

EXPERT OPINION

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New pharmacotherapy for the treatment of onychomycosis: an update

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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

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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

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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 aminolevulinic acid

The photosensitizers aminolevulinic acid (ALA) and methyl aminolevulinic acid (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/cm². 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/cm², 3100 mW/cm², 100 mW/cm²). 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/cm² 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 α -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 (%)
<i>Long-pulsed laser systems</i>													
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%	-
<i>Short-pulse laser systems</i>													
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%
<i>Q-switched laser systems</i>													
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., 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, Merck, Novartis, Janssen and Allergan. 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.

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