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# Advances in Tinea Pedis Management

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# Advances in Tinea Pedis Management

## INTRODUCTION



## ORIGINAL ARTICLES



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# Introduction to Advances in Tinea Pedis Management

Leon H. Kircik MD

Dermatophytes and humans have coexisted for millennia, and for those thousands of years, humans have suffered the consequences of dermatophyte infections. Only recently have clinicians had access to safe and effective treatments to combat dermatophytoses. In just the past few years, the field of topical antifungal therapy has seen tremendous advancements that are paving the way for better treatment outcomes and enhanced patient adherence.

Of note, the FDA has in recent years approved formulations that feature new antifungal drugs previously not available in the United States. This gives prescribers access to the widest possible range of topical treatment options for onychomycosis and suprficial cutaneous fungal infections. Devising an effective topically applied treatment for toenail onychomycosis had proven an elusive goal. Today, there are two novel topical formulations that show benefit in treating toenail onychomycosis and thus reduce the need for oral antifungal therapy with its associated risks, concerns for drug – drug interactions especially in older patients and required monitoring.

In addition to new chemical entities, several formulation advancements have also emerged recently for both new and established antifungal drugs. These formulation advancements have been demonstrated to provide more patient centric use and in some cases increased efficacy as compared to older formulations of the same active agents. Gels, foams, and other dosage forms now available may be especially suited for application to large body surfaces, hair bearing areas providing ease of spreadibility of the active agent. Additionally, newer formulations allow for less frequent dosing (once daily) or shorter courses of treatment, which may be associated with improved patient satisfaction and better adherence with topical therapy. For example, as discussed ahead, the newest gel formulation of Naftifine 2% for interdigital tinea pedis is applied once daily for 2 weeks. In clinical trials, patients had shown continuous improvement in the signs and symptoms of tinea for up to four weeks after the treatment stopped.

Dermatophyte infections of the nails and skin can have a tremendous impact on patients, effecting not only function but also quality of life. Affected skin can become tender, itchy, and macerated. In patients with certain pre-existing medical conditions, like diabetes, for example, dermatophytoses are a source of potential significant health impairment. Dystrophic nails can become painful and affect gait.

When patients seek treatment, they require accurate diagnosis, education, and a commitment from the prescriber to combat a significant health concern. Many patients may have tried over-the-counter or "alternative" remedies, and may be frustrated with lack of results. They need efficient treatments that can be applied to affected skin and nails without causing additional discomfort and once a day dosing with ease of use. The latest range of topical antifungal therapies in novel formulations provides prescribers many options to meet those patient needs.

The pages ahead explore the microbiology of topical antifungal drugs, the science behind vehicle formulations and delivery systems, and the data on topical treatment efficacy. Armed with this knowledge, clinicians can more effectively target superficial cutaneous fungal infections and ultimately increasing their patients' quality of life.

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# Advancements in Topical Antifungal Vehicles

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## ABSTRACT

The primary treatment for superficial fungal infections is antifungal topical formulations, and allylamines and azoles represent the two major classes of topical formulations that are used to treat these infections. The stratum corneum (SC) is composed of keratinocytes that are surrounded by a matrix of lipids. The efficacy of topically applied formulations depends on their ability to penetrate this lipid matrix, and the vehicle plays an integral role in the penetration of active molecule into skin. There are several challenges to formulating topical drugs, which include the biotransformation of the active molecules as they pass through the SC and the physical changes that occur to the vehicle itself when it is applied to the skin. This article will review current and emerging topical antifungal vehicles.

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## INTRODUCTION

Superficial cutaneous fungal infections (SCFIs) are commonly encountered in clinical practice in the United States, and comprise infections of the skin by dermatophytes and yeasts.[1-3] Although SCFIs are seldom life threatening, they can severely affect patients' quality of life.[1-3] The most common of the SCFIs are dermatophyte infections, which result from fungi and affect the keratinized tissues of the skin, hair, and nails.

The primary treatment for SCFIs is antifungal topical formulations.[4-5] Allylamines and azoles represent the two major classes of topical formulations that are used to treat SCFIs.[4,5] Although both classes of topical formulations are clinically effective, allylamines have fungicidal activity against dermatophytes.[4,5] Conversely, the azoles are known to have greater activity against yeasts such as Candida spp and Malassezia spp, but topical allylamines have also shown to be efficacious for cutaneous candidiasis.[4,5]

Allylamines inhibit squalene epoxidase, which is a vital enzyme in the ergosterol biosynthesis pathway of fungal cell membrane formation.[6] The subsequent alterations in the fungal cell membrane formation results in cellular permeability and growth inhibition.[6] The allylamine antifungal agents in clinical use include naftifine, butenafine, and terbinafine.[6]

Azole antifungals also inhibit the synthesis of ergosterol by inhibiting the enzyme 14 alpha demethylase and thus disrupting the fungal cell membrane.[6] The azole antifungal agents in clinical use contain either two or three nitrogens in the azole ring and are classified as imidazoles (eg, ketoconazole and miconazole, clotrimazole) or triazoles (eg, itraconazole and fluconazole).[6]

A meta-analysis conducted by Rotta et al evaluated the efficacy of topical antifungals used in dermatophytosis treatment.[7] The investigators performed a comprehensive search for randomized, controlled trials comparing topical antifungals with one another or with placebo in dermatophytosis treatment through July 31, 2012 for all entries in MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, Literatura Latino Americana e do Caribe em Ciências da Saúde, and International Pharmaceutical Abstracts.[7] The investigators concluded that there was not a statistically significant difference among the outcomes regarding mycologic cure rates at the end of treatment among the various antifungals, but the allylamines naftifine, butenafine, and terbinafine are possibly the best strategies for maintaining a cured status among patients.[7]

Although all of the Food and Drug Administration (FDA) approved antifungals prescribed today produce mycologic cure rates, a primary difficulty for antifungal topical drug delivery is the low diffusion rate of drugs across the stratum corneum (SC).[8] The SC is composed of keratinocytes that are surrounded by a matrix of lipids. The efficacy of topically applied formulations depends on their ability to penetrate the lipid matrix of the SC.[9,10] The primary lipids found in the stratum corneum are phospholipids, cholesterol-3-sulphate, cholesterol, ceramides, sterol esters, and free fatty acids. The sebaceous lipids in the SC include triglycerides, wax esters, and squalene. [9,10]

In the topical administration of antifungals, the active drug should pass the SC, particularly into the viable epidermis. Consequently, the vehicle plays an integral role in the penetration of the active molecule into skin and ultimate clinical efficacy.[11] Depending on the properties of the delivery vehicle, the penetration of the active drug can be quite variable.[12] For example,

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the potency of topical corticosteroids has been evaluated by vasoconstrictor assay, and the same concentration of a topical corticosteroid can have potency that varies significantly in different vehicles.[13]

Vehicles contain a myriad of different chemicals, and there are several challenges to formulating topical drugs, which include the biotransformation of the active molecules as they pass through the SC and the physical changes that occur to the vehicle itself when it is applied to the skin.[14,15] Vehicles generally include ingredients that disrupt the skin barrier as they fluidize the lipid channels between corneocytes and transport the active drug into the cutaneous structures.[14] Detergents and emulsifiers are often used as vehicle excipients, because they disrupt and penetrate the SC. Propylene glycol is probably the most common excipient in topical vehicles, because it has multifunctional properties that act as a solvent, humectant, penetration enhancer, in addition to antimicrobial characteristics. At high concentrations, propylene glycol induces desquamation, which widens the cellular pathways and also disrupts the epidermal barrier.

Topical delivery systems often have a rheologic agent that improves its spreadability.[16] Microorganisms can form and proliferate in the water phase of a topical product, so topical formulations regularly include preservatives.[16] Fragrance or coloring agents may also be incorporated into a vehicle to modify the cosmetic features of the product. The relationship of these various ingredients will determine the efficacy of the final product.[16]

For decades, dermatologists have relied on creams and ointments for the topical treatment of SCFIs, but patient dissatisfaction with these delivery vehicles can result in reduced patient compliance and exacerbate SCFIs. Consequently, newer delivery vehicles in dermatology have been developed to improve clinical efficacy, reduce adverse events such as irritation, and enhance patient adherence. The newer vehicles include gels and foams, which often provide better application properties, adherence, and patient satisfaction in comparison to traditional vehicles. In addition to the ease of spreadability, particularly in hair bearing areas, gels and foams are particularly well suited for application over larger areas.

## Current and Emerging Antifungal Vehicles

Naftifine hydrochloride gel and cream, a topical allylamine, is a fungicidal that has shown to be efficacious against a wide spectrum of dermatophyte.[17,18,19, 20,21] The active ingredient of naftifine gel and cream is naftifine hydrochloride. The gel vehicle contains alcohol, benzyl alcohol, edentate disodium, hydroxyethyl cellulose, purified water, propylene glycol, polysorbate 20 and trolamine.[22] Propylene glycol acts as its primary penetration enhancer. The cream vehicle contains benzyl alcohol, cetyl alcohol, cetyl esters wax, isopropyl myristate, polysorbate 60, purified water, sosium hydroxide, sorbitan monostearate, stearyl alcohol, and hydrochloric acid.[23] In this case, isopropyl myristate is the major penetration enhancer.

Naftifine inhibits squalene epoxidase, thus inhibiting the conversion of squalene to squalene epoxide in ergosterol biosynthesis. Naftifine has potent in vitro fungicidal activity against dermatophytes, which correlates with its clinical and mycological activity in patients with dermatophytosis, as well as some anti inflammatory properties.[19] Naftifine application has also demonstrated a significant improvement in clinical symptoms and therapeutic success after courses of therapy between 2 to 6 weeks in a high percentage of patients with interdigital tinea pedis, tinea cruris, or corporis.[17,18,9]

> "The efficacy of topically applied formulations depends on their ability to penetrate the lipid matrix of the SC."

Naftifine gel 2% is approved for the topical treatment of interdigital tinea pedis caused by Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum in patients 18 years of age or older.[22] Naftifine cream 2 % is indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by Trichophyton rubrum in patients 18 years of age or older.[23] Both treatment regimens are applied topically once daily for two weeks in clinical studies. However, post-treatment improvement has been seen for up to two weeks in the case of tinea cruris and up to four weeks in the case of interdigital tinea pedis.[17,18] Similar trends in post-treatment improvement for up to four weeks after treatment cessation have also been demonstrated using naftifine gel 2% in subjects with interdigital type tinea pedis with or without moccasin-type infection.[17,24]

Plaum et al conducted an open-label, single-exposure study that tested the hypothesis that one of the reasons for the efficacy of naftifine 2% cream or gel is that drug-levels remained in the SC after the cessation of therapy.[20] The investigators utilized a tape stripping methodology to assess the amount of drug available in the SC over a 28-day period following the cream or gel's last application.[20] Six subjects were given naftifine cream 2% and six subjects were given naftifine gel 2%. The 12 subjects had twelve application sites on their upper backs, and 11 of the sites were dosed with one of the test formulations for 14 days. The final site remained untreated to serve as the control site.[20]

On days 15, 29, and 43, a selected test site was tape stripped to glean cells from the SC. The tape strips enabled the investigators

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to quantify the amount of drug present on the subjects' backs.[20] Plaum et al found that naftifine was present on all tape strip samples collected over the 28-day period after the cream or gel's initial application.[20] Moreover, the most relevant, deeper tape strip sets showed the potentially clinically relevant presence of naftifine in the skin 28 days post-treatment.[20] The investigators' findings elucidate the progressive improvement in clinical and mycological response rates not only during the treatment period but also for up to four weeks post-treatment using naftifine cream or gel.[20]

Kircik and Onumah conducted an 8-week pilot study that examined the efficacy of naftifine hydrochloride cream 2% and urea cream 39% for the treatment of tinea pedis with hyperkeratosis.[21] The treatment of tinea pedis with hyperkeratosis has traditionally been difficult for dermatologists due to the presence of thick scaling after the resolution of the active fungal infection. So the investigators utilized urea, because it is a keratolytic agent that clears the skin of hyperkeratosis scaling.[21]The investigators followed 10 patients for 8 weeks.[21] At baseline, the subjects were given a 2-week supply of naftifine hydrochloride cream 2% and an 8-week supply of urea cream 39%.[21] At weeks, 2, 4, and 8, the subjects were evaluated for compliance, and they also completed a visual analog scale (VAS) for pruritus severity and a dermatology life quality index (DLQI) questionnaire in addition to verbal and clinical assessments.[21] At week 8, Kircik and Onumah recorded significant clinical improvements and also subject satisfaction.[21] Over the 8-week period, the subjects had a 1-point improvement in the resolution of their hyperkeratosis.[21] Moreover, the subjects experienced a statistically significant median 2-point improvement in VAS pruritus severity, and a median 3-point improvement over the 8 weeks in their DLQI from baseline.[21] The investigators concluded that naftifine hydrochloride cream 2% and urea cream 39% were effective for the treatment of tinea pedis with hyperkeratosis, because, in part, the urea cream mitigated hyperkeratotic scaling, which facilitated the penetration of naftifine hydrochloride.

A 2014 study, conducted by Erdal et al, assessed the absorption of another, allylamine , terbinafine in a gel formulation in the presence and absence of three chemical enhancers: nerolidol, dl-limonene, and urea.[25] The investigators applied terbinafine 1% to the SC of healthy subjects, and, after 8 hours, used tape stripping and ATR-FTIR spectroscopy to determine absorption rates.[25] Erdal et al found that the terbinafine gel formulation containing nerolidol produced significantly greater terbinafine permeation through the SC than formulations containing urea and dl-limonene.[25] ATR-FTIR spectroscopy demonstrated that the terbinafine gel formulation containing nerolidol induced lipid bilayer disruption in the SC.[25]The formulation with urea produced enhanced permeation of terbinafine into the SC, whereas dl-limonene produced a relatively minimal accumulation of terbinafine in the upper SC.[25] Erdal et al concluded that a terbinafine gel formulation with nerolidol could potentially be of benefit for both superficial and deep cutaneous fungal infections.[25]

A study published in 2015, conducted by Pillai et al, assessed various formulations of butenafine hydrochloride gel, and their affects on ex vivo skin permeation and antifungal activity when compared to marketed butenafine hydrochloride cream.[26] The investigators incorporated isopropyl palmitate for the oil phase, and aerosol OT and sorbitan monooleate as surfactants.[26] They found that incorporating the aforementioned ingredients into Carbopol 940 gel had greater efficacy when compared to sodium alginate or hydroxyl propyl methyl cellulose gels. Pillai et al concluded that the developed gel demonstrated superior ex vivo skin permeation and antifungal activity when compared to marketed butenafine hydrochloride cream.[26]

Several studies have evaluated the safety and efficacy of a formulation of luliconazole cream 1%, which contains benzyl alcohol, butylated hydroxytoluene, cetostearyl alcohol, isopropyl myristate, medium-chain triglycerides methylparaben, polysorbate 60, propylene glycol, purified water, and sorbitan monostearate. Benzyl alchohol, propylene glycol, and isopropyl myristate act as the vehicle's primary penetration enhancers. In the preclinical guinea pig studies, high levels of luliconazole were achieved in the stratum corneum of guinea pig plantar skin within three consecutive days of application and was maintained over 14 days of application.[27]

A phase III randomized, double-blind, vehicle-controlled study assessed the safety and efficacy of luliconazole cream 1% in subjects with tinea pedis who were 12 years of and older.[28]The study included 321 patients; 159 subjects were randomized to receive luliconazole cream 1% and 162 received the vehicle once daily for 14 days.[28]The efficacy of luliconazole cream 1% regarding erythema, scaling, pruritus and mycology was evaluated at days 28 and 42, which were 14 and 28 days post-treatment.[28] On day 42, investigators found that 26.4% of subjects receiving luliconazole cream 1% achieved a complete clearance of clinical signs and mycology, and 1.9% of patients treated with the vehicle achieved a complete clearance of clinical signs and mycology ($P< 0.001$)[28]Comparable safety profiles were also recorded for luliconazole cream and the vehicle.

Sertaconazole has shown efficacious antifungal activity against dermatophytes that may have reduced susceptibility to other azoles. Susilo et al conducted a study to assess the rate and extent of the penetration of sertaconazole nitrate 2% cream into the SC.[29] The study included 12 healthy volunteers who were exposed to 8 applications of sertaconazole nitrate 2% cream or placebo over time intervals ranging between 0 and 48 hours.[29] The investigators used tape stripping and an HPLC-assay to determine the penetration of sertaconazole into three layers of the

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epidermis. Sertaconazole nitrate cream penetrated the SC shortly after application, and a relevant amount of the applied dose was recovered from the SC within 30 minutes after its initial application.[29] A plateau of sertaconazole was achieved three hours after administration, and it was maintained for 48 hours.[29]The estimated average level of sertaconazole nitrate penetration of the SC following the application of 100 milligrams of the cream was 1409 micrograms immediately after application, and it plateaued to 9029 micrograms at 3 hours.[29]The relative proportion of sertaconazole penetrating the SC was 1% at 12 hours, 34.2% at 24 hours, and 37.6% after 48 hours.[29] Susilo et al concluded that the rapid penetration of sertaconazole nitrate cream into SC and its increasing penetration over time, without significant quantities being distributed into blood, made it a favorable antifungal preparation.[29]

In 2014, the FDA approved econazole nitrate 1% foam for the treatment of interdigital tinea pedis. Econazole nitrate 1% foam incorporates patented Proderm Technology®, which is a water-lipid based dermal delivery technology that has demonstrated the potential to repair and restore compromised skin barrier function while delivering active ingredients without disrupting skin barrier function.[30,31] To assess the safety and efficacy of econazole nitrate 1% foam compared to the foam vehicle for the treatment of interdigital tinea pedis, Elewski and Vlahovic conducted two randomized, double-blind, parallel-group, vehicle-controlled, multicenter trials.[31]The trials enrolled males and females ≥12 years old with a clinical diagnosis of interdigital tinea pedis who also had a baseline fungal culture that was positive for a dermatophyte.[31] The trials' subjects applied econazole nitrate 1%foam (n=246) or the foam vehicle (n=249) once daily for 4 weeks.[31]The trails' primary endpoint was the percentage of subjects achieving a complete cure, which included a negative KOH, negative fungal culture, and a complete resolution of all signs and symptoms at 2 weeks post-treatment or day 43.[31] Elewski and Vlahovic found that the complete cure rate by day 43 was 24.3% for the subjects receiving econazole nitrate foam compared to 3.6% for the subjects receiving the foam vehicle.[31] The investigators determined that econazole nitrate foam was highly efficacious over the foam vehicle for the primary and secondary endpoints, and it was safe and well tolerated with a safety profile similar to the foam vehicle.[31]

## CONCLUSION

Topical anti-fungal treatment for SCFIs is a primary component of the dermatologic armamentarium, and effective treatment of SCFIs depends on both the active drug and the vehicle. The efficacy of topical formulations for SCFIs is not exclusively contingent on the concentration of the active drug but also the vehicle which plays an integral role in the success of topical treatment. Depending on the vehicle, penetration of the active drug can be quite variable. In addition to enhancing an anti-fungal's effectiveness, a vehicle may itself cause adverse effects, so the development of a vehicle includes multiple considerations. A myriad of diverse and molecularly complex classes of new topical vehicles are continuously being studied and refined in dermatologic research arena.

In this review of topical antifungal vehicles, we found that certain vehicles enhances efficacy up to four weeks post treatment by enabling the retention of the active molecule in the stratum corneum as in the case of naftifine cream and gel. The depo effect in stratum corneum of naftifine or similar agents shortens the treatment period, which increases patient compliance. Additionally, certain properties of vehicles such as ease of use, increase spreadability, and tolerability with a moisturizing effect in case of econazole foam, also increase patient compliance hence efficacy. Thus, we can not emphasize enough the importance of vehicles not only in topical anti fungal treatment but also in all aspects of topical dermatologic therapy.

## DISCLOSURES

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## REFERENCES

1. Borgers M, Degreef H, Cauwenbergh G. Fungal infections of the skin: infection process and antimycotic therapy. *Curr Drug Targets.* 2005; 6(8):849 62.
2. Charles AJ. Superficial cutaneous fungal infections in tropical countries. *Dermatol Ther.* 2009; 22(6):550-9.
3. Garber G. An overview of fungal infections. *Drugs.* 2001;61(Suppl 1):1-12.
4. Gupta AK, Cooper EA. Update in antifungal therapy of dermatophytosis. *Mycopathologia.* 2008;166(5-6):353-67.
5. Meis JF, Verweij PE. Current management of fungal infections. *Drugs.* 2001;61(Suppl 1):13-25.
6. Zhang, Y, Camp WL, Elewski BE. Advances in topical and systemic antifungals. *Clin Dermatol.* 2007; 25(2):165-83.
7. Rotta I, Ziegelmann PK, Otuki MF, et al. Efficacy of topical antifungals in the treatment of dermatophytosis: a mixed-treatment comparison meta-analysis involving 14 treatments. *JAMA Dermatol.* 2013; 149(3):341-49.
8. Bouwstra JA, Honeywell-Nguyen PL. Skin structure and mode of action of vesicles. *Adv Drug Deliv Rev.* 2002;1(54) Suppl 1:S41-55.
9. Potts RO, Francoeur ML. The influence of stratum corneum morphology on water permeability. *J Invest Dermatol.* 1991; 96(4):495–99.
10. Rougier A, Dupuis D, Lotte C, et al. In vivo correlation between stratum corneum reservoir function and percutaneous absorption. *J Invest Dermatol.* 1983; 81(3):275–78.
11. Lee CM, Maibach, HI. Deep percutaneous penetration into muscles and joints. *Journ of Pharma Sci.* 2006; 95(7):1405-12.
12. Weiss SC. Conventional topical delivery systems. *Dermatol Ther.*_2011; 24(5):471-6.
13. Cornell RC, Stoughton RB: Correlation of the vasoconstriction assay and clinical activity in psoriasis. *Arch Dermatol.*1985; 121:63–7.
14. Kircik LH. Importance of vehicles in acne therapy. *J Drugs Dermatol.* 2011; 10(6):s17-23.
15. Surber C, Smith EW. The mystical effects of dermatological vehicles. *Dermatology.* 2005; 210(2):157-68.
16. Feldman SR. Principles of topical treatment: advancement in gel vehicle technology. *J Drugs Dermatol.* 2014; 13(4):423-27.
17. Parish LC, Parish JL, Routh HB, et al. A randomized, double-blind, vehicle controlled efficacy and safety study of naftifine 2% cream in the treatment of tinea pedis. *J Drugs Dermatol.* 2011; 10(11):1282-88.
18. Parish LC, Parish JL, Routh HB, et al. A double-blind, randomized, vehicle-controlled study evaluating the efficacy and safety of naftifine 2% cream in tinea cruris. *J Drugs Dermatol.* 2011; 10(10):1142-47.
19. Monk JP, Brogden RN. Naftifine. A review of its antimicrobial activity and therapeutic use in superficial dermatomycoses. *Drugs.*1991; 42(4):659-72.
20. Plaum S, Verma A, Fleischer AB Jr, et al. Detection and relevance of naftifine hydrochloride in the stratum corneum up to four weeks following the last application of naftifine cream and gel, 2%. *J Drugs Dermatol.* 2013; 12(9):1004-8.
21. Kircik LH, Onumah N. Use of naftifine hydrochloride 2% cream and 39% urea cream in the treatment of tinea pedis complicated by hyperkeratosis. *J Drugs Dermatol.* 2014; 13(2):162-5.

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22. NAFTIN (naftifine hydrochloride) Gel, 2% Prescribing information. Merz Pharmaceuticals, LLC. 2013; Rev 6/13.
23. NAFTIN (naftifine hydrochloride) Cream, 2% Prescribing information. Merz Pharmaceuticals, LLC. 2009; Rev 1/12.
24. Stein, Gold L, Vlahovic T, Verms A, et al. Naftifine Hydrochloride Gel 2% An effective topical treatment for moccasin typoe tinea pedis. *JDrugs in Dermatol.* 2015; 14(10):1138-1144
25. Erdal MS, Peköz AY, Aksu B, Araman A. Impacts of chemical enhancers on skin permeation and deposition of terbinafine. *Pharm Dev Technol.* 2014; 19(5):565-70.
26. Pillai AB, Nair JV, Gupta NK, Gupta S. Microemulsion-loaded hydrogel formulation of butenafine hydrochloride for improved topical delivery. *Arch Dermatol Res.* 2015 May 26. [Epub ahead of print]
27. Koga H, Nanjoh Y, Inoue K, et al. ISHAM June 2006. P-0090
28. Jarratt M, Jones T, Adelglass J, et al. Efficacy and safety of once-daily luliconazole 1% cream in patients ≥12 years of age with interdigital tinea pedis: a phase 3, randomized, double-blind,vehicle- controlled study. *J Drugs Dermatol.* 2014; 13(7):838-46.
29. Susilo R, Korting HC, Strauss UP, et al. Rate and extent of percutaneous absorption of sertaconazole nitrate after topical administration. *Arzneimittelforschung.* 2005; 55(6):338-42.
30. Bikowski J. Practical features and clinical applications of a non-steroidal anti-inflammatory foam. *Pract Dermatol.* 2009:69-71.
31. Elewski BE, Vlahovic TC. Econazole nitrate foam 1% for the treatment of tinea pedis: results from two double-blind, vehicle-controlled, phase 3 clinical trials. *J Drugs Dermatol.* 2014;13(7):803-8.

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# Mycological Considerations in the Topical Treatment of Superficial Fungal Infections

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## ABSTRACT

Trichophyton rubrum remains the most common pathogenic dermatophyte in the United States, Europe, and industrialized Asia, although other species are predminant elsewhere. Candida albicans is the most common pathogenic yeast, with other species occasionally encountered. Just a few of the 14 described species of Malassezia cause pityriasis versicolor worldwide. FDA approval does not always accurately reflect the potential utility of any given topical antifungal agent. Azole, hydroxypyridone, and allylamine agents are beneficial in the management of dermatophytosis; however, the allylamines may lead to faster symptom resolution and a higher degree of sustained response. Although in actual clinical use the allylamines have all shown some activity against superficial cutaneous candidiasis and pityriasis versicolor, the azole agents remain drugs of choice. Ciclopirox is an excellent broad-spectrum antifungal agent. Optimal topical therapy for superficial fungal infections cannot yet be reliably based upon in-vitro laboratory determination of sensitivity. Inherent antibacterial and anti-inflammatory properties possessed by some antifungal agents may be exploited for clinical purposes. Candida species may be azole-insensitive due to efflux pumps or an altered target enzyme. So-called "antifungal resistance" of dermatophyets is actually due to poor patient adherence (either in dosing or treatment duration), or to reinfection.

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## INTRODUCTION

Superficial fungal infections – those affecting the skin, hair and nails – are extraordinarily common worldwide. About 20% to 25% of the world's population will be affected by at least one superficial fungal infection during their lifetime.[1] Superficial mycoses are caused by Candida species, the yeast forms responsible for pityriasis versicolor, select nondermatophyte molds, and dermatophytes, with the latter being the most prevalent globally.[2,3] The justifications for treatment of superficial mycoses include: cosmetic distress, presence of pruritus or pain, potential for spread from one body site to another, possible transmission to unaffected individuals, and prevention of secondary bacterial superinfection or persistent nail dystrophy.[4-7] When measured, successful therapy of superficial mycoses is associated with an improved quality of life.[8-10]

For a variety of reasons detailed elsewhere,[11] it is likely that both the incidence and prevalence of superficial fungal infections will increase. Thus, health care practitioners (HCPs) remain in search of simple, safe, convenient, and effective therapeutic interventions. This manuscript reviews mycologic aspects of this subject, with a goal of offering concrete and clinically relevant suggestions. This review will not address superficial mycoses, which typically require oral therapy (such as tinea capitis).

### Epidemiology of Superficial Mycoses

It is difficult to reliably determine both the overall incidence and prevalence of the various superficial mycoses worldwide because epidemiologic studies performed in one city/locale may not be representative of the overall disease pattern of that country; similarly, findings in one country may not be representative of the overall disease pattern of that region/continent. Finally, fungal disease patterns differ greatly from continent to continent.[1,2] Moreover, the predominant pathogenic fungal species is somewhat dependent on which type of superficial mycosis is most common, tinea pedis or tinea capitis. Finally, the local pattern of highly prevalent dermatophyte organisms may be influenced or modified by such factors as: changes in socioeconomic conditions, alterations in typical lifestyle, recent migration, and expansion of tourism.[1] With the foregoing cautionary caveats in mind, some generalizations can be made[1,2,12-14]:

Some species are worldwide T. rubrum, T. mentagrophytes var. interdigitale (now simply called T. interdigitale), M. canis, and E. floccosum.

Other species are characteristically restricted to select geographic regions; examples include: T. schoenleinii (Eurasia, Africa), T. soudanense (Africa), T. violaceum (Africa, Asia, and Europe), and T. concentricum (Pacific Islands, Far East, and India). Patients presenting with dermatophytosis who are visiting or emigrating from these areas may well harbor an organism common in their native land. Cultural identification of the offending pathogen is advisable in order to properly direct treatment.

The vast majority of cases of onychomycosis, tinea cruris, tinea corporis, and tinea pedis are currently caused by T. rubrum, the

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most common dermatophyte in both industrialized countries and in urban settings of emerging nations; In North America, as well as in most of Europe and Asia, the second most commonly encountered dermatophyte is T. interdigitale.

By contrast, in Southern Europe, Arabic countries, and rural locations in the Americas, zoophilic dermatophytes, such as M. canis or T. verrucosum, may be common pathogens.

When dealing with dermatophytes, the HCP must always take into account specific, individualized circumstances. For example, a patient who is involved with breeding, caring for, or riding horses might develop a dermatophytosis due to T. equinum, an otherwise unusual isolate.

Improvements in sanitation and socio-economic status may accompany urbanization, and the latter is generally associated with a decline in zoophilic and geophilic dermatophyte and a concurrent increase in anthropophilic dermatophyte infections.

Dermatophytes traditionally and primarily associated with tinea capitis can cause tinea corporis and even tines pedis (eg, M. canis, T. tonsurans).

Clinical infections, which unequivocally suggest dermatophytosis, may, in fact, be due to non-dermatophyte molds. Examples include: Neoscytalidium dimidiatum and N. hyalinum-induced tines pedis and as well as onychomycosis due to Acremonium, Aspergillus species, Fusarium species, Scopulariopsis brevicaulis, and other opportunistic molds. Such infections are highly treatment resistant, and failure of routine therapy should prompt mycological investigation for such rare organisms.

Although Malassezia species were discovered over a century and a half ago, their fastidious nature coupled with difficult culture and speciation techniques, have restricted research. New molecular techniques have facilitated understanding these lipophilic, non-keratolytic fungi. There are now 14 species within the genus Malassezia; M. globosa, M. furfur, M. restrica, and M. sympodialis are the common etiologic organisms associated with pityriasis versicolor.[15] The prevalence of pityriasis versicolor varies from negligible to up to 50% of populations in tropical and subtropical environments.[16] It is also more common among physically active, young individuals.[17] Under the correct conditions, the fungi responsible for pityriasis versicolor can cause: catheter-associated fungal sepsis, peritoneal dialysis-associated peritonitis, mastitis, sinusitis, malignant otitis, and septic arthritis.[15]

There are somewhere between 150 and 200 species of Candida, speciation being performed by conventional mycologic methods, manual and automated commercial systems, and newer molecular analyses.[18] Common pathogens include: C. albicans (~75% of all pathogenic isolates), C. glabrata, C. tropicalis, C. guilliermondii , C. parapsilosis, and C. krusei. Cutaneous infection with Candida species causes many morphologically distinct entities, including: congenital candidiasis, dermal lesions associated with candida sepsis, chronic mucocutaneous candidiasis, candida onychomycosis, paronychia, perleche, vulvovaginal candidiasis, candida balanitis, erosio interdigitale blastomycetica, diaper dermatitis, and intertriginous candidiasis. The last five of those enumerated previously are particularly amenable to topical therapy. C. albicans is the major pathogen in all types of cutaneous candidiasis throughout the world.[19] Many individuals with cutaneous candidiasis have some form of underlying predisposition that must be addressed and, if possible, corrected in order to achieve maximum clinical outcome and to prevent prompt relapse. Some underlying conditions include: innate or acquired immunocompromise (including HIV/AIDS); administration of steroids, chemotherapeutic agents, or other immunosuppressive drugs; broad spectrum antibiotic treatment; endocrine disorders (eg, diabetes mellitus and Cushing's syndrome); debilitation, immobility and malnutrition; obesity and hyperhidrosis; and prolonged occupational exposure to water (eg, bartender, maid).[20]

## Epidemiologic Correlation with FDA-Approved Treatments

Table 1 lists the most readily available topical antifungal agents in the United States, including both prescription only and over-the-counter (OTC) formulations, along with corresponding FDA approved indications. The Table does not include the myriad of primarily OTC "peeling" agents based upon salicylic acid and other "non-specific" agents (such as selenium sulfide).

The three products solely formulated for nail application along with every topical antifungal agent in all chemical groups (excepting nystatin), are approved to deal with the most common dermatophye, T. rubrum. Most are also approved for use with the second most common causative dermatophyte, T. interdigitale. However, it behooves us to remember that FDA-approved indications listed in package insets are based entirely upon the results of pivotal trials. Just because an agent lacks an "indication" does not mean that the drug will fail. Most often, lacking an "indication" reflects the fact that too few patients in the pivotal studies yielded positive culture for the fungus that is not indicated. Another possibility is that the disease state was simply not studied, as FDA labeling was not sought. These factors create serious anomalies. For example, note the difference between FDA-approved indications for 1% naftifine cream/gel and the comparable 2% formulations. Does anyone seriously believe that increasing the concentration of active antifungal drug will lead to a reduced spectrum of activity? Clearly, 2% naftifine cream has not been "proven" effective, to the FDA's satisfaction, in management of any dermatophytosis other than those caused by T. rubrum, even though the 1% naftifine

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**TABLE 1.**

**Topical Antifungal Drugs and Approved Uses**

| Drug | Class | Tinea corporis/ cruris | Tinea pedis | Tinea versicolor | Onychomycosis | Cutaneous candidiasis |
|---|---|---|---|---|---|---|
| Butenafine 1% Cream | Allylamine* | 1,2,3,4 | 1,2,3,4 | Yes | No | No |
| Naftifine 1% Cream/ Gel | Allylamine | 1,2,3,4 | 1,2,3,4 | No | No | No |
| Naftifine 2% Cream | Allylamine | 1 | 1 | No | No | No |
| Naftifine 2% Gel | Allylamine | No | 1,2,4 | No | No | No |
| Terbinafine 1% Cream/Spray | Allylamine | 1,2,4 | 1,2,4 | Spray only | No | No |
| Clotrimazole 1% Cream | Azole | 1,2,4,5 | 1,2,4,5 | Yes | No | Yes |
| Econazole 1% Cream | Azole | 1,2,3,4,5,6 | 1,2,3,4,5,6 | Yes | No | Yes |
| Econazole 1% Foam | Azole | No | 1,2,4 | No | No | No |
| Efinaconazole 10% Sol | Azole | No | No | No | 1,2 | No |
| Ketoconazole 2% Cream | Azole | 1,2,4 | 1,2,4 | Yes | No | Yes |
| Luliconazole 1% Cream | Azole | 1,4 | 1,4 | No | No | No |
| Miconazole 2% Cream | Azole | 1,2,4 | 1,2,4 | Yes | No | Yes |
| Oxiconazole 1% Cream | Azole | 1,2,4 | 1,2,4 | Yes | No | No |
| Oxiconazole 1% Lotion | Azole | 1,2,4 | 1,2,4 | No | No | No |
| Sertaconazole 2% Cream | Azole | No | 1,2,4 | No | No | No |
| Sulconazole 1% Cream | Azole | 1,2,4,5 | 1,2,4,5 | Yes | No | No |
| Ciclopriox 0.77% Cream/Gel | Hydroxpyridone | 1,2,4,5 | 1,2,4,5 | Yes | No | Yes |
| Ciclopirox 8% lacquer | Hydroxpyridone | No | No | No | 1 | No |
| Tavaborole 5% Solution | Oxaborole | No | No | No | 1,2 | No |
| Nystatin Cream/ Ointment | Polyene | No | No | No | No | Yes |
| Tolnaftate | Thiocarbamate | 1,2,3,4,5,6 | 1,2,3,4,5,6 | No | No | No |

Key:
1. Trichophyton rubrum
2. Trichophyton mentagrophytes
3. Trichophyton tonsurans
4. Epidermophyton floccosum
5. Microsporum canis
6. Other Microsporum species

Notes: *Butenafine is technically a benzylamine, a close structural relative to allylamines

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cream has a wide range of indication. Nonetheless, this simply defies logic and common sense. In a similar manner, 2% naftifine gel is approved only for the treatment of interdigital tinea pedis. Considering that 1% naftifine gel is indicated for management of tinea corporis and cruris, is there any reason why the 2% formulation lacks the same indication, other than the fact that this study was not done? As another example of a glaring anomaly, consider the only current FDA-approved indication for sertaconazole cream: interdigital tinea pedis. Yet, in the European Union, sertaconazole is indicated for the treatment of tinea corporis, tinea cruris, tinea manum, tinea barbae, and tinea pedis, as well as both cutaneous candidiasis and pityriasis versicolor.[21] Should we believe that this agent somehow works less well in North America than in Europe, especially for the same causative fungi?

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FDA-approved indication also does not address relative (comparative) efficacy, safety, and tolerability. While tonaftate is "approved" for the treatment of tinea corporis, cruris, and pedis due to an extended range of dermatophyte species, clinical experience dictates that both azole and allylamine agents are more efficacious. When comparing the relative efficacy of azoles and allylamines, the situation becomes considerably less clear despite comprehensive and thoughtful attempts to do so. In such systematic and meta-analyses, the authors concluded two important things: 1. Allylamine, benzylamine, azole, hydroxypyridone, and thiocarbamate agents are all routinely superior to placebo and 2. Since no trials sort subjects who failed treatment by etiologic species, no conclusions can be drawn about clinical susceptibility of various fungi to individual drugs in a manner that meaningfully impacts decision making.[22-25] A few additional pearls can be gleaned from these heroic attempts to compare different topical agents. In a systematic review of 67 randomized-controlled trials (RCTs) of topical tinea pedis treatment, authors concluded that: allylamines produce slightly higher complete cure rates than do azoles, and that, for the same agent, longer durations of therapy tend to work somewhat better than shorter durations of therapy.[22] In a systematic review of 129 RCTs of topical treatments for tinea corporis and cruris, the authors concluded that naftifine and terbinafine were very effective, but that other classes (such as azoles and hydroxypyridones) are also quite beneficial.[25] Finally, in a pair of reports representing the most ambitious attempts to compare efficacy between various topical antifungal drugs, as well as between classes of topical antifungals, Rotta and co-wokers[23,24] concluded that: 1. There is no significant and consistent difference between classes of antifungal drugs in terms of short-term efficacy 2. Safety and tolerability is excellent across all classes of topical antifungals, with adverse events (burning, stinging, pruritus, true allergic contact dermatitis) being reported in about 1-3% of treated patients and 3. Allylamine agents (and the related benzylamine, butenafine) show a higher degree of sustained cure compared to classic imidazoles. It is noted that these exhaustive reviews included many RTC which were sub-optimally designed, inadequately reported, subject to considerable heterogeneity, and at risk for bias; none included newer formulations or concentrations of older agents or recently released agents (eg, luliconazole).

What is the clinical relevance of the foregoing? Basically, assuming diligent patient adherence to the prescribed treatment regimen, any approved agent will work for common dermatophyte infections due to the most common pathogens.[11] However, some interventions may be more "appealing" to both HCP and patient because they require fewer applications per day, fewer total applications, and/or shorter duration of therapy. For example, whereas four weeks of topical antifungal therapy were once considered required to achieve clinical benefit in tinea pedis, newer agents (1% luliconazole cream and 2% naftifine cream/gel) prove satisfactory after only two weeks of therapy.[26-28] Luliconazole cream has even been successfully administered once daily for only one week for tinea cruris.[29]

Although not apparent in large scale retrospective analysis, there is some evidence that dermatomycoses due to Microsporum species (in particular M. canis) may be somewhat less responsive to topical azole agents compared to topical allylamines, especially if one utilizes the older azoles such as clotrimazole.[30,31]

With respect to cutaneous candidiasis, the various approved azoles and ciclopirox are considered superior to allylamines and are deemed the appropriate drugs of choice.[32] That said, in contrast to accepted dogma and FDA approved indication, both butenafine and terbinafine have proven modestly successful (efficacy rates ranging from 73-85%) in the treatment of interdigital and intertriginous candidiasis.[33,34] Butenafine is particularly interesting in that it may not only block squalene epoxidase, but also possess a direct membrane damaging effect on Candida albicans.[35] Due to its potent anti-inflammatory effects and relative low cost (now being available OTC), butenafine may be a viable (off-label) alternative for rapid relief of symptomatic cutaneous candidiasis. Nystatin is the only specific topical anti-Candidal agent, and is available as a powder, cream and ointment (100,000 units per gram). The powder may be untenable in the face of excessive exudation, but may be an optimal method of topical prophylaxis in cases of recurrent intertriginous candidiasis. Nystatin regularly demonstrates a

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higher in-vitro MIC when compared to azole antifungals worldwide (studies cited from Brazil, Cuba and Singapore).[36-38]

Virtually no cases of pityriasis versicolor are investigated to determine the precise causative Malssezia species. The absence of standardized collection and reporting practices during clinical studies or during routine use, precludes any conclusions to be drawn regarding the relative efficacy of the many approved topical agents with regards to specific Malassezia species.[39] In general, topical azoles are felt to be superior to topical allylamines in the management of pityriasis versicolor. However, topical prescription treatments for pityriasis versicolor may be logistically and economically impractical in extensive disease. Several OTC preparations are suitable for treatment of pityriasis versicolor, including zinc pyrithione and selenium sulfide.[32] Short courses of generic oral antifungal agents (such as fluconazole, off-label) may actually be more cost effective, not to mention more convenient, than two-eight weeks of topical application of either prescription or OTC agents.[39] As another deviation from FDA approvals, both terbinafine and naftifine have been utilized successfully in pityriasis versicolor, although neither is considered a drug of choice for this superficial mycosis.

## In-vitro Data

Perhaps therapeutic decisions could (or should) be based upon in-vitro anti-fungal drug sensitivities of clinical isolates, akin to the manner in which bacterial diseases are treated? Alas, such is not the case. Stringent but cumbersome broth microdilution standards do exist: Clinical Laboratory Standards Institute (CLSI: M38-A1 and M38-A2) in the United States and the European Committee on Antimicrobial Susceptibility Testing (EUCAST: E.DEF 7.2 and 9.1) in Europe. However, even these reference techniques differ in inoculum size, incubation time and medium composition.[40] They are also designed and validated only for yeasts and molds and, as a consequence, do not directly address the antifungal susceptibility of dermatophyte species. While reference tests can be adapted for dermatophytes,[41-43] results may vary depending upon exact parameters employed during testing. There are also alternative methods in use, including: macro-dilution, agar-based disk diffusion, colorimetric modifications, bioluminescence assays, flow cytometry, ergosterol quantitation and a number of automated and semi-automated commercial kits.[44,45] The various techniques available for antifungal susceptibility testing do not always correlate with reference techniques or with eachother.[42,45] Finally, as pointed out repeatedly, correlation between in-vitro dermatophyte MICs and in-vivo clinical outcomes remains unclear and yet to be determined.[32,41,42,45] Even when dealing with Candida species, isolates from patients whose condition does not respond to azole therapy may be apparently sensitive based upon standardized in-vitro testing, whereas patients whose condition responds to treatment may have strains that show MIC values consistent with in-vitro resistance.[46] In short, when it comes to topical therapy for superficial fungal infections, in-vitro laboratory determination of sensitivity is not a "surefire" manner to predict clinical success.

Similarly, whether an agent is considered "fungicidal" or "fungistatic" has minimal real world importance. A high enough concentration of virtually any of the agents listed (except for nystatin and tonaftate) will result in in-vitro fungicidal activity for at least some dermatophytes and yeast. Moreover, as noted by a leading Japanese mycologist, we are far from understanding how to devise accurate, reproducible and standardized methods of determining minimal fungicidal drug concentrations for dermatophytes.[47] It is, however, generally accepted that, with the exception of luliconazole, sertaconazole, and possibly oxiconazole, the azoles are predominantly fungistatic; by contrast, butenafine, naftifine, terbinafine, and ciclopirox are considered fungicidal.[32] The possible benefit to a fungicidal agent is the potential for more rapid onset of action, and therefore somewhat more prompt relief of symptoms.

> "Many individuals with cutaneous candidiasis have some form of underlying predisposition that must be addressed and, if possible, corrected in order to achieve maximum clinical outcome and to prevent prompt relapse."

## Ancillary Antifungal Properties

These properties may influence, to some extent, the choice of specific agents in certain clinical settings. For example, when concurrent bacterial infection is probable, or already present (such as severe interdigital tinea pedis), an antifungal agent which helps eradicate bacterial superinfection might be preferable. In those situations where the inflammatory response to superficial mycoses is extreme and symptoms are overwhelming, an antifungal agent which is inherently anti-inflammatory may be preferable.

Some of the azole antifungal drugs are antibacterial: clotrimazole, econazole, miconazole, oxiconazole, sertaconazole, and sulconazole demonstrate inhibitory activity in vitro and in vivo against some Gram-positive and a few Gram-negative bacteria.[32] In particular, sertaconazole has a lower geometric mean MIC for Streptococcal and Staphylococcal species than other azoles.[48] Both naftifine and terbinafine have some demonstrable in-vitro and in-vivo anti-bacterial properties according to a German group of investigators.[49,50] Of all the anti-mycotic agents, ciclopirox olamine has the broadest spectrum of antibacterial

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activity, including low MICs for Pseudomonas aeruginosa, Proteus mirabilis, Escherichia coli, and Klebsiella pneumoniae, as well common Streptococcal and Staphylococcal species.[51,52] By contrast, butenafine has no activity against Gram-negative bacteria and Gram-positive activity limited only to Group A beta-hemolytic Streptococcus.[52] Despite evidence of antibacterial activity, none of these antifungal agents should be considered drugs of choice when treating either uncomplicated or complicated primary bacterial pyodermas.

Anti-inflammatory properties have been investigated in a variety of ways, including: inhibition of neutrophil chemotaxis, reduction in inflammation-associated skin temperature, reduction of croton oil or arachidonic acid-induced ear edema in a murine model, reduced erythema-wheal formation following intracutaneous histamine injection, direct inhibition of 5-lipoxygenase and/or cyclo-oxygenase activity and inhibition of UV-induced erythema. Although many antifungals possess some degree of inherent anti-inflammatory activity, when tested in a head-to-head manner, ciclopirox olamine, naftifine and terbinafine proved more effective than the any of the azole drugs.[53,54] This suggests, but does not prove, that these three antifungal agents might be more effective at reducing erythema and pruritus. An example would be tinea corporis or faciei due to M. canis acquired from a new pet kitten or puppy.

### Antifungal Resistance

Candida albicans resistance to antifungal drugs seems to be increasing, and such resistance appears to be related to prolonged exposure to these agents.[55,56] Candidal resistance appears primarily related to upregulation of CDR1, CDR2 genes, which enhance efflux (removal) of anti-infective drugs, as well as mutations in ergosterol biosynthesis gene (ERG11) leading to an altered (resistant) form of the azole target enzyme, 14C-lanosterol demethylase.

Dermatophyte resistance has been most widely studied in T. rubrum. Antifungal resistance to allylamines depends mostly upon an altered target enzyme, wherein amino acid substitutions in squalene epoxidase occur in the allylamine binding site.[57,58] In addition, there appears to be the potential for inducible upregulation of TruMDR1 and TruMDR2 genes which encode for drug efflux structures.[59,60] Finally, T. rubrum may over-express salicylate mono-oxygenase which is capable of degrading allylamines.[60] Dermatophyte resistance to azole agents depends on the same efflux mechanisms detailed above, and also to compensatory over-production of the target enzyme, 14C-lanosterol demethylase.[61] Despite the foregoing, naturally occurring resistant dermatophytes are exceedingly rare. One study estimated that innately azole resistant T. rubrum occurred in about 1 in $10^7$ organisms and innately terbinafine resistant T. rubrum in about 1 in $10^9$ organisms.[62] The same investigators noted that repeated exposures (10 passages) of T. rubrum to subinhibitory concentrations of azole and allylamine antifungal agents led to appearance of resistant strains. Thus, failure of one antifungal agent might be due to acquired resistance, even though innate resistance is rare. Interestingly, despite multiple exposures of T. rubrum to subinhibitory concentrations of ciclopirox olamine, no mutant resistant strains were isolated.[62]

In reality, most antifungal "resistance" is actually due to: poor patient adherence (either in dosing or treatment duration), or to reinfection following re-exposure.[63]

## CONCLUSION

The ideal topical antifungal agent for superficial mycoses should have broad-spectrum activity, high mycologic and clinical cure rates, efficacy at low concentrations, fungicidal activity with a convenient dosing schedule, keratinophilic and lipophilic properties, a reservoir effect in the stratum corneum, lack of potential for development of antifungal drug resistance, low relapse rate, few to no adverse effects, and a low cost. While this "ideal" agent does not yet exist, many of the FDA-approved topical agents have some of these characteristics.

## DISCLOSURES

The author has received honoraria from the following pharmaceutical companies in conjunction with participation in advisory boards: Anacor, Merz, and Valeant.

This article includes discussion of published and/or investigational use of agents that are not indicated by the United States FDA.

## REFERENCES

1. Ameen M. Epidemiology of superficial fungal infections. *Clin Dermatol.* 2010;28(2):197-201.
2. Havlickova B, Czaika VA, Friedrich M. Epidemiological trends in skin mycoses worldwide. *Mycoses.* 2008;51(suppl 4):s2-s15.
3. Pires CA, Cruz NF, Lobato AM, et al. Clinical, epidemiological, and therapeutic profile of dermatophytosis. *An Bras Dermatol.* 2014;89(2):259-264.
4. Zeichner JA. New topical therapeutic options in the management of superficial fungal infections. *J Drugs Dermatol.* 2015;14(suppl 10):s35-41.
5. Rich P. Efinaconazole topical solution, 10%: the benefits of treating onychomycosis early. *J Drugs Dermatol.* 2015;14(1):58-62.
6. Ghannoum MA, Mukherjee PK, Warshaw EM, et al. Molecular analysis of dermatophytes suggest spread of infection among household members. *Cutis.* 2013;91(5):237-246.
7. Zaias N, Rebell G. Chronic dermatophytosis syndrome due to Trichophyton rubrum. *Int J Dermatol.* 1996;35(9):614-617.
8. Kircik LH. Observational evaluation of sertaconazole nitrate cream 2% in the treatment of pruritus related to tinea pedis. *Cutis.* 2009;84(5):279-83.
9. Milobratović D, Janković S, Vukičević J, et al. Quality of life in patients with toenail onychomycosis. *Mycoses.* 2013;56(5):543-51.
10. Warshaw EM, Foster JK, Cham PM, et al. NailQoL: a quality-of-life instrument for onychomycosis. *Int J Dermatol.* 2007;46(12):1279-86.
11. Rosen T. Assessment of dermatophytosis treatment studies: Interpreting the data. *J Drugs Dermatol.* 2015;14(suppl 10):s48-54.
12. Seebacher C1, Bouchara JP, Mignon B. Updates on the epidemiology of dermatophyte infections. *Mycopathologia.* 2008;166(5-6):335-52.
13. Canavan TN, Elewski BE. Identifying signs of tines pedis: A key to understanding clinical variables. *J Drugs Dermatol* 2015;14(suppl 10):s42-47.
14. Martínez-Herrera EO, Arroyo-Camarena S, Tejada-García DL, et al. Onychomycosis due to opportunistic molds. An Bras Dermatol. 2015;90(3):334-7.

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15. Thayikkannu AB, Kindo AJ, Veeraraghavan M. Malassezia-Can it be Ignored? *Indian J Dermatol.* 2015;60(4):332-9.
16. Renati S, Cukras A, Bigby M. Pityriasis versicolor. *BMJ.* 2015 Apr 7;350:h1394.
17. Kyriakis KP, Terzoudi S, Palamaras I, et al. Pityriasis versicolor prevalence by age and gender. *Mycoses.* 2006;49(6):517-8.
18. Neppelenbroek KH, Seó RS, Urban VM, et al. Identification of Candida species in the clinical laboratory: a review of conventional, commercial, and molecular techniques. *Oral Dis.* 2014;20(4):329-44.
19. Fallahi AA, Korbacheh P, Zaini F, et al. Candida species in cutaneous candidiasis patients in the Guilan province in Iran; identified by PCR-RFLP method *Acta Med Iran.* 2013;51(11):799-804.
20. Hay RJ. The management of superficial candidiasis. *J Am Acad Dermatol.* 1999;40(6 Pt 2):S35-42.
21. Croxtall JD, Plosker GL. Sertaconazole: a review of its use in the management of superficial mycoses in dermatology and gynaecology. *Drugs.* 2009;69(3):339-59.
22. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. *Cochrane Database Syst Rev.* 2007 Jul 18;(3):CD001434.
23. Rotta I, Sanchez A, Gonçalves PR, et al. Efficacy and safety of topical antifungals in the treatment of dermatomycosis: a systematic review. *Br J Dermatol.* 2012;166(5):927-33.
24. Rotta I, Ziegelmann PK, Otuki MF, et al. Efficacy of topical antifungals in the treatment of dermatophytosis: a mixed-treatment comparison meta-analysis involving 14 treatments. *JAMA Dermatol.* 2013;149(3):341-49.
25. El-Gohary M, van Zuuren EJ, Fedorowicz, Z, et al. Topical antifungal treatments for tinea cruris and tinea corporis. *Cochrane Database Syst Rev.* 2014 Aug 4;8:CD009992.
26. Jarratt M, Jones T, Adelglass J. Efficacy and safety of once-daily luliconazole 1% cream in patients ≥12 years of age with interdigital tinea pedis: a phase 3, randomized, double-blind,vehicle-controlled study. *J Drugs Dermatol.* 2014;13(7):838-46.
27. 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):911-18.
28. Parish LC, Parish JL, Routh HB, et al. A randomized, double-blind, vehicle-controlled efficacy and safety study of naftifine 2% cream in the treatment of tinea pedis. *J Drugs Dermatol.* 2011;10(11):1282-28.
29. Jones TM, Jarratt MT, Mendez-Moguel I, et al. A randomized, multicenter, double-blind, vehicle-controlled study evaluating the efficacy and safety of luliconazole cream 1% once daily for 7 days in patients aged ≥ 12 years with tinea cruris. *J Drugs Dermatol.* 2014;13(1):32-38
30. Pierard GE, Pierard-Franchimont C, Estrada JA. Comparative study of the activity and lingering effect of topical antifungals. *Skin Pharmacol.* 1993;6(3):208- 14.
31. Rosen T, Elewski BE. Failure of clotrimazole-betamethasone dipropionate cream in treatment of Microsporum canis infections. *J Am Acad Dermatol.* 1995;32(6):1050-1
32. Phillips RM, Rosen T. Topical antifungal agents. In: Wolverton S. (ed). Comprehensive Dermatologic Therapy. 3rd edition. Dermatology in General Medicine. 4th ed. New York, NY: Elsevier Saunders. 2013: 460-472.
33. Villars V, Jones TC. Clinical efficacy and tolerability of terbinafine (Lamisil) – a new topical and systemic fungicidal drug for treatment of dermatomycoses. *Clin Exp Dermatol.* 1989;14(2):124-27
34. Fukushiro R, Urabe H, Kagawa S. Butenafine hydrochloride, a new antifungal agent: clinical and experimental study. In: Yamaguchi H, Kobayashi GS, Takahashi H (eds). Recent progress in antifungal therapy. New York, NY: Marcel Dekker. 1992: 147-157
35. Iwatani W1, Arika T, Yamaguchi H. Two mechanisms of butenafine action in Candida albicans. *Antimicrob Agents Chemother.* 1993;37(4):785-8.
36. Brito GN1, Inocêncio AC, Querido SM, et al. In vitro antifungal susceptibility of Candida spp. oral isolates from HIV-positive patients and control individuals *Braz Oral Res.* 2011;25(1):28-33
37. Suárez VL1, Fernández Andreu CM [In vitro susceptibility of vaginal isolates of Candida vs clotrimazole and nystatin]. *Rev Cubana Med Trop.* 2003;55(3):138-45. [Article in Spanish]
38. Kwok YK, Tay YK, Goh CL, Epidemiology and in vitro activity of antimycotics against candidal vaginal/skin/nail infections in Singapore. *Int J Dermatol.* 1998;37(2):145-9.
39. Gupta AK, Kogan N, Batra R. Pityriasis versicolor: a review of pharmacological treatment options. . *Expert Opin Pharmacother.* 2005;6(2):165-78
40. Alastruey-Izquierdo A, Melhem MS, Bonfietti LX, et al. Susceptibility test for fungi: Clinical and labratorial correlations in medical mycology. *Rev Inst Med Trop Sao Paulo.* 2015;57 Suppl 19:57-64.
41. Ghannoum MA, Arthington-Skaggs B, Chaturvedi V, et al. Interlaboratory study of quality control isolates for a broth microdilution method (modified CLSI M38-A) for testing susceptibilities of dermatophytes to antifungals. *J Clin Microbiol.* 2006;44(12):4353-6
42. Singh J, Zaman M, Gupta AK. Evaluation of microdilution and disk diffusion methods for antifungal susceptibility testing of dermatophytes. *Med Mycol.* 2007;45(7):595-602.
43. Risslegger B, Lass-Flörl C, Blum G, et al. Evaluation of a modified EUCAST fragmented-mycelium inoculum method for in vitro susceptibility testing of dermatophytes and the activity of novel antifungal agents. *Antimicrob Agents Chemother.* 2015;59(6):3675-82.
44. Rizi K, Murdan S, Danquah C, et al. Development of a rapid, reliable and quantitative method – "SPOTi" for testing antifungal efficacy. *J Microbiol Methods.* 2015;117:36-40
45. Arikan S. Current status of antifungal susceptibility testing methods. *Med Mycol.* 2007;45(7):569-87.
46. Sanguinetti M, Posteraro B, Lass-Flörl C. Antifungal drug resistance among Candida species: mechanisms and clinical impact. *Mycoses.* 2015;58 Suppl 2:2-13.
47. Koga H. Antifungal susceptibility testing method for dermatophytes -determination of MIC and MFC values. *Med Mycol J.* 2014;55(2):J57-63
48. Palacin C, Sacristan A, Ortiz JA. In vitro activity of sertaconazole. *Arzneimittelforschung.* 1992;42 (5A):699-705.
49. Nolting S. Investigation of the antibacterial effect of the antifungal agent naftifine: left versus right clinical comparative study between naftifine and gentamicin in pyoderma. *Mykosen.* 1987;30(suppl 1):70-77.
50. Nolting S, Brautigam M. Clinical relevance of the antibacterial activity of terbinafine: a contralateral comparison between 1% terbinafine cream and 0.1% gentamicin sulphate cream in pyoderma. *Br J Dermatol.* 1992;126(Suppl 39):56–60.
51. Riviera L, Bellotti M. Laboratory evaluation of ciclopirox olamine: In vitro and in vivo studies on its antimicrobial activity. *Chemotherapia.* 1983;2(2):97–102.
52. Kokjohn K, Bradley M, Griffiths B, et al. Evaluation of in vitro activity of ciclopirox olamine, butenafine HCL and econazole nitrate against dermatophytes, yeasts and bacteria. *Int J Dermatol.* 2003;42(Suppl 1):11–7.
53. Hanel H, Smith-Kurtz E, Pastowsky S. Therapy of seborrheic eczema with an antifungal agent with an antiphlogistic effect. *Mycoses.* 1991;34(Suppl 1):91–3.
54. Rosen T, Schell BJ, Orengo I. Anti-inflammatory activity of antifungal preparations. *Int J Dermatol.* 1997;36(10):788–92.
55. Araj GF, Asmar RG, Avedissian AZ. Candida profiles and antifungal resistance evolution over a decade in Lebanon. *J Infect Dev Ctries.* 2015;27;9(9):997-1003.
56. Bailly S, Maubon D, Fournier P, et al. Impact of Antifungal Prescription on relative distribution and susceptibility of Candida spp - Trends over 10 Years. *J Infect.* 2015;Oct 27. pii: S0163-4453(15)00342-4. (e-pub)
57. Favre B, Ghannoum MA, Ryder NS. Biochemical characterization of terbinafine-resistant Trichophyton rubrum isolates. *Med Mycol.* 2004;42(6):525-9.
58. Osborne CS, Leitner I, Favre B, et al. Amino acid substitution in Trichophyton rubrum squalene epoxidase associated with resistance to terbinafine. *Antimicrob Agents Chemother.* 2005 Jul;49(7):2840-4
59. Cervelatti EP, Fachin AL, Ferreira-Nozawa MS, et al. Molecular cloning and characterization of a novel ABC transporter gene in the human pathogen Trichophyton rubrum. *Med Mycol.* 2006;44(2):141-7.
60. Martinez-Rossi NM, Peres NT, Rossi A. Antifungal resistance mechanisms in dermatophytes. *Mycopathologia.* 2008;166(5-6):369-83.
61. Yu L, Zhang W, Wang L, et al. Transcriptional profiles of the response to ketoconazole and amphotericin B in Trichophyton rubrum. *Antimicrob Agents Chemother.* 2007;51(1):144-53
62. Ghelardi E, Celandroni F, Gueye SA, et al. Potential of Ergosterol synthesis inhibitors to cause resistance or cross-resistance in Trichophyton rubrum. *Antimicrob Agents Chemother.* 2014;58(5):2825-9.
63. Gupta AK, Cooper EA. Update in antifungal therapy of dermatophytosis. *Mycopathologia.* 2008;166(5-6):353-67.

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# The Role of Naftifine HCl 2% Gel and Cream in Treating Moccasin Tinea Pedis

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## ABSTRACT

In recent years, new topical antifungals have emerged for the treatment and management of tinea pedis, but all have been investigated and approved for the treatment of interdigital tinea pedis. Moccasin tinea pedis has not been recognized by governing bodies as a definable and treatable disease entity separate from interdigital tinea pedis at this time. Thus, creating randomized, controlled clinical trials to investigate moccasin tinea pedis is a challenge without an agreed upon definition of the disease state, treatment regimen, and treatment course. Considering systemic therapy issues and the lack of data from large trials demonstrating safety and efficacy in the topical management of this clinical presentation, an unmet need has been created for a topical antifungal agent that can treat moccasin tinea pedis. Naftifine 2% gel, an allylamine, was studied in a clinical trial that enrolled patients who had interdigital or both interdigital and moccasin-type tinea pedis. In the moccasin group, the primary efficacy endpoint of complete cure at week 2 (end of treatment) was 1.7% (gel) vs 0.9% (vehicle) and week 6 (four weeks post-treatment) was 19.2% (gel) vs 0.9% (vehicle). Naftifine 2% cream in combination with urea 39% also showed improvement in hyperkeratotic moccasin tinea pedis.

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## INTRODUCTION

In the US, tinea pedis is the most common inflammatory fungal infection that is mostly caused by dermatophytes.[1] These are the skin, hair, and nail-preferring fungi such as Trichophyton sp, Microsporum sp, and Epidermophyton sp, of which the top pedal pathogen is Trichophyton rubrum. Dermatophytes are highly contagious and may be transferred between soil, animals, humans, and fomites.

Wearing shoes, sneakers, and boots lead to creating a warm and moist environment, which is an optimal place for fungus to thrive. Traditionally, tinea pedis occurs in the pedal interdigital areas, where prolonged moisture will cause macerated tissue to occur, but it also presents on the plantar surface of the foot as dry, scaly, and itchy skin known as the moccasin type. Populations at risk to develop tinea pedis include: those who use communal facilities (pools, dorm showers, gyms); those who wear rubber or non-breathable material shoes at work; and those who are obese, diabetic, immunocompromised, vascularly compromised, or are unable to perform regular foot hygiene.

Treatment options have consisted of both prescription and over the counter topical medications as first line agents (such as naftifine, econazole, and ciclopirox), oral medications for recalcitrant and severe presentations (off label uses for terbinafine, itraconazole, and on label for griseofulvin ultra micro-sized), and patient education on proper foot hygiene. Even after educating the patient on the basics of pedal hygiene (drying between toes, changing socks and shoes daily, disinfecting family showering areas, and wearing shower shoes in communal areas), the physician will typically continue to manage the patient for a persistent and irritating plantar infection weeks to months after treating the initial infection.

Even though interdigital tinea pedis is classically described as the most common clinical presentation, many physicians agree that the moccasin type is widely seen and a challenge to treat.[2] As described earlier, moccasin tinea pedis presents on the plantar foot commonly extending from the digital sulcus to the medial, lateral, and posterior borders of the foot where it may reach superiorly towards the junction of the dorsal and plantar skin. It can present as dry serpiginous scale, but may also be hyperkeratotic and in some cases, fissure. Scaling can be fine or coarse, and erythema may be present. Long standing moccasin tinea pedis is often asymptomatic and can predispose the patient to developing onychomycosis. It may co-present with tinea manuum where the patient exhibits bilateral tinea pedis and unilateraly tinea manuum (2 feet–1 hand syndrome).

In the last few years, new topical antifungals have emerged for the treatment and management of tinea pedis, but all have been investigated and approved for the treatment of interdigital tinea pedis. Moccasin tinea pedis has not been recognized by the FDA as a definable and treatable disease entity separate from interdigital tinea pedis at this time. Thus, creating randomized, controlled clinical trials to investigate moccasin tinea pedis is a challenge without an agreed

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upon definition of the disease state, treatment regimen, and treatment course. Due to the chronicity and possible co-presentation of onychomycosis, systemic therapy is often recommended for this disease state. Oral antifungals may not be accessible for all patients due to risk vs benefit when factoring in co-morbidities and drug–drug interactions. Considering systemic therapy issues and the lack of data from large trials demonstrating safety and efficacy in the topical management of this clinical presentation, an unmet need has been created for a topical antifungal agent that can treat moccasin tinea pedis.

"Long standing moccasin tinea pedis is often asymptomatic and can predispose the patient to developing onychomycosis."

In a review of the literature, the first trial to investigate moccasin-type (along with interdigital tinea pedis) is the naftifine HCl gel 2% phase III clinical study. A member of the allylamine class, naftifine exhibits fungicidal, anti-inflammatory, and anti-bacterial properties.[3-6] In vitro, naftifine exhibits fungicidal activity against the dermatophytes and many Candida species. It stops fungal growth by inhibiting squalene epoxidase in the ergosterol synthesis pathway, which ultimately increases cell membrane fragility and permeability. The mycological and clinical cure rates for naftifine in the treatment of tinea are superior or equivalent to those of terbinafine, econazole, and tolnaftate.[7] In 2011, Parish et al showed that naftifine 2% cream (Naftin 2% cream, Merz) used once daily for two weeks in the management of interdigital tinea pedis had efficacy responses equivalent to naftifine 1% cream which was traditionally used for four weeks for the same infection.[8] Naftifine 2% gel (Naftin 2% gel, Merz) was approved for the same dosing regimen as the 2% cream. The 2% gel was studied in a clinical trial that enrolled patients who had interdigital or both interdigital and moccasin-type tinea pedis.[9]

The overall study design was a two six-week, double-blind, randomized, vehicle-controlled, multi-center, parallel-group for this phase III clinical trial examining the safety and efficacy of naftifine HCl 2% gel for interdigital and moccasin tinea pedis. Subjects were placed into the interdigital-type only or the interdigital with moccasin-type infection group. In order to focus on the moccasin-type only, a post-hoc analysis was completed to evaluate the safety and efficacy of a 2-week, once daily course of naftifine gel 2% versus vehicle for this sub-type.[10]

Over 40 sites were utilized in this study that enrolled male and female subjects aged 12–70 years old. A baseline clinical presentation of moderate erythema, moderate scaling, mild pruritus, and positive KOH/mycology culture on one or both feet. Patients were not enrolled if they had uncontrolled diabetes, plantar psoriasis, incapacitating tinea pedis, or atopic dermatitis.

As this is a fungal infection that is clinically symptomatic, investigators recorded two measurements to determine efficacy: mycological analysis and clinical signs and symptoms. Mycological analysis was reported after two weeks of use and at week 6 (four weeks post-treatment). Clinical assessment measured the amount of erythema, scaling, and pruritus on a four-point scale (0=absent, 1=mild, 2=moderate, 3=marked) at those same time points. The primary efficacy endpoint of complete cure was defined as negative mycology (KOH/culture) and a "0" score of erythema, scaling, and pruritus. In addition to complete cure, mycologic cure, treatment effectiveness, clinical cure, and clinical success were also reported (Table 1). Safety assessments consisting of adverse events (AE's), laboratory testing, and physical exam, were completed at defined visits.

A total of 1715 subjects were randomized, 1174 who had interdigital tinea pedis with or without moccasin-type and positive KOH and mycology culture at baseline were analyzed for efficacy. Subjects included applied the study drug or vehicle once daily for two weeks to affected areas. The study subjects were then followed for four weeks after discontinuation of the study drug. Those in the interdigital plus moccasin group applied the product both in the interspaces and the entire plantar foot. Of the 1174 subjects, 674 had interdigital tinea only while 500 had both moccasin and interdigital-type presentation. In the 500 moccasin/interdigital group, only 380 subjects satisfied the inclusion criteria to qualify for data analysis. The 380 subjects comprise the post-hoc analysis.

**TABLE 1.**

**Efficacy Endpoints for Naftifine Gel 2% Trial**

| | Mycology (KOH/Culture) | Clinical Assessment (erythema, scaling, pruritus) |
|---|---|---|
| Complete Cure* | negative KOH/Culture | Score of 0 |
| Mycologic Cure# | negative KOH/Culture | N/A |
| Treatment Effectiveness# | negative KOH/Culture | Score of 0 or 1 |
| Clinical Cure# | N/A | Score of 0 |
| Clinical Success# | N/A | Score of 0 or 1 |

*primary efficacy variable
#secondary efficacy variable

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**TABLE 2.**

| Demographics of Moccasin Group (Table similar to reference 10) | | |
|---|---|---|
| | Naftifine gel 2% n=253 | Vehicle n=127 |
| Male | 202 | 101 |
| Female | 51 | 26 |
| Age, Mean (SD) | 44.6 (13.6) | 47.7 (14.0) |
| Black/African American | 69 | 37 |
| White | 176 | 84 |
| Other | 8 | 6 |

Demographically, white, male subjects comprised the majority in the naftifine gel 2% and vehicle arms (Table 2). The mean age for the treatment group was 44.6 and the vehicle group was 47.7.

Results of the trial showed that the 2% gel was superior to vehicle at week 6 (four weeks post-treatment) for complete cure of the subject who had both interdigital and moccasin-type presentations. It was also shown to be significantly better than vehicle in achieving mycologic cure at week 6 in those same subjects. Overall, naftifine 2% gel was designed to provide a shorter and more convenient regimen while still maintaining the efficacy that practitioners have come to expect with the drug. Specifically for the moccasin group, the primary efficacy endpoint of complete cure at week 2 (end of treatment) was 1.7% (gel) vs 0.9% (vehicle) and week 6 (four weeks post-treatment) was 19.2% (gel) vs 0.9% (vehicle). The secondary efficacy endpoints for the moccasin group are listed in Table 3. At week 6, complete cure, mycological cure, treatment effectiveness, clinical cure, and clinical success were statistically superior when compared to the matching vehicle group.

Naftifine gel 2% was well tolerated in the 14-day treatment period. Three subjects in the 2% gel group experienced treatment emergent adverse events (TEAE) related to the study drug while no subjects in the vehicle group experienced TEAE related to the study treatment. TEAEs, which were rated by the investigator, included application site pruritus, rash, vesicles, and hypersensitivity.

As moccasin tinea pedis may present with plantar hyperkeratosis, this focal hyperkeratosis presents a therapeutic challenge to both the patient and the physician both during and after antifungal therapy. Hyperkeratotic tinea pedis accounts for 2-8% of tinea cases and presents as moccasin type tinea with hyperkeratosis confined to the weight bearing areas.[11] Hyperkeratosis in the presence of moccasin tinea pedis is typically bilateral and often only treated with a topical antifungal. Often, after the tinea infection has resolved, the hyperkeratosis remains, which leads the patient to believe

**TABLE 3.**

| Efficacy Endpoints for Moccasin Subjects (n=380) (Modified from reference 10) | | |
|---|---|---|
| | Gel | Vehicle |
| Complete Cure* | | |
| Week 2 | 1.7% | 0.9% |
| Week 6 | 19.2 | 0.9 |
| Mycologic Cure# | | |
| Week 2 | 29 | 15.2 |
| Week 6 | 65.8 | 7.9 |
| Treatment Effectiveness# | | |
| Week 2 | 11.7 | 5.3 |
| Week 6 | 51.4 | 4.4 |
| Clinical Cure# | | |
| Week 2 | 2.9 | 0.9 |
| Week 6 | 23.9 | 2.6 |
| Clinical Success# | | |
| Week 2 | 33.2 | 31.6 |
| Week 6 | 72.1 | 29.3 |

*primary efficacy variable
#secondary efficacy variable

the infection is still present. The addition of a keratolytic to reduce stratum corneum thickening is warranted in these cases. There is no combination product targeting both the hyperkeratosis and the tinea available at this time, but Kircik et al relates a pilot study of using naftifine 2% cream along with urea 39% cream on 18 subjects.[12] Patients were evaluated for 8 weeks during which they used the naftifine 2% cream for two weeks in the morning and the urea 39% cream to the affected area nightly. Ultimately, the evaluable subjects had improvements in hyperkeratosis, the active tinea infection, and pruritus. This dual therapy ultimately proved efficacious and cosmetically pleasing for the patients to use.

Considering the chronic and refractory course of moccasin tinea pedis, naftifine gel 2% and naftifine cream 2% (in combination with urea 39% cream) have been shown to be useful agents in the management of this subtype; however both are still only approved for the interdigital type, not the moccasin type. The post-hoc data reported for naftifine HCl gel 2% is a first step in creating awareness and a possible protocol to determine the safety and efficacy for a topical antifungal in the presence of moccasin tinea pedis. A once daily dosing regimen for a shorter course of therapy (2 weeks vs the standard 4-week twice daily dosing) is advantageous in patients with this chronic superficial skin infection. And, in adding a urea product, a patient can also achieve a cosmetically and therapeutically pleasing result with their topical antifungal regimen. Overall, the naftifine gel 2%

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data and cream 2% data show the possibility of managing moccasin tinea pedis in an efficacious, safe, and tolerable manner.

## DISCLOSURES

The author has been a principal investigator and has served as an advisory board member for Merz, Valeant, and Pharmaderm.

## REFERENCES

1. Habif TP. Superficial Fungal Infections. In: Clinical Dermatology: A Color Guide to Diagnosis and Therapy. 4th ed. Philadelphia (PA): Mosby (An affiliate of Elsevier); 2004: 409-56.
2. Canavan T and Elewski B. Identifying the Signs of Tinea Pedis: A Key to Understanding the Clinical Variables. *J Drugs Dermatol.* 2015; 14(suppl 10): s42-s47.
3. Evans EG, James IG, Seaman RA, Richardson MD. Does naftifine have anti-inflammatory properties? A double-blind comparative study with 1% clotrimazole/1% hydrocortisone in clinically diagnosed fungal infection of the skin. *Br J Dermatol.* 1993; 129(4):437-42.
4. Merz Pharmaceuticals, LLC. Naftifine product monograph. 2010.
5. Monk JP, Brogden RN. Naftifine: a review of its antimicrobial activity and therapeutic use as in superficial dermatomycoses. *Drugs.* 1991; 42(4):659-72.
6. Vago T, Baldi G, Columbo D, Barbareschi M, Norbiato G, Dallegri F, et al. Effects of naftifine, terbinafine, two allylamine antifungal drugs, on selected functions of polymorphonuclear leukocytes. *Antimicrob Agents Chemother.* 1994; 38(11):2605-11.
7. Ablon G, Rosen T, Spedale J. Comparative efficacy of naftifine, oxiconazole, and terbinafine in short-term treatment of tinea pedis. *Int J Dermatol.* 1996; 35(8):591-93.
8. Parish LC, Parish JL, Routh HB, Avakian EV, Olayinka B, Pappert EJ, et al. A double-blind, randomized, vehicle-controlled study evaluating the efficacy and safety of naftifine cream, 2% in tinea cruris. *J Drugs Dermatol.* 2011; 10(10):1142-48.
9. Stein Gold L, 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):911-18.
10. Stein Gold L, Vlahovic T, Verma A, et al. Naftifine Hydrochloride Gel 2%: An Effective Topical Treatment for Moccasin-Type Tinea Pedis. *J Drugs Dermatol.* 2015; 14(10):1138-44.
11. Tanuma H. Pathogenesis and treatment of hyperkeratotic tinea pedis in Japan. *Mycoses.* 1999; 42(1-2):21-28.
12. Kircik L and Onumah N. Use of naftifine hydrochloride 2% cream and 39% urea cream in the treatment of tinea pedis complicated by hyperkeratosis. *J Drugs Dermatol.* 2014; 13(2):162.

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