WHAT IS NEW IN PHARMACOTHERAPEUTICS?

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Hardware/Software Requirements: Any web browser

Statement of Need

Onychomycosis is a fungal infection of the nail bed, matrix or plate usually caused by a dermatophyte. Nails of the toes are affected more often than fingers and accounts for more than one-third of integumentary fungal infections and one-half of all nail disease. The incidence of onychomycosis has been increasing particularly in the elderly and patients with immunodeficiency diseases, diabetes and circularly disorders. It is estimated that onychomycosis affects up to 12% of the world population and as many as 35 million in the US. Onychomycosis may indirectly decrease peripheral circulation and may contribute to limited mobility and venous stasis and diabetic foot ulcers and constitutes an important public health problem because of its high prevalence and associated morbidity. The disease can have certain negative consequences for patients, such as pain, and can potentially undermine work and social lives. Dermatophytes are fungi that require keratin for growth; they may cause superficial infections of the skin, hair and nails and are spread from person, from soil to or from animal host to humans. Dermatophytes are the most prevalent of the 3 major classes of superficial infections. Clinically, dermatophytosis infections, also known as tinea, are classified according to the body regions involved and the type and severity of the host response is often related to the species and strain of the dermatophyte causing the infection. The dermatophytes are the only fungi that have evolved a dependency on human or animal infection for the survival and dissemination of their species. The most common of these organisms are *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Epidermophyton floccosum*.

Educational Objectives

The educational goal for this activity will be to present dermatologists, residents, and allied health professionals with a discussion of key information developed from scientific research and expert clinical experience on the accurate diagnosis, optimal management and available treatment options (topical and systemic) for patients with onychomycosis and other dermatophyte infections.

Upon completion of this enduring material, participants should be able to:

- Categorize the features of fungal infections encountered in the dermatology setting
- Distinguish clinical presentation of onychomycosis and other dermatophyte infections
- Evaluate treatment options by type of infection
- Formulate effective treatment strategies using topical and systemic therapies

Target Audience

Office- and hospital-based dermatologists, dermatology residents, fellows, and other healthcare practitioners with an interest in the care of patients with cutaneous diseases and disorders.

Accreditation Statement

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What Is New in Fungal Pharmacotherapeutics?

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ABSTRACT

Approximately 20-25% of the population worldwide is affected by superficial cutaneous mycoses (SCM). SCM are cutaneous fungal infections with a wide array of systemic and topical treatment options. However, successful therapeutic outcomes are limited by patient non-adherence, medication side effects, potential drug interactions, antifungal resistance and disease recurrence. Advances in formulation technology have allowed for the development of more effective and safer therapies. In this article we will review several new and emerging pharmacotherapeutics for onychomycosis and tinea pedis.

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INTRODUCTION

Superficial cutaneous mycoses (SCM) are frequently encountered skin infections affecting 20-25% of the population worldwide.[1] SCM are typically categorized by the location of fungal infection and further subdivided by its causative dermatophyte. Current therapies include an array of systemic and topical agents. Successful therapeutic outcomes are limited by patient non-adherence, medication side effects, potential drug interactions, antifungal resistance and disease recurrence. In the following, we will review several new and emerging pharmacotherapeutics for onychomycosis and tinea pedis.

Onychomycosis

Onychomycosis is a fungal infection of the nail unit (eg, nail plate, nail bed, and periungal tissue). Dermatophytes, yeasts, and nondermatophyte molds are common etiologic agents. Four onychomycosis variants exist: distal subungual onychomycosis, white superficial onychomycosis, proximal subungual onychomycosis, and candida onychomycosis. The dermatophyte Trichophyton rubrum is responsible for up to 90% of infections, followed by Trichophyton mentagrophytes.[2] Less common pathogenic organisms include other dermatophytes, eg, Trichophyton tonsurans, Microsporum canis, and Epidermophyton Floccosum; yeasts, eg, Candida albicans and Candida parapsilosis; and molds, eg, Acremonium spp, Fusarium spp, Aspergillus, and Scytalidium spp.[1]

Approximately 10-12% of the US population[3] suffers from onychomycosis and its incidence increases with advanced age. While most patients are asymptomatic, those who seek medical attention suffer from pain, paronychia, and interference with normal function.[4]

Several therapeutic options exist for onychomycosis, however it continues to be a challenge to clear and maintain. The primary endpoint in clinical trials evaluating onychomycosis treatment is the "complete cure," defined as a negative fungal culture and potassium hydroxide (KOH) prep, as well as restoring the normal appearance of the nail. "Mycologic cure," on the other hand, refers to onychomycotic nails, which are not 100% anatomically clear, but yield a negative fungal culture. Current systemic therapies include fluconazole, itraconazole, and terbinafine, while topically ciclopirox nail lacquer may be used.[5]

New Therapies for Onychomycosis

Itraconazole 200 mg single daily dose received FDA approval in April 2010 for the treatment of onychomycosis caused by *T. rubrum* or *T. mentagrophytes* in non-immunocompromised patients. Itraconazole is an azole antifungal agent with antifungal activity through cytochrome P450-dependent synthesis of ergosterol resulting in the disruption of fungal cell membrane and associated enzyme systems. The efficacy of the 200 mg single daily dose of itraconazole is comparable to two 100 mg itraconazole QD[6] (Table 1).

TABLE 1.

The Efficacy of 200mg Single Daily Dose of Itraconazole Compared to Two-100mg Itraconazole QD for the Treatment of Onychomycosis

	Complete Cure at Week 52 (%)	Mycological Cure at Week 52(%)	Clinical Cure at Week 52 (%)
Itraconazole 200 mg QD (1 tablet)	22.3	44	26
Itraconazole 100 mg QD (2 tablets)	21.7	37	28

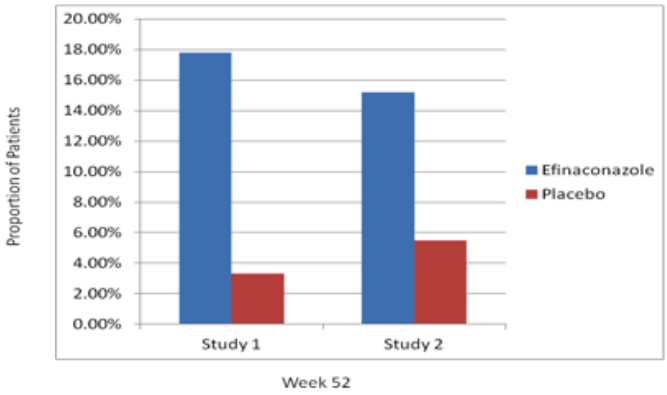
Prescribers must be aware of potential serious side effects, drug interactions, and laboratory monitoring associated with itraconazole. It is contraindicated in patients with current or history of congestive heart failure (CHF) as it exhibits negative inotropic effects. Additionally, rare cases of anaphylaxis, hepatotoxicity, and neuropathy (eg, transient or permanent hearing loss) have been reported.[6] Itraconazole is a potent inhibitor of the cytochrome P450 system and may affect the metabolism of other drugs. Cisapride, pimoxide, levacetylmethadol, methadone, and quinidine should be avoided because of the risk of serious cardiac adverse events such as QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death.[6] Additionally, calcium channel blocks should be avoided because of the additive risk for CHF exacerbation. All patients should have liver enzymes checked at baseline and periodically during therapy because of the risk of hepatotoxicity.[6] Finally, itraconazole is pregnancy category C, so caution should be exercised in treating female patients of childbearing potential.

The potential for serious adverse effects and drug interactions makes topical onychomycosis treatment preferable notwithstanding low efficacy of topical treatments and hence decreased adherence by patients. While ciclopirox 8% nail lacquer is FDA approved for the topical treatment of onychomycosis, its cure rate ranges from 5.5-8.5%[4] and requires frequent concurrent nail debridement. Other topical therapies are currently in development and may offer higher cure rates for patients. In October 2013, efinaconazole 10% topical solution became the first topical triazole antifungal solution approved by the Canadian regulatory authority, Health Canada, for the treatment of mild to moderate onychomycosis.

Efinaconazole has not yet received US FDA approval. Two phase 3 clinical trials have been conducted in the US to evaluate the safety and efficacy of efinaconazole 10% topical solution for onychomycosis. Efinaconazole had a complete cure rate approximately 5 times greater than placebo (P<0.001) (Figure 1). The mycological cure rate from efinaconazole was 53-55% compared to 16% from placebo (P<0.001).[7] Mild local skin reactions included application site dermatitis and vesicles. Systemic absorption of efinaconazole 10% solution topically applied to the nail is below the threshold for clinical drug-drug interactions, suggesting that it has limited or no potential for drug interactions[8]. Consequently, lab monitoring is not recommended.

Efinaconazole is a triazole antifungal, which inhibits sterol 14α-demethylase in the ergosterol biosynthesis pathway, thereby disrupting fungal cell membrane function.[9] Efinaconazole has a broad spectrum antifungal activity against dermatophytes, nondermatophyte molds, and yeast.[10] It has broad spectrum antifungal activity, with particular effectiveness

FIGURE 1. Complete cure rate of efinaconazole compared to placebo after 52 weeks for the treatment of onychomycosis.



against *T. rubrum and T. mentagrophytes* and *C. albicans.*[11] Additionally, efinaconazole has exhibited in-vitro antifungal activity against Trichophyton, Microsporum, Epidermophyton, Acremonium, Fusarium, Paecilomyces, Pseudallescheria, Scopulariopsis, Aspergillus, Cryptococcus, Trichosporon, and Candida.[9]

Efinaconazole 10% solution has several unique properties that explain its efficacy. Its non-lacquer, alcohol-based vehicle does not require debridement between applications and creates a low surface tension that provides easy access to the nail bed.[10,12] Moreover, efinaconazole possesses a low binding affinity to keratin, allowing for favorable nail plate penetration and quick drug release in its free, active form into the nail plate.[10,12] It is designed to be applied to a clean, dry nail plate surface, lateral and proximal nail folds, hyponychium, and undersurface of the nail plate once daily for 48 weeks.

Another new topical therapy for onychomycosis is tavaborole 5% solution. As of October 2013, the New Drug Application (NDA) for tavaborole 5% solution was accepted by the US FDA for review. This drug is in a new class of broad-spectrum antifungals, called benzoxaboroles, which inhibits fungal leucyl transfer RNA synthetase (LeuRS), an enzyme essential for protein synthesis.[13] Tavaborole demonstrates broad-spectrum antifungal activity against yeast, molds, dermatophytes, and filamentous fungi.[14] The degree of nail penetration of tavaborole 5% solution is 250 times greater than that of ciclopirox,[15] penetrating the lower ventral and intermediate layers of the nail plate 72 hours after application.[16] Additionally, tavaborole drug load that penetrated the lower layers of the nail plate was 5 times greater than ciclopirox.[17] Tavaborole 5% solution is safe; The most common side effects are local application reactions and no treatment-related systemic side effects were observed.[14] Tavaborole represents a new boron-based class of anti-fungals, which have a totally different mechanism of action than other anti-fungals on the market. Phase 3 clinical study results for this product are expected to be published soon.

TABLE 2.

Efficacy Results of Naftifin 2% Gel at Week 6 for the Treatment of Interdigital Tinea Pedis

	Trial 1		Trial 2	
Endpoint	Naftifine 2% Gel	Vehicle	Naftifine 2% Gel	Vehicle
Complete Cure Rate[a]	17%	2%	26%	3%
Mycological Cure Rate[b]	65%	14%	59%	10%
Treatment Effectiveness[c]	54%	6%	51%	7%

[a]Complete cure rate is defined as the mycological cure plus clinical cure which is defined as complete absence of erythema, scaling, and pruritis
[b]Mycological cure rate is defined as a negative KOH and dermatophyte culture
[c]Treatment effectiveness is defined as a negative KOH preparation and negative dermatophyte culture, and absent or nearly absent erythema, scaling and pruritus

New Therapies for Tinea Pedis

Tinea Pedis is an infection of the skin that affects the interdigital areas or soles of the feet and is caused by fungi, particularly dermatophytes and yeasts. Common fungal pathogens frequently associated with this disease include *T. rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*. Other etiological agents include Malassezia furfur, Microsporum canis, Coynebacterium minutissium, and Candida spp.[18] This condition affects approximately 10-25% of the population worldwide[19] and is characterized by pruritus, cracking, maceration, dry scaling, clusters of blisters/pustules, and/or erythema. The disease has various clinical patterns that may affect one or both feet.

Current therapies include a broad range of topical antifungal agents. The majority of topical anti-fungals currently in use are either in the allylamine or azole groups. The allylamine anti-fungals are fungicidal and kill the dermatophytes, whereas azole group anti-fungals mainly work by inhibiting dermatophyte growth as fungistatic agents. While cures can be achieved, reinfection occurs in up to 70% of patients.[20] Moreover, the increased use of topical azole antifungals has led to fungal resistance warranting the need for newer, more effective therapies.[21] In July 2013, naftifine 2% gel was approved by the US FDA for the treatment of interdigital tinea pedis. Additionally, in November 2013 the US FDA approved luliconazole 1% cream for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis.

Naftifine 2% gel is an allylamine antifungal that exhibits potent fungistatic and fungicidal activity against dermatophytes in vitro, unlike azole anti-fungals, which are only fungistatic. The exact mechanism of action is not yet clear, however naftifine hydrochloride interferes with sterol biosynthesis by inhibiting the enzyme squalene 2,3 epoxidase, depleting ergosterol and accumulating squalene cells, arresting fungal growth and disrupting the stability of the fungal cell membrane.[22] Naftifine also has anti-inflammatory effect by inhibiting polymorphonuclear leukocytes (PMN) chemotaxis and neutrophil adhesion[23]. In vitro antifungal activity of naftifine hydrochloride against dermatophytes demonstrated potent fungistatic and fungicidal activity against all dermatophytes (*T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *M. canis,* and Epidermophyton floccosum).[24] It has moderate activity against Aspergillus spp, Sporothrix schenckii, and some strains of Candida.[25]

Two multicenter trials have been conducted to evaluate the efficacy and safety of naftifine 2% gel for interdigital and moccasin-type tinea pedis. Naftifine 2% gel or vehicle was applied once daily for two weeks to the affected area of the foot. The primary endpoint for interdigital tinea pedis indication was the complete cure rate at the four-week follow-up visit after having used the study drug for two weeks (week 6). The complete cure rate, mycological cure rate, and treatment effectiveness at week six are seen in Table 2.[26] While local application site reactions occurred, there was no evidence of contact sensitization, phototoxicity, or photoallergenicity.[27] Systemic absorption ranged from 2-6%, but systemic adverse effects were not reported and consequently patients do not require laboratory monitoring.[28] Naftifine is pregnancy category B, but the safety and effectiveness in nursing women and pediatric patients have not been established.

The most interesting part of these results is continuous improvement during the study after stopping the study drug. For example, complete cure rate of composite scores from two studies increased from 5.4% at week 2 to 21.5% at week 6, four weeks after stopping the study drug; as well the mycologic cure rate increased from 39.1% at week 2 to 62% at week 6.[26] This progressive clinical and mycologic improvement over time, after stopping naftifine, implies the depot effect of naftifine in the skin. Furthermore, tape-stripping studies revealed that epidermal level of naftifine at application site remains relatively unchanged for several weeks post treatment.[29]

Additionally, naftifine 2% gel is the only anti-fungal that has been formally studied in moccasin-type tinea pedis. Although, naftifine 2% gel has not been approved by the FDA for this indication, a randomized double blinded vehicle controlled study showed that complete cure rate for moccasin-type tinea pedis at week 6 was 19.6% for naftifine vs 0.7% for the vehicle group. Treatment effectiveness at week 6 was 51% for naftifine vs 6% for the vehicle group.[26]

TABLE 3.

Efficacy of Luliconazole 1% Cream After 2 Weeks of Active Treatment for Interdigital Tinea Pedis		
	Active Treatment for 2 Weeks	Active Treatment for 2 Weeks
Endpoint	Luliconazole 1% cream at 2 weeks post treatment	Luliconazole 1% cream at 4 weeks post treatment
Complete Clearance Rate	26.8%	53.7%
Mycological Cure Rate	78%	82.9%

TABLE 4.

Efficacy of Luliconazole 1% Cream After 4 Weeks of Active Treatment for Interdigital Tinea Pedis		
	Active Treatment for 4 Weeks	Active Treatment for 4 Weeks
Endpoint	Luliconazole 1% cream at 2 weeks post treatment	Luliconazole 1% cream at 4 weeks post treatment
Complete Clearance Rate	45.7%	62.9%
Mycological Cure Rate	88.6%	91.4%

Luliconazole 1% cream is a once-daily topical medication for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis. Luliconazole is a topical imidazole that inhibits sterol 14α-demethylase and subsequently prevents ergosterol biosynthesis. It has broad-spectrum in-vitro antifungal activity against dermatophytes and candida.[30] As opposed to the 2-week treatment course needed for many other topical imidazoles, luliconazole treatment course is only one week for tinea cruris and tinea corporis indications. However, interdigital tinea pedis indication still requires a two-week treatment course. Topical luliconazole has been used for tinea pedis, tinea corporis, and tinea cruris in Japan since 2005.

Several clinical trials have been performed using luliconazole to treat tinea infections in the US. A double-blind vehicle control study in the US evaluated interdigital tinea pedis treated with luliconazole 1% cream. Patients used active drug or vehicle once daily for two or four weeks. Complete clearance rate and mycological cure rate after two or four weeks of therapy with luliconazole 1% cream is seen in Tables 3 and 4.[31-32] After two weeks of therapy, the mycological cure rate of luliconazole was 58.5%, which increased to 78% two weeks post-treatment, and then to 82.9% four weeks post-treatment in the two-week active treatment group.[32] After four weeks of therapy, the mycological cure rate of luliconazole was 77.1%, which increased to 88.6% two weeks post-treatment and then to 91.4% four weeks post-treatment in the four-week active treatment group.[32] Both treatment regimens were found to be safe and well-tolerated with limited systemic absorption and thus far no treatment related systemic side effects. Efficacy results were comparative to those observed in Japan.[33] Finally, a separate study evaluating luliconazole efficacy for tinea cruris revealed that once-daily application for one week treatment yielded a 21% complete clearance rate, as compared to 4% on vehicle at three weeks post-treatment.[34]

CONCLUSION

Both tinea pedis and onychomycosis are common skin infections that can be a challenge to treat. Side effects and monitoring need for oral anti-fungals have prompted the development of new and more effective topical medications. Advances in formulation technology has allowed for the development of more effective, safer therapies that offer higher cure rates with shorter treatment periods. These new medications offer additional options for patients with resistant or recurrent disease or in those populations who are noncompliant with previous longer therapies.

DISCLOSURES

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REFERENCES

1. James WD, Berger TG, Elston DM. Andrew's Disease of the Skin Clinical Dermatology. 11th Edition, Philadelphia, PA, Elsevier/Saunders, 2011.
2. Scher RK, Rich P, Pariser D, Elewski B. The epidemiology, etiology, and pathophysiology of onychomycosis. *Semin Cutan Med Surg.* 2013; 32(suppl):S2-S4.
3. Ghannoum MD, Hajjeh RA, Scher R. A large-scale North American study of fungal isolates from nails: The frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. *J Am Acad Dermatol.* 2000;43:641-648.
4. Pariser D. The rationale for renewed attention to onychomycosis. *Semin Cutan Med Surg.* 2013; 32(suppl): S1.
5. Elewski B, Pariser D, Rich P, Scher RK. Current and Emerging Options in the Treatment of Onychomycosis. *Semin Cutan Med Surg.* 2013;32:S9-12.
6. ONMEL (FDA package insert). Greensboro, NC:Merz Pharmaceuticals, LLC; 2012. Accessed 11/10/13 at http://onmel.com/wp-content/uploads/ONMEL-full-prescribing-information.pdf.
7. 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 Apr; 68(4):600-608.
8. Tosti A. Efinaconazole solution 10%: topical antifungal therapy for toenail onychomycosis. *Cutis.* 2013 Oct;92(4):203-8.
9. Tatsumi Y, Nagashima M, Shibanushi T et al. Mechanism of action of efinaconazole, a novel triazole antifungal agent. *Antimicrob Agents Chemother.* 2013 May; 57(5):2405-9.
10. Elewski BE. Efinaconazole 10% solution: a new topical antifungal therapy for onychomycosis. *Expert Rev Dermatol.* 2013; 8(4):347-356.
11. 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 Apr; 57(4):1610-6.
12. Patel T, Dhillon S. Efinaconazole: First Global Approval. *Drugs.* 2013; 73:1977-1983.
13. Fernando LR, Mao W, Yaremchuk A et al. An antifungal agent inhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site. *Science.* 2007; 316:1759-1761.
14. Zane LT, Pollak RA. Safety and Efficacy of Tavaborone (Formerly AN 2690), a Novel Boron-based Molecule, in phase 2 trials for the topical treatment of toenail onychomycosis. 2012 Aug.
15. Baker SJ , Hui X, Sanders V, et al. Nail Penetration of AN2690: Efficacy Coefficient and Effect of Formulation. 2006. Available at: http://www.anacor.com/pdf/ESDR_P91.pdf. Accessed 11/9/13.
16. Gupta AK, Simpson FC. New therapeutic options for onychomycosis. Expert Opin. *Pharmacother.* 2012;13(8): 1131-1142.
17. Hui X, Baker SJ, Wester RC, et al. In Vitro penetration of a novel oxaborole antifungal (AN2690) into the human nail plate. *J Pharm Sci.* 2007;96(10):2622-31.
18. Al Hasan M, Fitzgerald SM, Saoudian M, et al. Dermatology for the practicing allergist: Tinea pedis and its complications. *Clin Mol Allergy.* 2004, 2:5.
19. Havlickova B, Czaika VA, Freidrich M. Epidemiological trends in skin mycoses worldwide. *Mycoses.* 2008; 51(Suppl. 4):2-15.
20. Drake LA, Dinehart SM, Farmer ER, et al. Guidelines for care for superficial mycotic infections of the skin: tinea corporis, tinea cruris, tinea faciei, tinea manuum, and tinea pedis. Guiedelines/Outcomes Committee. American Academy of Dermatology. *J Am Acad Dermatol.* 1996; 34(2):282-286.
21. Maertens JA. History of the development of azole derivatives. *Clin Microbiol Infect.* 2004;10(Suppl 1):1-10.
22. Kosinski M, Joseph WS, Markinson B. Advances in the Treatment of Tinea Pedis. Podiatry Management. 2007 June/July; 227-242.
23. Choi TS, Solomon B, Nowakowski M, et al. Effect of naftifine on neutrophil adhesion. *Skin Pharmacol.* 1996; 9(3):190-6.
24. Ghannoum M, Isham N, Verma A, Plaum S, Fleischer A, Hardas B. In vitro Antifungal Activity of Naftifine Hydrochloride against Dermatophytes. *Antimicrob Agents Chemother.* 2013; 57(9):4369-4372.
25. Monk JP, Brogden RN. Naftifine: A review of its antimicrobial activity and therapeutic use in superficial dermatomycoses. *Drugs.* 1991; 42(4):659-672.
26. Stein Gold LF, Parish LC, Vlahovic T, et al. Efficacy and Safety of Naftifine HCL Gel 2% in the Treatment of Interdigital and Moccasin Type Tinea Pedis: Pooled Results from Two Multicenter, Randomized, Double-Blind, Vehicle-Controlled Trials. *J Drugs Dermatol.* 2013; 12(8):911-918.
27. NAFTIN Gel, 2% [package insert]. Greensboro, NC: Merz Pharmaceuticals, LLC; June 2013. 2. Data on file, Merz Pharmaceuticals, LLC. http://naftin.com/wp-content/uploads/NAFTIN-Gel-2-PI.pdf. Accessed 11/9/13
28. Del Rosso JQ, Kircik LH. Optimizing Topical Antifungal Therapy for Superficial Cutaneous Fungal Infections: Focus on Topical Naftifine for Cutaneous Dermatophytosis. *J Drugs Dermatol.* 2013; 12(11):S165-171.
29. Plaum S, Verma A, Fleischer A, Olayinka B, Hardas B: Detection and Relevance of Naftifine Hydrocloride in the Stratum Corneum Up to Four Weeks Following the Last Application of Naftifine Cream and Gel, 2%. *J Drugs Dermatol.* 2013; 12(9);1004-1008.
30. Koga H. Nanjoh Y, Makimura K et al. In vitro antifungal activities of luliconazole, a new topical imidazole. *Med Mycol.* 2009; 47(6):640-7.
31. Jarratt M, Jones T, Kempers S, et al. Luliconazole for the treatment of interdigital tinea pedis: a double-blind, vehicle controlled study. *Cutis.* 2013; 91:203-210.
32. Jones T, Tavakkol A. Safety and Tolerability of Luliconazole Solution, 10% in Patients with Moderate to Severe Distal Sunungual Onychomycosis. Antimicrob. *Agents Chemother.* 2013; 57(6):2684-9.
33. Watanabe S, Takahashi H, Nishikawa T, et al. Dose-finding comparative study of 2 weeks of luliconazole cream treatment for tinea pedis – comparison between three groups (1%, 0.5%, 0.1%) by a multi-center randomized double-blind study. *Mycoses.* 2007; 50:35-40.
34. Little LW. Valeant Pharmaceuticals Announces U.S. Approval of Luzu Cream, 1%. 2013 Nov. Available at: http://ir.valeant.com/investor-relations/news-releases/news-release-details/2013/Valeant-Pharmaceuticals-Announces-US-Approval-Of-Luzu-Cream-1/default.aspx. Accessed 11/19/13.

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1. Tavaborole is a:

a. Allylamine

b. Imidazole

c. Triazole

d. Boron based molecule

2. Luliconazole is:

a. Indicated for interdigital tinea pedis for one week therapy

b. Indicated for onychomycosis

c. Indicated for tinea cruris for one week therapy

d. Indicated for tinea capitis

3. Naftifine Gel 2% is:

a. Indicated for onychomycosis

b. Indicated for interdigital tinea pedis for four week therapy

c. Indicted for interdigital tinea pedis for two weeks therapy

d. Indicated for tinea capitis

4. Efinaconazole 10% solution:

a. Has been studied for tinea capitis

b. Has been studied for onychomycosis

c. Has been studied for tinea pedis

d. Has been studied for tinea cruris

5. Which one of the following anti-fungals has been used in Japan since 2005:

a. Luliconazole

b. Tavaborole

c. Naftifine

d. Efinaconazole

Evaluation Form

What is New in Fungal Pharmacotherapeutics?

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this Evaluation/Certificate Form. **For fastest results, please complete this form online at JDDonline.com** in the Medical Education Library. ***You must complete and submit this form or complete the CME activity online to receive credit for completing this activity. There is no fee for this CME activity.*** You must earn a passing score of at least 70% and complete the activity evaluation form in order to complete the course and receive a certificate for *AMA PRA Category 1 Credit™*. Alternatively, you may return this form to JDD by fax to (718) 407-0898, or by mail to 377 Park Avenue South, 6th Floor, NY, NY 10016.

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Post-test Answer Key

1	2	3	4	5

☐ I certify my actual time spent to complete this educational activity to be: _____

☐ I participated in the entire activity and claim 1 *AMA PRA Category 1 Credit™*.

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree	2 = Disagree	3 = Neutral	4 = Agree	5 = Strongly Agree

Was timely and will influence how I practice
1 2 3 4 5

Enhanced my current knowledge base
1 2 3 4 5

Addressed my most pressing questions
1 2 3 4 5

Provided new ideas or information I expect to use
1 2 3 4 5

Addressed competencies identified by my specialty
1 2 3 4 5

Avoided commercial bias or influence
1 2 3 4 5

Impact of the Activity

Name one new strategy you learned as a result of completing this activity:

_____

Name one thing you intend to change in your practice as a result of completing this activity:

_____

Additional comments about this activity:

_____

Please list any topics you would like to see addressed in future educational activities:

_____

continued on next page

Educational Gaps Evaluation

This activity was created to address the professional practice gaps listed below:

- Recognizing the impact of onychomycosis since fungal infections of the nails may spread to other areas of the body.
- Recognizing the clinical subtypes of onychomycosis and differentiate other conditions that can mimic onychomycosis.
- Accessing the latest evidence-based data and clinical experience in treatment options for onychomycosis and common dermatophyte infections.

	1=Disagree				5=Agree
1. Please respond regarding how much you agree or disagree that the gaps listed above were met.	**1**	**2**	**3**	**4**	**5**
Did participating in this educational activity change your KNOWLEDGE in the professional practice gaps that are listed above?	O	O	O	O	O
Did participating in this educational activity change your COMPETENCE in the professional practice gaps that are listed above?	O	O	O	O	O
Did participating in this educational activity change your PERFORMANCE in the professional practice gaps that are listed above?	O	O	O	O	O

2. Please elaborate on your previous answers.)

3. Please identify a change that you will implement into practice as a result of participating in this educational activity (new protocols, different medications, etc.).

4. How certain are you that you will implement this change?

5. Were the patient recommendations based on acceptable practices in medicine?

6. If you answered No on the question above, please explain which recommendation(s) were not based on acceptable practices in medicine?

continued on next page

7. Do you think the presentation was without commercial bias?

8. If you answered No on the above question, please list the topics that were biased.

9. Please provide any additional comments you may have about this educational activity.