Anthem

Medical Policy

Subject: Laser Treatment for Onychomycosis
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Description/Scope

This document addresses the proposed use of laser treatment for onychomycosis. Onychomycosis is a common and persistent fungal infection of the nail bed and plate, which is often challenging to treat. Conventional therapeutic options include topical or systemic antifungal agents; however, topical therapies are seldom effective since it is difficult to achieve local therapeutic concentrations, and individual adherence to long-term therapy is low. Systemic antifungal agents, while more effective, with approximately 50% of individuals achieving significant improvement or cure, are associated with higher rates of complications, including liver and kidney damage in some individuals with comorbidities. As a result, laser treatment has been introduced as an alternative, noninvasive treatment modality.

Position Statement

Investigational and Not Medically Necessary:

Laser treatment of onychomycosis is considered **investigational and not medically necessary.**

Rationale

Multiple randomized controlled trials (RCTs) have evaluated laser treatment for onychomycosis. Most RCTs have used neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers; RCTs have also evaluated a near infrared diode laser (Landsman, 2010; Landsman 2012) and a carbon dioxide (CO_2) laser (Rajbanshi, 2020). In the trials, lasers were compared with no laser treatment (Hollmig, 2014; Kandpal, 2021; Karsai, 2017), sham treatment (Landsman 2010; Landsman 2012) and oral or topical antifungal treatment (Bonhert, 2018; Kim, 2016; Park, 2017; Xu, 2014). In the Zhang, 2012 RCT, all individuals underwent laser treatment, but duration of therapy varied. Several RCTs also included groups receiving a combination of laser and oral or topical treatment (Bonhert, 2018; Kim, 2016; Park, 2017; Xu, 2014). Sample sizes in the RCTs ranged from 20 to 128 individuals.

Findings of the trials were mixed. Several trials (Hollmig, 2014; Karsai, 2017; Sabbah, 2019) did not find statistically significant differences between the Nd:YAG laser treatment and comparison groups in their key efficacy outcomes. Other RCTs found significantly better results in groups receiving laser therapy compared with comparison interventions on at least some clinical outcomes.

Sabbah (2019) conducted a double-blind RCT comparing treatment with Nd:YAG 1064 nm short-pulse lasers and sham in 51 individuals with toenail onychomycosis. Individuals received treatments at 0, 12 and 24 weeks. The primary endpoint was the proportion of individuals with complete cure, defined as clear nail and negative mycology, at 52 weeks. The primary endpoint was achieved by none of the individuals in the laser group and 2 (7.7%) individuals in the sham group, p=0.49. Secondary endpoints also did not differ significantly between groups. For example, 24% of individuals in the laser group and 42% of individuals in the sham group had negative mycology at 52 weeks, p=0.17. In conclusion, the study demonstrated that laser was not effective in treating onychomycosis, with results actually trending in favor of placebo sham laser.

Bonhert (2018) did not find a significant difference between groups in the primary outcome, complete cure, but did find a significant benefit of laser therapy for the outcome, improvement in onychomycosis. The trial randomized 30 individuals with toenail onychomycosis to treatment with 48 weeks of daily topical antifungal solution or antifungal solution plus 6 sessions of a 1064 nm Nd:YAG laser spaced 4 weeks apart. Outcome evaluation was blinded and all participants completed the study. The primary outcome was complete cure at week 52, defined as negative mycological culture, negative potassium hydroxide (KOH) test and no nail onychomycosis. The primary outcome did not differ significantly between groups. At 52 weeks, there were no statistically significant differences between groups in mycological cure or KOH test results and thus the proportion of individuals experiencing complete cure did not differ. Onychomycosis severity was assessed by a 30-point Scoring Clinical Index for Onychomycosis (SCIO Index). The laser group had significantly lower SCIO scores at weeks 36, 48 and 52 compared with the comparison group. Moreover, overall improvement rated by blinded investigators was significantly higher in the laser group at 48 and 52 weeks.

Combination therapy, lasers plus oral or topical antifungals, has also been studied in RCTs (Bunyaratavej, 2020; Khater, 2019; Kim, 2016; Park, 2017; Rajbanshi, 2020; Xu, 2014; Zhang, 2020). Most of these trials have found significant improvement in at least some clinical outcomes compared with oral or topical treatment alone. For example, Kim and colleagues (2016) compared 1064 nm Nd:YAG laser treatment, oral antifungal treatment and their combination in 56 individuals (217 nails). Blinding of outcome assessment was not discussed. The proportion of individuals who showed ‘marked improvement’ at 24 weeks in clinical response was 40.8% in the laser plus antifungal group, 31.6% in the laser-only group and 7.5% in the antifungal-only group. The difference in rates between each of the laser treatment groups and the antifungal-only group was statistically significant, $p<0.05$. Moreover, the rate of complete response with mycological cure was 22.5% in the laser-plus-antifungal group and 15.2% in the laser-only group, which was significantly higher than the 4.5% rate in the antifungal-only group. Limitations of this study were that it only had 24 weeks of follow-up and it did not appear to be blinded.

In the study by Park and colleagues (2017), 128 individuals were randomized to 16 weeks of treatment with topical antifungal treatment alone (n=64) or topical treatment plus 1064 nm Nd:YAG laser treatment at 4 week intervals (n=64). The authors stated that outcome assessment was objective and independently assessed by two dermatologists. One of the primary efficacy outcomes, percent change in the lesion-free area over 16 weeks, did not differ significantly between groups. Change in the lesion-free area was 33.7% in the combined treatment group and 23% in the control group (p=0.07). However, there was a large and statistically significant difference between groups in another primary efficacy outcome, cumulative cure rate, defined as the achievement of clinically normal nail or negative mycology, with nail plate involvement of less than 10%. Cure rates were 72% in the combined treatment group and 20% in the topical treatment-only group, $p<0.00001$.

However, a double-blind study by Bunyaratavej and colleagues (2020) did not find that Nd:YAG laser treatment of onychomycosis had superior outcomes to topical treatment alone or the combination of the two treatments. The study included 60 individuals, 20 per

group. Individuals assigned to laser treatment received 4 sessions, with a month between each session. After treatment, mycological cure rates were 35%, 60% and 65% in the laser, topical treatment and combination treatment groups, respectively. Rates in the topical and combination treatment groups were similar to one another and both were better than rates in the laser treatment group alone (p=0.05). Clinical cure rates were 10% in the laser group, 30% in the topical treatment group, and 30% in the combination treatment group; p-values for this analysis were not reported.

A 2019 meta-analysis of 24 prospective randomized and non-randomized trials evaluating laser treatment of onychomycosis (Yeung, 2019) found a pooled complete clinical cure rate of 7.2% (95% confidence interval [CI], 1.9-23.5%), clinical improvement rate of 67.2% (95% CI, 43.2-84.7%) and mycological cure rate of 70.4% (95% CI, 52.5-82.8%). The authors noted a high rate of heterogeneity among studies. The study did not report rates for any comparison intervention.

A 2022 meta-analysis of 12 RCTs compared the combination of laser treatment and topical antifungals with topical antifungals alone (Zhang, 2022). In pooled analyses, the authors found a significantly higher likelihood of clinical effectiveness (7 studies) (RR, 1.50, 95% CI, 1.24 to 1.83) and mycological cure (6 studies) (RR, 1.27, 95% CI, 1.10 to 1.48) in the group receiving the laser and topical antifungal treatment compared with antifungals alone. Only 2 studies addressed the complete cure rate. In their assessment of risk of bias, the authors noted that only 1 of 12 RCTs mentioned blinding of participants and personnel and only 3 of the 12 RCTs stated that outcome evaluation was blinded. The length of intervention and length of follow-up varied among studies.

A 2021 systematic review of literature on lasers for treating dermatophyte onychomycosis (Gupta, 2021) included clinical studies of laser monotherapy that evaluated the great toenail as the target nail, reported mycological confirmation of onychomycosis and included a clear definition of efficacy. A total of nine studies met the review's inclusion criteria. Outcome measures and definitions of efficacy varied among studies. Clinical cure defined as 100% clear nail was reported in one study and clinical cure defined as less than 10% clinical involvement was reported in four studies. Mycological cure defined as both negative microscopy and negative fungal culture was reported in two studies, mycological cure defined as negative microscopy only was evaluated in three studies, and mycological cure defined as negative fungal culture only was reported in five studies. The authors did not pool study results.

The British Association of Dermatologists' 2014 guideline on treatment of onychomycosis stated that "newer devices" including Nd:YAG lasers showed "promising results" but recommendations could not be made regarding their use at the time. No guideline updates were available.

In summary, a number of RCTs have evaluated laser treatment for onychomycosis. Study findings were mixed, as were the design quality of the trials; for example, not all studies had blinded assessment of outcomes. Study outcome measures were often of unclear clinical significance (e.g. percent change in lesion-free area or "marked improvement"), and did not include evaluation of outcomes considered to be complications of onychomycosis (e.g. soft tissue bacterial infection, pain; or even quality of life). Furthermore, only one study had at least 1 year of follow-up. Length of follow-up may not have been long enough to adequately determine cure rate or to assess rates of recurrence. Finally, the mechanisms of action and the optimal regimen for laser therapy, e.g. number and frequency of treatments, remain unclear. Additional data are needed before conclusions can be drawn about the durable, clinically meaningful efficacy of lasers for treating onychomycosis.

Background/Overview

Onychomycosis (also known as dermatophytic onychomycosis or tinea unguium) is a fungal infection of the nail. Most toenail onychomycosis is caused by dermatophytes; however, many cases of fingernail onychomycosis are due to yeast. This condition may affect toenails or fingernails, although toenails are more likely to be infected. One or more of the toenails or fingernails may be involved, but seldom are all involved (Becker, 2013).

Onychomycosis is very common, accounting for half of all nail disorders, and is considered the most common nail disease in adults. Its incidence ranges from 2% to 13% in North America. It has been reported that 30% of individuals with a cutaneous fungal infection also have onychomycosis. Onychomycosis has been reported to occur in 2.6% of children (younger than 18 years of age), and in 90% of the elderly. Even with optimal diagnosis and treatment, 1 in 5 individuals with onychomycosis fail to achieve full clearance and cure with current topical and systemic therapies. The long-term recurrence rates of onychomycosis are relatively high, and range from 20% to 50% (de Morais, 2013).

Risk factors that have been associated with onychomycosis include older age, swimming, tinea pedis, psoriasis, diabetes, immunodeficiency, genetic predisposition, and living with family members who have onychomycosis. Onychomycosis is usually asymptomatic. Individuals frequently initially seek treatment for cosmetic reasons without any physical complaints. However, as the disease progresses, onychomycosis may interfere with wearing shoes, standing, walking, and exercising. In more severe cases, individuals may report paresthesia, pain, discomfort, and loss of dexterity. They may also report loss of self-esteem and lack of social interaction. Providers may suggest treating toenail onychomycosis in individuals with a history of ipsilateral lower extremity cellulitis and in individuals with diabetes who have additional risk factors for cellulitis (that is, prior cellulitis, venous insufficiency or edema) (Gupta, 2012, 2013).

Onychomycosis is frequently treated with either systemic or topical antifungal medications, or a combination of both systemic and topical medications. However, because the infection is embedded within the nail and is difficult to reach, full resolution of symptoms is slow and may take a year or more, since a new nail must grow and entirely replace the infected nail. Also, some of the medications used to treat onychomycosis are associated with serious adverse events, including hepatotoxicity (Gupta, 2012, 2013).

Researchers are currently investigating the use of various laser systems in the clinical setting as a relatively noninvasive treatment for onychomycosis. Laser therapy has the potential to be an ideal treatment option with respect to its ability to deliver a high concentration of energy to a relatively small area, limiting systemic side effects, while enhancing its ability to penetrate more deeply into the nail plate.

A number of Nd:YAG laser systems have been cleared by the FDA for marketing for the temporary increase of clear nail in individuals with onychomycosis. CO_2 laser systems have also been cleared by the FDA for fungal nail treatment. The regulatory 510K clearance of device systems by the FDA are made on the basis of "substantial equivalence" to the technical specifications of pre-existing devices already approved for marketing for onychomycosis, not on the basis of clinical trials data.

Definitions

Dermatophytes: Fungi that require keratin to grow that cause superficial fungal infections on the nails, hair and skin.

Laser: The word is an acronym for "light amplification by the stimulated emission of radiation." Lasers are devices that emit amplified, single-color light.

Onychomycosis: Fungal infection of the nail.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:

CPT

17999	Unlisted procedure skin, mucous membrane and subcutaneous tissue [when specified as laser treatment of onychomycosis]
96999	Unlisted special dermatological services or procedures [when specified as laser treatment of onychomycosis]

ICD-10 Diagnosis

	All diagnoses including, but not limited to the following:
B35.1	Tinea unguium

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Government Agency, Medical Society, and Other Authoritative Publications:

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ClearSense™
GenesisPlus™
Long pulse laser
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Near Infrared Diode Lasers
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Short pulse laser
VARIABreeze™

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy and Technology Assessment Committee (MPTAC) review. Updated References section.
Reviewed	11/10/2022	MPTAC review. Rationale and References sections updated.
Reviewed	11/11/2021	MPTAC review. Rationale and References sections updated.
Reviewed	11/05/2020	MPTAC review. Rationale and References sections updated.
Reviewed	11/07/2019	MPTAC review. Rationale and References sections updated.
Reviewed	01/24/2019	MPTAC review. Description/Scope, Rationale, Background/Overview, Definitions and References sections updated.
Reviewed	02/27/2018	MPTAC review. The document header wording was updated from “Current Effective Date” to “Publish Date.” References were updated.
Reviewed	02/02/2017	MPTAC review. References were updated.
Reviewed	02/04/2016	MPTAC review. References were updated. Removed ICD-9 codes from Coding section.
Reviewed	02/05/2015	MPTAC review. Updated Description, Rationale, and References sections.
New	02/13/2014	MPTAC review. Initial document development.

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