Efficacy of Low-Level Laser Therapy for the Therapeutic Management of Neuropathic Orofacial Pain: A Systematic Review

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Aims: To evaluate the efficacy of low-level laser therapy (LLLT) for the therapeutic management of neuropathic orofacial pain. **Methods:** 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, third edition. The primary outcome was measurement of pain intensity. **Results:** A total of 997 studies were obtained with the initial search; 13 (8 randomized controlled trials, 2 prospective studies, and 3 case series) met the inclusion criteria and were analyzed for data extraction. Three provided data for the treatment of trigeminal neuralgia, 1 for occipital neuralgia, and 10 for burning mouth syndrome. 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. **Conclusion:** LLLT seems to be effective as a treatment option for different neuropathic orofacial pain entities such as trigeminal neuralgia, occipital neuralgia, and burning mouth syndrome as a single or combined treatment. However, 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 required to confirm the results of this systematic review. *J Oral Facial Pain Headache 2020;34:13–30. doi: 10.11607/ofph.2310*

Keywords: *low-level laser therapy, neuropathic pain, orofacial pain, systematic review*

The American Academy of Orofacial Pain (AAOP) defines orofacial pain as pain associated with the hard and soft tissues of the head, face, and neck. Neuropathic pain is defined as "pain arising as a direct consequence of a lesion or disease of the somatosensory system."[1] In section 13 (painful lesions of the cranial nerves and other facial pain) in the latest classification of headache disorders (ICHD-3),[2] the International Headache Society (IHS) describes all of the neuropathic orofacial pain entities (Table 1).

Due to the extensive number of neuropathic and idiopathic pain entities in the orofacial region and their different pathogeneses, a vast number of therapeutic options have been used. These therapeutic options include pharmacologic (prednisone, opioids, paroxetine, amitriptyline, amisulpride, venlafaxine, duloxetine, fluoxetine, gabapentin, pregabalin, clonazepam, bethanechol, lafutidine, carbamazepine, topical anesthetics, capsaicin, and dietary supplements such as alpha lipoic acid [ALA]),[3–8] interventional (microvascular decompression, alcohol injections, thermocoagulation, mechanical decompression, or stereotactic radiosurgery in the form of Gamma Knife),[5,9] and psychologic treatments.[3–8] In most cases, these treatment modalities render only moderate symptom relief and have significant surgical risks and adverse effects. Therefore, it is necessary to look for new therapies.[7]

Low-level laser therapy (LLLT) has emerged as an interesting treatment option in patients with neuropathic orofacial pain.[10] LLLT has

Table 1 Classification of Headache Disorders (ICHD-3), Section 13 (Painful Lesions of the Cranial Nerves and Other Facial Pain)

13.1.1 Trigeminal neuralgia	A disorder characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli. It may develop without apparent cause or be a result of another diagnosed disorder. Additionally, there may be concomitant continuous pain of moderate intensity within the distribution(s) of the affected nerve division(s).
13.1.2 Painful trigeminal neuropathy	Facial pain in the distribution(s) of one or more branches of the trigeminal nerve caused by another disorder and indicative of neural damage. The primary pain is usually continuous or near-continuous, and commonly described as burning or squeezing, or likened to pins and needles. Superimposed brief pain paroxysms may occur, but these are not the predominant pain type. This combination distinguishes painful trigeminal neuropathy from the subtypes of trigeminal neuralgia. There are clinically detectable sensory deficits within the trigeminal distributions, and mechanical allodynia and cold hyperalgesia are common, fulfilling IASP criteria for neuropathic pain. As a rule, allodynic areas are much larger than the punctate trigger zones present in trigeminal neuralgia.
13.2.1 Glossopharyngeal neuralgia	A disorder characterized by unilateral brief stabbing pain, abrupt in onset and termination, in the distributions not only of the glossopharyngeal branches of the vagus nerve. Pain is experienced in the ear, base of the tongue, tonsillar fossa and/or beneath the angle of the jaw. It is commonly provoked by swallowing, talking or coughing and may remit and relapse in the fashion of trigeminal neuralgia.
13.2.2 Painful glossopharyngeal neuropathy	Pain within the distribution of the glossopharyngeal nerve (posterior part of the tongue, tonsillar fossa, pharynx and/or beneath the angle of the lower jaw). In addition, pain is commonly perceived in the ipsilateral ear. The primary pain is usually continuous or near-continuous, and commonly described as burning or squeezing, or likened to pins and needles. Brief paroxysms may be superimposed, but they are not the predominant pain type. Sensory deficits may be present in the ipsilateral posterior part of the tongue and tonsillar fossa, and the gag reflex may be weak or missing.
13.3.1 Nervus intermedius neuralgia	A rare disorder characterized by brief paroxysms of pain felt deeply in the auditory canal, sometimes radiating to the parieto-occipital region. In the vast majority of cases, vascular compression is found at operation, occasionally with a thickened arachnoidea, but it may develop without apparent cause or as a complication of herpes zoster or, very rarely, multiple sclerosis or tumour. It is provoked by stimulation of a trigger area in the posterior wall of the auditory canal and/or periauricular region.
13.3.2 Painful nervus intermedius neuropathy	Pain within the distribution(s) of the intermedius nerve(s) (auditory canal, auricle or region of the mastoid process), usually described by the patient as dull, deep in the ear and continuous or near-continuous. Brief paroxysms may be superimposed, but they are not the predominant pain type. Sensory deficits, usually slight, may be present in the ear canal, auricle or skin overlying the mastoid process.
12.4 Occipital neuralgia	Unilateral or bilateral paroxysmal, shooting or stabbing pain in the posterior part of the scalp, in the distribution(s) of the greater, lesser and/or third occipital nerves, sometimes accompanied by diminished sensation or dysesthesia in the affected area and commonly associated with tenderness over the involved nerve(s).
13.5 Neck-tongue syndrome	Immediate-onset, unilateral, sharp or stabbing and usually severe occipital and/or upper neck pain brought on by sudden rotatory head movement, accompanied by abnormal sensation and/or posture of the ipsilateral tongue.
13.6 Painful optic neuritis	Pain behind one or both eyes caused by demyelination of the optic nerve(s) and accompanied by impairment of central vision.
13.7 Headache attributed to ischaemic ocular motor nerve palsy	Unilateral frontal and/or periorbital pain caused by and associated with other symptoms and/or clinical signs of ischaemic paresis of the ipsilateral IIIrd, IVth and/or VIth cranial nerve(s).
13.8 Tolosa-Hunt syndrome	Unilateral orbital or periorbital pain associated with paresis of one or more of the IIIrd, IVth and/or VIth cranial nerves caused by a granulomatous inflammation in the cavernous sinus, superior orbital fissure or orbit.
13.9 Paratrigeminal oculosympathetic (Raeder's) syndrome	Constant, unilateral pain in the distribution of the ophthalmic division of the trigeminal nerve, sometimes extending to the maxillary division, accompanied by ipsilateral Horner's syndrome and caused by a disorder in the middle cranial fossa or of the carotid artery.
13.10 Recurrent painful ophthalmoplegic neuropathy	Repeated attacks of paresis of one or more ocular cranial nerves (commonly the IIIrd), with ipsilateral headache.
13.11 Burning mouth syndrome	An intraoral burning or dysaesthetic sensation, recurring daily for more than two hours/day over more than three months, without clinically evident causative lesions.
13.12 Persistent idiopathic facial pain	Persistent facial and/or oral pain, with varying presentations but recurring daily for more than two hours/day over more than three months, in the absence of clinical neurological deficit.
13.13.1 Central neuropathic pain attributed to multiple sclerosis	Unilateral or bilateral craniocervical pain with variable presentation, with or without sensory changes, attributed to a demyelinating lesion of the central ascending connections of the trigeminal nerve in a person with multiple sclerosis. It commonly remits and relapses.
13.13.2 Central post-stroke pain	Usually unilateral facial and/or head pain, with varying presentations involving parts or all of the craniocervical region and associated with impaired sensation, occurring within six months of and caused by stroke. It is not explicable by a lesion of the peripheral trigeminal or other cranial or cervical nerves.

proven to be effective in other persistent painful conditions such as chronic back pain, myofascial pain syndrome, chronic cervical pain, and osteoarthritis.[11]

Several studies have demonstrated the role of LLLT in oral medicine to manage different diseases such as oral mucositis,[12] oral lichen planus,[13] recurrent herpes

simplex,[14] recurrent aphthous ulcerations,[15,16] xerostomia,[16] and temporomandibular disorders.[10] LLLT bases its analgesic, anti-inflammatory, and biostimulatory effects on the improvement of cellular function at the mitochondrial level, increasing serotonin levels, plasma levels of endorphins, synthesis of collagen, and the production of adenosine triphosphate, among others.[10] In addition, LLLT is a noninvasive, nonpharmacologic treatment with minimal adverse effects.[10]

The main objective of this systematic review was to evaluate the efficacy of LLLT in the therapeutic management of neuropathic orofacial pain. In addition to the main outcome of pain intensity improvement, treatment results were evaluated in other dimensions of pain, such as physical and emotional functioning, patient impression of improvement, and adverse events, among others.

Materials and Methods

Protocol and Registration

This systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (http://www.prisma-statement.org).[17]

Eligibility Criteria

Based on the PRISMA guidelines, a focused PICO (population, intervention, comparison, outcome) question was considered: In patients with neuropathic orofacial pain, is LLLT, compared to placebo or other treatments, an effective treatment in terms of pain reduction?

The selected studies had to be original studies, clinical trials, observational studies, or case series, only in humans, and published in English.

One group of individuals (study group) needed to receive only LLLT or LLLT associated with another intervention for treatment of neuropathic orofacial pain, and these results needed to be compared to a placebo treatment or to another treatment for orofacial neuropathic pain, if available. Studies that analyzed the use of LLLT for treatment of neuropathic pain in different parts of the body were included, but these studies had to adequately describe the outcomes for the orofacial region in order to be considered for this study. Studies that compared different wavelengths of LLLT in different groups of patients were also included. In every study, all of the patients in each group had to receive the exact same number of sessions with the same laser technique or treatment.

Studies excluded were those that did not use LLLT for orofacial treatment, those in which several pathologies were treated with LLLT, and those in which the results were not clearly separated.

		Neuropathic pain
		Orofacial pain
		Neuralgia
		Neuropathy
Low level laser therapy	AND	Trigeminal neuralgia
		Painful trigeminal neuropathy
		Glossopharyngeal neuralgia
		Painful glossopharyngeal neuropathy
		Nervus intermedius neuralgia
		Painful nervus intermedius neuropathy
		Occipital neuralgia
		Neck-tongue syndrome
		Painful optic neuritis
		Headache attributed to ischaemic ocular motor nerve palsy
		Tolosa-Hunt syndrome
		Paratrigeminal oculosympathetic (Raeder's) syndrome
		Recurrent painful ophthalmoplegic neuropathy
		Burning mouth syndrome
		Persistent idiopathic facial pain
		Central neuropathic pain attributed to multiple sclerosis
		Central post-stroke pain

Fig 1 Terms used in the search strategy. Most are taken from ICHD-3.

In some cases, in order to obtain additional information regarding methodology and outcomes, the authors were contacted directly by email.

Information Sources

A comprehensive search of the literature was conducted in the PubMed/MEDLINE (National Library of Medicine), Scopus, and Cochrane Library electronic databases up to March 8, 2018. No limits were placed on the search function. An additional hand search was performed to find potential eligible studies in the reference lists of review articles and relevant studies.

Search

The search strategy used the following combination of terms in the electronic databases: low level laser therapy AND neuropathic pain OR orofacial pain OR neuralgia OR neuropathy OR painful lesions of the cranial nerves and other facial pain (section 13 of ICHD-3[2]) (Fig 1).

Study Selection

The literature search was performed by two independent researchers (M.D.P. and R.M.L.P.), and their results were compared. Duplicates were removed, and full titles and abstracts of the remaining papers were screened individually. Differences in eligible studies were resolved via discussion with a third reviewer (G.H.).

Data Collection Process

M.D.P. and R.M.L.P. extracted the data independently. Any disagreements were solved via discussion with a third reviewer (J.L.D.L.H.).

Table 2 Risk of Bias in Individual Studies

	Possible source of bias (type of bias)						
Author, year, country	Random sequence generation (selection)	Allocation concealment (selection)	Blinding of participants and personnel (performance)	Blinding of outcome assessment (detection)	Incomplete outcome data (attrition)	Selective reporting (reporting)	Other bias
13.1 Trigeminal neuralgia							
Antonić et al,[19] 2017, Croatia	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Seada et al,[20] 2013, Saudi Arabia	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk
Aghamohammadi et al,[21] 2012, Iran	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	High risk	High risk
13.4. Occipital neuralgia							
Amoils and Kues,[22] 1991, USA	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	High risk	High risk
13.11 Burning mouth syndrome							
Antonić et al,[19] 2017, Croatia	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Unclear risk	High risk
Barbosa et al,[23] 2018, Brazil	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Arduino et al,[24] 2016 Italy	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Valenzuela and López-Jornet,[25] 2016, Spain	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Arbabi-Kalati et al,[26] 2015, Iran	Low risk	Low risk	Low risk	High risk	Unclear risk	Unclear risk	High risk
Spanemberg et al,[27] 2015, Brazil	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	High risk
Dos Santos et al,[29] 2015, Brazil	Unclear risk	Unclear risk	High risk	High risk	High risk	Unclear risk	High risk
Brailo et al,[30] 2013, Croatia	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk
Pezelj-Ribarić et al,[31] 2013, Croatia	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk
Dos Santos et al,[28] 2011, Brazil	Unclear risk	Unclear risk	High risk	High risk	High risk	Unclear risk	High risk

Data Items

To be selected, studies needed to evaluate at least the results of the different treatments using a visual analog scale (VAS) for pain, numeric rating scale (NRS) for pain, visual numeric scale (VNS) for pain, or to show improvement as percentage, and they needed to specify at least the baseline and posttreatment results. In addition, other outcome variables, such as unstimulated whole salivary flow (UWSF), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) salivary levels, McGill Pain Questionnaire (MPQ), pain intensity at time of visit, Oral Health Impact Profile 14 and 49 (OHIP-14, OHIP-49), Hospital Anxiety and Depression Scale (HADS), Geriatric Depression Scale (GDS), Xerostomia Inventory (XI), Patients Global Impression of Improvement (PGII), masseter muscle tension (MMT), maximum mouth opening (MMO), masseter compound action potentials (MCAP), temporalis compound action potentials (TCAP), and presence of nausea and/or photophobia were collected if available. Significant values and complications are presented if they were reflected in the selected studies.

Risk of Bias in Individual Studies

To assess the methodologic quality of eligible studies, two independent reviewers (M.D.P. and R.M.L.P.) used the Cochrane Collaboration tool for assessing risk of bias. Any disagreements were solved by discussion with a third reviewer (G.H.). The studies were classified in the following categories: low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for one or more key domains), and high risk of bias (high risk of bias for one or more key domains) (Table 2).[18]

Summary Measures

The selected articles were categorized according to the treated pathology: trigeminal neuralgia (TN),[19–21] occipital neuralgia (ON),[22] or burning mouth syndrome (BMS).[19,23–31] Antonić et al analyzed the effect of LLLT in both TN and BMS and was therefore included in both groups.[19]

The included data were: first author; year of publication; country; type of study; study population (patients per group, mean age, and gender); laser type and protocol (equipment, wavelength, fluency, power, beam area, power density, energy per point, application time per point, total number of points, distance between points, frequency, number of sessions per week, and number of weeks of treatment); placebo or other treatment protocol for neuropathic pain; type of pain measuring; other collected variables; results (pain level before and after treatment); significant associations (if available); and treatment complications.

The fundamental outcome variable, pain level, was measured on a 0 to 10 VAS,[19,21–23,25,28,29,31] 0 to 100 VAS,[24,27] 0 to 10 NRS,[20,26] 0 to 10 VNS,[27] or as a percentage of VAS improvement.[30]

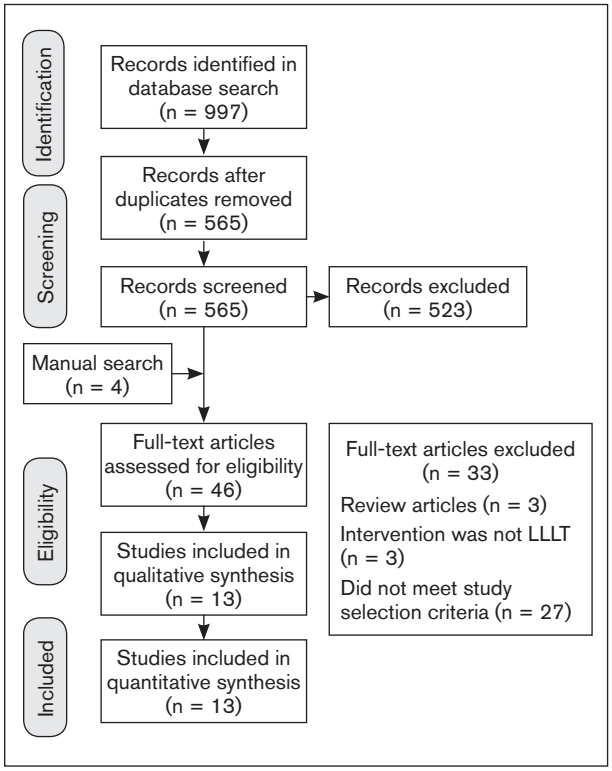
Risk of Bias Across Studies

The total data resulting from each domain of the Cochrane Collaboration tool were quantified and classified (Table 2).

Table 3 Rejected Articles with Reasons

Authors	Rejection reason(s)
Brunner at al[32]	No clinical trial
Coulthard et al[33]	No clinical trial
Fallah and Wang[34]	No clinical trial
Fan et al[35]	No LLLT
Lorenz et al[36]	No LLLT
de Oliveira Martins et al[37]	Study in rats
Chen et al[38]	No pain measured
Ebrahimi et al[39]	No pain measured
Khullar et al[40]	No pain measured
Khullar et al[41]	No pain measured
Eckerdal and Bastian[42]	Uncompleted pain measuring (no baseline pain values)
Sasaki et al[43]	Uncompleted pain measuring (no baseline pain values)
Kato et al[44]	Uncompleted pain measuring (considered VAS of the first appointment as the maximum VAS [100])
Sugaya et al[45]	Uncompleted pain measuring (considered VAS of the first appointment as the maximum VAS [100])
Romeo et al[46]	Uncompleted pain measuring (did not measure VAS in each session)
Hong et al[47]	Patients in the same group did not receive the same number of LLLT sessions
Midamba et al[48]	Patients in the same group did not receive the same number of LLLT sessions
Mizekami and Haanaes[49]	Patients in the same group did not receive the same number of LLLT sessions
Numazawa et al[50]	Patients in the same group did not receive the same number of LLLT sessions
Otsuka et al[51]	Patients in the same group did not receive the same number of LLLT sessions
Shiroto et al[52]	Patients in the same group did not receive the same number of LLLT sessions
Yang and Huang[53]	Patients in the same group did not receive the same number of LLLT sessions
Yang and Huang[54]	Patients in the same group did not receive the same number of LLLT sessions
Awad and Hosam[55]	No orofacial pain
Bashiri[56]	No orofacial pain
Matsumura et al[57]	No orofacial pain
Moore et al[58]	Several pathologies were treated with LLLT, and the results of orofacial region were not clearly separated
Amanat et al[59]	Several pathologies were treated with LLLT, and the results of orofacial region were not clearly separated
Yamada and Ogawa[60]	Several pathologies were treated with LLLT, and the results of orofacial region were not clearly separated
Pinheiro et al[61]	Several pathologies were treated with LLLT, and the results of orofacial region were not clearly separated
Kemmotsu et al[62]	Several pathologies were treated with LLLT, and the results of orofacial region were not clearly separated
Iijima et al[63]	Several pathologies were treated with LLLT, and the results of orofacial region were not clearly separated
Hansen and Thorøe[64]	Several pathologies were treated with LLLT, and the results of orofacial region were not clearly separated

Fig 2 *(right)* Flowchart of study selection process.



Results

Study Selection

An initial search yielded 997 references, and 46 full-text articles were assessed for eligibility. Thirty-three studies did not fulfill the eligibility criteria and were excluded (Table 3).[32–64] Finally, 13 articles were included and analyzed for data extraction. The selection procedure is presented in Fig 2.

Study Characteristics

A total of 13 articles were considered for data extraction: 8 randomized controlled trials (RCTs),[20,21,23–27,31] 2 prospective studies,[19,22] and 3 case series.[28–30]

Regarding the main outcome, 3 studies evaluated the use of LLLT for the treatment of TN (Table 4), 1 for the treatment of ON (Table 5), and 10 for the treatment of BMS (Table 6).

Table 4 Trigeminal Neuralgia Studies

Author, year, country	Type of study	Study population	Laser type and protocol
Antonić et al,[19] 2017, Croatia	Prospective study	20 patients (12 men/8 women, mean age 53 y [27–72]) LLLT1 group: 10 LLLT2 group: 10 Included: CTN according to ICHD for 6- to 12-mo duration	Equipment: GaAlAs Medio Laser Combi dental (Slovenia) Wavelength: 810 nm (LLLT1)/660 nm (LLLT2) Fluency: 3 J/cm^2 Power: 30 mW Beam area: 2 mm Power density: NS Energy per point: NS Application time per point: 10 min total Total no. of points: NS Distance between points: NS Frequency: Continuous mode Sessions per wk: 5 Wks: 4
Seada et al,[20] 2013, Saudi Arabia	RCT	LLLT: 15 patients (gender NS, mean age 48.8 ± 6.3 y) EMS: 15 (gender NS, mean age 46.6 ± 9.6 y) Included: Multiple sclerosis patients with CTN (all branches) according to ICHD for 6- to 12-mo duration, pain > 6 NRS Excluded: TN secondary to tumor, herpes zoster or any other causes, past invasive treatment, or coagulation dysfunction	Equipment: HeNe laser Wavelength: 830 nm Fluency: NS Power: 15 mW Beam area: NS Power density: 150–170 mW/cm^2 Energy per point: NS Application time per point: Intraorally 1–2 min, extraorally 10 min Total no. of points: Intraorally path of the nerve path, extraorally 4 tender points of the face Distance between points: NS Frequency: NS No. of sessions per wk: 3 Wks: 8
Aghamohammadi et al,[21] 2012, Iran	RCT	LLLT + GGB: 21 patients (gender NS, mean age 52.48 ± 17.76 y) GGB: 21 (gender NS, mean age 47.81 ± 16.73 y) Included: TN, VAS pain ≥ 6 Excluded: Coagulopathy, psychotic disease, increased cerebrospinal fluid pressure, lack of consent	Equipment: Mustang 026 (Russia) Wavelength: 890 nm Fluency: NS Power: NS Beam area: NS Power density: NS Energy per point: 3–10 J Application time per point: NS Total no. of points: NS Distance between points: NS Frequency: NS No. of sessions per wk: 1 Wks: 1

LLLT = low-level laser therapy; GaAlAs = gallium-aluminum-arsenide; HeNe = helium-neon; CTN = classical trigeminal neuralgia; TN = trigeminal neuralgia; ICHD = International Classification of Headache Disorders; VAS = visual analog scale; RCT = randomized clinical trial; EMS = electromagnetic stimulation; NRS = numeric rating scale; MMT = masseter muscle tension; MMO = maximum mouth opening; MCAP = masseter compound action potentials; TCAP = temporalis compound action potentials; GGB = Gasserian ganglion block.

Table 5 Occipital Neuralgia Studies

Author, year, country	Type of study	Study population	Laser type and protocol
Amoils and Kues,[22] 1991, USA	Prospective study	7 (1 man/6 women) (mean age 31.85 y) Included: Generalized headache syndrome compatible with occipital neuralgia or vascular headache. Associated nausea, photophobia, or autonomic symptoms less than 10-h duration. Minimal or no use of drug therapy prior to seeking medical help for the current episode. Excluded: History of prolonged use of narcotic analgesics or NSAIDs. Psychiatric illness or other severe concomitant systemic illness.	Equipment: Med 107 Laser, Lasotronic (Switzerland) Wavelength: 670 nm Fluency: NS Power: < 7 mW Beam area: 1 mm Power density: 0.89 W/cm^2 Energy per point: NS Application time per point: 30–40 s Total no. of points: NS Distance between points: NS Frequency: Continuous mode No. of sessions per wk: 1 Wks: 1

NSAIDs = nonsteroidal anti-inflammatory drugs; VAS = visual analog scale.

Measurement of pain	Other variables	Significant results	Complications
VAS (0–10)	No	Pain (0–10 VAS): LLLT1: Mean VAS changed from 7 (5–10) before treatment to 4 (1–5) after treatment (P = .005) LLLT2: Mean VAS changed from 7 (2–9) before treatment to 6.5 (2–8) after treatment (P = .043)	None
NRS (0–10)	MMT, MMO, MCAP, TCAP	Pain (0–10 NRS): LLLT changed from 7.5 ± 0.5 to 6.2 ± 0.5 (P < .05) EMS changed from 7.6 ± 0.4 to 5.3 ± 0.3 (P < .01) MMT: LLLT changed from 9.7 ± 2.5 to 17.8 ± 1.6 (P < .05) EMS changed from 9.5 ± 2.1 to 25.2 ± 1.1 (P < .01) MMO: LLLT changed from 16.7 ± 1.1 to 23.9 ± 1.8 (P < .05) EMS changed from 15.4 ± 1.7 to 28 ± 1.5 (P < .01) MCAP: LLLT changed from 0.6 ± 0.1 to 1.6 ± 0.1 (P < .01) EMS changed from 0.7 ± 0.1 to 2.1 ± 0.1 (P < .01) TCAP: LLLT changed from 0.9 ± 0.2 to 1.9 ± 0.2 (P < .05) EMS changed from 0.8 ± 0.5 to 2.4 ± 0.5 (P < .01)	None
VAS (0–10)	Complete pain relief	Pain (0–10 VAS): 1 d: LLLT + GGB: 8.71 ± 0.96 GGB: 8.29 ± 0.85 / 7 d: LLLT + GGB: 1.33 ± 1.77 GGB: 2.67 ± 1.83 (P = .017) / 1 mo: LLLT + GGB: 0.43 ± 0.48 GGB: 3.14 ± 1.46 (P < .001) / 3 mo: LLLT + GGB: 0.33 ± 0.73 GGB: 2.67 ± 1.25 (P < .001) / 6 mo: LLLT + GGB: 0.25 ± 0.64 GGB: 4.24 ± 1.51 (P < .001)	None
	No. of carbamazepine tablets	No. of carbamazepine tablets taken by the patients between groups: 1 d: LLLT + GGB: 6.24 ± 1.55 / GGB: 6.38 ± 1.36 1 mo: LLLT +GGB: 0.76 ± 1.18 / GGB: 2.71 ± 1.55 (P < .001) 3 mo: LLLT + GG b: 0.52 ± 0.87 / GGB: 3.10 ± 1.48 (P < .001)	
	Mean duration of a painless state	6 mo: LLLT + GGB: 0.33 ± 0.073 / GGB: 3.52 ± 1.69 (P < .001) Mean period of a painless state between groups (no. of patients): 1 d: 0 both groups / 7 d: LLLT + GGB: 12 / GGB: 3 (P = .004) 1 mo: LLLT + GGB: 17 / GGB: 2 (P < .001) / 3 mo: LLLT + GGB: 17 GGB: 1 (P < .001) / 6 mo: LLLT + GGB: 18 / GGB: 1 (P < .001)	

Measurement of pain	Other variables	Significant results	Complications
VAS (0–10)	Nausea (0–10) Photophobia (0–10)	No significant results were found. Efficacy of treatment, pre- and posttreatment score: VAS pain from 7.71 to 3.28 Nausea from 3.57 to 0.86 Photophobia from 1.28 to 0	None

Table 6 Burning Mouth Syndrome Studies

Author, year, country	Type of study	Study population	Laser type and protocol
Barbosa et al,[23] 2018, Brazil	RCT	15 BMS (6 men/9 women, mean age 45 ± 12.5 y) LLLT: 10 ALA: 5 Included: BMS diagnostic criteria established by the ICHD-3. Excluded: Patients with oral lesions or any other type of local alteration such as hyposalivation, trauma, hypersensitivity reactions, or action of physicochemical agents.	Equipment: 3B laser Bio Wave (Brazil) Wavelength: 660 nm Fluency: 3 J/cm^2 Power: 30 mW Beam area: 3 mm Power density: NS Energy per point: NS Application time per point: 10 s Total no. of points: NS Distance between points: 1 cm Frequency: continuous mode No. of sessions per wk: 1 Wks: 4
Antonić et al,[19] 2017, Croatia	Prospective study	40 (9 men/31 women, mean age 51 y, 25–80) LLLT1: 20 LLLT2: 20 Included: BMS diagnosis and the absence of any systemic disease or local oral factors that might be involved in the sensation of mouth burning. Normal values in blood count, blood glucose, and estrogen levels.	Equipment: GaAlAs Medio Laser Combi dental (Slovenia) Wavelength: 810 nm (LLLT1)/ 660 nm (LLLT2) Fluency: 3 J/cm^2 Power: 30 mW Beam area: 2 mm Power density: NS Energy per point: NS Application time per point: 10 m total Total no. of points: NS Distance between points: NS Frequency: Continuous mode No. of sessions per wk: 5 Wks: 4
Arduino et al,[24] 2016, Italy	RCT	LLLT: 18 (4 men/14 women, mean age 68.5 ± 9.31 y) CL: 15 (4 men/11 women, mean age 65.47 ± 7.6 y) Included: Oral burning sensation, 6-mo duration, no detection of oral mucosal lesions, ability to complete the present clinical trial. Excluded: Sjögren syndrome, head and neck radiotherapy, lymphoma, hepatitis C, pregnant or breastfeeding, antidepressants, anxiolytics, anticonvulsants.	Equipment: GaAlAs DMT device (Italy) Wavelength: 980 nm Fluency: 10 J/cm^2 Power: 300 mW Beam area: 0.28 cm^2 Power density: NS Energy per point: NS Application time per point: 10 s Total no. of points: NS Distance between points: NS Frequency: Continuous mode No. of sessions per wk: 2 Wks: 5
Valenzuela and López-Jornet,[25] 2017, Spain	RCT	LLLT4: 16 (1 man/15 women, mean age 63.8 ± 8.5 y) LLLT6: 16 women (mean age 69.7 ± 8.8 y) CG: 12 (2 men/10 women) (mean age 62.3 ± 9.2 y) Included: Diagnosis of BMS in accordance with ICHD-3 Excluded: Head and neck malignancy radiation, poorly managed diabetes mellitus, chronic thyroid disease, Sjögren syndrome, rheumatologic diseases, anemia, use of analgesics medications, pregnancy. Not excluded: Use of psychotropic drugs	Equipment: GaAlAs laser by LaserSmile (USA) Wavelength: 815 nm Fluency: 133.3 J/cm^2 (LLLT4)/ 200 J/cm^2 (LLLT6) Power: 1 W Beam area: 0.03cm^2 Power density: NS Energy per point: 4 J (LLLT4)/6 J (LLLT6) Application time per point: 4 s (LLLT4), 6 s (LLLT6) Total no. of points: 10 Distance between points: NS Frequency: Continuous mode No. of sessions per wk: 1 Wks: 4

RCT = randomized clinical trial; LLLT = low-level laser therapy; ALA = alpha lipoic acid; BMS = burning mouth syndrome; ICHD-3 = International Classification of Headache Disorders, ed 3; VAS = visual analog scale; UWSF = unstimulated whole salivary flow; TNF-α = tumor necrosis factor-alpha; CL = clonazepam; GaAlAs = gallium-aluminum-arsenide; DMT = N,N-Dimethyltryptamine; MPQ = McGill Pain Questionnaire; PPI = present pain intensity; OHIP-14/OHIP-49 = Oral Health Impact Profile; HADS = Hospital Anxiety and Depression Scale; GDS = Geriatric Depression Scale; CG = control group (placebo); XI = Xerostomia Inventory; PGII = Patient Global Impression of Improvement; NRS = numeric rating scale; VNS = visual numeric scale; InGaAlP = aluminum-gallium-indium-phosphide; IL-6 = interleukin-6.

Measurement of pain	Other variables	Significant results	Complications
VAS (0–10)	UWSF Salivary levels of TNF-α	Pain (0–10 VAS): No significant results for VAS; change in mean ranks: LLLT from 2.5 before treatment to 0 after treatment, ALA from 2 before treatment to 0 after treatment UWSF salivary levels: Increased in LLLT from 0.3 to 0.5 mL/min (P = .034)	None
VAS (0–10)	No	Pain (0–10 VAS): LLLT1 from 6 before treatment to 4 after treatment (P = .001) LLLT2 from 7 before treatment to 4.5 after treatment (P = .001)	None
VAS (0–100), MPQ, PPI	UWSF, OHIP-49, HADS, GDS	Pain (0–100 VAS, MPQ, and PPI): Decreasing sensation of pain after 12 wks: LLLT: VAS changed from 4.97 (2.69) to 2.19 (4.83) (P = .004) MPQ changed from 16.94 (10.21) to 6.89 (7.41) (P = .002) PPI changed from 2.39 (0.92) to 1.22 (1.00) (P = .002) OHIP-49 changed from 59.28 (37.95) to 48.22 (32.11) (P = .01) CL: MPQ changed from 17.93 (9.65) to 6.93 (4.57) (P = .005) PPI changed from 2.67 (1.11) to 1.40 (1.18) (P = .013) Statistical differences between the two groups in different times of follow-up period: After 8 wks (LLLT superior in improving pain perception CG) VAS = LLLT 1.81 vs CG 3.47 (P = .026) PPI: LLLT 1.11 vs CG 1.53 (P = .038)	With CL 32%: dizziness, fever, headache, lack of appetite
VAS (0–10)	OHIP-14, XI, HADS, PGII	Pain (0–10 VAS): LLLT significantly lower than CG (P < .001): LLLT4: 7.56 ± 1.5 pretreatment/6.56 ± 1.5 wk 2/6.38 ± 1.6 wk 4 LLLT6: 8.38 ± 1.7 pretreatment/7.44 ± 1.9 wk 2/7.06 ± 1.8 wk 4 CG: 7.83 ± 1.3 pretreatment/7.83 ± 1.1 wk 2/7.65 ± 1.2 wk 4 OHIP-14: LLLT significantly lower than CG (P < .001): LLLT4: 29.88 ± 3.6 pretreatment/28.81 ± 3.2 wk 2/28.5 ± 3.1 wk 4 LLLT6: 29.56 ± 5.9 pretreatment/28.62 ± 5.8 wk 2/28.25 ± 6.1 wk 4 CG: 29.33 ± 5.9 pretreatment/29.25 ± 5.7 wk 2/29.25 ± 6.3 wk 4	None

Table 6 Burning Mouth Syndrome Studies *(continued)*

Author, year, country	Type of study	Study population	Laser type and protocol
Arbabi-Kalati et al,[26] 2015, Iran	RCT	LLLT: 10 women (mean age 47.2 ± 5.3 y) CL: 10 women (mean age 46.6 ± 4.6 y) Included: Burning sensation in all or a part of the oral cavity with or without symptoms such as change in taste sensation for at least 4 mo, normal oral mucosa without any lesions, and absence of any local or systemic factors that produce the same symptoms. Excluded: Systemic problems, age < 18 y, pregnancy, smoking, oral lesions, not signing informed consent form.	Equipment: Iodine GaAs laser, Mustang laser device (Russia) Wavelength: 630 nm Fluency: 1 J/cm^2 Power: 30 mW Beam area: NS Power density: NS Energy per point: NS Application time per point: 10 s Total no. of points: 10 areas: 2 buccal mucosa, each side 2 tongue 2 floor of mouth 1 soft palate 1 hard palate Distance between points: NS Frequency: NS No. of sessions per wk: 2 Wks: 2
Spanemberg et al,[27] 2015, Brazil	RCT	LLLT1: 20 (3 men/17 women, mean age 63.6 ± 9.61 y) LLLT3: 20 (2 men/18 women, mean age 60.5 ± 6.42 y) LLLTr: 19 (1 man/18 women, mean age 63.2 ± 6.91 y) CG: 19 (5 men/14 women, mean age 61.5 ± 8.76 y) Included: Symptoms of burning or pain in the oral mucosa for at least 6 mo and presence of clinically normal mucosa. Excluded: Patients taking antidepressants, anxiolytics, anticonvulsant drugs, and/or with history of chemotherapy, radiotherapy, hyposalivation, or blood count alterations.	Equipment: GaAlAs Thera Lase (Brazil) Wavelength: 830 nm (LLLT1–LLLT3)/685 nm (LLLTr) Fluency: 176 J/cm^2 (LLLT1–LLLT3)/72J /cm^2 (LLLTr) Power: 100 mW (LLLT1–LLLT3)/35 mW (LLLTr) Beam area: 0.028 cm^2 Power density: NS Energy per point: 5 J (LLLT1–LLLT3)/2 J (LLLTr) Application time per point: 50 s Total no. of points: Apex of the tongue (3 points), side of the tongue (4 points), dorsum of the tongue (10 points), buccal mucosa (8 points), labial mucosa (5 points), hard palate (8 points), soft palate (3 points), and gums and alveolar ridge mucosa (3 points per sextant) Distance between points: NS Frequency: Continuous mode No. of sessions per wk: 1 (LLLT1)/3 (LLLT3–LLLTr) Wks: 10 LLLT1/3 (LLLT3–LLLTr)
dos Santos et al,[29] 2015, Brazil	Case series	20 (3 men/17 women, mean age 63.2 y, range 48–78) Included: Previous treatment with antifungal 21 d, 2% pilocarpine, lip balm, and clonazepam 1 mg 3 min 3 times/d Excluded: Systemic diseases (hematologic, thyroid, diabetes), systemic abnormalities (B12, iron, glucose, thyroid hormones), intraoral abnormalities (infections, hyposalivation, lichen planus, benign migratory glossitis, allergic contact, parafunctional habits, ill-adapted prosthesis)	Equipment: Diode laser InGaAlP (Photon Laser, DMC Brazil) Wavelength: 660 nm Fluency: 20 J/cm^2 Power: 40 mW Beam area: 0.04 cm^2 Power density: NS Energy per point: NS Application time per point: 10 s Total no. of points: 3 to 920 Distance between points: 1 cm Frequency: Continuous mode Sessions per wk: 1 Wks: 10

RCT = randomized clinical trial; LLLT = low-level laser therapy; ALA = alpha lipoic acid; BMS = burning mouth syndrome; ICHD-3 = International Classification of Headache Disorders, ed 3; VAS = visual analog scale; UWSF = unstimulated whole salivary flow; TNF-α = tumor necrosis factor-alpha; CL = clonazepam; GaAlAs = gallium-aluminum-arsenide; DMT = N,N-Dimethyltryptamine; MPQ = McGill Pain Questionnaire; PPI = present pain intensity; OHIP-14/OHIP-49 = Oral Health Impact Profile; HADS = Hospital Anxiety and Depression Scale; GDS = Geriatric Depression Scale; CG = control group (placebo); XI = Xerostomia Inventory; PGII = Patient Global Impression of Improvement; NRS = numeric rating scale; VNS = visual numeric scale; InGaAlP = aluminum-gallium-indium-phosphide; IL-6 = interleukin-6.

Measurement of pain	Other variables	Significant results	Complications
NRS (0–10)	OHIP-14	Pain (0–10 NRS): Differences between groups after intervention (P = .004): LLLT changed from 8 ± 2.3 to 3.6 ± 3 CL changed from 8.2 ± 1.7 to 8 ± 1.5 OHIP-14: Differences between groups after intervention (P = .01): LLLT changed from 27.8 ± 12 to 12.8 ± 11.4 CL changed from 28.3 ± 11.9 to 28.6 ± 11.5	None
VAS (0–100), VNS (0–10)	OHIP-14	Pain (0–10 VNS): Decrease of the symptoms at the end of the treatment maintained in the 8-wk follow-up: CG from 9.00 ± 1.00 to 6.47 ± 2.31 vs LLLT1 from 8.20 ± 1.57 to 3.75 ± 2.40 (P = .005) CG from 9.00 ± 1.00 to 6.47 ± 2.31 vs LLLT3 from 8.00 ± 1.33 to 2.90 ± 2.10 (P = .0001) Pain (0–100 VAS): Decrease of the symptoms at the end of the treatment maintained in the 8-wk follow-up: CG from 85.26 ± 14.25 to 62.84 ± 26.30 vs LLLT1 from 82.15 ± 14.47 to 32.95 ± 28.92 (P = .004) CG from 85.26 ± 14.25 to 62.84 ± 26.30 vs LLLT3 from 78.90 ± 15.25 to 25.90 ± 19.48 (P = .0001) OHIP-14: CG from 17.80 ± 5.37 to 13.39 ± 3.62 vs LLLT3 from 12.87 ± 7.78 to 6.89 ± 4.05 (P = .021)	None
VAS (0–10)	No	Pain (0–10 VAS): From wk 1 to wk 9, and all other wks: A statistically significant improvement was observed in wk 2 (P = .009), wk 3 (P = .001), and from wk 4 to wk 10 (P = .000). Comparing sessions with the previous one, there was a statistically significant pain reduction in wk 2 (P = .009) and wk 3 (P = .001). When comparing the evaluation at each session with the previous one, there was a statistically significant improvement in wk 5 (P = .010). Comparing the period of the conventional treatment to the period in which volunteers underwent laser phototherapy, there was a statistically significant improvement in wk 3 (P = .002), wk 4 (P = .001), wk 5 (P = .003), wk 6 (P = .000), wk 7 (P = .000), wk 8 (P = .000), wk 9 (P = .000), and wk 10 (P = .000). All patients showed reduced burning intensity in all sessions when compared to the previous one, and reduction in VAS scores by up to 49% was seen in the last clinical session when compared to the first session.	None

Table 6 Burning Mouth Syndrome Studies *(continued)*

Author, year, country	Type of study	Study population	Laser type and protocol
Brailo et al,[30] 2013, Croatia	Case series	16 (2 men/14 women, mean age 70.9 y, range 36–87) Included: Correct routine blood exam, no medication, previous treatment with clonazepam	Equipment: Medio Laser Kombi (Slovenia) Wavelength: 660 nm Fluency: 1.5–2 J/cm^2 Power: NS Beam area: NS Power density: NS Energy per point: NS Application time per point: 15 min (total) Total no. of points: 11 acupuncture points. ST1, ST3, ST4, ST5, LI4, LU7, GV14, CV17, SP10, SP9, SP6 Distance between points: NS Frequency: NS No. of sessions per wk: 4 Wks: 2
Pezelj-Ribarić et al,[31] 2012, Croatia	RCT	LLLT: 20 (5 men/15 women, mean age 60.2 ± 6.3 y) CG: 20 (8 men/12 women, mean age 61.1 ± 2.2 y) Included: Diagnosis of BMS and absence of any systemic disease or local factors, normal complete blood count.	Equipment: GaAlAs diode laser Medio Laser Combi dental (Slovenia) Wavelength: 685 nm Fluency: 3 J/cm^2 Power: 30 mW Beam area: 2 mm Power density: NS Energy per point: NS Application time per point: 100 s Total no. of points: NS Distance between points: NS Frequency: Continuous mode No. of sessions per wk: 5 Wks: 4
dos Santos et al,[28] 2011, Brazil	Case series	10 (1 man/9 women, mean age 65.8 y, 53–78) Included: Previous treatment with antifungal 21 d, 2% pilocarpine, lip balm, and clonazepam 1 mg 3 min 3 times/d. Excluded: Systemic diseases (hematologic, thyroid, diabetes), systemic abnormalities (B12, iron, glucose, thyroid hormones), intraoral abnormalities (infections, hyposalivation, lichen planus, benign migratory glossitis, allergic contact, parafunctional habits, ill-adapted prosthesis).	Equipment: Diode laser InGaAlP (Photon Laser, DMC Brazil) Wavelength: 660 nm Fluency: 20 J/cm^2 Power: 40 mW Beam area: 0.04 cm^2 Power density: NS Energy per point: NS Application time per point: 10 s Total no. of points: 3 to 920 Distance between points: 1 cm Frequency: Continuous mode No. of sessions per wk: 1 Wks: 10

RCT = randomized clinical trial; LLLT = low-level laser therapy; ALA = alpha lipoic acid; BMS = burning mouth syndrome; ICHD-3 = International Classification of Headache Disorders, ed 3; VAS = visual analog scale; UWSF = unstimulated whole salivary flow; TNF-α = tumor necrosis factor-alpha; CL = clonazepam; GaAlAs = gallium-aluminum-arsenide; DMT = N,N-Dimethyltryptamine; MPQ = McGill Pain Questionnaire; PPI = present pain intensity; OHIP-14/OHIP-49 = Oral Health Impact Profile; HADS = Hospital Anxiety and Depression Scale; GDS = Geriatric Depression Scale; CG = control group (placebo); XI = Xerostomia Inventory; PGII = Patient Global Impression of Improvement; NRS = numeric rating scale; VNS = visual numeric scale; InGaAlP = aluminum-gallium-indium-phosphide; IL-6 = interleukin-6.

Risk of Bias Within Studies

The Cochrane Collaboration tool for assessing risk of bias[18] was used to assess the methodologic quality of eligible studies. A vast majority of articles presented high risk of bias (Table 2): 10 presented high risk,[20–23,26–31] 2 unclear risk,[19,24] and only 1 showed low risk.[25]

Results of Individual Studies

Trigeminal Neuralgia. Two RCTs[20,21] and one prospective study[19] met the inclusion criteria (Table 4). Seada et al compared the use of LLLT to transcranial electromagnetic stimulation (EMS).[20] Aghamohammadi et al compared the use of Gasserian ganglion block (GGB) with LLLT to GGB without LLLT.[21] Finally, Antonić et al compared the results of two different LLLT wavelengths.[19]

With respect to the recruitment of patients, two studies selected their TN patients from university hospitals in Saudi Arabia[20] and Croatia,[19] and the other did not specify patients' origins. Antonić et al included 20 patients divided into two groups of 10[19]; Seada et al included 30 patients, 15 in the LLLT group and 15 in the EMS group[20]; and Aghamohammadi et al included 42 patients, 21 in the LLLT + GGB group and 21 in the GGB group.[21] All patients were diagnosed with TN according to the ICHD-3,[2] and patients suffered from TN for at least 6 months. The

Measurement of pain	Other variables	Significant results	Complications
VAS (0–10)	No	Pain (0–10 VAS): No significant results. The average decrease in burning symptoms after the treatment was 55.2%.	None
VAS (0–10)	Salivary level of TNF-α and IL-6	Pain (0–10 VAS): No significant results. From 7 (5–8) before treatment to 6 (5–8) in the LLLT group. Salivary levels: LLLT: Levels of TNF-α before therapy greater than levels after therapy; 0.437 ± 0.124 vs 0.234 ± 0.060 (P = .001). Levels of IL-6 before therapy greater than levels after therapy; 0.401 ± 0.151 vs 0.141 ± 0.037 (P = .001).	None
VAS (0–10)	No	Pain (0–10 VAS) For VAS baseline scores in first session compared to those of the other sessions, a statistically significant improvement was observed in wk 4 (P = .03), wk 5 (P = .03), wk 6 (P = .009), wk 7 (P = .003), wk 8 (P = .002), wk 9 (P = .002), and wk 10 (P = .002). All patients reported improvement in all sessions, with reduction in VAS scores by up to 58% in the 10th session.	None

studies excluded patients suffering from tumors, herpes zoster infections, coagulopathies, psychotic diseases, or increased cerebrospinal fluid pressure.[20,21]

Antonić et al used a gallium-aluminum-arsenide (GaAlAs) laser,[19] and Seada et al a helium-neon (HeNe) laser.[20] Aghamohammadi et al did not specify the type of laser.[21] Antonić et al used two different wavelengths: 810 nm and 660 nm[19]; Seada et al used an 830-nm wavelength[20]; and Aghamohammadi et al used a wavelength of 890 nm.[21]

Only Antonić et al[19] specified the fluency of 3 J/cm^2, as well as beam area (2 mm[19]) and mode (continuous frequency).[19] Aghamohammadi et al did not specify the laser power,[21] and the other authors applied the LLLT with powers of 15 mW[20] and 30 mW.[19] Only Seada et al specified the power density, 150 to 170 mW/cm^2.[20] Aghamohammadi et al was the only study that specified the energy per point: 3 to 10 J.[21] Seada et al applied LLLT for 1 to 2 minutes intraorally across the trigeminal nerve path and 10 minutes extraorally in four tender points of the face,[20] and Antonić et al used LLLT for 10 minutes but did not specify the number of points.[19] Aghamohammadi et al did not specify fluency, power, beam area, power density, frequency, application time per point, or total number of points.[21] Regarding the number of LLLT sessions, Aghamohammadi et al applied a single LLLT session,[21] Antonić et al 20

sessions in 4 weeks,[19] and Seada et al 24 sessions in 8 weeks.[20]

All authors except Seada et al, who measured pain with an NRS scale,[20] used a VAS from 0 to 10 to measure pain.[19,21] Seada et al showed a pain reduction (NRS) of 1.3 ± 0.5 points in the LLLT group after treatment (from 7.5 ± 0.5 to 6.2 ± 0.5), but achieved better results in the EMS group (from 7.6 ± 0.4 to 5.2 ± 0.3).[20] The reduction in VAS after treatment in Antonić et al[19] was 0.5 (from 7 to 6.5) in the 660-nm group and 3 (from 7 to 4) in the 810-nm group. In Aghamohammadi et al,[21] the VAS reduction was 8 points (from 8.71 ± 0.96 to 0.25 ± 0.64) when LLLT was associated with GGB. Other secondary results can be observed in Table 4.

None of the studies reported any complication with the LLLT treatment.[19–21]

Occipital Neuralgia. Only one prospective study met the inclusion criteria (Table 5).[22] Amoils and Kues included seven patients presenting a generalized headache syndrome compatible with ON or vascular headache with associated nausea, photophobia, or autonomic symptoms in a university hospital in the United States. Patients were excluded from the study if they had a previous history of prolonged use of narcotic analgesics, nonsteroid anti-inflammatory drugs (NSAIDs), psychiatric illness, or severe concomitant systemic illness.

Amoils and Kues applied LLLT with a wavelength of 670 nm in one session during 30 to 40 seconds per point, with a power < 7 mW and a beam area of 1 mm in a continuous mode.[22] They did not find significant results, but observed a VAS pain reduction from 7.71 to 3.28, nausea from 3.57 to 0.86, and photophobia from 1.28 to 0.

No complications were found.[22]

Burning Mouth Syndrome. Ten studies met the inclusion criteria (Table 6)[19,23–31]: 6 RCTs,[23–27,31] 1 prospective study,[19] and 3 case series.[28–30] The selected studies compared LLLT to placebo,[26,31] different LLLT techniques to each other and to placebo,[25,27] different LLLT techniques to each other,[19] and to LLLT plus another treatment.[23,24] The case series studied only LLLT treatment.[28–30]

The number of LLLT patients included in these studies varied from 10 to 78. Barbosa et al included 10 patients in the LLLT group and 5 in the ALA group.[23] Antonić et al included 40 patients in two groups of 20.[19] Arduino et al included an LLLT group of 18 patients and a clonazepam group of 15 patients.[24] Valenzuela and López-Jornet studied two groups of different types of LLLT with 16 patients each and a placebo group of 12 patients.[25] Arbabi-Kalati et al included 20 patients: 10 in the LLLT group and 10 in the CG (placebo).[26] Spanemberg et al included a total of 78 patients divided into two LLLT groups of 20 patients each (LLLT1 group, with one session per week for 10 weeks, and LLLT3 and LLLTr, groups with three sessions per week for 3 weeks), other LLLT with 19 patients, and a placebo group of 19.[27] Dos Santos et al published a case series of 20 patients[29] and a case series of 10 patients.[28] Brailo et al included 16 patients in their prospective study.[30] Finally, Pezelj-Ribarić et al included 40 patients divided into an LLLT group of 20 and a placebo group of 20.[31] The studies included BMS patients and excluded patients with Sjögren syndrome, previous treatment with head and neck radiotherapy, lymphoma, hepatitis C, pregnant or breastfeeding women, trauma, hypersensitivity reactions, action of physicochemical agents, use of analgesics, antidepressants, anxiolytics, and anticonvulsants (excluding Valenzuela and López-Jornet[25]), poorly managed diabetes mellitus, chronic thyroid disease, rheumatologic diseases, anemia, smoking, and other oral lesions.[23–29]

The types of laser used by the different authors were GaAlAs,[19,24,25,27,31] iodine gallium-arsenide (GaAs),[26] and aluminum-gallium-indium-phosphide (InGaAlP).[28,29] Barbosa et al and Brailo et al did not specify the type of laser used.[23,30] Different wavelengths were used in the studies: 630 nm,[26] 660 nm,[19,23,28–30] 685 nm,[27,31] 810 nm,[19] 815 nm,[25] 830 nm,[27] and 980 nm.[24] The same happened with fluency: 1 J/cm^2,[26] 1.5 to 2 J/cm^2,[30,31] 3 J/cm^2,[19,23] 10 J/cm^2,[24] 20 J/cm^2,[28,29] 72 J/cm^2,[27] 133.3 J/cm^2,[25] 176 J/cm^2,[27] and 200 J/cm^2.[25] Different power protocols were used in each study: 30 mW,[19,23,26,31] 35 mW,[27] 40 mW,[28,29] 100 mW,[27] 300 mW,[24] and 1 W.[25] Brailo et al did not specify the power protocol.[30] The beam area was specified in Barbosa et al (3 mm[23]), Antonić et al and Pezelj-Ribarić et al (2 mm[19,31]), Arduino et al[24] and Spanemberg et al[27] (0.28 cm^2), Valenzuela and López-Jornet[25] (0.03 cm^2), and dos Santos et al (0.04 cm^2).[28,29] None of the authors specified the power density. Only Valenzuela and López-Jornet and Spanemberg et al specified the energy per point: 2 J,[27] 4 J,[25] 5 J,[27] and 6 J.[25] Many differences in the application time per point were found: 4 seconds,[25] 6 seconds,[25] 10 seconds,[23,24,26,28,29] 50 seconds,[27] and 100 seconds.[31] Antonić et al applied 10 minutes total,[19] and Brailo et al 15 minutes total.[30]

All of the authors who specified the frequency of laser pulsation used a continuous mode.[19,23–25,27,28,31] Arbabi-Kalati et al[26] applied the LLLT for 4 sessions (2 sessions in 2 weeks); Barbosa et al[23] and Valenzuela and López-Jornet[25] 4 sessions in 4 weeks; Brailo et al 8 sessions (4 sessions per week for 2 weeks)[30]; Spanemberg et al[27] 9 sessions (3 sessions per week in 3 weeks) in one group and 10 sessions (1 session per week) in the other group; dos Santos et al 10 sessions in 10 weeks[28,29]; Arduino et al[24] 10 sessions

(twice per week for 5 weeks); and Pezelj-Ribarić et al[19] and Antonić et al[31] 20 sessions (5 sessions per week for 4 weeks).

The authors measured pain with a 0 to 10 VAS,[19,23,25,28–31] a 0 to 100 VAS,[24,27] and a 0 to 10 NRS.[26] Arduino et al also measured with the MPQ and the PPI.[24] With regard to 0 to 10 VAS: Antonić et al showed improvement in both LLLT groups after treatment (from 6 to 4 in 810-nm group and from 7 to 4.5 in 660-nm group)[19]; Valenzuela and López-Jornet obtained VAS scores that were significantly lower in both LLLT groups with respect to placebo in the second and fourth weeks of treatment[25]; in their first study,[28] dos Santos et al showed a significant VAS score improvement from weeks 4 to 10, and in their other study,[29] they observed a significant improvement in VAS scores in week 2, week 3, and from weeks 4 to 10; and no other studies achieved significant results in VAS.[23,30,31] Regarding VAS from 0 to 100: Arduino et al showed a decreasing sensation of pain reported in the LLLT group with respect to placebo[24]; and Spanemberg et al observed a decrease in symptoms at the end of the treatment maintained in the 8-week follow-up.[27] Regarding 0 to 10 NRS: Arbabi-Kalati showed a significant difference in pain reduction between the LLLT group and placebo, with the LLLT group going from 8 ± 2.3 to 3.6 ± 3 and the CG going from 8.2 ± 1.7 to 8 ± 1.5.[26] Some studies evaluated OHIP-14: Valenzuela and López-Jornet[25] and Arbabi-Kalati[26] et al described that OHIP-14 scores obtained in LLLT groups were significantly lower than placebo scores, and Spanemberg et al described a decrease of the OHIP-14 at the end of treatment that remained stable in the 8-week follow-up in the LLLT3 group (3 sessions per week for 3 weeks).[27] Other secondary results can be observed in Table 6.

Only one study referred some complications related to clonazepam.[24]

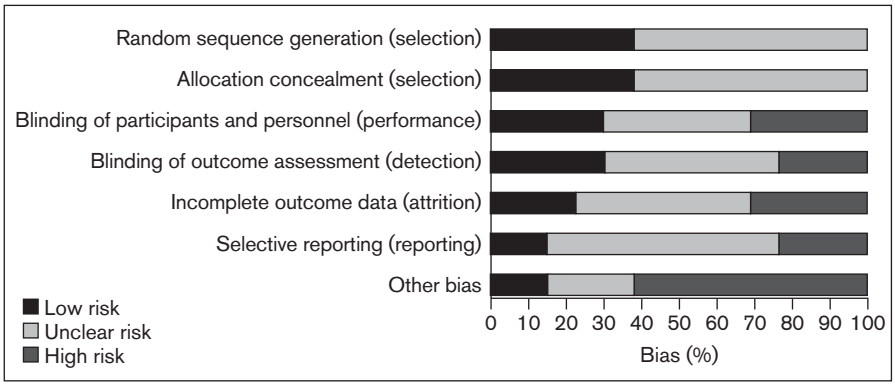


Fig 3 Distribution of studies at high, unclear, and low risk of bias according to the Cochrane Collaboration Risk of Bias tool.

Synthesis of Results

Performing a meta-analysis was not feasible because of the heterogeneity between studies using different laser systems and applying them with different techniques (wavelength, fluency, power, beam area, power density, energy per point, application time per point, total number of points, distance, frequency, and number of sessions) in the pathologies presented.

Risk of Bias Across the Studies

A high risk of bias was found across the studies. More than 60% have unclear risk of bias in selection. In terms of performance, more than 30% have high risk of bias, and almost 40% are unclear. The same applies to detection and attrition bias—almost 90% had low or unclear risk of bias in reporting, and more than 60% had high risk in other bias (Fig 3).

Discussion

Summary of Evidence

In recent years, several studies about the management of different neuropathic entities, such as TN,[19–21,52,59,61,64] painful trigeminal neuropathies,[38,43,47,50,51,55,57,58,60,62,63] ON,[22,49] BMS,[19,23–31] persistent idiopathic facial pain,[54,59] and improvement of posttraumatic dysesthesia and paresthesia in the orofacial region[40,41,48] with LLLT have been published; but only 13 articles about TN,[19,21] ON,[22] and BMS[19,23–31] met the inclusion criteria and were included in this systematic review.

As described in Results, different types of equipment, wavelengths, fluencies, power, beam areas, power densities, application time per point, number of points, distance between points, frequency, and number of sessions have been used to apply LLLT. All of the studies in one way or another confirmed an improvement in pain sensation, but it is necessary to form a protocol for future studies. Across the studies, LLLT has been shown to have no adverse effects or complications compared to other treatments.

A high number of painful entities affecting the orofacial region persists over time, influencing the patient's emotional and psychosocial health status. In addition, many of these entities, such as BMS and persistent idiopathic facial pain, usually present comorbid psychosocial and psychiatric disorders, so it is necessary to carry out an exhaustive analysis of patients' Axis II examination. Dimensions such as somatization, obsessiveness-compulsiveness, depression, and anxiety or psychoticism, among others, should be assessed prior to the treatments and also after, observing whether the therapy improves the quality of life of the patients from a biopsychosocial approach. In this regard, the IASP recommends the use of IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) to consider all dimensions of pain (pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition) in RCTs that analyze chronic pain.[65] In this sense, even if all the included articles have assessed the intensity of the pain, few have used general health questionnaires and perception of improvement on the part of the patient, and less have valued the Axis II examination in this systematic review. Regarding general health status, only Arduino et al assessed the OHIP-49,[24] and Valenzuela and López-Jornet, Arbabi-Kalati et al, and Spanemberg et al assessed the OHIP-14.[25–27] Regarding the assessment of Axis II, Arduino assessed HADS and GDS for depression and anxiety,[24] and Valenzuela and López-Jornet evaluated HADS and PGII for depression, anxiety, and perception of improvement of patients.[25] A short summary of the main results for each disease is presented.

Trigeminal Neuralgia

Two of the studies had high risk of bias,[20,21] and one was unclear.[19] The three papers on TN demonstrated statistically significant improvement in patients' pain sensations, but none of them compared LLLT to placebo: Antonić et al compared two different wavelengths,[19] Seada et al compared LLLT to EMS,[20] and Aghamohammadi et al compared LLLT combined with GGB to a GGB-only treatment group.[21]

The greatest decrease in pain sensation occurred in the LLLT1 group (with 10 patients) in Antonić et al (810 nm), which coincidentally had the highest number of sessions per week (5) and the highest power (30 mW). Aghamohammadi et al obtained a significant decrease in VAS as well, but only when LLLT was applied after GGB.[21]

As described in Results, different types of equipment, wavelengths, fluencies, power, beam areas, power densities, application time per point, number of points, distance between points, frequency, and number of sessions have been used to apply LLLT in TN. In this case, it can be seen that the more sessions and the higher the power, the better the results.

Occipital Neuralgia

The only study about LLLT for ON had a high risk of bias. This study concluded that there was a nonsignificant improvement in VAS pain in a group of seven patients.[22] Due to the absence of RCTs and studies comparing LLLT to placebo treatment and the low number of patients in this study, no conclusion can be drawn on the use of LLLT for ON.

Burning Mouth Syndrome

Only Valenzuela and López-Jornet, Arbabi-Kalati et al, Spanemberg et al, and Pezelj-Ribarić et al compared LLLT for BMS to a placebo group.[25–27,31] Barbosa et al compared LLLT to ALA,[23] Arduino et al compared it to clonazepam,[24] Antonić et al compared different wavelengths of LLLT,[19] and the rest of the authors did not compare LLLT to other treatment.[28–30] The study of Valenzuela and López-Jornet was the only study with low risk of bias[25]; the rest had high[20–23,26–31] or unclear risk.[19,24]

All articles showed significant improvement in pain with the use of LLLT, with the exception of Brailo et al Pezelj-Ribarić et al, which did not obtain significant results.[30,31] The results with LLLT are better than those achieved with clonazepam or ALA. The best results in pain reduction were those obtained by the LLLT3 group in Spanemberg et al, which was composed of 20 individuals who received three weekly sessions for 3 weeks of LLLT at 830 nm with a power of 100 mW.[27]

The OHIP-14 was analyzed in three studies.[25–27] The best results were found in the LLLT group in Arbabi-Kalati et al with 10 patients,[26] using a wavelength of 630 nm with a power of 30 mW in four sessions (two per week).

Despite the lack of standardized protocols of application in the studies analyzed, if the RCTs with higher quality and lower risk of bias[24,25,27] are analyzed, several coincidences are found. These three studies used a wavelength higher than 815 nm, with a beam area around 0.3 cm^2 in continuous mode.[24,25,27] Valenzuela and López-Jornet used a higher power, 1 W, with less exposure time, 6 seconds in 4 sessions,[25] while Arduino et al and Spanemberg et al used less power, 300 mW[24] and 100 mW,[27] but with higher exposure times, 10 seconds[24] and 50 seconds,[27] and during more sessions (both 10 sessions in total).[24,27] Thus, using LLLT with a wavelength higher than 815 nm, a power between 300 mW and 1 W, a beam area of 0.28 cm^2 in continuous frequency, and application for about 10 seconds per point in 10 sessions (2 per week for 5 weeks) could get satisfactory results in pain reduction.

Limitations

Even though three databases were fully searched, relevant studies may have been missed, especially due to publication bias and to the exclusion of articles written in languages other than English.

Regarding the methodology of the analyzed articles, several limitations were found. The first was the absence of consensus about an established protocol for LLLT. The authors did not always use the same treatment protocols and sometimes combined LLLT with other treatments, so extracting extrapolated results is complex. The second one is the lack of an adequate blinding strategy, as none of the included studies described a double-blinding methodology. Future studies should describe and apply stronger blinding strategies. Finally, regarding the methodology, a great limitation has been found in the follow-up of patients, since LLLT results have not been evaluated medium to long term.

Many painful orofacial entities of neuropathic origin are characterized by persistent pain, but most of the studies analyzed have not evaluated all core domains described in the IMMPACT recommendations that should be considered when studying patients with chronic pain (pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse effects, and participant disposition).

Conclusions

LLLT seems to be effective as a treatment option for different neuropathic orofacial pain entities such as TN, ON, and BMS as a single treatment or combined with other therapies (improving and prolonging the therapeutic effect). All studies showed an improvement in patients' pain sensation (VAS, NRS, or MPQ) and in other oral health variables (OHIP-49, OHIP-14), the majority of them with statistical significance.

More medium- and long-term quality studies evaluating all the outcome measures of chronic pain (pain, physical functioning, emotional functioning, participant ratings of global improvement and satisfactions with treatment, symptoms and adverse events, and participant disposition) are needed to confirm the results obtained in this systematic review.

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