

# ONYCHOMYCOSIS: A Review of New and Emerging Topical and Device-based Treatments

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## ABSTRACT

Onychomycosis is a challenging nail condition to treat. The gold standard treatment relies on long-term systemic therapy, which carries risks of potential side effects and drug interactions. Topical alternatives exist; however, treatment outcomes remain disappointing. In this article, we review newer topical formulations that are approved by the United States Food and Drug Administration, as well as other topical drugs that are still undergoing clinical trials. Lasers and energy-based devices have also been used for the treatment of onychomycosis; however, standardized parameters and clear treatment endpoints have yet to be specified. Currently, device-based therapies are considered as options for improving the cosmetic appearance of nails. The use of lasers to improve the penetration of topical antifungal treatments as possible combination treatments is also reviewed.

**KEYWORDS:** Antifungal, fungus, laser, nail, onychomycosis

Onychomycosis is estimated to affect 5.5 percent of the world's population.<sup>1</sup> Onychomycosis can be painful and have significant psychosocial effects, negatively impacting quality of life.<sup>2</sup> Fungal pathogens disrupt the integrity of the skin by means of scaling and fissure formation. These pathogens typically start by penetrating at the distal end of the nail bed, causing distal subungual onychomycosis, which is the most common form of fungal nail disease. Less frequently, infection at the surface of the nail plate can lead to white superficial onychomycosis; invasion near the cuticle can result in proximal subungual onychomycosis; and candidal infections of the nail can occur in case of human immunodeficiency virus and decreased immunity. This allows for penetration of pathogenic bacterial species, thus predisposing the patient to infections and cellulitis.<sup>3</sup> Risk factors for onychomycosis include age, peripheral vascular disease, diabetes, and immunosuppression.<sup>4</sup>

Various treatment modalities are available for onychomycosis. While mild (<20% nail involvement) and moderate (20%–60% nail involvement) forms of onychomycosis can benefit from topical therapies, severe cases require systemic antifungals. Nevertheless, long-term treatment success rates vary widely and relapse rates remain high.<sup>1,4</sup>

Currently, a 12-week course of oral terbinafine is considered the gold standard for the treatment of onychomycosis. However, the complete cure rate at 36 weeks after the completion

of terbinafine in the original approval study was reported to be only 38 percent, and the great toenail alone was used for outcomes assessments.<sup>5</sup> There are studies that report cure rates ranging from 14 to 90 percent with oral terbinafine for onychomycosis.<sup>6</sup> This range could be due to different parameters and outcomes measures used to evaluate cure rates.

Treatment failure with oral and topical antifungals is thought to be multifaceted.<sup>7</sup> While patient factors such as age, health status, adherence, and polypharmacy play a role in long-term clearance, drug and fungal properties are also responsible. For example, in a study assessing residual drug content of nail clippings after oral treatment cessation, the clippings showed persistence of drug levels for months after the cessation of systemic treatment.<sup>1</sup> A large discrepancy exists when comparing *ex-vivo* drug studies for fungal susceptibility to those with *in-vivo* results. In *ex-vivo* experiments, antifungal drugs tend to demonstrate much higher positive outcomes typically not seen when evaluating the efficacy of these drugs *in-vivo*.<sup>8</sup> The variation in outcomes can be due to multiple factors, including drug bioavailability, penetration, local actions by keratin, and fungal behavior at the site of infection. A study showed that terbinafine affinity to keratin reduced the bioavailability and ability to target fungus in the nail bed.<sup>9</sup> In the study by Ghannoum et al,<sup>9</sup> the drug was found to be sequestered within the nail plate, thus reducing its efficacy *in vivo*. Despite

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**TABLE 1.** Endpoints for treatment success

Antifungal medications	
Clinical cure	Complete nail clearance* or <10% nail still affected
Mycological cure	Negative culture** and negative microscopy
Complete cure	Clinical cure and mycological cure
Device-based treatment (assessed at six months after the first treatment)	
Fingernails	≥12-mm increase in clear nail, 90mm <sup>2</sup> of new clear nail growth (based on the width of the first toenail), or complete clearance if <12mm of distal nail was involved prior to treatment
Toenails	≥6-mm increase in clear nail, 60mm <sup>2</sup> of new clear nail growth (based on width of the first toenail), or complete clearance if <6mm of the distal nail was involved prior to treatment

\*Clear nail is defined as area from proximal nail fold till most proximal area of abnormality with evidence of persistent clear growth.  
Clearance must be progressively observed over two time points.  
\*\*Negative culture is defined by negative potassium hydroxide (KOH) test

changes in drug formulation to allow for better nail penetration, the drugs still appear to be less effective than expected. Fungal growth patterns within the nail and spore formation also lead to less favorable outcomes *in vivo*. The slow growth rate of nails further contributes to suboptimal treatment outcomes, as a high fungal load is harbored within the affected nail.

The assessment of treatment efficacy follows specified endpoints (Table 1). While some studies rely on subjective clinical cures, others are more objective, relying on mycological or complete cures. Additionally, while many studies utilize the great toenail as a targeted therapeutic site to evaluate complete cure rate, others include the remaining nails as well. Given the lower responsiveness of the great toenail compared to the other toenails, therapeutic responsiveness might appear higher when all nails are included, and therefore, must be considered when evaluating drug efficacy.<sup>6</sup> For example, in the case of oral terbinafine, the complete cure rate using the great toenail alone as the therapeutic response site was reported to be 23 percent,

while the cure rates when considering the second, third and fourth toenails in the same study were 65, 51, and 67 percent, respectively.<sup>6</sup>

Designated endpoints and selected target nails should be considered judiciously when comparing study results. Here, we provide a review on the uses and outcomes of new and upcoming topical therapies and energy-based devices for the treatment of distal subungual onychomycosis.

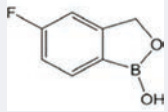
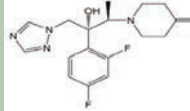
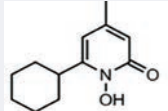
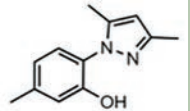
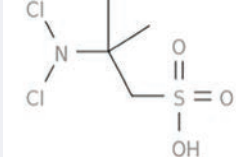
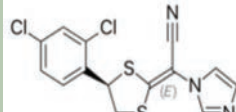
### TOPICAL ANTIFUNGALS

Numerous topical treatments are available in the form of nail lacquers or solutions, but the efficacy of these treatments remains low. Up until 2014, ciclopirox, which has been shown to have efficacy against both dermatophytes and yeast, was the only topical antifungal approved by the United States Food and Drug Administration (FDA) for the treatment of onychomycosis.<sup>10,11</sup> It was postulated that the inability of the drug to penetrate the hard nail plate hinders clinical efficacy, leading to its poor overall performance.<sup>10,11</sup> Therefore, the penetration capacity of ciclopirox with and without added diffusion enhancers was assessed in various studies. In one study using an *ex-vivo* experimental setup, it was demonstrated that ciclopirox reached sufficiently high concentrations within healthy nails, especially when using oil-based diffusion enhancers.<sup>12,13</sup> The limitations of this study were the use of nondiseased nails in an *ex-vivo* system. In another study, using *ex-vivo* models of diseased nails to evaluate fungicidal and fungistatic activity of ciclopirox against *Trichophyton mentagrophytes* (*T. mentagrophytes*) in the presence of keratin powder, it was shown that the drug was not active.<sup>14</sup> Under these conditions, the drug was not able to kill the fungal pathogens in the same way that it did in the absence of keratin, indicating, aside from optimal penetration into the nail plate and strong antifungal activity *ex vivo*, that the drug also needs to function within the infected nail in the presence of keratin. For that reason, newer antifungal options aim to achieve higher efficacy by making use of a combination of factors, such as good penetration, new low surface tension formulations, lower keratin affinity, and alternative mechanisms of action.<sup>14</sup> As a result, the efficacy of these novel drugs is often compared to ciclopirox as a reference. Table 2 summarizes the newer topical antifungals, with a focus on their mechanism of action and efficacy.

**Efinaconazole.** Efinaconazole (Jublia 10% solution; Ortho-Dermatologics, Bridgewater, New Jersey) is a topical imidazole active against dermatophytes and yeasts. It received FDA approval in 2014.<sup>15</sup> Having a low affinity for keratin, this drug is able to penetrate the nail plate easily and selectively target pathogenic fungi.<sup>15</sup> Despite having a higher molecular weight than ciclopirox, its low surface tension is thought to allow better penetration.<sup>11</sup> Once within the nail, efinaconazole is observed to have a better efficacy than what was noted for ciclopirox. In fact, the same *ex-vivo* infection model using keratin powder demonstrated complete eradication of *T. mentagrophytes* at concentrations of 5 and 20mcg/mL.<sup>13</sup> Studies using a fluorescein vehicle showed that a single application of efinaconazole to the hyponychium was able to reach the site of infection at the nail bed and underside of the nail plate.<sup>17</sup> Further studies were also conducted in cadaveric nails following the application of nail polish. In this case, the drug was able to penetrate the nail without disrupting the polish, resulting in a similar concentration as seen in control specimens free of polish.<sup>18,19</sup>

**Tavaborole.** Tavaborole (Kerydin, 5% solution; PharmaDerm, Princeton, New Jersey) is a boron-based antifungal containing oxaborole molecules approved in 2014. The increased affinity for fungal enzymes allows the drug to be selective against the pathogen without interfering with host protein synthesis. It is indicated for the treatment of onychomycosis caused by *T. rubrum* and *T. mentagrophytes*; however, it is also effective against an array of less commonly encountered pathogens, such as yeast.<sup>20</sup> The low molecular weight of tavaborole allows for easy nail penetration.<sup>21</sup> Drug levels in the nail remain high even at three months after treatment cessation. Using liquid chromatography and mass spectrometry, *ex-vivo* cadaveric nail studies showed significantly higher drug penetration of tavaborole compared to ciclopirox.<sup>22</sup> Moreover, studies evaluating the effects of nail polish on drug penetration determined that the presence of nail polish did not hinder the transungual delivery of tavaborole and might even enhance it.<sup>23</sup> Despite the concern of boron-related toxicity, tavaborole appears to have an excellent safety profile, showing no cytochrome enzyme inhibition and negligible plasma levels after topical use.<sup>22</sup> Rodent studies assessing potential carcinogenic effects also determined that the product was suitable for long-term use in humans.<sup>22</sup>

**TABLE 2.** Topical antifungals treatments

DRUG NAME (TRADE NAME)	REGIMEN	STRUCTURE	MECHANISM OF ACTION	MOLECULAR WEIGHT (G/MOL)	REPORTED CURE RATE (%)
Tavaborole (Kerydin)	Solution applied daily for 48 weeks		Inhibition of fungal protein synthesis by binding to cytoplasmic leucyl-tRNA	151.93	Mycologic: 30–36 Complete: 6–10
Efinaconazole (Jublia)	Solution applied daily for 48 weeks		Blocking of ergosterol synthesis by inhibition of lanosterol 14- $\alpha$ -demethylase	348.39	Mycologic: 53.4–55.2 Complete: 15.2–17.8
Ciclopirox (Penlac)	Nail lacquer Debridement + daily application		Chelation of metal cations needed as enzyme cofactors Modification of fungal plasma membrane of fungi	207.27	Mycologic: 29–36 Complete: 5.5–8.5
ME 1111	TBD		Targeting of fungal electron transport chain at complex II	202.25	TBD
Auriclosene	TBD		Protein inactivation via modification of sulfur-containing amino acids	222.08	TBD
Luliconazole	TBD		Inhibition of ergosterol synthesis Inhibition of extracellular protease secretion	354.28	Mycologic: 53.4–55.2 Complete: 14.9

TBD: To be determined

### OTHER TOPICAL ONYCHOMYCOSIS TREATMENTS UNDER INVESTIGATION

**Auriclosene.** NVC 422 (auriclosene) is a broad-spectrum antibacterial and antifungal agent belonging to a family of compounds known as aganocides.<sup>24</sup> Current clinical studies are focusing mainly on the treatment of impetigo, conjunctivitis, and urinary catheter infections (clinicaltrials.gov; NCT00781339, NCT01532336, NCT01367314, NCT01243125, NCT01877694). However, preclinical studies have assessed its utility in the treatment of onychomycosis; an *in-vitro* evaluation on a cadaveric model utilized nanoemulsion

lacquers and gel formulations to assess the growth inhibition of dermatophytes, which showed significant drug penetration and fungal eradication.<sup>25</sup>

**ME1111.** ME1111 is a fungicidal compound effective against dermatophytes, reaching sufficiently high concentrations in the nail to overcome the minimum inhibitory concentration (MIC) of these organisms.<sup>26</sup> The ability of this drug to exert antifungal activity in the presence of keratin has not been assessed. However, the effect of ME1111 showed selective toxicity to the fungal organisms.<sup>27</sup> Phases I and II clinical trials

assessing the pharmacokinetics and safety of ME1111 were recently completed, but results have not been published yet (Table 3).

**Luliconazole.** Luliconazole is an imidazole antifungal with an added ketone dithioacetate component. In spite of its higher molecular weight, a modified molecular structure endows this novel antifungal with lower keratin affinity and, in turn, potentially improved potency.<sup>28</sup> This drug is FDA-approved in a cream formulation for the treatment of fungal infections of the skin. Studies pertaining to onychomycosis used solutions of 5% applied daily for 48 weeks and assessed outcomes at the end of the treatment

**TABLE 3.** Registered clinical trials investigating novel onychomycosis treatments

TREATMENT	CLINICALTRIALS.GOV IDENTIFICATION NO.
ME1111	NCT01841996 NCT02022215
MOB-015	NCT02866032 NCT02859519 NCT01246518 NCT03244280 NCT01814020
P-3058	NCT02549001 NCT02547701 NCT03094468
HTU-520	NCT01400594
TDT 067	NCT01145807 NCT01790165

course;<sup>29</sup> at this concentration, randomized control studies showed similar efficacy for Luliconazole and other approved topical treatments, reporting around a 14.9 percent complete cure rate. A 10% solution was tested for safety and tolerability; however, it has not yet been assessed for treatment efficacy.<sup>30</sup>

#### Non-oral terbinafine alternatives.

Given the well-known efficacy of terbinafine, novel formulations of the drug are also being evaluated. This includes topical, transungual routes, and patches (MOB-015, P-3058, and HTU-520, respectively; Table 3). Additionally, compounding terbinafine with new vehicles such as transferosome (TDT 067) is also being investigated as these lipid vesicles are thought to allow improved transport through the nail barrier.<sup>11,31</sup>

**Summary.** Although the aforementioned drugs provide alternatives to systemic treatments, optimal efficacy has not yet been achieved. Due to the thick keratin structure of the onychomycotic nail, drugs must be able to effectively penetrate the nail plate in order to reach the deeper site of infection.<sup>14</sup> Nevertheless, reaching mycological MIC is insufficient for efficacy given the potential interaction between drugs and the keratinized structure.<sup>14</sup> Higher concentrations might be needed before the drug is able to act *in vivo* as it does *ex vivo*. Furthermore, penetration studies focusing on healthy nails fail to consider morphological changes accompanying the diseased nail, such as increased porosity and hyperkeratosis.<sup>13,18</sup> These factors warrant potential

changes in how drugs are evaluated. Additionally, the propensity of fungal organisms to move to a spore stage makes them resistant to treatment. A better method of targeting spores within the nail plate is needed to eradicate the disease.

#### LASER TREATMENT

Lasers are widely used in the field of dermatology for the treatment of various skin conditions. Difficulties associated with topical treatments and high side effect profile linked to oral therapies have led researchers to test laser treatments as a novel therapy for onychomycosis. These are only FDA-approved for cosmetic endpoints and are judged based on the ability to “temporarily increase the amount of clear nail.”<sup>32</sup> Various lasers have been used for the treatment of onychomycosis. We have summarized some of the major laser modalities, treatment regimens, and outcomes in Table 4. Given the lack of standardized parameters, expected clinical outcomes vary from one study to the next, and therefore, cannot be generalized.

**Neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers.** The utility of laser treatments is thought to rely on heat transfer to fungal mycelium, reaching fungicidal temperatures of 43°C to 51°C for 2 to 3 minutes; lower temperatures can lead to stimulation of fungal growth.<sup>33</sup> Such high temperatures can promote increased local circulation and ultimately strengthen the body’s natural immunological response.<sup>33</sup> The heat-induced mitochondrial production of reactive oxygen species within the fungal pathogens also pushes these cells to undergo apoptosis.<sup>32</sup> Within the fungal cell, target chromophores are thought to be melanin for the 1,064-nm Q-switched Nd:YAG laser, and xanthomegnin in the case of the 532-nm Q-switched Nd:YAG laser. Currently, long-pulsed Nd:YAG is one of the most commonly used laser modalities for onychomycosis.<sup>33</sup> Nevertheless, it does not have a clearly specified optimized treatment regimen. While some studies suggest weekly treatments, others recommend one-month intervals.<sup>34–39</sup> The number of total sessions required ranges from 3 to 8, with 2 to 3 passes performed each time depending on operator preference and experience.<sup>34–39</sup> Treatment parameters, such as wavelengths, spot sizes, fluence, and pulse duration differ also in various studies, suggesting that the laser effect is not chromophore-dependent.<sup>34–36</sup> Some studies evaluating the utility of Nd:YAG relied solely

on the laser treatment, while others called for concomitant antifungal use or pretreatment with keratolytics in cases of dystrophic nails.<sup>37–39</sup> In spite of the FDA’s preset definition of treatment success, this is defined differently from one study to the next, making adequate comparisons difficult. Most patients undergoing laser treatments for onychomycosis noted that multiple treatments were needed before any visible improvements could be observed.<sup>36–39</sup> With regard to safety and tolerability, patients noted mild burning or pain during the sessions; however, such did not prevent them from continuing treatment.<sup>36,37</sup>

**Fractional CO<sub>2</sub> lasers.** The mechanism of action of this laser modality is thought to be twofold: it can lead to fungal cell injury and death by photothermal effect and can also create pores in the nail plate, allowing for better penetration of combined topical treatments.<sup>33</sup> Again, the optimal number and frequency of treatment sessions and selected parameters have not been established, and are thus selected based on operator experience. For the most part, terbinafine is the combined topical treatment of choice, with few studies evaluating the utility of other agents.<sup>35,40</sup> Although early results are promising, studies that included longer follow-up posttreatment periods reported significant relapse rates.<sup>33</sup>

**Other laser treatments under consideration.** Near-infrared diode laser application is thought to achieve a cure via its thermal effect on the fungal pathogen, increasing the amount of reactive oxygen species and ultimately leading to apoptosis.<sup>33</sup> A dual-wavelength 870-/930-nm laser at 4,074 J/cm<sup>2</sup> was tried for four sessions and showed complete irradiation of both bacteria and yeasts.<sup>41</sup>

Nonthermal low-level laser devices have also been tested for the treatment of onychomycosis in toenails. This method employs 635-/405-nm dual-diode laser application. Although the mechanism of action is not clearly understood, it is thought to involve photobiomodulation leading to increased cellular respiration. For the time being, the only published data are from a retrospective study sponsored by the laser developer and used for FDA approval procedures.<sup>42</sup>

#### CONCLUSION

Ideally, treatments for onychomycosis should boast effective nail penetration and broad-spectrum antifungal activity within the nail, with



TABLE 4: Energy-based onychomycosis treatments

TREATMENT MODALITY	ARTICLE REFERENCE	PARAMETERS	NUMBER OF TREATMENTS (INTERVAL)	ADDITIONAL TREATMENTS	REPORTED CURE RATES
Nd:YAG	Kalokasidis et al <sup>36</sup>	First pass: 1,064nm, 14 J/cm <sup>2</sup> Second pass: 532nm, 14 J/cm <sup>2</sup>	2 (4 weeks)	None	At one month • Mycological: 95.4% • Clinical: 10.6% women, 5.4% of men No long-term results
	Hochman et al <sup>37</sup>	2 passes: 1,064nm, 223 J/cm <sup>2</sup> , no cooling	2–3 (3 weeks)	Antifungal cream	After last treatment: • Mycological: 87.5% No long term results
	Okan et al <sup>38</sup>	2 passes: 1,064nm, 40–60 J/cm <sup>2</sup>	4 (1 week)	40% urea cream under occlusion 1 week pretreatment	At 6 months: • Mycological: 60% • Clinical: 47%
	Carney et al <sup>39</sup>	1,064nm, 16 J/cm <sup>2</sup>	4 (1 week) + single additional session at Week 7	Topical antifungal	At 15 weeks: • Mycological: 42.8% At 24 weeks: • 33% recurrence
Fractional CO <sub>2</sub>	Bhatta et al <sup>33</sup>	2–6 passes : E=9 mJ, 410 spot/ cm <sup>2</sup>	3 (4 weeks)	1% terbinafine cream daily for 3 months	At last treatment: • Mycological: 92%–94.6% At 6 months: • Mycological: 80%–84%
	Shi et al <sup>40</sup>	Multiple passes: E=15 mJ, 15% spot density	12 (2 weeks)	1% terbinafine cream daily, under occlusion overnight for 6 months	At last treatment: • Clinical: 58.87% At 3 months: • Mycological: 74.19% • Clinical: 68.55%
Nonthermal	Zang et al <sup>42</sup>	635-/405-nm dual-diode laser	4 (1 week)	None	At 6 months: • Clinical: 67%
Near infrared light	Landsman et al <sup>41</sup>	4,074 J/cm <sup>2</sup> , 870 and 930 nm	Treatments at Days 1, 14, 42, and 120	None	At 2 months: • Clinical: 65%

\*Clinical cure refers to >75% nail clearance or > 3mm of clear nail growth

convenient dosing and limited side effects. This should translate into high overall cure rates and longer effectiveness.

Novel topical and device-based treatments for onychomycosis have brought forth possible alternatives to systemic therapy. The efficacy of these options remains questionable, as cure rates are often still low compared to current standards of care. It is important to note that, currently, very few studies offer a head-to-head, *in-vivo* comparison of available topical treatments. As a result, reviews of the literature are suboptimal due to the differing treatment endpoints between the various studies. Even when comparing clinical cure, for instance, while some trials consider complete clearance of the nail as the desired goal, others consider clearance of a given percentage of the affected nail (<5%–10%) to be acceptable. Additionally, nonadherence to long treatment courses and daily applications can also hinder

the clearance process, so adherence to treatment must be considered.

Laser-based treatments are only considered for cosmetic improvements and not for treatment; thus, their addition to the market offers new challenges in the assessment of improvements. For this reason, treatment success in the setting of laser application is not comparable to that achieved with standard therapies. Variations in laser parameters, treatment frequency, and causative pathogens lead to differences in perceived outcomes. Further standardized treatment regimens are required before the utility of these lasers can truly be evaluated.

Although some studies have evaluated the combination of topical treatments and laser therapy, no such data exist for the novel antifungals. Despite the ability of efinaconazole and tavaborole to better penetrate the nail plate, it is not clear whether thermal injury or

microhole creation would act synergistically with this process. Additionally, the effects of thermal injury on fungal spores should also be evaluated, as eradication of these might improve outcomes if combined with effective fungicidal topical therapies.

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