

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

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

n 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

Semin Cutan Med Surg 35(supp3):S51-S55
© 2016 Frontline Medical Communications

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

* Professor of Dermatology, Baylor College of Medicine, Houston, Texas.

† Director of Dermatology Research, Henry Ford Health System, Detroit, Michigan.

Publication of this CME/CE article was jointly provided by the University of Louisville, and Global Academy for Medical Education, LLC with Skin Disease Education Foundation (SDEF) and is supported by an educational grant from PharmaDerm, a Fougera Pharmaceuticals company.

Dr Rosen and Dr Stein Gold have received an honorarium for their participation in this activity. They acknowledge the editorial assistance of Joanne Still, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal supplement.

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.

Theodore Rosen, MD, *Consultant:* Anacor Pharmaceuticals and Valeant Pharmaceuticals North America LLC.

Address reprint requests to: Theodore Rosen, MD, 2815 Plumb, Houston, TX 77005; vampireted@aol.com.

and Recurrence Prevention: An Update,” on pages S56-S59, addresses the topic of onychomycosis comorbidities in detail.]

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 colleagues³ 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 colleagues⁵ reported efficacy rates of 37% with 150 mg/week, 46% with 300 mg/week, and 48% with 450 mg/week.

In addition, Gupta and colleagues⁶ 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		Approved regimen for toenail onychomycosis, with/without fingernail involvement.
200 mg/day x 12 weeks ³	14%	
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%	
Fluconazole⁴		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 antihistamines⁷ (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 investigational in alopecia areata. Fluconazole inhibits tofacitinib’s metabolism and,

therefore, may lead to gastrointestinal disturbances, such as severe diarrhea. Furthermore, inhibition of tofacitinib's metabolism may potentiate tofacitinib-related infections, particularly pharyngitis, sinusitis, and bacterial infections; some of these infections may be severe.¹⁰

Topical Agents: Efficacy and Safety

Currently, three topical agents are approved for the treatment of onychomycosis: ciclopirox 8% solution, efinaconazole 10%, and tavaborole 10%. No systemic adverse events have been reported with these topical agents, and the incidence of serious local reactions generally is quite low. Because the pivotal studies of these agents were not conducted using standardized protocols, each medication must be considered on its own merits in determining which topical agent to choose for an individual patient. The efficacy rates from the pivotal trials of these three agents are listed in Table 3.

Ciclopirox

Ciclopirox has antifungal, antibacterial, and anti-inflammatory effects. The lacquer is painted on the nail plates of the affected nails daily for 48 weeks. It has demonstrated good fungicidal activity in vitro against the dermatophytes *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*; *Candida* spp; and the nondermatophyte molds *Scopulariopsis brevicaulis*, *Aspergillus* spp, and *Scytalidium hyalinum*.⁶

The phase III pivotal trial protocol included patients between the ages of 18 and 70, with distal subungual onychomycosis of at least one great toenail (target nail) and positive KOH examination and culture for dermatophytic onychomycosis. Involvement of the target nail was no less than 20% and no greater than 65%. The lacquer was painted once daily on the entire nail plate of the target nail(s), along with approximately 5 mm of adjacent skin, the hyponychium, and the accessible ventral surface of the nail plate. The lacquer was removed once weekly with an alcohol wipe. In addition, subjects were required to report each month for professional trimming and debridement of the nails.¹¹ The guidelines for use specified in the prescribing information for ciclopirox include weekly removal of the lacquer and regular visits to a health care professional for debridement.¹²

In the two phase III pivotal trials, the complete cure rates reported were 5.5% and 8.5%.¹²

Efinaconazole

Efinaconazole is an azole drug with good potency against *T. rubrum*, *T. mentagrophytes*, and *C. albicans*. The formulation has a low surface tension, causing a "wicking" action that draws the medication around the nail. Studies of in vivo penetration showed that daily application of 10% and 5% solutions to all 10 toenails for 28 days demonstrated high levels of nail deposition and low systemic exposure to efinaconazole and its metabolite.¹³

In two parallel, 52-week, phase III, multicenter trials of efinaconazole,¹⁴ a total of 1,655 subjects were randomized, in a 3:1 ratio, to receive either efinaconazole or placebo. Included were subjects between 18 and 70 years of age with mild to moderate onychomycosis affecting 20% to 50% of at least one great toenail, with at least 3 mm of uninfected nail as measured from the proximal nail fold, and a nail plate thickness no greater than 3 mm. Nail trim-

n TABLE 2. Systemic Antifungals: Potential Drug-Drug Interactions

Terbinafine¹

- Beta-blockers
- Antiarrhythmics
- Tricyclic antidepressants
- Selective serotonin reuptake inhibitors (SSRIs)
- Monoamine oxidase inhibitors (MAOIs)

Itraconazole⁴

- Antiarrhythmics
- Statins
- Antihypertensives
- Benzodiazepines
- Opioids
- Antipsychotics
- Vasoconstrictors (ie, migraine therapy)

Fluconazole⁷

- Antiarrhythmics
- Antipsychotics
- Antihistamines
- Tofacitinib¹⁰ (fluconazole inhibits tofacitinib's metabolism)

ming, to any extent, was permitted but not required.

The cure rates in the efinaconazole pivotal trials were 15% and 18%.^{14,15}

Tavaborole

Tavaborole represents a new class of antifungal agent, a boron-based therapy. Boron is a low-molecular-weight, highly reactive molecule that targets protein synthesis.¹⁶ In preclinical studies, tavaborole demonstrated excellent and rapid penetration through the nail plate and into the nail bed.¹⁷

The inclusion criteria for the two parallel, phase III pivotal trials of tavaborole had several of the same or similar inclusion criteria as the pivotal trials of the other two topical antifungals: laboratory-confirmed onychomycosis of at least one great toenail; nail involvement of between 20% and 60%; at least 3 mm of uninvolved nail, as measured from the proximal nail fold; and nail thickness of 3 mm or less.¹⁸

However, these tavaborole studies differed from the ciclopirox

n TABLE 3. Topical Antifungals: Efficacy in Phase III Pivotal Trials

Medication	Complete Cure Rates*
Ciclopirox 8% ¹²	5.5% and 8.5%
Efinaconazole 10% ¹⁵	15% and 18%
Tavaborole 10% ¹⁶	7% and 9%

Regimens: All of these medications are approved for daily application for 48 weeks.

*Results of two phase III trials, respectively.

and efinaconazole trials in three important respects, which should be considered when comparing cure rates. First, in the tavaborole studies, no upper age limit was established (whereas the upper age limit in the other two studies was 70). Second, in the tavaborole studies, the medication was to be applied without debridement. Third, the final nail trimming prior to the final assessment allowed no less than 1 mm of growth at the distal edge of the target nail(s); in the other studies, the nail could be trimmed to the distal edge of the nail, which could affect the grading results.

The complete cure rates in the tavaborole pivotal trials were 9.5% and 6.5%.^{16,18}

Mechanisms of Action

The antifungal activities of the medications used to treat onychomycosis vary by class (Figure). The systemic agents itraconazole and fluconazole and the topical agent efinaconazole are in the azole class—specifically, in the triazole category. Triazoles work by inhibiting 14 α -demethylase of the P450 enzyme, blocking conversion of lanosterol to ergosterol in fungal cells; ergosterol is essential to fungal cell growth.^{4,7,15}

Terbinafine, in the allylamine class, also inhibits ergosterol biosynthesis, but at a different point in the pathway. Rather than affecting P450 and lanosterol-converting enzymes, the allylamines

inhibit squalene oxidase, resulting in lethal fungal cell membrane changes.¹

Ciclopirox is a synthetic antifungal agent. Its mechanism of action has not been clearly established but seems to involve both the inhibition of the metal-dependent enzymes responsible for the degradation of peroxides within the fungal cell as well as upregulation of fungicidal reactive oxygen formation within the fungal cytoplasm.^{19,20}

Tavaborole’s mechanism of action also is not completely understood, but it is thought to most likely involve inhibition of the enzyme leucine aminoacyl-transfer ribonucleic acid synthetase. Tavaborole is active against most strains of *T. rubrum* and *T. mentagrophytes*, the two species most commonly found in onychomycosis. No resistance to tavaborole has been observed.¹⁶

Efinaconazole shows in vitro activity against *T. rubrum* and *T. mentagrophytes*. No clinically significant evidence of drug resistance to efinaconazole has been reported.

Conclusion

In the pivotal trials for antifungal therapy for onychomycosis, the FDA-mandated criterion for efficacy is “complete cure.” This is defined as negative results on both direct microscopic examination of samples prepared with 10% to 20% KOH and on mycologic

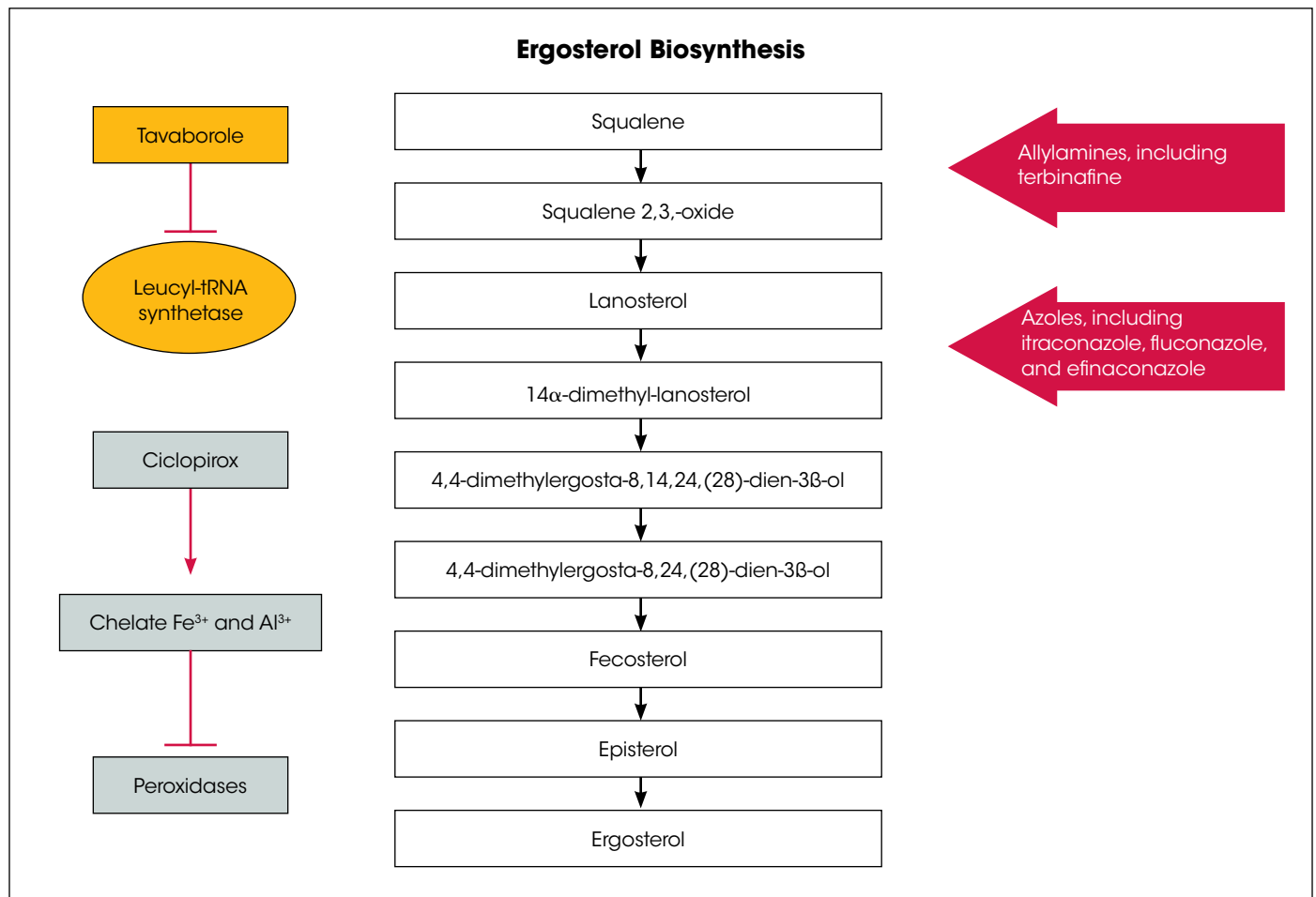


FIGURE. Antifungal Medications: Mechanisms of Action

Source: Theodore Rosen, MD.

culture, plus a substantially clinically improved nail (although not necessarily 100% normal appearance). In contrast, what might be called “effective treatment” is marked by a negative culture (regardless of the result of microscopic KOH examination, as a false-positive test may occur when nonviable hyphae are present), and substantial clinical improvement in the appearance of the nail.

In some patients, particularly those with early disease and little or no nail discoloration or deformity, a complete cure may be a realistic expectation. In those with infection of longer duration and a moderate degree of discoloration and deformity, a good result—ie, a clinical cure—is resolution of the infection, documented on direct microscopy and culture, and an appreciable improvement in the appearance of the nail. Effective treatment should be the baseline goal for the majority of patients. Resolution of infection, documented by a negative culture, and substantial improvement in nail appearance are achievable benchmarks in most cases, assuming that the medication chosen is effective against the infecting organism(s) and that the patient uses the treatment as prescribed.

References

1. Lamisil® (terbinafine) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2013.
2. Drake LA, Shear NH, Arlette JP, et al. Oral terbinafine in the treatment of toenail onychomycosis: North American multicenter trial. *J Am Acad Dermatol*. 1997;37(5 pt 1):740-745.
3. Evans EGV, Sigurgeirsson B, for the LION Study Group. Double blind, randomised study of continuous terbinafine compared with intermittent itraconazole in treatment of toenail onychomycosis. *BMJ*. 1999;318:1031-1035.
4. Sporanax® (itraconazole) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2014.
5. Scher RK, Breneman D, Rich P, et al. Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. *J Am Acad Dermatol*. 1998;38(6 pt 2):S77-S86.
6. Gupta AK, Paquet M, Simpson FC. Therapies for the treatment of onychomycosis. *Clin Dermatol*. 2013;31:544-554.
7. Diflucan® (fluconazole) [package insert]. New York, NY: Roerig, Division of Pfizer Inc; 2014.
8. Bebawi E, Jouni SS, Tessler AA, Frenette AJ, Brindamour D, Doré M. A metoprolol-terbinafine combination induced bradycardia. *Eur J Drug Metab Pharmacokinet*. 2015;40:295-299.
9. NoorZurani MH, Vicknasingam B, Narayanan S. Itraconazole-induced torsade de pointes in a patient receiving methadone substitution therapy. *Drug Alcohol Rev*. 2009;28:688-690.
10. Lahiri M, Dixon WG. Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2015;29:290-305.
11. Gupta AK, Fleckman P, Baran R. Ciclopirox nail lacquer topical solution 8% in the treatment of toenail onychomycosis. *J Am Acad Dermatol*. 2000;43(4 suppl):S70-S80.
12. Penlac® (ciclopirox) [package insert]. Bridgewater, NJ: Dermik Laboratories; 2006.
13. Jo Siu WJ, Tatsumi Y, Senda H, et al. Comparison of in vitro antifungal activities of efinaconazole and currently available antifungal agents against a variety of pathogenic fungi associated with onychomycosis. *Antimicrob Agents Chemother*. 2013;57:1610-1616.
14. Elewski BE, Rich P, Pollak R, et al. Efinaconazole 10% solution in the treatment of toenail onychomycosis: Two phase III multicenter, randomized, double-blind studies. *J Am Acad Dermatol*. 2013;68:600-608.
15. Jublia® (efinaconazole) [package insert] Bridgewater, NJ: Valeant Pharmaceuticals North America, LLC; 2015.
16. Kerydin® (tavaborole) [package insert]. Palo Alto, CA: Anacor Pharmaceuticals, Inc.; 2014.
17. Gupta AK, Daigle D. Potential role of tavaborole for the treatment of onychomycosis. *Future Microbiol*. 2014;9:1243-1250.
18. Elewski BE, Aly R, Baldwin SL, et al. Efficacy and safety of tavaborole topical solution, 5%, a novel boron-based anti fungal agent, for the treatment of toenail onychomycosis: Results from 2 randomized phase-III studies. *J Am Acad Dermatol*. 2015;73:62-69.
19. Belenky P1, Camacho D, Collins JJ. Fungicidal drugs induce a common oxidative-damage cellular death pathway. *Cell Rep*. 2013;3:350-358.
20. Subissi A, Monti D, Togni G, Mailland F. Ciclopirox: Recent nonclinical and clinical data relevant to its use as a topical antimycotic agent. *Drugs*. 2010;70:2133-2152.