Laser Treatment of Onychomycosis

Policy Number: 2.01.89
Origination: 11/2015
Last Review: 5/2020
Next Review: 11/2020

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Laser Treatment of Onychomycosis. This is considered investigational.

When Policy Topic is covered
n/a

When Policy Topic is not covered
Laser treatment of onychomycosis is considered investigational.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With onychomycosis</td>
<td>• Laser therapy</td>
<td>• Topical antifungal nail lacquer</td>
<td>• Symptoms</td>
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<tr>
<td></td>
<td></td>
<td>• Oral antifungal therapy</td>
<td>• Change in disease status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Medication use</td>
</tr>
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<td></td>
<td></td>
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<td>• Treatment-related morbidity</td>
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</table>

Onychomycosis is a common fungal infection of the nail. Currently available treatments for onychomycosis, including systemic and topical antifungal medications, have relatively low efficacy and require a long course of treatment. Laser systems are proposed as another treatment option.

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.

**Background**

**Onychomycosis**

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. Also, 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 the quality of life. Patients with onychomycosis have reported pain, uncomfortable nail pressure, embarrassment, and discomfort wearing shoes.

**Diagnosis**

The diagnosis of onychomycosis can be confirmed by potassium hydroxide preparation, culture, or histology.

**Treatment**

Treatments for onychomycosis include topical antifungals such as nail paints containing ciclopirox (ciclopiroxolamine) or amorolfine and oral antifungals such as terbinafine and itraconazole. These 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 the 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 one or several sessions and, thus, requires less long-term patient compliance.

Laser treatment of onychomycosis uses the principle of selective photothermolysis. This is defined as the precise targeting of 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°-60°C)
and at the same time avoid pain and necrosis to surrounding tissues.5

Characteristics of laser systems used to treat onychomycosis are listed in Table 1.5

Table 1. Characteristics of Lasers for Treating Onychomycosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wavelength</td>
<td>Lasers are single-wavelength light sources. There needs to be sufficient tissue penetration to adequately treat nail fungus. The near-infrared spectrum tends to be used because this part of the spectrum has maximum tissue penetrance in the dermis and epidermis and the nail plate is similar to the epidermis. To date, most laser systems for treating onychomycosis have been Neodymium yttrium aluminum garnet (Nd:YAG) lasers that typically operate at 1064 nm; 940- to 1320-nm and 1440-nm wavelengths are also options.</td>
</tr>
<tr>
<td>Pulse duration</td>
<td>Pulses need to be short to avoid damaging the tissue surrounding the target area. For example, short-pulse systems have microsecond pulse durations and Q-switched lasers have nanosecond pulse durations.</td>
</tr>
<tr>
<td>Repetition rate (frequency of pulses, in hertz)</td>
<td>Spot size to the diameter of the laser beam. For treating onychomycosis, laser spot sizes range from 1 to 10 nm.</td>
</tr>
<tr>
<td>Fluence (in J/cm²)</td>
<td>Fluence refers to the amount of energy delivered into the area</td>
</tr>
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</table>

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

Table 2. Select Laser Systems Approved for Temporary Increase of Clear Nail in Patients With Onychomycosis

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nd:YAG 1064-nm laser systems</td>
<td>PinPointe USA (acquired by NuvoLase 2011)</td>
<td>2010</td>
</tr>
<tr>
<td>PinPointe™ FootLaser™</td>
<td>PinPointe USA (acquired by NuvoLase 2011)</td>
<td></td>
</tr>
<tr>
<td>GenesisPlus™</td>
<td>Cutera</td>
<td>2011</td>
</tr>
<tr>
<td>VariaBreeze™</td>
<td>CoolTouch</td>
<td>2011</td>
</tr>
<tr>
<td>JOULE ClearSense™</td>
<td>Sciton</td>
<td>2011</td>
</tr>
<tr>
<td>GentleMax Family of Laser Systems</td>
<td>Candela</td>
<td>2014</td>
</tr>
<tr>
<td>Nordlys</td>
<td>Ellipse A/S</td>
<td>2016</td>
</tr>
<tr>
<td>Dual wavelength Nd:YAG 1064-nm and 532-nm laser system</td>
<td>Light Age</td>
<td>2011</td>
</tr>
<tr>
<td>Q-Clear™</td>
<td>Light Age</td>
<td>2011</td>
</tr>
</tbody>
</table>

**Rationale**

This evidence review was created in May 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through October 14, 2019.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function—such as benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**Laser treatment for onychomycosis**

**Clinical Context and Therapy Purpose**

The purpose of laser treatment in patients who have onychomycosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of laser treatment improve the net health outcome compared with topical antifungal nail lacquer or oral antifungal therapy in patients who have onychomycosis?

The following PICOs were used to select literature to inform this review.

**Patients**

The relevant population of interest are patients with onychomycosis.

**Interventions**

The therapy being considered is laser treatment. Laser treatment allows for precise targeting of the fungal areas with enough heat to disrupt growth while avoiding damage to surrounding tissues. Two types of lasers have been developed...
to treat onychomycosis: neodymium-doped:yttrium aluminum garnet (Nd:YAG) and diode lasers.

Laser treatments are performed in outpatient centers.

Comparators
Current treatments for onychomycosis include topical antifungal nail lacquer and oral antifungal therapy. These treatments typically require long courses, which result in poor patient compliance and high relapse rates. Nail lacquers contain ciclopirox or amorolfine. Oral medications are terbinafine and itraconazole, which have been associated with a risk of hepatotoxicity.

Outcomes
The general outcomes of interest are symptom relief (eg, clear nail growth), change in disease status (eg, mycologic remission or Onychomycosis Severity Scale scores), reduction in medication use, and treatment-related morbidity. Clinical response can be measured after laser treatment (three-six months). To determine remission rates, follow-up may last a year or more.

Study Selection Criteria
To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

Systematic Reviews
A systematic review by Bristow et al (2014) identified 12 published studies on laser treatment for onychomycosis in a literature search conducted in June 2014. Two were RCTs, four were nonrandomized comparative studies with no placebo or control group, and six were case series. Bristow et al (2014) did not pool study findings, concluding the evidence was limited and of poor methodologic quality.

Randomized Controlled Trials
Representative RCTs published after the systematic review, with the largest sample sizes, and comparing laser treatment with placebo or a different intervention are described next.

Karsai et al (2017) 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 four treatments at intervals of four to six weeks. The trial’s primary endpoint (the proportion of nails with mycologic remission) was not achieved in either group after 12 months. The trial’s secondary endpoint was the clinical appearance of the nails using the Onychomycosis Severity Index, which was assessed by two independent blinded investigators. There were no differences in Onychomycosis Severity Index scores at baseline or at 12-month follow-up. The Onychomycosis Severity Index 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).

Kim et al (2016) compared 1064-nm Nd:YAG laser therapy alone (n=19) with a laser plus topical antifungal therapy (n=18) and topical antifungal therapy alone (n=19) (in the final group; original N enrolled not specified) 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 alone group (p<0.05 for laser and laser plus topical groups 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 laser and laser plus topical groups vs topical-only group). There was no mention of blinded outcome assessment.

El-Tatawy et al (2015) 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). The clinical efficacy outcome measure categorized patients into those with a marked improvement (>75%), moderate improvement (50%-75%), mild improvement (25%-50%), or no improvement (<25%). The authors did not state whether the outcome assessment was blinded. At 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, eight patients had mild improvement, two had moderate improvement, and ten had no improvement. Lack of blinding could have introduced bias in the clinical assessment of patients.

Xu et al (2014) in China randomized 53 patients with toenail onychomycosis to 1 of 3 treatment groups: daily oral terbinafine 250 mg (16 patients, 30 nails), weekly long-pulsed 1064-nm Nd:YAG laser (Luminis One) (18 patients, 31 nails), or a combination of both therapies (n=16 patients, 29 nails). The 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 vs laser group did not differ significantly. Findings were similar for the mycological clearance rate. A trial limitation was its reporting of outcomes on a per-nail basis, which did not account for correlated measurements.

An industry-sponsored study by Landsman et al (2010) 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 trial 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 mycologic 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 linear nail growth. The difference between groups was statistically significant, favoring the active treatment group (p=0.011). Ten (39%) of 26 toes in the active treatment group and 1 (9%) of 11 in the control group had both a negative mycologic culture and at least 3 mm of clear nail growth at 180 days; the difference between groups was not statistically significant (p=0.119). Differences between these two outcomes might be attributed to the subjective nature of the visual assessments.

Landsman and Robbins (2012) reported 270-day results in 36 of 40 treated toes.12 (This included clinically eligible toes as well as companion toes.) When photographs of 34 toes were evaluated, 35% were considered to have continuous improvement, 38% were considered not to have changed for 180 days, and 20% were considered to have worsened. Authors did not report 270-day findings for patients assigned to the sham control group.

Limitations of the 2 Landsman and Robbins (2012) studies included the intermediate outcome measures used (eg, 3 mm of clear linear nail growth), which are of uncertain clinical significance. Also, 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. The relevant outcomes are symptoms, change in disease status, medication use, and treatment-related morbidity. The randomized controlled trials reported inconsistent results and had methodologic limitations. Clinical and mycologic outcomes differed across the trials, lacked consistent blinding of outcome assessments, and often reported outcomes on a per-nail basis without accounting for correlated measurements. 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 randomized controlled trials are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION
Practice Guidelines and Position Statements
British Association of Dermatologists
The British Association of Dermatologists (2014) issued guidelines on the management of onychomycosis. Due to the limited nature of the evidence, the Association concluded that “lasers are showing promising results in the treatment of onychomycosis, but recommendations cannot be made at this stage” (level of evidence 1-).

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02812043</td>
<td>Comparison Between Long-pulsed Nd:YAG, Amorolfine and Combination Treatment in Treating Non-dermatophyte Onychomycosis</td>
<td>60</td>
<td>Aug 2018* (ongoing)</td>
</tr>
<tr>
<td>NCT02019446</td>
<td>Laser Treatment for Onychomycosis in Diabetes</td>
<td>60</td>
<td>Dec 2021</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01996995</td>
<td>Laser Therapy for Onychomycosis in Patients with Diabetes at Risk for Diabetic Foot Complications (LASER-1)</td>
<td>64</td>
<td>Jul 2017 (completed)</td>
</tr>
<tr>
<td>NCT01915355</td>
<td>Pulsed Dye Laser Treatment of Onychomycosis</td>
<td>11</td>
<td>Jul 2015 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial; Nd:YAG: neodymium yttrium aluminum garnet.
a Denotes industry-sponsored or cosponsored trial.
* No results published as of October 2019

REFERENCES

Billing Coding/Physician Documentation Information
17999 Unlisted procedure, skin, mucous membrane and subcutaneous tissue
96999 Unlisted special dermatological service or procedure

ICD10 Codes
B35.1 Dermatophytosis - Tinea unguium (includes onychomycosis)

Additional Policy Key Words
N/A

Policy Implementation/Update Information
11/1/15 New Policy; considered investigational.
5/1/16 No policy statement changes.
11/1/16 No policy statement changes.
5/1/17 No policy statement changes.
11/1/17 No policy statement changes.
5/1/18 No policy statement changes.
11/1/18 Edits to Policy section to align with PICOT table; statements otherwise unchanged.
5/1/19 No policy statement changes.
11/1/19 No policy statement changes.
5/1/20 No policy statement changes.

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