#### **HOT TOPICS**



# Effectiveness of Laser Acupuncture for Reducing Pain and Increasing Mouth Opening Range in Individuals with Temporomandibular Disorder: A Systematic Review and Network Meta-Analysis

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#### Abstract

**Purpose of Review** Laser acupuncture (LA) demonstrates promising results in the treatment of musculoskeletal disorders. However, its effects on temporomandibular disorder (TMD) are not yet fully understood. Thus, the aim of this systematic review and network meta-analysis was to assess the effectiveness of LA on pain intensity and maximum mouth opening range (MMO) related to TMD. A search was carried out in 11 electronic databases and references of included studies to locate randomized clinical trials (RCTs) that evaluated LA as a primary treatment for TMD. The risk of bias was assessed using the RoB 2 tool. Network meta-analysis was conducted on the MetaInsight platform, considering the pain intensity and counseling (C) as the outcome of reference. The GRADE system was used to assess the certainty of the evidence. **Recent Findings** Five studies evaluated pain intensity, four with a high risk of bias and one with a low risk. Two studies evaluated pain intensity on palpation (one with high and one with low risk of bias), and one study with high risk of bias evaluated MMO. Laser parameters were: 690–810 nm, 40–150 mW, and 7.5–112.5 J/cm<sup>2</sup>. Occlusal splint (OS) [-2.47; CI 95%-3.64, -1.30] and Physiotherapy (PT) [-2.64; CI 95%-3.94, -1.34] reduced pain intensity compared to C. The ranking of treatments in order of effectiveness was PT > OS > LA > C > CR (craniopuncture). The certainty of the evidence was very low or low. **Summary** The data do not support the indication of LA for the treatment of TMDs and new placebo-controlled RCTs must be conducted to demonstrate its effectiveness more precisely.

Keywords Temporomandibular oint isorders · Laser acupuncture · Low-evel ight herapy · Acupuncture herapy

# Introduction

Temporomandibular disorders (TMDs) refer to a wide range of musculoarticular clinical conditions related to the stomatognathic apparatus [1, 2]. The main related symptoms are

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muscle or joint pain during function, headache, preauricular pain, joint noises, and changes on jaw movements [1-5]. Moreover, TMD is considered the main cause of orofacial pain with non-odontogenic origin [1, 2].

It presents a multifactorial etiology. Direct and indirect trauma, microtraumas, genetics, occlusion, and psychological conditions should be highlighted and can act as triggering, perpetuating, or predisposing factors [1–3]. Due to this plurality of diagnoses and etiological factors, the treatment of these conditions represents a great challenge for clinicians and specialists in this area [1, 6]. Furthermore, there are several treatment options, from conservative interventions to surgical and invasive approaches [1, 7, 8].

Current scientific evidence has supported the use of conservative multimodal approaches [8, 9] and minimally invasive [7] for the initial management of patients with TMD. Conservative treatments have demonstrated significant effectiveness in reducing symptoms, in addition to presenting lower costs and risks to patients [10].

In this scenario, there is evidence that traditional acupuncture is effective in reducing pain intensity and improving the quality of life of patients with TMD, especially those with muscular symptoms [11-13]. However, the need to insert needles can be a limiting factor for pediatric patients, geriatric patients, those with needle phobias, those hospitalized, or those at risk of bleeding or infection [14, 15]. Thus, the effectiveness of other acupuncture modalities has been evaluated [16, 17].

As an alternative to traditional acupuncture, laser acupuncture (LA) appears, which is characterized by the photobiostimulation of acupuncture points with a low-level laser [15, 17, 18] and has the advantages of being a non-invasive, atraumatic method, easy to perform, and features low risk of infection [19]. Some studies have shown that this modality of acupuncture exhibits substantial potential for reducing pain and improving function in different musculoskeletal disorders [15, 17, 18]. However, the effects of LA on TMD are not yet completely understood.

Observational studies have shown that LA can reduce pain intensity at rest [20–22] and palpation of the temporomandibular joint (TMJ) [21], in addition to improving the maximum mouth opening amplitude (MMO) [21, 22]. Although data from these studies suggest a promising effect of LA on TMD symptoms, there is a lack of evidence from studies with appropriate design to evaluate the effectiveness of this therapy. Therefore, the aim of this systematic review and network meta-analysis was to evaluate the effectiveness of LA on pain intensity and pain-free MMO amplitude in adult individuals with TMD, based on data from randomized clinical trials (RCTs).

# **Materials and Methods**

A systematic review and network meta-analysis was conducted from October/2022 to October/2023, in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [23] and the *Cochrane Handbook for Systematic Reviews* [24]. The present review was registered at International Prospective Register of Systematic Reviews (PROSPERO; ID number CRD42022372896) based on the following focused question: is LA effective, compared to other conservative treatments, non-treatment or placebo, for reducing pain and increasing MMO range in adult individuals with TMD?

The following electronic databases were searched by two independent investigators with a search updated on October 16, 2023: Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed, Web of Science, Scopus, Excerpta Medica Database (Embase), Latin American and Caribbean Health Sciences Literature (LILACS), Cochrane CENTRAL, Physiotherapy Evidence Database (PEDro), and ClinicalTrials.gov. For gray literature, the following databases were consulted: Networked Digital Library of Theses and Dissertations/Global Electronic Theses and Dissertations Service (NDLTD/Global EDT Search), Catalog of Theses and Dissertations—Coordination for the Improvement of Higher Education Personnel (CAPES), and Google Scholar. The search strategies used involved terms related to TMD and LA, as well as their synonyms, which were associated using the Boolean operators AND and OR. Search strategies for each database are shown in Supplementary Material 1.

RCTs that compared the use of LA with other conservative treatments, no treatment or placebo were included, regardless of language, period, or place of publication. Furthermore, RCTs should include adult participants, diagnosed with TMD through clinical examination or RDC/TMD and DC/TMD diagnostic criteria, without limitations on sex and ethnicity.

The following were excluded: studies that evaluated individuals with fibromyalgia, arthritis, or other musculoskeletal disorders; studies in which the experiment was not completed, or full text could not be obtained; and studies that did not provide complete data, and these could not be obtained by other means, such as contacting the corresponding author or using software to collect information contained in figures or graphs.

The study selection process was conducted by two independent researchers (I. H. A. A. and M. M. L. M.), who selected studies in two stages: (1) titles and abstracts were screened and studies considered ineligible were excluded; (2) potentially eligible studies were fully read and evaluated according to the eligibility criteria. After this stage, consensus meetings were held to discuss possible inconsistencies regarding the selection of studies. If inconsistencies remained, a third evaluator (G. A. L.) would be consulted. The Kappa statistic was used to assess inter-rater agreement. Additionally, the reference list of included studies was also evaluated to identify potential studies of interest that were not detected through the main search strategy. The excluded studies were registered separately, indicating the reasons for their exclusion. Duplicate studies were identified and removed using reference management software Mendeley (Mendeley Desktop, version 1.19.8, Elsevier).

Data were extracted by two independent researchers (I. H. A. A. and M. M. L. M.) and organized in a standardized spreadsheet in the Microsft Excel. A third researcher (G. A. L.) acted as a mediator in case of discrepancies or when a consensus was not established. The following data were collected: information about the studies (authors, year of publication, and country of origin), methodological aspects of the studies (sample size, sampling, randomization, blinding, eligibility criteria, age and gender of participants, time of segment, and adverse

events), LA parameters (type of laser, wavelength, output power, energy density, applied points, frequency, application interval, and duration of treatment), parameters of the comparator/control groups (type of treatment, duration, frequency, doses, and adverse effects), and measures of mean and standard deviation (SD) of pain intensity (subjective/self-reported and on palpation) and MMO without pain and without assistance at the end of treatments. The authors of the primary studies were contacted for additional clarification whenever necessary.

The primary outcome was subjective/self-reported pain intensity, expressed by VAS (0–10 cm) in the LA and comparator groups at the end of treatment. The intensity of pain on palpation in the TMJ and masticatory muscles (masseter and temporal muscles) was also evaluated using VAS, MMO without pain and without assistance, and the presence of adverse events after completion of treatment. VAS values 0–100 were directly transformed into a scale of 0–10, dividing by 10.

#### **Risk of Bias Assessment of Included Studies**

The risk of bias was assessed by two independent researchers (E. C. M. and G. A. L.), using the Cochrane tool for randomized clinical trials (RoB 2) [25]. A third researcher acted as a mediator (O. B. O. N.) in cases of discrepancy and as a third evaluator if a consensus was not established. The level of agreement between evaluators was also determined using the Kappa coefficient.

## **Data Synthesis**

Qualitative data synthesis was performed and then summarized in tables and graphs for a better understanding on relevant clinical issues such as sample characteristics, LA parameters, and measures of pain intensity and MMO after completion of treatment.

Quantitative data were analyzed using a frequentist network meta-analysis, in order to directly and indirectly compare all interventions addressed in the included studies. The network was created on the free online platform MetaInsight (https://crsu.shinyapps.io/metainsightc/) [26]. Network meta-analysis was conducted for the subjective pain intensity outcome, using mean difference (MD) as a measure of effect, data from the counseling group (C) as a reference, and a random effects model.

For studies in which the SD was not available, its calculation was performed using data from the 95% confidence interval (CI 95%), number of participants in each group (n), and critical values of the *t* distribution table  $(t^*)$ , with a significance level of 5%, according to Chapter 6 of the Cochrane Handbook for Systematic Reviews of Interventions [27].

#### **Certainty of the Evidence Assessment**

The certainty of the evidence assessment was carried out by two independent researchers (I. H. A. A. and M. M. L. M.) using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system [28, 29]. A third researcher (G. A. L.) mediated possible disagreements and was consulted if a consensus was not reached. The Kappa test was also used to evaluate the agreement between evaluators.

Effect measures were determined from network metaanalysis. For comparisons that were not included in the meta-analysis, continuous effect estimates were considered for evaluation in the GRADE system, considering the isolated study. To this end, the MD and CI 95% were calculated using the PEDro calculator (https://pedro.org.au/portuguese/ resources/confidence-interval-calculator/).

For the subjective pain intensity and palpation pain intensity outcomes, a 1.9 cm reduction in VAS was considered the minimum important difference for current pain intensity [30].

## Results

Searches on online databases yield 238 results. Of which, 123 were duplicates and, hence, excluded; 94 were excluded and one publication was not located. Thus, 20 studies were fully read and assessed for eligibility and 15 of them were excluded (Fig. 1). Thus, five studies were included on the systematic review. In addition, references of included studies comprised 310 records, which were assessed for potential interest; however, no additional studies were included (Fig. 1). The Kappa coefficient regarding search and selection processes was 0.869. A consensus was established between reviewers; thus, the assessment of the third reviewer was not necessary.

### **Characteristics of Included Studies**

Table 1 presents data regarding general characteristics of included RCTs. One may notice that five RCTs [31–35] evaluated participants of diagnosis of TMD using the RDC/TMD criteria and used the VAS before treatment and up to 3 months after its conclusion. Mean age varied from 28.75 to 41 years of age and LA was compared to C, occlusal splint (OS) and physiotherapy (PT) [31], C, OS, PT, and craniopuncture (CR) [35], Placebo LA +OS [32], Placebo LA [33], or low-level laser therapy (LLLT) [34].

#### **Risk of Bias of Included Studies**

Five RCTs evaluated the outcome subjective intensity of pain [31-35]. As seen in Fig. 2, the overall risk of bias was considered high for the following comparisons: (1) LA x C,

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



\*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n/71.

Fig. 1 Flow diagram of studies assessed for eligibility

OS, and PT [31], (2) active LA x open LA (non-blinded) [33], (3) LA x LLLT [34], and (4) LA x C, OS, PT, and CR [35]. On the other hand, the overall risk of bias was low for the comparison LA + OS x Placebo LA + OS [32].

Two RCTs evaluated the outcome pain intensity on palpation [32, 34]. For the comparison between LA + OS x Placebo LA + OS, the overall risk of bias was low in the outcomes of pain on palpation of the masseter muscle, temporalis muscle, and TMJ [32]. However, for the comparison LA x LLLT, the risk of bias for the outcome pain intensity on palpation in the masseter and temporalis muscles was high [34]. Only one RCT evaluated the pain-free and unassisted MMO outcome [34] and the overall risk of bias was considered high (Fig. 2). The Kappa coefficient was of 0.7 for this stage. After team meetings, a consensus was established, with no need for evaluation by a third researcher.

## **Qualitative Synthesis of Included Studies**

One may notice in Table 2 that four RCTs applied diode lasers (GaAlAs), with wavelengths between 780 nmand 810 nm (infrared) and output power between 40and 150 mW [31, 32, 34, 35]. Another RCT applied a red laser (690 nm) and an output power of 40 mW [33]. The energy density ranged from 7.5 Jto 112.5 J/cm<sup>2</sup> [31, 32, 34, 35], with one RCT specifying only the applied energy (40–60 J) [33]. Three RCTs operated the laser in

Study ID	Country	Sex (F/M)	Age (mean, minimum, maximum, SD)	Diagnosis and instruments	Intervention	Comparators	Sample size (groups/n)	Method to assess pain	Follow-up period
Bezerra [31]	Brazil	52/8	28.75y (18–60 y) (±10.11)	Articular, muscular, or mixed TMD (RDC/TMD)	LA in points of the head	C OS PT	LA /15 C /15 OS /15 PT /15	VAS (0-10)	Before and 1 month after completion of treatment
Ferreira et al. [32]	Brazil	40/0	34.17 y (±8.83)	Myofascial pain and arthralgia (RDC/TMD)	LA+OS	Placebo LA + OS	LA + OS /20 Placebo LA + OS/20	VAS (0-10)	Before, once a month treatment (M1 and M2) and immediately after completion of treatment (M3)
Katsoulis et al. [33]	Switzerland	10/1	33 y(22–61 y)	Myofascial pain (RDC/ TMD)	LA (blinded)	LA (non-blinded) Placebo LA	LA (blinded) /3 LA (non-blinded) /4 LA placebo /4	VAS (0–100)/Ver- bal scale	Before and 3 months after completion of treatment
Khalighi et al. [34]	Iran	20/4	41 y(24–59 y)	Myofascial pain (RDC/ TMD)	LA	LLLT	LA /12 LLLT/ 12	VAS (0-10)	Before each laser irradiation and 2 months after completion of treatment
Melo [35]	Brazil	66/12	28.8 y (18–60 y) (±9.5)	Articular, muscular, or mixed TMD (RDC/TMD)	LA in points of the head	cs CS CS	LA/13 C/15 OS/17 PT/20 CR/13	VAS (0-10)	Before, 1 month and 3 months after completion of treatment
F female, $M$ male, $S$ ture, $LLLT$ low-level	D standard de laser therapy	viation, y yea	ars, VAS visual analog scal	e, n number of p	articipants, C couns	elling, OS occlusal s	plint, <i>PT</i> physiothera	apy, LA laser acupunc	ture, CR craniopunc-

 Table 1
 Characteristics of included studies

1	Intention-to-														
t	treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	Overall		
		ID1	Study 1	Laser acupuncture	Counselling, Occlusal splint and Physical therapy	Subjecive pain intensity	1	•	•	Ŧ	•	•	•	•	Low risk
		ID2	Study 2	Laser acupuncture	Placebo laser acupuncture	Subjective pain intensity	1	•	•	Ŧ	!	1	•	•	Some concerns
		ID3	Study 3	Laser acupuncture	Low-level light therapy	Subjetive pain intensity	1	•	Ŧ	Ŧ	•	Ŧ	•	•	High risk
		ID4	Study 4	Laser acupuncture + Occlusal splint	Placebo laser acupuncture + Occlusal splint	Subjective pain intensity	1	•	•	Ŧ	•	•	$\bullet$		
		ID5	Study 5	Laser acupuncture	Counselling, Occlusal splint, Physical therapy or Craniopuncture	Subjective pain intensity	1	•	•	•	•	•	•	D1	Randomisation process
		ID6	Study 3	Laser acupuncture	Low-level light therapy	Pressure pain threshold masster muscle	1	•	•	÷	•	•	•	D2	Deviations from the intended interventions
		ID7	Study 4	Laser acupuncture + Occlusal splint	Placebo laser acupuncture + Occlusal splint	Pressure pain threshold masseter muscle	1	•	•	÷	•	•	•	D3	Missing outcome data
		ID8	Study 3	Laser acupuncture	Low-level light therapy	Pressure pain threshold temporalis muscle	1	•	•	•	•	•	•	D4	Measurement of the outcome
		ID9	Study 4	Laser acupuncture + Occlusal splint	Placebo laser acupuncture + Occlusal splint	Pressure pain threshold temporalis muscle	1	Ŧ	Ŧ	Ŧ	÷	Ŧ	$(\mathbf{+})$	D5	Selection of the reported result
		ID10	Study 4	Laser acupuncture + Occlusal splint	Placebo laser acupuncture + Occlusal splint	Pressure pain threshold TMJ	1	÷	•	Ŧ	•	•	•		
		ID11	Study 3	Laser acupuncture	Low-level light therapy	Pain-free maximum mouth opening	1	•	•	Ŧ	•	•	•		

Fig. 2 Overall risk of bias

continuous mode [31, 32, 35] and two others did not report the emission mode [33, 34].

The application time per LA point varied from 5 s to 15 min. The number of applications varied between 8 and 12, with a frequency of one [32], two [31, 33, 35], or three sessions per week [34]. The acupuncture points irradiated exhibited great variation, with points ST6, located on the head and LI4, located on the hand, being the most frequently irradiated (Table 2).

Table 3 demonstrates the results of the included RCTs. Bezerra [31] found that only the groups treated with OS and PT reduced pain after treatment. Melo [35] observed that OS, C, and PT reduced the intensity of subjective pain in 1 month and 3 months after completion of treatment. CR reduced pain intensity just 1 month after treatment. Ferreira et al. [32] observed that treatments with LA + OS and Placebo LA + OS reduced pain intensity. However, the reduction in the group treated with active LA was statistically greater. In the study by Katsoulis et al. [33], subjective pain levels after treatment were higher in the blind LA group. However, they were lower in the group treated with nonblinded LA. Khalighi et al. [34] observed that treatments with LA or LLLT reduced pain intensity, with no differences in the intergroup comparison (Table 3).

Regarding the intensity of pain on palpation, Ferreira et al. [32] observed that treatments with active LA or Placebo LA, associated with OS, reduced pain on palpation in the masseter muscle, temporalis muscle, lateral pole of the TMJ, and posterior region of the TMJ, with this reduction being statistically greater in the active LA group. Khalighi et al. [34] demonstrated that treatments with LA or LLLT reduced the intensity of pain on palpation in the masseter and temporalis muscles from the second or third session onwards, with no statistically significant difference between the two groups (Table 3).

Regarding pain intensity in other muscle groups, Ferreira et al. [32] demonstrated that both active LA and Placebo LA associated with OS reduced pain on palpation in the posterior region of the mandible, submandibular region, lateral pterygoid area, and temporalis tendon at the end of treatment. They also observed that pain reduction was statistically greater for the same palpation sites in the group treated with active LA. The researchers also observed that most patients in the active LA group achieved complete remission of symptoms after treatment in all palpation sites, while the majority of patients in the Placebo LA group achieved only a partial reduction in symptoms in the same structures. Khalighi et al. [34] observed that treatments with LA or LLLT reduced the intensity of pain on palpation in the medial pterygoid and lateral pterygoid muscles from the second or third session onwards. However, there was no statistically significant difference between the two groups up to 2 months after completion of treatment.

Khalighi et al. [34] also evaluated the effects of LA on pain-free and unassisted MMO. They found that treatments with LA and LLLT statistically increased mouth opening, compared to the baseline, with no differences between the two treatments.

No adverse effects were reported in the included studies (Table 3).

#### **Network Meta-Analysis**

Two RCTs showed similarities in relation to the sample, as well as the methodological aspects and LA parameters [31, 35] and were therefore included in the network meta-analysis. The network involved five interventions, 10 comparisons with direct paired data, and 138 patients (Fig. 3A).

As seen in Fig. 3B, treatments with OS [MD = -2.47; CI 95% -3.64, -1.30] and PT [MD = -2.64; CI 95% -3.94, -1.34] reduced subjective pain intensity compared to C. Regarding the ranking of treatments in order of effectiveness, the following decreasing sequence was observed: PT > OS > LA > C > CR (Fig. 3C).

The inconsistency test demonstrated that there were no important estimated differences between direct and indirect

Study ID	LA parameters							Parameters of comparators
	Type of laser/wavelength	Output power	Energy density (J/ cm <sup>2</sup> )	Emission mode	Time per point	Frequency	Application site	
Bezerra [31]	GaAlAs diode laser /780 mm	50 mW	112.5	Continuous	60 s	Total of 8 applications /2 sessions per week /during 4 weeks	VG20 (Baihui), VG21 (Qianding), VG22 (Shenting), NG24 (Shenting), motor and sensory areas of the face of the Jiao Shunfa school	<ul> <li>- C</li> <li>Oral and written guidance in a single consultation and reinforced after 15 and 30 days</li> <li>- OS</li> <li>- OS</li> <li>Creation of a stabilizing splint, guidance on clean- ing and maintenance of the splint, return within</li> <li>15 days for adjustments, if necessary</li> <li>- PT</li> <li>- PT</li> <li>Use of thermal agents (heat and cryotherapy), therapeu- tic exercises and massages (8 sessions in total, twice a week for 4 weeks) + stretch- ing exercises and com- presses at home every day</li> </ul>
Ferreira et al. [32]	GaAlAs diode laser /780 nm	50 mW	112.5	Continuous	s 06	Creation of stabiliz- ing splint (dura- tion of treatment: 3 months) + Active Laser acupuncture: 12 applications/once a week /during 12 weeks (3 months)	ST6, S119, GB20, L14, LR3, TE3, GB34 and EX-HN3	- Placebo LA + OS The same parameters with the laser not activated
Katsoulis et al. [33]	MA /690 nm	40 mW	NA (Energy varied from 40-60 J)	NA	15 min	Total of 6 applications /2 sessions per week /during 3 weeks	ST6, SI18, S13 and L14 (in both sides of the body and simultaneously stimulated)	- LA (blinded) - LA placebo The same parameters with the laser not activated

 Table 2
 Parameters of interventions on included studies

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Study ID	LA parameters							Parameters of comparators
	Type of laser/wavelength	Output power	Energy density (J/ cm <sup>2</sup> )	Emission mode	Time per point	Frequency	Application site	
Khalighi et al. [34]	GaAlAs diode laser/810 nm	150 mW	7.5-26.25	Υ N	5 s (points ST6, ST7 and L14) 40 s (point Ashi)	Total of 12 applica- tions / every other day (3 sessions per week) /during 4 weeks	ST6 and ST7 (same side of the affected muscle), L14 on the opposite side and points Ashi (points of pain)	- LLLT Infrared laser (810 nm), total of 12 applications, over 4 weeks: 9 First week: 5 applications with decreasing output power of 0.5–0.1W o Second week: 3 applica- tions with increasing output power of 0.2–0.4W o Third week: 2 applications with decreasing output power of 0.3–0.2W o Fourth week: 2 applica- tions with increasing output power of 0.1–0.2W o Fourth week: 2 applica- tions with increasing output power of 0.1–0.2W in continuous mode, for 60 s on the pain points. Energy density between 6 and 24 J/ cm <sup>2</sup>

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Study ID	LA parameters							Parameters of comparators
	Type of laser/wavelength	Output power	Energy density (J/ cm <sup>2</sup> )	Emission mode	Time per point	Frequency	Application site	
Melo [35]	GaAlAs diode laser/780 nm	50 mW	112.5	Continuous	60 s	Total of 8 applications /2 sessions per week /during 4 weeks	VG20 (Baihui), VG21 (Qianding), VG22 (Xinhui), VG24 (Shenting), motor and sensory areas of the face of the Jiao Shunfa school	<ul> <li>- C</li> <li>Oral and written guidance in a single consultation and reinforced after 15 days</li> <li>- OS</li> <li>- OS</li> <li>Creation of a stabilizing plate and guidance on cleaning and maintenance of the plate. Return consultations for control and adjustments</li> <li>15 days, 1 (one) month, and 3 (three) months after installation</li> <li>- PT</li> <li>Therapeutic exercises and massages (8 sessions in total, twice a week for 4 weeks) + stretching exer- cises and warm compresses at home every day</li> <li>- CR</li> <li>Applied points: VG20 (Baihui), VG21 (Qiand- ing), VG22 (Xinhui), VG24 (Shenting), point known as "head," motor and sensory areas of the face of the Jiao Shunfa school</li> </ul>

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Table 2 (continued)

Study ID	Intensity of spontaneous	s pain	Intensity of pai on palpa	tion	MMO with no p	ain after treatment	Adverse events
	Mean and SD (Intervention/baseline/ end of treatment)	Intragroup and intergroup comparisons	Mean and SD (Intervention/baseline/ end of treatment)	Intragroup and intergroup comparisons	Mean and SD (Intervention/ baseline/end of treatment)	Intragroup and intergroup comparisons	
Bezerra [31]	LA /5.78 ( $\pm 2.91$ ) /4 ( $\pm 2.48$ ) C /4.53( $\pm 2.61$ ) /4.40 ( $\pm 2.82$ ) OS /4.53 ( $\pm 3.11$ ) /2.33 ( $\pm 1.54$ ) PT /3.60 ( $\pm 2.22$ ) /1.46 ( $\pm 2.06$ )	OS (p=0.001) and PT (p=0.014) reduce pain. PT is better than LA (p=0.006).	NA	NA	NA	NA	Non reported
Ferreira et al. [32]	LA + OS/7.65 (±1.63) /0.05 (±0.22) Placebo LA + OS /7.30 (±2.0) /2.75 (±2.71)	Active LA (p=0.001) and Placebo LA (p=0.001) associated to OS reduce pain. Active LA was better than Placebo LA (p<0.01)	- Masseter muscle LA + OS /7.95 ( $\pm$ 1.53)/ 0.1 ( $\pm$ 0.44) Placebo LA + OS /8.55 ( $\pm$ 1.5) /2.3 ( $\pm$ 1.86) - Temporalis muscle LA + OS /6.7 ( $\pm$ 1.89) /0 Placebo LA + OS /7.30 ( $\pm$ 2.29) /1.75 ( $\pm$ 1.91) - Lateral pole of TMJ LA + OS /8.15 ( $\pm$ 1.53) / 0.25 ( $\pm$ 0.71) Placebo LA + OS /8.7 ( $\pm$ 0.97) /2.05 ( $\pm$ 2.16) - Posterior attachment of TMJ LA + OS /7.4 ( $\pm$ 1.71) /0.05 ( $\pm$ 0.22) Placebo LA + OS /8.05 ( $\pm$ 1.87) /2.25 ( $\pm$ 2.38)	Active LA and Placebo LA associated to OS reduce pain. Active LA was better than Placebo LA	Ч. Х	Ŋ	Non reported
Katsoulis et al. [33]*	LA (blinded) /6.1 (±3.29) /4.5 (±2.25) LA (non-blinded) /6.7 (±2.27) /1.6 (±1.28) Placebo LA/6.8 (±2.2) /2.2 (±1.83)	Did not perform statistical tests to compare groups.	NA	NA	NA	NA	Non reported

 Table 3
 Outcomes on included studies

Table 3 (continued)							
Study ID	Intensity of spontaneou	s pain	Intensity of pai on palpa	tion	MMO with no pa	ain after treatment	Adverse events
	Mean and SD (Intervention/baseline/ end of treatment)	Intragroup and intergroup comparisons	Mean and SD (Intervention/baseline/ end of treatment)	Intragroup and intergroup comparisons	Mean and SD (Intervention/ baseline/end of treatment)	Intragroup and intergroup comparisons	
Khalighi et al. [34]	LA /7.08 (±1.37) /0 LLLT /6.58 (±1.31) /0.33 (±0.65)	LA (P < 0.0001) and LLLT (P < 0.0001) reduce pain. LA = LLLT	-Masseter muscle LA/ 6.35 (± 2.42) /0 LLLT / 7.57 ± 1.27 / 0.35 ± 0.62 - Temporalis muscle LA / 5.25 (± 1.17) /0 LLLT /6.66 (± 0.57) /0	LA and LLLT reduce pain from the second or third session onwards LA = LLLT	LA /33 (± 6.57) /45.67 (± 3.86) 3.86) 3.86) 8.76) / 42.58 (± 4.75)	LA (P < 0.0001) and LLLT (P= 0.001) increased MMO LA = LLLT	Non reported
Melo [35]	LA $(5.9 (\pm 4.29) / 3.4 (\pm 4.7)$ C $(5.6 (\pm 2.52) / 3.6 (\pm 3.06)$ OS $(4.1 (\pm 3.59) / 0.8 (\pm 1.36)$ PT $(3.8 (\pm 2.45) / 1.3 (\pm 2.56)$ PT $(3.8 (\pm 2.45) / 1.3 (\pm 2.56)$ CR $(5.1 (\pm 3.88) / 4.4 (\pm 2.8)$	OS. PT and C reduce pain after 3 months CR reduces pain after 1 month OS and PT were better than C. CR and LA after 3 months	NA	Ą	Ϋ́	ΥX	Non reported
NA non assessed, SD	standard deviation, C cour	nselling, OS occlusal splint, H	<sup>oT</sup> physiotherapy, LA laser	acupuncture, CR craniopunc	ture, <i>LLLT</i> low-lev	el laser therapy, TMJ ter	nporomandibular

ŝ â ר ד joint \*VAS from 0 to 100 converted in 0–10 5

Fig. 3 A Network involving five interventions. **B** Treatments with OS and PT. **C** Ranking of treatments in order of effectiveness



information (Supplementary Material 2). Due to the small number of studies included in the meta-analysis, it was not possible to perform subgroup and sensitivity analyses.

## **Certainty of Evidence**

Table 4 shows that the certainty of evidence for all comparisons and outcomes was very low or low. The main reasons for downgrading the certainty of the evidence were the high risk of bias in the included studies, imprecision, and indirect evidence. The latter related only to the studies included in the network meta-analysis.

# Discussion

This systematic review and network meta-analysis evaluated the effectiveness of LA on TMD symptoms. It was demonstrated in the network meta-analysis that LA did not significantly reduce subjective pain intensity when compared to AC (very low certainty of evidence). It was also demonstrated that LA alone or associated with PO reduced the intensity of pain on palpation of the masseter muscle (very low and low certainty of evidence, respectively), temporalis muscle (very low and low certainty of evidence, respectively), and TMJ (slow certainty of evidence). Furthermore, LA increased pain-free MMO amplitude (very low certainty of evidence). There were also no reported adverse reactions resulting from treatment with LA.

de Oliveira et al. [19] conducted a literature review aiming to gather evidence on the application of LA in Dentistry. The researchers included 10 studies, seven of which evaluated patients with TMD. Observational clinical studies and RCTs were included, demonstrating better results from LA. The researchers concluded that although LA is safe and presents promising results, there is a lack of standardization of parameters, especially those related to laser irradiation, and more RCTs are needed to determine an LA application protocol.

On the other hand, Peixoto et al. [36] performed a systematic review to evaluate the effects of traditional acupuncture and LA on pain intensity and MMO in adult patients with TMD, compared to other therapies, with no treatment or placebo. Six RCTs involving patients with TMD through the RDC/TMD or DC/TMD were included. These researchers concluded that traditional acupuncture seems to reduce TMD symptoms, as well as LA associated with PO. However, due to the small number of included studies, the researchers argued that there is a lack of evidence to prove the best type of acupuncture. However, unlike the present review, researchers did not perform a meta-analysis and did not assess the level of certainty of the evidence using an appropriate instrument. Furthermore, only one study that evaluated LA was included.

In the present systemic review and network meta-analysis, using a comprehensive search strategy, a greater number of databases and no language restrictions, five RCTs were included that specifically evaluated LA on TMD symptoms. Aligning the results of this review with the findings of De Oliveira et al. [19] and Peixoto et al. [36], it can be suggested that there is a lack of robust evidence to prove the effectiveness of LA for the remission of TMD symptoms.

However, systematic reviews involving patients with different musculoskeletal disorders have demonstrated promising results from LA. In this sense, a study reviewed data from 18 RCTs involving adult individuals, whose primary intervention was LA and the outcomes evaluated were pain intensity and/or a global measure of patient improvement

Table 4 Level	l of certainty of	evidence using	the GRADE syst	tem								
Certainty asse	ssment						Nº of patients		Effect		Certainty	Importance
<u>Ne</u> of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo, no treatment or other therapies	Relative (95% CI)	Absolute (95% CI)		
Subjective pair	ι intensity (Laser	acupuncture vs (	Counselling) (foll	ow-up: mean 3	months; assesse	ed with: VAS; Sca	ale from 0 to 10					
5	Randomised trials	Very serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Very serious <sup>c</sup>	None	28	30		MD 0.42 VAS lower (1.98 lower to 1.13 higher)	<b>DOO</b>	CRITICAL
Subjective pair	1 intensity (Occlu	ısal splint vs Cou	ınselling) (follow-	-up: mean 3 moi	nths; assessed v	with: VAS; Scale f	from 0 to 10)					
5	Randomised trials	Very serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Very serious <sup>d</sup>	None	32	30		MD 2.47 VAS lower (3.64 lower to 1.3 lower	<b>DOO</b>	CRITICAL
Subjective pair	1 intensity (Physi	cal therapy vs Ct	ounselling) (follov	w-up: mean 3 m	onths; assessed	l with VAS)						
7	Randomised trials	Very serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Very serious <sup>d</sup>	None	35	30		MD 2.64 VAS lower (3.94 lower to 1.34 lower	<b>DOO</b>	CRITICAL
Subjetive pain	intensity (Cranio	puncture vs Cou	nselling) (follow-	up: mean 3 mon	iths; assessed w	vith: VAS; Scale fi	rom 0 to 10)					
7	Randomised trials	Very serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Very serious <sup>c</sup>	None	13	30		MD 0.93 VAS higher (0.97 lower to 2.83 higher)	<b>DOO</b>	CRITICAL
Subjective pair	1 intensity (Occlu	ısal splint vs Las	er acupuncture) (1	follow-up: mean	1 3 months; asse	essed with: VAS;	Scale from 0 to	10)				

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Table 4 (conti	inued)											
Certainty asse	ssment						Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo, no treatment or other therapies	Relative (95% CI)	Absolute (95% CI)		
0	Randomised trials	Very serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Very serious <sup>d</sup>	None	32	28		MD 2.05 VAS lower (3.31 lower to 0.78 lower	⊕OOO Very low	CRITICAL
Subjective pain	intensity (Physic	al therapy vs La	tser acupuncture)	(follow-up: mea	an 3 months; as	sessed with: VAS	; Scale from 0 to	0 10)				
6	Randomised trials	Very serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Very serious <sup>d</sup>	None	35	28		MD 2.22 VAS lower (3.6 lower to 0.84 lower	⊕OOO Very low	CRITICAL
Subjective pain	intensity (Laser	acupuncture vs (	Craniopuncture) (	(follow-up: mear	n 3 months; ass	essed with: VAS;	Scale from 0 to	10)				
0	Randomised trials	Very serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Very serious <sup>c</sup>	None	28	13		MD 1.35 VAS lower (3.35 lower to 0.64 higher)	⊕OOO Very low	CRITICAL
Subjective pain	intensity (Laser	acupuncture + O	Acclusal splint vs l	Placebo laser ac	upuncture + Oc	clusal splint) (ass	essed with: VAS	S; Scale from 0 to	10)			
-	Randomized trials	Not serious	Not serious	Not serious	Very serious <sup>d</sup>	None	20	20		MD 2.7 VAS lower (3.93 lower to 1.47 lower	Low $\Theta \Theta O$	CRITICAL
Subjective pain	i intensity (Laser	acupuncture vs l	Low-level light th	ıerapy) (follow-ı	up: mean 2 mor	ths; assessed witl	1: VAS; Scale fr	om 0 to 10)		~		

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Table 4 (con	tinued)											
Certainty ass	essment						Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo, no treatment or other therapies	Relative (95% CI)	Absolute (95% CI)		
_	Randomized trials	Very serious <sup>e</sup>	Not serious	Not serious	Very serious <sup>c</sup>	None	12	12		MD 0.33 VAS lower (0.72 lower to 0.06 higher)	⊕⊖⊖⊖⊖ Very low	CRITICAL
Subjective pai	in intensity (Laser	acupuncture vs.	Placebo laser acu	ipuncture) (follo	w-up: mean 3 n	nonths; assessed v	with: VAS; Scale	e from 0 to 10)				
_	Randomized trials	Very serious <sup>e</sup>	Not serious	Not serious	Very serious <sup>d</sup>	None	ς	4		MD 2.3 VAS higher (0.56 higher to 4.04 higher	<b>DOO</b>	CRITICAL
Pressure pain	threshold massete	sr muscle (Laser	acupuncture + Oc	cclusal splint vs	Placebo acupun	acture + Occlusal a	splint) (assessed	l with: VAS; Scale	from 0 to 10	~		
_	Randomized trials	Not serious	Not serious	Not serious	Very serious <sup>d</sup>	None	20	20		MD 2.2 VAS lower (0.72 higher to 1.33 higher)	DOW DO	CRITICAL
Pressure pain	threshold massete	er muscle (Laser	acupuncture vs L	ow-level light th	herapy) (follow-	up: mean 2 month	hs; assessed with	h: VAS; Scale fron	1 0 to 10)			
1 Pressure pain	Randomized trials threshold temoors	Very serious <sup>e</sup> alis muscle (Lase	Not serious	Not serious Occlusal solint v	Very serious <sup>e</sup> s. Placeho laser	None acumuncture + Oc	12 clisal snlint) (as	12 sessed with: VAS:	- Scale from (	MD 0.35 VAS lower (0.72 lower to 0.02 higher) 0 to 10)	⊕⊖⊖⊖ Very low	CRITICAL
-	Randomized triâls	Not serious	Not serious	Not serious	Very serious <sup>d</sup>	None	20	20		MD 1.75 VAS lower (2.61 lower to 0.88		CRITICAL
										lower)		

Table 4 (continued)											
Certainty assessment						Nº of patients		Effect		Certainty	Importance
Nº of studies Study design Ris	sk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo, no treatment or other therapies	Relative (95% CI)	Absolute (95% CI)		
Pressure pain threshold temporalis n	nuscle (Laser	acupuncture vs	Low-level light	therapy) (follow	v-up: mean 2 mor	ths; assessed w	ith: VAS; Scale fr	om 0 to 10)			
1 Randomized Ver trials	ry serious <sup>e</sup>	Not serious	Not serious	Very serious <sup>f</sup>	None	12	12	ı	MD 0 VAS (0 to 0)		CRITICAL
Pressure pain threshold TMJ lateral	pole (Laser a	cupuncture + Oc	clusal splint vs H	Placebo laser ac	upuncture + Occ]	usal splint) (ass	essed with: VAS;	Scale from 0	to 10)	•	
1 Randomized No trials	t serious	Not serious	Not serious	Very serious <sup>d</sup>	None	20	20	1	MD 1.8 VAS lower (2.83 lower to 0.77 lower	₽ Tow 0 0 0	CRITICAL
Pressure pain threshold TMJ posterio	or attachment	: (Laser acupunc	ture + Occlusal	splint vs Placeb	o laser acupuncti	rre+Occlusal sj	plint) (assessed wi	th: VAS; Sca	lle from: 0 to	10)	
1 Randomized No trials	t serious	Not serious	Not serious	Very serious <sup>d</sup>	None	20	20	,	MD 2.2 VAS lower (3.28 lower to 1.12 lower	DO Low	CRITICAL
Pain-free maximum mouth opening	(Laser acupu	ncture vs Low-le	evel light therapy	/) (follow-up: n	nean 2 months; as	sessed with: m	m)				
1 Randomized Ver trials	ry serious <sup>e</sup>	Not serious	Not serious	Very serious <sup>c</sup>	None	12	12		MD 3.09 mm higher (0.57 lower to 6.75 higher)	<b>DOO</b>	IMPORTANT
CI confidence interval, MD mean	difference										
<sup>a</sup> Included studies present a high ris	sk of bias in	important dom	ains								
<sup>b</sup> Presence of indirect evidence in n	network mets	ı-analysis									
<sup>c</sup> (1) Small sample size. (2) Confid	ence interval	touches the nu	ıll line								
<sup>d</sup> (1) Small sample size. (2) Confid	lence interva	l of the effect es	stimate includes	s the minimal	important differe	nce in current	pain intensity (1.	9 cm reduct	ion in VAS)		
<sup>e</sup> Study presents high risk of bias ir	n important e	lomains									
f(1) Small sample size. (2) Effect e	estimate is ze	cro									

[37]. Moderate evidence has been demonstrated to support the use of this therapy in the treatment of myofascial pain, using a minimum output power of 10 mW and at least 0.5 J of energy per point. Other parameters could not be established due to the great heterogeneity of the laser parameters used in the included studies.

The same group of researchers updated the systematic review described previously and added meta-analysis data related to the effects of LA on pain associated with musculo-skeletal disorders, reviewing 49 RCTs [18]. The researchers demonstrated that, overall, LA compared to placebo reduced the intensity of pain determined by VAS immediately after treatment [SMD = -0.49; CI 95% -0.79, -0.35] and in the period of up to 6 months of follow-up [SMD = -0.95; CI 95% -1.55, -0.35]. Subgroup analysis demonstrated that LA reduced the intensity of pain related to myofascial pain immediately after completion of treatment [SMS = -0.49; CI 95% -0.79, -0.23]. However, they did not demonstrate a significant reduction in lateral epicondylitis and TMD.

The systematic review conducted by Law et al. [18] included studies that applied low-level laser at acupuncture points, at trigger points, or other sensitive points of traditional Chinese medicine, making it difficult to separate LA from traditional LLLT, in which the laser is applied on pain points. In the qualitative assessment and TMD-related meta-analysis, these authors used study data that applied the laser at trigger points or pain points [38, 39] and inside the external auditory conduit [40]. Since these points are not acupuncture-related, the data presented on the effects of LA may under or overestimate TMDs.

Another systematic review evaluated the effectiveness of LA for remission of knee osteoarthritis symptoms [17]. Seven RCTs were included involving adult patients in which LA was compared to placebo. The researchers demonstrated that LA reduced pain intensity determined by VAS compared to placebo at short-term follow-up [SMD = -1.03; CI 95% -1.93, -0.13]. However, LA did not demonstrate significant effects on pain reduction in the long-term follow-up period.

Hung et al. [15] performed a systematic review and metaanalysis to evaluate the effectiveness of LA on the levels of pain reduction, disability, and impairment in patients with musculoskeletal disorders. These researchers demonstrated that LA promoted considerable pain reduction compared to Sham treatment overall [g = 0.88; CI 95% 0.35, 1.42], in short-term assessments [g = 0.96; CI 95% 0.57, 1.36] and in more than a month [g = 0.87, CI 95% 0.12, 1.62]. LA promoted a significant reduction in the level of disability [g = 0.68; CI 95% 0.29, 1.08]; however, it was not effective in a follow-up longer than 1 month. LA also decreased the level of functional impairment compared to Sham treatment [g = 0.67; CI 95% 0.32, 1.03]. Regarding LA parameters, this review demonstrated a great heterogeneity in relation to acupuncture points and laser parameters. Most of the included RCTs applied infrared laser with a wavelength between 780 nmand 810 nm. An RCT applied a red laser with a wavelength of 690 nm. The output power varied from 40 to 150 mW and the energy density varied between 7.5 Jand 112.5 J/cm<sup>2</sup>. Corroborating the results of this review, De Oliveira et al. [19] argue that these parameters are crucial, as they can directly interfere with the effectiveness of the treatment.

Current evidence has demonstrated that LLLT has analgesic, anti-inflammatory, and regenerative effects [41-44], being able to promote vasodilation, stimulate the formation of fibroblasts and collagen, inhibit pro-inflammatory mediators and matrix metalloproteinases, facilitate neural regeneration, and increase the pain threshold and production of endogenous opioids [14, 42, 45-48]. However, the mechanism by which low-level laser/photobiostimulation can stimulate acupuncture points is not yet completely understood. Differences in laser characteristics such as wavelength, output power, energy, and energy density are known to affect the level of dispersion and penetration of light through skin tissue [14, 41, 49]. Furthermore, light penetration is difficult to standardize due to the complex optical properties of the skin and heterogeneity in skin characteristics at different treatment sites or between different individuals [14, 49]. Therefore, a unified protocol as well as laser parameters can be difficult to establish.

Due to the depth of the acupuncture points, red and infrared lasers with wavelengths in the range of 650 nmto 900 nm are more suitable, as shorter lengths are absorbed by melanin and wavelengths greater than 900 nm are absorbed by water [14]. In addition, higher energy density results in greater penetration into the skin [14, 41, 42, 49]. Nevertheless, more studies are needed, addressing different laser parameters, to better understand its mechanism of action on acupuncture points and the most suitable parameters for each point.

It was observed in this review that the irradiated acupuncture points also exhibited great variation, with the most frequent points being ST6 and LI4. Points ST6, ST7, SI18, GV20, GB20, and BL10, located in the head and neck region, and the distant point LI4 are traditionally stimulated in traditional acupuncture to promote pain relief in the face and neck [21, 22, 50]. The photobiostimulation of these points must be evaluated in new placebocontrolled studies to confirm its effectiveness in reducing symptoms associated with TMD. On the other hand, photobiostimulation of craniopuncture points did not promote a statistically significant reduction in pain, suggesting that these points may not positively influence the symptoms of this disorder.

As a limitation of this systematic review, we can highlight the small number of studies included and the impossibility of sensitivity and subgroup analyses in network meta-analysis. However, a broad search strategy was used, without language restrictions, in 11 electronic databases, 3 of which were related to gray literature. Furthermore, the references of the studies included were evaluated in the search for studies that were not located in the main strategy. Thus, the main studies that addressed the effectiveness of LA for TMD symptoms were reviewed.

One RCT evaluated the efficacy of LA and LLLT compared to placebo in treating TMD symptoms [47]. The researchers found that both LA and LLLT reduced the intensity of subjective pain and pain on palpation of the TMJ and masticatory muscles, except for the temporalis muscle. The treatments did not promote significant changes in MMO, but LA and LLLT increased the range of left laterality and protrusion movements. Nevertheless, this study was not included in this review, as it involved patients aged between 15 and 71 years and it was not possible to identify whether individuals under 18 years of age were part of all groups, even after contact with the researchers. This systematic review gathered data only from studies involving adult patients diagnosed with TMD through the RDC/TMD, DC/ TMD, or clinical examination.

Two clinical trial registries whose results were not part of this review were also identified. The first was conducted by a team from China and has an estimated completion date of December 31, 2022. However, no related publication or technical report was found, even after contacting the responsible researchers. The second was registered on July 2, 2023, by a team of Brazilian researchers and is currently in the participant recruitment phase. This demonstrates that the topic continues to be explored by different groups of researchers. The results of these studies and others that may be initiated may be used to update this review in the future and clarify the effect of LA on TMD symptoms.

# Conclusions

LA is a promising, safe, and atraumatic treatment as it does not require the use of needles. However, its application cannot be supported for the treatment of TMDs according to the results of RCTs, due to the low certainty of the available evidence. New placebo-controlled RCTs should be conducted to more precisely demonstrate its effectiveness in remitting TMD symptoms, as well as the most appropriate laser parameters.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11916-024-01251-5.

Author Contributions The idea for the study was determined by ASL. The literature search and data extraction were performed by MMLM

and IHAA. Data analysis was performed by ECMi and GAL. The work was written by GAL. ECM, OBON and PLPS critically reviewed the work.

**Data Availability** No datasets were generated or analysed during the current study.

## **Compliance with Ethical Standards**

**Conflict of Interest** The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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