REVIEW PAPER

Physiotherapy Quarterly (ISSN 2544-4395)
2022, 30(4), 14–26

Efficacy of low-intensity laser therapy in trigeminal neuralgia: a systematic review

DOI: https://doi.org/10.5114/pq.2022.121152

Hernán Andrés de la Barra Ortiz, Carola Freire Gavilan, María Aurelia Rojas
Exercise and Rehabilitation Sciences Institute, School of Physical Therapy, Faculty of Rehabilitation Sciences, Universidad Andres Bello, Santiago, Chile

Abstract

Introduction. Trigeminal neuralgia (TN) is a highly prevalent cranial neuropathy, recognized as one of the main chronic orofacial neuropathic pain conditions. Low-intensity laser therapy (LILT) has been proposed as an analgesic alternative for treating neuropathic orofacial pain, although studies appear to be limited, without a consensus on dose. The study aim was to describe the efficacy of LILT in TN treatment.

Methods. Randomized clinical trials and controlled trials were identified in the PubMed, Scopus, Web of Science, and ScienceDirect databases for May 8, 2021. Three independent researchers reviewed titles and abstracts to determine their eligibility. Risk of bias and quality were assessed with the RoB 2 tool (Cochrane) and PEDro scale. Decreased pain was considered the main outcome, and changes in the temporomandibular joint range of motion, strength, or disability were secondary outcomes.

Results. The search yielded 1078 articles after eliminating duplicates, reduced to 13 when applying the selection criteria. Nine articles were ascribed a low risk of bias or remained without consensus (69.23%), obtaining an average score of 6 (PEDro). Thirteen trials showed pain reduction at the end of treatment and in follow-up, although with statistical significance for 8 articles only ($p < 0.005$). A decrease in drug consumption and an increase in serotonin levels were observed in experimental groups, which supports the systemic analgesic effects of local and remote LILT.

Conclusions. LILT is effective in reducing pain in TN. However, more research is needed to establish a referential dose consensus for TN and other neuropathic pain conditions.

Key words: systematic review, lasers, phototherapy, low-level light therapy, trigeminal neuralgia, neuralgia

Introduction

Chronic pain is a frequent medical consultation, standing out as one of the main causes of disability in the adult population, with a prevalence of 16–70% [1–2]. Chronic pain, persisting for more than 3 months despite medication or treatment, is associated with high drug dependence, anxiety, depression, poor quality of life, and limitations in daily living activities [2–5].

Neuropathic pain is a chronic pain condition resulting from lesions or diseases of central or peripheral nervous system. In some cases, it manifests without nociceptor stimulation or a nerve lesion [6, 7]. The updated definitions recognize it as any pain caused by a lesion or disease of the somatosensory nervous system, a conceptualization based on its pathophysiology and the diversity of diseases with which it is related [8–10]. Its prevalence in the population is 7%, affecting 25% of diabetics and 35% of patients with a human immunodeficiency virus infection [9, 11]. Clinically, neuropathic pain is characterized by spontaneous pain (continuous or paroxysmal) or pain evoked by peripheral stimulation, associated with sensitivity alterations, such as hyperalgesia, allodynia, and hypoesthesia, and muscle weakness [12–14].

Trigeminal neuralgia (TN) is a neuropathic orofacial condition aroused by injuries, compressions, or demyelinating diseases of the 5th cranial nerve [15–18]. This neuropathy affects the adult population with a prevalence of 10–300 per 100,000 inhabitants [16, 17], with a higher incidence in women (2:1 ratio compared with men) aged 50–60 years [16–18]. TN manifests as orofacial pain in the distribution of one or more trigeminal nerve branches, compromising maxillary (V2) and mandibular (V3) nerves in 65% of cases [19, 20]. TN is clinically described as sudden, severe, brief, stabbing and recurrent, generally predominantly unilateral pain, and classified as type 1 (intermittent) or type 2 (continuous) pain, representing different clinical, pathological, and prognostic entities [15–21]. TN medical treatment has been oriented mainly to its clinical symptoms, including first-line antiepileptic drugs, such as carbamazepine and oxcarbazepine, and, as a second option, microvascular decompression surgeries, radiosurgery, or nerve blocks in patients resistant to drug treatments [22–24]. Although these interventions prove to be effective, a 50% relapse has been documented after a few months, in addition to adverse effects of medications, such as dizziness, nausea, vomiting, or ataxia, or conditions where these treatments cannot be applied owing to individual contraindications [16, 23–28]. Physical therapy is a non-pharmacological option for pain management in TN, using such modalities as ultrasound, transcutaneous electrical nerve stimulation, radiofrequency, transcranial magnetic stimulation (TMS), electroacupuncture, or mirror therapy [24, 29–32]. Another alternative is low-intensity laser therapy (LILT) or low-level laser therapy (LLLT), a safe and non-invasive intervention supported by various studies for pain management in TN and a variety of orofacial pain disorders [33–37].

LILT is a phototherapy modality that consists of the application of low-power non-ionizing electromagnetic radiation (less than 500 mW for a single source: categorized as

Correspondence address: Hernán Andrés de la Barra Ortiz, Exercise and Rehabilitation Sciences Institute, School of Physical Therapy, Faculty of Rehabilitation Sciences, Universidad Andres Bello, Santiago, 7591538, Chile,
e-mail: hdelabarra@unab.cl, handresdelabarra@yahoo.es, https://orcid.org/0000-0002-3927-1743

Received: 18.07.2021
Accepted: 20.09.2021

Citation: de la Barra Ortiz HA, Freire Gavilan C, Rojas MA. Efficacy of low-intensity laser therapy in trigeminal neuralgia: a systematic review. Physiother Quart. 2022;30(4):14–26; https://doi.org/10.5114/pq.2022.121152.

class IIIb devices) in the spectral band of visible light or infrared, used in physical therapy for tissue repair, wound healing, and pain reduction [33, 37–42]. Laser production is based on the physical phenomenon of stimulated emission of radiation, in which atoms in a medium emit photons when it is stimulated by an electrical source [41–43]. Laser energy is absorbed by chromophores, that is, molecules or cells that absorb light radiation, such as haemoglobin, water, fibroblasts, and melanocytes [38, 41–45]. LILT is known as 'photobiomodulation' because its biological effects can be stimulatory or inhibitory, depending on the magnitude of radiated energy, but without increasing tissue temperature. LILT is commonly generated from gaseous mixtures of helium-neon (HeNe; wavelength of 632 nm) or semiconductor diodes of arsenide-gallium-aluminum (ArGaAl; wavelength of 630–950 nm), conditioning different tissues depths depending on the wavelength [41–48].

Although the biological effects of LILT are not entirely clear, anti-inflammatory and repair responses are based on angiogenesis, increased microcirculation, neurogenesis, and increased collagen synthesis, while analgesia would be related to adenosine triphosphate production, increased resting membrane potential, increased serotonin levels, and endogenous opioid peptide release [36, 44–50].

Although the World Association for Laser Therapy supports the use and dosage of LILT for different clinical conditions, its application for TN or other orofacial pain conditions has not been incorporated into the recommendations, even though various clinical trials have reported analgesic benefits, supporting LILT as a non-invasive treatment for neuropathic pain without the adverse effects of drugs [22–24, 36, 50–62]. Thus, the objective of this systematic review was to evaluate the existing scientific evidence concerning the efficacy of LILT in TN management.

Subjects and methods

Study design

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (available at http://www.prisma-statement.org) [63]. The research was uploaded electronically to the International Prospective Register of Systematic Reviews (PROSPERO) of the National Institute for Health Research (https://www.crd.york.ac.uk/prospero) and received the registration number CRD42021256727.

The systematic review used the PICO acronym (participants, intervention, comparison, and outcome) to structure the research question and search algorithm on the basis of the following elements: patients with the diagnosis of TN; treated with LILT (LLLT); compared with a control group (another treatment, sham application, or placebo); and evaluation of pain reduction as the main outcome, and changes in function/disability, the temporomandibular joint range of motion, muscle strength or electromyographic activity as secondary outcomes.

Search strategy

A systematic review was carried out considering the electronic databases of PubMed, Scopus, Web of Science, ScienceDirect, SciELO, and Physiotherapy Evidence Database (PEDro), with the last update on May 8, 2021. Keywords were chosen from the Medical Subject Headings (MeSH) dictionary (https://www.ncbi.nlm.nih.gov/mesh/), used for indexing scientific articles to the PubMed database. The search terms included "Neuralgia", "Trigeminal Neuralgia", "Trigeminal Nerve", "Lasers", "Laser Therapy", and "Low Level Light Therapy" connected through the Boolean operators "OR" and "AND"; the following algorithm was obtained: ((("Neuralgia") OR ("Trigeminal Neuralgia")) OR ("Trigeminal Nerve")) AND ((("Lasers") OR ("Laser Therapy")) OR ("Low Level Light Therapy")) OR ("Phototherapy")).

The searches were downloaded for each database (nbib, ris, or ciw formats). The files were analysed with the Rayyan tool, developed for the preliminary selection of article abstracts and titles (https://rayyan.qcri.org) [64]. Three independent researchers (HD, CF, and MR) analysed article titles and abstracts with reference to the selection criteria, classifying them in the categories 'included,' 'possible,' and 'excluded'. In addition, study references were examined, with the extraction and revision of their country, author, affiliated institutions, and enrolment periods to identify and exclude duplicate publications. Articles in the 'possible' category were reviewed by a researcher team to be included or not in the final count. Articles with incomplete abstracts were discarded from the analysis and each investigator recorded their exclusion reasons.

For included articles, study objective, PEDro score, participants' demographic data, follow-up sessions, treatment protocol, LILT dose, and results in the variables of interest were analysed [65, 66].

Selection criteria

The inclusion criteria involved: (1) randomized clinical trials or controlled trials; (2) studies in humans; (3) participants older than 18 years; (4) articles in the English or Spanish language; (5) studies that used LILT or LLLT alone or with another intervention for treatment of TN; and (6) comparison with another treatment, sham application, or placebo. The following were excluded: (i) case report studies, systematic reviews, meta-analyses, and literature reviews; (ii) animal or in vitro studies; (iii) reports on LILT in orofacial pain without clinical condition specification; (iv) reports on LILT in other cranial neuropathies (e.g., facial nerve neuropathy, hypoglossal neuropathy); and (v) studies with incomplete abstracts or texts.

Article quality and risk of bias

Article quality was evaluated with the PEDro scale (Cohen's kappa coefficient of 0.5–0.79 for groups of 2 or 3 evaluators) [65–67]. Each researcher performed an independent assessment, and any disagreements were subsequently discussed to establish a consensus. Randomized clinical trials with scores ≤ 5 were classified as 'low quality,' while those with scores ≥ 6 were considered 'high quality'.

Article risk of bias was assessed with the RoB 2 tool, proposed by the Cochrane Collaboration for randomized clinical trial analysis in systematic reviews for the following domains [68, 69]: (1) bias arising from the randomization process; (2) bias due to deviations from the planned interventions; (3) bias due to missing outcome data; (4) outcome measurement bias; (5) bias in the reported outcome selection; and (6) overall article bias. The investigators rated the risk of bias for each criterion as high, low, unclear, or no information if the data provided were not sufficient to decide [68–70]. Box and summary plots were constructed with the Risk-of-bias Visualization (robvis) tool (https://www.riskofbias.info/welcome/robvis-visualization-tool) (see Figure 2) [71].

Studies with 2 or more high risks of bias were considered as low quality [72].

Ethical approval

The conducted research is not related to either human or animal use.

Results

Search results

The initial search strategy yielded 9970 articles from the selected databases (PubMed, *n* = 212; Scopus, *n* = 4776; Web of Science, *n* = 42; ScienceDirect, *n* = 4490; SciELO, *n* = 450). Subsequently, duplicates were eliminated by using the Rayyan detection tool [64], and 1078 articles were obtained. The main reasons for exclusion were other treatments application, different main outcome, other types of studies, articles in languages other than English or Spanish, and LILT applied in cranial neuropathies or orofacial pain other than TN. After reviewing titles and abstracts, 21 articles were rated between 'possible' and 'included' when applying the selection criteria. The researchers adopted consensus for these articles, discarding 8 and finally obtaining 13 for analysis. Causes of exclusion were as follows: other reviews (*n* = 3), other interventions (*n* = 1), and other orofacial pain conditions (*n* = 4). Figure 1 shows the PRISMA flow chart with a summary of the selection results, while Figure 2 presents the article risk of bias [63, 71].

Risk of bias and quality

The results show that 23.07% of the articles (*n* = 3) were rated as high risk of bias [56, 58, 59], especially in domains 1 and 5 for the RoB 2 tool [56–59, 62]. On the other hand, 7.69% (*n* = 1) of studies had 2 or more high risks of bias [56], while 38.46% (*n* = 5) presented no risk of bias for any of the domains [36, 51, 52, 54, 60].

Table 1 shows the PEDro score for the 13 articles, while Table 2 summarizes the characteristics of the study groups, treatment sessions, and outcome measures. Internal validity implies a high quality for 61.54% of the articles (*n* = 7) (score ≥ 6 for the PEDro scale) [36, 52–55, 60–62], with an average of 6 points [65, 66].

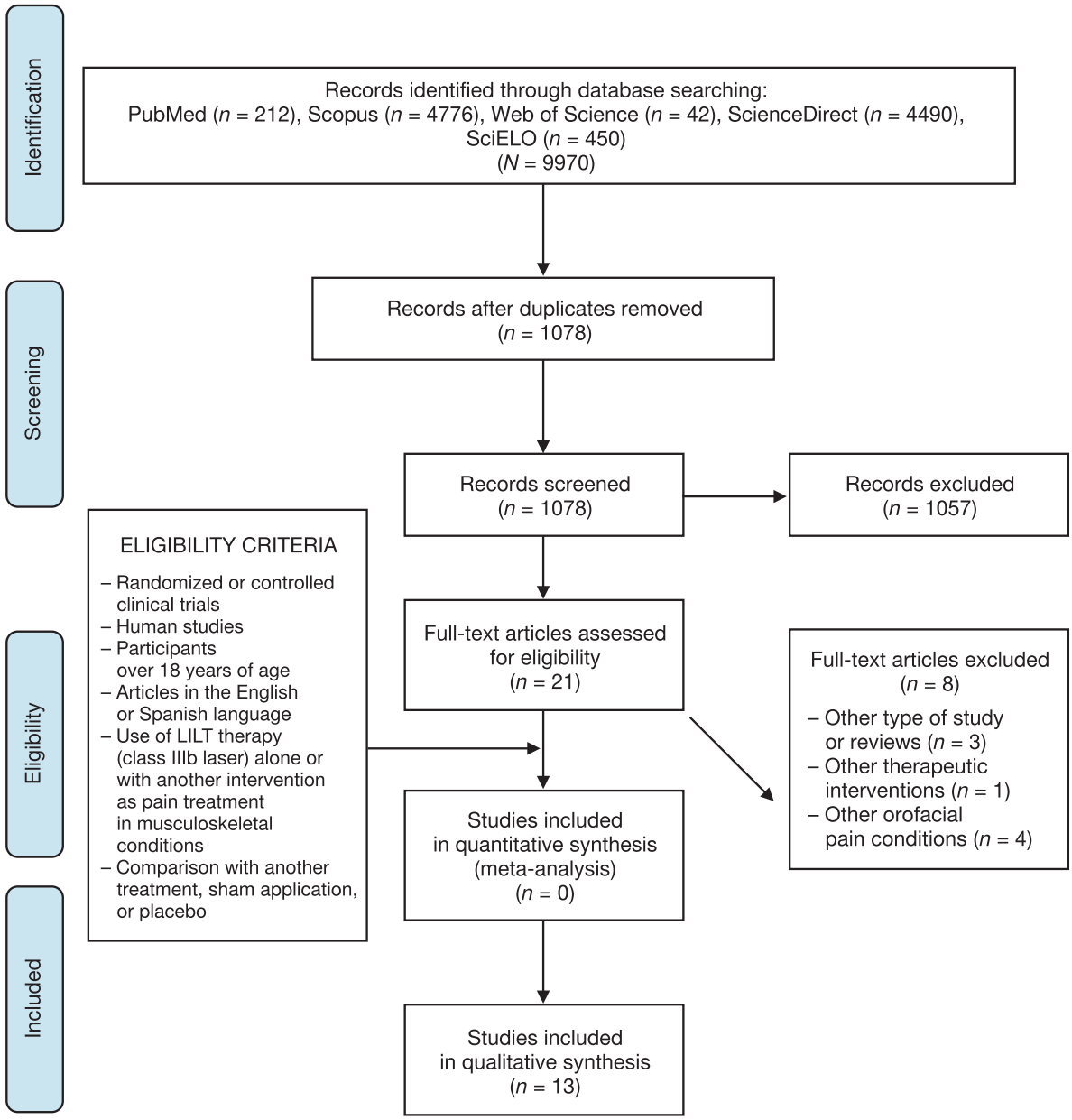

Figure 1. Flowchart of the studies included in the review in accordance with the PRISMA 2009 guidelines [63, 72]

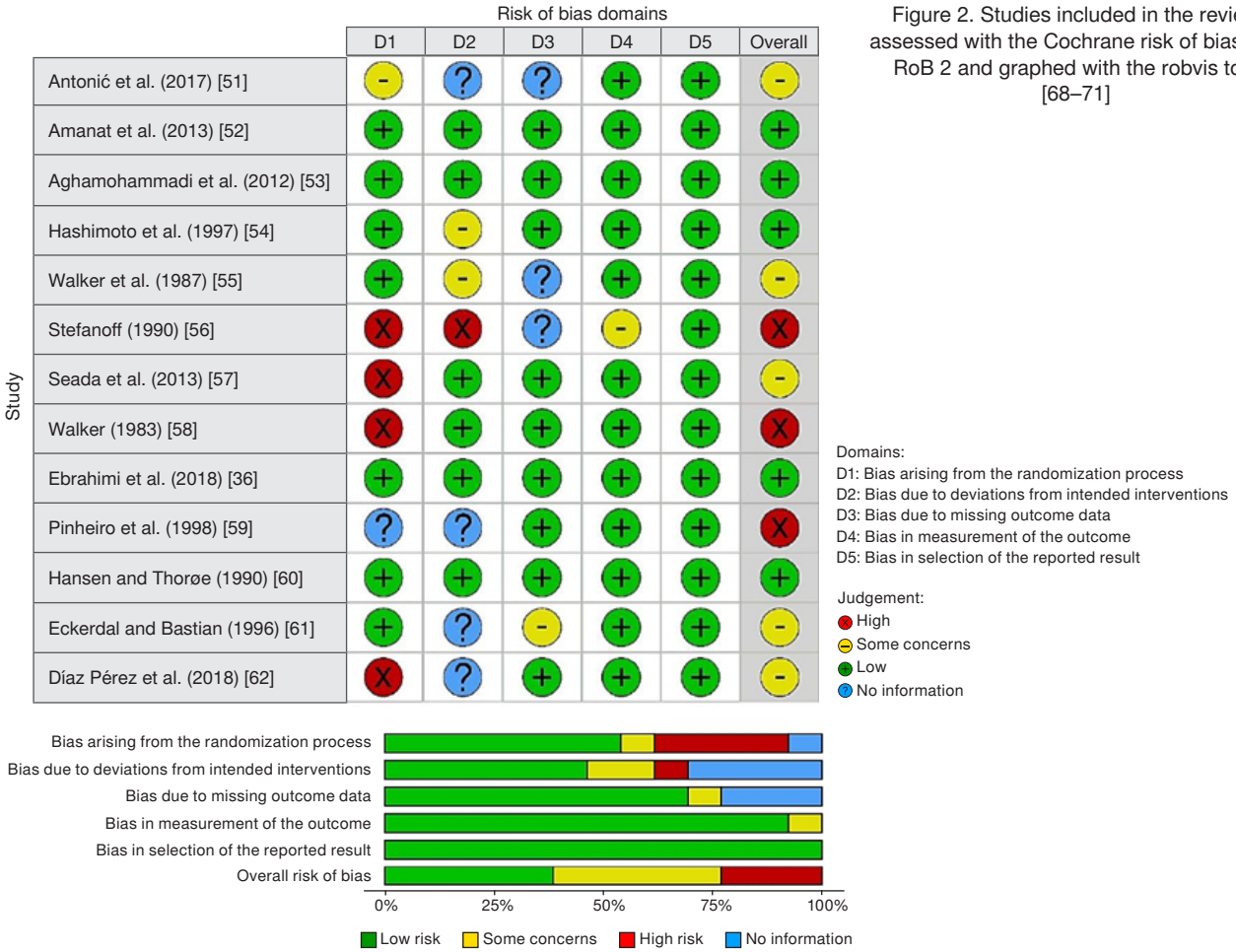

Figure 2. Studies included in the review assessed with the Cochrane risk of bias tool RoB 2 and graphed with the robvis tool [68–71]

Table 1. PEDro scale score of the analysed studies [65, 66]

Clinical trial number	Author, year of publication	PEDro scale criteria											Total score
		1	2	3	4	5	6	7	8	9	10	11	
1	Antonić et al. (2017) [51]	1	0	0	1	0	0	0	1	0	1	1	5
2	Amanat et al. (2013) [52]	1	1	0	1	1	1	1	1	0	1	1	9
3	Aghamohammadi et al. (2012) [53]	1	1	0	1	1	0	1	1	0	1	1	8
4	Hashimoto et al. (1997) [54]	1	1	0	1	1	1	1	1	0	1	1	9
5	Walker et al. (1987) [55]	1	1	0	1	1	0	0	1	0	1	1	7
6	Stefanoff (1990) [56]	1	0	0	1	0	0	0	1	1	0	0	4
7	Seada et al. (2013) [57]	1	1	1	1	0	0	0	1	0	1	1	7
8	Walker (1983) [58]	1	0	0	1	1	1	1	1	0	1	1	8
9	Ebrahimi et al. (2018) [36]	1	1	0	0	1	0	1	0	0	1	1	6
10	Pinheiro et al. (1998) [59]	1	1	0	1	0	0	0	1	0	0	0	4
11	Hansen and Thorøe (1990) [60]	1	1	1	1	1	0	1	1	0	1	1	9
12	Eckerdal and Bastian (1996) [61]	1	1	1	1	1	1	0	1	0	1	0	8
13	Díaz Pérez et al. (2018) [62]	1	0	0	1	0	0	0	1	0	1	1	5

PEDro (Physiotherapy Evidence Database) scale criteria:
(1) The selection criteria were specified.
(2) Subjects were randomized into groups (in a crossover study, subjects were randomized as they received treatments).
(3) The assignment was hidden.
(4) The groups were similar at the beginning in relation to the most important prognostic indicators.
(5) All subjects were blinded.
(6) All therapists who administered the therapy were blinded.
(7) All assessors who measured at least 1 key outcome were blinded.
(8) Measures of at least 1 of the key outcomes were obtained from more than 85% of the subjects initially assigned to the groups.
(9) Results were presented for all subjects who received treatment or were assigned to the control group, or, when this could not be the case, data for at least 1 key outcome were analysed by 'intention to treat'.
(10) Results of statistical comparisons between groups were reported for at least 1 key outcome.
(11) The study provides point and variability measures for at least 1 key outcome.

Table 2. Characteristics of the included studies

Clinical trial number	Author, year of publication	Study	Sample size (men, women)	EG and CG	Intervention	Laser type (wavelength)	Application area	LILT sessions	Evaluation time	Outcomes (measuring instrument)	Conclusion
1	Antonić et al. (2017) [51]	The effects of low level laser therapy on the management of chronic idiopathic orofacial pain: trigeminal neuralgia, temporomandibular disorders and burning mouth syndrome	*n* = 20 men: *n* = 12, 60% women: *n* = 8, 40%	EG 1: 10 (NS by sex) EG 2: 10 (NS by sex)	EG 1: LILT (10 min) EG 2: LILT (10 min) The total treatment time varied depending on the number of application points for each participant	EG 1: ArGaAl diode laser (660 nm) EG 2: ArGaAl diode laser (810 nm)	EG 1: face EG 2: face	20 sessions (5 per week, 4 weeks)	T0: baseline, T1: 4 weeks	Main outcome: pain intensity (VAS)	Pain intensity (VAS): EG 2 < EG 1 at T1* and < T0
2	Amanat et al. (2013) [52]	The adjunct therapeutic effect of lasers with medication in the management of orofacial pain: double blind randomized controlled trial	*n* = 26 men: *n* = 9, 34.62% women: *n* = 17, 65.38%	EG: 12 (4 men, 8 women) CG: 14 (5 men, 9 women)	EG: LILT (5 min) + medication (carbamazepine) CG: sham LILT + medication (carbamazepine) The total treat-ment time varied depending on the number of application points for each participant	ArGaAl diode laser (980 nm)	EG: face CG: face	10 sessions (3 per week, 3 weeks)	T0: baseline, T1: 3 weeks (after 10 sessions), T2: 2–4 months	Main outcome: pain intensity (VAS)	Pain intensity (VAS): EG < CG at T1* EG = CG at T2 and < T0
3	Aghamoham-madi et al. (2012) [53]	Gasserian ganglion block with or without low-intensity laser therapy in trigeminal neuralgia: a comparative study	*n* = 42 NS by sex	EG: 21 (NS by sex) CG: 21 (NS by sex)	EG: LILT (NS time point) + trigeminal ganglion block (bupivacaine and methylprednisolone, 4 blocks every other day) CG: trigeminal ganglion block (bupivacaine and methylprednisolone, 4 blocks every other day) All participants received analge-sic medication (carbamazepine) and did not interrupt drug treatment during the study	ArGa diode laser (890 nm)	EG: face	12 sessions (4 per week, 3 weeks)	T0: baseline, T1: 1 day after ganglia block (after 4 blocks), T2: 3 days after ganglia block, T3: 5 days after ganglia block, T4: 7 days after ganglia block, T5: 1 month after treatment, T6: 3 months after treatment, T7: 6 months after treatment	Main outcome: pain intensity (VAS) Secondary outcome: analgesic medication dose (carbamazepine)	Pain intensity (VAS): EG = CG at T0, T1, T2, and T3 EG < CG at T4*, T5*, T6*, and T7*
4	Hashimoto et al. (1997) [54]	Efficacy of laser irradiation on the area near the stellate ganglion is dose dependent: a double-blind crossover placebo-controlled study	*n* = 8 men: *n* = 6, 75% women: *n* = 2, 25%	EG: 4 (NS by sex) CG: 4 (NS by sex)	EG 1: LILT (3 min) EG 2: LILT (3 min) CG: sham LILT (3 min)	EG 1: ArGaAl diode laser (830 nm) EG 2: ArGaAl diode laser (830 nm) Difference between groups was the power output	EG 1: transverse process of C7 EG 2: transverse process of C7 CG: transverse process of C7	3 sessions (1 week)	T0: baseline, T1: after treatment (9 min), T2: 5 min after treatment, T3: 10 min after treatment, T4: 15 min after treatment, T5: 30 min after treatment	Main outcome: pain intensity (VAS) Secondary outcome: average temperature of the forehead (thermography)	Pain intensity (VAS): EG 1 < CG at T1–T5* EG 2 < CG at T1–T5* Average forehead temperature: EG 1 > CG at T1–T5* EG 2 > CG at T1–T5

5	Walker et al. (1987) [55]	Laser therapy for pain of trigeminal neuralgia	*n* = 35 men: *n* = 16, 45.7% women: *n* = 19, 54.3%	EG: 18 (9 men, 9 women) CG: 17 (7 men, 10 women)	EG: LILT(30 s, 15-s increase per week) CG: sham LILT (20 s) EG was divided into 3 categories (mild, moderate, and severe) depending on the baseline pain level	HeNe laser (632.5 nm)	EG: face CG: face	30 sessions (3 per week, 10 weeks)	T0: baseline, T1: week 1, T2: week 2, T3: week 6, T4: week 7, T5: week 10	Main outcome: pain intensity (VAS), weekly number of pain episodes in EG (mild, moderate, and severe subgroups)	Pain intensity (VAS): EG = CG at T0, T1, and T2 EG < CG at T3* and T4* EG = CG at T5 Weekly pain self-report: mild pain: EG without changes in T1–T5, moderate pain: EG shows changes in T1*, T2*, and T10*, severe pain: EG – no par- ticipants classified for this group
6	Stefanoff (1990) [56]	Treatment of trigeminal neuralgia (TN) with local laser irradiation and laser puncture	*n* = 34 men: *n* = 15, 44.1% women: *n* = 19, 55.9%	EG: 34 (15 men, 19 women)	EG: LILT (20–30 s) Participants had already undergone drug treatments, physical therapy, and surgeries in the previous 15 years	HeNe laser (632.8 nm)	EG: face, mouth, and ear (auriculotherapy)	10–12 sessions (daily, 2 weeks)	T0: baseline, T1: at the end of 10–12 sessions (2 weeks), T2: 6 months after treatment	Main outcome: pain (self-report of symptoms)	Pain (self-report of symptoms): T0 < T1 < T2 (32 patients without symptoms)
7	Seada et al. (2013) [57]	Comparison between trans-cranial electromagnetic stimulation and low-level laser on modulation of trigeminal neuralgia	*n* = 30 NS by sex	EG: 15 (NS by sex) CG: 15 (NS by sex)	EG: LILT (1–2 min intraoral and 10 min extraoral) CG: repeated TMS (20 min)	HeNe laser (830 nm)	EG: mouth and face (intraoral and extraoral)	24 sessions (3 per week, 8 weeks)	T0: baseline, T1: 8 weeks	Main outcome: pain intensity (NPRS) Secondary outcomes: temporal and masseter muscle action potential (EMG), mouth opening distance (calliper), masseter muscle tension (tensiometer)	Pain intensity (NPRS): CG < EG in T1* and < T0* Masseter and temporal muscle action potential: CG > EG at T1* and > T0* Mouth opening distance: CG > EG at T1* and > T0* Muscle tension: CG < EG at T1* < T0*
8	Walker (1983) [58]	Relief from chronic pain by low power laser irradiation	*n* = 12 NS by sex	EG 1: 9 (NS by sex) EG 2: 3 (NS by sex)	EG 1: LILT (20 s for first week and 30-s increments for each week) + medication (anticonvulsants and barbiturates) EG 2: LILT (20 s for first week and 30-s increments for each week) + medication (anticonvulsants and barbiturates)	HeNe laser (632 nm)	EG 1: cutaneous territory inner- vated by the saphenous, median, radial, and ulnar nerves, and all the pain points of the face or temporoman- dibular joint EG 2: cutaneous territory inner- vated by the saphenous, median, radial, and ulnar nerves	30 sessions (3 per week, 10 weeks)	T0: baseline, T1: 4–8 sessions (2–3 weeks) – pain intensity / T1: session 5 (week 2) – urinary excretion of 5HIAA, T2: 12–30 sessions (4–10 weeks) – pain intensity / T2: session 10 (week 3) – urinary excretion of 5-HIAA	Main outcome: pain intensity (participant self-report) Secondary outcome: 5-HIAA excretion (urine test at 24 hours)	Pain intensity (self-report): EG 1 < EG 2 at T1 and T2 5-HIAA excretion (urine test at 24 hours): EG 1 > EG 2 at T1 and T2

9	Ebrahimi et al. (2018) [36]	Therapeutic and analgesic efficacy of laser in conjunction with pharmaceutical therapy for trigeminal neuralgia	*n* = 30 men: *n* = 11, 36.67% women: *n* = 19 63.33%	EG: 15 (5 men, 10 women) CG: 15 (6 men, 9 women)	EG: LILT (25 s per point) + medication (carbamazepine) CG: sham LILT + medication (carbamazepine) The total treatment time varied depending on the number of sore spots found in each participant	ArGaAl laser (810 nm)	EG: face CG: face	9 sessions (3 per week, 3 weeks)	T0: baseline, T1: 3 weeks, T2: 7 weeks	Main outcome: pain intensity (VAS)	Pain intensity (VAS): EG < CG at T1* EG < CG at T2* and < T0*
10	Pinheiro et al. (1998) [59]	Low-level laser therapy is an important tool to treat disorders of the maxillofacial region	*n* = 53 NS by sex	EG: 53 (NS by sex)	EG: LILT cluster (emission of 3 lasers)	ArGaAl diode laser (cluster application with 3 types of lasers: 632.8 nm, 670 nm, and 830 nm)	EG: face	12 sessions (2 per week, 6 weeks)	T0: baseline, T1: session 12 (week 6)	Main outcome: pain (symptomatic/ asymptomatic)	Pain: EG at T1 < T2 (30 asymptomatic, 9 show improvement, and 14 remain symptomatic at the end of study)
11	Hansen and Thorøe (1990) [60]	Low power laser biostimulation of chronic oro-facial pain. A double-blind placebo controlled cross-over study in 40 patients	*n* = 40 men: *n* = 3, 7.5% women: *n* = 37, 92.5%	EG: 20 (NS by sex) CG: 20 (NS by sex)	EG: LILT (60–120 s per point) CG: sham LILT	ArGaAl diode laser (904 nm)	EG: face and mouth (intraoral)	8 sessions (2 per week, 4 weeks)	T0: baseline, T1: 4 sessions (week 2), T2: 8 sessions (week 4)	Main outcome: pain intensity (VAS) Secondary outcome: 5-HIAA excretion (urine test)	Pain intensity (VAS): EG < CG at T2 and T1 5-HIAA excretion (urine test): EG > CG at T2* and T1*
12	Eckerdal and Bastian (1996) [61]	Can low reactive-level laser therapy be used in the treatment of neurogenic facial pain? A double-blind, placebo-controlled investigation of patients with trigeminal neuralgia	*n* = 32 men: *n* = 12, 37.5% women: *n* = 20, 62.5%	EG: 14 (4 men, 10 women) CG: 18 (8 men, 10 women)	EG: LILT (62.5 s per point) + medication (carbamazepine, oxcarbazepine, ibuprofen) CG: sham LILT + medication (carbamazepine, oxcarbazepine, ibuprofen)	ArGaAl diode laser (832 nm)	EG: face and neck CG: face and neck	5 sessions (1 per week, 5 weeks)	T0: baseline, T1: session 5	Main outcome: pain intensity (VAS) Secondary outcome: medication intake (self-report; number of medications ingested)	Pain intensity (VAS): EG < CG at T1 and < T0 Medication intake: EG < CG at T1
13	Díaz Pérez et al. (2018) [62]	Therapeutic laser effectiveness in ailment with orofacial pain	*n* = 6 men: *n* = 0, 0% women: *n* = 6, 100%	EG: 6 (0 men, 6 women)	EG: LILT (NS time per point)	ArGaAl diode laser (904 nm)	EG: face	12 sessions (2 per month, 6 months)	T0: baseline, T1: 4 weeks, T2: 8 weeks, T3: 12 weeks, T4: 16 weeks, T5: 20 weeks, T6: 24 weeks	Main outcome: pain intensity (VAS)	Pain intensity (VAS): EG at T6* < T5* < T4* < T3* < T2* < T1* < T0

5-HIAA – 5-hydroxyindoleacetic acid, ArGaAl – arsenide-gallium-aluminum, ArGa – arsenide-gallium, EMG – electromyography, VAS – visual analogue scale, EG – experimental group, CG – control group, HeNe – helium-neon, LILT – low-intensity laser therapy, NS – not specified, NPRS – numeric pain rating scale, TMS – transcranial magnetic stimulation, T0 – initial evaluation time point before treatment (baseline), T1, T2, ... – post-baseline evaluation time points
* $p < 0.05$

Study characteristics

Table 2 shows that 7 studies used LILT alone in experimental groups (EG) [51, 54–57, 59, 60, 62], while 4 applied LILT and drugs (carbamazepine, oxcarbazepine, barbiturates, and ibuprofen) [36, 52, 53, 58, 61] and only 1 utilized LILT and trigeminal ganglion block (bupivacaine and methylprednisolone) [53]. On the other hand, control groups (CG) received treatments with simulated LILT and drugs (n = 4) [36, 52, 58, 61], isolated simulated laser (n = 3) [53, 55, 60], TMS application (n = 1), and trigeminal ganglion block (n = 1) [53, 57], while 4 studies did not use CG [51, 56, 59, 62].

The reported number of treatment sessions was in the range of 9–12, except for the studies by Seada et al. [57] and Walker [58], who applied the highest number of 24 and 30 sessions, respectively. It should be noted that for most studies, 12 sessions were performed with intervals (1–3 times a week), except for Antonić et al. [51], who implemented LILT 5 times a week.

Regarding the place of treatment, 7 articles (53.84%) reported laser application directly on the face [36, 51–53, 59, 62], 3 (23.07%) on face and mouth (intraoral) [56, 57, 60], and 2 (15.38%) in extremity peripheral nerves (saphenous, median, radial, and ulnar nerves) plus temporomandibular joint [58], and cervical spine (transverse process of C7) [53]. In addition, Stefanoff et al. [56] reported auriculotherapy point application (ear) in addition to face and mouth treatment.

Main outcome

Pain intensity was evaluated in all included articles. The visual analogue scale (VAS) stands out as the most useful instrument (n = 9, 69.23%) applied to assess pain at rest [36, 51–55, 60–62], while some studies determined pain reduction through self-report (n = 3, 23.07%) [56, 58, 59], weekly pain episodes [55], and pain changes with numeric pain rating scale (NPRS) [57]. All studies present a decrease in pain in EG in relation to the initial evaluation (T0 or baseline), except for Aghamohammadi et al. [53] and Walker et al. [55], who did not observe pain decrease before treatment for the first and second evaluations (T1 and T2), although it was lower for subsequent evaluations. Pain reduction was statistically significant ($p < 0.05$) in favour of EG when comparing the evolution between sessions (intragroup) and with CG (intergroup) (n = 8, 61.53%) [36, 51–55, 57, 62]. On the other hand, Stefanoff [56], Walker [58], Pinheiro et al. [59], Hansen and Thorøe [60], and Eckerdal and Bastian [61] reported pain reduction in EG, but without an analysis indicating statistical significance for this change.

Only Walker [58] demonstrated secondary effects after the application of HeNe LILT, describing an exacerbation of symptoms in 1 participant between 3 and 24 hours after treatment.

Secondary outcomes

Secondary outcomes included drug use frequency [53], changes in facial skin temperature (thermography) [54], masticatory muscle electromyographic activity (surface electromyography) [57], temporal and masseter muscle tension (tensiometer) [57], mouth opening distance [57], and urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion [58, 60]. Hashimoto et al. [54] reported a statistically significant increase in face temperature at 15 and 30 minutes when comparing the irradiated side before and after laser treatment ($p < 0.01$) and when comparing it with the contralateral half-face (not irradiated) ($p < 0.05$). Seada et al. [57] indicated lower masticatory muscle tension ($p < 0.01$) and a greater mouth opening (interincisal distance) in EG between evaluation sessions ($p = 0.014$), although when compared with TMS, a greater statistically significant improvement was observed in favour of CG ($p < 0.01$). The same study describes a statistically significant improvement ($p = 0.01$) in masseter and temporal muscle electromyographic activity [57].

Walker [58] and Hansen and Thorøe [60] implied an increase in 5-HIAA excretion at 24 hours in favour of EG between sessions, although without reporting the statistical analysis for the first and with statistically significant changes for the second one ($p < 0.05$).

LILT dosage in included studies

Table 3 shows LILT modalities and dosage. A greater use of diode-type lasers was observed (n = 9, 69.23%) [36, 51–54, 59–62] compared with HeNe (n = 4, 30.76%) [55–58], most of these being infrared lasers with wavelengths of 810–980 nm (n = 10, 76.92%), while 3 studies documented LILT HeNe application with a common wavelength of 632 nm [55, 56, 58]. The studies revealed an output power range of 0.001 [55, 58] and 0.25 W [53], with 0.03 W as the most widely applied power [51, 59–61].

Continuous (100% duty cycle; n = 6, 46.15%) [36, 51, 53, 56, 59, 61] and pulsed delivery cycles (n = 7, 53.84%) [57, 58, 63] were administered, although in 3 studies the percentage of pulsed emission cycle was not specified. Given the output powers and emission cycles, the irradiance range (power density) obtained was 0.3–200 mW/cm^2 [36, 60], with an average of 64.33 mW/cm^2 [36, 60]. Only the studies by Stefanoff [56] and Seada et al. [57] coincide in irradiance in the range of 150–170 mW/cm^2. Regarding fluence (energy density), various values can be seen, with the range of 0.02–214 J/cm^2 [53, 58], the most common being 3–10 J/cm^2 [51–53, 59, 61]. The output power, irradiance, or fluence values were not reported in the study by Diaz Pérez et al. [62].

It was found that treatment times per point differed. The most frequent time was 20–60 seconds (n = 6, 46.15%) [36, 55, 56, 58, 60, 61], and the parameter was not reported in 3 articles (23.07%) [53, 59, 62]. The longest irradiation time per point was reported by Amanat et al. [52] (300 seconds), while the lowest irradiation times were described by Stefanoff [56] and Walker [58], who used 20 seconds. Walker [55] was the only one who applied a progressive weekly increase in irradiation time, observing an exacerbation of symptoms if treatment started with times of 60 seconds or more.

In most studies (n = 11), the number of pain points treated was not specified, except for Seada et al. [57] and Walker et al. [55], who applied LILT in 4 and 3 face points, respectively.

The contact application technique was the most used (n = 10, 76.92%) [36, 51, 52, 54, 55, 57–60, 62], while 3 trials (23.07%) did not report the application technique [53, 56, 61].

Discussion

The purpose of this systematic review was to investigate the scientific evidence on the efficacy of LILT as an analgesic treatment in TN. The results suggest that LILT is a therapeutic option reducing pain in this clinical condition.

This systematic review included 13 clinical trials, showing a low risk of bias in 38.46% of the studies (n = 5) [36, 52–54, 60] and a high risk of bias for 23.07% (n = 3) [56, 58, 59], which is an indicator of good methodological quality for

Table 3. Types of lasers and parameters used in the included studies

Study	Laser type	Wave-length	Output power	Duty cycle (emission modality)	Power density (irradiance)	Energy density	Treatment time per point	Total energy per point	Number of treated points	Application technique
Antonić et al. (2017) [51]	Laser 1: ArGaAl diode Laser 2: ArGaAl diode	Laser 1: 660 nm Laser 2: 810 nm	Laser 1: 0.03 W Laser 2: 0.03 W	Laser 1: 100% (continuous emission) Laser 2: 100% (continuous emission)	30 mW/cm^2	Laser 1: 3.0 J/cm^2 Laser 2: 3.0 J/cm^2	Laser 1: 100 s Laser 2: 100 s	3 J	NS	Contact
Amanat et al. (2013) [52]	ArGaAl diode	980 nm	0.012 W	1.2% (pulsed emission)	120 mW/cm^2	3.6 J/cm^2	300 s	3.6 J	NS	Contact
Aghamo-hammadi et al. (2012) [53]	ArGa diode	890 nm	< 0.25 W	100% (continuous emission)	NS	3–10 J/cm^2	NS	NS	NS	NS
Hashimoto et al. (1997) [54]	Laser 1: ArGaAl diode Laser 2: ArGaAl diode	Laser 1: 830 nm Laser 2: 830 nm	Laser 1: 0.06 W Laser 2: 0.15 W	100% (continuous emission)	Laser 1: 60 mW/cm^2 Laser 2: 15 mW/cm^2	Laser 1: 85.9 J/cm^2 Laser 2: 214.8 J/cm^2	180 s	Laser 1: 10.8 J Laser 2: 27 J	NS	Contact
Walker et al. (1987) [55]	HeNe	632.5 nm	0.001 W	50% (pulsed emission)	10 mW/cm^2	1.43 J/cm^2 (week 1) 2.14 J/cm^2 (week 2) 2.86 J/cm^2 (week 3) 4.28 J/cm^2 (week 4)	30 s 45 s 60 s 90 s	42.9 J (week 1) 96.4 J (week 2) 171.6 J (week 3) 385.2 J (week 4)	3	Contact
Stefanoff (1990) [56]	HeNe	632.8 nm	0.012 W	100% (continuous emission)	150–170 mW/cm^2	3–5.1 J/cm^2	20–30 s	60–153 J	NS	NS
Seada et al. (2013) [57]	HeNE	830 nm	0.015 W	NS delivery cycle (pulsed emission)	150–170 mW/cm^2	0.9–2.04 J/cm^2	60–120 s	54–244.8 J	4	Contact
Walker (1983) [58]	Laser 1: HeNe Laser 2: HeNe	632 nm	0.001 W	NS delivery cycle (pulsed emission)	1 mW/cm^2	Laser 1: 0.02 J/cm^2 Laser 2: 0.03 J/cm^2	Laser 1: 20 s Laser 2: 30 s	Laser 1: 0.04 J Laser 2: 0.09 J	NS	Contact
Ebrahimi et al. (2018) [36]	ArGaAl	810 nm	0.20 W	100% (continuous emission)	200 mW/cm^2	5 J/cm^2	25 s	5 J	NS	Contact
Pinheiro et al. (1998) [59]	ArGaAl diode (cluster)	632.8 nm 670 nm 830 nm	0.003 W 0.005 W 0.040 W	100% (continuous emission)	3 mW/cm^2 5 mW/cm^2 40 mW/cm^2	0.1–9.6 J/cm^2	NS	NS	NS	Contact
Hansen and Thorøe (1990) [60]	ArGaAl diode	904 nm	0.003 W	0.02–0.2% (pulsed emission)	0.3 mW/cm^2	0.078 J/cm^2	60–120 s	4.7–9.4 J	NS	Contact
Eckerdal and Bastian (1996) [61]	ArGaAl diode laser	832 nm	0.032 W	100% (continuous emission)	32 mW/cm^2	9.2 J/cm^2	60 s	552 J	NS	NS
Díaz Pérez et al. (2018) [62]	ArGaAl diode	904 nm	NS	NS delivery cycle (pulsed emission)	NS	NS	NS	NS	NS	Contact

ArGaAl – arsenide-gallium-aluminum, ArGa – arsenide-gallium, HeNe – helium-neon, NS – not specified

5 articles. The main problems in those at a high risk of bias are related to their blinding processes (participants and evaluators) and randomization, which constitute an aspect to consider despite the reported analgesic benefits [56–58]. It should be noted that 3 of these articles were published in the previous 10 years, so it is suggested that they be considered as the first reference owing to their methodological quality to evaluate the benefits of LILT in TN [36, 52, 53]. A statistically significant decrease in pain was observed for the 5 studies of a low risk of bias in favour of EG [36, 52–54, 60]. Regardless of the risk of bias, analgesic benefits of LILT in TN patients stand out for 100% of the remaining clinical trials (n = 8) [51, 55–59, 61, 62], which supports the literature that promotes the efficacy of this treatment in neuropathic pain conditions and other cranial neuropathies [73–76].

For most studies, the systematic review shows direct applications on the face, following the painful points in the sensitive territories of the trigeminal nerve, especially in the V2 branch (n = 11) [36, 51–53, 55–57, 59–62]. This assumes that the researchers supported the analgesic effects of LILT in relation to local physiological modifications such as increased synthesis of adenosine triphosphate, DNA, and cellular RNA, and increased resting membrane potential of free nerve endings, although they should not rule out systemic effects such as endogenous opioid peptide release or increased serotonin availability [36, 44–50]. It should be noted that the authors of 3 of these trials performed complementary intraoral treatments [56, 57, 60], trying to approach the superior and inferior alveolar nerves with dental applications to achieve the same extraoral physiological changes in the

V2 and V3 branches that these nerves originate. However, even though intraoral applications led to a reduction in pain, this was only statistically significant for Seada et al. [57]. Other problems for intraoral applications include more stringent hygiene protocols (e.g., protection of the probe with a disposable plastic), joint discomfort, or other discomfort from prolonged mouth opening while undergoing treatment. Although no studies reported details of the intraoral procedure, the probe isolation could attenuate the irradiance on target tissues, reducing the effectiveness of LILT, which could be the reason for not finding statistical significance in pain decrease [56, 57, 60]. Therefore, it is suggested to carry out new trials that would compare extraoral and intraoral techniques to assess the real benefits of the latter. On the other hand, Hashimoto et al. [54] and Eckerdal and Bastian [61] reported LILT application in the 7th cervical vertebra (transverse process of C7) and painful points associated with upper cervical spine, showing decreased pain, although with statistical significance only for the study by Hashimoto et al. [54]. These applications would be supported by cervicothoracic ganglia irradiation (stellate ganglion, in C7) and upper cervical (levels C2 and C3) seeking to improve synaptic transmission and decrease the exacerbated sympathetic nerve activity [54, 61, 77–79]. Although these physiological mechanisms are not clear, they may be associated with other systemic effects such as opioid peptide release (beta-endorphins) and greater serotonin availability [36, 44–50].

In turn, Walker [58] was the only one who reported a LILT intervention at the peripheral level in the cutaneous territories of saphenous, median, radial, and ulnar nerves, in addition to a temporomandibular joint specific application. The author sought local and systemic benefits, confirming them with a decrease in joint pain and increase in the systemic serotonin level through greater 5-HIAA urine excretion [58, 60, 80].

The number of treated pain spots was reported only by Walker [55] and Seada et al. [57], who applied LILT on the face in 3 and 4 spots, respectively, showing a significant pain reduction. The other articles did not specify the number of intervened points. Therefore, a minimum of 3 points can be suggested to start treatment, thus agreeing with the World Association for Laser Therapy recommendations for the treatment of temporomandibular disorders [44].

The systematic review shows a comparison between LILT and a simulated application for 53.8% of trials (n = 7), revealing a decrease in pain in both groups for 6 studies, although always with statistical significance in favour of LILT [36, 52–55, 60, 61]. The possible analgesic effect obtained for CG would be supported by placebo mechanisms, although these would be less effective than analgesic effects induced by LILT itself [81]. Although LILT and placebo generate opioid peptide release, the levels of these peptides with laser could be higher and bear a more prolonged effect [52, 60, 81].

It should be noted that 38.46% of the trials (n = 5) used a base drug treatment for both comparison groups, which included anticonvulsants (n = 4) [36, 52, 53, 58, 61], barbiturates (n = 1) [58], trigeminal ganglion block with bupivacaine and methylprednisolone (n = 1) [53], and non-steroidal anti-inflammatory drugs (ibuprofen) (n = 1) [61]. These drugs have different inhibitory effects on the nervous system such as calcium channel blockage (anticonvulsants), greater release of gamma-aminobutyric acid (barbiturates), less membrane sodium permeability (bupivacaine), and anti-inflammatory effects (methylprednisolone and ibuprofen) [22–24]. The base pharmacological treatment safeguarded bioethical principles, ensuring that both groups received equally effective treatment regardless of the effects of LILT. Likewise, the systematic review shows pain reduction in LILT groups, which makes it possible to assume additional laser analgesic effects beside those obtained with pharmacological treatment [36, 52, 53, 58, 61]. On the other hand, the paper by Seada et al. [57] reported the use of TMS as an active comparator, standing out as the only one where a physical agent for CG was applied. TMS is a non-invasive technique that involves the emission of low-frequency magnetic pulses over certain areas of the brain; it has been suggested as a treatment for chronic neuropathic pain [82]. Although Seada et al. [57] revealed a decrease in pain with statistical significance for both groups, greatest reduction was reported for CG (p = 0.001), which suggests that both treatments are effective. Despite this, LILT could be a better therapeutic option than TMS as it is less expensive, easier to apply, and more widely available, in addition to the fact that discomfort during application has been documented for TMS [57, 82].

This systematic review presents VAS as the most widely used instrument for assessing changes in pain (n = 9) [36, 51–55, 60–62]. It is characterized by good psychometric properties as validity (r: 0.62–0.91, correlation with NPRS), reliability (r: 0.71–0.94, test-retest), sensitivity (0.6), and specificity (0.74), standing out for pain variation detection in patients of all ages [83]. Seven of the presented studies showed a statistically significant pain reduction as evaluated with this instrument in LILT groups [36, 51–55]. On the other hand, 2 studies assessed self-report pain changes (pain relief or not) [56, 58] and Pinheiro et al. [59] rated participants dichotomously into symptomatic and asymptomatic. Although all trials determined a pain decrease, it is suggested to consider mostly those that used VAS, given its greater objectivity [36, 51–55, 62].

Two studies considered 5-HIAA excreted in the urine at 24 hours after LILT in the middle and at the end of treatment as a secondary outcome [58, 60], which is interesting because this substance represents serotonin degradation by the body. This hormone plays an important role in pain modulation, and a higher excretion relates to a greater analgesic effect of the laser [80]. Although both studies show an increase in 5-HIAA, supporting the systemic effects of LILT, this increase was statistically significant only in the paper by Hansen and Thorøe [60]; therefore, it is suggested to incorporate this outcome measure into new protocols.

All studies reported the number of the treatment sessions, with varied ranges between 3 to 30 at intervals [36, 51–62]. Although the studies describe analgesic benefits during follow-up sessions, pain reduction was observed from the 2nd week [36, 52, 56, 58, 60]. Interval sessions are highly recommended since the average duration of an LILT analgesic effect is 9–72 hours; besides, they allow avoiding cumulative results that could lead to a paradoxical effect (Arndt-Schulz law) [36, 41, 52].

Most trials used an infrared laser (wavelength > 760 nm) (n = 10) [36, 51–54, 57, 59–62]. The researchers probably chose these wavelengths to ensure a sufficient irradiation depth in the target tissues (2 cm for these types of lasers) [41–45].

This systematic review shows that LILT is a safe resource, without adverse effects and with analgesic benefits. However, 1 study reported exacerbation of pain for 9–24 hours after treatment in 1 participant, despite pain reduction in subsequent sessions [58]. This event could be due to the low power used (0.001 W), not reaching the therapeutic dose.

Although the results support the use of LILT, the diversity of parameters applied is considered a great limitation. The

papers report a wide range of output powers, irradiance (mW), fluence (J/cm^2), and treatment times (minutes), which makes it difficult to recognize a reliable dosage.

However, after analysing the studies, the following can be recommended for LILT in TN: diode-type lasers, infrared wavelengths, average output powers of 120–170 mW, and energy densities of 3–5 J/cm^2 for each treatment point, considering at least 3–4 points.

Finally, it is suggested for future LILT studies in this and other areas to clearly inform the LILT parameters, including mean powers, energy densities, and the number of points, since these variables are determinant for a dosage consensus and comparisons among clinical trials.

Conclusions

LILT is a safe and non-invasive treatment for different neuropathic pain disorders, including TN. This systematic review indicates that LILT is effective in reducing pain in the short and long term in patients with TN, being well tolerated, with no reported side effects in the studies analysed. Results are promising and promote the need to incorporate LILT in treatment protocols for TN and other types of orofacial pain, minimizing the consumption of medications. In addition, LILT shows advantages in the management of TN compared with other techniques such as TMS, extracorporeal shock waves, or dry needling, given its high availability, low cost, easy application, and lower risk than in the case of invasive techniques.

However, it is convenient to review the doses used, informing with greater clarity in new studies the mean powers (W_m), energy densities (J/cm^2), treatment times, and the number of points, in order to obtain reliable parameters to establish a dosage consensus. Likewise, this systematic review allowed the researchers to establish a dosage recommendation that can be revised and used for further research.

Disclosure statement

No author has any financial interest or received any financial benefit from this research.

Conflict of interest

The authors state no conflict of interest.

Funding

The study was not funded.

References

1. Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, et al. Prevalence of chronic pain and high-impact chronic pain among adults – United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67(36):1001–1006; doi: 10.15585/mmwr.mm6736a2.
2. Kohrt BA, Griffith JL, Patel V. Chronic pain and mental health: integrated solutions for global problems. Pain. 2018;159(Suppl. 1):85–90; doi: 10.1097/j.pain.0000000000001296.
3. Smith BH, Torrance N. Epidemiology of neuropathic pain and its impact on quality of life. Curr Pain Headache Rep. 2012;16(3):191–198; doi: 10.1007/s11916-012-0256-0.
4. Karst M, Jasper S, Bernateck M, Stephan M. Clinical diagnostics and therapy of chronic pain syndromes [in German]. Psychother Psychosom Med Psychol. 2012; 62(8):320–330; doi: 10.1055/s-0032-1305160.
5. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2019;160(1): 19–27; doi: 10.1097/j.pain.0000000000001384.
6. Ro L-S, Chang K-H. Neuropathic pain: mechanisms and treatments. Chang Gung Med J. 2005;28(9):597–605.
7. Planjar-Prvan M, Bielen I, Baraba R, Buljan R. Pathophysiologic basis of the treatment of neurogenic pain [in Croatian]. Acta Med Croatica. 2004;58(3):197–205.
8. Murnion BP. Neuropathic pain: current definition and review of drug treatment. Aust Prescr. 2018;41(3):60–63; doi: 10.18773/austprescr.2018.022.
9. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice ASC, et al. A new definition of neuropathic pain. Pain. 2011;152(10):2204–2205; doi: 10.1016/j.pain.2011.06.017.
10. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain. 2006;7(4):281–289; doi: 10.1016/j.jpain.2005.11.008.
11. International Association for the Study of Pain. Epidemiology of neuropathic pain: how common is neuropathic pain, and what is its impact? Washington: IASP; 2014.
12. Smith BH, Torrance N. Epidemiology of neuropathic pain. Pain Manag. 2011;1(1):87–96; doi: 10.2217/pmt.10.5.
13. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 2010;9(8):807–819; doi: 10.1016/S1474-4422(10)70143-5.
14. Szok D, Tajti J, Nyári A, Vécsei L. Therapeutic approaches for peripheral and central neuropathic pain. Behav Neurol. 2019;2019:8685954; doi: 10.1155/2019/8685954.
15. Jones MR, Urits I, Ehrhardt KP, Cefalu JN, Kendrick JB, Park DJ, et al. A comprehensive review of trigeminal neuralgia. Curr Pain Headache Rep. 2019;23(10):74; doi: 10.1007/s11916-019-0810-0.
16. Bendtsen L, Zakrzewska JM, Heinskou TB, Hodaie M, Lacerda Leal PR, Nurmikko T, et al. Advances in diagnosis, classification, pathophysiology, and management of trigeminal neuralgia. Lancet Neurol. 2020;19(9):784–796; doi: 10.1016/S1474-4422(20)30233-7.
17. Spina A, Mortini P, Alemanno F, Houdayer E, Iannaccone S. Trigeminal neuralgia: toward a multimodal approach. World Neurosurg. 2017;103:220–230; doi: 10.1016/j.wneu.2017.03.126.
18. Lake WB, Neimat J. Trigeminal neuralgia. In: Harbaugh RE, Shaffrey C, Couldwell WT, Berger MS (eds.), Neurosurgery knowledge update: a comprehensive review. New York: Thieme Medical Publishers; 2015; 293–299.
19. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal neuralgia – a prospective systematic study of clinical characteristics in 158 patients. Headache. 2014;54(10): 1574–1582; doi: 10.1111/head.12441.
20. Bennetto L, Patel NK, Fuller G. Trigeminal neuralgia and its management. BMJ. 2007;334(7586):201–205; doi: 10.1136/bmj.39085.614792.BE.
21. Yadav YR, Nishtha Y, Sonjjay P, Vijay P, Shailendra R, Yatin K. Trigeminal neuralgia. Asian J Neurosurg. 2017; 12(4):585–597; doi: 10.4103/ajns.AJNS_67_14.
22. Cruccu G, Di Stefano G, Truini A. Trigeminal neuralgia. N Engl J Med. 2020;383(8):754–762; doi: 10.1056/NEJMra1914484.
23. Maarbjerg S, Di Stefano G, Bendtsen L, Cruccu G. Trigeminal neuralgia – diagnosis and treatment. Cephalalgia.2017;37(7):648–657;doi:10.1177/0333102416687280.
24. Xu L, Zhang Y, Huang Y. Advances in the treatment of neuropathic pain. Adv Exp Med Biol. 2016;904:117–129; doi: 10.1007/978-94-017-7537-3_9.

25. Ariai MS, Mallory GW, Pollock BE. Outcomes after microvascular decompression for patients with trigeminal neuralgia and suspected multiple sclerosis. World Neurosurg. 2014;81(3–4):599–603; doi: 10.1016/j.wneu.2013.09.027.
26. Han KR, Kim C, Chae YJ, Kim DW. Efficacy and safety of high concentration lidocaine for trigeminal nerve block in patients with trigeminal neuralgia. Int J Clin Pract. 2008;62(2):248–254;doi:10.1111/j.1742-1241.2007.01568.x.
27. Pollock BE. Radiosurgery for trigeminal neuralgia: is sensory disturbance required for pain relief? J Neurosurg. 2006;105(Suppl.):103–106; doi: 10.3171/sup.2006.105.7.103.
28. Sade B, Lee JH. Microvascular decompression for trigeminal neuralgia. Neurosurg Clin N Am. 2014;25(4):743–749; doi: 10.1016/j.nec.2014.06.007.
29. Vanneste T, Van Lantschoot A, Van Boxem K, Van Zundert J. Pulsed radiofrequency in chronic pain. Curr Opin Anaesthesiol. 2017;30(5):577–582; doi: 10.1097/ACO.0000000000000502.
30. Weber K. Neuromodulation and devices in trigeminal neuralgia. Headache. 2017;57(10):1648–1653; doi: 10.1111/head.13166.
31. Singla S, Prabhakar V, Singla RK. Role of transcutaneous electric nerve stimulation in the management of trigeminal neuralgia. J Neurosci Rural Pract. 2011;2(2):150–152; doi: 10.4103/0976-3147.83580.
32. Sun J, Li R, Li X, Chen L, Liang Y, Zhang Q, et al. Electroacupuncture therapy for change of pain in classical trigeminal neuralgia. Medicine. 2020;99(16):e19710; doi: 10.1097/MD.0000000000019710.
33. Bjordal JM, Couppé C, Chow RT, Tunér J, Ljunggren EA. A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders. Aust J Physiother. 2003;49(2):107–116; doi: 10.1016/s0004-9514(14)60127-6.
34. Kalhori KAM, Vahdatinia F, Jamalpour MR, Vescovi P, Fornaini C, Merigo E, et al. Photobiomodulation in oral medicine. Photobiomodul Photomed Laser Surg. 2019;37(12):837–861; doi: 10.1089/photob.2019.4706.
35. Pandeshwar P, Roa MD, Das R, Shastry SP, Kaul R, Srinivasreddy MB. Photobiomodulation in oral medicine: a review. J Investig Clin Dent. 2016;7(2):114–126; doi: 10.1111/jicd.12148.
36. Ebrahimi H, Najafi S, Khayamzadeh M, Zahedi A, Mahdavi A. Therapeutic and analgesic efficacy of laser in conjunction with pharmaceutical therapy for trigeminal neuralgia. J Lasers Med Sci. 2018;9(1):63–68; doi: 10.15171/jlms.2018.13.
37. Parker S, Cronshaw M, Anagnostaki E, Bordin-Aykroyd SR, Lynch E. Systematic review of delivery parameters used in dental photobiomodulation therapy. Photobiomodul Photomed Laser Surg. 2019;37(12):784–797; doi: 10.1089/photob.2019.4694.
38. Clijsen R, Brunner A, Barbero M, Clarys P, Taeymans J. Effects of low-level laser therapy on pain in patients with musculoskeletal disorders: a systematic review and meta-analysis. Eur J Phys Rehabil Med. 2017;53(4):603–610; doi: 10.23736/S1973-9087.17.04432-X.
39. Cotler HB, Chow RT, Hamblin MR, Carroll J. The use of low level laser therapy (LLLT) for musculoskeletal pain. MOJ Orthop Rheumatol. 2015;2(5):00068; doi: 10.15406/mojor.2015.02.00068.
40. Khalkhal E, Razzaghi M, Rostami-Nejad M, Rezaei-Tavirani M, Beigvand HH, Tavirani MR. Evaluation of laser effects on the human body after laser therapy. J Lasers Med Sci. 2020;11(1):91–97; doi: 10.15171/jlms.2020.15.
41. Cameron MH. Lasers and light. In: Cameron MH (ed.), Physical agents in rehabilitation: an evidence-based approach to practice, 6th ed. Philadelphia: Elsevier; 2022; 305–324.
42. Xu G-Z, Jia J, Jin L, Li J-H, Wang Z-Y, Cao D-Y. Low-level laser therapy for temporomandibular disorders: a systematic review with meta-analysis. Pain Res Manag. 2018;2018:4230583; doi: 10.1155/2018/4230583.
43. Choy DS. History of lasers in medicine. Thorac Cardiovasc Surg. 1988;36(Suppl. 2):114–117; doi: 10.1055/s-2007-1022985.
44. Bjordal JM. Low level laser therapy (LLLT) and World Association for Laser Therapy (WALT) dosage recommendations. Photomed Laser Surg. 2012;30(2):61–62; doi: 10.1089/pho.2012.9893.
45. De la Barra Ortiz HA, Acevedo Cangas S, Cumio Herrera A, Oñate García F, Velásquez Velásquez S. Efficacy of class IV laser in the management of musculoskeletal pain: a systematic review. Physiother Quart. 2021;29(2):1–11; doi: 10.5114/pq.2021.105882.
46. Karu TI, Hode L. Ten lectures on basic science of laser phototheraphy. Grängesberg: Prima Books; 2007.
47. Bjordal JM, Johnson MI, Iversen V, Aimbire F, Lopes-Martins RAB. Low-level laser therapy in acute pain: a systematic review of possible mechanisms of action and clinical effects in randomized placebo-controlled trials. Photomed Laser Surg. 2006;24(2):158–168; doi: 10.1089/pho.2006.24.158.
48. Tomazoni SS, Costa LOP, Joensen J, Stausholm MB, Naterstad IF, Leal-Junior ECP, et al. Effects of photobiomodulation therapy on inflammatory mediators in patients with chronic non-specific low back pain: protocol for a randomized placebo-controlled trial. Medicine. 2019;98(15):e15177; doi: 10.1097/MD.0000000000015177.
49. Munguia FM, Jang J, Salem M, Clark GT, Enciso R. Efficacy of low-level laser therapy in the treatment of temporomandibular myofascial pain: a systematic review and meta-analysis. J Oral Facial Pain Headache. 2018;32(3):287–297; doi: 10.11607/ofph.2032.
50. Naeser MA, Hamblin MR. Potential for transcranial laser or LED therapy to treat stroke, traumatic brain injury, and neurodegenerative disease. Photomed Laser Surg. 2011;29(7):443–446; doi: 10.1089/pho.2011.9908.
51. Antonić R, Brumini M, Vidović I, Muhvić Urek M, Glažar I, Pezelj-Ribarić S. The effects of low level laser therapy on the management of chronic idiopathic orofacial pain: trigeminal neuralgia, temporomandibular disorders and burning mouth syndrome. Med Flum. 2017;53(1):61–67; doi: 10.21860/medflum2017_173373.
52. Amanat D, Ebrahimi H, Lavaee F, Alipour A. The adjunct therapeutic effect of lasers with medication in the management of orofacial pain: double blind randomized controlled trial. Photomed Laser Surg. 2013;31(10):474–479; doi: 10.1089/pho.2013.3555.
53. Aghamohammadi D, Amirnaseri R, Peirovifar A, Hossainzadeh H, Eidi M, Ehsaei M, et al. Gasserian ganglion block with or without low-intensity laser therapy in trigeminal neuralgia: a comparative study. Neurosurg Q. 2012;22(4):228–232; doi: 10.1097/WNQ.0b013e3182571c93.
54. Hashimoto T, Kemmotsu O, Otsuka H, Numazawa R, Ohta Y. Efficacy of laser irradiation on the area near the stellate ganglion is dose dependent: a double-blind cross-

over placebo-controlled study. Laser Ther. 1997;9(1): 7–12; doi: 10.5978/islsm.9.7.
55. Walker JB, Akhanjee LK, Cooney MM, Goldstein J, Tamzyoshi S, Segal-Gidan F. Laser therapy for pain of trigeminal neuralgia. Clin J Pain. 1987;3(4):183–188.
56. Stefanoff V. Treatment of trigeminal neuralgia (TN) with local laser irradiation and laser puncture. Int J Oral Maxillofac Surg. 1990;19(6):379–380.
57. Seada YI, Nofel R, Sayed HM. Comparison between trans-cranial electromagnetic stimulation and low-level laser on modulation of trigeminal neuralgia. J Phys Ther Sci. 2013;25(8):911–914; doi: 10.1589/jpts.25.911.
58. Walker J. Relief from chronic pain by low power laser irradiation. Neurosci Lett. 1983;43(2–3):339–344; doi: 10.1016/0304-3940(83)90211-2.
59. Pinheiro AL, Cavalcanti ET, Pinheiro TI, Alves MJ, Miranda ER, De Quevedo AS, et al. Low-level laser therapy is an important tool to treat disorders of the maxillofacial region. J Clin Laser Med Surg. 1998;16(4):223–226; doi: 10.1089/clm.1998.16.223.
60. Hansen HJ, Thorøe U. Low power laser biostimulation of chronic oro-facial pain. A double-blind placebo controlled cross-over study in 40 patients. Pain. 1990;43(2): 169–179; doi: 10.1016/0304-3959(90)91070-Y.
61. Eckerdal A, Bastian L. Can low reactive-level laser therapy be used in the treatment of neurogenic facial pain? A double-blind, placebo-controlled investigation of patients with trigeminal neuralgia. Laser Ther. 1996;8(4): 247–251; doi: 10.5978/islsm.8.247.
62. Díaz Pérez R, Guzmán Ruiz A, Gutiérrez Valdez DH. Therapeutic laser effectiveness in ailment with orofacial pain [in Spanish]. Av Odontoestomatol. 2018;34(2):87–93.
63. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339: b2535; doi: 10.1136/bmj.b2535.
64. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan – a web and mobile app for systematic reviews. Syst Rev. 2016;5:210; doi: 10.1186/s13643-016-0384-4.
65. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003;83(8): 713–721; doi: 10.1093/ptj/83.8.713.
66. De Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Aust J Physiother. 2009;55(2):129–133; doi: 10.1016/s0004-9514(09)70043-1.
67. Albanese E, Bütikofer L, Armijo-Olivo S, Ha C, Egger M. Construct validity of the Physiotherapy Evidence Database (PEDro) quality scale for randomized trials: item response theory and factor analyses. Res Synth Methods. 2020;11(2):227–236; doi: 10.1002/jrsm.1385.
68. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898; doi: 10.1136/bmj.l4898.
69. Minozzi S, Cinquini M, Gianola S, Gonzalez-Lorenzo M, Banzi R. The revised Cochrane risk of bias tool for randomized trials (RoB 2) showed low interrater reliability and challenges in its application. J Clin Epidemiol. 2020; 126:37–44; doi: 10.1016/j.jclinepi.2020.06.015.
70. Minozzi S, Cinquini M, Gianola S, Castellini G, Gerardi C, Banzi R. Risk of bias in nonrandomized studies of interventions showed low inter-rater reliability and challenges in its application. J Clin Epidemiol. 2019;112:28–35; doi: 10.1016/j.jclinepi.2019.04.001.
71. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021; 12(1):55–61; doi: 10.1002/jrsm.1411.
72. Stovold E, Beecher D, Foxlee R, Noel-Storr A. Study flow diagrams in Cochrane systematic review updates: an adapted PRISMA flow diagram. Syst Rev. 2014;3:54; doi: 10.1186/2046-4053-3-54.
73. De Andrade ALM, Bossini PS, Parizotto NA. Use of low level laser therapy to control neuropathic pain: a systematic review. J Photochem Photobiol B. 2016;164:36–42; doi: 10.1016/j.jphotobiol.2016.08.025.
74. Anju M, Ummer VS, Maiya AG, Hande M. Low level laser therapy for the patients with painful diabetic peripheral neuropathy – a systematic review. Diabetes Metab Syndr. 2019;13(4):2667–2670; doi: 10.1016/j.dsx.2019.07.035.
75. Lin L, Li J, Lin J, Tang S, Li Y. Effectiveness and safety of low-level laser therapy in diabetic peripheral neuropathy: a protocol for a systematic review and meta-analysis. Syst Rev. 2021;10(1):96; doi: 10.1186/s13643-021-01656-y.
76. Ordahan B, Karahan AY. Role of low-level laser therapy added to facial expression exercises in patients with idiopathic facial (Bell's) palsy. Lasers Med Sci. 2017;32(4): 931–936; doi: 10.1007/s10103-017-2195-9. Erratum in: Lasers Med Sci. 2019;34(6):1281–1282; doi: 10.1007/s10103-019-02828-y.
77. Walker JB, Akhanjee LK. Laser-induced somatosensory evoked potentials: evidence of photosensitivity in peripheral nerves. Brain Res. 1985;344(2):281–285; doi: 10.1016/0006-8993(85)90805-4.
78. Tsuchiya K, Kawatani M, Takeshige C, Matsumoto I. Laser irradiation abates neuronal responses to nociceptive stimulation of rat-paw skin. Brain Res Bull. 1994;34(4): 369–374; doi: 10.1016/0361-9230(94)90031-0.
79. Lambert GW, Kaye DM, Cox HS, Vaz M, Turner AG, Jennings GL, et al. Regional 5-hydroxyindoleacetic acid production in humans. Life Sci. 1995;57(3):255–267; doi: 10.1016/0024-3205(95)00269-c.
80. Deacon AC. The measurement of 5-hydroxyindoleacetic acid in urine. Ann Clin Biochem. 1994;31(Pt 3):215–232; doi: 10.1177/000456329403100302.
81. Rossettini G, Carlino E, Testa M. Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. BMC Musculoskelet Disord. 2018;19(1):27; doi: 10.1186/s12891-018-1943-8.
82. Coarkin PE, Wall CA, King JD, Kozel FA, Daskalakis ZJ. Pain during transcranial magnetic stimulation in youth. Innov Clin Neurosci. 2011;8(12):18–23.
83. Sokka T. Assessment of pain in patients with rheumatic diseases. Best Pract Res Clin Rheumatol. 2003;17(3): 427–449; doi: 10.1016/s1521-6942(03)00020-2.