EXPERT OPINION



# New pharmacotherapy for the treatment of onychomycosis: an update

Aditya K Gupta[†] & Fiona C Simpson
[†]*Mediprobe Research, Inc., London, ON, Canada*

***Introduction:*** Onychomycosis is an infection of the nail plate that is an important priority area for the development of antifungal drugs. The high incidence of relapse and reinfection often makes onychomycosis a chronic condition. The current gold standard is oral therapy, but the development of effective topical agents remains a priority as they have fewer systemic interactions.
***Areas covered:*** This review summarizes development of antifungals from early phase development through Phase III clinical trials for onychomycosis. The oral molecules in development are azole molecules. Topical drugs in development include azoles, allylamines, benzoxaboroles and nanoemulsions. Photosensitizers for photodynamic therapy and new laser systems are also emerging therapeutic options. There is a diverse array of antifungal drugs in the early phases of development.
***Expert opinion:*** The goals of onychomycosis therapy are a mycological cure and a normal appearing nail. The recent development of topical antifungals has been successful at improving the nail permeation and efficacy. The diversification of molecular targets is the next primary goal of antifungal development. Incomplete treatment of onychomycosis provides an environment conducive to the development of antifungal resistance. New topical agents and device-based therapies expand the therapeutic options. Combination therapy using multiple drug classes may improve the overall efficacy of antifungal treatment in onychomycosis.

**Keywords:** allylamine, antifungal, azole, dermatophyte, non-dermatophyte mold, onychomycosis

*Expert Opin. Pharmacother. (2015)* ***16****(2):227-236*

## 1. Introduction

Onychomycosis is an infection of the nail apparatus caused by dermatophytes, yeasts and/or non-dermatophyte molds (NDM) [1]. It can cause nail plate discoloration, thickening and onycholysis. It also poses a risk of infection to secondary sites on the body [2]. Onychomycosis has a number of presentations including distal and lateral subungual onychomycosis (DLSO), superficial white onychomycosis and proximal subungual onychomycosis. Severe onychomycosis may present with severe subungual hyperkeratosis, lunula or matrix involvement or dermatophytoma and progress to total dystrophic onychomycosis [2]. It is critical to treat onychomycosis for both medical and cosmetic purposes. The incidence of onychomycosis is higher in elderly patients and patients with diabetes, peripheral vascular disease, HIV, immunosuppression, obesity and smoking [3-9].

In the status quo, the therapeutic options for onychomycosis include oral and topical allylamines, azoles, benzoxaboroles, ciclopirox and amorolfine [10]. These therapies range in efficacy, but oral terbinafine is the current gold standard with a mycological cure rate of 74% [11,12]. Even when initial therapy is successful at achieving a complete or mycological cure, there is a high rate of relapse and

informa
healthcare



10.1517/14656566.2015.993380 © 2015 Informa UK, Ltd. ISSN 1465-6566, e-ISSN 1744-7666

**Article highlights.**

- Oral drugs in development include albaconazole, posaconazole and pramiconazole.
- Topical drug development includes azoles, allylamines, benzoxaboroles, nanoemulsions and photosensitizers.
- Two new topical drugs efinaconazole and tavaborole have received FDA approval.
- Device-based therapies such as photodynamic therapy and lasers provide new options for treating onychomycosis.
- Diversification of antifungal molecular mechanisms should be a priority to combat the development of antifungal resistance.

This box summarizes key points contained in the article.



recurrence due to the continued presence of fungal material in the patient's environment [13,14]. The relapse may be due to the presence of drug-resistant arthroconidia in the nail plate, as well as hyphae, which germinate in post-treatment period [15,16]. This means that onychomycosis often becomes a chronic condition with disease durations in the range of several years.

There are a number of new drug therapies in the developmental pipeline for onychomycosis. The goal of new treatments is to improve on topical drug efficacy using new molecules or permeation enhancers, to diversify drug targets and to expand on previously successful base molecules to produce new drugs. This article summarizes pharmacotherapies for onychomycosis that have reached Phase II/III clinical trials or have been used in off-label trials. The definitions of clinical trial outcome measures can be found in **Table 1**.

## 2. Orals

### 2.1 Azoles

#### *2.1.1 Albaconazole*

Albaconazole is a triazole antifungal formulated for a once-weekly dosing schedule. A Phase II, double-blind, placebo-controlled study was conducted to compare four regimens of albaconazole [17]. Patients with KOH and culture confirmed distal subungual onychomycosis (n = 582) were randomized to once-weekly doses of 100 mg (36 weeks), 200 mg (36 weeks), 400 mg (36 weeks), 400 mg (24 weeks plus 12 weeks placebo) or placebo (36 weeks) at a 1:1:1:1:1 ratio. The primary outcome was global change in target toenail condition, evaluated at week 52. The secondary outcome measures were mycological cure, percentage of affected target nail, linear clear nail growth and number of affected nails. The study completion rate for the full protocol was 82%. Effective treatment was achieved at the highest rate in participants receiving 400 mg/week for 36 weeks. The full outcome measures are presented in **Table 2**.

#### *2.1.2 Posaconazole*

Posaconazole is a triazole antifungal that is formulated as an oral suspension. It is currently FDA-approved for the treatment of invasive *Candida* and *Aspergillus* infections [18]. Posaconazole has completed a Phase II dose-ranging clinical trial [19]. Adult participants (n = 218) with mycologically confirmed mild-to-moderate (25 – 75% nail plate involvement) DLSO were enrolled in this active comparator-controlled clinical trial. The participants were randomized to a daily dose of one of the following regimens: 100, 200 or 400 mg posaconazole for 24 weeks, 400 mg posaconazole for 12 weeks, 250 mg terbinafine for 12 weeks or vehicle for 24 weeks. The primary outcome measure was complete cure at 48 weeks. Full trial results are shown in **Table 3**. The highest complete cure rate was achieved by 200 mg/day posaconazole at 54.1%. Treatment-emergent adverse events (TEAEs) reported during the trial included headache, diarrhea, nausea and fatigue. Posaconazole is not registered for future trials for onychomycosis.

## 3. Topicals

### 3.1 Azoles

#### *3.1.1 Efinaconazole*

Efinaconazole is a triazole antifungal that is formulated as a daily topical nail solution [20,21]. A Phase II dose-ranging study compared efinaconazole 10% with or without semi-occlusion, efinaconazole 5% without semi-occlusion and vehicle [22]. Participants applied their treatment daily for 36 weeks and outcome measures were evaluated at 40 weeks. The full outcome measures are presented in **Table 4**. The most effective trial arm was efinaconazole 10% without semi-occlusion.

Duplicate Phase III trials were conducted for efinaconazole 10% solution [23]. Participants with mycologically confirmed DLSO (20 – 50% of the nail plate) were randomized to receive efinaconazole or vehicle once daily for 48 weeks. Follow up was conducted for 4 subsequent weeks and the outcome measures were assessed at week 52. The primary outcome measure was complete cure. The full outcome measures from the two trials are presented in **Table 5**. The complete cure rates were 17.8 and 15.2% for participants receiving efinaconazole and 3.3 and 5.5% for participants receiving vehicle. The TEAEs reported were mild and resolved with cessation of treatment. Efinaconazole 10% nail solution received FDA approval for the treatment of onychomycosis in 2014 [20].

### 3.2 Allylamines

#### *3.2.1 TDT-067*

TDT-067 is terbinafine formulated in a Transfersome at a concentration of 15 mg/ml [24,25]. *In vitro* the Transfersome's capabilities showed increased efficacy over terbinafine alone for *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, *Trichophyton rubrum* and terbinafine-resistant *Trichophyton rubrum* [25]. A Phase II, open-label study was conducted in

**Table 1. Outcome measures.**

| Outcome measure | Description |
|---|---|
| Complete cure | 0% nail plate involvement and mycological cure |
| Complete or almost complete cure | ≤ 5% clinical involvement and mycological cure |
| Mycological cure | Negative KOH and culture |
| Treatment success | < 10% nail plate involvement of the target nail |
| Effective treatment | 0% nail involvement or > 3 mm proximal nail growth from baseline |
| Clinical efficacy | < 20% nail plate involvement |
| Treatment efficacy | Negative culture plus ≥ 2 mm clear nail growth or an Investigator Global Assessment score of clear or almost clear |
| Unaffected toenail growth | Linear change from baseline |
| Treatment-emergent adverse event | Any adverse event that manifests during the course or treatment |

**Table 2. Albaconazole Phase II trial outcomes.**

| Treatment duration | Treatment arm | Number of participants | Complete cure rate | Mycological cure rate |
|---|---|---|---|---|
| 36 weeks | Placebo | 115 | 0% | 6% |
| | 100 mg | 117 | 12% | 34% |
| | 200 mg | 117 | 21% | 43% |
| | 400 mg | 116 | 33% | 71% |
| 24 weeks | 400 mg | 117 | 26% | 54% |

Data taken from [17].

**Table 3. Posaconazole Phase II trial outcomes.**

| Treatment duration | Treatment arm | Number of participants | Mycological cure rate | Complete cure rate |
|---|---|---|---|---|
| 24 weeks | Placebo | 36 | 3.1% | 0% |
| | Posaconazole 100 mg | 37 | 37.1% | 22.9% |
| | Posaconazole 200 mg | 37 | 70.3% | 54.1% |
| | Posaconazole 400 mg | 36 | 78.8% | 45.5% |
| 12 weeks | Posaconazole 400 mg | 36 | 42.9% | 20.0% |
| | Terbinafine 250 mg | 36 | 71.4% | 37.1% |

Data taken from [19].

participants with mycologically confirmed bilateral onychomycosis of the great toenail [26]. Participants applied TDT-067 to the nails and surrounding skin twice daily for 12 weeks. Outcome measures were assessed at week 48. The mycological cure rate was 38%. In addition, 9% of participants achieved ≥ 5 mm of clear nail growth and 24% achieved ≥ 2 mm clear nail growth. TEAEs were mild to moderate and resolved with cessation of treatment.

### 3.3 Benzoxaborole

#### *3.3.1 Tavaborole*

Tavaborole is a benzoxaborole molecule that is formulated as a 5% topical solution [27]. Tavaborole is the first benzoxaborole molecule to achieve FDA approval and has a novel mechanism of action as a tRNA synthetase inhibitor [28]. Three Phase II clinical trials were conducted for tavaborole. Two were open-label trials and the other was a double-blind, placebo-controlled trial [29]. The disposition of study participants is shown in **Table 6**. The most effective trial arm in Phase II was 7.5% tavaborole at 53% treatment efficacy at 6 months in an open-label trial.

Duplicate multicenter, double-blind, randomized, vehicle-controlled Phase III trials were conducted for tavaborole 5% nail solution [27]. Adult subjects with DLSO of at least one great toenail with 20 – 60% nail plate involvement without dermatophytoma or lunula involvement were enrolled. Participants applied tavaborole 5.0% solution or placebo once daily for 48 weeks, with a 4-week follow-up period. The primary outcome measure was complete cure assessed at week 52. The full trial results are summarized in **Table 7**. The complete cure rates were 6.5 and 9.1% for tavaborole versus 0.5 and 1.5% in vehicle for the two trials, respectively. The most

**Table 4. Efinaconazole Phase II trial outcomes [22].**

| Trial arm | Number of participants | Complete cure | Mycological cure | Clinical efficacy | Treatment efficacy | Unaffected nail growth |
|---|---|---|---|---|---|---|
| Efinaconazole 10% with semi-occlusion | 36 | 22.2% | 83.3% | 67% | 61% | 4.7 mm |
| Efinaconazole 10% | 39 | 25.6% | 87.2% | 69% | 64% | 4.7 mm |
| Efinaconazole 5% | 38 | 15.8% | 86.0% | - | 55% | 3.8 mm |
| Vehicle | 22 | 9.1% | - | 32% | 23% | 1.8 mm |

**Table 5. Efinaconazole Phase III trial outcomes.**

| | | Number of participants | Complete cure | Mycological cure | Complete or almost complete cure | Treatment success: % nail plate involvement | | | | Unaffected nail growth |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 0% | ≤ 5% | < 10% | ≤ 10% | |
| Study 1 | Efinaconazole 10% | 656 | 17.8% | 55.2% | 26.4% | 45% | 35.7% | 35% | 21% | 5.0 mm |
| | Vehicle | 214 | 3.3% | 16.8% | 7.0% | 17% | 11.7% | 11% | 6% | 1.6 mm |
| Study 2 | Efinaconazole 10% | 583 | 15.2% | 53.4% | 23.4% | 40% | 31.0% | 29% | 18% | 3.8 mm |
| | Vehicle | 202 | 5.50 | 16.9% | 7.5% | 15% | 11.9% | 11% | 7% | 0.9 mm |

Data taken from [23].

**Table 6. Tavaborole Phase II studies.**

| Trial | 200 | | | | 201 | | | 203 | |
|---|---|---|---|---|---|---|---|---|---|
| Trial design | Double-blind, placebo-controlled | | | | Open-label | | | Open-label | |
| Inclusion criteria | DLSO of at least 1 great toenail, 20 – 60% nail plate involvement, KOH and culture positive, history of nail growth | | | | DLSO of at least 1 great toenail, 20 – 60% nail plate involvement, history of nail growth | | | DLSO of at least 1 great toenail, 20 – 60% nail plate involvement, history of nail growth | |
| Trial arms | 2.5% | 5% | 7.5% | Vehicle | 5.0% | 7.5% | 5.0% | 1.0% | 5.0% |
| Treatment duration | 6 months | | | | 6 months | 6 months | 12 months | 6 months | |
| Participants (n) | 63 | 33 | 31 | 60 | 30 | 30 | 29 | 30 | 30 |
| Treatment efficacy | 27% | 26% | 32% | 14% | 43% | 53% | 14% | 30% | 50% |

Data taken from [29].
DLSO: Distal and lateral subungual onychomycosis.

common adverse events were application site exfoliation, ingrown toenail and application site erythema and dermatitis. Tavaborole 5% solution received FDA approval for the treatment of onychomycosis in 2014 [27].

### 3.4 Photosensitizers for photodynamic therapy

Photosensitizers are topically applied drugs that are activated by narrow spectrum light to cause the generation of reactive oxygen species and apoptosis [30]. Photosensitizers are used to perform photodynamic therapy (PDT), which involves pretreating the infection with the photosensitizer followed by irradiation with light at a specific wavelength and energy fluence. The light activates the photosensitizers leading to the generation of reactive oxygen species which damage cellular structures leading to apoptosis.

#### *3.4.1 5-Aminolevulinic acid and methyl aminolevulinate*

The photosensitizers aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) are topically applied protoporphyrin

**Table 7. Tavaborole Phase III trial outcomes.**

| Trial | Trial arm | Number of participants | Complete cure | Complete or almost complete cure | Mycological cure |
|---|---|---|---|---|---|
| Trial 1 | Tavaborole | 399 | 6.5% | 15.3% | 31.1% |
| | Vehicle | 194 | 0.5% | 1.5% | 7.2% |
| Trial 2 | Tavaborole | 396 | 9.1% | 17.9% | 35.9% |
| | Vehicle | 205 | 1.5% | 3.9% | 12.2% |

Data taken from [27].



photosensitizers. ALA is the first step in the heme biosynthesis pathway. Cellular uptake of ALA causes an increase in the production of protoporphyrins, specifically protoporphyrin IX (PPIX), due to the limited capacity of the enzyme ferrochelatase to convert PPIX into heme [30]. MAL is a derivative of ALA that acts as a prodrug for this pathway [31]. *In vitro* dose–response curve experiments on the effect of ALA activated by 10 J of unfiltered white light in *T. rubrum* showed decreased fungal growth in comparison to non-irradiated controls after 7-day incubation [32]. Several case studies and clinical trials have summarized the effects of ALA and MAL PDT for onychomycosis (**Table 8**) [33-36]. These results are largely positive, but a later review suggests that ALA and MAL may not be ideal photosensitizers for the treatment of onychomycosis [30].

#### 3.4.2 *Hematoporphyrin derivatives*

Hematoporphyrin derivatives (HpD) are a mixture of monomeric and oligomeric porphyrins derived from blood [37]. The HpD formulation Photogem® (5 mg/ml) was tested in a male patient with mycologically confirmed onychomycosis. A 20% urea pretreatment was applied for 10 min prior to debridement using a pneumatic diamond drill. The photosensitizer was applied for 1 h followed by irradiation at 630 nm for 9 min with a fluence of 54 J/cm$^2$. The patient received six sessions of PDT at weekly intervals. At 6 weeks, complete healing and a mycological cure were achieved.

#### 3.4.3 *Methylene blue*

Methylene blue (MB) is a dye that has been formulated as topical 2% aqueous solution [38]. MB has strong absorption from 600 to 660 nm. A clinical trial of MB-PDT was conducted in 11 participants with severe DLSO (lunula or nail matrix involvement or 50% nail plate involvement with > 2 mm subungual hyperkeratosis or dermatophytoma) and 11 participants with mild-to-moderate DLSO. Participants were required to have a mycological diagnosis of *T. rubrum* as the infectious agent. Participants underwent therapy for 6 months with 15-day intervals between treatments. Participants applied 2% MB followed by irradiation with a 630 nm red light (36 J/cm$^2$, 3100 mW/cm$^2$, 100 mW/cm$^2$). A complete clinical response occurred in 100% of mild-to-moderate participants and 63.6% of severe participants. There were no TEAEs reported. An additional trial following the same protocol was conducted in four participants with endonyx onychomycosis [39]. Complete clinical cure and mycological cure was achieved in all participants. No TEAEs were observed.

#### 3.4.4 *Toluidine blue*

Toluidine blue (TBO) is a topical photosensitizer formulated as a 100 µg/ml gel [40]. TBO is activated by a 635 nm light source with a light dose of 200 J/cm$^2$ per session. TBO was 100% effective against *T. rubrum in vitro* at two concentrations and any light dose from 5 to 20 min. In an onychomycosis model of micronized nail incubated with *T. rubrum*, a dose response to the length of irradiation was observed with reduced fungal growth at 10 and 20 min and complete suppression after 30 min. A case study was conducted in a woman with DLSO caused by *Trichophyton interdigitale* [40]. TBO was applied for 15 min followed by 10 min irradiation at 635 nm and 500 mW. The patient was treated for 3 consecutive days until a clinical cure was reached. The only TEAE was transient staining of the nail following the treatment. Nail morphology improved at 11 weeks and remained improved at 6 months.

## 4. Laser therapy

Laser therapy is a non-pharmacologic treatment for onychomycosis. Laser systems are approved by the FDA based on similarity to predicate devices and they are approved for 'the temporary increase of clear nail in onychomycosis' [41].

### 4.1 Neodymium-yttrium garnet lasers

#### 4.1.1 *Long-pulsed laser systems*

The study by Kozarev is the only instance of the use of a long-pulsed (35 ms) laser (**Table 9**) [42,43]. Long-pulsed laser systems are more likely to result in volumetric heating due to their temporal pulse format. This is more likely to result in transient pain for the patient, so this design is uncommon for onychomycosis lasers.

#### 4.1.2 *Short-pulsed systems*

Short-pulsed lasers have pulse durations in the 300 – 650 µs range [44-53]. These are the most common commercial models approved for onychomycosis. The majority of systems are 1064 nm lasers, but a single clinical trial has also been conducted with a 1320 nm laser [53].These studies have the widest range of efficacy with mycological cure rates ranging from 0 to

**Table 8. ALA and MAL photodynamic therapy.**

| Study | Watanabe 2008 | Pirracini 2008 | Gilaberte 2010 | Sotiriou 2010 |
|---|---|---|---|---|
| Number of participants | 2 | 1 | 2 | 30 |
| Pretreatment | 20% urea for 10 h | 50% urea under occlusion for 7 days | 40% urea under occlusion for 12 h | 20% urea under occlusion for 10 nights |
| Photosensitizer | ALA for 5 h | MAL for 3 h | MAL for 4 h | ALA for 3 h |
| Light source | 630 nm, 100 J/cm$^2$ | 630 nm, 37 J/cm$^2$ | 635 nm, 37 J/cm$^2$ | 570 – 670 nm, 40 J/cm$^2$ |
| Number of treatments | 1 | 3 | 2 | 2 |
| Treatment interval | - | 15 | 2 weeks | 2 weeks |
| Follow-up period | 6 months | 24 months | 6 months | 18 months |
| Mycological cure | 100% | 100% | 100% | 37% |
| Treatment-emergent adverse event | Transient pain | - | Transient pain | Erythema, edema, blistering |

Data taken from [33-36].
ALA: Aminolevulinic acid; MAL: Methyl aminolevulinate.



100%. Several reviews of these laser systems have indicated that randomized, double-blind trials will be required to ascertain if these models are in fact fungicidal [54,55].

#### 4.1.3 *Q-Switched laser systems*

An additional three studies have used the Q-Clear Q-switched laser that has a 3 – 10 ns pulse duration [56-58]. The smaller temporal pulse length in this laser is less than the thermal relaxation time of the fungi, which allows for more contained heating of the fungi in the nail plate. Two were single assignment open-label studies [56,57]. The third was a comparative study where participants were randomized to the Q-Clear or Monalisa devices [58]. The mycological cure rate for all three studies was > 95%.

## 5. Conclusion

There is a diverse array of new therapies for onychomycosis. The oral drug development pipeline is limited, as the developmental priority is topical drugs. There is a diverse array of azoles, allylamines, nanoemulsions and photosensitizers that have been developed and tested for the treatment of onychomycosis. In addition, there are numerous molecules in the early developmental stages that build on the existing azole platform or target new biosynthesis pathways to achieve their effects.

## 6. Expert opinion

There are two primary goals for onychomycosis therapy. The first is to eradicate the fungal infection and the second is to restore a normal-appearing nail plate. Many patients focus primarily on the second goal, but nail damage due to trauma may result in long-term damage to the nail apparatus. The first goal is more medically relevant, achievable goal and it is unlikely that a normally appearing nail can be achieved without full resolution of the fungal infection. Recent developments in pharmacotherapy have primarily focused on the development of topical monotherapies for use in patients who cannot take oral medication or prefer a topical drug. After many years of focus on expanding the options for topical therapies, significant progress has been made in improving these formulations [59,60]. The recent FDA approval of the topical monotherapies efinaconazole and tavaborole shows that improvements have been made in the development of solutions with permeation enhancers for drug delivery. Renewed attention to the routes of topical drug administration may also expand the efficacy of topical drugs, as subungual drug administration may play as significant a role as transungual drug administration for the administration of topical antifungals such as efinaconazole and in future formulations [61]. These molecules will also offer the possibility of new combination therapies with oral drugs and/or devices to expand the current treatment possibilities.

The next challenge facing the development of antifungals is drug target diversification. The azole and allylamine drug platforms have produced a number of effective antifungals, but they are also associated with the possible accumulation of drug resistance [62-64]. Given that it is very difficult to completely eradicate onychomycosis, treatment failures may present ideal conditions for the development of drug resistance. Treatment failures allow for extended exposure of dermatophytes, yeasts and NDMs to sublethal doses of antifungal drugs. However, thus far, resistance of dermatophytes to azole agents has not been an issue that is of clinical relevance [63]. Diversifying the molecular targets of antifungal drugs will hopefully allow for increased mycological cure and decreased opportunities for drug resistance at common molecular targets like sterol 14$\alpha$-demethylase. The introduction of tavaborole provides the opportunity not only to use a novel monotherapy but also to combine the efficacy of benzoxaboroles against leucyl tRNA synthetase with existing molecular targets. The molecules in early development provide novel mechanisms of action from mimicking the action of the leukocyte cell burst to inhibiting fatty acid biosynthesis. Many also have unknown mechanisms at this time. These new

**Table 9. Neodymium-yttrium garnet 1064 nm laser system clinical trials.**

| Study | Laser system | Wavelength (nm) | Participants (n) | Diagnosis | Pulse duration | Frequency (Hz) | Energy Fluence (J/cm$^2$) | Spot Size (mm) | # of Tx | Tx interval | Follow-up period | MCR (%) | CCR (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Long-pulsed laser systems* | | | | | | | | | | | | | |
| Kozarev and Vizintin (2010) [42], Kozarev (2011) [43] | Dualis SP, Fotona | 1064 | 162 | Culture and KOH | 35 ms | 1 | 35 – 40 | 4 | 4 | 1 week | +12 months | 100% | - |
| *Short-pulse laser systems* | | | | | | | | | | | | | |
| Harris *et al.* (2009) [44] | PinPointe Foot-Laser, Nuvolase, Inc. | 1064 | 14 | - | - | - | - | 2.5 | 1 | - | 6 months | - | 80% |
| Weiss (2011) [45] | GenesisPlus, Cutera | 1064 | 7 | - | 300 µs | 2 | 16 | 5 | 2 | 6 weeks | 12 months | - | 70% |
| Hochman (2011) [46] | Aerolase, LightPod Neo | 1064 | 8 | Culture or PAS | 650 µs | - | 223 | 2 | 3 | 3 weeks | 4 – 6 months | 87.5% | - |
| Kimura *et al.* (2012) [47] | GenesisPlus, Cutera | 1064 | 13* | KOH | 300 µs | 5 | 14 | 5 | 1 – 3 | 4 or 8 weeks | 16 weeks | 51%* | 81%* |
| Waibel *et al.* (2013) [48] | Sciton, Joule ClearSense | 1064 | 7 | Culture or PAS | 300 µs | 6 | 13 | - | 4 | 1 week | 6 months | 100% | - |
| Carney *et al.* (2014) [49] | Laser Genesis, Cutera | 1064 | 14 | Culture | 300 µs | 2 | 16 | 5 | 1 | - | 24 weeks | 29% | - |
| Noguchi *et al.* (2013) [50] | GentleYAG, Candela | 1064 | 12 | Culture | 500µs | 2 | 10 | 6 | 3 | 4 weeks | 6 months | 0% | - |
| Moon *et al.* (2014) [51] | ClearSense, Sciton | 1064 | 13 (43 nails) | Culture and KOH | 300µs | 5 | 5 | 6 | 5 | 4 weeks | 6 months | 70%* | |
| Gupta and Paquet (2014) [52] | PinPointe Foot-Laser, Nuvolase, Inc. | 1064 | 23 | KOH, Culture, PCR | 1/3s | 30 | - | - | 4 | 2 – 4+ weeks | 31 weeks | - | 17% |
| Ortiz *et al.* (2014) [53] | CoolTouch CT3 Plus laser with CoolBreeze Zoom handpiece; Cool-Touch | 1320 | 10 | Culture | 350 µs | 20 | - | 5 | 4 | Days 1, 7, 14 and 60 | 180 days | 50%‡ | 40% |
| *Q-switched laser systems* | | | | | | | | | | | | | |
| 510(k) K110370, (2011) [56] | Q-Clear, Light Age | 1064 | 100 | - | 3 – 10 ns | 1 | | 2.5 – 6 | 1 | - | - | - | 95% |
| Kalokasidis *et al.* (2013) [57] | Q-Clear, Light Age, Inc. | 1064 | 100 | Culture | 9e$^{-9}$s | 5 | 14 | 2.5 | 2 | 30 days | 3 months | 95.42% | - |
| Galvan Garcia (2014) [58] | Monalisa Laser, Sincoheren Co.; Q-Clear, Light Age, Inc. | 1064 | 120 | KOH | - | 3 | 0.6 | 3 | 1 | - | 9 months | 100% | - |

*Reported as nails not participants.

‡Reported at day 90.

CCR (%): Liner nail growth or ≤ 10% nail involvement; MCR: Mycological cure rate; PAS: Periodic acid-Schiff; PCR: Polymerase chain reaction; Tx: Treatment.

molecules and drug classes are an important developmental goal for the future treatment of onychomycosis.

The development of device-based therapies is an important step in the diversification of treatments for onychomycosis. PDT and laser therapy have the advantage of being inpatient procedures, which are less reliant on patient compliance to achieve the desired outcome. In the long term, PDT or laser therapy may be an ideal primary treatment in combination with a topical as a preventative measure.

The key to successful onychomycosis treatment is to fully eradicate the fungi not only from the patient's nail plate but also from their surroundings. The continued presence of fungal spores in clothing and footwear presents strong risks of reinfection once patients have ceased treatment. From a clinical perspective, the education of patients about these risks and solutions, such as ozone sanitization for shoes and ensuring laundry is washed in high heat, is equally important to prescribing the ideal pharmacotherapy.

## Declaration of interest

AK Gupta has been a clinical trial investigator for Valeant Canada, Bristol Meyers Squibb, Eli Lilly, Merk, Novartis, Janssen and Allergen. AK Gupta has also served as a speaker for Valeant Canada, Janssen and Bayer. FC Simpson is an employee of Mediprobe Research, Inc., which conducts clinical trials. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.



## Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Zaias N. Onychomycosis. Arch Dermatol 1972;105(2):263-74
2. Welsh O. Onychomycosis. Clin Dermatol 2010;28(2):151-9
3. Baran R. The nail in the elderly. Clin Dermatol 2011;29(1):54-60
4. Gupta AK, Konnikov N, MacDonald P, et al. Prevalence and epidemiology of toenail onychomycosis in diabetic subjects: a multicentre survey. Br J Dermatol 1998;139(4):665-71
5. Gupta AK, Humke S. The prevalence and management of onychomycosis in diabetic patients. Eur J Dermatol 2000;10(5):379-84
6. Gupta AK, Gupta MA, Summerbell RC, et al. The epidemiology of onychomycosis: possible role of smoking and peripheral arterial disease. J Eur Acad Dermatol Venereol 2000;14(6):466-9
7. Gupta AK, Taborda P, Taborda V, et al. Epidemiology and prevalence of onychomycosis in HIV-positive individuals. Int J Dermatol 2000;39(10):746-53
8. Bakr NI, El-Sawy E, Hamdy AF, Bakr MA. Skin infections in Egyptian renal transplant recipients. Transpl Infect Dis 2011;13(2):131-5
9. Döner N, Yaşar Ş, Ekmekçi TR. Evaluation of obesity-associated dermatoses in obese and overweight individuals. Turkderm 2011;45(3):146-51
10. Gupta AK, Simpson FC. Investigational drugs for onychomycosis. Expert Opin Investig Drugs 2014;23(1):97-106
11. Gupta AK, Paquet M, Simpson FC. Therapies for the treatment of onychomycosis. Clin Dermatol 2013;31(5):544-54
12. Novartis. LAMISIL (terbinafine hydrochloride) Tablets, 250 mg [Internet]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020539s021lbl.pdf
13. Tosti A, Piraccini BM, Stinchi C, Colombo MD. Relapses of onychomycosis after successful treatment with systemic antifungals: a three-year follow-up. Dermatology 1998;197(2):162-6
14. Arrese JE, Piérard GE. Treatment failures and relapses in onychomycosis: a stubborn clinical problem. Dermatology 2003;207(3):255-60
15. Pierard GE, Pierard-Franchimont C, Arrese JE. The boosted antifungal topical treatment (BATT) for onychomycosis. Med Mycol 2000;38(5):391-2
16. Pierard GE. Spores, sporodochia and fomites in onychomycosis. Dermatology 2006;213(2):169-72
17. Sigurgeirsson B, van Rossem K, Malahias S, Raterink K. A phase II, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study to investigate the efficacy and safety of 4 dose regimens of oral albaconazole in patients with distal subungual onychomycosis. J Am Acad Dermatol 2013;69(3):416-25

•• **Phase II trial for albaconazole.**

18. Schering Plough. NOXAFIL® (Posaconazole) oral suspension 40 mg/mL [Internet]. 2012. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022003s011s012,022027s002s003lbl.pdf
19. Elewski B, Pollak R, Ashton S, et al. A randomized, placebo- and active-controlled, parallel-group, multicentre, investigator-blinded study of four treatment regimens of posaconazole in adults with toenail onychomycosis. Br J Dermatol 2012;166(2):389-98
20. Valeant Pharmaceuticals. JUBLIA® (efinaconazole) topical solution, 10% [Internet]. 2014. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/203567s000lbl.pdf
21. Valeant Canada LP. PrJUBLIATM Efinaconazole Topical Solution, 10% w/w. 2013
22. Tschen EH, Bucko AD, Oizumi N, et al. Efinaconazole solution in the treatment of toenail onychomycosis: a phase 2, multicenter, randomized, double-blind study. J Drugs Dermatol 2013;12(2):186-92
23. Elewski BE, Rich P, Pariser DM, 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(4):600-8

•• **Pivotal trial for efinaconazole.**

24. Sigurgeirsson B, Ghannoum M. Therapeutic potential of TDT 067 (terbinafine in Transfersome®): a carrier-based dosage form of terbinafine for onychomycosis. Expert Opin Investig Drugs 2012;21(10):1549-62

25. Ghannoum M, Isham N, Herbert J, et al. Activity of TDT. 067 (Terbinafine in Transfersome) against agents of onychomycosis, as determined by minimum inhibitory and fungicidal concentrations. J Clin Microbiol 2011;49(5):1716-20

26. Dominicus R, Weidner C, Tate H, Kroon H-A. Open-label study of the efficacy and safety of topical treatment with TDT 067 (terbinafine in Transfersome®) in patients with onychomycosis. Br J Dermatol 2012;166(6):1360-2

27. Anacor Pharmaceuticals, Inc. KERYDIN (TM) (tavaborole) topical solution, 5% [Internet].
2014. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails

28. Rock FL, Mao W, Yaremchuk A, et al. An antifungal agent inhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site. Science 2007;316(5832):1759-61

29. Zane L, Pollak R. Safety and efficacy of tavaborole (Formerly AN2690), a novel boron-based molecule, in phase 2 trials for the topical treatment of toenail onychomycosis [Internet]. Anacor Pharmaceuticals, Washington, DC; 2012. Available from: http://www.anacor.com/pdf/APMA%20Tavaborole%20Phase%202%20Poster.pdf [Cited 11 April 2013]

- **Phase II trial for tavaborole.**

30. Harris F, Pierpoint L. Photodynamic therapy based on 5-aminolevulinic acid and its use as an antimicrobial agent. Med Res Rev 2012;32(6):1292-327

31. Galderma Labs. METVIXIA® (methyl aminolevulinate) Cream, 16.8% [Internet].
2004. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021415s004lbl.pdf

32. Kamp H, Tietz H-J, Lutz M, et al. Antifungal effect of 5-aminolevulinic acid PDT in trichophyton rubrum. Mycoses 2005;48(2):101-7

33. Watanabe D, Kawamura C, Masuda Y, et al. Successful treatment of toenail onychomycosis with photodynamic therapy. Arch Dermatol 2008;144(1):19-21

34. Piraccini BM, Rech G, Tosti A. Photodynamic therapy of onychomycosis caused by Trichophyton rubrum. J Am Acad Dermatol 2008;59(5 Suppl):S75-6

35. Gilaberte Y, Aspiroz C, Martes MP, et al. Treatment of refractory fingernail onychomycosis caused by nondermatophyte molds with methylaminolevulinate photodynamic therapy. J Am Acad Dermatol 2011;65(3):669-71

36. Sotiriou E, Koussidou-Eremonti T, Chaidemenos G, et al. Photodynamic therapy for distal and lateral subungual toenail onychomycosis caused by Trichophyton rubrum: preliminary results of a single-centre open trial. Acta Derm Venereol 2010;90(2):216-17

37. Silva AP, Kurachi C, Bagnato VS, Inada NM. Fast elimination of onychomycosis by hematoporphyrin derivative-photodynamic therapy. Photodiagn Photodyn Ther 2013;10(3):328-30

38. Souza LW, Souza SV, Botelho AC. Distal and lateral toenail onychomycosis caused by Trichophyton rubrum: treatment with photodynamic therapy based on methylene blue dye. An Bras Dermatol 2014;89(1):184-6

39. Souza LW, Souza SV, Botelho AC. Endonyx toenail onychomycosis caused by Trichophyton rubrum: treatment with photodynamic therapy based on methylene blue dye. An Bras Dermatol 2013;88(6):1019-21

40. Mehra T, Schaller M, Walker B, et al. Efficacy of antifungal PACT in an in vitro model of onychomycosis. J Eur Acad Dermatol Venereol 2014. [Epub ahead of print]

41. Pinpointe USA. 510(k) Summary K093547. PinPointe FootLaser, Pinpointe USA, Inc. [Internet] 2010. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf9/K093547.pdf

42. Kozarev J, Vižintin Z. Novel laser therapy in treatment of onychomycosis. J Laser Health Acad 2010;2010(1):1-8

43. Kozarev J. Clearsteps – laser onychomycosis treatment: assessment of efficacy 12 months after treatment and beyond. J Laser Health Acad 2011;2011(1):S07

44. Harris DM, McDowell BA, Strisower J. Laser treatment for toenail fungus. Proc SPIE 2009;7161:71610M1-7

45. Weiss D. 3 month clinical results using sub-millisecond 1064 nm Nd:YAG laser for the treatment of onychomycosis [Internet].
2011. Available from: http://conejofeet.com/wp-content/uploads/2011/06/David-Weiss-DPM-report.pdf

46. Hochman LG. Laser treatment of onychomycosis using a novel 0.65-millisecond pulsed Nd:YAG 1064-nm laser. J Cosmet Laser Ther 2011;13(1):2-5

47. Kimura U, Takeuchi K, Kinoshita A, et al. Treating onychomycoses of the toenail: clinical efficacy of the sub-millisecond 1,064 nm Nd: YAG laser using a 5 mm spot diameter. J Drugs Dermatol 2012;11(4):496-504

48. Waibel J, Rudnick A, Wulkan AJ. Prospective efficacy and safety evaluation of laser treatments with real-time temperature feedback for fungal onychomycosis. J Drugs Dermatol 2013;12(11):1237-42

49. Carney C, Cantrell W, Warner J, Elewski B. Treatment of onychomycosis using a submillisecond 1064-nm neodymium:yttrium-aluminum-garnet laser. J Am Acad Dermatol 2013;69(4):578-82

50. Noguchi H, Miyata K, Sugita T, et al. Treatment of onychomycosis using a 1064nm Nd:YAG laser. Med Mycol J 2013;54(4):333-9

51. Moon SH, Hur H, Oh YJ, et al. Treatment of onychomycosis with a 1,064-nm long-pulsed Nd:YAG laser. J Cosmet Laser Ther 2014;16(4):165-70

52. Gupta AK, Paquet M. A retrospective chart review of the clinical efficacy of Nd:YAG 1064-nm laser for toenail onychomycosis. J Dermatolog Treat 2014;5:1-3

53. Ortiz AE, Truong S, Serowka K, Kelly KM. A 1,320-nm Nd: YAG laser for improving the appearance of onychomycosis. Dermatol Surg 2014;40(12):1356-60

54. Gupta AK, Simpson FC. Laser therapy for onychomycosis. J Cutan Med Surg 2013;17(5):301-7

55. Bristow IR. The effectiveness of lasers in the treatment of onychomycosis: a systematic review. J Foot Ankle Res 2014;7:34

56. Light Age, Inc. 510(k) Summary K110370. Q-Clear, Light Age [Internet]. 2011. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf11/K110370.pdf

57. Kalokasidis K, Onder M, Trakatelli M-G, et al. The effect of Q-switched Nd:YAG 1064 nm/532 nm laser in the treatment of onychomycosis in vivo. Dermatol Res Pract 2013;2013:1-10

58. Galvan Garcia HR. Onychomycosis: 1064-nm Nd:YAG q-switch laser treatment. J Cosmet Dermatol 2014;13(3):232-5

- **Clinical trial for Q-switched vs. short pulse laser.**

59. Murdan S. Enhancing the nail permeability of topically applied drugs. Expert Opin Drug Deliv 2008;5(11):1267-82

60. Del Rosso JQ. The role of topical antifungal therapy for onychomycosis and the emergence of newer agents. J Clin Aesthet Dermatol 2014;7(7):10-18

61. Pariser DM, Pollak R, Pillai R, Olin JT. Efinaconazole topical solution may reach the onychomycosis infection site by spreading through the space between the nail plate and nail bed. MauiDerm NP+PA Fall Meeting, Boston, MA; 2014

- **Subungual route of delivery for efinaconazole.**

62. De Assis Santos D, de Carvalho Araújo RA, Kohler LM, et al. Molecular typing and antifungal susceptibility of Trichophyton rubrum isolates from patients with onychomycosis pre- and post-treatment. Int J Antimicrob Agents 2007;29(5):563-9

63. Gupta AK, Kohli Y. Evaluation of in vitro resistance in patients with onychomycosis who fail antifungal therapy. Dermatology 2003;207(4):375-80

64. Mukherjee P, Leidich S, Isham N, et al. Clinical Trichophyton rubrum strain exhibiting primary resistance to terbinafine. Antimicrob Agents Chemother 2003;47(1):82-6

## Affiliation

Aditya K Gupta[†1,2] MD PhD FAAD FRCPC & Fiona C Simpson[1]
[†]Author for correspondence
[1]Mediprobe Research, Inc., 645 Windermere Rd, London, ON, N5X 2P1, Canada
Tel: +1 519 851 9715;
Fax: +1 519 657 4233;
E-mail: agupta@execulink.com
[2]University of Toronto, Department of Medicine, Toronto, ON, Canada