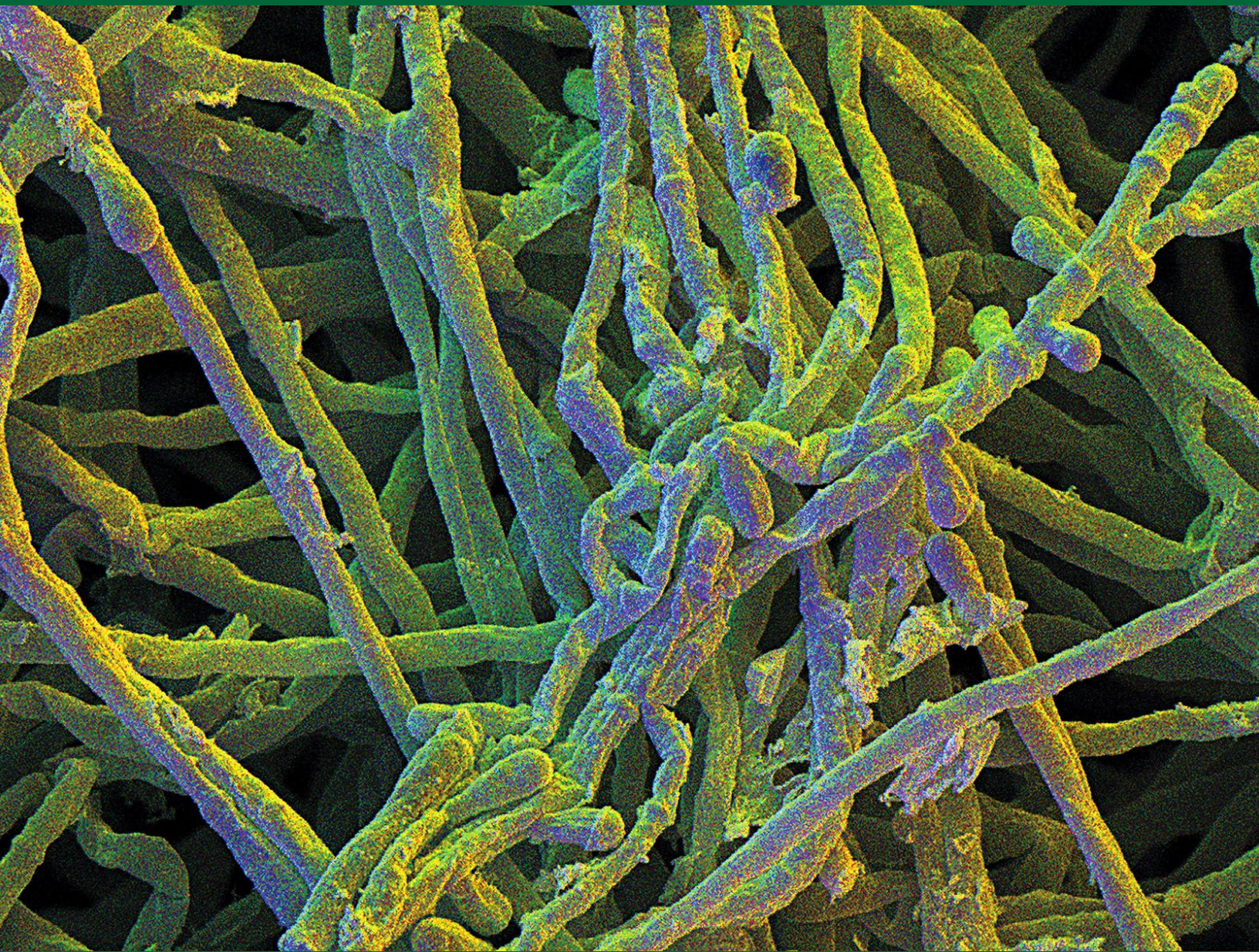


# Understanding Treatment Goals for Patients With Onychomycosis **CME/CE**

Supported by an independent educational grant from Valeant Pharmaceuticals North America LLC.





This article is a CME/CE certified activity.  
To earn credit for this activity visit:  
[www.medscape.org/spotlight/onychomycosis](http://www.medscape.org/spotlight/onychomycosis)

CME/CE Released: 12/22/2014; Valid for credit through 12/22/2015

### Target Audience

This activity is intended for dermatologists, podiatrists, primary care physicians, nurses, nurse practitioners, and other clinicians who treat patients with onychomycosis.

### Goal

The goal of this activity is to review the rationale, goals, and options for early, effective treatment of onychomycosis.

### Learning Objectives

Upon completion of this activity, participants will be able to:

1. Interpret clinical trial results on the efficacy of topical solutions for the treatment of onychomycosis
2. Identify realistic treatment goals for patients with onychomycosis, for both oral and topical therapies, based on available clinical trial results and current clinical practices
3. Review the rationale for early, effective treatment of onychomycosis

### Credits Available

**Physicians** - maximum of 0.50 AMA PRA Category 1 Credit(s)<sup>™</sup>

**Nurses** - 0.50 ANCC Contact Hour(s) (0.5 contact hours are in the area of pharmacology)

All other healthcare professionals completing continuing education credit for this activity will be issued a certificate of participation.

### Accreditation Statements

#### For Physicians

**Medscape** Medscape, LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Medscape, LLC designates this enduring material for a maximum of **0.50 AMA PRA Category 1 Credit(s)<sup>™</sup>**. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

#### For Nurses

**Medscape** Medscape, LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Awarded 0.50 contact hour(s) of continuing nursing education for RNs and APNs; 0.50 contact hours are in the area of pharmacology.

## Instructions for Participation and Credit

There are no fees for participating in or receiving credit for this online educational activity. For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing board.

This activity is designed to be completed within the time designated on the title page; physicians should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity online during the valid credit period that is noted on the title page. To receive *AMA PRA Category 1 Credit™*, you must receive a minimum score of 75% on the post-test.

Follow these steps to earn CME/CE credit\*:

1. Read the target audience, learning objectives, and author disclosures.
2. Study the educational content online or printed out.
3. Online, choose the best answer to each test question. To receive a certificate, you must receive a passing score as designated at the top of the test. We encourage you to complete the Activity Evaluation to provide feedback for future programming.

You may now view or print the certificate from your CME/CE Tracker. You may print the certificate but you cannot alter it. Credits will be tallied in your CME/CE Tracker and archived for 6 years; at any point within this time period you can print out the tally as well as the certificates from the CME/CE Tracker.

\*The credit that you receive is based on your user profile.

## Hardware/Software Requirements

To access activities, users will need:

- A computer with an Internet connection.
- Internet Explorer 8.x or higher, the latest versions of Firefox or Safari, or any other W3C standards compliant browser.
- Adobe Flash Player and/or an HTML5 capable browser may be required for video or audio playback.
- Occasionally other additional software may be required such as PowerPoint or Adobe Acrobat Reader.

## Faculty and Disclosures

As an organization accredited by the ACCME, Medscape, LLC, requires everyone who is in a position to control the content of an education activity to disclose all relevant financial relationships with any commercial interest. The ACCME defines “relevant financial relationships” as financial relationships in any amount, occurring within the past 12 months, including financial relationships of a spouse or life partner, that could create a conflict of interest.

Medscape, LLC, encourages Authors to identify investigational products or off-label uses of products regulated by the US Food and Drug Administration, at first mention and where appropriate in the content.

### **Boni E. Elewski, MD**

Professor, University of Alabama, Birmingham

Disclosure: Boni E. Elewski, MD, has disclosed the following relevant financial relationships:

Served as an advisor or consultant for: Valeant Pharmaceuticals International; Anacor Pharmaceuticals, Inc.

Dr Elewski does intend to discuss **off-label** uses of drugs, mechanical devices, biologics, or diagnostics *approved* by the FDA for use in the United States.

Dr Elewski does not intend to discuss **investigational** drugs, mechanical devices, biologics, or diagnostics *not approved* by the FDA for use in the United States.

**James Q. Del Rosso, DO**

Adjunct Clinical Professor of Dermatology, Touro University College of Osteopathic Medicine, Henderson, Nevada

Disclosure: James Q. Del Rosso, DO, has disclosed the following relevant financial relationships:

Served as an advisor or consultant for: Valeant Pharmaceuticals International; Anacor Pharmaceuticals, Inc.; Merz Pharmaceuticals; Ranbaxy Pharmaceuticals Limited; Innocutis

Served as a speaker or a member of a speakers bureau for: Valeant Pharmaceuticals International; Merz Pharmaceuticals; Ranbaxy Pharmaceuticals Limited; Innocutis

Dr Del Rosso does intend to discuss **off-label** uses of drugs, mechanical devices, biologics, or diagnostics *approved* by the FDA for use in the United States.

Dr Del Rosso does not intend to discuss **investigational** drugs, mechanical devices, biologics, or diagnostics *not approved* by the FDA for use in the United States.

**Warren Joseph, DPM**

Podiatrist, Roxborough Memorial Hospital, Philadelphia, Pennsylvania

Disclosure: Warren Joseph, DPM, has disclosed the following relevant financial relationships:

Served as an advisor or consultant for: Valeant Pharmaceuticals International; Anacor Pharmaceuticals, Inc.; Sandoz

Served as a speaker or a member of a speakers bureau for: Valeant Pharmaceuticals International

Dr Joseph does intend to discuss **off-label** uses of drugs, mechanical devices, biologics, or diagnostics *approved* by the FDA for use in the United States.

Dr Joseph does not intend to discuss **investigational** drugs, mechanical devices, biologics, or diagnostics *not approved* by the FDA for use in the United States.

**Editor**

**Kristin M. Richardson**

Scientific Director, Medscape, LLC

Disclosure: Kristin M. Richardson has disclosed no relevant financial relationships.

**Steering Committee**

**Boni E. Elewski, MD**

As listed above.

**Aditya K. Gupta, MD, PhD, FRCPC, MBA**

Professor, Division of Dermatology, Department of Medicine, Sunnybrook Health Sciences Center of the University of Toronto, Toronto, Ontario, Canada

Disclosure: Aditya K. Gupta, MD, PhD, FRCPC, MBA, has disclosed the following relevant financial relationships:

Served as an advisor or consultant for: Valeant Pharmaceuticals International; Novartis Pharmaceuticals Corporation; Janssen Pharmaceutical Companies of Johnson & Johnson

Served as a speaker or member of a speakers bureau for: Valeant Pharmaceuticals International; Bayer Corporation; Novartis Pharmaceuticals Corporation; Janssen Pharmaceutical Companies of Johnson & Johnson

Received grants for clinical research from: Valeant Canada; Bristol-Myers Squibb; Lilly

**Jeffrey M. Robbins, DPM**

Professor of Podiatric Medicine, Kent State University College of Podiatric Medicine, Kent, Ohio; Clinical Assistant Professor, Case Western Reserve University School of Medicine, Cleveland, Ohio

Disclosure: Jeffrey M. Robbins, DPM, has disclosed no relevant financial relationships.

**Tracey C. Vlahovic, DPM**

Associate Professor, Temple University School of Podiatric Medicine, Philadelphia, Pennsylvania

Disclosure: Tracey C. Vlahovic, DPM, has disclosed the following relevant financial relationships:

Served as an advisor or consultant for: Valeant Pharmaceuticals International; Merz Pharmaceuticals; Anacor Pharmaceuticals, Inc.  
Served as a speaker or a member of a speakers bureau for: Valeant Pharmaceuticals International; Merz Pharmaceuticals; Innocutis  
Received grants for clinical research from: Merz Pharmaceuticals

**CME Reviewer/Nurse Planner**

**Amy Bernard, MS, BSN, RN-BC**

Lead Nurse Planner, Medscape, LLC

Disclosure: Amy Bernard, MS, BSN, RN-BC, has disclosed no relevant financial relationships.

**Peer Reviewer**

This activity has been peer reviewed and the reviewer has disclosed no relevant financial relationships.

**Medscape**  
EDUCATION

**Understanding Treatment Goals  
for Patients With  
Onychomycosis**

**Moderator**  
**Boni E. Elewski, MD**  
Professor of Dermatology  
University of Alabama, Birmingham

**Boni E. Elewski, MD:** I'm Boni Elewski, professor of dermatology at the University of Alabama in Birmingham, Alabama. Welcome to this CME-CE program on onychomycosis.

**Medscape**  
EDUCATION

**Panelists**  
**James Q. Del Rosso, DO**  
Clinical Professor of Dermatology  
Touro University College of Osteopathic Medicine  
Henderson, Nevada

**Warren Joseph, DPM**  
Podiatrist and Infectious Disease Specialist  
Roxborough Memorial Hospital  
Philadelphia, Pennsylvania

Joining me today are Jim Del Rosso, clinical professor of dermatology at Touro University College of Osteopathic Medicine in Henderson, Nevada, and Warren Joseph, a podiatrist and infectious disease specialist at Roxborough Memorial Hospital in Philadelphia, Pennsylvania.

## Program Goals

- Describe treatment goals for patients with onychomycosis
- Review the 2 recently approved topical agents for the treatment of onychomycosis
- Review the rationale for early, effective treatment of onychomycosis

**Dr Elewski:** In this program, we will describe treatment goals for patients with onychomycosis and review the 2 recently approved topical agents for the treatment of onychomycosis. I would also like to mention that this program will include a discussion of off-label treatment options.

## What Is Onychomycosis?

- Common fungal infection of the nail unit: nail bed, nail plate, and some periungual tissue
- Usually caused by a dermatophyte
- Most frequently affects the toenails in adults

Let's start with some basics. Onychomycosis is a common fungal infection of the nail unit: the nail bed, nail plate, and some periungual tissue. It is usually caused by a dermatophyte fungus, and it most frequently affects the toenails in adults.

## What Is Onychomycosis? (cont)

- Distal lateral subungual onychomycosis is the most common form
- Most frequent causative organism is *Trichophyton rubrum* (90%)
- *T mentagrophytes* is the causative organism in the balance of cases

Ghannoum MA, et al. *J Am Acad Dermatol*. 2000;43:641-648.<sup>[1]</sup>

**Dr Elewski:** Distal lateral subungual onychomycosis, or simply distal subungual onychomycosis, is the most common form. The most frequent causative organism is *Trichophyton rubrum*, which causes approximately 90% of cases.<sup>[1]</sup> *T mentagrophytes*, also known as *T interdigitale*, is the other causative organism in the balance of cases.<sup>[1]</sup>

Jim and Warren, let's look at some images of onychomycosis and discuss the clinical presentation.



## Mild Onychomycosis



Image courtesy of Boni E. Elewski, MD.

**Warren Joseph, DPM:** I would classify this case as relatively mild onychomycosis. There is some toenail discoloration, but there is not a lot of thickening. There is perhaps 40% involvement.

**James Q Del Rosso, DO:** I think you have to consider if it *is* onychomycosis; you need to be sure that you have the correct diagnosis.

**Dr Elewski:** How would you know clinically that this is onychomycosis?

**Dr Del Rosso:** I would determine if the patient has concomitant tinea pedis, usually moccasin or dry plantar tinea pedis. You can certainly do a potassium hydroxide (KOH) test and fungal culture. The sensitivities of those tests are sometimes reported to not be very good, but I think a lot depends on how the operator obtains the specimen or performs the culture.

**Dr Joseph:** We have to look at the evidence. Fletcher and colleagues<sup>[2]</sup> and, more recently, Garcia-Doval and colleagues<sup>[3]</sup> found that the positive predictive values for clinical diagnosis, especially if you have a patient with suspected onychomycosis and plantar desquamation suggesting tinea pedis, are better than for some of the other tests. I think it is a combination of using your clinical acumen plus the laboratory tests.

**Dr Del Rosso:** Especially if there is evidence of concomitant tinea pedis; that really supports the diagnosis of onychomycosis.

**Dr Joseph:** Yes. I think that is the key.

**Dr Elewski:** This patient would be a perfect candidate for treatment, because the onychomycosis is not that bad and the patient would likely be cured.

**Dr Del Rosso:** Right. The earlier you diagnose onychomycosis, the better the patient will do with treatment.

## Moderate Onychomycosis



Image courtesy of Boni E. Elewski, MD.

**Dr Elewski:** Let's look at another case. What do you think of this case, Warren?

**Dr Joseph:** I think this is the next step. In the earlier case, we did not see a lot of thickening. There was 40% to 50% involvement, if that. Here you are starting to see more onycholysis: the nail is lifting up off the nail bed. You have a thicker-looking nail. This case is going to be more difficult to treat. I'll echo what Jim said: the earlier you treat, the better the result. Once the nail starts looking like the nail in this photograph, you are going to have to debride to thin and shorten the nail, so treatment is going to be more difficult.

**Dr Elewski:** Let's look at another case.

## Severe Onychomycosis With Tinea Pedis



Image courtesy of Boni E. Elewski, MD.

**Dr Joseph:** We have shown a nice progression from mild to moderate to severe onychomycosis, although the terms are not really well defined. I would call this case severe onychomycosis. I might even go as far as to call it totally dystrophic onychomycosis. What is interesting is the evidence of tinea pedis along with the onychomycosis. You see the scaling of the skin of the hallux. I'm a firm believer that this is the natural history of onychomycosis. It starts as tinea pedis and then invades up underneath the toenail. This is a perfect example of concomitant tinea pedis and onychomycosis.

**Dr Del Rosso:** When we say toenail, we are talking about the toenail plate. It is really a disease of the nail bed first, when it starts to invade the nail unit. The onychodermal band can be violated very easily by simple trauma, and once that portal of entry is broken, the organism has an easier time invading the nail bed.

## Presentation of Onychomycosis

- Onycholysis (loosening or separation of the nail from the nail bed)
- Thickening, crumbling, and discoloration (usually nontransparent white or yellow) of the nail plate
- Subungual debris
- Concomitant tinea pedis

**Dr Elewski:** Clinically we see onycholysis, subungual debris, and thickening of the nail plate. You also look for tinea pedis. These are the take-home points.

Onychomycosis is common. Approximately 10% of the population has this infection.<sup>[4]</sup> It also has the reputation of being difficult to treat, partly because it is not correctly diagnosed. Jim, can you discuss some of the challenges we face when treating onychomycosis?



## Treatment Challenges

- Slow growth of the toenail
- Presence of the nail plate interferes with access to the nail bed
- Pharmacologic profile of the medication
- Attaining therapeutic drug levels after topical or oral administration

Del Rosso JQ. *J Clin Aesthet Dermatol.* 2014;7:10-18.<sup>[5]</sup>

**Dr Del Rosso:** Patients would like onychomycosis to go away quickly, but toenails grow very slowly, especially as people age.<sup>[5]</sup> We cite the average of 1 year, but not everyone's toenails grow out from proximal to distal in 1 year. Some people's toenails take longer, especially if the person is older or has peripheral vascular disease. It takes a long time for the new nail plate to grow in and replace the affected nail plate. Patients have to be patient, and so do practitioners.

Another challenge is that the presence of the nail plate interferes with penetration to the nail bed, and that is assuming that the medication has transungual penetration.<sup>[5]</sup> With the newer topical agents, because they are solutions, we may not be dependent only on that feature. The solutions may actually be getting through the air gaps, along the sides of the nail, under the cuticle, and also under the hyponychium, which may be how they are able to better penetrate the nail unit. But treatment still takes time.

The pharmacologic profile of the medication is important.<sup>[5]</sup> If you are trying to get transungual penetration through the nail plate and into the nail bed, the medications have to be small molecules with the correct partition coefficient.

It is important to get therapeutic concentrations, because I agree totally with Warren Joseph's philosophy that you have to eradicate the fungus. Although it can come back, you have to eradicate the organism, so you must get adequate antifungal concentrations either from a topical medication, an oral medication, or both.

## Treatment Challenges (cont)

- Vehicle formulation
- High incidence of reinfection/recurrence
- Environmental exposure to dermatophytes
- Practice-related challenges

Del Rosso JQ. *J Clin Aesthet Dermatol.* 2014;7:10-18.<sup>[5]</sup>

**Dr Del Rosso:** For topical medications, the vehicle is important.<sup>[5]</sup> The first topical drug approved for onychomycosis, ciclopirox, is a very effective antifungal agent, but the vehicle does not penetrate well because it is a lacquer. It does not get into crevices and cracks, which is very important for a topical antifungal.

Reinfection and recurrence are important obstacles.<sup>[5]</sup> If you do not get rid of the concomitant *T rubrum*, let's say, on the skin around the affected toenail, it is going to reinvade later. You can clear patients, they can go through all of this trouble, but if they are carriers of *T rubrum* or if they are re-exposed, they can become reinfected fairly easily. You cannot blame the initial treatment; it worked, but now the patient is reinfected.

Environmental exposure to dermatophytes can be an issue. I don't get too crazy about people throwing out their shoes, but I think it is important to control concomitant tinea pedis.

Today, we also have to deal with practice-related challenges. We have great medications, but patients have higher copays. They do not want to come in as often to see the clinician. They may not be able to get access to medications, so that becomes a challenge. We need to make certain that patients get the therapy they need.

## Why Treat Onychomycosis?

**“Treating onychomycosis is challenging, but it *is* an infection. I cannot think of another infection that we ignore.”**

**Dr Elewski:** We know that treating onychomycosis is challenging, but it is an infection. We have to keep remembering that. I cannot think of another infection that we ignore, yet many clinicians just ignore onychomycosis. Warren, could you review some of the consequences of *not* treating onychomycosis?

## Why Treat Onychomycosis? (cont)

- It is an infection that can spread within a nail, across toes, and to other parts of the foot or body
- Progressive destruction and deformity of the nails
- Development of secondary infections, especially in people with diabetes

**Dr Joseph:** I think you used the key word -- infection -- and because my training is in infectious diseases, I always think of onychomycosis not as a disease of the nail or the skin but as an infection. We do not think twice about using an antibiotic when there is a bacterial infection; we should be using an antifungal when there is a fungal infection. It is an infection that needs to be treated, and as an infection, it can progress. We know that onychomycosis starts on one part of one toenail. It can spread to the rest of that toenail. It can spread from one toenail to other toenails and from the toenails to other parts of the body. Zaias showed that.<sup>[6]</sup> He was talking about tinea pedis, tinea cruris, and tinea corporis being associated with onychomycosis. It is progressive. It can cause destruction of the nail. You may never get a good-looking nail back if you wait too long to treat.

There are other issues. There can be secondary infections, bacterial infections, especially in populations such as patients with diabetes. You take a thick onychomycotic nail, put it on a neuropathic toe, and then place it in a shoe that might be a little bit too tight, and subungual ulcerations can develop. These can go down to the bone, and then you have osteomyelitis as a result of onychomycosis. That is another reason to treat.



## Why Treat Onychomycosis? (cont)

### Effects on quality of life:

- Pain
- Embarrassment (more frequent in women)
- Interference with social relationships

Drake LA, et al. *J Am Acad Dermatol*. 1998;38:702-704.<sup>[7]</sup>

**Dr Joseph:** Lynn Drake, MD, did a classic study looking at quality of life and found that 48% of patients with onychomycosis have pain.<sup>[7]</sup> Many insurers would want to say to us that they don't want to pay for onychomycosis because it is a cosmetic disease. But how can onychomycosis be a cosmetic condition when half the patients have pain? Seventy-four percent of patients experience embarrassment; 40% cannot wear shoes.<sup>[7]</sup> Onychomycosis places a major burden on the healthcare system. Onychomycosis is an infection that we need to treat because it has effects on all aspects of life.

**Dr Del Rosso:** An infection by definition cannot be just cosmetic. It is an infectious disease.

**Dr Joseph:** It's an infectious disease but people tend to pooh-pooh it, perhaps because it is hidden in the shoe. No; it is progressive and recurrent and can cause major issues. Onychomycosis needs to be treated.

## Clinical Trial End Points: Complete Cure

- Primary end point for all onychomycosis studies
- Completely cured nail with 0% clinical involvement, plus a negative KOH test result and a negative fungal culture result achieved simultaneously

**Dr Elewski:** To help us understand the clinical trials we will be discussing, it is important to review the 2 clinical trial end points that are mandated by the US Food and Drug Administration (FDA).

Complete cure is the primary end point for all onychomycosis studies. Complete cure means a completely cured nail with 0% clinical involvement plus a negative KOH test result and a negative fungal culture result achieved simultaneously.

## Clinical Trial End Points: Mycologic Cure

**Negative fungal culture result plus a negative KOH test result achieved simultaneously**

The second end point is mycologic cure, which is a negative fungal culture result plus a negative KOH test result achieved simultaneously. To me, this is an objective test and the practical end point when treating a fungal infection. What do you think?

## Clinical Trial End Points: Questions and Issues

- Is complete cure achievable?
- Investigator subjectivity
- Condition and appearance of the nail before development of onychomycosis

**Dr Joseph:** What I tell people is that in the definition of complete cure not only does the condition have to be mycologically cured, with negative KOH and culture results, but the nail has to be perfect, which is an end point that is almost unachievable. This is why some of the complete cure data across all drugs, oral and topical, have not been particularly impressive.

Mycologic cure tends to be an easier end point to reach. Boni, I agree with you that it is an important and objective end point because we are looking to get rid of the fungus. And the hope is that, as Jim mentioned earlier, if we kill the fungus then the nail has the opportunity to grow out over time. We have to look at some intermediate end points that make patients happy, and if they are happy, we are happy and we still kill the fungus.

**Dr Del Rosso:** We have to remember that clinical assessments are based on the investigator's eye, which can be subjective and cause variability in the clinical numbers.

**Dr Elewski:** Clinical cure, to me, is like stipulating in an acne study that the objective is perfectly smooth skin without any scarring or redness, and you cannot achieve that.

**Dr Del Rosso:** The other problem is that you do not know what the nail looked like before the patient developed onychomycosis and sought treatment. There can be many reasons why the patient has an imperfect nail, which may prevent the patient from achieving a perfect nail after treatment.

**Dr Elewski:** Right, but there are other end points that are flexible. These end points may not be the same from study to study. We'll look at some of these end points when we discuss the clinical trials.

## A New Era

- Until recently, the armamentarium included oral drugs and one topical (a lacquer)
- Two topical solutions were approved by the FDA in 2014

**Dr Elewski:** Until recently, we have had 2 approved oral drugs and a nail lacquer to treat onychomycosis. The recent approval of 2 new topical drugs is exciting. We are at the beginning of a new era of effective topical treatment. Before we discuss the newer options, let's review what has been available.

Jim, do you want to refresh us on the oral agents?



## Oral Antifungals

### Griseofulvin

- Indicated but not recommended

### Terbinafine<sup>a</sup>

- 250 mg/d for 12 weeks
- Mycologic cure: 70% in toenails

### Itraconazole<sup>b</sup>

- 200 mg/day for 12 weeks
- Mycologic cure: 54% in toenails

a. Lamisil® PI 2013.<sup>[8]</sup>

b. Sporanox® PI 2001.<sup>[9]</sup>

**Dr Del Rosso:** Griseofulvin is approved for the treatment of onychomycosis, but we do not recommend it because it does not work very well in adults with toenail onychomycosis.<sup>[5]</sup>

Oral terbinafine has been around for quite some time. The recommended regimen based on approved labeling is 250 mg/day for 12 weeks.<sup>[8]</sup> It has a reservoir effect in the nail unit, and the nail continues to grow and clear, although the patient takes the drug for only 12 weeks. In the pivotal trials, the mycologic cure at 1 year was 70% in toenails.<sup>[8]</sup>

Oral itraconazole is also approved for the treatment of onychomycosis. The approved regimen is 200 mg/day for 12 weeks.<sup>[9]</sup> Dosing can be with two 100-mg capsules or a newer 200-mg tablet. The mycologic cure rate was 54% at 1 year.<sup>[9]</sup>

## Oral Antifungals (cont)

### Itraconazole pulse therapy

- 200 mg twice daily for 1 week per month
- Not an approved regimen for toenail disease
- No pivotal trial data for toenail disease

### Fluconazole (not an approved indication)

- Once-weekly dosing (150, 300, or 450 mg)<sup>a</sup>
- Mycologic cure: 47% to 62%

a. Scher RK, et al. *J Am Acad Dermatol*. 1998;38:S77-S86.<sup>[10]</sup>

**Dr Del Rosso:** Itraconazole has also been used in a pulse regimen, although this regimen was never approved for toenail dermatophyte onychomycosis. A pulse regimen was approved for fingernails at 200 mg twice a day for 1 week each month, 2 pulses for fingernails.<sup>[9]</sup> Three pulses have been used off label for toenails, but we do not have any pivotal trial data on that regimen.

Fluconazole never received FDA approval for the treatment of toenail dermatophyte onychomycosis. In a clinical trial of dosing at 150, 300, and 450 mg once a week until the nail plate grew out completely, mycologic cure rates of 47% to 62% were achieved.<sup>[10]</sup>

## Oral Antifungals: Monitoring

- Baseline hepatic panel and CBC for terbinafine, itraconazole, and fluconazole
- Repeat monitoring if therapeutic course is repeated
- Periodic monitoring of patients with certain comorbidities, taking certain concomitant drugs, and in those at risk for adverse events

**Dr Elewski:** When we use oral drugs in the treatment of onychomycosis, there is some laboratory monitoring we have to perform. I generally do a baseline hepatic function panel and a complete blood count before treatment. If I prescribe a second course of treatment, I do another baseline hepatic panel and complete blood count. In patients with certain comorbidities -- for example, patients with diabetes, immunocompromised patients, or patients taking medications that might irritate the liver -- I check these levels in the middle of treatment.

## Oral Antifungals: Safety Issues

- Systemic antifungals have been associated with hepatic injury<sup>a,b</sup>
- Itraconazole<sup>b</sup>
  - Boxed warning about congestive heart failure, cardiac effects, and drug interactions

a. Lamisil® PI 2013.<sup>[8]</sup>

b. Sporanox® PI 2001.<sup>[9]</sup>

**Dr Elewski:** There are adverse effects that we have to consider: drug-drug interactions, drug eruptions, potential loss of taste, and cardiac issues such as congestive heart failure.

**Dr Del Rosso:** Which was an issue that came up with itraconazole.

**Dr Elewski:** It did.

**Dr Del Rosso:** We did not see it frequently in patients with onychomycosis, but there was some worsening of congestive heart failure, and it created a significant warning for itraconazole.

## Oral Antifungals: Safety Issues

### Terbinafine<sup>a</sup>

- Potential taste and/or smell disturbances
- Depressive symptoms, skin reactions, and exacerbation of lupus erythematosus have been reported
- Drug interactions

a. Lamisil® PI 2013.<sup>[6]</sup>

**Dr Del Rosso:** I think the most significant issue with oral drugs for onychomycosis is drug-drug interactions. Most of the adverse effects, such as hepatotoxicity, are quite rare, but there are a significant number of drug interactions and contraindications. We all know the oral drugs and use them, but there is a lot more to think about when you are prescribing oral treatment.

**Dr Joseph:** I think there is an unwarranted fear of the use of oral antifungals, not only on the part of patients who read something on the Internet but also prescribing clinicians. There is a lot of misunderstanding because the adverse events are relatively rare, but as you pointed out, they are out there.

**Dr Del Rosso:** I also get concerned that people are going to be too cavalier with topical drugs. You still have to look at the patient, evaluate what is going on, and educate the patient -- not just prescribe a topical. I look at that as a real-world concern.

## Ciclopirox

- Nail lacquer
- Daily application
- Requires nail debridement
- Mycologic cure rates: 29% to 36%
- Complete cure rates: 5.5% to 8.5%

Penlac™ PI 2006.<sup>[11]</sup>

**Dr Elewski:** Don't forget about ciclopirox lacquer. Warren, many of my friends who are podiatrists use it. Can you talk about ciclopirox?

**Dr Joseph:** We were excited when the drug first came out about 15 years ago. Everyone was concerned about the oral antifungals, and they wanted a topical. There is no question that for the right patient, someone who is motivated, with 25% to 40% nail involvement without a lot of thickening, the drug did work.<sup>[11]</sup> The problem with the drug was poor patient selection. A patient with a big thick nail is not going to get better on a topical. Another problem with the drug is the lacquer vehicle. Until now, it was the only FDA-approved topical we had.

**Dr Del Rosso:** It is interesting because they were thinking only in terms of transungual penetration through the nail plate into the nail bed by having a lacquer. They were not recognizing that you need to get to the portal of entry underneath the nail plate.



## New Topical Antifungals

- Efinaconazole 10% solution: triazole antifungal<sup>a</sup>
- Tavaborole 5% solution: oxaborole antifungal<sup>b</sup>

a. Jublia® PI 2014.<sup>[12]</sup>  
b. Kerydin™ PI 2014.<sup>[13]</sup>

**Dr Elewski:** Let's turn our attention to the 2 new topical antifungal treatments. We have efinaconazole 10% solution, which is a triazole antifungal, and tavaborole 5% solution, which is an oxaborole antifungal.<sup>[12,13]</sup>

## New Topical Antifungals (cont)

- Both indicated for the topical treatment of onychomycosis of the toenails due to *T rubrum* and *T mentagrophytes*
- Both products indicated for once-daily treatment
- Neither requires debridement

Both are indicated for the topical treatment of onychomycosis of the toenails due to *T rubrum* and *T mentagrophytes*. Both are indicated for once-daily treatment. Neither requires debridement; debridement was not performed in the clinical studies.

## Clinical Trials: Efinaconazole

- Two phase 3 studies: identical, multicenter, randomized, double-blind, vehicle-controlled
- Approximately 1200 participants applied active drug and 400 applied vehicle, a 3:1 randomization

Elewski BE, et al. *J Am Acad Dermatol.* 2013;68:600-608.<sup>[14]</sup>

**Dr Elewski:** The safety and efficacy of efinaconazole were established in 2 identical multicenter, randomized, double-blind, vehicle-controlled phase 3 studies.<sup>[14]</sup> Approximately 1200 participants received active drug and 400 received vehicle, which is roughly a 3:1 randomization.

## Clinical Trials: Efinaconazole (cont)

- Patients had distal lateral subungual onychomycosis of the toenails, with 20% to 50% clinical involvement
- Self-applied solution once-daily for 48 weeks
- 4-week posttreatment follow-up

Elewski BE, et al. *J Am Acad Dermatol.* 2013;68:600-608.<sup>[14]</sup>

The patients had distal lateral subungual onychomycosis of the toenails, with 20% to 50% clinical involvement. Patients self-applied the drug once daily for 48 weeks, followed by a 4-week posttreatment follow-up.

## Efinaconazole Cure Rates

	Study 1 (N = 870) <sup>a</sup>	Study 2 (N = 785) <sup>a</sup>	Pooled Analysis <sup>b</sup> (mITT)
Mycologic Cure	Active: 55.2% Vehicle: 16.8% ( <i>P</i> < .001)	Active: 53.4% Vehicle: 16.9% ( <i>P</i> < .001)	Active: 56.3% Vehicle: 16.6% ( <i>P</i> < .001)
Complete Cure	Active: 17.8% Vehicle: 3.3% ( <i>P</i> < .001)	Active: 15.2% Vehicle: 5.5% ( <i>P</i> < .001)	Active: 18.5% Vehicle: 4.7% ( <i>P</i> < .001)

a. Elewski BE, et al. *J Am Acad Dermatol*. 2013;68:600-608.<sup>[14]</sup>

b. Gupta AK, et al. *J Drugs Dermatol*. 2014;13:815-820.<sup>[15]</sup>

**Dr Elewski:** Let's look at the 2 prime efficacy analyses. Mycologic cure rate from the pooled data was 56.3%. Complete cure rate from the pooled data was 18.5%.<sup>[15]</sup>

**Dr Del Rosso:** You could look at that data and say that those numbers are better than what we had in the past [with topical treatment], but they are still low. However, the mandated clinical efficacy end points set a high bar.

## Efinaconazole Cure Rates (Cont)

	Study 1 (N = 870) <sup>a</sup>	Study 2 (N = 785) <sup>a</sup>	Pooled Analysis <sup>b</sup> (mITT)
Complete or Almost Complete*	Active: 26.4% Vehicle: 7.0% ( <i>P</i> < .001)	Active: 23.4% Vehicle: 7.5% ( <i>P</i> < .001)	Active: 27.7% Vehicle: 7.9% ( <i>P</i> < .001)
Treatment Success <sup>†</sup>	Active: 35.7% Vehicle: 11.7% ( <i>P</i> < .001)	Active: 31.0% Vehicle: 11.9% ( <i>P</i> < .001)	Active: 47.2% Vehicle: 18.2% ( <i>P</i> < .001)

mITT = modified intention-to-treat analysis.

\*≤5% affected target toenail area involved + mycological cure.

†<10% clinical involvement of the large toenail.

a. Elewski BE, et al. *J Am Acad Dermatol.* 2013;68:600-608.<sup>[14]</sup>

b. Gupta AK, et al. *J Drugs Dermatol.* 2014;13:815-820.<sup>[15]</sup>

**Dr Elewski:** Let's look at the "complete or almost complete cure" measure: KOH negative, fungal culture negative, and 5% or less visible clinical involvement of the nail. So the nail is almost totally perfect and there is a smidgen of dystrophy somewhere, probably onycholysis. The "complete or almost complete cure" measure for efinaconazole was nearly 28%. Treatment success, measured as less than 10% involvement of the large toenail, was 47.2%.

## Efinaconazole Safety

### Adverse Reactions Reported by at Least 1% of Participants Treated for up to 48 Weeks

	Efinaconazole	Vehicle
Ingrown toenail, %	2.3	0.7
Application site dermatitis, %	2.2	0.2
Application site vesicles, %	1.6	0.0
Application site pain, %	1.1	0.2

Jublia® PI 2014.<sup>[12]</sup>

**Dr Elewski:** Safety was quite good. The majority of adverse events were mild or moderate and were not considered related to the study drug.<sup>[12]</sup> The incidence of treatment-related adverse events was comparable to vehicle. The most common adverse event leading to discontinuation was treatment-related application site reactions such as irritation. Rates of discontinuation were very low, approximately 2% to 3%.<sup>[12]</sup>

## Clinical Trials: Tavaborole

- Two phase 3 studies: identical, multicenter, randomized, double-blind, vehicle-controlled
- Patients had distal lateral subungual onychomycosis of the great toenail (20%-60% clinical involvement)
- 795 patients applied tavaborole; 399 applied vehicle
- Patients self-applied the solution once daily for 48 weeks; no debridement
- 4 week posttreatment follow-up

Kerydin™ PI 2014.<sup>[13]</sup>

**Dr Elewski:** Let's turn our attention to tavaborole.

**Dr Del Rosso:** Tavaborole was studied in a similar way: two identical phase 3, multicenter, randomized, double-blind, vehicle-controlled studies.<sup>[13]</sup> Patients were treated once a day with no debridement for 48 weeks and were then tested 4 weeks later. Patients had up to 60% involvement of the nail plate (in the efinaconazole studies, patients had up to 50% involvement).

There were 795 patients applying the active drug and 399 applying the vehicle. Keep in mind that tavaborole is a new type of compound; it is in the oxaborole class, and the integration of boron into the molecular structure helps get the compound to the target site.<sup>[16]</sup>



## Tavaborole Cure Rates

	Study 1 (N = 593)	Study 2 (N = 601)
Complete cure, %	Active: 6.5 Vehicle: 0.5 ( <i>P</i> < .001)	Active: 9.1 Vehicle: 1.5 ( <i>P</i> < .001)
Mycologic cure, %	Active: 31.1 Vehicle: 7.2 ( <i>P</i> < .001)	Active: 35.9 Vehicle: 12.2 ( <i>P</i> < .001)

Kerydin™ PI 2014.<sup>[13]</sup>

**Dr Del Rosso:** In study 1, the complete cure rates were 6.5% for tavaborole and 0.5% for vehicle.<sup>[13]</sup> In study 2, the complete cure rates were 9.1% for tavaborole vs 1.5% for vehicle. In study 1, the mycologic cure rates were 31.1% for tavaborole vs 7.2% for vehicle. In trial 2, the mycologic cure rates were 35.9% for tavaborole vs 12.2% for vehicle.<sup>[13]</sup> Those were the primary end points in the studies.

**Dr Elewski:** I gave the pooled data for efinaconazole because we have it, but the pooled data are not in the package insert for tavaborole.

## Tavaborole Cure Rates (cont)

	Study 1 (N = 593)	Study 2 (N = 601)
Complete or almost complete* <sup>a</sup>	Active: 26.1% Vehicle: 9.3% ( <i>P</i> < .001)	Active: 27.5% Vehicle: 14.6% ( <i>P</i> < .001)
Complete or almost complete plus mycologic cure <sup>†b</sup>	Active: 15.3% Vehicle: 1.5% ( <i>P</i> < .001)	Active: 17.9% Vehicle: 3.9% ( <i>P</i> < .001)

\*≤ 10% affected target toenail area involved.

†≤ 10% affected target toenail area involved plus negative KOH and culture results.

a. Gupta AK, et al. *Expert Rev Anti Infect Ther*. 2014;12:735-742.<sup>[17]</sup>

b. Kerydin™ PI 2014.<sup>[13]</sup>

**Dr Del Rosso:** If we look at complete or almost complete cure (≤10% affected target toenail area involved), the results were 26.1% for tavaborole vs 9.3% for vehicle in study 1.<sup>[13,17]</sup> In study 2, results were 27.5% for tavaborole vs 14.6% with the vehicle.<sup>[13,17]</sup> Complete/almost complete cure rates plus mycologic cure rates were 15.3% in study 1 for tavaborole vs 1.5% for vehicle, and in study 2, results were 17.9% for tavaborole vs 3.9% for vehicle.<sup>[13]</sup>

There were some differences in the efinaconazole and tavaborole trials that may affect some of the results. Some people agree; some people do not. However, I think we have to find out what these drugs are going to do in the real world.

**Dr Joseph:** The take-home message is that for the first time in 15 years, we have 2 new FDA-approved drugs for the treatment of onychomycosis, and they both have solid data showing that they are statistically significantly better than vehicle. That is major for our patients.

## Tavaborole Safety

### Adverse Reactions Occurring in $\geq 1\%$ of Participants

AE	Tavaborole	Vehicle
Application site exfoliation, %	2.7	0.3
Ingrown toenail, %	2.5	0.3
Application site erythema, %	1.6	0
Application site dermatitis, %	1.3	0

Kerydin™ PI 2014.<sup>[13]</sup>

**Dr. Del Rosso:** Similar to efinaconazole, tavaborole was well tolerated. There were no safety signals. There was no systemic toxicity from absorption or anything of that nature. Some patients may get some local irritation, but there was not anything significant to be concerned about.

## New Antifungal Solutions in Practice

- Monotherapy for mild to moderate toenail onychomycosis
- Alternative treatment of patients who will not or cannot use oral antifungals
- Combination therapy with oral antifungals (no clinical trials)
- Prevention of recurrence (no clinical trials)

**Dr Elewski:** Let's discuss the place of these new topical drugs in our practice. Warren, where do you think you will use these new drugs?

**Dr Joseph:** I have always said that topical agents are not appropriate for the treatment of thick, totally dystrophic nails, what we would call severe onychomycosis. Topicals are appropriate for mild to moderate onychomycosis: the patient who has 20% to 50% involvement without a lot of thickening.

**Dr Del Rosso:** You are talking about monotherapy.

**Dr Joseph:** As monotherapy, yes. I think about very mild to moderate disease, although, interestingly, neither drug is labeled for mild to moderate disease. Both drugs are labeled for onychomycosis of the toenails due to *T rubrum* or *T mentagrophytes*. Another use I see for these drugs is as alternative therapy. What I mean by that are patients who, for whatever reason, will not take or cannot take oral therapy. Perhaps such patients have the potential for one of the drug-drug interactions or a history of liver toxicity, hepatitis C for instance. So these drugs can be an alternative for patients who cannot take an oral drug.

I also would like to talk about adjunctive therapy, combination therapy. There are no studies to prove this, but think about it: If you use an oral drug, it works from the inside out. The topical drug works from the outside in. The fungus gets caught in the middle, and hopefully it gets killed. You would think that, at least empirically, that would be a better way to go.

Finally, I think an interesting use of these drugs would be for preventing recurrence. Again, there is no evidence to support this, but if you have a patient who has been cleared either through the use of an oral or one of these topicals and you want them to remain clear, you need to treat the tinea pedis and you need to keep the nails clear of fungus. I joke around about "toenail Tuesday" or "fungal Friday" -- apply a topical perhaps twice a week to keep the fungus away.

**Dr Del Rosso:** I think we have a great opportunity if we step back and, as clinicians, really look at our patients. We should also look at the clinical presentation and make certain that patients understand their condition and its treatment.

**Dr Elewski:** This is a great time for patients with onychomycosis because now they have options. They can take an oral drug or they can use a topical drug. Also, as you mentioned, Warren, maybe they can use both an oral and a topical drug. I would like to thank you, Jim and Warren, for this very interesting discussion.

And thank you for participating in this activity. Click on the Earn CME/CE Credit link to revisit the questions presented at the beginning of the program to see what you have learned. The posttest and evaluation will follow. Thank you.

*This transcript has been edited for style and clarity.*

This article is a CME/CE certified activity. To earn credit for this activity visit:

[www.medscape.org/spotlight/onychomycosis](http://www.medscape.org/spotlight/onychomycosis)

## Abbreviations

AE = adverse event

FDA = US Food and Drug Administration

KOH = potassium hydroxide

mITT = modified intention-to-treat analysis

## References

1. Ghannoum MD, Hajjeh RA, Scher R, et al. 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.
2. Fletcher CL, Hay RJ, Smeeton NC. Observer agreement in recording the clinical signs of nail disease and the accuracy of a clinical diagnosis of fungal and non-fungal nail disease. *Br J Dermatol*. 2003;148:558-562.
3. Garcia-Doval I, Cabo F, Monteagudo B, et al. Clinical diagnosis of toenail onychomycosis is possible in some patients: cross-sectional diagnostic study and development of a diagnostic rule. *Br J Dermatol*. 2010;163:743-751.
4. Scher RK, Rich P, Pariser D, Elewski B. The epidemiology, etiology, and pathophysiology of onychomycosis. *Semin Cutan Med Surg*. 2013;32(2 Suppl 1):S2-S4.
5. Del Rosso JQ. The role of topical antifungal therapy for onychomycosis and the emergence of newer agents. *J Clin Aesthet Dermatol*. 2014;7:10-18.
6. Zaias N, Rebell G. Chronic dermatophytosis caused by *Trichophyton rubrum*. *J Am Acad Dermatol*. 1996;35:S17-S20.
7. Drake LA, Scher RK, Smith EB, et al. Effect of onychomycosis on quality of life. *J Am Acad Dermatol*. 1998;38:702-704.
8. Lamisil [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2013.
9. Sporanox [package insert]. Raritan, NJ: PriCare, Division of Ortho-McNeil-Janssen Pharmaceuticals; 2001.
10. Scher RK, Breneman D, Rich P, et al. Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. *J Am Acad Dermatol*. 1998;38:S77-S86.
11. Penlac™ [package insert]. Bridgewater, NJ: Dermik Laboratories; 2006.
12. Jublia® [package insert]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; 2014.
13. Kerydin™ [package insert]. Palo Alto, CA: Anacor Pharmaceuticals, Inc.; 2014.
14. Elewski BE, Rich P, Pollak R, et al. Efinaconazole 10% solution in the treatment of toenail onychomycosis: two phase III multicenter, randomized, double-blind studies. *J Am Acad Dermatol*. 2013;68:600-608.
15. Gupta AK, Elewski BE, Sugarman JL, et al. The efficacy and safety of efinaconazole 10% solution for treatment of mild to moderate onychomycosis: a pooled analysis of two phase 3 randomized trials. *J Drugs Dermatol*. 2014;13:815-820.
16. Del Rosso JQ, Plattner JJ. From the test tube to the treatment room: fundamentals of boron-containing compounds and their relevance to dermatology. *J Clin Aesthet Dermatol*. 2014;7:13-21.
17. Gupta AK, Daigle D. Tavaborole (AN-2690) for the treatment of onychomycosis of the toenail in adults. *Expert Rev Anti Infect Ther*. 2014;12:735-742.

## Disclaimer

The educational activity presented above may involve simulated case-based scenarios. The patients depicted in these scenarios are fictitious and no association with any actual patient is intended or should be inferred.

The material presented here does not necessarily reflect the views of Medscape, LLC, or companies that support educational programming on medscape.org. These materials may discuss therapeutic products that have not been approved by the US Food and Drug Administration and off-label uses of approved products. A qualified healthcare professional should be consulted before using any therapeutic product discussed. Readers should verify all information and data before treating patients or employing any therapies described in this educational activity.

Medscape Education © 2014 Medscape, LLC