Aetna considers low-level laser therapy medically necessary for prevention of oral mucositis in persons undergoing cancer treatment associated with increased risk of oral mucositis, including chemotherapy and/or radiotherapy, and/or hematopoietic stem cell transplantation.

Aetna considers cold laser therapy (also known as low-level laser therapy or class III laser), high-power laser therapy (class IV therapeutic laser), low-level laser therapy using dynamic photonic and dynamic thermokinetic energies experimental and investigational for the following indications (not an all-inclusive list) because there is inadequate evidence of the effectiveness of cold laser therapy and high-power laser therapy for these indications:

- Alzheimer's disease
- Bone regeneration/bone healing
- Breast implant capsular contracture
- Cardio-protection following myocardial infarction
- Carpal tunnel syndrome
• Colorectal cancer
• Dementia
• Dental pain
• Dentin hypersensitivity
• Depression
• Elbow disorders
• Fibromyalgia
• Hair loss (including alopecia areata and androgenic alopecia)
• Head and neck cancer
• Heart failure
• Herpes labialis
• Hypothyroidism induced by autoimmune thyroiditis
• Inferior alveolar nerve and lingual nerve injuries
• Knee osteoarthritis
• Lymphedema
• Musculoskeletal dysfunction
• Myofascial pain syndrome
• Neurological dysfunctions
• Neuropathic orofacial pain (e.g., burning mouth syndrome, occipital neuralgia, and trigeminal neuralgia)
• Obesity
• Oral lichen planus
• Pain relief (e.g. acute and chronic low back pain/neck pain, orthodontic pain, neuropathic pain, shoulder pain)
• Parkinson's disease
• Patella-femoral pain syndrome
• Pemphigus vulgaris
• Peri-implant mucositis
• Peri-odontitis
• Physical therapy (including rehabilitation following carpal tunnel release)
• Recurrent aphthous stomatitis/ulcers
• Rheumatoid arthritis
• Shoulder impingement syndrome
• Skin burn
• Stroke
▪ Temporomandibular joint disorders
▪ Tendon repair
▪ Tinnitus
▪ Traumatic brain injury
▪ Wound healing (including diabetic ulcers, following hammertoe surgery, gingival healing, and pressure ulcers).

See also CPB 0604 - Infrared Therapy (../600_699/0604.html).

Background

Low Level Laser Therapy

Low level laser therapy (LLLT), also known as "cold" laser therapy, refers to a wide variety of procedures involving several laser types and treatment methods. LLLT uses red beam or near infrared nonthermal lasers with a wavelength between 600 and 1000 nanometers and from five to 500 milliwatts. In contrast, lasers used for surgery typically use 300 watts. When applied, the lasers penetrate the surface of the skin without a heating (burning) effect, produce no sensation and do not damage the skin. It is believed that due to the low skin absorption and no side effects, the laser light can penetrate deeply into tissues and can reach the site of damage or injury.

Low-energy lasers (also known as cold lasers or class III lasers) have been promoted as an effective way to produce analgesia and accelerate healing of a variety of clinical conditions. By definition, low energy laser therapy uses irradiation intensities that induce minimal temperature elevation (not more than 0.1 to 0.5 °C), if any. For practical purposes, this restricts treatment energies to a few J/cm² and laser powers to 500 mW or less.
Despite these constraints, a wide variety of types of lasers, treatment schedules, and techniques have been used. Consequently, apparently conflicting results from studies of low-intensity lasers may not be in conflict, and may represent fundamental, but poorly understood, differences in treatment approaches.

LLLT may be administered by a physician, physical therapist, occupational therapist or Doctor of Chiropractic (DC) in a physician’s office or other outpatient setting and requires no sedation or anesthesia. It is theorized that LLLT may cause a biostimulatory healing effect for the treatment of a range of conditions, including arthritis, chronic pain commonly associated with carpal tunnel syndrome, tissue injuries (eg, tendinopathy, tendonitis) and severe wounds.

Examples of LLLT devices include Acculaser Pro4, Axiom BioLaser LLLT Series-3, Bioptron 2, Luminex LL Laser System, MicroLight 830, RianCorp LTU-904, Thor DDII 830 CL3 Laser System, Thor DDII IR Lamp System and TerraQuant. The TerraQuant device uses a combination of a "super pulsed" laser, pulsed infrared, red light and static magnetic field, which is purported to accelerate pain relief.

Although the results from large, uncontrolled, open trials of low-energy lasers in inducing wound healing have shown benefit, controlled trials have shown little or no benefit. The analgesic effects of low-energy lasers have been most intensely studied in rheumatoid arthritis. Recent well-designed, controlled studies have found no benefit from low-energy lasers in relieving pain in rheumatoid arthritis or other musculoskeletal conditions. Furthermore, although positive effects were found in some earlier studies, it was not clear that the pain relief achieved was large enough to have either clinical significance or to replace conventional therapies.
Published systematic reviews of the evidence have concluded that there is a lack of adequate evidence of effectiveness of cold laser therapy for treatment of chronic wounds (e.g., Schneider and Hailey, 1999; Cullum and Petherick, 2007; Flemming and Cullum, 1999; Samson et al, 2004; Simon et al, 2004; Wang, 2004; Nelson and Jones, 2006), arthritis (Brosseau et al, 2007; Brosseau et al, 2005; Marks and de Palma, 1999; Puett and Griffin, 1994; Wang, 2004), tuberculosis (Vlassov et al, 2006; Ziganshina and Garner, 2005), tinnitus (Waddell, 2004), pain (Gross et al, 1998; van der Heijden et al, 2002; Binder, 2002; Speed, 2006; Green et al, 2003), smoking cessation (White et al, 2006), epicondylitis (Chapell et al, 2002), Achilles tendinitis (McLauchlan et al, 2001), plantar heel pain (Crawford and Thomson, 2003; Landorf and Menz, 2007), back pain (Yousefi-Nooraie et al, 2008), and other musculoskeletal disorders (de Bie et al, 1998; de Bie et al, 2001; Ohio BWC, 2004; Wang, 2004).

Systematic evidence reviews have also concluded that low-energy laser therapy (e.g., Microlight 830, Microlight Corporation of America, Missouri City, TX) is ineffective in treating carpal tunnel syndrome (Gerritsen et al, 2002; O'Connor et al, 2003; Ohio BWC, 2004; Wang, 2004; CTAF, 2006).

A recent study (Hirschl et al, 2004) evaluated the effectiveness of low-level laser therapy in patients with primary Raynaud's phenomenon (n = 48). Laser and sham therapy each were applied 5 days a week for 3 weeks. The authors found that low-level laser therapy reduced the frequency and severity of Raynaud attacks. The findings of this study were interesting but need to be validated by further investigation with more patients and follow-up.

Kreisler et al (2004) assessed the effect of low-level laser application on post-operative pain after endodontic surgery in a double-blind, randomized clinical study. A total of 52 healthy adults undergoing endodontic surgery were included into the study. After suturing, 26 patients had the operation site
treated with an 809 nm-GaAlAs-laser at a power output of 50 mW and an irradiation time of 150 seconds. Laser treatment was simulated in another 26 patients. Patients were instructed to evaluate their post-operative pain on 7 days following surgery by means of a visual analogue scale. The results revealed that the pain level in the laser-treated group was lower than in the placebo group throughout the 7 day follow-up period. The differences, however, were significant only on the first post-operative day. The authors stated that low-level laser therapy can be beneficial for the reduction of post-operative pain. However, its clinical effectiveness and applicability with regard to endodontic surgery need further investigation, especially in terms of the optimal energy dosage and the number of laser treatments needed after surgery.

In a randomized controlled study, Bingol et al (2005) examined the effect of low-power gallium-arsenide laser treatment on the patients with shoulder pain. A total of 40 patients with shoulder pain and complied with the selection criteria were included in the study. They were randomly assigned into 2 groups: (i) laser treatment (n = 20), and (ii) control (n = 20). In group (i), patients were given laser treatment and an exercise protocol for 10 sessions during a period of 2 weeks. In group (ii), placebo laser and the same exercise protocol was given for the same period. Patients were evaluated according to the parameters of pain, palpation sensitivity, algometric sensitivity, and shoulder joint range of motion before and after treatment. Analysis of measurement results within each group showed a significant post-treatment improvement for some active and passive movements in both groups, and also for algometric sensitivity in group (i) (p < 0.05 to 0.01). Post-treatment palpation sensitivity values showed improvement in 17 patients (85 %) for group (i) and 6 patients (30 %) for group (ii). Comparison between 2 groups showed superior results (p < 0.01 and p < 0.001) in group (i) for the parameters of passive extension and palpation sensitivity but no significant difference for other parameters. These
researchers concluded that this study have shown better results in palpation sensitivity and passive extension, but no significant improvement in pain, active range of motion, and algometric sensitivity in laser treatment group compared to the control group in the patients with shoulder pain.

Markovic and Todorovic (2007) compared the effectiveness of dexamethasone and low-power laser (LPL) after surgical removal of impacted lower third molars under local anesthesia (2 % lidocaine / epinephrine). A total of 120 healthy patients were divided into 4 groups of 30 each: (i) group 1 received LPL irradiation immediately after operation (energy output 4 J/cm2 with constant power density of 50 mW, wavelength 637 nm); (ii) group 2 also received intra-muscular (i.m.) injection of 4 mg dexamethasone (Dexason) into the internal pterygoid muscle; (iii) group 3 received LPL irradiation supplemented by systemic dexamethasone, 4 mg i.m. in the deltoid region, followed by 4 mg of dexamethasone intra-orally 6 hours post-operatively; and (iv) control group received only the usual post-operative recommendations (i.e., cold packs, soft diet, etc.). Low-power laser irradiation with local use of dexamethasone (group 2) resulted in a statistically significant reduction of post-operative edema in comparison to the other groups. No adverse effects of the procedure or medication were observed. The authors concluded that LPL irradiation after lower third molar surgery can be recommended to minimize swelling. The effect is enhanced by simultaneous local intra-muscular use of dexamethasone. The drawbacks of this study were 2-fold: (i) the effects of LPL, if any, was confounded by the simultaneous use of dexamethasone, and (ii) while the combination of LPL and dexamethasone achieved a statistical significant reduction in edema, its clinical benefit is unclear.

Stergioulas (2007) compared the effectiveness of a protocol of combination of laser with plyometric exercises and a protocol
of placebo laser with the same program, in the treatment of tennis elbow. A total of 50 patients were randomized into 2 groups: (i) group A (n = 25) was treated with a 904 nm Ga-As laser, frequency 50 Hz, intensity 40 mW and energy density 2.4 J/cm², plus plyometric exercises, and (ii) group B (n = 25) that received placebo laser plus the same plyometric exercises. During 8 weeks of therapy, patients of the 2 groups received 12 sessions of laser or placebo, 2 sessions per week (weeks 1 to 4) and 1 session per week (weeks 5 to 8). Pain at rest, at palpation on the lateral epicondyle, during resisted wrist extension, middle finger test, and strength testing was evaluated using visual analog scale (VAS). Also, the grip strength, the range of motion (ROM) and weight test were evaluated. Parameters were determined before treatment, at the end of the 8th week course of treatment (week 8), and 8th (week 8) after the end of treatment. Relative to group B, group A had (i) a significant decrease of pain at rest at the end of 8 weeks of the treatment (p < 0.005) and at the end of following up period (p < 0.05), (ii) a significant decrease in pain at palpation and pain on isometric testing at 8 weeks of treatment (p < 0.05), and at 8 weeks follow-up (p < 0.001), (iii) a significant decrease in pain during middle finger test at the end of 8 weeks of treatment (p < 0.01), and at the end of the follow-up period (p < 0.05), (iv) a significant decrease of pain during grip strength testing at 8 weeks of treatment (p < 0.05), and at 8 weeks follow-up (p < 0.001), (v) a significant increase in the wrist ROM at 8 weeks follow-up (p < 0.01), (vi) an increase in grip strength at 8 weeks of treatment (p < 0.05) and at 8 weeks follow-up (p < 0.01), and (vii) a significant increase in weight-test at 8 weeks of treatment (p < 0.05) and at 8 weeks follow-up (p < 0.005). The authors concluded that these findings suggested that the combination of laser with plyometric exercises was more effective treatment than placebo laser with the same plyometric exercises at the end of the treatment as well as at the follow-up. Moreover, they stated that future studies are
needed to establish the relative and absolute effectiveness of
the above protocol.

Kaviani and colleagues (2006) examined the effects of low-
level laser therapy (LLLT) in the treatment of post-mastectomy
lymphedema. A total of 11 women with unilateral post-
mastectomy lymphedema were enrolled in a double-blind
controlled trial. Patients were randomly assigned to laser and
sham groups and received laser or placebo irradiation (Ga-As
laser device with a wavelength of 890 nm and fluence of 1.5
J/cm²) over the arm and axillary areas. Changes in patients'
limb circumference, pain score, ROM, heaviness of the
affected limb, and desire to continue the treatment were
measured before the treatment and at follow-up sessions
(weeks 3, 9, 12, 18, and 22) and were compared to pre-
treatment values. Results showed that of the 11 enrolled
patients, 8 completed the treatment sessions. Reduction in
limb circumference was detected in both groups, although it
was more pronounced in the laser group up to the end of 22nd
week. Desire to continue treatment at each session and
baseline score in the laser group was greater than in the sham
group in all sessions. Pain reduction in the laser group was
more than in the sham group except for the weeks 3 and 9.
No substantial differences were seen in other 2 parameters
between the 2 treatment groups. The authors concluded that
despite the encouraging results, further studies of the effects
of LLLT in management of post-mastectomy lymphedema
should be undertaken to determine the optimal physiological
and physical parameters to obtain the most effective clinical
response.

In a systematic review of common conservative therapies for
arm lymphoedema secondary to breast cancer treatment,
Moseley et al (2007) stated that secondary arm lymphoedema
is a chronic and distressing condition which affects a
significant number of women who undergo breast cancer
treatment. A number of health professional and patient
instigated conservative therapies have been developed to help
with this condition, but their comparative benefits are not clearly known. This systematic review undertook a broad investigation of commonly instigated conservative therapies for secondary arm lymphoedema including: complex physical therapy, manual lymphatic drainage, pneumatic pumps, oral pharmaceuticals, LLLT, compression bandaging and garments, limb exercises and limb elevation. It was found that the more intensive and health professional based therapies, such as complex physical therapy, manual lymphatic drainage, pneumatic pump and laser therapy generally yielded the greater volume reductions, whilst self-instigated therapies such as compression garment wear, exercises and limb elevation yielded smaller reductions. All conservative therapies produced improvements in subjective arm symptoms and quality of life issues, where these were measured. Despite the identified benefits, there is still the need for large scale, high level clinical trials in this area.

Information on lymphedema from the BC Cancer Agency (2007) notes that laser therapy "may or may not work but need [s] further study."

Carrasco et al (2009) noted that limited studies have demonstrated that LLLT may have a therapeutic effect on the treatment of myofascial pain syndrome (MPS). In this study, 60 patients with MPS and having 1 active trigger point in the anterior masseter and anterior temporal muscles were selected and assigned randomly to 6 groups (n = 10 in each group): Groups I to III were treated with GaAlAs (780 nm) laser, applied in continuous mode and in a meticulous way, twice-weekly, for 4 weeks. Energy was set to 25 J/cm², 60 J/cm² and 105 J/cm², respectively. Groups IV to VI were treated with placebo applications, simulating the same parameters as the treated groups. Pain scores were assessed just before, then immediately after the 4th application, immediately after the 8th application, at 15 days and 1 month following treatment. A significant pain reduction was observed over time (p < 0.001). The analgesic effect of the LLLT was
similar to the placebo groups. The authors stated that using the parameters described in this experiment, LLLT was effective in reducing pain experienced by patients with MPS. Thus, it was not possible to establish a treatment protocol.

Yelden and colleagues (2009) examined the effectiveness of LLLT in addition to exercise program on shoulder function in subacromial impingement syndrome (SAIS). A total of 67 patients with SAIS were randomly assigned to either a group that received laser (n = 34) or a group that received placebo laser (n = 26). Pain, functional assessment, disability and muscle strength of shoulder were assessed before and after a 3-week rehabilitation program. Besides laser or placebo laser, superficial cold and progressive exercise program were administered to both groups, 5 days a week, for 3 weeks. A progressive exercise program that was done twice-daily under supervision in clinic and at home was given to the patients. After the treatment, all outcome measurements had shown significant improvement except muscle strength in both the groups. When the parameters of the improvement were compared, there were no significant differences between the 2 groups after treatment. The authors concluded that there is no fundamental difference between LLLT and placebo LLLT when they are supplementing an exercise program for rehabilitation of patients with shoulder impingement syndrome.

In a prospective, randomized double-blind study, Teggi et al (2009) examined the effectiveness of LLLT for tinnitus. A total of 60 outpatients with tinnitus presenting sensorineural hearing loss in the affected ear were included in the study. They were randomly divided into 2 groups: (i) active laser therapy 20 mins a day for 3 months with a 650-nm, 5-mW soft laser (group L), and (ii) control group with dummy device, which duplicated all aspects of active laser therapy except for the activation of the laser beam. One subject in both groups dropped out due to an increase in tinnitus loudness. Two more patients in each group ceased to comply with the
protocol due to familiar problems. Main outcome measure was the Tinnitus Handicap Inventory (THI); no statistical difference was detected between the 2 groups in the THI total score \( (p = 0.97) \), and its functional \( (p = 0.89) \), emotional \( (p = 0.89) \) and catastrophic \( (p = 0.89) \) subscales. Moreover, a VAS for self-perceived loudness of the tinnitus showed no difference between the groups \( (p = 0.69) \). Regarding psychoacoustic parameters, the minimum masking level showed no difference \( (p = 0.42) \), while loudness expressed in sensation level exhibited lower values in the treatment group \( (p = 0.0127) \).

Subjects in the treatment group also reported a decreased rate of hyperacusis \( (p = 0.02) \). No changes were detected in the audiometric threshold in both groups. The authors concluded that soft laser therapy demonstrated no efficacy as a therapeutic measure for tinnitus.

A systematic evidence review by Chow et al. (2009) concluded that lowLLLT reduced pain immediately after treatment in acute neck pain, and up to 22 weeks after completion of treatment, in patients with chronic neck pain. The authors included randomized controlled trials (RCTs) or quasi-RCTs of LLLT, for participants aged 16 or over with acute or chronic neck pain, were eligible for inclusion. Sixteen RCTs \( (n = 820 \text{ participants}) \) met inclusion criteria, with sample sizes ranging from 20 to 90 participants. The authors reported significant effects of LLLT on acute and chronic neck pain. An evaluation of the systematic evidence review by Chow et al. by the Centre for Reviews and Dissemination (2009) found that, although suitable methods were employed to reduce the risks of reviewer error and bias for the processes of study selection and data extraction, the authors did not report on whether such methods were used to assess study quality, which was assessed using the Jadad scale. The CRD also found that this did not assess methods of allocation concealment, so the risk on investigator bias affecting trial results could not be ruled out. Furthermore, no information was provided on the actual levels of withdrawals and drop-outs. The CRD also found that all trials included in this systematic review had
relatively small sample sizes and information was not provided on whether treatment groups (in individual trials) were comparable at baseline for likely confounders. The CRD noted that the authors of the systematic review acknowledged the considerable clinical heterogeneity in laser treatment parameters, but this also seemed apparent with regard to the sites treated, diagnoses, frequencies of treatment, and uses of cointerventions; it is therefore questionable whether meta-analysis was the most appropriate method of synthesis. The CRD concluded: "Although many aspects of this review were well-conducted, the considerable clinical heterogeneity seen, coupled with uncertainty regarding possible bias in the small trials included, mean the authors’ conclusions should be interpreted with a degree of caution."

In a randomized, double-blind, placebo-controlled study, Ay and colleagues (2010) compared the effectiveness of LLLT on pain and functional capacity in patients with acute and chronic low back pain caused by lumbar disk herniation (LDH). A total of 40 patients with acute (26 females/14 males) and 40 patients with chronic (20 females/20 males) low back pain caused by LDH were included in the study. Patients were randomly allocated into 4 groups: (i) group 1 (acute LDH, n = 20) received hot-pack + laser therapy; (ii) group 2 (chronic LDH, n = 20) received hot-pack + laser therapy; (iii) group 3 (acute LDH, n = 20) received hot-pack + placebo laser therapy, and (iv) group 4 (chronic LDH, n = 20) received hot-pack + placebo laser therapy, for 15 sessions during 3 weeks. Assessment parameters included pain, patients’ global assessment, physician's global assessment, and functional capacity. Pain was evaluated by VAS. Patients’ and physician’s global assessment were also measured with VAS. Modified Schober test and flexion and lateral flexion measures were used in the evaluation of ROM of lumbar spine. Roland Disability Questionnaire (RDQ) and Modified Oswestry Disability Questionnaire (MODQ) were used in the functional evaluation. Measurements were done before and
after 3 weeks of treatment. After the treatment, there were statistically significant improvements in pain severity, patients’ and physician’s global assessment, ROM, RDQ scores, and MODQ scores in all groups (p < 0.05). However, no significant differences were detected between 4 treatment groups with respect to all outcome parameters (p > 0.05). There were no differences between laser and placebo laser treatments on pain severity and functional capacity in patients with acute and chronic low back pain caused by LDH.

In a randomized double-blind controlled trial, Meireles and associates (2010) assessed the effectiveness of LLLT on pain reduction and improvement in function in the hands of patients with rheumatoid arthritis. A total of 82 patients with rheumatoid arthritides were included in this study. The experimental group was submitted to the application of laser therapy, whereas the control group received a placebo laser. Aluminum gallium arsenide laser was used, at a wavelength of 785 nm, dose of 3 J/cm(2) and mean power of 70 mW. The groups were homogenous at the beginning of the study with regard to the main variables (p > 0.05). There were no statistically significant differences between groups in most of the measurements taken at the end of the intervention including the primary variables; the following variables were the exceptions: favoring the experimental group -- inflammation of the inter-phalangeal joint of the right thumb (p = 0.012) and perimetry of the inter-phalangeal joint of the left thumb (p = 0.013); and favoring the control group -- flexion of the proximal inter-phalangeal joint of the right fifth finger (p = 0.021), perimetry of the third proximal inter-phalangeal joint of the right hand (p = 0.044), grip strength in the left hand (p = 0.010), and the work domain of the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire (p = 0.010). The authors concluded that low-level aluminum gallium arsenide laser therapy is not effective at the wavelength, dosage, and power studied for the treatment of hands among patients with rheumatoid arthritis.
The Blue Cross and Blue Shield Association Technology Evaluation Center (2010) concluded that LLLT for either carpal tunnel syndrome or for chronic neck pain does not meet the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria. Furthermore, the Work Loss Data Institute's clinical practice guideline on "Carpal tunnel syndrome" (2011) does not recommend LLLT as a therapeutic option.

Kadhim-Saleh et al (2013) examined the effectiveness of LLLT in reducing acute and chronic neck pain as measured by the VAS. A systematic search of 9 electronic databases was conducted to identify original articles. For study selection, 2 reviewers independently assessed titles, abstracts, and full text for eligibility. Methodological quality was assessed using the Detsky scale. Data were analyzed using random-effects model in the presence of heterogeneity and fixed-effect model in its absence. Heterogeneity was assessed using Cochran's Q statistic and quantifying $I^2$. Risk ratios (RR) with 95% confidence intervals (CI) were reported. Eight RCTs involving 443 patients met the strict inclusion criteria. Inter-rater reliability for study selection was 92.8% (95% CI: 80.9 to 100%) and for methodological quality assessment was 83.9% (95% CI: 19.4 to 96.8%). Five trials included patients with cervical myofascial pain syndrome (CMPS), and 3 trials included different patient populations. A meta-analysis of 5 CMPS trials revealed a mean improvement of VAS score of 10.54 with LLLT (95% CI: 0.37 to 20.71; heterogeneity $I^2 = 65\%$, $p = 0.02$). The authors concluded that this systematic review provided inconclusive evidence because of significant between-study heterogeneity and potential risk of bias. They stated that the benefit seen in the use of LLLT, although statistically significant, does not constitute the threshold of minimally important clinical difference.

van Middelkoop et al (2011) determined the effectiveness of physical and rehabilitation interventions (i.e. exercise therapy, back school, transcutaneous electrical nerve stimulation
(TENS), LLLT, education, massage, behavioral treatment, traction, multi-disciplinary treatment, lumbar supports, and heat/cold therapy) for chronic low back pain (LBP). The primary search was conducted in MEDLINE, EMBASE, CINAHL, CENTRAL, and PEDro up to 22 December 2008. Existing Cochrane reviews for the individual interventions were screened for studies fulfilling the inclusion criteria. The search strategy outlined by the Cochrane Back Review Groups (CBRG) was followed. The following were included for selection criteria: (i) RCTs, (ii) adult (greater than or equal to 18 years) population with chronic (greater than or equal to 12 weeks) non-specific LBP, and (iii) evaluation of at least one of the main clinically relevant outcome measures (pain, functional status, perceived recovery, or return to work).

Two reviewers independently selected studies and extracted data on study characteristics, risk of bias, and outcomes at short, intermediate, and long-term follow-up. The GRADE approach was used to determine the quality of evidence. In total, 83 RCTs met the inclusion criteria: exercise therapy (n = 37), back school (n = 5), TENS (n = 6), LLLT (n = 3), behavioral treatment (n = 21), patient education (n = 1), traction (n = 1), and multi-disciplinary treatment (n = 6).

Compared to usual care, exercise therapy improved post-treatment pain intensity and disability, and long-term function. Behavioral treatment was found to be effective in reducing pain intensity at short-term follow-up compared to no treatment/waiting list controls. Finally, multi-disciplinary treatment was found to reduce pain intensity and disability at short-term follow-up compared to no treatment/waiting list controls. Overall, the level of evidence was low. Evidence from RCTs demonstrated that there is low quality evidence for the effectiveness of exercise therapy compared to usual care, there is low evidence for the effectiveness of behavioral therapy compared to no treatment and there is moderate evidence for the effectiveness of a multi-disciplinary treatment compared to no treatment and other active treatments at reducing pain at short-term in the treatment of chronic LBP.
Based on the heterogeneity of the populations, interventions, and comparison groups, the authors concluded that there are insufficient data to draw firm conclusion on the clinical effect of back schools, LLLT, patient education, massage, traction, superficial heat/cold, and lumbar supports for chronic LBP.

Lake and Wofford (2011) examined the effectiveness of therapeutic modalities for the treatment of patients with patella-femoral pain syndrome (PFPS). Medline was searched using the following databases: PubMed, CINAHL, Web of Science Citation Index, Science Direct, ProQuest Nursing & Allied Health, and Your Journals@OVID. Selected studies were RCTs that used a therapeutic modality to treat patients with PFPS. The review included articles with all outcome measures relevant for the PFPS patient: knee extension and flexion strength (isokinetic and isometric), patella-femoral pain assessment during activities of daily life, functional tests (e.g., squats), Kujala patella-femoral score, and electromyographic recording from knee flexors and extensors and quadriceps femoris cross-sectional areas. Authors conducted independent quality appraisals of studies using the PEDro Scale and a system designed for analysis of studies on interventions for patella-femoral pain. A total of 12 studies met criteria: 1 on the effects of cold and ultrasound together, ice alone, iontophoresis, and phonophoresis; 3, neuromuscular electrical stimulation; 4, electromyographic biofeedback; 3, electrical stimulation for control of pain; and 1, laser. Most studies were of low to moderate quality. Some reported that therapeutic modalities, when combined with other treatments, may be of some benefit for pain management or other symptoms. There was no consistent evidence of any beneficial effect when a therapeutic modality was used alone. Studies did not consistently provide added benefit to conventional physical therapy in the treatment of PFPS. The authors concluded that none of the therapeutic modalities reviewed has sound scientific justification for the treatment of PFPS when used alone.
The American College of Occupational and Environmental Medicine’s clinical guideline on “Elbow disorders” (ACOEM, 2012) listed low-level laser therapy as one of the interventions/procedures that were considered, but are not currently recommended.

In a meta-analysis, Sgolastra et al (2013) evaluated the effectiveness of lasers in reducing dentin hypersensitivity (DH) as compared with placebo or no treatment. Seven electronic databases and a manual search resulted in 2,538 unique publications. After selection, 13 studies were included in the meta-analysis. A CONSORT-based quality assessment revealed that 3 and 10 studies were at low- and high-risk of bias, respectively. A random-effects model with the generic inverse variance standardized mean difference (SMD) was used because of expected heterogeneity. Meta-analyses of the baseline-end of follow-up changes in pain revealed no differences for Er,Cr:YSSG versus placebo (SMD = 2.49; 95% CI: -0.25 to 5.22; p = 0.07) but did reveal differences in favor of lasers for Er:YAG versus placebo (SMD, 2.65; 95% CI: 1.25 to 4.05; p = 0.0002), Nd:YAG versus placebo (SMD, 3.59; 95% CI: 1.49 to 5.69; p = 0.02), and GaAlAs versus placebo (SMD, 3.40; 95% CI: 1.93 to 4.87; p < 0.00001). High and significant heterogeneity was found for all comparisons. The authors concluded that Er:YAG, Nd:YAG, and GaAlAs lasers appear to be effective in reducing DH. However, given the high heterogeneity of the included studies, future RCTs are needed to confirm these results.

(January 1982 to March 2012), PsycINFO (January 1806 to March 2012), PEDRO (January 29, 2013) and clinical trials registers (January 29, 2013). Randomized or quasi-randomized clinical trials that compared any post-operative rehabilitation intervention with no intervention, placebo or another post-operative rehabilitation intervention in individuals who had undergone CTS surgery were selected for analysis. Two reviewers independently selected trials for inclusion, extracted data and assessed the risk of bias according to standard Cochrane methodology. These researchers included 20 trials with a total of 1,445 participants. They studied different rehabilitation treatments including immobilization using a wrist orthosis, dressings, exercise, controlled cold therapy, ice therapy, multi-modal hand rehabilitation, laser therapy, electrical modalities, scar desensitization, and arnica. Three trials compared a rehabilitation treatment to a placebo comparison; 3 trials compared rehabilitation to a no treatment control; 3 trials compared rehabilitation to standard care; and 14 trials compared various rehabilitation treatments to one another. Overall, the included studies were very low in quality. Eleven trials explicitly reported random sequence generation and, of these, 3 adequately concealed the allocation sequence. Four trials achieved blinding of both participants and outcome assessors. Five studies were at high-risk of bias from incompleteness of outcome data at one or more time intervals. Eight trials had a high-risk of selective reporting bias. The trials were heterogeneous in terms of the treatments provided, the duration of interventions, the nature and timing of outcomes measured and setting. Therefore, these researchers were not able to pool results across trials. Four trials reported the authors’ primary outcome, change in self-reported functional ability at 3 months or longer. Of these, 3 trials provided sufficient outcome data for inclusion in this review. One small high quality trial studied a desensitization program compared to standard treatment and revealed no statistically significant functional benefit based on the Boston Carpal Tunnel Questionnaire (BCTQ) (MD -0.03; 95 % CI: -0.39 to 0.33). One moderate quality trial assessed
participants 6 months post-surgery using the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire and found no significant difference between a no formal therapy group and a 2-week course of multi-modal therapy commenced at 5 to 7 days post-surgery (MD 1.00; 95 % CI: -4.44 to 6.44). One very low quality quasi-randomized trial found no statistically significant difference in function on the BCTQ at 3 months post-surgery with early immobilization (plaster wrist orthosis worn until suture removal) compared with a splint and late mobilization (MD 0.39; 95 % CI: -0.45 to 1.23). The differences between the treatments for the secondary outcome measures (change in self-reported functional ability measured at less than 3 months; change in CTS symptoms; change in CTS-related impairment measures; presence of iatrogenic symptoms from surgery; return to work or occupation; and change in neurophysiological parameters) were generally small and not statistically significant. Few studies reported adverse events. The authors concluded that there is limited and, in general, low-quality evidence for the benefit of the reviewed interventions. People who have had CTS surgery should be informed about the limited evidence of the effectiveness of post-operative rehabilitation interventions. Until the results of more high-quality trials that evaluate the safety and effectiveness of various rehabilitation treatments have been reported, the decision to provide rehabilitation following CTS surgery should be based on the clinician's expertise, the patient's preferences and the context of the rehabilitation environment. It is important for researchers to identify patients who respond to a certain treatment and those who do not, and to undertake high-quality studies that evaluate the severity of iatrogenic symptoms from the surgery, measure function and return-to-work rates, and control for confounding variables.

He and co-workers (2013) examined the effectiveness of LLLT in the management of orthodontic pain. This systematic review and meta-analysis was carried out in accordance with Cochrane Handbook and the PRISMA statement. An
extensive literature search for RCTs, quasi-RCTs, and controlled clinical trials (CCTs) was performed through CENTRAL, PubMed, Embase, Medline, CNKI, and CBM up to October 2011. Risk of bias assessment was performed via referring to the Cochrane tool for risk of bias assessment. Meta-analysis was implemented using Review Manager 5.1. As a result, 4 RCTs, 2 quasi-RCTs, and 2 CCTs were selected from 152 relevant studies, including 641 patients from 6 countries. The meta-analysis demonstrated that 24 % risk of incidence of pain was reduced by LLLT (RR = 0.76, 95 % CI: 0.63 to 0.92, p = 0.006). In addition, compared to the control group, LLLT brought forward "the most painful day" (MD = -0.42, 95 % CI: -0.74 to -0.10, p = 0.009). Furthermore, the LLLT group also implied a trend of earlier end of pain compared with the control group (MD = -1.37, 95 % CI: -3.37 to 0.64, p = 0.18) and the pseudo-laser group (MD = -1.04, 95 % CI: -4.22 to 2.15, p = 0.52). However, the authors concluded that because of the methodological shortcomings and risk of bias of included trials, LLLT was proved with limited evidence in delaying pain onset and reducing pain intensity. Moreover, they stated that in the future, larger and better-designed RCTs are needed to provide clearer recommendations.

Thornton et al (2013) stated that shoulder pain is a common musculo-skeletal condition that affects up to 25 % of the general population. Shoulder pain can be caused by any number of underlying conditions including subacromial impingement syndrome, rotator-cuff tendinitis, and biceps tendinitis. Regardless of the specific pathology, pain is generally the number 1 symptom associated with shoulder injuries and can severely affect daily activities and quality of life of patients with these conditions. Two of the primary goals in the treatment of these conditions are reducing pain and increasing shoulder ROM. Conservative treatment has traditionally included a therapeutic exercise program targeted at increasing ROM, strengthening the muscles around the joint, proprioceptive training, or some combination of those activities. In addition, these exercise programs have been
supplemented with other interventions including non-steroidal anti-inflammatory drugs, corticosteroid injections, manual therapy, activity modification, and a wide array of therapeutic modalities (e.g., cryotherapy, EMS, ultrasound). Recently, LLLT has been used as an additional modality in the conservative management of patients with shoulder pain. However, the authors noted that true effectiveness of LLLT in decreasing pain and increasing function in patients with shoulder pain is unclear.

Amid et al (2014) reviewed the data published in the field of the effects of LLLT on proliferation and differentiation of the cells contributing in bone regeneration. These researchers performed an electronic search in PubMed from 2001 to April 2014. English language published papers on LLLT were found using the selected keyword. The full texts of potentially suitable articles were obtained for final assessment according to the exclusion and inclusion criteria. A total of 240 articles were found from 2001 to April 2014. Following the initial screening of titles and abstracts as well as the final screening of full texts, 22 articles completely fulfilled the inclusion criteria of this study. Wavelength used in LLLT irradiation varied between 600 to 1,000 nm with an energy density of 0.04 to 60 J/cm². Although almost all studies agreed on getting positive effects from LLLT, some had opposing results. The authors concluded that low level laser with low-energy density range appears to exert a bio-stimulatory effect on bone tissue, enhance osteoblastic proliferation as well as differentiation on cell lines used in in-vitro studies. They stated that despite the fact that many researches have been recently done on the effects of LLLT on different cell lines, without knowing the precise mechanism and effects, they were not able to offer a clinical treatment protocol.

Doeuk et al (2015) noted that LLLT is currently being used for various disorders, but with no convincing scientific evidence. Most recently these investigators have noticed an increase in published RCTs that have focused on its applications in wound
healing, scarring, disorders of the temporomandibular joint (TMJ), oral mucositis, and dental pain. These researchers evaluated the scientific evidence about its effectiveness in maxillofacial surgery. They reviewed PubMed from January 2003 to January 2013 using the key phrase "low level laser treatment". The inclusion criterion was intervention studies in humans of more than 10 patients. The authors excluded animal studies and papers in languages other than English, French, and German. These researchers found 45 papers that they screened independently. The resulting full texts were scrutinized by 2 authors who awarded a maximum of 5 points using the Jadad scale for assessing the quality of RCT, and extracted the data according to sample size, variables of LLLT, the authors' conclusions, and the significance of the result. The authors concluded that LLLT seems to be effective for the treatment of oral mucositis after treatment for head and neck cancer. However, it cannot yet be considered a valid treatment for disorders of the TMJ; and it seems to improve gingival healing, and myofascial and dental pain.

Huang et al (2015) examined the effectiveness of LLLT of knee osteoarthritis (KOA) by a systematic literature search with meta-analyses on selected studies. MEDLINE, EMBASE, ISI Web of Science and Cochrane Library were systematically searched from January 2000 to November 2014. Included studies were RCTs written in English that compared LLLT (at least 8 treatment sessions) with sham laser in KOA patients. The efficacy effective size was estimated by the SMD. Standard fixed or random-effects meta-analysis was used, and inconsistency was evaluated by the I-squared index (I(2)). Of 612 studies, 9 RCTs (7 double-blind, 2 single-blind, totaling 518 patients) met the criteria for inclusion. Based on 7 studies, the SMD in VAS pain score right after therapy (RAT) (within 2 weeks after the therapy) was not significantly different between LLLT and control (SMD = -0.28 [95% CI: -0.66 to 0.10], I(2) = 66 %). No significant difference was identified in studies conforming to the World Association of Laser Therapy (WALT) recommendations (4 studies) or on the basis of OA
severity. There was no significant difference in the delayed response (12 weeks after end of therapy) between LLLT and control in VAS pain (5 studies). Similarly, there was no evidence of LLLT effectiveness based on Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain, stiffness or function outcomes (5 and 3 studies had outcome data right after and 12 weeks after therapy respectively). The authors concluded that the findings of this study indicated that the best available current evidence does not support the effectiveness of LLLT as a therapy for patients with KOA.

Pavlic et al (2015) stated that recurrent aphthous stomatitis (RAS) is defined as multi-factor immunologic inflammatory lesions in the oral cavity, characterized by painful, recurrent single/multiple, shallow, round or ovoid ulcerations of mucosal tissues. To-date, a considerable number of RAS treatment protocols have been suggested, but since the etiology of RAS is idiopathic, these therapeutic options have symptomatic rather than curative or preventive effect. Recently, it has been suggested that laser therapy could be successfully used as an efficient treatment approach in therapy of RAS. These investigators estimated the effects of laser therapy in treatment of RAS analyzing results of clinical studies published in peer-reviewed journals. The studies published until December 31, 2013 were obtained from the Medline/PubMed, Science Direct and Cochrane Library of the Cochrane Collaboration (CENTRAL) online databases, using following search terms and key words: "laser" and "recurrent aphthous stomatitis", "laser" and "aphthous", and "laser" and "aphthae". A total of 4 original research articles met the all required inclusion/exclusion criteria, and were used for this review. The main outcome measures assessed were: a reduction of pain associated with RAS and a reduction in episode duration (faster RAS healing). The assessed literature demonstrated the benefits of laser therapy mainly due to immediate analgesia and ability to speed up a RAS healing process. The authors concluded that although the assessed literature suggested beneficial outcomes of laser therapy in treatment of
RAS, these results should be interpreted with caution. They stated that the issues related to the study designs and different sets of laser irradiation parameters of a limited number of available studies with the same treatment outcomes prevented them from making definite conclusions.

Vale et al (2015) noted that recurrent aphthous ulcers (RAUs) are the most common lesion found in the oral cavity. There is no definitive cure for RAUs and current treatments are aimed at minimizing symptoms. Since LLLT modulates inflammatory responses, and promotes pain reduction and cellular bio-stimulation, LLLT can be suggested as an alternative treatment for RAUs. The literature concerning the potential of LLLT in the treatment of RAUs was evaluated. A systematic literature review identified 22 publications, of which only 2 studies were adopted. The eligibility criteria consisted of RCTs. Both RCTs achieved significant results concerning LLLT and pain-level reductions and reduced healing times. Despite the variance in irradiation conditions applied in both studies, very similar wavelengths were adopted. There is accordingly strong evidence that wavelength plays an important role in RAU treatment. Taking into account the different parameters applied by selected RCTs, it is not possible to suggest that a specific protocol should be used. However, in light of the significant results found in both studies, LLLT can be suggested as an alternative for RAU treatment. The authors concluded that additional RCTs should be performed in order to reach a clinical protocol and better understand the application of LLLT in RAU treatment.

Bone Regeneration / Bone Healing

Atasoy and colleagues (2017) evaluated the effectiveness of low-level 940 nm laser therapy with energy intensities of 5, 10 and 20 J/cm2 on bone healing in an animal model. A total of 48 female adult Wistar rats underwent surgery to create bone defects in the right tibias. Low-level laser therapy was applied immediately after surgery and on post-operative days 2, 4, 6,
8, 10 and 12 in 3 study groups with energy intensities of 5 J/cm², 10 J/cm² and 20 J/cm² using a 940 nm Gallium-Aluminum-Arsenide (Ga-Al-As) laser, while 1 control group underwent only the tibia defect surgery. All animals were sacrificed 4 or 8 weeks post-surgery. Fibroblasts, osteoblasts, osteocytes, osteoclasts and newly formed vessels were evaluated by a histological examination. No significant change was observed in the number of osteocytes, osteoblasts, osteoclasts and newly formed vessels at either time period across all laser groups. Although LLLT with the 10 J/cm² energy density increased fibroblast activity at the 4th week in comparison with the 5 and 20 J/cm² groups, no significant change was observed between the laser groups and the control group. The authors concluded that these findings showed that low-level 940 nm laser with different energy intensities may not have marked effects on the bone healing process in both phases of bone formation.

In a systematic review, Skondra and colleagues (2018) evaluated the evidence on the effects of LLLT on bone healing following rapid maxillary expansion (RME). Electronic search was performed in Medline, Scopus, and Embase databases using appropriate Medical Subject Heading terms, with no time restriction. ClinicalTrials.gov (www.clinicaltrials.gov) was also searched using the terms "low level laser therapy" and "maxillary expansion". Original research articles on human clinical trials that involved both RME and LLLT were included. Animal studies were also assessed on an exploratory basis. The search strategy resulted in 12 publications (4 RCTs, 8 animal studies). In human studies, bone density was assessed radiographically (either 2-DI or 3-D imaging). Regardless of the discrepancies in the intervention protocols, the total of the trials revealed that LLLT had stimulatory effects on bone regeneration following RME. The studies in animal models measured the formation and maturation of new bone qualitatively or quantitatively. The authors concluded that despite the limited evidence, LLLT appeared to be a promising intervention for stimulating immediate bone regeneration and
healing following mid-palatal suture expansion. Moreover, these researchers stated that long-term, RCTs are needed to formulate safe results and establish a reliable clinical protocol, rendering the method clinically applicable.

Carpal Tunnel Syndrome

Li and colleagues (2016) evaluated the effectiveness of LLLT in the treatment of mild-to-moderate CTS using a Cochrane systematic review. The authors concluded that the findings of this study revealed that LLLT improved hand grip, VAS, and SNAP after 3 months of follow-up for mild-to-moderate CTS. However, they stated that more high-quality studies using the same laser intervention protocol are needed to confirm the effects of LLLT in the treatment of CTS.

Bekhet and associates (2017) performed a meta-analysis to investigate the efficacy of LLLT in the management of mild-to-moderate CTS. These investigators searched PubMed, Web of Knowledge, Scopus, Cochrane Central, and Virtual Health Library for RCTs that compared the effects of LLLT with or without splinting versus placebo on functional and electromyographic (EMG) outcomes in CTS. All outcomes were pooled as mean differences (MD) under the inverse variance or random effects model, using the statistical add-in (MetaXL, version 5.0). A total of 8 RCTs (473 patients/631 wrists) were eligible for the final analysis. The overall effect estimates did not favor LLLT therapy group over placebo in all primary outcomes: VAS (MD -1.11, 95 % CI: -2.58 to 0.35), symptom severity scale score (MD -1.41, 95 % CI: -5.12 to 2.29), and functional status scale score (MD -1.33, 95 % CI: -3.27 to 0.61). However, LLLT was superior to placebo in terms of grip strength (MD 2.19, 95 % CI: 1.63 to 2.76) and inferior to placebo in terms of sensory nerve action potential (MD -2.74, 95 % CI: -3.66 to -1.82). The authors concluded that laser therapy was superior to placebo in terms of improving the grip strength; however, no significant difference was found between both groups in terms of functional status.
improvement, pain reduction, or motor electro-diagnostic evaluations. They stated that further high-quality trials with longer follow-up periods are needed to establish the efficacy of LLLT for CTS treatment.

Temporomandibular Joint Disorders

Shukla and Muthusekhar (2016) evaluated the effectiveness of LLLT in patients with temporomandibular disorders (TMDs). Medline search was done from 1997 to 2011 using search terms appropriate to establishing a relation between LLLT and TMD. Only RCTs were included in this study. Outcome variables related to pain, muscle tenderness, mandibular movements, and EMG activity were considered. Of the 242 articles examined, 13 were finally included in the critical analysis conducted as a part of the present systematic review; 7 articles showed significant improvement in the study group, whereas 5 showed no significant improvement between the study and control groups. The primary outcome of most of the studies was pain. Other variables considered were muscle tenderness, mandibular movements; EMG activity was considered. The authors concluded that LLLT appeared to be effective in reduction of pain in TMDs. The hypothesis that LLLT acts through a dose-specific anti-inflammatory effect in the irradiated joint capsule is a possible explanation of the positive results. However, due to the limitations of this review, findings must be interpreted with caution. Moreover, they stated that there is a need for more well-conducted RCTs examining LLLT as interventions for TMDs. These studies need to be clear in the reporting of allocation, blinding, sequence generation, withdrawals, intention-to-treat analysis, and any other potential source of bias in the study. In addition, there should be use of well-validated standardized outcomes so that the RCTs could be compared with other similar trials. The sample size of the RCTs should also be calculated beforehand so that the study has adequate statistical power.
Magri and colleagues (2017) noted that women with TMD frequently report pain areas in body regions. This process is associated with central sensitization phenomena, present in chronic pain; LLLT has been reported as a therapeutic option for the painful TMD treatment. These investigators analyzed the effect of LLLT on pain intensity (VAS), pain sensitivity in orofacial and corporal points (pressure pain threshold, PPT), and on Short Form-McGill Pain Questionnaire (SF-MPQ) indexes of women with myofascial pain (subtype of muscle TMD). A total of 91 women (18 to 60 years) were included in the study, among which 61 were diagnosed with myofascial pain (Research Diagnostic Criteria for Temporomandibular Disorder-Ia and Ib) and were divided into laser (n = 31) and placebo group (n = 30), and 30 were controls; LLLT was applied at pre-established points, twice-weekly, 8 sessions (780 nm; masseter and anterior temporal = 5 J/cm2, 20 mW, 10 s; TMJ area = 7.5 J/cm2, 30 mW, 10 s). Pain intensity, pain sensitivity, and the SF-MPQ indexes were measured at the baseline, during laser sessions, and 30 days after treatment. For intra-group comparisons, the Friedman test was performed, and for inter-group, the Mann-Whitney test. Increased pain sensitivity was found in women with myofascial pain when compared to controls (p < 0.05). There was a reduction in pain intensity for both groups after LLLT. However, LLLT did not change the PPT for any group (p>0.05). Active laser and placebo reduced the indexes of sensory, total pain, and VAS, maintaining the results after 30 days; there was a reduction in the affective pain rating index for both groups, with no maintenance after 30 days for placebo, and the present pain intensity decreased in the laser group and did not change in the placebo after LLLT. The authors concluded that LLLT active or placebo were effective in reducing the overall subjective perception of myofascial pain (VAS and SF-MPQ indexes); however, they had no effectiveness in reducing the pain sensitivity in orofacial and corporal points (PPT increase).
Syndrome, Occipital Neuralgia, and Trigeminal Neuralgia)

Arbabi-Kalati and colleagues (2015) evaluated the effectiveness of LLLT in improving the symptoms of burning mouth syndrome (BMS). A total of 20 patients with BMS were enrolled in this study; they were divided in 2 groups randomly. In the laser group, in each patient, 10 areas on the oral mucosa were selected and underwent LLL irradiation at a wavelength of 630 nm, and a power of 30 mW for 10 seconds twice-weekly for 4 weeks. In the placebo group, silent/off laser therapy was carried out during the same period in the same areas. Burning sensation and quality of life were evaluated. Burning sensation severity and quality of life in the 2 groups after intervention were different significant (p = 0.004, p = 0.01, respectively). Patients in laser group had better results. The authors concluded that LLLT might decrease the intensity of BMS. However, the present study had some limitations, including the small sample size and long duration of the application of LLL, which decreases the cooperation of patients. These researchers stated that further research is needed to validate our findings.

Al-Maweri and colleagues (2017) stated that BMS is a chronic pain condition with indefinite cure, predominantly affecting post-menopausal women. These researchers reviewed the effectiveness of LLLT in the treatment of BMS. PubMed, Embase and Scopus were searched from date of inception till and including October 2016 using various combinations of the following keywords: burning mouth syndrome, BMS, stomatodynia, laser therapy, laser treatment and phototherapy. The inclusion criteria were: prospective, retrospective and case series studies. Letter to editors, reviews, experimental studies, studies that were not published in English, theses, monographs, and abstracts presented in scientific events were excluded. Due to heterogeneity of data no statistical analyses were performed. A total of 10 clinical studies fulfilled the eligibility criteria, 5 of which were randomized clinical trials. In these studies, the laser
wavelengths, power output and duration of irradiation ranged between 630 to 980 nm, 20 to 300 mW, 10 seconds to 15 minutes, respectively. Most of studies reported laser to be an effective therapy strategy for management of BMS. The authors concluded that the majority of the studies showed that laser therapy seemed to be effective in reducing pain in BMS patients. However, they stated that due to the varied methodologies and substantial variations in laser parameters among these studies, more clinical trials are needed to determine the effectiveness of laser for treating BMS.

In a systematic review, de Pedro and colleagues (2020) examined the efficacy of LLLT for the management of neuropathic orofacial pain. This systematic review was conducted according to PRISMA guidelines. A comprehensive search of the literature was conducted in the PubMed/Medline, Scopus, and Cochrane Library databases up to March 8, 2018, using terms such as low-level laser therapy, neuropathic pain, orofacial pain, neuralgia, neuropathy, and all the entities described in section 13 of the International Classification of Headache Disorders, 3rd edition. The primary outcome was measurement of pain intensity. A total of 997 studies were obtained with the initial search; 13 (8 RCTs, 2 prospective studies, and 3 case series) met the inclusion criteria and were analyzed for data extraction; 3 provided data for the treatment of trigeminal neuralgia (TN), 1 for occipital neuralgia, and 10 for BMS. All studies showed a reduction in pain intensity (most of them significant). The different studies analyzed LLLT alone and compared to placebo, to another treatment, or to different LLLT application protocols. The authors concluded that LLLT appeared to be effective as a therapeutic option for different neuropathic orofacial pain entities such as TN, occipital neuralgia, and BMS as a single or combined treatment. Moreover, these researchers stated that more quality studies assessing all outcome measures of chronic pain are needed in the medium- and long-terms. Furthermore,
due to the lack of standardization of the application technique, more well-designed studies are needed to confirm the results of this systematic review.

Cardio-Protection Following Myocardial Infarction / Heart Failure

Carlos and colleagues (2016) systematically reviewed the role of LLLT in cardiac remodeling after myocardial infarction (MI). Literatures were systematically searched in several electronic databases. These researchers included only studies with a well-standardized coronary occlusion model in-vivo LLLT application. After screening, a total of 14 studies were eligible for review. The study heterogeneity was described in terms of rationality, gender, irradiation parameters, treatment numbers and moment of LLLT application; 3 studies showed a null role of LLLT on infarct size, and only 1 study found positive LLLT effects on the cardiac performance. The cardio-protective role of LLLT was mediated by anti-inflammatory, pro-angiogenic and anti-oxidant actions. The authors concluded that the reduction in infarct size was a major finding. The stated that LLLT cardio-protection may be mediated by several molecular and cellular mechanisms; although these results are exciting, there are many limitations that must be resolved before LLLT clinical trials.

Manchini and associates (2017) noted that LLLT has been targeted as a promising approach that can mitigate post-infarction cardiac remodeling. There is some interesting evidence showing that the beneficial role of the LLLT could persist long-term even after the end of the application, but it remains to be systematically evaluated. These researchers tested the hypothesis that LLLT beneficial effects in the early post-infarction cardiac remodeling could remain in overt heart failure (HF) even with the disruption of irradiations. Female Wistar rats were subjected to the coronary occlusion to induce MI or sham operation. A single LLLT application was carried out after 60 seconds and 3 days post-coronary occlusion,
respectively. Echocardiography was performed 3 days and at the end of the experiment (5 weeks) to evaluate cardiac function. After the last echocardiographic examination, LV hemodynamic evaluation was performed at baseline and on sudden afterload increases. Compared with the sham group, infarcted rats showed increased systolic and diastolic internal diameter as well as a depressed shortening fraction of LV. The only benefit of the LLLT was a higher shortening fraction after 3 days of infarction. However, treated-LLLT rats showed a lower shortening fraction in the 5th week of study when compared with sham and non-irradiated rats. A worsening of cardiac function was confirmed in the hemodynamic analysis as evidenced by the higher left ventricular end-diastolic pressure and lower +dP/dt and -dP/dt with 5 weeks of study. Cardiac functional reserve was also impaired by infarction as evidenced by an attenuated response of stroke work index and cardiac output to a sudden afterload stress, without LLLT repercussions. No significant differences were found in the myocardial expression of Akt1/VEGF pathway. The authors concluded that these findings showed that LLLT improved LV systolic function in the early post-infarction cardiac remodeling; however, this beneficial effect may be dependent on the maintenance of phototherapy. They stated that long-term studies with LLLT application are needed to establish whether these effects ultimately translate into improved cardiac remodeling.

Hair Loss

Zarei and colleagues (2016) noted that despite the current treatment options for different types of alopecia, there is a need for more effective management options. Recently, LLLT was evaluated for stimulating hair growth. These investigators reviewed the current evidence on the LLLT effects with an evidence-based approach, focusing more on RCTs by critically evaluating them. In order to examine if in individuals presenting with hair loss (male pattern hair loss (MPHL), female pattern hair loss (FPHL), alopecia areata (AA), and
chemotherapy-induced alopecia (CIA)) LLLT is effective for hair re-growth, several databases including PubMed, Google Scholar, Medline, Embase, and Cochrane Database were searched using the following keywords: alopecia, hair loss, Hair growth, low level laser therapy, low level light therapy, low energy laser irradiation, and photobiomodulation (PBM). From the searches, 21 relevant studies were summarized in this review including 2 in-vitro, 7 animal, and 12 clinical studies. Among clinical studies, only 5 were RCTs, which evaluated LLLT effect on male and female pattern hair loss. The RCTs were critically appraised using the created checklist according to the Critical Appraisal for Therapy Articles Worksheet created by the Center of Evidence-Based Medicine, Oxford. The results demonstrated that all the performed RCTs have moderate to high quality of evidence. However, only 1 out of 5 studies performed intention-to-treat analysis, and only another study reported the method of randomization and subsequent concealment of allocation clearly; all other studies did not include this very important information in their reports. None of these studies reported the treatment effect of factors such as number needed to treat. Based on this review on all the available evidence about effect of LLLT in alopecia, these researchers found that the FDA-cleared LLLT devices are both safe and effective in patients with MPHL and FPHL who did not respond or were not tolerant to standard treatments. The authors concluded that future RCTs of LLLT are strongly encouraged to be conducted and reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement to facilitate analysis and comparison.

In a Cochrane review, van Zuuren and associates (2016) evaluated the safety and effectiveness of the available options for the treatment of female pattern hair loss in women. These investigators updated their searches of the following databases to July 2015: the Cochrane Skin Group Specialized Register, CENTRAL in the Cochrane Library (2015, Issue 6), Medline (from 1946), Embase (from 1974), PsycINFO (from 1872), AMED (from 1985), LILACS (from 1982), PubMed (from
1947), and Web of Science (from 1945). They also searched 5 trial registries and checked the reference lists of included and excluded studies. They included RCTs that assessed the effectiveness of interventions for FPHL in women; 2 review authors independently assessed trial quality, extracted data and carried out analyses. The authors concluded that although there was a predominance of included studies at unclear to high risk of bias, there was evidence to support the safety and effectiveness of topical minoxidil in the treatment of FPHL (mainly moderate-to-low quality evidence). Furthermore, there was no difference in effect between the minoxidil 2 % and 5 % with the quality of evidence rated moderate-to-low for most outcomes. Finasteride was no more effective than placebo (low quality evidence). They stated that there were inconsistent results in the studies that evaluated laser devices (moderate-to-low quality evidence), but there was an improvement in total hair count measured from baseline. These investigators stated that further RCTs of other widely-used treatments, such as spironolactone, finasteride (different dosages), dutasteride, cyproterone acetate, and laser-based therapy are needed.

Gupta and Foley (2017) consolidated evidence and established which data are still required for the widespread acceptance of LLLT for hair loss therapy. A thorough search of the PubMed database was conducted to obtain studies investigating LLLT for androgenetic alopecia (AGA) in men and women. A total of 9 trials were identified for comb and helmet/cap devices, 5 of which were RCTs. Data comparison across LLLT trials and with traditional hair loss therapy (minoxidil, finasteride) was not straightforward because there was a lack of visual evidence, sample sizes were low, and there were large variations in study duration and effectiveness measurements. The authors concluded that there are a number of unanswered questions about the optimum treatment regimen, including maintenance treatment and the long-term consequences of LLLT use. They stated that
moving forward, protocols should be standardized across trials; and it is recommended that future trials include visual evidence and trial duration be expanded to 12 months.

Afifi and co-workers (2017) reviewed the existing research studies to examine if LLLT is an effective therapy for AGA based on objective measurements and patient satisfaction. These researchers performed a systematic literature review to identify articles on Medline, Google Scholar, and Embase that were published between January 1960 and November 2015. All search hits were screened by 2 reviewers and examined for relevant abstracts and titles. Articles were divided based on study design and assessed for risk of bias. A total of 11 studies were evaluated, which investigated a total of 680 patients, consisting of 444 males and 236 females; 9 out of 11 studies assessing hair count/hair density found statistically significant improvements in both males and females following LLLT treatment. Additionally, hair thickness and tensile strength significantly improved in 2 out of 4 studies. Patient satisfaction was investigated in 5 studies, and was overall positive, though not as profound as the objective outcomes. The authors concluded that the majority of studies covered in this review found an overall improvement in hair re-growth, thickness, and patient satisfaction following LLLT therapy. They stated that although caution is needed when interpreting these findings, LLLT therapy appeared to be a promising monotherapy for AGA and may serve as an effective alternative for individuals unwilling to use medical therapy or undergo surgical options.

Darwin and colleagues (2018) examined the clinical trials to determine whether the body of evidence supports the use of low-level laser therapy (LLLT) to treat androgenic alopecia (AGA). A literature search was conducted through PubMed, Embase, and Clinicaltrials.gov for clinical trials using LLLT to treat AGA. Thirteen clinical trials were assessed. Review articles were not included. Ten of 11 trials demonstrated significant improvement of androgenic alopecia in comparison
to baseline or controls when treated with LLLT. In the remaining study, improvement in hair counts and hair diameter was recorded, but did not reach statistical significance. Two trials did not include statistical analysis, but showed marked improvement by hair count or by photographic evidence. Two trials showed efficacy for LLLT in combination with topical minoxidil. One trial showed efficacy when accompanying finasteride treatment. LLLT appears to be a safe, alternative treatment for patients with androgenic alopecia. Clinical trials have indicated efficacy for androgenic alopecia in both men and women. It may be used independently or as an adjuvant of minoxidil or finasteride. More research needs to be undertaken to determine the optimal power and wavelength to use in LLLT as well as LLLT's mechanism of action.

Delaney and Zhang (2018) stated that alopecia is a common disorder affecting over 50% of the world's population. Within this condition, androgenic alopecia (AA) is the most common type, affecting 50% of men over 40 years of age and 75% of women over 65. Anecdotal paradoxical hypertrichosis noted during laser epilation has generated interest in the possibility of using laser to stimulate hair growth. These investigators evaluated the application of LLLT for the treatment of AA in adults. They carried out a systematic review on studies identified on Medline, Embase, Cochrane database, and clinicaltrials.org. Double-blinded RCTs were selected and analyzed quantitatively (meta-analysis) and qualitatively (quality of evidence, risk of bias). The authors concluded that LLLT appeared to be a promising non-invasive treatment for AA in adults that is safe for self-administration in the home-setting. These researchers stated that although shown to effectively stimulate hair growth when compared to sham devices, these results must be interpreted with caution. They stated that further studies with larger samples, longer follow-up, and independent funding sources are needed to determine the clinical effectiveness of this novel therapy.
Liu and colleagues (2019) examined the effectiveness of LLLT in the treatment of adult AA (AAA). A systematic search of studies on LLLT for AAA was conducted mainly in PubMed, Embase, and Cochrane Systematic Reviews. The SMD in the changes of hair density treated by LLLT versus sham devices was analyzed. The meta-analysis included 8 studies comprising a total of 11 double-blinded RCTs. The quantitative analysis showed a significant increase in hair density for those treated by LLLT versus sham group (SMD 1.316, 95 % CI: 0.993 to 1.639). The subgroup analysis demonstrated that LLLT increased hair growth in both genders, in both comb- and helmet-type devices, and in short- and long-term treatment course. The subgroup analysis also showed a more significant increase of hair growth for the LLLT versus sham in the low-frequency treatment group (SMD 1.555, 95 % CI: 1.132 to 1.978) than in the high-frequency group (SMD 0.949, 95 % CI: 0.644 to 1.253). The review was limited by the heterogeneity of included trials; LLLT significantly increased hair density in AAA. The authors concluded that the findings of this meta-analysis suggested that low treatment frequency by LLLT had a better hair growth effect than high treatment frequency. They stated that LLLT represents a potentially effective treatment for AAA in both male and female.

Marchitto and colleagues (2019) noted that alopecia areata (AA) is a common form of patchy, non-scarring hair loss. Although intralesional steroid injections are currently the mainstay therapy for AA, other non-steroid-based therapies, including platelet-rich plasma (PRP), ultra-violet radiation (UVR), and laser-based modalities, are emerging as management options. These researchers systematically reviewed non-steroid-based therapies for the treatment of AA. They carried out a systematic review of the literature searching PubMed/Medline databases identifying studies examining PRP, UVR, and laser-based modalities for the treatment of AA. Literature search yielded 644 articles entailing PRP, UVR, and laser treatment modalities for AA. Of the 644 articles, 46
met inclusion criteria. Although numerous reports demonstrated strong potential for PRP, UVR, and laser modalities in treating AA, high-quality evidence supporting their efficacy is still lacking. The authors concluded that there is an abundance of evidence for non-steroid-based therapies in the treatment of AA. Moreover, these researchers stated that RCTs comparing these therapeutic options head-to-head should be conducted to better understand the true effectiveness of these therapies.

Head and Neck Cancer

Zecha and colleagues (2016) noted that recent advances in PBM technology, together with a better understanding of mechanisms involved, may expand the applications for PBM in the management of other complications associated with head and neck cancer (HNC) treatment. This article (part 1) described PBM mechanisms of action, dosimetry, and safety aspects and, in doing so, provided a basis for a companion paper (part 2), which described the potential breadth of potential applications of PBM in the management of side-effects of (chemo)radiation therapy in patients being treated for HNC and proposed PBM parameters. These investigators reviewed PBM mechanisms of action and dosimetric considerations. Virtually, all conditions modulated by PBM (e.g., ulceration, inflammation, lymphedema, pain, fibrosis, neurological and muscular injury) are thought to be involved in the pathogenesis of (chemo)radiation therapy-induced complications in patients treated for HNC. The impact of PBM on tumor behavior and tumor response to treatment has been insufficiently studied. In-vitro studies assessing the effect of PBM on tumor cells report conflicting results, perhaps attributable to inconsistencies of PBM power and dose. However, the biological bases for the broad clinical activities ascribed to PBM have also been noted to be similar to those activities and pathways associated with negative tumor behaviors and impeded response to treatment. While there are no anecdotal descriptions of poor tumor outcomes in
patients treated with PBM, confirming its neutrality with respect to cancer responsiveness is a critical priority. The authors concluded that based on its therapeutic effects, PBM may have utility in a broad range of oral, oropharyngeal, facial, and neck complications of HNC treatment. They stated that although evidence suggested that PBM using LLLT is safe in HNC patients, more research is imperative and vigilance remains warranted to detect any potential adverse effects of PBM on cancer treatment outcomes and survival.

Furthermore, National Comprehensive Cancer Network’s clinical practice guideline on “Head and neck cancers “ (Version 1.2017) does not mention LLLT as a management option.

Neuropathic Pain

de Andrade and colleagues (2016) reviewed the literature on the use of LLLT in neuropathic pain with the goal of establishing a “therapeutic window” for the effective use of this treatment. These researchers analyzed 14 articles, 10 in experimental animals and 4 in humans. The results were presented in 3 tables, the first being for comparison of the studies’ application parameters, the second showing the average and median parameters experimental studies and third showing the clinical studies embodiment. The experimental studies revealed better results for LLLT and infrared laser powers above 70 mW. Clinical studies were inconclusive as to the application parameters, due to the discrepancy; however all demonstrated the effectiveness of LLLT. According to the data presented, the authors concluded that LLLT had positive effects on the control of analgesia for neuropathic pain, but further studies with high scientific rigor are needed in order to define treatment protocols that optimize the action LLLT in neuropathic pain.
Oral Mucositis

Bayer and colleagues (2017) stated that oral mucositis (OM) induces severe pain and limits fundamental life behaviors such as eating, drinking, and talking for patients receiving chemotherapy or radiotherapy. In addition, through opportunistic microorganisms, OM frequently leads to systemic infection, which then leads to prolonged hospitalization. Severe lesions often adversely affect curative effects in cancer cases. Thus, the control of OM is important for oral health quality of life and prognosis. Low-level laser therapy and ozone may be useful to accelerate wound healing. In this study, 24 Sprague-Dawley rats were divided into 3 groups: (i) control, (ii) ozone, and (iii) laser groups. All groups received 5-fluorouracil intra-peritoneally and trauma to the mouth pouch with a needle. After the formation of OM in the mouth, the control group had no treatment; the ozone group was administered ozone, and the laser group, LLLT. Then, all groups were sacrificed and basic fibroblast growth factor (bFGF), transforming growth factor (TGF-β), and platelet-derived growth factor (PDGF) were evaluated in all groups; LLLT was found to be statistically significantly more effective than ozone on FGF and PDGF. However, in respect of TGF-β, no statistically significant difference was observed between the groups. The authors concluded that within the limitations of this study, LLLT was more effective than ozone; however, further studies on this subject are needed.

de Lima, et al. (2020) reported on a systematic review and meta-analysis to determine the effectiveness of low-level laser therapy in preventing oral mucositis in patients undergoing chemoradiotherapy for head and neck cancer. The following databases were searched through September 2018, with last search performed on May 2019, for clinical trials: MEDLINE via PubMed, Cochrane Central, Scopus, Lilacs, ISI Web of Science and SIGLE via Open Grey. From 14,525 records, 4 studies were included in the review and 3 studies were included in meta-analysis. Data from 500 patients (mean age
of 53.595 and 54.14 for intervention and control groups, respectively) were analyzed. Meta-analysis showed that laser therapy prevents oral mucositis incidence in 28% and 23% of cases during the third and fourth follow-up week, respectively, in comparison to a placebo-treated control group. There was no statistically significant difference the prevention of pain; dysphagia and quality of life were not analyzed due to missing data. The authors concluded that laser therapy was effective in preventing oral mucositis from the 15th to the 45th days of chemoradiotherapy. However, new primary studies with low risk of bias are needed so a higher scientific evidence can be obtained.

Peralta-Mamani and colleagues (2019) noted that dosimetry for LLLT depends on several parameters, such as target tissue type, lesion type and laser equipment used. These researchers determined the most used LLLT dosimetry for the treatment and prevention of OM resulting from radiation therapy (RT) in head and neck cancer patients (HNCP). This research was conducted according to the PRISMA guidelines using the PICO framework. After extensively searching PubMed, Web of Science, Embase, Scopus, BVS and Cochrane Library databases, these investigators found 130 records and selected 7 studies, involving 363 HNCP with an average age of 60.6 years who received RT. Briefly, sites affected by tumors were the following: oral cavity (n = 170), oropharynx (n = 91), throat (n = 42), larynx (n = 32), nasopharynx (n = 11), hypopharynx (n = 9), and in 8 cases, sites were not reported. These studies used several classifications for OM (RTOG/EORTC, WHO, NCI-CTC) and pain (NRS, VAS and modified VAS). These various researchers performed the LLLT punctual application of different forms using several protocols making analysis difficult. However, LLLT was effective regardless of the parameters used (632.8 nm to 685 nm, 1.8 J/cm² to 3.0 J/cm², 10 mW to 60 Mw, 0.8 J to 3.0 J). The meta-analysis showed a better results with preventive LLLT 660 nm, 3.8 J/cm², 15 mW; 0.15 J compared to preventive LLLT 660 nm, 1.3 J/cm², 5 mW;
0.05 J (OMS: p = 0.03; NCI-CTC: p = 0.027). The authors concluded that there is, as of yet, no evidence of better laser dosimetry being more effective; RCTs to determine which doses of LLLT are most appropriate for treating and preventing OM due to RT are lacking and should be further investigated.

Pressure Ulcers

Machado and colleagues (2017) evaluated the effects of LLT in pressure ulcers (PU) in humans through a systematic review of randomized studies. The search includes the databases Medline, PEDro, Cochrane CENTRAL, and Lilacs, as well a manual search until May, 2016. This included randomized clinical trials of LLT compared with other interventions, different types of LLT, LLT placebo, or control in the treatment of PU. The outcomes evaluated were the ulcer area, healing rate, and overall healing rate. The risk of bias was evaluated using the tool of the Cochrane Collaboration, and the results were analyzed descriptively. From the 386 articles identified, only 4 studies were included, with 2 LLT used with single wavelength (1: 904 nm versus control and 2: 940 nm versus 808 nm versus 658 nm versus placebo) and 2 LLT used to probe cluster. One study compared to different single wavelengths showed a significant 71% reduction of the PU and an improved healing rate in which 47% of PU healed completely after 1 month of therapy with the use of LLT with a wavelength of 658 nm compared with other lengths. The other analyzed wavelengths were not significant in the assessed outcomes. Significant results were observed in the use of LLT with a 658 nm wavelength, and no evidence was found for use of wavelengths above that for the treatment of PU. The authors also found no evidence in the laser used to probe the cluster.

Furthermore, an UpToDate review on “Overview of treatment of chronic wounds” (Evans and Kim, 2017) does not mention LLLT as a therapeutic option.
Traumatic Brain Injury

Thunshelle and Hamblin (2016) LLLT or PBM is a possible treatment for brain injury, including traumatic brain injury (TBI). These investigators reviewed the fundamental mechanisms at the cellular and molecular level and the effects on the brain were discussed. There are several contributing processes that have been proposed to lead to the beneficial effects of PBM in treating TBI such as stimulation of neurogenesis, a decrease in inflammation, and neuroprotection. Both animal and clinical trials for ischemic stroke were outlined. A number of articles have shown how transcranial LLLT (tLLLT) is effective at increasing memory, learning, and the overall neurological performance in rodent models with TBI. The authors’ laboratory has conducted 3 different studies on the effects of tLLLT on mice with TBI. The 1st studied pulsed against continuous laser irradiation, finding that 10 Hz pulsed was the best. The 2nd compared 4 different wavelengths, discovering only 660 and 810 nm to have any effectiveness, whereas 732 and 980 nm did not. The 3rd looked at varying regimens of daily laser treatments (1, 3, and 14 days) and found that 14 laser applications was excessive. The authors also reviewed several studies of the effects of tLLLT on neuroprogenitor cells, brain-derived neurotrophic factor and synaptogenesis, immediate early response knockout mice, and tLLLT in combination therapy with metabolic inhibitors.

Furthermore, an UpToDate review on “Management of acute severe traumatic brain injury” (Hemphill and Phan, 2017) does not mention LLLT as a therapeutic option.

Breast Cancer-Related Lymphedema

In a systematic review, Baxter and associates (2017) evaluated the effectiveness of LLLT (also known as photobiomodulation (PBM)) in the management of breast cancer related lymphedema (BCRL). Clinical trials were
searched in PubMed, AMED, Web of Science, and China National Knowledge Infrastructure up to November 2016; 2 reviewers independently assessed the methodological quality and adequacy of LLLT in these clinical trials. Primary outcome measures were limb circumference/volume, and secondary outcomes included pain intensity and ROM. Because data were clinically heterogeneous, best evidence synthesis was performed. A total of 11 clinical trials were identified, of which 7 RCTs were chosen for analysis. Overall, the methodological quality of included RCTs was high, whereas the reporting of treatment parameters was poor. Results indicated that there was strong evidence (3 high quality trials) showing LLLT was more effective than sham treatment for limb circumference/volume reduction at a short-term follow-up. There was moderate evidence (1 high quality trial) indicating that LLLT was more effective than sham laser for short-term pain relief, and limited evidence (1 low quality trial) that LLLT was more effective than no treatment for decreasing limb swelling at short-term follow-up. The authors concluded that based upon the current systematic review, LLLT may be considered an effective treatment approach for women with BCRL. However, they stated that due to the limited numbers of published trials available, there is a clear need for well-designed high-quality trials in this area. The optimal treatment parameters for clinical application have yet to be elucidated.

Obesity

Silva and colleagues (2018) noted that obesity represents a continuously growing global epidemic and is associated with the development of type 2 diabetes mellitus (T2DM). The etiology of T2DM is related to the resistance of insulin-sensitive tissues to its action leading to impaired blood glucose regulation. Photobiomodulation therapy might be a non-pharmacological, non-invasive strategy to improve insulin resistance. It has been reported that PBM therapy in combination with physical exercise reduces insulin resistance. These researchers examined the effects of PBM therapy on
insulin resistance in obese mice. Male Swiss albino mice received low-fat control diet (n = 16, LFC) or high-fat diet (n = 18, HFD) for 12 weeks. From 9th to 12th week, the mice received PBM therapy (laser) or sham (light-off) treatment and were allocated into 4 groups: LFC sham (n = 8), LFC PBM (n = 8), HFD sham (n = 9), and HFD PBM (n = 9). The PBM therapy was applied in 5 locations: to the left and right quadriceps muscle, upper limbs and center of the abdomen, during 40 s at each point, once-daily, 5 days a week, for 4 weeks (780 nm, 250 mW/cm², 10 J/cm², 0.4 J per site; 2 J total dose per day). Insulin signaling pathway was evaluated in the epididymal adipose tissue. PBM therapy improved glucose tolerance and phosphorylation of Akt (Ser473) and reversed the HFD-induced reduction of GLUT4 content and phosphorylation of AS160 (Ser588). Also, PBM therapy reversed the increased area of epididymal and mesenteric adipocytes. The authors concluded that these findings showed that chronic PBM therapy improved parameters related to obesity and insulin resistance in HFD-induced obesity in mice.

Oral Lichen Planus

Al-Maweri and co-workers (2017) stated that oral lichen planus (OLP) is a chronic inflammatory disease of unknown etiology and indefinite cure. In a systematic review, the investigators assessed the efficacy LLLT in the treatment of symptomatic OLP. Electronic databases (PubMed, Scopus, and Web of Science) were searched from date of inception till and including December 2016, using various combinations of the following keywords: oral lichen planus, laser therapy, low-level laser therapy, and phototherapy. Owing to heterogeneity of data, no statistical analyses were conducted. Initially, 227 publications were identified. After selection, only 6 studies were included in this systematic review. In these studies, the laser wavelengths, power output, and duration of irradiation ranged between 630 to 980 nm, 20 to 300 mW, and 10 s to 15 min, respectively. All of the included studies found laser to be
effective in management of OLP, without any reported adverse effects. The authors concluded that the results of the included studies confirmed that LLLT was effective in management of symptomatic OLP and could be used as an alternative to corticosteroids. However, they stated that due to variety of methods and substantial variations in laser parameters among these studies, more RCTs with large sample sizes are needed.

In a systematic review, Akram and colleagues (2018) evaluated the efficacy of LLLT, in comparison with corticosteroid therapy, in the treatment of OLP. This systematic review aimed to address the following focused question: "Does LLLT yield better clinical outcomes than corticosteroid therapy in the treatment of OLP"? Indexed databases were searched up to and including April 2017. Clinical trials in humans diagnosed clinically and/or histologically with OLP allocated to test (LLLT) versus control (steroid therapy) groups were included. A total of 5 clinical studies were included. The risk of bias was considered high in 4 studies and moderate in 1 study. Laser wavelengths, power, spot size, and duration of laser exposure ranged between 630 and 970 nm, 10 to 3,000 mW, 0.2 to 1.0 cm², and 6 to 480 seconds, respectively. The follow-up period ranged from 4 to 48 weeks. All included studies reporting clinical scores showed that LLLT was effective in the treatment of OLP in adult patients at follow-up; 3 studies showed significantly higher improvements with topical use of corticosteroids compared to LLLT, while 1 study showed significant improvement with LLLT; 1 study showed comparable outcomes between LLLT and corticosteroid application. The authors concluded that it remained debatable whether LLLT is more effective as compared to corticosteroids in the treatment of OLP, given that the scientific evidence was weak. Moreover, they stated that these findings were preliminary and further RCTs are recommended.

Pemphigus Vulgaris
Yousef and associates (2017) stated that pemphigus vulgaris is a chronic blistering skin disease. Management of recalcitrant pemphigus ulcers is a great problem; LLLT is known to supply direct bio-stimulative light energy to body cells. In a pilot study, these investigators evaluated the efficacy of low power laser in the healing of pemphigus lesions. A total of 10 patients with pemphigus vulgaris were enrolled in the trial. The LED-LLLT system used was the Thor LED clusters (109, 69 or 19 diode) with 660-nm wavelength in continuous wave (CW) and 30 mW energy. Both sides of the patients' lesion were photographed prior to the study and in each laser therapy session. The pattern of changes in qualitative wound score (QWS) patterns differed significantly over time between the 2 therapies (treatment × time interactions, p < 0.0001). When compared to the routine therapy, the laser therapy showed more decrease in mean QWS in all sessions in comparison with baseline. The authors concluded that application of LLLT simultaneously with conventional therapy could result in sensational healing of ulcers especially in patients who did not respond to conventional treatment or suffering from recalcitrant lesions. Moreover, they stated that since this was a pilot study with a small sample size (n = 10), it is suggested that further research be performed. In order to determine the real efficacy of LLLT (the optimal set of laser irradiation parameters and well-defined duration and frequency of intervals), further carefully designed long-term clinical trials with a larger sample size (possibly international) are needed as well as prolonged follow-up period.

Diabetic Foot Ulcers

Beckmann et al (2014) stated that diabetic foot ulcers (DFUs) are one of the most common complications of diabetes mellitus are defined as non-healing or long-lasting chronic skin ulcers in diabetic patients. Multi-disciplinary care for the diabetic foot is common, but treatment results are often unsatisfactory. Low level laser therapy on wound areas as
Cold Laser and High-Power Laser Therapies

well as on acupuncture points, as a non-invasive, pain-free method with minor side effects, has been considered as a possible treatment option for the diabetic foot syndrome. A systematic literature review identified 1,764 articles on this topic. These researchers adopted 22 eligible references; 8 of them were cell studies, 6 were animal studies, and 8 were clinical trials. Cell studies and animal studies gave evidence of cellular migration, viability, and proliferation of fibroblast cells, quicker re-epithelization and reformed connective tissue, enhancement of microcirculation, and anti-inflammatory effects by inhibition of prostaglandins, interleukin, and cytokine as well as direct anti-bacterial effects by induction of reactive oxygen species (ROS). The transferal of these data into clinical medicine is under debate. The majority of clinical studies showed a potential benefit of LLLT in wound healing of diabetic ulcers. But there are a lot of aspects in these studies limiting final evidence about the actual output of this kind of treatment method. The authors concluded that all studies gave enough evidence to continue research on laser therapy for diabetic ulcers, but clinical trials using human models do not provide sufficient evidence to establish the usefulness of LLLT as an effective tool in wound care regimes at present. They stated that further well-designed studies are needed to determine the true value of LLLT in routine wound care.

In a systematic review and meta-analysis, Li and colleagues (2018) examined if LLLT is effective at healing DFU and provided evidence-based recommendations and clinical guidelines for the future clinical treatment of DFUs. Medline, Embase, Scopus, Cochrane Library, and Web of Science databases were searched for studies published up to June 30, 2017, without language or data restrictions; RCTs that examined the use of LLLT for DFU treatment were included. Standard methods of meta-analysis were performed to evaluate outcomes of LLLT on the healing of DFU. A total of 7 RCTs involving 194 participants were eligible for this systematic review and meta-analysis. The results of meta-analysis showed that LLLT has emerged as a potential non-
invasive treatment for DFUs, as LLLT was found to effectively reduce the ulcer area [weighted MD (WMD) 34.18, 95% CI: 19.38 to 48.99, p < 0.00001], improve the complete healing rate [odds ratio (OR) 6.72, 95% CI: 1.99 to 22.64, p = 0.002]. Qualitative analysis of the included RCTs found that LLLT also played a role in the treatment of DFUs through promoting rapid granulation formation and shortening ulcer closure time, as well as alleviating foot ulcer pain. None of the treatment-related adverse event (AE) was reported. The authors concluded that LLLT was recognized as a potential method in the comprehensive treatment of DFUs. These researchers stated that further well designed and high-quality studies are needed to confirm the role of LLLT in the management of DFUs.

Herpes Labialis

de Paula Eduardo et al (2014) noted that recurrent herpes labialis (RHL) is a worldwide life-long oral health problem that remains unsolved. It affects approximately 1/3 of the world population and causes frequent pain and discomfort episodes, as well as social restriction due to its compromise of esthetic features. In addition, the available anti-viral drugs have not been successful in completely eliminating the virus and its recurrence. Currently, different kinds of laser treatment and different protocols have been proposed for the management of recurrent herpes labialis. These investigators reviewed the literature regarding the effects of laser irradiation on recurrent herpes labialis and identified the indications and most successful clinical protocols. The literature was searched with the aim of identifying the effects on healing time, pain relief, duration of viral shedding, viral inactivation, and interval of recurrence. According to the literature, none of the laser treatment modalities is able to completely eliminate the virus and its recurrence. However, laser phototherapy appears to strongly decrease pain and the interval of recurrences without causing any side effects. Photodynamic therapy can be helpful in reducing viral titer in the vesicle phase, and high-
power lasers may be useful to drain vesicles. The main advantages of the laser treatment appear to be the absence of side effects and drug interactions, which are especially helpful for older and immune-compromised patients. The authors concluded that although these results indicated a potential beneficial use for lasers in the management of recurrent herpes labialis, they are based on limited published clinical trials and case reports. They stated that the literature still lacks double-blind, controlled clinical trials verifying these effects and such trials should be the focus of future research.

Al-Maweri and associates (2018) stated that RHL is a highly prevalent viral infection that affects the orofacial region. Current therapeutic options have limited efficacy in reducing healing time and recurrence rate of the disease. Recently, LLLT has been proposed as a potential treatment alternative for the management of RHL with no side effects. These investigators examined the effectiveness of laser therapy in the management and prevention of RHL. A comprehensive search of Medline/PubMed, Scopus, and Web of Science was carried out to identify published clinical trials comparing laser intervention to active and/or non-active controls for the treatment of RHL. Due to marked heterogeneity of available data, studies were assessed qualitatively, and no statistical analysis was performed. Of the retrieved 227 articles, 6 clinical trials met the eligibility criteria. The wavelengths, the power output, and energy density ranged between 632.5 to 870 nm, 5 to 80 W, and 2.04 to 48 J/cm², respectively. All included studies found laser to be effective in the management and prevention of RHL, without any side effects. The authors concluded that the findings of this review suggested that laser is potentially a safe and effective treatment alternative for the management of RHL. However, these researchers stated that due to high variability in study designs and inconsistency in laser parameters among the included studies, more well-designed RCTs with standardized laser parameters are needed.
Low Back Pain and Neck Pain

In a clinical practice guideline on “Management of neck pain and associated disorders” from the Ontario Protocol for Traffic Injury Management (OPTIMA) Collaboration, Cote et al (2016) concluded that “For neck pain and associated disorders (NAD) grade III of less than or equal to 3 months duration, clinicians may consider supervised strengthening exercises in addition to structured patient education. In view of evidence of no effectiveness, clinicians should not offer structured patient education alone, cervical collar, low-level laser therapy, or traction”.

In a clinical practice guideline for “Physical therapy assessment and treatment in patients with nonspecific neck pain” (Bier et al, 2018) stated that “The physical therapist is advised not to use dry needling, low-level laser, electrotherapy, ultrasound, traction, and/or a cervical collar”.

The Agency for Healthcare Research and Quality (AHRQ)’s systematic review on “Noninvasive nonpharmacological treatment for chronic pain” (Skelly et al, 2018) stated that for chronic neck pain, low-level laser therapy was associated with a moderate improvement in short-term function (2 trials, pooled difference -14.98, 95% CI: -23.88 to -6.07, I² = 39%, 0 to 100 scale) and pain (3 trials [n = 26, 45, and 30 for laser treatment; and the quality of the study was fair, good, and fair, respectively], pooled difference -1.81 on a 0-10 scale, 95% CI: -3.35 to -0.27, I² = 75%) compared with sham (Strength of evidence (SOE): Moderate for function and pain). However, there is no evidence to support its effectiveness for improvement of intermediate-term and long-term function and pain. For LBP, SOE on the use of cold laser therapy for the treatment of LBP was low (short-term improvement in function and pain). No clear improvement in function was observed at intermediate-term for low-level laser therapy (SOE: Low); and there is no evidence to support its effectiveness for improvement of long-term function and pain.
Breast Implant Capsular Contracture

Azimi and colleagues (2018) stated that breast reconstruction with implants can be complicated by symptomatic capsular contracture, especially after radiotherapy. A phase-I, non-randomized clinical trial reported improvement in capsular contracture and avoidance of revision surgery with LLLT. In a phase-II, double-blind, RCT, these investigators examined the efficacy of LLLT for treating capsular contracture in women with breast reconstruction following mastectomy for breast cancer. Participants had completed their definitive implant-based reconstruction a minimum of 6 months previously and were randomized to weekly treatments over 6 weeks with either an active or inactive LLL hand-piece (Riancorp LTU-904). Pain, tightness, arm movement, and appearance were assessed by patient questionnaires. Breast symmetry, shape, naturalness, softness, and grade of contracture were assessed by clinician reports. Participants were assessed at 1 and 6 months after completion of the treatments. A total of 42 patients (intervention arm, n = 20; placebo, n = 22) were assessed in the trial; 32 had post-mastectomy radiotherapy. There was no significant difference in the change in any patient-reported outcomes or clinician-reported outcomes of breast symmetry, shape, or naturalness for the 2 groups. There was a significantly greater improvement in clinician-reported breast softness (p < 0.05) and degree of contracture (p < 0.05) in the placebo group at both 1- and 6-month follow-up. The authors concluded that LLLT was not an effective therapy for breast implant capsular contracture in reconstruction patients. Level of evidence = I.

Hypothyroidism Induced by Autoimmune Thyroiditis

In a RCT, Hofling and colleagues (2018) examined the efficacy of LLLT for hypothyroidism induced by chronic autoimmune thyroiditis (CAT). These researchers evaluated the safety and actions of LLLT 6 years after completion of the RCT. A total of 43 participants were invited to participate in this study 6 years
after completion of the RCT; 25 were subjected to LLLT (group L), and 18 were subjected to placebo (group P). Primary outcome measure was frequency of thyroid nodules, which were subjected to fine-needle aspiration biopsy. Secondary outcome measures included dose of levothyroxine needed to treat hypothyroidism, thyroid peroxidase antibodies (anti-TPO), and anti-thyroglobulin antibodies (anti-Tg). In group L, a nodule was observed in 3 patients, who all had a Bethesda II classification. In group P, a nodule was also observed in 3 patients, with 2 classified as Bethesda II and 1 as Bethesda III. The levothyroxine dose needed by group L was significantly lower than that required by group P (p = 0.002). The anti-TPO and anti-Tg levels did not differ between the 2 groups. The authors concluded that the findings of this study suggested that LLLT was safe for the treatment of patients with CAT-induced hypothyroidism under the specified conditions, and thus, subsequent applications may be considered for the purpose of maintaining or improving the obtained results. These researchers stated that future research will be important to corroborate these findings.

The authors stated that this study had several drawbacks. The vascularization was evaluated by means of a subjective method, with classification of the vascularization into 4 different patterns. Although the evaluation of thyroid vascularization pattern TVP was performed by a single experienced examiner, there may be intra-observer variations in interpretation in the case of borderline patterns. However, 2 separate analyses by 2 independent investigators could also be employed to improve this evaluation. The use of different anti-TPO and anti-Tg measurement kits during the RCT and the present study made comparative analysis impossible at those moments. The safety analysis was based on a small sample of patients. Thus, further research is needed to confirm these results.

Inferior Alveolar Nerve and Lingual Nerve Injuries
Miloro and Criddle (2018) noted that iatrogenic damage to the inferior alveolar nerve (IAN) and lingual nerve (LN) may occur during routine oral and maxilla-facial surgeries. In a prospective, double-blind RCT, these investigators examined if the proportion of nerve-injured patients with post-operative neurosensory improvement over a 3-month period differed significantly between a LLLT group and a control group. The study sample consisted of 35 patients with iatrogenic nerve injury due to 3rd molar odontectomy, dental implant placement, or local anesthetic injection. The investigators used a randomized, double-blind laser delivery system to administer either placebo or LLLT to patients who met the inclusion criteria. The outcome variable of neurosensory improvement was defined as a minimum 1-unit increase from baseline in VAS rating and was based on standard objective clinical neurosensory testing. Study variables included the affected nerve (IAN or LN) and time from injury to treatment (3 to 12 months or greater than 12 months). Uni-variate statistical analysis ($\chi^2$ test) was performed to determine significance between the 2 groups. Neurosensory improvement was observed in 46.7% of the LLLT patients, who showed at least a 1-unit improvement at 3 months, compared with 38.5% improvement for controls ($p = 0.66$), regardless of the specific nerve involved (IAN or LN). In addition, no observed difference was noted between the study groups based on time from injury to treatment. The authors concluded that this study failed to provide sufficient evidence to conclude that a difference in neurosensory improvement exists between the LLLT and placebo groups with IAN or LN injuries. However, this study was unique in the prospective double-blind study design and comprehensive neurosensory testing protocols. These researchers stated that there is a continued need for further clinical studies on LLLT in oral and maxillofacial surgery nerve injuries.

**Peri-Implant Mucositis**
In a systematic review, Albaker and colleagues (2018) examined the effect of photodynamic therapy (PDT) or laser therapy (LT) in the management of peri-implant mucositis (p-iM). The electronic databases were searched until October 2017. Outcome measures were bleeding on probing (BOP), plaque index (PI), or probing depth (PD). The addressed PICO (population-intervention-comparator-outcome) question was: "Is PDT and LT effective in the management of p-iM?" A total of 5 studies included in the qualitative analysis, 2 of which had a low-risk of bias; 3 studies used PDT while 2 studies used LT. All studies reported a significant improvement in clinical peri-implant inflammatory parameters in p-iM. For PDT, 1 study demonstrated a significant reduction for PDT group as compared to manual debridement (MD), while 1 study indicated comparable outcomes when tested with probiotics at follow-up. One study used PDT alone and indicated significant improvements in peri-implant parameters at follow-up. However, in the studies using LT, one study demonstrated a significant improvement in peri-implant parameters as compared to scaling and root planing alone, while other study indicated comparable outcomes when compared with manual debridement / chlorhexidine group at follow-up. The authors concluded that this systematic review demonstrated inconclusive findings to show the effect of PDT or LT in the management of p-iM due to methodological heterogeneity such as non-standard control groups, laser parameters and short follow-up period. These researchers stated that the findings of this review should be considered preliminary and further, more robust, well-designed studies with long-term follow-up and standardized comparators with laser parameters are needed.

Peri-Odontitis

In a systematic review, Mokeem (2018) examined the efficacy of LLLT as an adjunct to scaling and root planing (SRP) versus SRP alone in the treatment of aggressive periodontitis (AgP). The addressed PICO (Population, Interventions, Comparisons
and Outcomes) question was: Is LLLT as an adjunct to SRP effective in the treatment of AgP? Electronic databases, including Medline via PubMed, Cochrane Central Register of Controlled Trials and Cochrane Oral Health Group Trials, and Embase, were searched until March 2018. A total of 4 clinical studies were included; 3 studies showed significant improvement in periodontal outcomes among LLLT group compared to SRP alone, whereas only 1 study showed comparable periodontal outcomes between the adjunctive LLLT and SRP groups at follow-up. The overall MD for clinical attachment level gain (WMD = -1.69, 95 % CI: -3.46 to 0.07, p < 0.061) was non-significant. However, significant difference for probing depth reduction (WMD = -0.95, 95 % CI: -1.66 to 0.23, p = 0.009) was noticed between groups at follow-up. Whether LLLT as an adjunct to SRP is more effective than SRP alone in the treatment of AgP remains debatable. The authors concluded that further RCTs with long follow-up periods and standard laser parameters are needed to reach a strong conclusion.

Skin Burn

Brassolatti and colleagues (2018) noted that burn is defined as a traumatic injury of thermal origin, which affects the organic tissue; and LLLT has gained great prominence as a treatment in this type of injury; however, the application parameters are still controversial in the literature. These investigators reviewed the literature studies that use LLLT as a treatment in burns conducted in an experimental model, discussed the main parameters used, and high-lighted the benefits found in order to choose an appropriate therapeutic window to be applied in this type of injury. The selection of the studies related to the theme was performed in the main databases (PubMed, Cochrane Library, LILACS, Web of Science, and Scopus in the period from 2001 to 2017). Subsequently, the articles were then chosen that fell within the inclusion criteria previously established. A total of 22 studies were evaluated, and the main parameters were presented. The analyzed
studies presented both LLLT use in continuous and pulsed mode. Differences between the parameters used (power, fluence, and total energy) were observed. In addition, the protocols were distinct as to the type of injury and the number of treatment sessions. Among the results obtained by the authors were the improvements in the local micro-circulation and cellular proliferation; however, a study reported no effects with LLLT as a treatment. The authors concluded that LLLT was effective in accelerating the healing process; however, there is immense difficulty in establishing the most adequate protocol, due to the great discrepancy found in the applied dosimetry values.

Tendon Repair

Lucke and colleagues (2019) noted that the cellular therapy using adipose-derived mesenchymal stem cells (ASCs) aims to improve tendon healing, considering that repaired tendons often result in a less resistant tissue. These researchers examined the effects of the ASCs combined with a LLLT for the healing processes. Rats calcaneal tendons were divided into 5 groups: normal (NT), transected (T), transected and ASCs (SC) or LLLT (L), or with ASCs and LLLT (SCL). All treated groups presented higher expression of Dcn and greater organization of collagen fibers. In comparison with T, LLLT also up-regulated Gdf5 gene expression, ASCs up-regulated the expression of Tnmd, and the association of LLLT and ASCs down-regulated the expression of Scx. No differences were observed for the expression of Il1b, Timp2, Tgfb1, Lox, Mmp2, Mmp8 and Mmp9, neither in the quantification of hydroxyproline, TNF-α, PCNA and in the protein level of Tnmd. A higher amount of IL-10 was detected in SC, L and SCL compared to T, and higher amount of collagen I and III was observed in SC compared to SCL. The authors concluded that transplanted ASCs migrated to the transected region, and all treatments altered the re-modelling genes expression. The LLLT was the most effective in the collagen reorganization, followed by its combination with
ASCs. These researchers stated that further investigations are needed to elucidate the molecular mechanisms involved in the LLLT and ASCs combination during initial phases of tendon repair.

**Brain Photobiomodulation Therapy / Transcranial LLLT**

Hennessy and colleagues (2017) noted that transcranial PBM also known as tLLLT relies on the use of red/near-infrared (NIR) light to stimulate, preserve and regenerate cells and tissues. The mechanism of action entails photon absorption in the mitochondria (cytochrome c oxidase), and ion channels in cells leading to activation of signaling pathways, up-regulation of transcription factors, and increased expression of protective genes. These researchers have studied PBM for treating TBI in mice using a NIR laser spot delivered to the head. Mice had improved memory and learning, increased neuro-progenitor cells in the dentate gyrus and sub-ventricular zone, increased brain-derived neurotrophic factor (BDNF) and more synaptogenesis in the cortex. These highly beneficial effects on the brain suggested that the applications of tLLLT are much broader than at first conceived. Other groups have studied Alzheimer's disease (AD), depression, Parkinson's disease (PD), stroke (animal models and clinical trials), as well as cognitive enhancement in healthy subjects. The authors concluded that due to the extremely positive results obtained in studies in animal models, and the small clinical trials that have been conducted thus far, broader clinical testing of PBM and its applications for neurological conditions is certainly needed, as much as it is necessary if PBM is to ever become a widely accessible treatment.

Salehpour and co-workers (2018) stated that brain PBM therapy enhances the metabolic capacity of neurons and stimulates anti-inflammatory, anti-apoptotic, and antioxidant responses, as well as neurogenesis and synaptogenesis. Its therapeutic role in disorders such as dementia and PD, as well as to treat brain trauma, depression, and stroke has gained
increasing interest. In the transcranial PBM approach, delivering a sufficient dose to achieve optimal stimulation is challenging due to exponential attenuation of light penetration in tissue. Alternative approaches such as intracranial and intranasal light delivery methods have been suggested to overcome this limitation.

Fibromyalgia

de Carvalho Pde et al (2012) noted that LLLT has been widely used as an adjuvant strategy for treatment of musculo-skeletal disorders. The light-tissue interaction (photo-biostimulation) promotes analgesic and anti-inflammatory effects and improves tissue healing, which could justify the recommendation of this therapy for patients with fibromyalgia, leading to an improvement in pain and possibly minimizing social impact related to this disease. These researchers proposed to evaluate the effect of LLLT on tender points in patients with fibromyalgia, correlating this outcome with quality of life and sleep. A total of 120 patients with fibromyalgia will be treated at the Integrated Health Center and the Sleep Laboratory of the Post Graduate Program in Rehabilitation Sciences of the Nove de Julho University located in the city of Sao Paulo, Brazil. After fulfilling the eligibility criteria, a clinical evaluation and assessments of pain and sleep quality will be carried out and self-administered quality of life questionnaires will be applied. The 120 volunteers will be randomly allocated to an intervention group (LLLT, n = 60) or control group (CLLLT, n = 60). Patients from both groups will be treated 3 times per week for 4 weeks, totaling 12 sessions. However, only the LLLT group will receive an energy dose of 6 J per tender point. A standardized 50-min exercise program will be performed after the laser application. The patients will be evaluated regarding the primary outcome (pain) using the following instruments: VAS, McGill Pain Questionnaire and pressure algometry. The secondary outcome (quality of life and sleep) will be assessed with the following instruments: Medical Outcomes Study 36-Item Short-Form Health Survey,
Fibromyalgia Impact Questionnaire, Berlin Questionnaire, Epworth Sleepiness Scale and polysomnography. ANOVA test with repeated measurements for the time factor will be performed to test between-groups differences (followed by the Tukey-Kramer post hoc test), and a paired t-test will be performed to test within-group differences. The level of significance for the statistical analysis will be set at 5% (p ≤ 0.05).

Winkelmann et al (2012) stated that the scheduled update to the German S3 guidelines on fibromyalgia syndrome by the Association of the Scientific Medical Societies was planned starting in March 2011. The development of the guidelines was coordinated by the German Interdisciplinary Association for Pain Therapy, 9 scientific medical societies, as well as 2 patient self-help organizations. Eight working groups with a total of 50 members were evenly balanced in terms of gender, medical field, potential conflicts of interest and hierarchical position in the medical and scientific fields. Literature searches were performed using the Medline, PsycInfo, Scopus and Cochrane Library databases (until December 2010). The grading of the strength of the evidence followed the scheme of the Oxford Center for Evidence-Based Medicine. The formulation and grading of recommendations was accomplished using a multi-step, formal consensus process. The guidelines were reviewed by the boards of the participating scientific medical societies. The authors concluded that low-to-moderate intensity aerobic exercise and strength training are strongly recommended; chiropractic, laser therapy, magnetic field therapy, massage, and transcranial current stimulation are not recommended.

In a systematic review and meta-analysis, Yeh and colleagues (2019) examined the efficacy of LLLT on patients with fibromyalgia. These researchers carried out a systematic review and meta-analysis of RCTs evaluating the effect of LLLT on patients with fibromyalgia. PubMed, Embase, and the Cochrane Library were searched for articles published
before August 2018; RCTs meeting the selection criteria were included. The methodological quality of the RCTs was evaluated according to the Cochrane risk-for-bias method. Review Manager version 5.3 was used to perform the meta-analysis. The primary outcomes were the total scores on the Fibromyalgia Impact Questionnaire (FIQ), pain severity, and number of tender points. The secondary outcomes were changes in fatigue, stiffness, anxiety, and depression; SMD, 95 % CI, and p values were calculated for outcome analysis. These investigators identified 9 RCTs that included 325 fibromyalgia patients undergoing LLLT or placebo laser treatment with or without an exercise program. The meta-analysis showed that patients receiving LLLT demonstrated significantly greater improvement in their FIQ scores (SMD: 1.16; 95 % CI: 0.64 to 1.69), pain severity (SMD: 1.18; 95 % CI: 0.82 to 1.54), number of tender points (SMD: 1.01; 95 % CI: 0.49 to 1.52), fatigue (SMD: 1.4; 95 % CI: 0.96 to 1.84), stiffness (SMD: 0.92; 95 % CI: 0.36 to 1.48), depression (SMD: 1.46; 95 % CI: 0.93 to 2.00), and anxiety (SMD: 1.46; 95 % CI: 0.45 to 2.47) than those receiving placebo laser. Furthermore, when compared with the standardized exercise program alone, LLLT plus the standardized exercise program provided no extra advantage in the relief of symptoms. On the other hand, the results of the only RCT using combined LLLT/LED phototherapy showed significant improvement in most outcomes except for depression when compared to placebo. When compared with pure exercise therapy, combined LLLT/LED phototherapy plus exercise therapy had additional benefits in reducing the severity of pain, number of tender points, and fatigue. The authors concluded that the findings of this systematic review and meta-analysis indicated that LLLT is an emerging, non-invasive, well-tolerated treatment for fibromyalgia to relieve discomfort, particularly in patients who do not exercise regularly.

The authors stated that this study had several drawbacks; mostly because of the low-to-middle methodological quality of the selected studies. First, most studies did not report the
allocation process clearly and only blinded the patients; neither phototherapy programmer nor outcome assessor were blinded. Considering that nearly all outcomes were subjective parameters, the above shortcomings may introduce allocation bias, performance bias, and detection bias. Second, one study used per-protocol analysis because of a 20% loss to follow-up without reporting the reasons for, or the distribution of, the loss to follow-up; this may have introduced attrition bias. Third, although LLLT was used in all trials, the differences in laser types, energy sources, and exposure times used in the studies may have resulted in some heterogeneity. Fourth, although patients with fibromyalgia did not take associated medications in most RCTs, patients in 1 trial maintained their usual pharmacological therapies, another trial included some patients continuing their regular medications, and the other 3 RCTs did not mention whether subjects were under concurrent medication; thus, these investigators could not clarify the separate roles of medication or phototherapy in fibromyalgia. Finally, long-term follow-up up to 6 months was only conducted in 1 RCT.

High Powered Lasers

High power laser therapy devices, also referred to as high does laser therapy (HDLT), (class IV therapeutic lasers) are purported to stimulate accelerated healing energy from superficial to deep levels (six to nine inches) over a larger surface treatment area. Its proposed use includes conditions such as arthritis, carpal tunnel syndrome, epicondylitis, sprains/strains, trigger points and various other musculoskeletal disorders. These devices are not to be confused with class IV surgical lasers. Examples of high power laser therapy devices that have received US Food and Drug Administration (FDA) approval are the AVI HP-7.5, AVI HPLL-12 and Diowave Laser System.
High-power lasers (class IV therapeutic lasers; not to be confused with class IV surgical lasers) have power output of up to 7,500 mW; and supposedly offer more power, deeper penetration (can penetrate up to 10 cm² instead of 0.5 to 2.0 cm² for class III lasers) and a larger surface treatment area (cover up to 77 cm² instead of 0.3 to 5.0 cm² for class III lasers). Despite little scientific support, high-power lasers have been employed for various indications including musculoskeletal disorders (e.g., carpal tunnel syndrome and lateral epicondylitis), pain relief, and wound healing.

Plaghki and Mouraux (2005) noted that laser heat stimulators selectively activate Adelta and C-nociceptors in the superficial layers of the skin. Their high-power output produces steep heating ramps, which improve synchronization of afferent volleys and thus allow the recording of time-locked events (e.g., laser-evoked brain potentials). Study of the electrical brain activity evoked by Adelta- and C-nociceptor afferent volleys revealed the existence of an extensive, sequentially activated, cortical network. These electro-physiological responses are modulated by stimulus-driven and, even more extensively, top-down processes. The specificity and validity of these components for pain research are currently under intense scrutiny.

In a systematic review on treatment of pressure ulcers, Reddy and colleagues (2008) concluded that there is little evidence to support routine nutritional supplementation or adjunctive therapies including laser therapy compared with standard care.

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**CPT Codes / HCPCS Codes / ICD-10 Codes**

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

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<thead>
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<th>Code</th>
<th>Code Description</th>
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Proprietary
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<td>Needle insertion(s) without injection(s); 1 or 2 muscle(s)</td>
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<tr>
<td>S8948</td>
<td>Application of a modality (requiring constant provider attendance) to one or more areas; low-level laser; each 15 minutes</td>
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<td>Intracranial injury</td>
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Cold Laser and High-Power Laser Therapies

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<td>Open wound [Codes not listed due to expanded specificity]</td>
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</table>

The above policy is based on the following references:


46. de Lima VHS, de Oliveira-Neto OB, da Hora Sales PH, et al. Effectiveness of low-level laser therapy for oral mucositis prevention in patients undergoing chemoradiotherapy for the treatment of head and


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There are no amendments for Medicaid.