Laser Treatment of Onychomycosis

Policy # 00371
Original Effective Date: 07/17/2013
Current Effective Date: 08/23/2017

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Based on review of available data, the Company considers laser treatment of onychomycosis to be investigational.*

Background/Overview
Onychomycosis is a common chronic fungal infection of the nail. It is estimated to cause up to 50% of all nail disease and 33% of cutaneous fungal infections. The condition can affect toenails or fingernails but is more frequently found in toenails. Primary infectious agents include dermatophytes (eg, *Trichophyton* species), yeasts (eg, *Candida albicans*), and nondermatophytic molds. In temperate Western countries, infections are generally caused by dermatophytes.

Aging is the most common risk factor for onychomycosis, most likely due to decreased blood circulation, longer exposure to fungi, and slower nail growth. In addition, various medical conditions increase the risk of comorbid onychomycosis. They include diabetes, obesity, peripheral vascular disease, immunosuppression, and HIV infection. In certain populations, onychomycosis may lead to additional health problems. Although there is limited evidence of a causal link between onychomycosis and diabetic foot ulcers, at least 1 prospective study with diabetic patients found onychomycosis to be an independent predictor of foot ulcer. Moreover, onychomycosis, especially more severe cases, may adversely impact quality of life. Patients with onychomycosis have reported pain, uncomfortable nail pressure, embarrassment, and discomfort wearing shoes.

The diagnosis of onychomycosis can be confirmed by potassium hydroxide preparation, culture, or histology. Treatments for onychomycosis include topical antifungals such as nail paints containing ciclopirox (ciclopiroxolamine) or amorolfine, and oral antifungals such as terbinafine and itraconazole. These generally have low-to-moderate efficacy and a high relapse rate. Topical antifungals and some long-available oral medications (eg, griseofulvin) require a long course of treatment, which presents issues for patient compliance. Moreover, oral antifungal medications have been associated with adverse effects such as a risk of hepatotoxicity.

Several types of device-based therapies are under investigation for treatment of onychomycosis, including ultrasound, iontophoresis, photodynamic therapy, and laser systems. A potential advantage of lasers is that they have greater tissue penetration than antifungal medication and thus may be more effective at treating infection embedded within the nail. Another potential advantage is that laser treatments are provided in a clinical setting in only 1 or several sessions and, thus, requires less long-term patient compliance.
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Laser treatment of onychomycosis uses the principle of selective photothermolysis. This is defined as the precise targeting of a tissue using a specific wavelength of light. The premise is that light is absorbed into the target area and heat generated by that energy is sufficient to damage the target area while sparing the surrounding area. The aim of laser treatment for onychomycosis is to heat the nail bed to temperatures required to disrupt fungal growth (approximately 40°C-60°C) and at the same time avoid pain and necrosis to surrounding tissues.

Characteristics of laser systems used to treat onychomycosis are listed in Table 1.

<table>
<thead>
<tr>
<th>Characteristics of Lasers for Treating Onychomycosis</th>
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<tbody>
<tr>
<td><strong>Wavelength</strong></td>
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<tr>
<td><strong>Pulse duration</strong></td>
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<tr>
<td><strong>Repetition rate</strong> (frequency of pulses, in hertz):</td>
</tr>
<tr>
<td><strong>Fluence</strong></td>
</tr>
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</table>

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

Multiple Nd:YAG laser systems have been cleared by the U.S. Food and Drug Administration (FDA) for marketing for the temporary increase of clear nail in patients with onychomycosis. FDA determined that these devices were substantially equivalent to existing devices. Table 2 lists select approved laser systems.

<table>
<thead>
<tr>
<th>Table 2. Select Laser Systems Approved for Temporary Increase of Clear Nail in Patients With Onychomycosis</th>
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</thead>
<tbody>
<tr>
<td><strong>Device</strong></td>
</tr>
<tr>
<td>Nd:YAG 1064-nm laser systems</td>
</tr>
<tr>
<td>PinPointe™ FootLaser™</td>
</tr>
<tr>
<td>GenesisPlus™</td>
</tr>
<tr>
<td>VariaBreeze™</td>
</tr>
<tr>
<td>JOULE ClearSense™</td>
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</tbody>
</table>

©2017 Blue Cross and Blue Shield of Louisiana
GentleMax Family of Laser Systems

Candela

2014

Nordlys

Ellipse A/S

2016

Dual wavelength Nd:YAG 1064-nm and 532-nm laser system

Q-Clear™

Light Age

2011

Nd:YAG 1064-nm laser systems (FDA product code: GEX); dual wavelength Nd:YAG 1064-nm and 532-nm laser system (FDA product code: PDX).

**Rationale/Source**

The main question for this evidence review is whether laser treatment is an efficacious treatment for onychomycosis and whether it is at least as effective as alternatives. Randomized controlled trials (RCTs) with appropriate comparison groups are the best study design to evaluate the effectiveness of laser treatment for onychomycosis. The most important outcomes for onychomycosis treatments are clinical cure of onychomycosis (ie, complete clearing without recurrence) and mycological cure. Other useful outcomes would be symptoms and functional measures related to onychomycosis. Partial healing and accelerated nail growth are intermediate outcomes that may or may not be associated with the ultimate cure rate. The most appropriate comparator interventions are sham laser treatment, if patient blinding is considered necessary, and best alternative care (eg, topical antifungals).

**LASER TREATMENT FOR ONYCHOMYCOSIS**

**Systematic Reviews**

A 2014 systematic review by Bristow et al identified 12 published studies on laser treatment for onychomycosis. Two were RCTs, 4 were nonrandomized comparative studies, and the other 6 were case series. Reviewers did not pool study findings but concluded that the evidence was limited and of poor methodologic quality. Representative RCTs with the largest sample sizes that compared laser treatment to placebo or to a different intervention are described next.

**Randomized Controlled Trials**

Karsai et al (2016) reported on a prospective randomized pilot trial with blinded outcome assessment comparing laser treatment (short-pulsed 1064-nm-ND:YAG laser) with control (no laser treatment) in 20 patients with 82 mycotic toenails. All patients received treatment with amorolfine cream over the soles of the feet, their intertriginous areas, and the skin directly surrounding the nails. Patients in the laser group received 4 treatments at intervals of 4 to 6 weeks. The trial’s primary end point (the proportion of nails with mycological remission) was not achieved in either group after 12 months. The study’s secondary end point was the clinical appearance of the nails using the Onychomycosis Severity Index (OSI), which was assessed by 2 independent blinded investigators. There were no differences in OSI scores at baseline or at 12-month follow-up. The OSI score worsened by a mean of 2.0 points in the treatment group compared with 3.6 points in the control group (between group change, 1.6 points; 95% confidence interval, -0.7 to 3.9; p=0.553).

In another RCT, Kim et al (2016) compared 1064-nm Nd:YAG laser therapy alone (n=19) to laser with topical antifungal therapy (n=18) and topical antifungal therapy (n=19) among 56 patients (in the final group;
original N enrolled not specified). Topical antifungal therapy included naftifine spray. Laser sessions were repeated at 4-week intervals for 12 weeks. Clinical response rates at 12 weeks were 70.9% in the laser only group, 73.2% in the laser plus topical group, and 14.9% in the topical group (p<0.05 for difference vs topical-only group). Cure rates at 24 weeks were 15.2% in the laser only group, 22.5% of the laser plus topical group, and 4.5% of the topical group (p<0.05 for difference vs topical-only group). There was no mention of blinded outcome assessment.

In 2015, El-Tatawy et al in Egypt reported on 40 patients with toenail onychomycosis randomized to 4 sessions of treatment with a 1064-nm Nd:YAG laser (n=20) or topical terbinafine twice daily for 6 months (n=20). The laser was a Dualis SP device (Fotona, Slovenia). The clinical efficacy outcome measure categorized patients into those with marked improvement (>75%), moderate improvement (50%-75%), mild improvement (25%-50%), or no improvement (<25%). The authors did not state that outcome assessment was blinded. At the end of the 6 months, 100% of patients in the laser group and none in the medication group showed marked improvement (p<0.002). In the medication group, 8 patients had mild improvement, 2 had moderate improvement, and 10 had no improvement. Lack of blinding could have introduced bias in the clinical assessment of patients.

A 2014 trial by Xu et al in China randomized 53 patients with toenail onychomycosis to 1 of 3 treatment groups: daily oral terbinafine 250 mg, weekly long-pulsed 1064-nm Nd:YAG laser (Luminis One), or a combination of the 2 therapies. The medication-only group included 16 patients with 30 infected nails, the laser group included 18 patients with 31 infected nails, and the combination treatment group included 16 patients with 29 infected nails. Analysis was done on a per-nail basis. All patients completed the 24-month follow-up. At this final evaluation point, the clinical clearance rate (defined as ≤5% nail plate involvement in onychomycosis) was 22 (73.3%) of 30 nails in the medication-only group, 20 (64.5%) of 31 nails in the laser group, and 28 (96.6%) of 29 nails in the combination treatment group. The rate was significantly higher in the combined treatment group than in either treatment alone; clinical clearance in the medication versus laser group did not differ significantly. Findings were similar for the mycological clearance rate. A limitation of this study was its reporting of outcomes on a per-nail basis, which did not account for correlated measurements.

In 2010, an industry-sponsored study by Landsman et al, used a dual-wavelength near-infrared diode laser that has not been cleared by the U.S. Food and Drug Administration for treatment of onychomycosis. The study included 36 patients with mycologically confirmed onychomycosis. Patients were randomized to actual laser treatment (n=26) or sham treatment (n=10). The sham treatment group received the same number of sessions, but laser power was set to zero. Thirty-four (94%) of 36 patients completed the study. These 34 patients had a total of 59 toes treated with an active or sham laser. Thirty-seven toes met all of the clinical eligibility criteria (26 in the active treatment group, 11 in the control group).

The primary study outcomes were the proportion of patients who had at least 3 mm of clear nail growth and who attained a negative mycological finding. As assessed by the blinded expert panel, at 180 days, 17 (65%) of 26 toes in the active treatment group and 1 (9%) of 11 in the control group attained at least 3 mm of clear lineal nail growth. The difference between groups was statistically significant, favoring the active
treatment group \((p=0.011)\). Moreover, 10 (39%) of 26 toes in the active treatment group and 1 (9%) of 11 in the control group had both a negative mycological culture and at least 3 mm of clear nail growth at 180 days; the difference between groups was not statistically significant \((p=0.119)\).

In the subjective clinical visual assessment of improvement at 180 days, investigators judged 5 (19%) of 26 toes in the active treatment group and 2 (18%) of 11 in the control group to be markedly improved. No toes were judged to be completely cleared. Reviewing photographs, the expert panel judged 1 (4%) toe in the active treatment group and 2 (18%) toes in the control group to be markedly improved and 1 toe (4%) in the active treatment group to be completely cleared. (Statistical comparisons of the treatment vs sham group were not reported for the visual assessment outcome.)

In 2012, Landsman and Robbins reported 270-day results in 36 of 40 treated toes. (This included clinically eligible toes as well as companion toes.) When photographs of 34 toes were evaluated, 35% were considered to have continued improvement, 38% were considered not to have changed since 180 days, and 20% were considered to have worsened. Authors did not report 270-day findings in patients assigned to the sham control group.

Limitations of the 2 Landsman studies included the intermediate outcome measures used (eg, 3 mm of clear lineal nail growth), which are of uncertain clinical significance. In addition, investigators randomized patients to a treatment group and a control group, yet presented their findings on a per-nail basis, which did not account for correlated measurements. Three (9%) of the 34 patients evaluated at 180 days contributed data from 2 toes to the analysis.

**SUMMARY OF EVIDENCE**

For individuals who have onychomycosis who receive treatment with laser therapy, the evidence includes small randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, medication use, and treatment-related morbidity. Some of the available RCTs have reported improvements in clinical outcomes with laser treatment, but these trials have mixed results and methodologic limitations. Clinical and mycological outcomes sometimes differed in the trials, which may be due in part to lack of consistent blinding of outcome assessment. The published evidence to date does not permit determining whether laser treatment improves health outcomes in patients with onychomycosis. Additional well-designed, adequately powered, and well-conducted RCTs are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

**References**


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Original Effective Date: 07/17/2013
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06/27/2013 Medical Policy Committee review
07/17/2013 Medical Policy Implementation Committee approval.
07/10/2014 Medical Policy Committee review
07/16/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2015 Medical Policy Committee review
08/19/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2016 Medical Policy Committee review
08/17/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017 Medical Policy Committee review
Next Scheduled Review Date: 08/2018

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<tr>
<td>CPT</td>
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<td>B35.1</td>
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