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Onychomycosis: Diagnosis, Treatment, and Prevention Strategies

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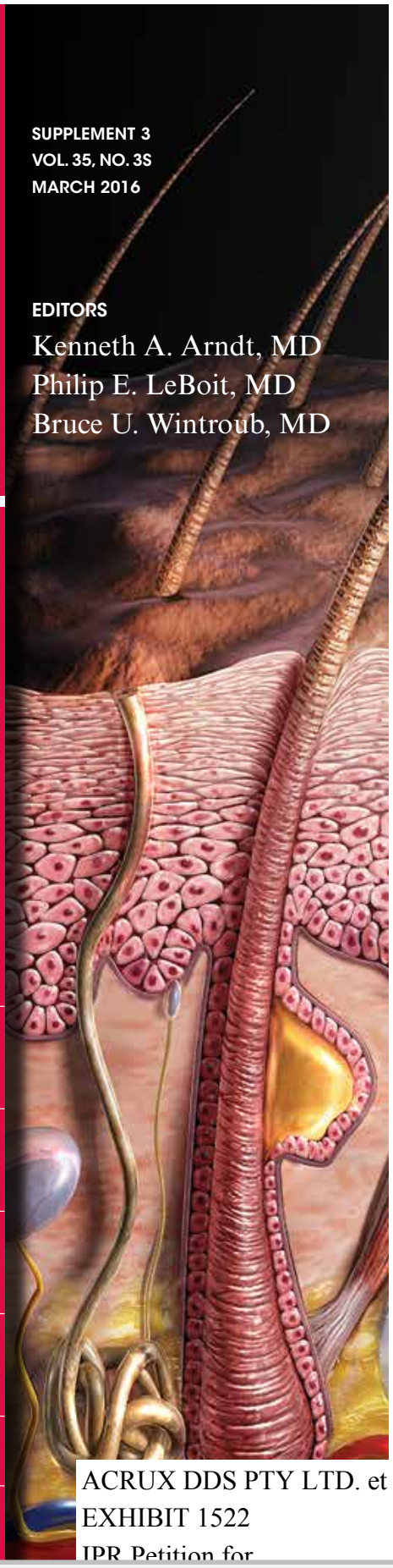

Onychomycosis: Diagnosis, Treatment, and Prevention Strategies

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Target Audience

This journal supplement is intended for dermatologists, family practitioners, internists, nurse practitioners, physician assistants, and other clinicians who treat patients with onychomycosis.

Educational Needs

For many years, the treatment of onychomycosis was frustrating for clinicians and patients alike, and the perceived futility of addressing fungal nail infections meant that many patients failed to seek treatment, and many others with suspected infections were neither definitively diagnosed nor treated. With the introduction of oral terbinafine in 1996 and the approval of the first topical agent in 1999, more effective control—if not cure—became possible, and clinicians showed increased interest in diagnosing and treating the condition. The introduction of two new topical agents in 2014 broadened the therapeutic options.

The optimum results with these agents requires the correct diagnosis, which cannot be made reliably on visual inspection alone. To use antifungals most effectively, clinicians must test to confirm the presence of infecting organisms and, in appropriate cases, identify the species involved so that the most appropriate antifungal can be prescribed. Patient selection also is important: for example, the potential for drug-drug interactions with systemic antifungals must be considered, the presence of certain comorbid conditions may affect the choice of antifungal employed, and the patient's ability to adhere to the long treatment regimens required must be addressed.

Clinicians must remain up-to-date on these issues, and must be able to effectively and safely use the available antifungal, evaluate the emerging data on medications and devices now being investigated, and educate patients to improve adherence.

Learning Objectives

After reading and studying this journal supplement, participants will be better able to:

- Establish or improve practice protocols for identifying patients with onychomycosis, particularly in special populations (eg, the elderly, pediatric patients, immunocompromised patients, patients with psoriasis, and those with diabetes mellitus).
- Discuss techniques, including obtaining good culture specimens, that permit more accurate diagnosis of the infecting organisms and the most appropriate choice of therapy.
- Explain the drug classes and mechanisms of action for the currently available therapeutic options, including differences in formulation and associated efficacy.
- More effectively use currently available oral and topical medications to treat various patient populations.
- Review and, if necessary, improve patient education materials designed to enhance patient adherence with the treatment regimen and to change habits that increase the chances of good long-term management of onychomycosis.
- Determine and help each patient recognize the realistic expectations for improvement in his or her individual case.
- Evaluate the results of clinical studies on new and emerging and available treatments for onychomycosis based on an understanding of possible differences in testing protocols (eg, inclusion or exclusion of patients with psoriasis or diabetes mellitus).

Disclosure Declarations

As a provider accredited by the ACCME, the Office of CME & PD, School of Medicine, University of Louisville must ensure balance, independence, objectivity, and scientific rigor in all its sponsored educational activities. All planners, faculty, reviewers, and other persons that affected the content of this CME activity were required to submit a financial disclosure form from which relevant conflicts of interest were determined. The persons below disclosed the following:

Linda F. Stein Gold, MD, Consultant: Anacor Pharmaceuticals Inc., Eli Lilly and Company, Galderma Laboratories, L.P., LEO Pharma Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc., Sandoz, Taro Pharmaceutical Industries Ltd., and Valeant Pharmaceuticals North America LLC. Speaker: Galderma, LEO, Novartis, and Valeant. Grant Research/Support: Anacor, Galderma, GlaxoSmithKline, LEO, Novartis, Pfizer Inc., Sandoz, Taro, and Valeant.

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Global Academy for Medical Education Staff: Sylvia H. Reitman, MBA, DipEd; Shirley V. Jones, MBA; Jenny Campano; and Joanne Still have no relevant financial relationships to disclose.

Off-Label/Investigational Use Disclosure

This CME/CE activity discusses the off-label use of fluconazole for the treatment of onychomycosis. Also discussed are off-label, alternative dosing schedules for itraconazole, as well as the use in pediatric patients of medications approved for the treatment of onychomycosis in adults; currently, no medication is approved for the treatment of onychomycosis in pediatric patients.

This continuing education supplement was developed from a satellite symposium held at Skin Disease Education Foundation (SDEF)`s 16th Annual Las Vegas Dermatology Seminar, which took place Friday, November 6, 2015, in Las Vegas, Nevada. The Guest Editors acknowledge the editorial assistance of Global Academy for Medical Education and Joanne Still, medical writer, in the development of this supplement. The manuscript was reviewed and approved by the Guest Editors as well as the Editors of Seminars in Cutaneous Medicine and Surgery. The ideas and opinions expressed in this supplement are those of the Guest Editors and do not necessarily reflect the views of the supporters, Global Academy for Medical Education, the University of Louisville, or the Publisher.

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EDITORS

STATEMENT OF PURPOSE

Seminars in Cutaneous Medicine and Surgery presents well-rounded and authoritative discussions of important clinical areas, especially those undergoing rapid change in the specialty. Each issue, under the direction of the Editors and Guest Editors selected because of their expertise in the subject area, includes the most current information on the diagnosis and management of specific disorders of the skin, as well as the application of the latest scientific findings to patient care.

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Antifungal Drugs for Onychomycosis: Efficacy, Safety, and Mechanisms of Action

Theodore Rosen, MD*, and Linda F. Stein Gold, MD†

Abstract

In 1996, oral terbinafine joined itraconazole and fluconazole on the short list of systemic medications that could be used to treat onychomycosis (although fluconazole was not approved for this indication by the US Food and Drug Administration [FDA], it was commonly used for this purpose). In 1999, ciclopirox was the first topical treatment to be FDA approved. The addition of the topical antifungal agents efinaconazole and tavaborole in 2014 expanded the roster of medications available to more effectively manage onychomycosis in a wide range of patients, including those for whom comorbid conditions, concomitant medications, or patient preference limited the use of systemic antifungals.

Keywords

Candidiasis; ciclopirox; efinaconazole; dermatophytosis; fluconazole; itraconazole; onychomycosis; tavaborole; terbinafine

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In selecting an antifungal agent to treat onychomycosis, clinicians must consider several factors: efficacy, side effect profile, drug-drug interactions, and the presence of comorbid diseases and conditions. This article focuses on the efficacy, safety, and drug-drug interactions associated with the systemic and topical medications used in the treatment of onychomycosis. [The third article in this supplement, "Concepts in Onychomycosis Treatment and Recurrence Prevention: An Update," on pages S59-S61, addresses the topic of onychomycosis comorbidities in detail.]

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Systemic Therapy: Efficacy Rates

Clinical trials have established the efficacy of terbinafine, itraconazole, and fluconazole in dermatophyte infections, using the FDA standard of complete cure—ie, negative mycology (both direct microscopy of a potassium hydroxide [KOH] wet-mount preparation) and normal nail plate appearance as the end point (Table 1).

Terbinafine has been the drug of choice since its introduction in 1996. The initial clinical trials comparing terbinafine with itraconazole showed that terbinafine was more effective. Those studies demonstrated a 38% complete cure rate using what became the FDA-approved dosage regimen for oral terbinafine—250 mg/day for 12 weeks.[1,2] Subsequently, Evans and colleagues[3] investigated the use of pulsed dosing of terbinafine, using either three or four pulses of 250 mg/day (ie, 1 week of daily treatment followed by 3 weeks off, repeated either once or twice). The reported cure rates were 49% for the three-pulse regimen and 54% for the four-pulse regimen. Pulsed dosing of terbinafine is not approved by the FDA.

Itraconazole, at a dosing schedule of 200 mg/day for 12 weeks, has been reported to yield a cure rate of 14%.[4] The results of clinical trials of pulsed dosing of itraconazole in patients with fingernail onychomycosis—a complete cure in 47% of patients—led to FDA approval of a regimen of two pulses of 400 mg/day for this indication (ie, 1 week of treatment followed by 3 weeks off, repeated once).[3] Studies of pulsed dosing of itraconazole in patients with toenail onychomycosis yielded efficacy rates of 23% for three pulses and 26% for four pulses.[3] Although not approved by the FDA for this indication, pulsed dosing of itraconazole frequently is used to treat toenail onychomycosis.

Fluconazole is not FDA approved for onychomycosis, but it is used quite commonly to treat both fingernail and toenail fungal infections. The typical regimen is a single weekly dose of 150 to 450 mg, for at least 6 months. Scher and colleagues[5] reported efficacy rates of 37% with 150 mg/week, 46% with 300 mg/week, and 48% with 450 mg/week.

In addition, Gupta and colleagues[6] reviewed other clinical trials that examined the efficacy of these medications with some smaller or noncontrolled trials yielding higher efficacy rates than those seen in the phase III trials. Although none of these medications is FDA approved for onychomycosis caused by *Candida* species, clinical studies have demonstrated that these oral antifungals do have some efficacy.[6]

Systemic Therapy: Safety

Oral antifungal agents generally are considered safe, but the prescribing information for each medication should be considered with respect to individual patient characteristics, and careful atten-

TABLE 1. Systemic Antifungals: Efficacy in Phase III Pivotal Trials

Medication/Regimen	Complete Cure Rates	Comments
Terbinafine		Pulsed dosing of terbinafine is not FDA approved.
250 mg/day x 12 weeks[1]	38%	
250 mg/day x 1 week/month[2]		
Repeated for 3 pulses	49%	
Repeated for 4 pulses	54%	
Itraconazole		
200 mg/day x 12 weeks[3]	14%	Approved regimen for toenail onychomycosis, with/without fingernail involvement.
400 mg/day x 1 week/month[2]		This regimen is not approved for either toenail or fingernail onychomycosis.
Repeated for 3 pulses	23%	
Repeated for 4 pulses	26%	
Fluconazole[4]		Fluconazole is not FDA approved for use in onychomycosis.
150 mg/week	37%	
300 mg/week	46%	
450 mg/week	48%	

tion should be paid to recommendations for baseline and follow-up testing and clinical monitoring.

For example, terbinafine has been associated with hepatic failure, and the prescribing information recommends that liver function tests be performed both at baseline and periodically during treatment. Other adverse events previously reported with the use of terbinafine include taste and smell disturbances that may become permanent, depression, severe neutropenia, and skin diseases such as Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), and lupus erythematosus–like illness.[1]

The prescribing information for itraconazole contains cautions about heart failure, other cardiac effects, including life-threatening arrhythmias, and sudden death (especially when itraconazole is used concomitantly with certain cytochrome P450 inhibitors—see "Drug-Drug Interactions," below). Hearing loss has been reported with the use of this medication, and hepatotoxicity rarely has been reported to occur as early as the first week of treatment.[4] Moreover, in vitro drug resistance has been demonstrated with this and the other azole drug, fluconazole.[4,7]

In addition to in vitro drug resistance, fluconazole use has been associated with hepatotoxicity, significant skin diseases, and prolongation of the QT interval on electrocardiogram. Fluconazole also has been associated with congenital defects, and its use should be avoided during the first trimester of pregnancy.[7]

Drug-Drug Interactions

No drug interactions have been reported with the use of any of the topical antifungal agents approved for the treatment of onychomycosis.

A number of drug-drug interactions—many of which are theoretical—are listed for each of the systemic antifungal medications (Table 2). The prescribing information for each of these medications should be consulted before choosing an oral antifungal. A detailed description of the mechanisms by which these interactions may occur is beyond the scope of this article, so one or two illustrative examples have been chosen for terbinafine, itraconazole, and fluconazole.

Terbinafine, which is metabolized by the cytochrome p450 (CYP450) enzyme 2D6 (CYP2D6), may interact in particular with drugs that are also metabolized by CYP2D6.[1] Although the class of beta-blockers is listed in the prescribing information, not all beta-blockers may interact to the same degree. Metoprolol—the most commonly prescribed beta-blocking agent in the United States—is the most likely drug in this class to interact with terbinafine. Terbinafine may inhibit the metabolism of metoprolol, resulting in excess systemic levels of metoprolol and a risk for bradycardia, low blood pressure, and, possibly, cardiogenic shock.[8]

Itraconazole is metabolized by the CYP3A4 enzyme, a characteristic it shares with several other medications.[4] One interaction of note is itraconazole's inhibition of metabolism of statin drugs, particularly simvastatin and lovastatin; this action can result in rhabdomyolysis. In addition, a potentially fatal interaction can occur when itraconazole is given concomitantly with opioids, particularly methadone; the combination is associated with a high likelihood of a fatal arrhythmia.[9]

Fluconazole has been widely studied and demonstrated to be effective against onychomycosis, and, although it is not FDA approved for this indication, it is widely used for treating this infection. Potential interactions include antiarrhythmic drugs, antipsychotics, and antihistamines[7] (although the most problematic among these, terfenadine, is no longer marketed).

However, not on the list derived from the fluconazole prescribing information is an interaction that has been demonstrated recently with tofacitinib—a medication currently approved for rheumatoid arthritis, well studied and likely to be approved for psoriasis and psoriatic arthritis, and being used investigationally in alopecia areata. Fluconazole inhibits tofacitinib's metabolism and

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