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A Risk-Benefit Assessment of the Newer Oral Antifungal Agents Used to Treat Onychomycosis

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Abstract

The newer antifungal agents itraconazole, terbinafine and fluconazole have become available to treat onychomycosis over the last 10 years. During this time period these agents have superseded griseofulvin as the agent of choice for onychomycosis. Unlike griseofulvin, the new agents have a broad spectrum of action that includes dermatophytes, *Candida* species and nondermatophyte moulds.

Each of the 3 oral antifungal agents, terbinafine, itraconazole and fluconazole, is effective against dermatophytes with relatively fewer data being available for the treatment of *Candida* species and nondermatophyte moulds. Itraconazole is effective against *Candida* onychomycosis. Terbinafine may be more effective

against *C. parapsilosis* compared with *C. albicans*; furthermore with *Candida* species a higher dose of terbinafine or a longer duration of therapy may be required compared with the regimen for dermatophytes. The least amount of experience in treating onychomycosis is with fluconazole. Griseofulvin is not effective against *Candida* species or the nondermatophyte moulds. The main use of griseofulvin currently is to treat tinea capitis. Ketoconazole may be used by some to treat tinea versicolor with the dosage regimens being short and requiring the use of only a few doses.

The preferred regimens for the 3 oral antimycotic agents are as follows: itraconazole – pulse therapy with the drug being administered for 1 week with 3 weeks off treatment between successive pulses; terbinafine – continuous once daily therapy; and fluconazole – once weekly treatment. The regimen for the treatment of dermatophyte onychomycosis is: itraconazole – 200mg twice daily for 1 week per month × 3 pulses; terbinafine – 250 mg/day for 12 weeks; or, fluconazole – 150 mg/wk until the abnormal-appearing nail plate has grown out, typically over a period of 9 to 18 months. For the 3 oral antifungal agents the more common adverse reactions pertain to the following systems, gastrointestinal (for example, nausea, gastrointestinal distress, diarrhoea, abdominal pain), cutaneous eruption, and CNS (for example, headache and malaise).

Each of the new antifungal agents is more cost-effective than griseofulvin for the treatment of onychomycosis and is associated with high compliance, in part because of the shorter duration of therapy. The newer antifungal agents are generally well tolerated with drug interactions that are usually predictable.

Onychomycosis is primarily a disease of the nail bed with secondary involvement of the nail plate. It has been estimated that onychomycosis is present in 7 to 8.5% of the North American population.[1,2] Until the late 1950s, there was no recognised oral therapy for onychomycosis with patients often being resigned to the fact that their onychomycosis may be a lifelong infection. In the late 1950s, griseofulvin became available and was quickly used to treat onychomycosis and other dermatomycoses in humans.[3,4]

Griseofulvin has a narrow spectrum of action with activity against dermatophytes but not *Candida* species.[5] Griseofulvin is effective against tinea capitis, and in fact, approximately 40 years later, is still widely used for this condition.[6,7] One of the shortcomings of griseofulvin is its relative ineffectiveness in toenail onychomycosis.

Ketoconazole was approved for use in the early 1980s and was the first significant broad spectrum oral antifungal agent.[8,9] There were rare reports of hepatotoxicity associated with this agent. The reported incidence of hepatotoxicity is about 1 per 10 000 exposed patients.[10-12] In 1 report, the mean duration of ketoconazole therapy in patients who developed symptomatic hepatotoxicity was about 28 days.[13] For pedal onychomycosis the duration of therapy with ketoconazole is generally several months. With the availability of the newer oral antifungal agents ketoconazole is no longer a preferred treatment for onychomycosis of the toenails.[5,14]

The newer oral antifungal agents itraconazole, terbinafine and fluconazole became available in the early 1990s and have superseded both griseofulvin and ketoconazole in the management of onychomycosis, particularly pedal infections.[15-31]

The risk-benefit assessment of the newer antifungal agents used to treat onychomycosis is a function of several variables: (i) reasons for wanting treatment for the onychomycosis; (ii) the extent to which the patient is familiar with the nature of onychomycosis, the available treatments, their benefits and risks (perceived benefits and risk by the patient); (iii) the treatment regimen (patients are more likely to choose short-duration therapy thereby exhibiting a higher degree of compliance);

(iv) efficacy of the available agents; (v) adverse effect profile of the agent; (vi) pharmacoeconomic issues relating to the drug acquisition cost of the agent, the expected cost of therapy and the relative cost-effectiveness of available therapies; (vii) the frequency of laboratory monitoring; and, (viii) relapse rates.

1. Reasons for Treating Onychomycosis

1.1 Cosmetic

Onychomycosis can often cause disfigurement of nails. They may become thickened, hyperkeratotic, onycholytic and discoloured. Abnormal-appearing fingernails are more difficult to conceal than toenails. Onychomycosis may decrease the quality of life by having a negative effect on social functioning, mental health and social confidence.[32-36] Fungal nail disease, especially fingernail, onychomycosis may result in discrimination at work or even in termination of employment.

1.2 Noncosmetic

Onychomycosis may be associated with pain, discomfort and a diminished ability to perform activities of daily living. Thickened, dystrophic toenails may make it difficult to wear shoes and ambulate. Fingernail disease may reduce dexterity. Onychomycosis is often associated with tinea pedis and the disease complex may predispose to bacterial infection. Onychomycosis with thickened and dystrophic nail may cause abrasions, ulcers and necrosis in the surrounding skin, especially in a patient with peripheral neuropathy.[37] The presence of peripheral vascular disease may predispose to further complications.[38] Bacterial and fungal infection can act as a reservoir for the spread of infection to distal sites, e.g. resulting in tinea cruris. In some instances the tinea unguium may be associated with erythema nodosum,[39] urticaria,[40] atopic dermatitis,[41] and asthma or sensitisation of the bronchial and upper airways to dermatophyte antigen.[42-44]

2. Familiarity of Patient with the Nature of Onychomycosis and Available Therapies

In North America there has been a push for direct-to-consumer advertising. As well, with the widespread use of the electronic media, patients are often familiar to some extent with the nature of onychomycosis and possible treatment options. The level and depth of knowledge pertaining to the benefits and risks of the treatment options for onychomycosis may vary from patient to patient. Misconceptions can develop depending upon the body of knowledge that the patient has been exposed to. It is therefore important for the physician to discuss the nature of onychomycosis and possible treatment options as applicable to the patient with data that reflect realistic cure rates, relapse rates, minor adverse effects and the more serious adverse effects.

3. Treatment Regimens for Dermatophyte Onychomycosis

The preferred treatment regimens for onychomycosis using the 3 newer oral antifungal agents are as follows.

- Fluconazole (intermittent therapy). For fingernails and toenails use 150mg once weekly until the nail unit normalises (typically 6 to 9 months for fingernail onychomycosis, and 9 to 18 months for toenail onychomycosis) [this is a common dosage used in many countries].
- Itraconazole (pulse). For fingernails and toenails use 200mg twice daily for 1 week per month with 3 weeks off therapy between successive pulses, and 2 pulses for fingernails and 3 pulses for toenails.
- Terbinafine. For fingernails and toenails use 250 mg/day for 6 and 12 weeks, respectively.

When griseofulvin is used to treat onychomycosis, the regimen is continuous therapy with 500 to 1000 mg/day microsize given for 6 to 9 months for fingernails and 12 to 18 months for toenails. The corresponding durations of active therapy for pedal onychomycosis are 52 to 104 weeks with

Table I. Mycological cure rates for griseofulvin, itraconazole (pulse), terbinafine (continuous) and fluconazole for the treatment of dermatophyte, toenail onychomycosis

Agent and study	Type of study	Dosage (mg/day)	Duration (mo)	Mycological cure rate [no. of patients successfully treated/total no. treated (%)]
Griseofulvin				
Arenas et al.[49]	Open, comparative	500	6	5/15 (33.3)
Baran et al.[50]	Double-blind, comparative	1000	12	32/73 (43.8)
Davies et al.[51]	Open	1000	24	9/31 (29.0)
Faergemann et al.[52]	Double-blind, comparative	500	12	19/41 (46.3)
Hofmann et al.[53]	Double-blind	1000	12	59/72 (81.9)
Korting et al.[54]	Open-controlled	660 (ultramicrosize)	18	2/36 (5.6)
		990 (ultramicrosize)	18	2/36 (5.6)
Russell et al.[55]	Open	1500	12	3/11 (27.2)
Svejgaard[56]	Open	500-1000	30	0/7 (0)
Walsøe et al.[57]	Double-blind, comparative	500	6	0/10 (0)
Itraconazole (pulse)				
Bonifaz et al.[58]	Open	400mg x 1wk	3 pulses	41/50 (82.0)
Canadian itraconazole package insert[59]	Double-blind, placebo controlled	400mg x 1wk	3 pulses	48/78 (61.5)
De Doncker et al.[60]	Open	400mg x 1wk	3 pulses	5/5 (100.0)
De Doncker et al.[61]	Open	400mg x 1wk	3 pulses	16/25 (64.0)
Evans et al.[62]	Double-blind, comparative	400mg x 1wk	3 pulses	41/107 (38.3)
Ginter et al.[63]	Open	400mg x 1wk	3 or 4 pulses	152/197 (77.0)
Haneke et al.[64]	Open	400mg x 1wk	3 or 4 pulses	465/567 (82.0)
Haneke et al.[65]	Double-blind randomised	400mg × 1wk	3 pulses	400/540 (74%)
Havu et al.[66]	Double-blind, comparative	400mg x 1wk	3 pulses	41/59 (69.5)
Kejda[67]	Open, randomised, comparative	400mg × 1wk	3 pulses	20/26 (75.0)
Negroni et al.[68]	Open, comparative	400mg × 1wk	3 pulses	83/117 (71.0)
Svejgaard et al.[69]	Double-blind, comparative	400mg x 1wk	3 pulses	74/158 (47.0)
Tosti et al.[70]	Open, comparative	400mg x 1wk	4 pulses	15/20 (75.0)
Wang et al.[71]	Open	400mg x 1wk	3 pulses	377/385 (98.0)
Wu et al.[72]	Open	400mg x 1wk	3 pulses	22/26 (83.3)
Terbinafine (continuous)				
Alpsoy et al.[73]	Open, comparative	250	3	19/24 (79.2)
Arenas et al.[74]	Open, comparative	250	3	17/17 (100.0)
Bräutigam et al.[75]	Double-blind, comparative	250	3	70/86 (81.4)
De Backer et al.[76]	Double-blind, comparative	250	3	119/163 (73.0)
De Backer et al.[77]	Double-blind, randomised	250	4	41/49 (84.4)
Degreef et al.[78]	Double-blind, randomised	250	3	73/109 (67.0)
Evans et al.[62]	Double-blind, comparative	250	3	81/107 (75.7)
Faergemann et al.[52]	Double-blind, randomised	250	4	36/43 (83.7)
Galimberti et al.[79]	Open	250	3	19/22 (86.4)
Goodfield et al.[80]	Double-blind, placebo controlled	250	3	37/45 (82.2)
Havu et al.[81]	Double-blind, comparative	250	3	41/46 (89.1)
Honeyman et al.[82]	Double-blind, comparative	250	4	78/82 (95.3)
Kejda[67]	Open, randomised, comparative	250	3	19/25 (76.0)
Negroni et al.[68]	Open, comparative	250	3 or 4	60/111 (53.1)
Svejgaard et al.[83]	Double-blind, placebo controlled	250	3	19/48 (39.6)
Svejgaard et al.[69]	Double-blind, comparative	250	3	93/158 (59.0)
Tausch et al.[84]	Double-blind	250	3	46/56 (82.1)

Table I. Contd

Agent and study	Type of study	Dosage (mg/day)	Duration (mo)	Mycological cure rate [no. of patients successfully treated/total no. treated (%)]
Török et al.[85]	Open	250	3	19/20 (95.0)
Tosti et al.[70]	Open, randomised, comparative	250	4	16/17 (94.1)
Terbinafine package insert (US)[86]	Double-blind, placebo controlled	250	3	99/141 (70.2)
Van Der Schroeff et al.[87]	Open	250	3	24/34 (70.6)
Watson et al.[88]	Double-blind, placebo controlled	250	3	33/56 (58.9)
Fluconazole				
Fräki et al.[89]	Open	150mg once weekly	5-12 (mean: 9.3)	78/102 (76.5)
Montero-Gei et al.[90]	Open	150mg once weekly	3-12 (mean: 7.6)	56/71 (79.0)
Havu et al.[81]	Double-blind, comparative, randomised	150mg once weekly	3	22/43 (51.2)
Kuokkanen et al.[91]	Open	150mg once weekly	9.3 (mean)	17/20 (84.0)[a]
Scher et al.[92]	Double-blind, placebo controlled, randomised	150mg once weekly	Up to 12 (mean: 10.1)	38/72 (52.8)

a With urea pedicure.

griseofulvin, 5.6 and 7.4 weeks over 9 and 12 months, respectively, for fluconazole, 3 weeks over 3 months for pulse itraconazole and 12 weeks over 3 months for terbinafine. These shorter durations of therapy compared with griseofulvin result in high patient compliance. Patient or physician preference for a certain type of therapy may play a role in the decision to prescribe a particular antifungal agent.

4. Efficacy of the Oral Antifungal Agents

One of the benefits of the newer oral antifungal agents is their superior efficacy compared with griseofulvin in the treatment of onychomycosis, in particular toenail disease. Furthermore, in contrast to the narrow spectrum of activity of griseofulvin against dermatophytes only, the newer antifungal agents have a broad action spectrum.

Dermatophytes are the most common agent implicated in onychomycosis in North America.[1,2] As a result the majority of trials evaluating the efficacy of oral antifungal agents in onychomycosis have been conducted in patients with dermatophyte onychomycosis. Large randomised, controlled trials are valuable in evaluating the efficacy of clinical interventions; however, such trials are often not available. Furthermore, when the data from different studies are in conflict with each other, the practising physician may find it difficult to make a rational decision regarding the most effective agent. An alternative may be to conduct a meta-analysis of similarly conducted studies.[45-48] While pooled data can eliminate some biases and allow for a larger number of patients to be considered, new sources of bias may be introduced depending upon the criteria used to select the studies and the degree of heterogeneity among the trials.

In order to evaluate efficacy of the oral antifungal agents for the treatment of dermatophyte toenail onychomycosis we conducted a Medline search (January 1966 to August 1999) for published studies in the English literature. The bibliographies and associated reference sources were consulted in order to ensure that all relevant studies had been reviewed. Included in table I are studies where itraconazole has been used for 3 to 4 pulses and terbinafine has been given as continuous therapy for 3 to 4 months. Mycological cure rate is an objective way of assessing efficacy of therapy. In dermatophyte onychomycosis of the toenails, there is a range of mycological cure rates observed with each of the drug comparators (table I).[49-92] We are aware of 5 comparative studies between itra-

Table II. Spectrum of action of itraconazole, terbinafine and fluconazole

Organism	Itraconazole	Terbinafine	Fluconazole
Dermatophytes	+	+	+
Candida species	+	±[a]	+[b]
Nondermatophyte moulds	+/Limited experience	+/Limited experience	Limited experience

a Therapy may be required for a longer duration or at a higher dose compared with dermatophytes.

b Few data on the use of fluconazole to treat *Candida* onychomycosis.

+ indicates effective; ± indicates conflicting reports on efficacy.

conazole (pulse) and terbinafine,[62,67-70] and 1 between terbinafine and fluconazole.[81] In comparative studies on the treatment of dermatophyte toenail onychomycosis, the mycological cure rates are: Evans et al.[62] [itraconazole (pulse) *vs* terbinafine, 38.3 *vs* 75.7%], Svejgaard et al.[69] [itraconazole (pulse) *vs* terbinafine, 47.0 *vs* 59.0%], Tosti et al.[70] [itraconazole (pulse) *vs* terbinafine, 75.0 *vs* 94.1%], Kejda[67] [itraconazole (pulse) *vs* terbinafine, 75.0 *vs* 76.0%], Negroni et al.[68] [itraconazole (pulse) *vs* terbinafine, 71.0 vs 53.1%], and Havu et al.[81] (fluconazole *vs* terbinafine, 51.2 *vs* 81.9%) [table I]. From table I it is observed that there is a range of mycological cure rates for each of the antifungal agents. The range of mycological cure rates for griseofulvin is 0 to 81.9%, itraconazole (pulse) 38.3 to 100%, terbinafine 39.6 to 100%, and fluconazole 51.0 to 87.0%. The number of studies with mycological cure rates <66 and ≥66% are: griseofulvin (n = 9 studies) [<65 vs ≥66% = 8 : 1 studies); itraconazole (pulse) [n = 15 studies] (<65 vs ≥66% = 4 : 11 studies); terbinafine (continuous) [n = 22 studies] (<65 vs ≥66% = 4 : 18 studies); and fluconazole (n = 5 studies) [<65 *vs* ≥66% = 2 : 3 studies].

5. Onychomycosis Associated with *Candida* Species

Onychomycosis may also be associated with *Candida* species or other nondermatophytes.[1,2,93,94] The action spectrum of fluconazole, itraconazole and terbinafine is given in table II. Onychomycosis caused by *Candida* species is classically observed in individuals with chronic mucocutaneous candidiasis. *Candida* species, in particular *C. albicans*, are more likely to be associated with paronychia than onychomycosis. Authentic evidence of yeast invasion of a nail is characterised by the appearance under light microscopic examination of yeast in its pseudomycelium growth phase with moniliform filaments and lateral blastoconidia.[95] The appearance of budding yeast cells alone, regardless of the degree of abundance, may merely reflect pockets of saprobic colonisation in nails. In many instances the examiner is given scrapings from both nails and peripheral skin. Invasion of skin by *Candida* species does not imply invasive nail disease. The paucity of studies on the treatment of *Candida* onychomycosis may partly reflect the difficulty in obtaining mycological confirmation of invasive *Candida* nail plate disease.

Itraconazole, fluconazole and terbinafine may be effective in onychomycosis due to *Candida* species.[96-103] When terbinafine is prescribed for *Candida* species a higher dose and/or a longer duration of therapy may be required, compared with the regimen used for dermatophytes.[99-102] Onychomycosis due to *Candida albicans* may respond less well to terbinafine compared with infection with *Candida parapsilosis*.[99-102]

6. Nondermatophyte Moulds

There is limited experience with the treatment of nondermatophyte moulds using oral antifungal agents. In the literature there are reports of nondermatophyte moulds responding to each of the 3 agents, fluconazole, itraconazole and terbinafine.[100,104-108] Once again, it is important to establish the diagnosis of invasive disease by a successional or primary invader.[95] Species that are contaminants, normal mammalian surface contaminants, transient saprobic colonisers and persistent secondary colonisers should be excluded.

It is important to obtain the identity of the nondermatophyte mould implicated in onychomycosis by examining 1 or more successive repeat samples from the involved nail.[94,95] If the organism is a long term coloniser of the nail then irregular fila-

ments may be observed on light microscopic examination of the nail with pure growth of the same organism on successive samplings.

There may be organisms which are poorly responsive or even unresponsive to the available oral antifungal agents. Examples include *Scytalidium dimidiatum* and possibly *Onychocola canadensis*.[108]

7. Experience with the Newer Oral Antifungal Agents in Other Types of Onychomycosis

Distal and lateral onychomycosis is the most common type of onychomycosis and is the subset of onychomycosis whose management has been most thoroughly investigated in the literature.

White superficial onychomycosis is less common and will usually respond to the application of topical antifungal agents, e.g. ketoconazole or terbinafine creams. Proximal white subungual onychomycosis is usually observed in patients who are immunocompromised (e.g. patients with AIDS) and no large studies have reported on the treatment of proximal subungual onychomycosis.

8. Use of the Newer Oral Antifungal Agents in Special Populations

The efficacy of the oral antifungal agents, fluconazole, itraconazole and terbinafine in the treatment of special populations e.g. patients with the yellow nail syndrome,[109] Down's syndrome,[110] renal transplants,[111,112] AIDS,[113] psoriasis[114] and diabetes mellitus[37,38] will not be considered further because use of antifungals in such patients can be particularly problematic.

9. Relapse Rates of Onychomycosis

When considering the cost-effectiveness of the newer oral antifungal agents for the management of toenail onychomycosis, not only are they more effective than griseofulvin, but the former also have lower relapse rates.[115]

Reappearance or recurrence of onychomycosis following apparently successful mycological and clinical cure may be due to 'delayed failure' or reinfection.[116-118] Delayed failure[116] describes the situation where there is apparent clinical and mycological cure at a certain time-point following completion of therapy; however, because of incomplete eradication of the fungal organism, within a few months the nail demonstrates clinical or mycological evidence of onychomycosis (the fungal organism at this time-point and baseline should be genetically identical). Relapse rates of onychomycosis (i.e. rates of recurrence/reappearance of disease) have been reported at the 12-, 24- and 36-month time-points following the start of therapy.[85,92,115,119-126] The recurrence of onychomycosis at a time-point longer than 18 months from the start of therapy, following apparently successful cure from the initial therapy, may not reflect delayed failure attributable to the antifungal agent, but reinfection (the fungal organism may not be genetically identical to the 1 isolated at baseline). The choice of the time-point of 18 months is an arbitrary time-frame for distinguishing between delayed failure and reinfection.

Clinical recurrence of onychomycosis should be confirmed by mycological examination. When evaluating the long term efficacy of an oral antifungal agent for onychomycosis, mycological cure should refer to negative light microscopic examination and culture. In some instances the clinical relapse rate refers to patients who were clinically cured at the end of therapy but not at the 6-month follow-up visit.[92] Relapse has also been reported as ≥90% clear nail at any time and <90% at the last visit.[125] In another trial, patients who achieved overall clinical and mycological success were evaluated for relapse [worsening of the global rating or conversion of light microscopic examination for fungal filaments (KOH) or culture to positive].[126]

In 1 trial, itraconazole pulse and terbinafine had a relapse rate of approximately 17 to 36% 2 years after completion of active drug therapy.[119] In a 3 year follow-up study, Tosti et al.[120] reported that 22.2% (8 of 36) patients with onychomycosis successfully treated with systemic antifungal agents

relapsed. The relapse rate increased from 8.3% at month 12, to 19.4% at month 24, and to 22.2% at month 36.

10. Adverse Effect Profiles of the Newer Antifungal Agents

Adverse effects due to the newer oral antifungal agents may be subdivided into the 'pill effect', less serious adverse effects and the more serious adverse effects. The pill effect reflects the adverse effects experienced by the patient while receiving a medication, regardless of the type. If a patient experiences, for example, a headache, a runny nose or a gastrointestinal upset, it is likely that these would be attributed to the drug although the antifungal agent may not actually be responsible. The duration of active therapy with the newer antifungal agents using the preferred dosage schedules (as stated in section 3) ranges from 21 to 84 days compared with 546 days (18 months) for griseofulvin. In some cases, the frequency of adverse effect, particularly the pill effect, may be related to the duration of therapy.

In some reports an attempt has been made to determine the causal relationship between the antifungal agent and the adverse effect. A possible scheme is whether the adverse effect is: probably or possibly related to the agent, unlikely or not related, or not assessed. In many cases the relationship between the adverse effect and the drug in question has been assessed by the investigator and classified as above.

In general, the newer oral antifungal agents are well tolerated with serious adverse effects occurring uncommonly. This is evidenced by the low attributable number of adverse effects to the oral antifungal agents and by the small number of patients who have to discontinue treatment due to an adverse effect or because of a laboratory abnormality.[86,92,127] The more common adverse effects reported with the newer oral antifungal agents, fluconazole, itraconazole and terbinafine are outlined below.

In a representative study where terbinafine was used to treat dermatophyte toenail onychomycosis, the number of patients experiencing an adverse effect in the terbinafine (n = 465) and placebo (n = 142) groups was, 46.7 *vs* 29.2%, respectively.[86] The corresponding figure for patients discontinuing due to an adverse event was 6.3 and 2.2%, respectively.[86] The more common adverse events involved the gastrointestinal system (diarrhoea, dyspepsia, abdominal pain, nausea, flatulence) [terbinafine, 17.1% *vs* placebo, 12.4%], dermatological symptoms (rash, pruritus, urticaria) [terbinafine, 9.5% *vs* placebo, 3.7%], and headache (terbinafine, 12.9% *vs* placebo, 9.5%). Asymptomatic liver enzyme abnormalities occurred in 3.3% of terbinafine recipients *vs* 1.4% of placebo recipients.[86] The estimated reporting incidence of the development of clinically significant symptoms and signs of hepatobiliary dysfunction for which no other cause was apparent, and in which terbinafine was considered the possible cause was 1 : 45 000 to 1 : 120 000.[128,129] Taste disturbance was reported in 2.8% of terbinafine recipients *vs* 0.7% of placebo recipients.[86]

With itraconazole (pulse) therapy, in a representative trial, the number of patients experiencing an adverse effect was 48.6% for itraconazole (n = 208) *vs* 40.3% for placebo (n = 124).[127] The corresponding figure for patients discontinuing therapy due to an adverse effect was 7.7 *vs* 0.8%, respectively.[127] The more common adverse events involved the gastrointestinal system (diarrhoea, dyspepsia, abdominal pain, nausea, flatulence) and occurred in 17.4% of itraconazole recipients *vs* 12.9% of placebo recipients, respectively.[127] Dermatological symptoms (rash, pruritus, urticaria) was observed in 8.7% of itraconazole recipients *vs* 0.8% of placebo recipients.[127] Headaches occurred in 7.2% of itraconazole (pulse) recipients *vs* 6.5% of placebo recipients.[127] Asymptomatic liver enzyme abnormalities were reported in 3.8 % of itraconazole recipients *vs* 1.6% of placebo recipients.[127] Symptomatic hepatitis, possibly or probably due to itraconazole, is estimated to occur in 1 : 500 000 patients.[129]

With fluconazole 150mg once weekly therapy, a representative trial revealed that in the flu-

conazole (n = 89) and placebo (n = 92) groups, the number of patients experiencing an adverse event was 83 and 78%, respectively.[92] The number of patients discontinuing therapy due to adverse event or laboratory abnormality in the fluconazole group was 4 *vs* 6% in the placebo group.[92] The more common adverse events in the fluconazole *vs* placebo groups were, headache (8 *vs* 2%), gastrointestinal symptoms or signs (7 *vs* 8%) and rash (4 *vs* 2%).[92]

Overall, each of the 3 oral antifungal agents, terbinafine, itraconazole and fluconazole is well tolerated when used to treat onychomycosis. The frequency of adverse effects with these agents is of a similar order compared with placebo. It is important to compare the adverse effects of each drug against placebo or another comparator, and to review the attributable risk to the antimycotic agent (that is, frequency of a particular adverse event seen with active drug minus the frequency of that adverse event with placebo). It is inaccurate to directly compare the adverse effects frequency for the drug comparators when the individual trials may have important differences e.g. site at which study was conducted, population studied, protocol used, evaluators for the study, etc.

11. Drug Interactions

Before initiating therapy with the oral antifungal agents a detailed drug history should be obtained of both prescription and nonprescription medications that the patient may be taking. Also, it may be prudent to inquire about the use of recreational and herbal medications. The history should also include information regarding any adverse reaction to drugs, in particular allergic reactions. A history of hepatitis or other liver diseases, especially in association with drug intake, should be elicited. Known hepatotoxins are best avoided or used with caution when taken concurrently with the oral antifungal agents as they may increase the potential for hepatotoxicity.

The contraindicated drugs with itraconazole are terfenadine, astemizole, cisapride, simvastatin, lovastatin, oral triazolam and oral midazolam. These drugs are metabolised by the cytochrome P450 3A4 enzyme system. Coadministration of these agents with itraconazole may lead to an elevated concentration of the former drugs with potentially serious consequences. Terfenadine is contraindicated with fluconazole when the triazole is administered at multiple doses of 400mg or higher. Cisapride is also contraindicated with fluconazole. The potentially important drug interactions with itraconazole and fluconazole are outlined in table III.[130-141] Possible alternative drugs to the contraindicated drugs with itraconazole are listed in table IV. Drug interactions reported in association with terbinafine are listed in table V.[86,142-152] The incidence of clinically important drug interactions is unclear; in general, drug interactions are meaningful if they interfere with the efficacy or safety of treatment. In some cases the coadministration of 2 interacting drugs (excluding contraindicated drugs) is possible as long as the effects are monitored appropriately and any necessary dosage modifications carried out.

12. Monitoring

In North America there is a wide variation in the frequency of monitoring treatment with the newer antifungal agents when treating onychomycosis. Some of the factors that play a role in the frequency of laboratory monitoring adopted by a physician when using an oral antifungal agent to treat pedal onychomycosis are: (i) monitoring recommendations; (ii) perceived safety of the antifungal agents; (iii) standard of practice both locally and nationally; (iv) features in the history and examination (e.g. history of hepatitis) that suggest the need for more careful monitoring; (v) development of symptoms and signs that indicate additional monitoring is required; and, (vi) fiscal and other guidelines laid down by the local healthcare system.

Baseline (pretherapy) monitoring is performed by a variable proportion of physicians ranging from testing in all patients to doing so in only a selected portion of patients.[153] The above is also true for monitoring during and after therapy.

Table III. Potentially important drug interactions with itraconazole and fluconazole[a][126,130-141]

	Itraconazole	Fluconazole
Antacids, histamine H_2-receptor antagonists, proton pump inhibitors or oral didanosine	Increased gastrointestinal pH, may result in reduced itraconazole absorption. Itraconazole capsules should be taken after a full meal or an acidic beverage (e.g. Coca Cola Classic, Pepsi Classic) 240ml so that the pH is 2.5.[141] Administer itraconazole 1 to 2 hours before antacids, H_2-receptor antagonists or oral didanosine. Caution is advised when administering itraconazole with proton pump inhibitors; taking itraconazole after drinking a classic cola beverage may help absorption	
Anticoagulants: coumarin-type e.g. warfarin	Plasma concentrations of coumarin-type anticoagulants may be elevated with increased anticoagulant effect	Plasma concentrations of coumarin-type anticoagulants may be elevated with increased anticoagulant effect
Anticonvulsants		
Phenytoin	Associated with decreased itraconazole plasma concentration by enhancing both the first-pass metabolism and hepatic metabolism by CYP3A4	May increase plasma concentration of phenytoin by inhibiting its metabolism via CYP2C9
Phenobarbital (phenobarbitone), carbamazepine	May decrease itraconazole plasma concentration	
Antidepressants, tricyclic (e.g. amitriptyline, nortriptyline)		3 case reports where fluconazole appeared to raise serum concentrations of amitriptyline
Antimycobacterial agents		
Rifampicin (rifampin)	May decrease itraconazole plasma concentrations	May decrease fluconazole plasma concentrations, increase in apparent oral clearance of fluconazole. Increased metabolism of fluconazole
Isoniazid	May decrease itraconazole plasma concentrations	
Rifabutin		
Astemizole or terfenadine	Contraindicated. Terfenadine: coadministrations associated with elevated concentrations of terfenadine. Rarely cardiac dysrhythmia and death, significantly prolonged QTc interval. Astemizole: elevated concentrations of astemizole and its major metabolite, desmethylastemizole	Terfenadine: use of fluconazole at multiple doses of 400mg or higher is contraindicated Astemizole: caution when coadministering fluconazole
Benzodiazepines e.g. midazolam, triazolam, alprazolam	Elevated concentrations of midazolam and triazolam – potential for prolonged hypnotic and sedation effects. Contraindicated because of prolonged sedative effect. Coadministration with alprazolam not recommended	
Busulfan	Busulfan concentrations may be increased	
Buspirone	Buspirone concentrations may be increased	
Calcium antagonists (dihydropyridine class e.g. amlodipine, felodipine, nicardipine, nifedipine)	Oedema may develop	
Cyclosporin	Increased cyclosporin concentrations	May significantly increase cyclosporin concentrations in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporin concentrations and serum creatinine level is recommended in patients receiving fluconazole and cyclosporin
Digoxin	Increase in dioxin concentrations may occur	
Fluoxetine	One case report of probable interaction between itraconazole and fluoxetine	
Gastrointestinal motility agents	Cisapride contraindicated. Itraconazole inhibits metabolism of cisapride with elevated concentrations of the latter. May result in prolonged QT interval on ECG and cardiac events including torsade de pointes	Cisapride contraindicated. Reports of cardiac events including torsade de pointes during concurrent fluconazole and cisapride administration

Table III. Contd

	Itraconazole	Fluconazole
HIV protease inhibitors: ritonavir, indinavir	Ritonavir and indinavir plasma concentrations may be increased	
HMG-CoA reductase inhibitors e.g. lovastatin, simvastatin	Inhibition of metabolism of simvastatin and lovastatin with elevated concentrations May increase the risk of rhabdomyolysis. The use of atorvastatin and cerivastatin with itraconazole may not be recommended since both are also metabolised by hepatic CYP3A4	
Hydrochlorothiazide		Increase in fluconazole plasma concentrations attributed to decreased renal clearance
Methylprednisolone	Metabolism of methylprednisolone may be inhibited	
Oral contraceptives	An isolated case of contraceptive failure though there may be no scientific basis for such an interaction.[137,138] In 1 study after oral administration of itraconazole 200 mg/day for 15 days the pharmacokinetics of ethinylestradiol were not affected.[137] Itraconazole did not reveal any inducing effects on the metabolism of ethinylestradiol and norethisterone. The report concluded that itraconazole may not affect contraceptive effectiveness	Fluconazole coadministered with oral contraceptive containing ethinylestradiol and levonorgestrel: overall mean increase in concentrations of both reported; however, in some instances decreased concentrations may occur. Clinical significance of these effects is presently not known
Oral hypoglycaemic agents: sulfonylurea-type e.g. tolbutamide, glipizide, glibenclamide (glyburide)	Blood glucose levels should be monitored because of possible hypoglycaemia Severe hypoglycaemia has been reported in patients receiving itraconazole concomitantly with oral hypoglycaemic agents (sulfonylurea-type) Recent reports suggest that drug interactions between itraconazole and the oral hypoglycaemic agents tolbutamide and glimepiride may not be expected since they are metabolised by CYP2C9 rather than CYP3A4[134-136]	Fluconazole reduces the metabolism of tolbutamide, glibenclamide and glipizide, and increases the plasma concentration of these agents. When fluconazole is used concomitantly with these or other sulfonylurea oral hypoglycaemic agents, blood glucose levels should be monitored and the dose of the sulfonylurea adjusted as needed
Oxybutin	Increase in serum concentrations of oxybutin	
Quinidine	Tinnitus and decreased hearing have been reported	
Sildenafil	Metabolism of sildenafil is mediated by CYP isoforms 3A4 (major route) and 2C9 (minor route). When sildenafil is administered concomitantly with itraconazole, plasma concentration of itraconazole may be increased by 200%, in such an instance reduce starting dose of sildenafil from 50 to 25mg	
Tacrolimus	Increase in plasma tacrolimus concentrations may occur	Nephrotoxicity has been reported
Theophylline		Increased serum concentrations of theophylline
Vincristine	Itraconazole may aggravate vincristine-induced neurotoxicity	
Zidovidine		Increase in zidovudine concentrations. Decrease in the metabolite to parent drug ratio

a Note: the table provides a guideline only of the main drug interactions. The reader should consult appropriate product-monographs and up-to-date listings before prescribing medications to patients. In some instances a drug interaction is cited for 1 azole and it may be prudent to observe for the similar interaction with other azoles. The drug interactions discussed above have been generally reported with continuous administration schedules. In some instances differences may be observed when intermittent administration schedules (e.g. active drug therapy once weekly or 1wk per month) are used. Data may be modified once relevant drug interaction studies with intermittent administration schedules are reported.

CYP = cytochrome P450; **ECG** = electrocardiogram; **HMG-CoA** = hydroxymethylglutaryl coenzyme A; **QTc** = corrected QT interval.

Table IV. Contraindicated drugs with itraconazole and possible alternatives[a]

Contraindicated drug	Possible alternatives
Antihistamines: Astemizole, terfenadine	Hydroxyzine, cetirizine, fexofenadine, loratadine, other antihistamines
GI motility agent: Cisapride	Antacids or H_2 antagonists (with itraconazole administered 1 to 2 hours beforehand), lifestyle modifications
Cholesterol-lowering agents:[b] Simvastatin, lovastatin	Pravastatin,[141] fluvastatin[140] or temporarily withhold cholesterol-lowering agent
Benzodiazepines: Oral triazolam, midazolam	Zolpidem[126]

a Note: the above is only a guideline. Consult product monograph or up-to-date source for contraindicated drugs as list may change with time. The list of possible alternatives may be updated as more information regarding drug interactions becomes available. Authoritative and current sources should be consulted before patient use.

b Atorvastatin and cerivastatin are metabolised in the liver by cytochrome P450 3A4. Therefore, the use of these 2 agents with itraconazole is not recommended.

GI = gastrointestinal.

In the US package insert for terbinafine it is stated that hepatic function tests are recommended in patients administered terbinafine continuously for more than 6 weeks.[86] Furthermore, the US package insert indicates that in patients with known or suspected immunodeficiency, physicians should consider monitoring complete blood counts in individuals receiving terbinafine for longer than 6 weeks.

For itraconazole continuous therapy the US package insert indicates that hepatic enzyme levels should be monitored in patients receiving therapy for more than 4 weeks.[126] For itraconazole pulse therapy given for fingernail onychomycosis, the US package insert has no recommendations for monitoring.[126] Itraconazole (pulse) is approved for the treatment of onychomycosis of the toenail in Canada there is no monitoring requirement when using itraconazole (pulse) for fingernail or toenail onychomycosis.[59]

Fluconazole is not approved for the treatment of onychomycosis in the US or Canada.

13. Pharmacoeconomics

In this age of shrinking healthcare dollars increasing attention is being paid towards rationalising treatment and paying more attention not only to the factors outlined in the previous sections but also to the relative cost of the different treatment options. Pharmacoeconomic studies help in the decision making process when choosing the most appropriate antifungal agent to treat onychomycosis.

Table V. Drug interactions reported in association with terbinafine[86,142-152]

Caffeine	Terbinafine decreases intravenously administered caffeine clearance by 19%
Cimetidine	Decreases terbinafine clearance by 33%
Cyclosporin	Terbinafine increases cyclosporin clearance by 15%
Nortriptyline	Single case report of nortriptyline intoxication in a patient receiving terbinafine. Rechallenge test was positive[148]
Rifampicin (rifampin)	Increases terbinafine clearance by 100%
Terfenadine	Decreases terbinafine clearance by 16%
Theophylline	Oral clearance of theophylline decreased by 14% and half-life increased by 24%[149]
Warfarin	In a study no pharmacokinetic or pharmacodynamic interactions between terbinafine and warfarin when healthy volunteers took single doses of warfarin after taking multiple doses of terbinafine.[150] In postmarketing surveillance studies no drug interactions reported between terbinafine and warfarin.[146,147] One case report of decreased anticoagulant effect when terbinafine given together with warfarin.[151] In another case report there may have been an interaction between terbinafine and warfarin, or terbinafine in the presence of cimetidine or thyroxine may have had an effect on warfarin[152]

Results from pharmacoeconomic studies should not replace clinical decision-making, but rather supplement other inputs and considerations, as well as good judgement and common sense.

There has been a relative increase in the number of pharmacoeconomic studies looking at the most cost-effective treatment for dermatophyte onychomycosis, especially pedal disease.[154-161] The studies indicate that the newer oral antifungal agents are more cost-effective than griseofulvin despite the lower drug acquisition cost per unit dosage of the latter.[154-156,158-160] Important factors that need to be considered are the higher efficacy, short treatment duration and lower relapse rates of the newer oral antifungal agents compared with griseofulvin, especially in onychomycosis of toenails.

Pulse therapy is the preferred regimen over continuous treatment for itraconazole. In contrast, the manufacturer recommends that terbinafine should be given as continuous therapy. Earlier phar-

Table VI. Risk-benefit evaluation of itraconazole, terbinafine and fluconazole in the management of onychomycosis

Parameter	Itraconazole	Terbinafine	Fluconazole
Approved indications in the US	Continuous therapy: aspergillosis: pulmonary and extra-pulmonary in patients intolerant of or refractory to amphotericin B therapy Histoplasmosis Blastomycosis: pulmonary and extra-pulmonary Fingernail and toenail onychomycosis due to dermatophytes Pulse therapy: fingernail onychomycosis due to dermatophytes	Continuous therapy: fingernail and toenail onychomycosis due to dermatophytes	Treatment of: vaginal candidiasis Oropharyngeal and oesophageal candidiasis Cryptococcal meningitis Prophylaxis: to decrease incidence of candidiasis in bone marrow transplant patients receiving cytotoxic chemotherapy and/or radiation therapy
Efficacy against dermatophytes	Yes	Yes	Yes
Efficacy against *Candida* species	Yes	Yes. Conflicting reports	Yes. Limited data
Efficacy against nondermatophyte moulds[a]	Yes Limited data	Yes Limited data	Yes. Very limited data
Adverse effects	Favourable adverse effect profile	Favourable adverse effect profile	Favourable adverse effect profile
Most common adverse effects	Gastrointestinal, cutaneous, nervous system	Gastrointestinal, cutaneous, nervous system	Gastrointestinal, cutaneous, nervous system
Drug interactions	Several	Few	Several
Contraindicated drugs	Astemizole, terfenadine, cisapride, simvastatin, lovastatin, oral midazolam, oral triazolam	None	Cisapride, terfenadine, when fluconazole is used at multiple doses of 400mg or higher
Monitoring guidelines for management of onychomycosis	Pulse therapy: none Continuous: LFTs after 4 wk of continuous therapy	Continuous therapy: LFTs after 6 wk; complete blood count after 6 wk in patients with known or suspected immunodeficiency, or secondary bacterial infection	Intermittent therapy: no formal requirement but not approved for onychomycosis
Onychomycosis: compliance of regimens	High	High	High
Benefit to risk ratio in the treatment of superficial mycoses	High	High	High

a Some moulds may not respond, or respond poorly, to the 3 oral antifungal agents.

LFTs = liver function tests.

Table VII. Potential interactions involving cytochrome P450–mediated metabolism (personal communication, Iain Smith, Drug Information Pharmacist, QEII Health Sciences Centre, Halifax, Nova Scotia, Canada, with permission)[a,b]

Cytochrome P450	Metabolises	Inhibited by
1A2	Acetanilide, amitriptyline, caffeine, clomipramine, clozapine, cyclobenzaprine, imipramine, paracetamol (acetaminophen), propafenone, propranolol, riluzole, *r*-warfarin (inactive), tacrine, theophylline, trimipramine, verapamil	Cimetidine, ciprofloxacin[c], diltiazem, enoxacin, erythromycin, fluvoxamine, grapefruit juice, mexilitine, norfloxacin, tacrine, ticlopidine
2C9/10	Celecoxib, diclofenac, naproxen, ibuprofen, phenytoin, piroxicam, *s*-warfarin (active), tolbutamide	Amiodarone, cimetidine, cotrimoxazole (trimethoprim-sulfamethoxazole), disulfiram, fluconazole, fluvastatin, metronidazole, phenylbutazone
2C19	Citalopram, clomipramine, diazepam, hexobarbital (hexobarbitone), imipramine, lansoprazole, mephenytoin, methylphenobarbital (methlyphenobarbitone), omeprazole, pantoprazole, proguanil, propranolol	Cimetidine?, felbamate, fluoxetine, omeprazole, sertraline
2D6	**Antiarrythmics** Amiodarone, encainide, flecainide, mexiletine, propafenone **Antipsychotics** Clozapine, haloperidol, olanzapine, perphenazine, remoxipride, risperidone, thioridazine, zuclopenthixol **β-Blockers** Alprenolol, bufuralol, metoprolol, propranolol, timolol **Antidepressants** Amitriptyline, clomipramine, desipramine, imipramine, fluoxetine, maprotiline, norfluoxetine, nortriptyline, paroxetine, trazodone,[c] trimipramine, venalfaxine **Miscellaneous** Buspirone, captopril, codeine, dextromethorphan, diphenhydramine, domperidone, ethylmorphine, 4-hydroamphetamine, phenformin, selegiline, terfenadine	Amiodarone, amitriptyline, domipramine, desipramine, doxepin, fluphenazine, fluoxetine, haloperidol, imipramine, moclobemide, nortriptyline, paroxetine, propafenone, quinidine, ritonavir, sertraline (weak), thioridazine, venalfaxine (weak)
3A3/4	**Antiarrythmics** Amiodarone, disopyramide, lidocaine (lignocaine), propafenone, quinidine **Anticonvulsants** Carbamazepine **Antidepressants** Amitriptyline, clomipramine, fluvoxamine, imipramine, nefazodone, sertraline, trazodone, venalfaxine **Benzodiazepines** Alprazolam, diazepam, midazolam, triazolam **Calcium antagonists** Diltiazem, felodipine, nifedipine, verapamil **Antihistamines** Astemizole, terfenadine **Miscellaneous** Atorvastatin, buspirone, cerivastatin, ciprofloxacin, cisapride, clozapine, cortisol, cyclobenzaprine, cyclosporin, dexamethasone, domperidone, erythromycin, ethinylestradiol, indinavir, lovastatin, pimozide, ritonavir, simvastatin, tamoxifen	Amiodarone, amprenavir, astemizole, cimetidine, clarithromycin, cyclosporin, danazol, diltiazem, erythromycin, fluconazole (large doses), fluvoxamine, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, norfluoxetine, quinidine, ritonavir, sertraline, sotalol, troleandomycin

a This chart is not an indication of documented interactions, nor does it replace the use of a current drug interactions reference. It may be useful in problem-solving in the clinical setting or in identifying potential areas of concern in combination of drug therapy. This chart does not imply that any combination of inhibitor and substrate for a particular isoenzyme will result in an interaction of clinical significance. This is not a complete list. Metabolic data for many drugs is either unavailable or undetermined.

b Smoking tobacco or marijuana may induce certain metabolic enzymes, increasing clearance of theophylline and other drugs. The culprit appears to be combustion products in the smoke, not nicotine. Similar effects may result from ingestion of charbroilled meats.

c Applies to metabolite rather than the parent drug.

macoeconomic studies either did not consider itraconazole (pulse) regimen because of insufficient published data on its efficacy or combined studies using the continuous and pulse regimens.[154-156] One study did not compare itraconazole (pulse) and terbinafine therapies;[157] another evaluated 4 pulses of itraconazole only and not 3 to treat toenail onychomycosis.[158] In 1 report a meta-analysis of all relevant studies was not performed and the pharmacoeconomic evaluation was based on single studies.[159] Some evaluations have suggested that terbinafine and itraconazole (pulse) regimens have a similar cost-effectiveness.[160-162] The results of pharmacoeconomic analyses may change over time as the values of the parameters used in the pharmacoeconomic analysis become modified.

14. Risk-Benefit Assessment of the Newer Antifungal Agents in the Management of Onychomycosis

The 3 most commonly used oral antifungal agents in the management of onychomycosis are itraconazole, terbinafine and fluconazole, with each drug demonstrating a favourable benefit to risk ratio (table VI).

The preferred treatment regimen with terbinafine is continuous therapy. After a 12-week course of continuous therapy the drug may be detectable in the plasma for a further 8 to 12 weeks.[163] This allylamine is extremely effective against dermatophytes. Terbinafine may have relatively poor efficacy against *Candida* species with limited experience in treating nondermatophyte mould onychomycosis. In other instances, when treating invasive infection due to *Candida* species, particularly *Candida albicans*, the dosage of terbinafine may need to be higher or the duration of therapy longer, compared with the regimen used to treat dermatophyte infection. Terbinafine has been used approximately 7.5 million times worldwide, predominantly for the treatment of superficial mycoses. Information obtained from large databases suggests that terbinafine is a well tolerated drug with only rare case reports of serious adverse effects. There are relatively few drug interactions and no contraindicated drugs associated with terbinafine (table V). Terbinafine has recently been reported to inhibit cytochrome P450 2D6.[164,165] Abdel-Rahman et al.[165] indicate that the disposition of cytochrome P450 2D6 substrates coadministered with terbinafine may be significantly altered in individuals (approximately 93% of the population) who are extensive metabolisers for this cytochrome P450 isoform. The drug interactions reported with itraconazole and fluconazole are listed in table III and those with terbinafine in table V. For reference purposes only we have included a list of some potential interactions involving the cytochrome P450–mediated system (table VII). It should be stressed that table VII is not an indication of documented drug interactions. Also, the chart does not imply that any combination of inhibitor and substrate for a particular isoenzyme will result in an interaction of clinical significance. In the US, there are monitoring guidelines when the drug is used on a continuous basis for periods exceeding 6 weeks.

Itraconazole is a triazole which can be used as either continuous or pulse therapy, with the latter being the preferred regimen. After completing a 'pulse' of therapy lasting 7 days, plasma concentration of itraconazole decrease to almost undetectable concentrations within 7 days.[166] This may result in 'drug-free' intervals of approximately 2 weeks between successive 1-week pulses, with each pulse started 4weeks apart. This may in part explain why itraconazole pulse therapy may be associated with fewer adverse effects compared with continuous treatment with this triazole.[24,127] Itraconazole is effective not only against dermatophytes but also *Candida* species with limited experience in treating onychomycosis due to nondermatophyte moulds. Itraconazole has been used approximately 40 million times worldwide (approximately two-thirds for superficial mycoses and one-third for deep mycoses). Data from the use of itraconazole in large numbers of patients suggest that the drug is well tolerated with only rare case reports of serious adverse effects. There are contraindicated drugs and several drug interactions with itraconazole (tables III and IV). In general,

these are predictable and manageable, e.g. using an alternative agent that does not interact with itraconazole or monitoring more frequently. Many of the drug interactions manifest themselves because itraconazole is an inhibitor of cytochrome P450 3A4 in the liver and small bowel. In the US, with continuous therapy there are monitoring guidelines when the drug is used continuously for periods exceeding 4 weeks. For the itraconazole (pulse) regimen to treat fingernail onychomycosis there are no monitoring requirements. Furthermore, in countries where itraconazole (pulse) therapy is approved for toenail onychomycosis there are no monitoring guidelines.

Fluconazole is also a triazole and has the fewest studies of the drug comparators for the treatment of superficial fungal infections. The preferred regimen is once weekly administration. It has efficacy against dermatophytes and *Candida* species that most commonly cause onychomycosis. However, there are only a few reported studies where fluconazole is the monotherapy for dermatophyte toenail onychomycosis without the use of adjunctive chemical avulsion. Similarly, there are few reported data on the use of fluconazole to treat onychomycosis of the toenails caused by *Candida* species and nondermatophyte moulds. Fluconazole appears to be well tolerated in the treatment of superficial fungal infections, bearing in mind that there are few data available from reported studies in the dermatology literature. There are drugs contraindicated with fluconazole and several drug interactions (table III). Since in most cases the drug interaction is predictable, management options include using an alternative drug that does not interact with fluconazole, or monitoring more frequently. The drug interactions may develop because of the inhibitory affect of this triazole on the cytochrome P450 3A4 and 2C9 pathways. Since fluconazole is not approved for use in the treatment of superficial skin infections in the US or Canada, there are no guidelines regarding laboratory monitoring in these countries.

Once mycological and clinical cure has been achieved, it is important to try and ensure that onychomycosis does not recur. This may be due to delayed failure, i.e. incomplete eradication of the fungal organism in the first instance, or due to re-infection.[116]

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