

Medical Policy



Title: Low-Level Laser Therapy

Professional

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| Populations | Interventions | Comparators | Outcomes |
|---|---|--|---|
| Individuals: <ul style="list-style-type: none"> With orthopedic pain (eg, neck pain, osteoarthritis knee pain, low back pain, carpal tunnel syndrome) | Interventions of interest are: <ul style="list-style-type: none"> Low-level laser therapy | Comparators of interest are: <ul style="list-style-type: none"> Conservative therapy (eg, physical therapy) Medication Surgery | Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Functional outcomes Quality of life Treatment-related morbidity |
| Individuals: <ul style="list-style-type: none"> With shoulder conditions, heel pain, or temporomandibular joint pain | Interventions of interest are: <ul style="list-style-type: none"> Low-level laser therap | Comparators of interest are: <ul style="list-style-type: none"> Conservative therapy (eg, physical therapy) Medication Surgery | Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Functional outcomes Quality of life Treatment-related morbidity |
| Individuals: <ul style="list-style-type: none"> With bone, ligament, and joint conditions (eg, rheumatoid arthritis, fibromyalgia) | Interventions of interest are: <ul style="list-style-type: none"> Low-level laser therapy | Comparators of interest are: <ul style="list-style-type: none"> Conservative care (eg, exercise) Medication | Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Functional outcomes Quality of life Treatment-related morbidity |

| Populations | Interventions | Comparators | Outcomes |
|---------------------------------------|---|--|---|
| Individuals: • With Bell palsy | Interventions of interest are: • Low-level laser therapy | Comparators of interest are: • Conservative care (eg, exercise) • Medication | Relevant outcomes include: • Change in disease status • Functional outcomes • Quality of life • Treatment-related morbidity |
| Individuals: • With lymphedema | Interventions of interest are: • Low-level laser therapy | Comparators of interest are: • Conservative care (eg, exercise) • Pneumatic compression • Complete decongestive therapy | Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity |
| Individuals: • With chronic wounds | Interventions of interest are: • Low-level laser therapy | Comparators of interest are: • Standard wound care | Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related morbidity |

DESCRIPTION

Low-level laser therapy (LLLT), also called photobiomodulation, is being evaluated to treat various conditions including oral mucositis, myofascial pain, joint pain, lymphedema, and chronic wounds.

Objective

The objective of this evidence review is to evaluate the safety and efficacy of low-level laser therapy for treating patients at increased risk of mucositis and other conditions (eg, soft tissue injuries, myofascial pain, tendinopathies, nerve injuries, joint pain, lymphedema).

Background

Oral Mucositis

Oral mucositis describes inflammation of the oral mucosa and typically manifests as erythema or ulcerations that appear 7 to 10 days after initiation of high-dose cancer therapy. Oral mucositis can cause significant pain and increased risk of systemic infection, dependency on total parenteral nutrition, and use of narcotic analgesics.

Treatment

Treatment planning may also need to be modified due to dose-limiting toxicity. There are a number of interventions for oral mucositis that may partially control symptoms, but none is considered a criterion standard treatment. When uncomplicated by infection, oral mucositis is self-limited and usually heals within 2 to 4 weeks after cessation of cytotoxic chemotherapy. Low-level laser therapy (LLLT) has been used in cancer therapy–induced oral mucositis in patients treated with radiotherapy and/or chemotherapy and hematopoietic cell transplantation.

Musculoskeletal and Neurologic Disorders

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy and the most commonly performed surgery of the hand. The syndrome is related to the bony anatomy of the wrist. The carpal tunnel is bound dorsally and laterally by the carpal bones and ventrally by the transverse carpal ligament. Through this contained space run the 9 flexor tendons and the median nerve. Therefore, any space-occupying lesion can compress the median nerve and produce the typical symptoms of CTS—pain, numbness, and tingling in the distribution of the median nerve. Symptoms of more severe cases include hypesthesia, clumsiness, loss of dexterity, and weakness of pinch. In the most severe cases, patients experience marked sensory loss and significant functional impairment with thenar atrophy.

Treatment

Mild-to-moderate cases of CTS are usually first treated conservatively with splinting and cessation of aggravating activities. Other conservative therapies include oral steroids, diuretics, nonsteroidal anti-inflammatory drugs, and steroid injections into the carpal tunnel itself. Patients who do not respond to conservative therapy or who present with severe CTS with thenar atrophy may be considered candidates for surgical release of the carpal ligament, using either an open or endoscopic approach. LLLT is also used to treat CTS.

Low-Level Laser Therapy

LLLT is the use of red-beam or near-infrared lasers with a wavelength between 600 and 1000 nm and power between 5 and 500 MW. (By comparison, lasers used in surgery typically use 300 W.) When applied to the skin, LLLT produces no sensation and does not burn the skin. Because of the low absorption by human skin, it is hypothesized that the laser light can penetrate deeply into the tissues where it has a photobiostimulative effect. The exact mechanism of its effect on tissue healing is unknown; hypotheses have included improved cellular repair and stimulation of the immune, lymphatic, and vascular systems.

LLLT is being evaluated to treat a wide variety of conditions, including soft tissue injuries, myofascial pain, tendinopathies, nerve injuries, joint pain, and lymphedema.

Regulatory Status

A number of low-level lasers have received clearance for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for the treatment of pain. Data submitted for the MicroLight 830® Laser consisted of application of the laser over the carpal tunnel 3 times a week for 5 weeks. The labeling states that the "MicroLight 830 Laser is indicated for adjunctive use in the temporary relief of hand and wrist pain associated with Carpal Tunnel Syndrome." In 2006, GRT LITE™ was cleared for marketing, listing the TUCO Erchonia PL3000, the Excalibur System, the MicroLight 830® Laser, and the Acculaser Pro as predicate devices. Indications of the GRT LITE™ for carpal tunnel syndrome are similar to the predicate devices: "adjunctive use in providing temporary

relief of minor chronic pain.” In 2009, the LightStream™ LLL device was cleared for marketing by FDA through the 510(k) process for adjunctive use in the temporary relief of pain associated with knee disorders treated in standard chiropractic practice. A number of clinical trials of low-level laser therapy are underway in the United States, including studies of wound healing. Since 2009, many more similar LLT devices have received 510(k) clearance from FDA; most recently, in 2018, Super Pulsed Laser technology (Multi Radiance Medical) was approved by FDA through the premarket approval process for use in neck and shoulder pain.

POLICY

- A. Low-level laser therapy may be considered **medically necessary** for prevention of oral mucositis in patients undergoing cancer treatment associated with increased risk of oral mucositis, including chemotherapy and/or radiotherapy, and/or hematopoietic cell transplantation (see Policy Guidelines).

- B. Low-level laser therapy is considered **experimental / investigational** for all other indications, including but not limited to:
 - 1. Carpal tunnel syndrome
 - 2. Neck pain
 - 3. Subacromial impingement
 - 4. Adhesive capsulitis
 - 5. Temporomandibular joint pain
 - 6. Low back pain
 - 7. Osteoarthritis knee pain
 - 8. Heel pain (ie, Achilles tendinopathy, plantar fasciitis)
 - 9. Rheumatoid arthritis
 - 10. Bell palsy
 - 11. Fibromyalgia
 - 12. Wound healing
 - 13. Lymphedema

Policy Guidelines

- 1. In the meta-analysis of 18 trials comparing low-level laser therapy (LLLT) to chemotherapy or chemoradiation for prevention of oral mucositis (Oberoi et al [2014]), the course of LLLT was generally from day 0 through treatment. In studies of hematopoietic cell transplant, the course of LLLT began between day -7 and day 0 and continued as long as day 14 or 15. In studies that began LLLT at day -7 or day -5 before hematopoietic cell transplant, the course of laser therapy ended at day -1 or day 0.
- 2. Other protocols have applied low-level laser energy to acupuncture points on the fingers and hand. This technique may be referred to as *laser acupuncture*. Laser acupuncture is not reviewed in this policy.

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through April 26, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to 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 a technology, 2 domains are examined: the relevance and the 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.

Prevention of Oral Mucositis

Clinical Context and Therapy Purpose

The purpose of low-level laser therapy (LLLT) in patients who have oral mucositis due to some cancer treatments and/or hematopoietic cell transplantation (HCT) 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 use of LLLT improve the health outcomes in those who have oral mucositis due to some cancer treatments and/or HCT?

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

Patients

The relevant population of interest is those who have oral mucositis due to some cancer treatments and/or HCT.

Interventions

The therapy being considered is LLLT.

Comparators

The following therapies are currently being used: conservative therapy (eg, oral hygiene, hydration) and pharmacologic agents.

Outcomes

The general outcomes of interest are reductions in symptoms and morbidity.

Timing

The effects of LLLT to promote healing are expected to occur from weeks to months.

Setting

LLLT is provided in an outpatient setting and may be administered by physical therapists and other practicing alternative medicine.

Systematic Reviews

In 2014, the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) issued guidelines that reiterated findings from their 2012 systematic review recommending LLLT for the prevention of oral mucositis in patients receiving HCT conditioned with high-dose chemotherapy and for patients undergoing head and neck radiotherapy, without concomitant chemotherapy.¹ The 2014 systematic review included 24 trials on a variety of prophylactic treatments. Recommendations for the use of LLLT for prevention of oral mucositis in patients receiving HCT were based on what reviewers considered to be the well-designed, placebo-controlled, randomized trial by Schubert et al (2007),² together with “weaker evidence” from 3 observational studies that showed positive results. This phase 3 trial was double-blind and sham-controlled evaluating 70 patients.² Patients were randomized to 650 nm laser, 780 nm laser, or placebo. Patients in the 650-nm laser group were more likely to have received a total body irradiation-containing regimen than the other 2 groups; otherwise, the groups were comparable. LLLT began on the first day of conditioning and continued for 3 days posttransplant. Of the 70 patients, 47 (67%) had complete or nearly complete mucositis measurements over time; the average number of visits per patient was similar among the 3 groups. The difference between groups in mean oral mucositis scores was greatest at day 11 (650 nm, 16.7; 780 nm, 20.6; placebo, 24.3), but this difference between the 650-nm group and placebo group was not statistically significant ($p=0.06$). Patient-specific oral mucositis scores differed significantly between the 2 groups only when adjusted for total body irradiation exposure. Of the 70 patients in the trial, 17 (24%) were assessed for oral pain. With group sizes of 5 and 6, the 650-nm group had significantly lower patient-specific average pain scores (15.6) than the placebo group (47.2). No adverse events from LLLT were noted. Trial limitations included lack of statistically significant findings for the primary outcome measure and a very small percentage of patients with pain assessments. Overall, as relates to the 3 observational studies, reviewers noted that, due to the range of laser devices and variations in individual protocols, results of each study applied exclusively to the cancer population studied and the specific wavelength and settings used.

Additional systematic reviews have been published since the 2012 MASCC/ISOO systematic review.³⁻⁵ Oberoi et al (2014) reported on a systematic review and meta-analysis of 18 RCTs comparing LLLT with no treatment or placebo for oral mucositis.⁴ Eight RCTs assessed patients undergoing HCT, 8 evaluated head and neck cancer patients receiving radiotherapy or chemoradiation, and the rest studied patients with other conditions receiving chemotherapy. Reviewers used the Cochrane risk of bias tool to evaluate the RCTs. Most were considered at low risk of bias on most domains. For example, 68% were at low risk of bias for blinding of patients and personnel, and 89% were at low risk of bias on incomplete outcome data. The primary outcome measure for the review was the incidence of severe mucositis. Ten studies ($n=689$ patients) were included in a pooled analysis for this outcome. The overall incidence of severe mucositis (grades 3-4) decreased with prophylactic LLLT, with a relative risk of 0.37 (95% confidence interval [CI], 0.20 to 0.67; $p=0.001$). Moreover, the absolute risk reduction in the

incidence of severe mucositis (-0.35) significantly favored LLLT (95% CI, -0.48 to -0.21; $p < 0.001$). Among secondary outcomes, LLLT also significantly reduced the overall mean grade of mucositis (standardized mean difference, -1.49; 95% CI, -2.02 to -0.95), duration of severe mucositis (weighted mean difference [WMD], -5.32; 95% CI, -9.45 to -1.19), and incidence of severe pain as measured on a visual analog scale (VAS; relative risk, 0.26; 95% CI, 0.18 to 0.37). In a subgroup analysis of the primary outcome (incidence of severe mucositis), the investigators did not find a statistically significant interaction between the type of condition treated and the efficacy of LLLT.

Randomized Controlled Trials

Two of the larger RCTs evaluating LLLT for prevention of oral mucositis were published by Gautam et al (2012).^{6,7} One reported on LLLT for the prevention of chemoradiotherapy-induced oral mucositis in 121 oral cancer patients.⁷ The other reported on LLLT for the prevention of chemoradiotherapy-induced oral mucositis in 221 head and neck cancer patients.⁶ There is an apparent overlap in patients in these 2 reports, with the head and neck cancer study including the 121 patients with a primary tumor site in the oral cavity. Patients in these studies received LLLT before radiotherapy at 66 gray delivered daily in 33 fractions, 5 days per week, and concurrent with cisplatin. LLLT was delivered at a wavelength of 632.8 nm, power density of 24 mW/cm², and a dosage of 3 to 3.5 J. In the report on oral cancer, LLLT before radiotherapy led to significant reductions in the incidence of severe oral mucositis (29% vs 89%) and its associated pain (18% vs 71%, with a VAS score > 7), opioid analgesic use (7% vs 21%), and total parenteral nutrition (30% vs 39%), all respectively, during the last weeks of chemoradiotherapy. LLLT also reduced the duration of severe oral mucositis (4.07 days vs 13.96 days), severe pain (5.31 days vs 9.89 days), and total parenteral nutrition (14.05 days vs 17.93 days), all respectively. In the 221 patients treated for head and neck cancer, LLLT led to significant reductions in the incidence and duration of severe oral mucositis (8.19 days vs 12.86 days) and its associated pain (VAS score, 4 vs 7), total parenteral nutrition (45.0% vs 65.5%), and opioid analgesic use (9% vs 26% for step III), all respectively. Gautam et al (2013) assessed patient-reported outcomes from the same study of 221 head and neck cancer patients using the Oral Mucositis Weekly Questionnaire–Head and Neck and the Functional Assessment of Cancer Treatment–Head and Neck questionnaire.⁸ Patients received LLLT as described above. Patients in the LLLT group reported significantly better outcomes than the placebo group, with lower scores on both the Oral Mucositis Weekly Questionnaire–Head and Neck ($p < 0.001$) and Functional Assessment of Cancer Treatment–Head and Neck questionnaire ($p < 0.05$).

In 2015 and 2016, 3 relatively small (ie, each < 50 patients), double-blind, sham-controlled, randomized trials on prevention of oral mucositis in patients undergoing cancer treatment were published. Gautam et al (2015) reported on 46 patients with head and neck cancer scheduled for radiotherapy and found significant reductions in the incidence and duration of severe oral mucositis ($p = 0.002$) and severe pain ($p = 0.023$) after LLLT vs sham.⁹ Oton-Leite (2015) reported on 30 head and neck cancer patients undergoing chemoradiation and found that oral mucositis grades were significantly lower in the LLLT group than in the control group at the week 1, 3, and 5 evaluations.¹⁰ For example, at the last clinical evaluation (week 5), the rates of grade 3 oral mucositis were 25% in the LLLT group and 54% in the control group. Ferreira et al (2016) evaluated 36 patients with hematologic cancer undergoing HCT.¹¹ The overall incidence of oral mucositis did not differ significantly between groups ($p = 0.146$). However, the rate of severe oral mucositis (grade 3 or 4) was significantly lower in the laser group (18%) than in the control group (61%; $p = 0.015$).

Section Summary: Prevention of Oral Mucositis

The literature on LLLT for the prevention of oral mucositis includes several systematic reviews, including a 2012 review by MASCC/ISOO, with a resulting recommendation for LLLT for adults receiving HCT conditioned with high-dose chemotherapy. Review of the key study evaluated by the MASCC/ISOO investigators for this recommendation revealed limitations that included statistically nonsignificant findings for the primary outcome measure. The MASCC/ISOO recommendation for LLLT for preventing oral mucositis in patients undergoing radiotherapy for head and neck cancer was based on lower level evidence. A 2014 systematic review of LLLT for prevention of oral mucositis included 18 RCTs, generally considered at low risk of bias, and found statistically significantly better outcomes with LLLT than with control conditions on primary and secondary outcomes. Also, 3 double-blind RCTs published in 2015 and 2016 found significantly better outcomes in patients undergoing LLLT compared with sham treatment before or during cancer treatment.

Musculoskeletal and Neurologic Disorders**Clinical Context and Therapy Purpose**

The purpose of LLLT in patients who have various musculoskeletal and neurologic disorders 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 use of LLLT improve the health outcomes in those who have various musculoskeletal and neurologic disorders?

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

Patients

The relevant population of interest is those who have various musculoskeletal and neurologic disorders.

Interventions

The therapy being considered is LLLT.

Comparators

The following therapies are currently being used: conservative therapy (eg, physical therapy, exercise), pharmacologic agents, and surgery.

Outcomes

The general outcomes of interest are pain relief and functional improvements.

Timing

The effects of LLLT to promote healing or pain relief are expected to occur from weeks to months.

Setting

LLLT is provided in an outpatient setting and may be administered by physical therapists and other practicing alternative medicine.

Carpal Tunnel Syndrome

A TEC Assessment (2010) evaluated LLLT for carpal tunnel syndrome (CTS) and chronic neck pain.¹² For inclusion in the Assessment, studies had to: be published in a peer-reviewed journal; be a randomized, sham-controlled trial, and, if adjunctive therapies were used, they had to have been applied to both groups; and measure outcomes at least 2 weeks beyond the end of the treatment period. Four RCTs met the inclusion criteria. Reviewers concluded that the studies had serious limitations, including small sample sizes and limited follow-up, and no study was so methodologically sound as to provide definitive results.

Li et al (2016) published a meta-analysis of RCTs on LLLT for CTS.¹³ Reviewers identified 7 RCTs. Meta-analyses evaluated outcomes for hand grip strength, pain measured by a VAS, symptom severity scores, and functional status scores. Short-term follow-up was defined as less than 6 weeks after treatment and long-term follow-up as at least 12 weeks after treatment. For 6 of the 8 meta-analyses, there were no statistically significant between-group differences in outcomes. They included short-term assessment of hand grip, short-term assessment of pain (VAS), and short- and long-term assessment of symptom severity and functional status scores. Meta-analyses found stronger hand grip (3 studies) and greater improvement in VAS scores (2 studies) at the long-term follow-up in the LLLT group than in the control. Most data for these 2 positive analyses were driven by a single RCT (Fusakul et al [2014]¹⁴). Reviewers concluded that additional high-quality trials with similar LLLT protocols would be needed to confirm that the intervention significantly improves health outcomes.

Section Summary: Carpal Tunnel Syndrome

A number of RCTs and several systematic reviews have been published. The most recent systematic review (2016) identified 7 RCTs. Meta-analyses did not find a significant benefit of LLLT compared with a control condition for most of the outcome measures (6 of 8). Previously, a TEC Assessment (2010) had concluded that the evidence from sham-controlled randomized trials was insufficient. More recent RCTs have not found that LLLT significantly improves outcomes.

Neck Pain

The TEC Assessment (2010), which included 6 trials of LLLT for chronic neck pain, found inconsistent results.¹² In the largest study (Chow et al [2006]), 90 patients were randomized to active LLLT or sham treatment.¹⁵ Five weeks after the 7-week treatment period, patients in the active treatment group reported a 2.7-point improvement in VAS pain score vs a 0.3-point worsening for the sham group. A calculated mean improvement of 43.8% was reported for the active LLLT group while the sham-treated group improved by 2.1%. The Assessment noted that baseline VAS pain scores were significantly higher in the active treatment group, possibly biasing results in favor of LLLT. Overall, reviewers concluded that the trials were characterized by small sample sizes, limited statistical power, and limited long-term follow-up, and thus the evidence was insufficient.

In a systematic review and meta-regression, Gross et al (2013) evaluated 17 trials on LLLT for neck pain.¹⁶ Ten trials demonstrated a high risk of bias. Two trials (n=109 subjects) were considered of moderate quality and found LLLT produced better outcomes than placebo for chronic neck pain treatment. Other trials showed improved outcomes with LLLT compared with placebo for acute neck pain, acute radiculopathy, and cervical osteoarthritis, but they were considered to be low quality. There was conflicting evidence on chronic myofascial neck pain.

Section Summary: Neck Pain

A number of RCTs and several systematic reviews have been published. A 2013 systematic review identified 17 trials. Only 2 trials considered of moderate quality found that LLLT led to better outcomes than placebo for chronic neck pain. Other trials were considered low quality. A 2010 TEC Assessment found conflicting evidence. While some studies showed positive benefits with LLLT over placebo, others did not. Additionally, laser types, dosages, and treatment schedules varied in the available evidence.

Subacromial Impingement Syndrome

Several RCTs evaluating LLLT for treatment of subacromial impingement syndrome have been published. Two sham-controlled studies, by Yeldan et al (2009)¹⁷ and by Dogan et al (2010),¹⁸ did not find statistically significantly better pain or functional outcomes with active treatment than with sham. A third RCT, by Abrisham et al (2011), compared exercise plus pulsed LLLT with sham laser 5 times a week for 2 weeks in 80 patients who had a subacromial syndrome (rotator cuff and biceps tendinitis).¹⁹ At the end of treatment, while both groups had improved VAS scores for pain and shoulder range of motion (ROM), the improvements were significantly better for the active LLLT group than for the sham laser group for pain (VAS score, 4.4 vs 2.9) and all measures of ROM (active and passive flexion, abduction, external rotation). The durability of this effect was not assessed.

Other RCTs have not shown statistically significant benefits of LLLT vs conservative treatment. In a study designed to assess the effectiveness of LLLT in patients with subacromial impingement syndrome, Bal et al (2009) randomized 44 patients to a 12-week home exercise program with or without LLLT.²⁰ Outcome measures of night pain, Shoulder Pain and Disability Index, and University of California-Los Angeles shoulder pain end-result scores were assessed at weeks 2 and 12 of the intervention. No distinct advantage was demonstrated by LLLT over exercise alone. Both groups showed significant reductions in night pain and Shoulder Pain and Disability Index scores at 2- and 12-week assessments, but the differences between groups were not statistically significant.

Calis et al (2011) randomized 52 patients with subacromial impingement syndrome to LLLT, ultrasound, or exercise.²¹ Patients were treated 5 days a week for 3 weeks with hotpack plus ultrasound plus exercise, hotpack plus LLLT plus exercise, or hotpack plus exercise. All 3 groups showed improvements from baseline to posttreatment in pain at rest, ROM, and function, but between-group improvements with LLLT were not statistically significant.

Section Summary: Subacromial Impingement Syndrome

The literature on LLLT for subacromial impingement syndrome consists of several RCTs. Most trials failed to show a significant benefit of LLLT compared with sham treatments or alternative interventions (eg, exercise).

Adhesive Capsulitis (Frozen Shoulder)

A Cochrane review by Page et al (2014) evaluated LLLT and other electrotherapy modalities for adhesive capsulitis (ie, frozen shoulder).²² Reviewers found limited evidence on which to conclude whether electrotherapy modalities are effective for frozen shoulder. Only 1 RCT (N=40 patients) compared LLLT with placebo. That trial administered LLLT for 6 days. On day 6, patients receiving LLLT showed some improvements on a global assessment of treatment success compared with patients receiving placebo. However, this trial was considered of low quality, and

its small sample size and short follow-up limited interpretation of results. Another RCT on LLLT discussed in the 2014 Cochrane review was assessed as moderate quality. In that RCT, Stergioulas et al (2008) randomized 63 patients with frozen shoulder to an 8-week program of LLLT (n=31) or placebo (n=32).²³ Both groups also participated in exercise therapy. Compared with the sham group, the active laser group had a significant decrease in overall, night, and activity pain scores after 4 and 8 weeks of treatment, and at the end of 8 more weeks of follow-up. At the same assessment intervals, significant decreases in Shoulder Pain and Disability Index and Croft Shoulder Disability Questionnaire scores were observed, while significant decreases in Disability of Arm, Shoulder, and Hand Questionnaire scores were observed at 8 weeks of treatment and 16 weeks postrandomization; significant decreases in Health Assessment Questionnaire scores were observed at 4 weeks and 8 weeks of treatment.

Section Summary: Adhesive Capsulitis

A Cochrane review evaluating treatments for adhesive capsulitis identified 2 RCTs on LLLT for adhesive capsulitis and, due to the small number of trials and study limitations, concluded that the evidence was insufficient to conclude whether LLLT is effective for adhesive capsulitis.

Temporomandibular Joint Pain

Several meta-analyses of RCTs on LLLT for temporomandibular joint (TMJ) pain have been published. A meta-analysis by Chen et al (2015) assessed pain and functional outcomes after LLLT for TMJ pain.²⁴ Fourteen placebo-controlled randomized trials were identified. Ten provided data on pain, as measured by a VAS. Pooled analysis of these studies found no significant differences between active treatment and placebo for VAS scores at final follow-up (WMD = -19.39; 95% CI, -40.80 to 2.03; p=0.08). However, meta-analyses did find significantly better functional outcomes (ie, maximum active mouth opening, maximum passive mouth opening) favoring LLLT. For example, the mean difference in maximum active mouth opening for active treatment vs placebo was 4.18 (95% CI, 0.73 to 7.63).

Chang et al (2014) published a meta-analysis of 7 RCTs on LLLT for TMJ pain.²⁵ Single- or double-blind RCTs included in the review compared LLLT with no treatment or placebo. The primary outcome of interest was pain measured by a VAS. Six studies (total N=223 patients) were eligible for inclusion in the meta-analysis. In a meta-analysis, reduction in VAS scores after treatment was significantly greater in the LLLT group than in the control group (pooled effect size, -0.6, 0.6; 95% CI, -0.47 to -0.73).

In a double-blind, placebo-controlled randomized trial, Shobha et al (2017) investigated the effectiveness of LLLT in patients with TMJ pain.²⁶ Forty TMJ patients were evenly randomized to an active or a placebo group. Treatment included 2 to 3 weekly sessions of LLLT for a total of 8 sessions. Patients were evaluated at baseline, after treatment, and at a 30-day follow-up. Both groups experienced pain reduction at all evaluation points. The most significant pain reduction was reported at the 30-day follow-up (p=0.001). There were no significant differences between groups at baseline (p=0.214), final session (p=0.000), or the 30-day follow-up (p=0.230). For a secondary outcome (the ability to open one's mouth), while both groups showed improvement, the difference between groups was not significant (p=0.330). Therefore, LLLT was determined to have no greater impact on healing or pain reduction over placebo. A study limitation is that MRI was not used, which is the traditional method for diagnosing TMJs.

Section Summary: Temporomandibular Joint Pain

A number of RCTs and several systematic reviews have evaluated LLLT for TMJ pain. Meta-analyses of these trials had mixed findings. The most recent meta-analysis, which included 14 placebo-controlled randomized trials, did not find a statistically significant impact of LLLT on pain but did find that LLLT significantly improved function outcomes (eg, mouth opening). RCTs have not compared the impact of LLLT with physical therapy on health outcomes.

Low Back Pain

A number of RCTs and several systematic reviews of RCTs have assessed LLLT for low back pain. For example, Glazov et al (2016) published a meta-analysis of blinded sham-controlled trials evaluating LLLT for treatment of chronic low back pain.²⁷ Fifteen RCTs (total n=1039 patients) met reviewers' eligibility criteria. Reviewers found that 3 of the 15 trials were at higher risk of bias (using a modified Cochrane risk of bias tool), mainly due to lack of blinding. The primary outcomes of interest to reviewers were pain measured by a VAS or a numeric rating scale, and a global assessment measure evaluating overall improvement and/or satisfaction with the intervention. Outcomes were reported immediately posttreatment (<1 week) and at short-term (1-12 weeks) follow-up. Longer term outcomes (ie, at 6 and 12 months) were secondary measures. For the pain outcomes, a meta-analysis of 10 trials found a significantly greater reduction in pain scores in the LLLT group at immediate follow-up (WMD = -0.79 cm; 95% CI, -1.22 to 0.36 cm). In a meta-analysis of 6 trials, there was no significant difference in pain reduction at short-term follow-up. However, in subgroup analyses, there was significantly greater reduction in pain with LLLT in trials that used a higher dose (>3 J/point), but not a lower dose, and in trials that included patients with a short duration of back pain (5-27 months) but not long duration (49 months to 13 years). Decisions on the cutoff to use for laser dose and duration of back pain were made post hoc and considered review findings. Findings were similar for the global assessment outcome. Meta-analyses found significantly higher global assessment scores at immediate follow-up (5 trials) but not at short-term follow-up (3 trials). Only 2 trials reported pain or global assessment at 6 and 12 months, and neither found statistically significant differences between the LLLT and sham groups.

Huang et al (2015) published a systematic review of RCTs on LLLT for treating nonspecific chronic low back pain.²⁸ Reviewers included trials comparing LLLT with placebo that reported pain and/or functional outcomes and a PEDro quality score. Seven trials (total N=394 patients; 202 assigned to LLLT, 192 assigned to placebo) were included. Six of the 7 trials were considered high quality (ie, a PEDro score ≥ 7 ; maximum score, 11 points). Primary outcomes of interest were posttreatment pain measured by VAS score and disability measured by the Oswestry Disability Index (ODI) score. ROM and change in pain scores were secondary outcomes. In pooled analyses, reviewers found a statistically significant benefit of LLLT on pain outcomes, but not disability or ROM. For the primary outcome (posttreatment pain scores) in a meta-analysis of all 7 trials, mean VAS scores were significantly lower in the LLLT group than in the placebo group (WMD = -13.57; 95% CI, -17.42 to -9.72). In a meta-analysis of 4 studies reporting the other primary outcome (ODI score), there was no statistically significant difference between the LLLT and the placebo groups (WMD = -2.89; 95% CI, -7.88 to 2.29). Outcomes were only reported immediately after treatment.

In a double-blind RCT, Koldas Dogan et al (2017) compared the effectiveness of 2 laser therapy regimens on pain, lumbar ROM, and functional capacity in patients with chronic low back pain.²⁹ This trial assessed 49 patients with chronic low back pain who were randomized to a hot pack

and the 2 different laser therapies for a total of 15 sessions. A series of assessments were conducted before and after treatment, including a modified Schober test; right and left lateral flexion measurements; VAS; and a modified ODI. After treatment, both groups saw a significant improvement in VAS, ODI, and lumbar ROM ($p < 0.05$). However, group 2 saw significantly better results in lateral flexion measurements and ODI scores ($p < 0.05$). Trial limitations included: (1) the short duration of follow-up; and (2) use of hot packs, which might have biased the pain measurements. No superiority was found for 1 laser treatment over the other regarding pain relief; however, regarding functionality, patients might find the Helium-Neon laser to be superior.

Section Summary: Low Back Pain

The literature on LLLT for low back pain consists of RCTs and several systematic reviews of RCTs. Meta-analyses found that LLLT resulted in significantly greater reductions in pain scores and global assessment scores than a placebo control in the immediate posttreatment setting. Meta-analyses also found that other outcomes (eg, disability index, ROM) were significantly better immediately after treatment with active vs placebo LLLT, though not at longer-term follow-up.

Osteoarthritic Knee Pain

Several RCTs and systematic review of RCTs have evaluated LLLT for treatment of knee osteoarthritis. Huang et al (2015) published a systematic review comparing at least 8 treatment sessions of LLLT with sham laser treatment in knee osteoarthritis patients.³⁰ To be eligible for inclusion, trials had to report pain and/or functional outcomes and a PEDro quality score. Nine trials (total N=518 patients) met eligibility criteria. In these studies, interventions included between 8 and 20 laser or sham sessions over 2 to 6 weeks. All 9 trials were considered high quality, as assessed using the PEDro scale (score of ≥ 7 ; maximum score, 11 points). Primary outcomes were posttreatment pain measured by VAS scores and the Western Ontario and McMaster Universities Arthritis Index scores (pain, function). Meta-analyses did not find that LLLT led to significantly lower pain scores than the sham control, either immediately after treatment or at the 3-month follow-up. For example, a meta-analysis of 5 studies that reported 12-week pain scores did not find a statistically significant between-group difference (standardized mean difference, -0.06; 95% CI, -0.30 to 0.18). Moreover, there were no statistically significant differences between active and sham laser interventions on Western Ontario and McMaster Universities Arthritis Index stiffness scores or function scores. The secondary outcome (ROM after therapy) also did not significantly favor LLLT over a sham intervention.

Bjordal et al (2017) published a systematic review of placebo-controlled randomized trials to determine the short-term efficacy of physical interventions for pain associated with knee osteoarthritis.³¹ They selected 36 RCTs. The largest proportion of trials evaluated transcutaneous electrical nerve stimulation ($n=11$), followed by 8 trials on LLLT and 7 on pulsed electromagnetic fields. Also included were trials on electroacupuncture, manual acupuncture, static magnets, and ultrasound. Reviewers did not report pooled analyses for LLLT for knee osteoarthritis. In a general qualitative analysis, they found that all the physical interventions except manual acupuncture and ultrasound showed better results with active treatment over placebo.

Section Summary: Osteoarthritic Knee Pain

The literature on LLLT for osteoarthritis includes RCTs and 2 systematic reviews of RCTs. The more recent systematic review, which pooled study findings, did not find that LLLT significantly reduced pain and improved function compared with a sham intervention.

Heel Pain

Achilles Tendinopathy

Stergioulas et al (2008) randomized 52 recreational athletes with chronic Achilles tendinopathy symptoms to an 8-week (12-session) program of eccentric exercises with LLLT or sham LLLT.³² By intention-to-treat analysis, results for the primary outcome of pain during physical activity assessed on a VAS were significantly lower in the exercise with LLLT group at 4 ($p<0.001$), 8 ($p<0.001$), and 12 weeks ($p=0.007$) after randomization.

Tumilty et al (2012) reported on a randomized, double-blinded, sham-controlled trial of LLLT as an adjunct to 3 months of exercise training in 40 patients with Achilles tendinopathy.³³ Active or sham LLLT was administered 3 times a week for 4 weeks, and exercises performed twice daily for 12 weeks. The primary outcome was the Victorian Institute of Sport Assessment–Achilles Questionnaire at 12 weeks. The only significant difference between groups using intention-to-treat analysis was at 4 weeks for Victorian Institute of Sport Assessment–Achilles Questionnaire scores, and that difference favored the sham control group. The Victorian Institute of Sport Assessment–Achilles Questionnaire and pain numeric rating scale scores did not differ significantly between the active and the sham groups at 12-week or 1-year follow-ups.

Plantar Fasciitis

A double-blind RCT by Macias et al (2015) assessed 69 patients with unilateral chronic plantar fasciitis and chronic heel pain of 3 months or longer that was unresponsive to conservative treatments (eg, rest, stretching, physical therapy).³⁴ Patients were randomized to twice weekly treatment for 3 weeks of LLLT or sham treatment. The primary efficacy outcome (reduction of heel pain pre- to posttreatment) differed significantly between groups ($p<0.001$). Mean VAS scores decreased from 69.1 to 39.5 in the LLLT group and from 67.6 to 62.3 in the sham group. The difference in Foot Function Index scores did not differ significantly between groups.

An RCT on LLLT for plantar fasciitis was reported by Kiritsi et al (2010).³⁵ The trial was double-blind and sham-controlled and assessed 30 patients. Twenty-five (83%) patients completed the trial, with treatment 3 times a week over 6 weeks. At baseline, plantar fascia thickness, measured by ultrasound, was significantly greater in symptomatic feet (5.3 mm) compared with asymptomatic feet (3.0 mm). Plantar fascia thickness decreased in both the LLLT and the sham groups during the trial. Although plantar fascia thickness after 6 weeks of treatment did not differ significantly between groups (3.6 mm in LLLT vs 4.4 mm in sham), there was a significant between-groups difference in the reduction in thickness (1.7 mm LLLT vs 0.9 mm sham). VAS scores after night rest or daily activities improved significantly more in the LLLT group (59% improvement) than in the sham group (26% improvement). At baseline, pain after daily activities was rated as 67 out of 100 by both groups. At the end of treatment, VAS scores for daily activities were rated as 28 out of 100 for LLLT and 50 out of 100 for sham.

Cinar et al (2018) conducted a prospective single-blinded RCT investigating combination therapy consisting of LLLT plus exercise and orthotic care vs orthotic care alone in persons with plantar fasciitis.³⁶ Forty-nine individuals were randomized to LLLT ($n=27$) or a control therapy ($n=22$). Each person performed a home exercise routine and received orthotic care; persons in the LLLT group received treatment 3 times a week for a total of 10 sessions. The function subscale of the American Orthopedic Foot and Ankle Society Score, a VAS, and the 12-minute walk test were used to measure progress. Scores were recorded at baseline, 3 weeks, and 3 months after treatment. At week 3, both groups saw a significant improvement in American Orthopedic Foot

and Ankle Society total score (LLLT, $p < 0.001$; control, $p = .002$). However, at the 3-month follow-up, only the LLLT group progressed as assessed on the American Orthopedic Foot and Ankle Society total score ($p = 0.04$). At all check-ins, the group scores for the 12-minute walk test were comparable. Both groups showed significant pain reductions at the 3-month follow-up (LLLT, $p < 0.001$; control, $p = 0.01$); however, the LLLT group had a more significant reduction in pain at month 3 ($p = 0.03$). Thus, reviewers concluded that combination therapy plus LLLT was more effective in reducing pain and improving function for patients with plantar fasciitis than orthotic care alone. Limitations included a lack of a control group, which would have accounted for the natural progression of recovery in patients with plantar fasciitis; another limitation is that the LLLT dose may or may not have been precise enough for the conditions of this study.

Section Summary: Heel Pain

At least 2 sham-controlled randomized trials have evaluated LLLT for heel pain (Achilles tendinopathy, plantar fasciitis)- but findings were inconsistent. One RCT compared LLLT plus therapy with orthotic care alone, and while a significant advantage was observed in LLLT treatment, LLLT treatment was used as a combination therapy. None of the studies presented long-term follow-up data. Given all factors, further studies are needed to validate the technology.

Rheumatoid Arthritis

A Cochrane review by Brosseau et al (2005) included 5 placebo-controlled randomized trials and found that, relative to a separate control group, LLLT reduced pain by 1.10 points on a VAS compared with placebo, reduced morning stiffness duration by 27.5 minutes, and increased tip-to-palm flexibility by 1.3 cm.³⁷ Other outcomes, such as functional assessment, ROM, and local swelling, did not differ between groups. For rheumatoid arthritis, relative to a control group using the opposite hand (1 study), no difference was observed between the control and treatment hand for morning stiffness duration, and no significant improvement was reported in pain relief. Reviewers noted that “despite some positive findings, this meta-analysis lacked data on how LLLT effectiveness is affected by four important factors: wavelength, treatment duration of LLLT, dosage, and site application over nerves instead of joints.”

A randomized, double-blind, placebo-controlled trial assessing outcomes for pain reduction and improvement in hand function in 82 patients with rheumatoid arthritis treated with LLLT or placebo laser was reported by Meireles et al (2010).³⁸ There were no statistically significant differences between groups for most outcome measurements, including the primary variables, though a few measures significantly favored either the active or placebo treatment. Reviewers concluded that LLLT at the dosage used in the trial was ineffective for treating rheumatoid arthritis.

Section Summary: Rheumatoid Arthritis

A Cochrane review of 5 placebo-controlled randomized trials found a significant benefit of LLLT on some outcomes (eg, VAS) but not others (eg, functional assessment). A 2010 RCT, published after the Cochrane review, did not find that LLLT was significantly better than a placebo treatment for most outcomes.

Bell Palsy

Alayat et al (2014) reported on a randomized, double-blind, placebo-controlled trial of laser therapy for the treatment of 48 patients with Bell palsy.³⁹ Facial exercises and massage were given to all patients. Patients were randomized to 1 of 3 groups: high-intensity laser therapy,

LLLT, or exercise only. Laser treatment was given 3 times a week to 8 points on the affected side for 6 weeks. At 3 and 6 weeks posttreatment, outcomes were assessed using the Facial Disability Index and the House-Brackmann Scale. Significant improvements in recovery were seen in both laser therapy groups over exercise alone, with the greatest improvement seen with a high-intensity laser.

Ordahan and Karahan (2017) investigated the efficacy of LLLT when used in combination with traditional facial exercises to treat facial paralysis.⁴⁰ Forty-six patients with Bell palsy were randomized to 2 groups: 1 group underwent LLLT plus facial exercise therapy (FET; n=23); the other group underwent FET alone (n=23). Laser therapy was administered 3 times a week for 6 weeks. Patients were evaluated during the treatment and at 3 and 6 weeks posttreatment. The Facial Disability Index was used to evaluate progress. No significant improvement was observed at week 3 in the FET-alone treatment group ($p<0.05$), but significant improvement was noted at week 6 ($p<0.001$). In the LLLT plus FET group, significant improvement was noted at 3 and 6 weeks ($p<0.001$); moreover, improvements in the Facial Disability Index scores in the LLLT plus FET group were significantly greater than those of the FET-alone treatment group at week 3 and week 6 ($p<0.05$). Study limitation included lack of long-term follow-up and use of combination therapy, which obscures the contribution of LLLT.

Section Summary: Bell Palsy

One RCT found a significant short-term benefit of LLLT over exercise, but long-term outcomes were not available. Another RCT found significant short-term benefit with FET plus LLLT over FET alone, but again, no long-term data were available. The limited evidence on laser therapy for Bell palsy is insufficient to draw conclusions. Because Bell palsy often improves within weeks and may resolve completely within months, it is difficult to isolate specific improvements from laser therapy over the natural resolution of the illness. Also, no sham-controlled trials are available.

Fibromyalgia

Several small RCTs evaluating LLLT for fibromyalgia have been published. Ruaro et al (2014) reported on 20 patients randomized to LLLT or sham treatment 3 times a week for 4 weeks (12 total treatments).⁴¹ Outcomes included scores in the Fibromyalgia Impact Questionnaire (FIQ), which measures physical function, ability to work, pain, fatigue, and depression; the McGill Pain Questionnaire; and a pain VAS. All 3 outcomes were significantly better with active than with sham LLLT posttreatment. Mean overall FIQ scores were 18.6 in the LLLT group and 5.2 in the sham group ($p=0.003$). Mean change scores also differed significantly between groups for McGill Pain Questionnaire score ($p=0.008$) and VAS score ($p=0.002$).

Matsutani et al (2007) randomized 20 patients with fibromyalgia to laser treatment plus stretching exercises or stretching alone.⁴² Outcome measures were VAS scores and dolorimetry at tender points, quality of life on the FIQ, and the 36-Item Short-Form Health Survey scores. At the end of treatment, both groups demonstrated pain reductions, higher pain thresholds at tender points (all $p<0.01$), lower mean FIQ scores, and higher 36-Item Short-Form Health Survey mean scores (all $p<0.05$). No significant differences were found between groups.

Section Summary: Fibromyalgia

Few RCTs evaluating LLLT for fibromyalgia are available; the existing trials are small (ie, <25 patients each). One RCT (N=20 patients) found significantly better outcomes with LLLT than with

sham, and another RCT (N=20 patients) did not find statistically significant between-group differences for similar outcomes. Additional RCTs with sufficient numbers of patients are needed.

Wound Care and Lymphedema

Clinical Context and Therapy Purpose

The purpose of LLLT in patients who have chronic nonhealing wounds or lymphedema 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 use of LLLT improve the health outcomes in those who have chronic nonhealing wounds or lymphedema?

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

Patients

The relevant population of interest is those who have various chronic nonhealing wounds or lymphedema.

Interventions

The therapy being considered is LLLT.

Comparators

The following therapies are currently being used: standard wound care or conservative care (eg, exercise), compression, and decongestive therapy.

Outcomes

The general outcomes of interest, for wound care, is complete wound healing, and for lymphedema, symptom reduction and functional improvements.

Timing

The effects of LLLT to promote healing or pain relief are expected to occur from weeks to months.

Setting

LLLT is provided in an outpatient setting and may be administered by physical therapists and other practicing alternative medicine.

Chronic Nonhealing Wounds

An evidence assessment by Samson et al (2004), which evaluated vacuum-assisted and low-level laser wound therapies for treatment of chronic nonhealing wounds and was prepared for the Agency for Healthcare Research and Quality, was based on 11 studies of LLLT.⁴³ It stated: "The best available trial [of low-level laser wound therapy] did not show a higher probability of complete healing at 6 weeks with the addition of low-level laser compared with sham laser treatment added to standard care. Study weaknesses were unlikely to have concealed existing effects. Future studies may determine whether different dosing parameters or other laser types may lead to different results."

A Cochrane review by Chen et al (2014) evaluated RCTs on light therapy, including phototherapy, ultraviolet, and laser, for pressure ulcers.⁴⁴ The few trials available for analysis were of small size

and very low quality. Reviewers found the available evidence overall insufficient to conclude whether light therapy is effective on pressure ulcers.

Machado et al (2017) also published a systematic review evaluating the treatment of pressure ulcers with LLLT.⁴⁵ Reviewers identified 4 studies meeting eligibility requirements (total N=210 patients). Outcomes were the ulcer area, healing rate, and overall healing rate. Two of the 4 studies used LLLT with a single wavelength^{46,47}; and the other two used LLLT with probe cluster, which employs the simultaneous assimilation of different types of diodes and wavelengths.^{48,49} In the study that employed the 658 nm wavelength, reviewers found that particular frequency reduced pressure ulcers by 71%. The other wavelengths did not produce any significant findings related to the study outcome; moreover, the studies using the probe cluster technique were also not successful in producing significant findings. While studies should be conducted to investigate further the success found in single wavelength at 658 nm, at this time there is insufficient evidence to suggest LLLT can significantly benefit patients with pressure ulcers.

Section Summary: Chronic Nonhealing Wounds

Three systematic reviews of the literature did not find sufficient evidence from controlled studies demonstrating that LLLT is effective for wound healing.

Lymphedema

Several systematic reviews of RCTs and observational studies have been published. For example, Smoot et al (2015) published a systematic review of studies on the effect of LLLT on symptoms in women with breast cancer–related lymphedema.⁵⁰ Reviewers identified 9 studies, 7 RCTs and 2 single-group studies. Three studies had a sham control group, 1 used a waitlist control, and 3 compared LLLT with an alternative intervention (eg, intermittent compression). Only 3 studies had blinded outcomes assessments and, in 3 studies, participants were blinded. A pooled analysis of 4 studies found significantly greater reductions in upper-extremity volume with LLLT than with the control condition (pooled effect size, -0.62; 05% CI, -0.97 to -0.28). Only 2 studies were suitable for a pooled analysis of the effect of LLLT on pain. This analysis did not find a significant difference in pain levels between LLLT and control (pooled effect size, -1.21; 95% CI, -4.51 to 2.10).

Omar et al (2012) published a qualitative systematic review of LLLT for the management of breast cancer–related lymphedema.⁵¹ They selected 8 studies (total N=230 patients) for their review. Five studies were graded as Sackett evidence level II (small randomized trial with high false-positive or false-negative errors), 2 were graded as level III (nonrandomized comparative study), and 1 study was graded as level V evidence (case series). Reviewers noted major methodologic flaws and little uniformity in trial designs.

One of the larger double-blind RCTs was published by Omar et al (2011); it reported on 50 patients with postmastectomy lymphedema.⁵² The average length of time that patients had swelling was 14 months (range, 12-36 months). They were treated with active or sham laser 3 times a week for 12 weeks over the axillary and arm areas. Also, all participants were instructed to perform daily arm exercises and to wear a pressure garment. Limb circumference, shoulder mobility, and grip strength were measured before treatment and at 4, 8, and 12 weeks. Limb circumference declined over time in both groups, with significantly greater reductions in the active laser group at 8 (20.0 cm vs 16.4 cm), 12 (29 cm vs 21.8 cm), and 16 (31 cm vs 2 cm) weeks. Shoulder flexion and abduction were significantly better in the active laser group at 8 and

12 weeks. Grip strength was significantly better in the active laser group after 12 weeks (26.2 kg vs 22.4 kg). The durability of these effects was not assessed.

Section Summary: Lymphedema

Two systematic reviews of RCTs and observational studies found methodologic flaws in the available studies and collectively these studies did not consistently report better outcomes in patients receiving LLLT vs a control condition for treatment of lymphedema.

Summary of Evidence

Oral Mucositis

For individuals who have increased risk of oral mucositis due to some cancer treatments (eg, chemotherapy, radiotherapy) and/or HCT who receive LLLT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related morbidity. A 2014 systematic review included 18 RCTs and found better outcomes with LLLT used to prevent oral mucositis than with control treatments. RCTs published after the systematic review had similar findings. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Musculoskeletal and Neurologic Disorders

For individuals who have CTS who receive LLLT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Both a 2016 systematic review and a TEC Assessment (2010) did not find sufficient evidence from RCTs that LLLT improves outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have neck pain who receive LLLT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. A 2013 systematic review identified 17 trials, most of which were considered low quality. Only 2 trials were considered moderate quality, and they found that LLLT led to better outcomes than placebo for chronic neck pain. A TEC Assessment (2010) found conflicting evidence. Additionally, laser types, application dosages, and treatment schedules vary in the available evidence and require further study. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have subacromial impingement syndrome who receive LLLT, the evidence includes RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Most trials did not show a significant benefit of LLLT compared with sham treatment or with an alternative intervention (eg, exercise). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have adhesive capsulitis who receive LLLT, the evidence includes RCTs and a systematic review. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. A Cochrane review evaluating treatments for adhesive capsulitis identified 2 RCTs assessing LLLT. Due to the small number of trials and study limitations, reviewers concluded that the evidence was insufficient to permit conclusions about the effectiveness of LLLT for adhesive capsulitis. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have TMJ who receive LLLT, the evidence includes RCTs and several systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Meta-analyses of RCTs had mixed findings. A 2015 meta-analysis, which included 14 placebo-controlled randomized trials, did not find a statistically significant impact of LLLT on pain, but did find that LLLT significantly improved functional outcomes (eg, mouth opening). RCTs have not compared the impact of LLLT with physical therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have low back pain who receive LLLT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Meta-analyses of RCTs found that LLLT resulted in a significantly greater reduction in pain scores and global assessment scores than a placebo control in the immediate posttreatment setting. Meta-analyses also found that other outcomes (eg, disability index, range of motion) were significantly better immediately after treatment with active rather than placebo LLLT, but not at longer term follow-up. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have osteoarthritic knee pain who receive LLLT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. A 2015 systematic review, which pooled study findings, did not find that LLLT significantly reduced pain or improved function outcomes compared with a sham intervention. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have heel pain (ie, Achilles tendinopathy, plantar fasciitis) who receive LLLT, the evidence includes RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Findings of 2 sham-controlled randomized trials were inconsistent, and while an RCT compared LLLT with standard care lacked long-term follow-up. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have rheumatoid arthritis who receive LLLT, the evidence includes RCTs and a systematic review. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. A systematic review of RCTs found inconsistent benefit of LLLT for a range of outcomes. A 2010 RCT, published after the systematic review, did not find that LLLT was significantly better than a placebo treatment on most outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have Bell palsy who receive LLLT, the evidence includes 2 RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The RCT found significant short-term benefit of LLLT over exercise. Longer term outcomes (>6 weeks) were not available. Because Bell palsy often improves within weeks and may completely resolve within months, it is difficult to isolate specific improvements from laser therapy over the natural resolution of the illness. Also, no sham-controlled trials are available. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have fibromyalgia who receive LLLT, the evidence includes RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The RCTs evaluating LLLT for treatment of fibromyalgia are small (ie, <25 patients each). One

RCT (N=20 patients) found significantly better outcomes with LLLT than with sham, while another (N=20 patients) did not find statistically significant between-group differences for similar outcomes. Additional RCTs with sufficient numbers of patients are needed to establish the efficacy of LLLT for fibromyalgia. The evidence is insufficient to determine the effects of the technology on health outcomes.

Wound Care and Lymphedema

For individuals who have chronic nonhealing wounds who receive LLLT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The few existing RCTs tend to have small sample sizes and potential risk of bias. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have lymphedema who receive LLLT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Two systematic reviews detected methodologic flaws in the available studies and did not consistently find better outcomes for patients receiving LLLT than those receiving a control condition for treatment of lymphedema. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

Mucositis Prevention Guideline Development Group

In 2017, the Mucositis Prevention Guideline Development Group published guidelines on preventing oral and oropharyngeal mucositis in children undergoing hematopoietic cell transplantation.⁵³ The guidelines were based on an evidence review consisting of randomized controlled trials that evaluated interventions such as cryotherapy and low-level laser therapy (LLLT). The guidelines suggested that LLLT could be offered to children but classified this recommendation as weak.

Multinational Association of Supportive Care in Cancer et al

The Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (2014) published joint guidelines on the management of mucositis secondary to cancer therapy.¹

For the prevention of oral mucositis, the 2 associations recommended the following treatments, based on strong evidence: LLLT (650 nm, power of 40 mW) in patients receiving hematopoietic cell transplantation conditioned with high-dose chemotherapy with or without total body irradiation; oral cryotherapy in patients receiving bolus 5-fluorouracil chemotherapy; recombinant human keratinocyte growth factor-1 in patients receiving high-dose chemotherapy and total body irradiation, followed by autologous cell transplantation for hematologic malignancy; and benzydamine mouthwash in patients with head and neck cancer receiving moderate-dose radiotherapy without concomitant chemotherapy.

Additionally, the following treatments were recommended for the prevention of oral mucositis based on weaker evidence: LLLT (≈ 632.8 nm) in patients undergoing radiotherapy, without concomitant chemotherapy, for head and neck cancer; oral care protocols for patients undergoing any cancer treatment; oral cryotherapy in patients receiving high-dose melphalan as

conditioning for hematopoietic cell transplantation; and oral zinc supplements in oral cancer patients receiving radiotherapy or chemoradiation.

American Physical Therapy Association

The American Physical Therapy Association (2010) published guidelines on the diagnosis and treatment of Achilles tendinitis.⁵⁴ LLLT received a level B recommendation (based on moderate evidence) for decreasing pain and stiffness in patients with Achilles tendinopathy. The guidelines concluded that “given the limited number of studies employing LLLT in this population, additional study is warranted.” In 2014, the Association stated in a press release, based on a Cochrane review,²² that “It could be that low-level laser therapy (LLLT) is a useful electrotherapy modality for treatment of adhesive capsulitis, but the effects are marginal, and evidence is a long way from conclusive...”⁵⁵

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2009) issued guidance on early management of persistent, nonspecific low back pain and did not recommend laser treatment, citing limited evidence.⁵⁶ The 2016 updated guidance does not mention laser therapy.⁵⁷ In 2018, the Institute released guidance stating that it was considering LLLT and that it would issue an interventional procedures consultation document regarding the safety and efficacy of the treatment; at the time of this writing, the Institute was still in progress of releasing their disclosure.

American College of Physicians and American Pain Society

The joint guidelines by the American College of Physicians and American Pain Society (2007) stated that there is insufficient evidence to recommend LLLT for treatment of low back pain.⁵⁸ The 2009 updated guidelines did not mention LLLT.⁵⁹

The American College of Physicians (2017) released guidelines relating to noninvasive treatments for chronic low back pain.⁶⁰ The guidelines strongly recommended that patients with chronic low back pain should first seek nonpharmacologic treatment such as exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction—all based on moderate quality evidence. The recommendation also stated that patients with chronic low back pain should seek treatments such as tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, LLLT, operant therapy, cognitive behavioral therapy, or spinal manipulation—all based on low-quality evidence. While the College stated that LLLT has a small effect on pain and function, it found the evidence insufficient for the use of LLLT.

American Academy of Orthopaedic Surgeons

The American Academy of Orthopaedic Surgeons’ 2016 guidelines on the management of carpal tunnel syndrome indicated the: “limited evidence supports that laser therapy might be effective compared to placebo.”⁶¹

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------|--|--------------------|-----------------------|
| Ongoing | | | |
| NCT02696408 | Efficacy of Prophylactic Low Level Laser Therapy (LLLT) for Decreasing Severity of Oral Mucositis During Hematopoietic Stem Cell (HSC) Transplantation (STOP MUCITES) | 194 | May 2018 |
| NCT02296697 | Low-level Laser Therapy Versus High Frequency on Pressure Ulcers Treatment | 75 | Dec 2018 |
| NCT01772706 | Laser Mucite ORL : Effectiveness of Laser Therapy for Mucositis Induced by a Radio-chemotherapy in Head and Neck Cancer (LaserMucite) | 100 | Mar 2019 |
| NCT02682992 | A Phase II Prospective Trial of Low-Level Laser Therapy for Prevention of Oral Mucositis in Patients Receiving Chemotherapy and Radiation for Head and Neck Cancer | 50 | Mar 2020 |
| Unpublished | | | |
| NCT03080207 | Comparison of Efficacy of Platelets / Platelet Enriched Plasma Regard (PRP) Method, Complex Decongestive Physiotherapy and Low Level Laser in Treatment of Lower Extremity Lymphoedema | 45 | Jan 2018 (unknown) |

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy 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. 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.

CPT/HCPCS

S8948 Application of a modality (requiring constant provider attendance) to one or more areas; low-level laser; each 15 minutes

- In January 2004, a HCPCS code was added that is specific to this therapy: S8948.
- There is no specific CPT code for low-level laser therapy LLLT.
- There is no ICD-10-CM diagnosis code for risk of oral mucositis. Codes such as K12.31, T45.1X5, and Y84.2 would require that the mucositis or adverse events had occurred. Medically necessary claims for patients receiving cancer treatment would be coded with a code from the Neoplasms (C00-D49) code range.

ICD-10 Diagnoses

C00.0-C14.8 Malignant neoplasms of lip, oral cavity and pharynx
 C15.3-C26.9 Malignant neoplasm of digestive organs
 C30.0-C39.9 Malignant neoplasms of respiratory and intrathoracic organs
 C40.0-C41.9 Malignant neoplasms of bone and articular cartilage
 C43.0-C44.99 Melanoma and other malignant neoplasms of skin

| | |
|-----------------|--|
| C45.0-C49.A9 | Malignant neoplasms of mesothelial and soft tissue |
| C50.011-C50.929 | Malignant neoplasm of breast |
| C51.0-C58 | Malignant neoplasms of female genital organs |
| C60.0-C63.9 | Malignant neoplasms of male genital organs |
| C64.1-C68.9 | Malignant neoplasms of urinary tract |
| C69.00-C72.9 | Malignant neoplasms of eye, brain and other parts of central nervous system |
| C73-C75.9 | Malignant neoplasms of ill-defined, other secondary and unspecified sites |
| C7A.010-C7A.8 | Malignant neuroendocrine tumors |
| C7B.00-C7B.8 | Secondary neuroendocrine tumors |
| C76.00-C80.2 | Malignant neoplasms of ill-defined, other secondary and unspecified sites |
| C81.00-C96.9 | Malignant neoplasms of lymphoid, hematopoietic and related tissue |
| D00.00-D09.9 | In situ neoplasms |
| D37.01-D48.9 | Neoplasms of uncertain behavior, polycythemia vera and myelodysplastic syndromes |
| D49.0-D49.9 | Neoplasms of unspecified behavior |

| REVISIONS | |
|------------------|---|
| 2005 | Policy added to the bcbsks.com web site. |
| 03-12-2013 | Title Revised from "Low-Level Laser Infrared Therapy (also known as soft laser therapy, Microlight 830, and cold laser therapy)" to "Low-Level Laser Therapy" |
| | Description section updated |
| | In Policy section: <ul style="list-style-type: none"> ▪ Revised policy language from, "Low-level laser treatment is considered experimental/investigational for all indications, including but not limited to carpal tunnel syndrome and other pain disorders, edema, and to enhance wound healing due to the lack of sufficient studies and published scientific literature." to, " Low-level laser therapy is considered experimental/investigational for all indications, including but not limited to carpal tunnel syndrome." This policy language change does not change the intent of the policy position. ▪ Added the Policy Guidelines of: "Other protocols have used low-level laser energy applied to acupuncture points on the fingers and hand. This technique may be referred to as "laser acupuncture." Laser acupuncture is not reviewed in this policy." |
| | Added Rationale section |
| | In Coding section: <ul style="list-style-type: none"> ▪ Added coding notations. |
| | Added Revision section |
| | Added References |
| 02-10-2015 | Description section updated |
| | In the Policy section: <ul style="list-style-type: none"> ▪ Added to policy statement "treatment of" to read, "Low-level laser therapy is considered experimental / investigational for all indications, including but not limited to treatment of carpal tunnel syndrome." This wording change does not change the intent of the policy. |
| | Rationale section updated |
| | References updated |
| 07-20-2016 | Description section updated. |
| | In Policy section: <ul style="list-style-type: none"> ▪ In the policy statement moved "treatment of carpal tunnel syndrome" to a list of experimental / investigational indications, adding indications 2 through 13: |

| REVISIONS | |
|------------------|---|
| | <p>"1. Carpal tunnel syndrome 2. Neck pain 3. Subacromial impingement 4. Adhesive capsulitis 5. Temporomandibular joint pain 6. Low back pain 7. Osteoarthritis knee pain 8. Heel pain (ie, Achilles tendinopathy, plantar fasciitis) 9. Rheumatoid arthritis 10. Bell palsy 11. Fibromyalgia 12. Wound healing 13. Lymphedema"</p> |
| | Rationale section updated |
| | References updated |
| 11-12-2018 | Description section updated |
| | <p>In Policy Section: ▪ Added "Low-level laser therapy may be considered medically necessary for prevention of oral mucositis in patients undergoing cancer treatment associated with increased risk of oral mucositis, including chemotherapy and/or radiotherapy, and/or hematopoietic cell transplantation (see Policy Guidelines)."</p> <p>In Policy Guidelines: ▪ Added "In the meta-analysis of 18 trials comparing low-level laser therapy (LLLT) to chemotherapy or chemoradiation for prevention of oral mucositis (Oberoi et al [2014]), the course of LLLT was generally from day 0 through treatment. In studies of hematopoietic cell transplant, the course of LLLT began between day -7 and day 0 and continued as long as day 14 or 15. In studies that began LLLT at day -7 or day -5 before hematopoietic cell transplant, the course of laser therapy ended at day -1 or day 0."</p> |
| | Rationale section updated |
| | <p>In Coding section: ▪ Added the following ICD-10 neoplasm Code Ranges: C00.0-C14.8, C15.3-C26.9, C30.0-C39.9, C40.0-C41.9, C43.0-C44.99, C45.0-C49.A9, C50.011-C50.929, C51.0-C58, C60.0-C63.9, C64.1-C68.9, C69.00-C72.9, C73-C75.9, C7A.010-C7A.8, C7B.00-C7B.8, C76.00-C80.2, C81.00-C96.9, D00.00-D09.9, D37.01-D48.9, D49.0-D49.9 ▪ Removed "Experimental / Investigational for all diagnoses related to this medical policy." Statement.</p> |
| | References updated |

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