnormal LFT's. Hepatoxicity is usually reversible.	7-12.5%; Nausea (2.4%), abdominal pain (1.4%), vomiting (0.8%), diarrhea (0.6%), anorexia (0.3%), headaches (1.5%), dizziness (0.7%), rash (1.1%), pruritus (0.7%), fatigue (0.5%), fever (0.3%), and malaise (0.1%). Elevation of liver function tests (LFTs) has occurred in 0.3% to 5% of patients. It has been rarely reported to cause symptomatic hepatic injury. Serum cholesterol concentration decreased in 81% of patients. Therefore, inhibition of sterol synthesis is not fungus specific.	10.4-11% ; 50% are GI disturbances: Gastritis (2.2%), fullness (0.5%), nausea/vomiting (1.1%), diarrhea/cramps (1.0%), and sickness (0.1%); Skin reactions (2.7%): erythema/rash (0.9%), urticaria (0.5%), eczema (0.1%), pruitus (0.4%) and isolated cases of Stevens-Johnson syndrome and toxic epidermal necrolysis; Other side effects: headache (0.9%), inability to concentrate (0.3%), tiredness/ fatigue (0.3%), and pain (0.1%). Reversible taste disturbances occur in 1 per 800 people. Liver enzyme abnormalities (>2X the upper limit of normal range) is 3.3%	16%; GI system: nausea (3.7%), abdominal pain (1.7%), vomiting (1.7%), diarrhea (1.5%); Headache (1.9%); Rash (1.8%) Laboratory side effects (1.3%)
Interaction with cytochrome P450	Inducer	Inhibitor	Inhibitor	None	Inhibitor
DRUG INTERACTIONS	Decreased efficiency with griseofulvin of • Oral contraceptives Decreased absorption and activity of griseofulvin with: • Phenobarbital and barbiturates Decreased activity of: • Warfarin Griseofulvin action may be enhanced with: • Cimetidine Combination with alcohol can result in a disulfiram-like reaction (potentiation) with tachycardia and flush	Potentiation of effect of: • Warfarin • Oral hypoglycemics Decreased absorption of ketoconazole with: • Rifampin • Isoniazid May increase levels of: • Cyclosporin • Methylprednisolone Interaction leads to cardiac dysrhythmia: • Terfenadine • Astemizole May alter level of both drugs: • Phenytoin Inhibition of drug-metabolizing enzyme may elevate itraconazole levels: • Cimetidine Combination with alcohol and ketoconazole may produce a disulfiram-like reaction	Drugs which are metabolized by cytochrome P-450 enzyme system may have their plasma concentration increased due to the interaction of itraconazole with the P-450 system, creating an increased therapeutic level and/or adverse effect. • Digoxin • Cyclosporin • Phenytoin • Oral hypoglycemics • Warfarin Contraindicated due to increased plasma levels which may result in life-threatening cardiac dysrhythmias: • Terfenadine • Astemizole • Cisapride Contraindicated due to potentated and prolonged hypnotic side effect: • Midazolam • Triazolam Induction of hepatic drug-metabolizing enzymes will decrease itraconazole concentration thereby making it less effective and prone to failure: • Rifampin • Isoniazid • Phenobarbital • Carbamazepine • Phenytoin Inhibits the metabolism, thereby increasing the levels causing rhabdomyalysis in renal transplant patients: • Lovastatin • Simvastatin	Terbinafine does not interact with the cytochrome P-450 enzyme system thereby minimizing drug interactions. Terbinafine is metabolized by the hepatic cytochrome P-450 enzyme system. Therefore, Decreased elimination of terbinafine with: • Cimetidine (33%) • Terfenadine (16%) Increased elimination of terbinafine with: • Rifampin (100%) • Phenobarbital	High specificity for fungal cytochrome P-450. Drugs which are metabolized by cytochrome P-450 enzyme system may have their plasma concentration increased due to the interaction of fluconazole with the P-450 system, creating an increased therapeutic level and/or adverse effect: • Digoxin • Cyclosporin • Phenytoin • Oral hypoglycemics • Warfarin • Cisapride • Astemizole Fluconazole metabolism is enhanced by: • Rifampin May increase fluconazole concentration: • Hydrochlorothiazude Fluconazole increases serum concentration of: • Theophylline • Zidovudine Fluconazole decreases the bioavailability of: • Ethinylestradiol oral contraceptives Decreased bioavailability of fluconazole with: Cimetidine

DRUG	GRISEOFULVIN	KETOCONAZOLE	ITRACONAZOLE	TERBINAFINE	FLUCONAZOLE
INDICATIONS AND USES	• Dermatophytosis	• Candidiasis and CMC • Blastomycoses • Coccidioidomycosis • Histoplasmosis • Cutaneous dermatophytosis	In immunocompromised patients: • Blastomycoses • Histoplasmosis • Aspergilosis In non-immunocompromised patients: • Onychomycosis of the toenail or fingernail due to dermatophytes	Onychomycosis of the toenail or fingernails due to dermatophytes	• Vaginal, esophageal and oropharyngeal candidiasis • Cryptococcus meningitis Fluconazole is not FDA for the treatment of onychomycosis in the United States
SPECTRUM	Dermatophytes	Dermatophytes, Yeasts (Candida) Non-dermatophyte molds	Dermatophytes, Yeasts (Candida), Non-dermatophyte molds	Dermatophytes (dec. activity against yeasts & molds)	Dermatophytes, Yeasts (Candida), some Molds
SCALE OF IN VITRO	++fungicidal	+fungistatic or efficacious	+/- somewhat efficacious	- not active or lacks efficacy	
Dermatophytes	+/-	+/-	+	++	+
Aspergillus spp.	-	+/-	+	++	+
Blastomyces spp.	-	+/-	+	++	+
Histoplasma spp.	-	+/-	+	++	+
Candida albicans	-	+	+	+/-	+
Candida tropicalis	-	+	+	+	+
Candida parapsilosis	-	+	+	++	+
S. Schenckii	-	+/-	+	++	+
Scopulariopsis brev.	-	+/-	+	++	+
Hendersonula	-	+/-	+	++	+
Acremonium	-	+/-	+	+	+
Coccidiioides ssp.	-	+	+		
Cryptococcus spp.	-	+	+	+	+
CURE RATE***	10-20%	30-50%	70-90%	70-80%	80-90%
RELAPSE	>40%	High relapse rate	8-11%	15%	Not enough data
CONCLUSION	Safe but not effective!	Roughly equivalent to griseofulvin with an increased risk!	Safe and effective; beware of drug interactions!	Safe and effective!	Safe and effective; beware of drug interactions.

***This is a summary of data reported in Table II as well as information from the product package inserts.

TABLE II A SUMMARY OF STATISTICS OF VARIOUS DRUG STUDIES

Author	Location	Drug	Dosage	Length/pulses	# of patients	Clinical response*	Mycological Cure	Relapse	Side Effects	Misc. Comments
ASSAF (25)	USA	Fluconazole	300mg/week	6 months	6	100%	100%		0%	
BONIFAX (26)	Mexico	Itraconazole	200mg BID	3 pulses	50	82%	93%		10%	
BRAUTIGAM (6,19)	Germany	Terbinafine Itraconazole	250mg/day 200mg/day	12 weeks 12 weeks	86 84	69% 61%	81% 63%		9% 6%	
DE BACKER (27)	Belgium	Terbinafine Itraconazole	250mg/day 200mg/day	12 weeks 12 weeks	186 186	76 % 58 %	73% 46%		10% 10%	
DE CUYPER (28)	Belgium	Terbinafine	250mg 500mg	16 weeks 16 weeks	19 18	89% 94%	84% 94%	5% 5%		
De DONCKER (11)	Multi-study	Itraconazole	200mg/day or 200mg BID 200 mg BID	12 weeks 2-4 pulses 2-4 pulses	9* 12** 15***	89% 83% 87%	89% 83% 67%			*Single mold infection/cont tx **Single mold infection/pulse tx *** Mixed mold/dermatophyte infection/pulse tx
De DONCKER (29)	Belgium	Itraconazole	200mg/day	3 months 4 months	25 25	70% 80	64% 72	9% 10%	19% 19%	
De DONCHER (30)	Belgium	Itraconazole	200mg BID	4 pulses	28	93%	100%		4%	
ELEWSKI (31)	USA	Itraconazole	200mg/day	12 weeks	110	65%	54%	21%	6%	
FAERGEMAN (32)	Sweden	Terbinafine Griseofulvin	250mg/day 1000mg/day	16 weeks 12mos	85 total	42% 2%	84% 45%		11% 29%	
FRAKI (7,33)	Germany	Fluconazole	150mg/week	9.3 months	111	74% 65%	80% 60%			With urea Without urea
GALIMBERTI (34)	Argentina	Terbinafine	250mg/day	12 weeks	22	82%	86%		18%	
HAVU (35)	Finland	Itraconazole	200mg/day 200mg BID	3 months 3 pulses	65 64	69% 81%	66% 69%		17% 14%	*if < 75% of nail involved ** if > 75% of nail involved
HEIKKILA (36)	Finland	Itraconazole	200mg/day	12 weeks	88	39%	57%		14%	
HOFMANN (37)	Germany	Terbinafine Griseofulvin	250mg/day 1000mg/day	24 weeks 48 weeks	195 total	67% 56%	81% 62%		12% 18%	
JONES (1)	USA	Itraconazole	200mg/day	12 weeks	36	77%	69%	28%	53%	
KUOKKANEN & FLAVA(38)		Fluconazole	150mg/week	9.3months	20	92%	92%	9%		Pre-treatment with 40% urea cream
Multi-study (3)		Itraconazole	200mg/day	3 months	558	82%	74%	14%		
Multi-study (39)		Itraconazole Terbinafine	200mg/day 250mg/day	3 months 3 months	53 total	61% 65%		21% 47%		
Multi-study (3)		Itraconazole	200mgBID	3 pulses 4 pulses	673 236	92% 92%	85% 77%	4% 0%		
ODOM (40)	USA	Itraconazole	200mg/day	12 weeks	75	84%	83%	7%	62%	
SEGAL (9)	Israel	Terbinafine	250mg/day	16 weeks	20	60%	70%		39%	Candida albicans infections
SVEJGAARD (41)	Denmark	Terbinafine	250mg/day 250mg/day	3 months 6 months	63 total	67% 81%	40% 66%	14%	14%	
TOSTI (42)	Italy	Terbinafine Terbinafine Itraconazole	250mg/day 500mg/day 400mg/day	3 months 3 pulses 3 pulses	21 21 21	94% 80% 75%	77% 80% 65%		5% 5% 0%	

* Clinical response is patients cured plus those who achieved marked improvement minimal nail involvement with significantly decreased signs.

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APPENDIX:

Common Trade Names of Generic Drugs

Oral Anti-Fungal Agents

Gris-peg: Allergan, Inc., Irvine CA
Fulvicin: Schering Corporation, Kenilworth NJ
Grisfulvin: Ortho Pharmaceutical Corporation, Raritan NJ
Grisactin: Wyeth-Ayerst Laboratories, Philadelphia PA
Nizoral: Janssen Pharmaceutica Inc., Titusville NJ
Sporonox: Janssen Pharmaceutica Inc., Titusville NJ
Lamisil: Novartis Pharmaceutical Corp, East Hanover NJ
Diflucan: Pfizer Inc, New York, NY

Topical Anti-Fungal Agents

Ketoconazole: Nizoral, Janssen Pharmaceutical Inc., Titusville NJ
Clotrimazole: Lotrimin, Schering Corp., Kenilworth NJ
Miconazole: Micatin, Ortho Dermatological, Raritan NJ
Fungoid tincture and Fungoid Cream, Pedinol, Farmingdale NY
Sulconazole: Exelderm, Westwood-Squibb, Buffalo NY
Oxconazole: Oxistat, Glaxo Wellcome Inc., Research Triangle Park NC
Econazole: Spectazole, Ortho Dermatological, Raritan NJ
Ciclopiroxolamine: Loprox, Hoechst-Roussel, Somerville NJ
Amorolfine: not available or manufactured in the United States
Naftifine: Naftin, Allergan Inc., Irvine CA
Terbinafine: Lamisil, Novartis Pharmaceutical, East Hanover NJ
Undecylenic acid: Fungoid Tincture, Pedinol, Farmindale NY
Tolnaftate: Tinactin, Schering Corp., Kenilworth NJ
Nystatin: Mycostatin, Westwood-Squibb, Buffalo NY

Miscellaneous Oral Agents

Warfarin: Coumidin, Dupont Pharma, Wilmington DE
Cimetidine:Tagamet, Smith Kline Beecham, Phildelphia PA
Cyclosporin: Neoral, Sandimmune, Sandoz Pharmaceutical, East Hanover NJ
Terfenadine: Seldane, Marion Merrell Dow, Kansas City MO
Astemizole: Hismanal, Janssen Pharmaceutical Inc., Titusville NJ
Phenytoin: Dilantin, Parke-Davis, Morris Plains NJ
Digoxin: Lanoxin, Burroughs Wellcome/Glaxo Wellcome Inc., Research Triangle Park NC
Cisapride: Propulsid, Janssen Pharmaceutica Inc., Titusvile NJ
Midazolam: Versed, Roche Laboratories, Nutley NJ
Triazolam: Halcion, The Upjohn Company, Kalamazoo MI
Carbamazepine: Tegretol, Ciba Geneva Pharmaceuticals, Summit NJ
Zidovudine: Retrovir, Burroughs Wellcome/Glaxo Wellcome, Inc., Research Triangle Park NC
Lovastin: Zocor, Merck & Co, West Point PA
Simvastatin: Mevacor, Merck & Co, West Point PA