Efficacy of Low-Level Laser Therapy in chronic Temporomandibular Disorders: Systematic review and meta-analysis of randomized placebo-controlled trials

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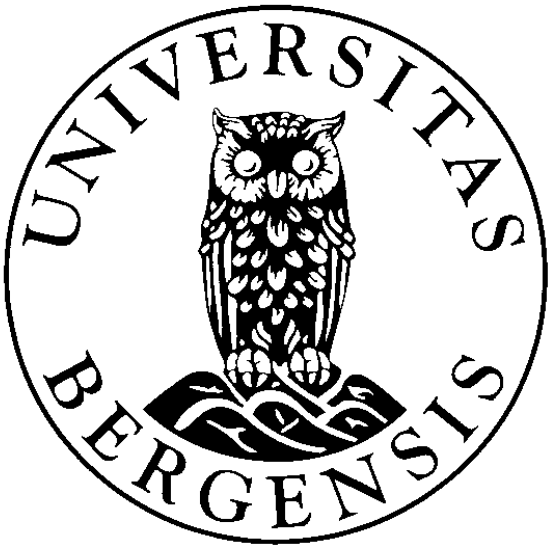

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Abstract

Objectives: Temporomandibular disorders (TMD) are perhaps as prevalent as low back pain, fibromyalgia, and migraine. Inflammation has shown to play a key role in the pathogenesis of TMD. Low-level laser therapy (LLLT) is generally not recommended in clinical guidelines for TMD. I investigated the effectiveness of LLLT in TMD and whether a dose-response relationship exists.

Design: Systematic review and meta-analysis.

Data sources: Eligible studies were identified through PubMed and Embase on 3 June 2022. The search was restricted to maximum 10 of the most recently published studies reported in English/Nordic language.

Eligibility criteria for selecting studies: Only randomized placebo-controlled trials (RCT) involving participants with chronic TMD who had their temporomandibular joint and/or masticatory muscles irradiated by LLLT were included.

Data extraction and synthesis: A random effects meta-analysis of self-reported pain was performed. The trials were subgrouped in adherence to the World Association for Laser Therapy (WALT)´s treatment recommendations.

Results: 10 RCTs (n = 423) were included in this review and meta-analysis, two with recommended doses and eight with non-recommended doses. The overall pain result immediately after completed therapy favored LLLT over placebo, but the difference was only borderline significant (SMD = -0.63 (95%CI -1.26 to 0.01), I^2 = 85%, n = 338). The overall follow-up pain result 1-8 weeks after completed therapy highly significantly favored LLLT over placebo (SMD = -1.51 (95% CI -2.56 to -0.47), I^2 = 92%, n = 279).

The pain results of the subgroup analysis of recommended laser doses favored LLLT over placebo, but not significantly (SMD = -4.05 (95% CI -11.22 to 3.13) I^2 = 97%, n = 44). The same applied to the non-recommended laser doses (SMD = -0.39 (95% CI -0.86 to 0.08) I^2 = 73%, n = 336).

Conclusion: The results indicate that LLLT can reduce TMD pain. The statistical heterogeneity was high, but it was caused by a single trial with a moderate sample size. More trials with WALT´s recommended doses are needed in the search for a possible dose-response relationship.

Prospero protocol: Supplementary material.

Keywords: TMD, temporomandibular disorder, orofacial pain, LLLT, low-level laser therapy, systematic review, meta-analysis

Sammendrag

Hensikt: Temporomandibulær dysfunksjon (TMD) rapporteres med tilsvarende prevalens som fibromyalgi, korsryggsmerter og migrene. Inflammasjon spiller en viktig rolle i patogenesen og opprettholdelsen av sykdommen. Low-level laser therapy (LLLT) anbefales ikke i anerkjente kliniske retningslinjer for behandling av TMD. Jeg undersøkte effekten av LLLT på TMD for selvrapportert smerte, og betydningen av et dose-respons-forhold for behandlingseffekt.

Studiedesign: Systematisk oversikt med metaanalyse.

Materiale og metode: Relevante artikler ble identifisert gjennom søk i PubMed og Embase 3. juni 2022. Jeg begrenset søket til de 10 nyeste publiserte studiene rapportert på engelsk eller nordisk språk. Kun randomiserte, placebokontrollerte studier (RCT) av deltakere med kronisk TMD – behandlet for smerte med LLLT påført enten temporomandibulærleddet eller kjevemuskulatur – ble inkludert. Det ble utført en random-effects metaanalyse av alle inkluderte studier. Studiene ble subgruppert etter etterlevelse til doseanbefalingene fra World Association for Laser Therapy (WALT).

Resultater: 10 RCTer (N = 423) ble inkludert i denne systematiske oversikten og metaanalysen, to med anbefalte doser og åtte med ikke-anbefalte doser. Hovedfunnene viste større smertereduksjon av laser sammenliknet med placebo umiddelbart etter siste behandling, men forskjellen kun grenset til statistisk signifikans (SMD = -0.63 (95%CI -1.26 to 0.01), I^2 = 85%, n = 338). Ved oppfølgingstidspunkt 1-8 uker etter gjennomført behandling gav LLLT en høyst signifikant bedring sammenliknet med placebo (SMD = -1.51 (95% CI -2.56 to -0.47), I^2 = 92%, n = 279). Resultatene fra subgruppeanalysen av anbefalte doser viste at LLLT reduserte smerte i større grad enn placebo, dog ikke signifikant (SMD = -4.05 (95% CI -11.22 to 3.13) I^2 = 97%, n = 44). Det samme gjaldt for de ikke-anbefalte dosene (SMD = -0.39 (95% CI -0.86 to 0.08) I^2 = 73%, n = 336).

Konklusjon: Resultatene indikerer at LLLT kan redusere TMDsmerter. Den statistiske heterogeniteten var høy, men var forårsaket av én enkelt, mindre studie. Flere studier med anbefalte doser fra WALT behøves i kartleggingen av et dose-respons-forhold.

Prospero-protokoll: Vedlegg.

Nøkkelord: TMD, temporomandibulær dysfunksjon, orofacial smerte, LLLT, lavenergi medisinsk laser, systematisk oversikt, metaanalyse

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1. INTRODUCTION

1.1. Rationale

1.1.1 Orofacial pain

Orofacial pain (OFP) ranks among the most common pain disorders and is experienced by over a quarter of the adult population (Macfarlane, Blinkhorn, Davies, Kincey, & Worthington, 2002). An association exists between orofacial pain and psychological distress (De La Torre Canales et al., 2018), which in turn can contribute to impair the patients`s quality of life and induce disability, loss of sleep, depression and anxiety (Natu, Yap, Su, Irfan Ali, & Ansari, 2018). Consequently, due to loss of workdays and increased use of healthcare, this condition is also considered to have a detrimental effect on society (Shueb, Nixdorf, John, Alonso, & Durham, 2015), with 100 billion dollars being spent yearly in the United States alone (List & Jensen, 2017).

1.1.2 Temporomandibular disorder

The international association for the study of pain (IASP) has declared temporomandibular joint disorder (TMD) as the most prevalent reason for chronic OFP (Benoliel et al., 2019), and its prevalence is perhaps comparable to that of low backpain, fibromyalgia and migraine (National Academies of Sciences et al., 2020). As the etiology and pathophysiology of it is not completely understood, TMD is an umbrella term, covering a set of symptoms stemming from both biological, biomechanical, physiological and neuromuscular factors (Tunér, Hosseinpour, & Fekrazad, 2019). IASP has defined the condition as pain, stiffness and fatigue of the jaws which involve both the temporomandibular joint (TMJ) with associated extraarticular structures and masticatory muscles as well (Hanna, Dalvi, Bensadoun, & Benedicenti, 2021).

While the incidence of TMD in Norway hasn’t been studied, reports from other countries show an incidence of approximately 3-15%. All age groups suffer from this, but young adults between the age of 20-45 years are overrepresented (Helsedirektoratet, 2016a). Rarely is TMD indicative of serious pathology, but in the cases where treatment is indicated, the aim is pain reduction and satisfactory gaping and chewing ability (Helsedirektoratet, 2016c)

1.2 Fundamental theory

1.2.1 Definition and symptoms

TMD is usually generated and maintained by several pathogenic drivers, both general and local. Examples of these are inflammatory conditions, trauma, psychosocial health, genetic predispositions and habits like pressing of the tongue against the teeth or jaw (Helsedirektoratet, 2016a).

Masticatory myalgia (muscle pain) is the most common symptom, experienced by 80% of patients with TMD. Typically, the pain can refer beyond the masticatory muscles to the eyes, ears or teeth (List & Jensen, 2017). Arthralgia (joint pain) frequently occurs alongside myalgia, but rarely as the only symptom (2% of cases). Arthralgia can be present with or without osteoarthritis (loss of joint cartilage). Another common joint related symptom is displacement of the temporomandibular meniscus, which often lead to clicking sounds during jaw movements. This is rarely a problem unless associated with catching and reduced mobility (List & Jensen, 2017). Other common symptoms include joint hypermobility, headaches, dizziness and changes in sound sensitivity (Helsedirektoratet, 2016a).

1.2.2 Inflammation

The Norwegian directorate of health emphasizes that TMD is a complicated multidimensional condition needed to be treated from a biopsychosocial framework (Helsedirektoratet, 2016a). Even so, clear evidence exists that inflammation plays an important role both in symptoms related to the joint and in the extra-articular structures. (Kopp, 2001). Larger quantities of the nociceptive neuropeptide serotonin have been found in hyperalgesic TMJs, as well as increased amounts of substance P (SP), calcitonin gene-related peptide (CGRP) and neuropeptide Y (NPY) in the synovial fluid of the joint. The cytokines tumor necrosis factor alpha (TNF- α) and interleukin-1 (IL-1) as well as the prostaglandins leukotriene B4 (LTB4), and Prostaglandin E2 (PGE2) have all been linked to pain and arthritis in the TMJ (Kopp, 2001).

1.2.3 Oxidative stress

Reactive oxygen species (ROS) are by-products of metabolic processes and mitochondrial activity in the body (Pizzino et al., 2017). These are associated with benign cellular functions, but can lead to oxidative stress with adverse effects if not detoxified appropriately by

antioxidants (Wade-Vallance et al., 2017). Oxidative stress (OS) is defined as this imbalance between the levels of ROS and antioxidants, which may result in tissue damage (Betteridge, 2000). OS and ROS have proven to be key factors in the pathogenesis of TMD, which happens trough several different pathways interchangeably interacting with inflammatory processes (Kawai, Lee, & Kubota, 2008). These include hypoxia reperfusion from mechanical stress, disruption of mitochondrial function and arachidonic acid catabolism (Wade-Vallance et al. 2017), that can lead to cartilage deterioration, increased joint friction and even anterior displacement of the articular meniscus in the TMJ (Wade-Vallance et al., 2017).

1.2.4 Treatment for TMD

Due to the complexity of TMD, several treatments have been applied to treat the disorder, including surgery (Reston & Turkelson, 2003), cognitive-behavioral therapy (Ferrando et al., 2012), acupuncture (Jung, Shin, Lee, Sim, & Ernst, 2011), non-steroidal anti-inflammatory drugs (NSAIDs), antidepressant medicines (Mujakperuo, Watson, Morrison, & Macfarlane, 2010), exercise therapy and manual therapy (Medlicott & Harris, 2006).

1.2.5 Photobiomodulation therapy

Photobiomodulation therapy (PBMT) in the form of light-emitting diode therapy (LEDT) and low-lever laser therapy (LLLT) in the red (600-700 nm) to near-infrared (770-1200 nm) spectrum has gained increasing interest over the years for its ability to induce healing, reduce pain and decrease inflammation (Hamblin, 2017). Shortly after the invention of laser in 1960, its potential for medical purposes was explored and demonstrated by accelerating fur-growth in mice and wound-healing in humans (Chung et al., 2012).

Since then, PBMT has developed into a therapeutic strategy for a wide array of conditions, including the treatment of inflammation and pain in chronic joint disorders (Jan M. Bjordal, Couppé, Chow, Tunér, & Ljunggren, 2003), regeneration of injured nerves (Gigo-Benato, Geuna, & Rochkind, 2005), stimulating healing of wounds (Posten et al., 2005) decreasing acute and chronic musculoskeletal pain (Chow, Johnson, Lopes-Martins, & Bjordal, 2009), and even enhancing sports performance of athletes and accelerating post-exercise recovery (Leal-Junior, Lopes-Martins, & Bjordal, 2019).

An increasingly recognized cellular pathway responsible for these effects are mediated by chromophores in our tissue molecules capable of absorbing photons, catalyzing biochemical processes (Leal-Junior et al., 2019). Cytochrome C-Oxidase, a chromophore in mitochondria, absorbs red and near-infrared light, which leads to increased oxygen consumption, enzyme activity and adenosine triphosphate (ATP) production (Hamblin, 2017).

1.2.5.1 PBMT´s effect on inflammation

The anti-inflammatory properties of PBMT have been quite reliably demonstrated (Hamblin, 2017). LLLT has shown to inhibit the inflammatory outcome of dendritic cells, which is plausible due to decreased activity of the transcription factor NF-Kb (A. C. H. Chen, Huang, Sharma, & Hamblin, 2011). In an experiment done on in vitro synoviocytes from rheumatoid arthritis patients showed that PBMT diminished TNF-α, IL-1 and 8 (Yamaura et al., 2009), and in a Norwegian randomized controlled trial (RCT) a reduction in prostaglandin E_2 from applying LLLT to patients with achilles tendonitis was observed (J. M. Bjordal, Lopes-Martins, & Iversen, 2006). The macrophage phenotype M1, which is associated with high production of inflammatory cytokines, has also been found to be reduced by PBMT in a study of rats inflicted with acute muscle injury (Souza et al., 2018).

1.2.5.2 Oxidative stress and the dose-response relationship of PBMT

One of the ways in which PBMT has been shown to work as an anti-inflammatory agent is trough decreasing OS and the production of ROS in inflammatory cells (Hamblin, 2017). Curiously, it is only when inflammation is present that biomarkers of OS decreases when PBMT is applied. Contrastingly, PBMT applied to healthy cells has shown to increase the production of ROS. Furthermore, both low (3 $J/cm^{2)}$ and high (30 J/cm^2) doses of laser applied to neurons have shown to increase ROS production to peak values compared to a moderate dosage of 10 J/cm^2 (A. C. H. Chen et al., 2011). This biphasic dose-response relationship is a well-known occurrence in PBMT experiments, where low levels of light regenerates tissues better than higher levels (Huang, Chen, Carroll, & Hamblin, 2009). The dose-response curve by Arndt-Schulz serves as an explanatory model for PBMT as well as many other medical and chemical substances (Huang et al., 2009).

1.3 Previous research on the topic

At least four systematic reviews concerning the effect of PBMT on TMD-induced pain have been published (Maia et al., 2012) (Xu et al., 2018) (Tunér et al., 2019) and (Hanna et al., 2021).

The most recent study was published on the 25.06.2021 under the title "Role of Photobiomodulation Therapy in Modulating Oxidative Stress in Temporomandibular Disorders. A Systematic Review and Meta-Analysis of Human Randomised Controlled Trials". This review included the results of 44 RCTs and featured a meta-analysis of 32 of them. The primary aims of the investigators were to identify the reasons for inconsistent findings of RCTs referring to lack of methodological quality, and to create clinical treatment guidelines and methodological instructions for the conduction of future higher quality RCTs.

They concluded that PBMT, including both LLLT and LEDT and the combination of these have a considerable positive effect on chronic pain, functional improvement and quality of life. In addition, the authors succeeded in constructing a framework for the above mentioned recommendations (Hanna et al., 2021).

However, no dose-response relationship investigation based on the World Association for Laser Therapy (WALT) treatment guidelines was conducted (Therapy). In a systematic review and meta-analysis from 2017 it was found that adhering to the WALT recommendations enhanced pain reduction in adults with musculoskeletal disorders (Clijsen, Brunner, Barbero, Clarys, & Taeymans, 2017). Such a dose-response relationship analysis could potentially reveal new insights into the optimal parameters of PBMT in TMJ as well, which was last revised in 2010 (Therapy).

2. OBJECTIVES

2.1 Motivation for choosing this topic

The Norwegian directorate of health do not find the evidence for LLLT satisfactory to recommend it as a treatment for TMD, as last revised in 2016 (Helsedirektoratet, 2016b). Moreover, only a scarce number of reputed guidelines recommend LLLT for musculoskeletal disorders (Lopes-Martins, Marcos, Leal-Junior, & Bjordal, 2018).

However, the LLLT research field is growing at a fast rate (Leal-Junior et al., 2019), as well does awareness and knowledge of the crucial importance of dose variables for successful clinical outcomes (Hanna et al., 2021). Stausholm et. Al. demonstrated this point prominently when a meta-analysis in a systematic review changed from negative to positive results from subgrouping the WALT-adherent trials together (Stausholm & Bjordal, 2021).

NSAIDs are commonly used for its analgesic effects in chronic pain from osteoarthritis and several other musculoskeletal disorders. A risk for fatal events relating to the cardiovascular, gastrointestinal and central nervous systems exists, and increases with age (Marcum & Hanlon, 2010).

Contrary to this, side effects reported from LLLT are neglectable (Chung et al., 2012). As a master student in musculoskeletal physiotherapy and a clinician of physical medicine, I recognize this potentially low-risk high-benefit treatment modality as an exciting supplement to our profession. The research group of physiotherapy at the University of Bergen has extensive research experience with LLLT and inflammation, and I consider this a great resource when choosing this topic for my master thesis.

2.2 Objective and hypothesis

- **Context**: Optimal variables relating to dossing of LLLT for treating people suffering from TMD have not been well established.
- **Objective**: To estimate the effectiveness of LLLT on pain in chronic TMD.
- **Hypothesis**: LLLT reduces pain in people with chronic TMD.
- **Focused question**: What is the optimal energy density and irradiation time for reducing pain in people with chronic TMD?

3. METHODS:

3.1 Protocol and registration

To reduce the risk of reviewer selection bias, a prospectively registered review protocol has been published via PROSPERO (reference number). It should be noted that the protocol describes a more comprehensive project planned for publication as a journal article. Due to this master thesis´ limited scope of 30 credits, it deviates from the protocol in the following ways:

1. Only the ten most recent studies were selected
2. Eligibility criteria restricted to “chronic TMD”
3. No additional outcomes concerning disability
4. No objective measures of pain besides self-reported scales
5. No comparison with conservative treatment
6. No follow-up assessment beyond 8 weeks
7. No assisting reviewer for trial selection, data extraction and risk of bias assessment
8. No sources for literature search beyond PubMed and Embase. No screening of reference lists of included trial articles and systematic reviews. No contacting of field experts.

The review was reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to ensure that the most common generic information was available (Page et al., 2021). The 27-item checklist is attached as a supplementary file. In addition, where presented with methodological difficulties, the Cochrane handbook of systematic reviews was utilized. The Cochrane collaboration is a network of researchers dedicated to increase the methodological quality of health-promoting science, with the end goal of promoting evidence-based decision-making (Jacqueline Chandler, 2022).

3.2 Research design

The research design in this thesis was a systematic review of randomized placebo-controlled trials. The RCT compares two or more groups receiving an intervention or control treatment over a set period of time, comparing intergroup-outcome and evaluating the effectiveness of the treatment (Helsebiblioteket, 2016). The RCT is considered the gold-standard for examining the effects of treatments (Svartdal, 2018), and is classified as a prospective, experimental study-design (Hariton & Locascio, 2018).

The power of the RCT lies in, for example, the randomization process, because potential confounding variables presented in participant characteristics is balanced between the groups, allowing us in the most certain degree possible to establish a causal relationship between the independent (intervention) and dependent (outcome) variables (Hariton & Locascio, 2018). Observational designs like cohorts and case-control studies are often cheap, practical options for uncovering correlations for etiological purposes, but are not valid for establishing

direction/causation, due to participant exposures not being controlled for, a significant risk of bias and to result validity (Hess & Abd-Elsayed, 2019).

The statistical power of the RCT will increase the more participants who participate in it. These criteria must to a large extent be adapted to the framework of what is practically feasible in reality. For example, an RCT with 10000 participants divided into 100 intervention groups is not realistic to conduct. A systematic review provides the opportunity of summarizing all the empirical evidence from every available study that fits our pre-specified eligibility criteria to test our hypothesis (Liberati et al., 2009a). The international group behind PRISMA defines the key characteristics of a systematic review as: "*1) a clearly stated set of objectives with an explicit, reproducible methodology; (2) a systematic search that attempts to identify all studies that would meet the eligibility criteria; (3) an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and (4) systematic presentation, and synthesis, of the characteristics and findings of the included studies.*" (Liberati et al., 2009a). In evidence-based medicine, a hierarchy of evidence has been illustrated as a pyramid with increasing validity from bottom to top, ranking the systematic review of RCTs the highest quality evidence (Murad, Asi, Alsawas, & Alahdab, 2016).

3.3 Eligibility criteria

Table I: PICOs

Population	Both genders of adult age diagnosed with temporomandibular disorder with a mean duration of ≥3 months
Intervention	Low-Level Laser Therapy
Comparison	Placebo/sham Low-Lever Laser Therapy
Outcome	Patient-reported pain intensity
Study design	Randomized controlled trials

Inclusion criteria

- Any identified study was included if it was a RCT involving participants with a mean age of ≥18 years with a mean duration of symptoms of ≥ 3 months, in which the effectiveness of LLLT was compared to placebo/sham LLLT, and outcome measures for patient-reported TMJ-related or masticatory muscle-pain was reported.

Study characteristics:

- Articles published in English or Nordic languages.
- The 10 most recent published articles found eligible for inclusion were chosen.
- There were two timepoints of assessment for the meta-analysis, that is 1) immediately after completed therapy and 2) last timepoint of assessment 1-8 weeks after completed therapy.

3.4 Outcome measures

Primary outcome: The primary outcome was pain intensity measured with patient-reported psychometric tools, for example, the visual analogue scale (VAS) or numeric rating scale (NRS) (Chiarotto et al., 2019).

If more than one pain scale were available from a record, a scale was selected for data-extraction in the following prioritized order:

1) Visual Analogue Scale (VAS) pain
2) Numeric Rating Scale (NRS)
3) Other pain scales

Secondary outcomes:

No additional outcomes were selected, as the predicted total volume of data would be too substantial to handle in this thesis.

3.5 Information sources:

A literature search for eligible articles indexed in PubMed and Embase was conducted 3 June 2022. No restrictions were checked off in the database search engines, nor was any restrictions on publication year imposed.

3.6 Search

The search terms were developed using medical subject headings (MeSH), Embase subject headings (Emtree) and text words related to PBMT and TMD listed in the two databases thesauruses. From this, the following search string was fabricated and applied for the PubMed search and adjusted to Embase respectively:

(Low-Level Light Therapy [Mesh] OR LLLT [Title/Abstract] OR low level [Title/Abstract] OR low power [Title/Abstract] OR laser therap*[Title/Abstract] OR laser acupuncture [Title/Abstract] OR HeNe [Title/Abstract] OR 632 nm [Title/Abstract] OR Ga-Al-As [Title/Abstract] OR 820 nm [Title/Abstract] OR 830 nm [Title/Abstract] OR 850 nm [Title/Abstract] OR GaAs [Title/Abstract] OR 904 nm [Title/Abstract]) AND (Temporomandibular Joint Disorders [MeSH Terms] OR temporomandibular [Title/Abstract] OR TMJ disorder* [Title/Abstract] OR TM disorder* [Title/Abstract] OR TM pain [Title/Abstract] OR TMJ pain [Title/Abstract] OR TMD [Title/Abstract] OR myofascial pain [Title/Abstract] OR craniomandibular disorder* [Title/Abstract] OR mandibular dysfunction* [Title/Abstract] OR osteoarthr* [Title/Abstract])

3.7 Study selection:

Phase one consisted of eliminating records based of reading only titles and abstracts of all combined articles collected from PubMed and Embase, with close attention to the eligibility criteria. The “EndNote 20” software was applied for this purpose, which also allowed quick removal of duplicate records.

As some abstracts did not provide adequate information, phase two involved the retrieval of these articles in full-text format for a thorough examination.

Only I as a single reviewer conducted the complete process of selecting studies for inclusion. Not involving a second reviewer increases the risk of overlooking relevant articles, and for misjudging the methodological suitability of eligibility (Page et al., 2021). Thus, validity is somewhat threatened. Compensating for this, consulting my supervisor when in doubt allowed for some degree of inter-rater agreement. The final decision for inclusion was mine.

3.8 Data collection process and data items

The process of extracting data was conducted by me alone. Inspiration for relevant data-items concerning study characteristics and laser-treatment characteristics was obtained from a systematic review of similar design to mine (M. B. Stausholm et al., 2019).

Items related to study characteristics encompassed both the intervention and control groups and consisted of: number of participants, number of women, mean age of participants, BMI of participants, baseline pain score, a description of and durations of intervention and control programs, outcome-measure scales utilized, and the relevant timepoints of assessment according to this review's objectives.

Items related to laser therapy consisted of: area treated, wavelength in nanometers (nm), joules per treatment spot, mean output power (mW), seconds per treated spot, number of spots treated and session/sessions per week.

In addition to the summarized analysis, the results of individual studies are reported in the supplementary files-section. This makes it easier to identify potential data extraction errors in the meta-analysis, a commonly occurring phenomenon (Page et al., 2021).

As self-reported pain on the VAS and NPRS follows a continuing sequence, the required data for a meta-analysis of this outcome are mean (M), standard deviation, and sample of each group at the time of analysis (Page et al., 2021). Mean final scores were selected, not mean change scores. Where numerical values were only presented graphically in figures, data was extracted manually by the use of a ruler, in accordance with the Cochrane handbook (Li T, 2022).

Challenges with missing data were handled by the following methods:

1. Where neither SD or alternative variance data were reported, SD was imputed from the mean SD of the other included trials´ (with similar assessment timepoints) respective intervention or control groups, a standardized method for handling missing variance data (Follmann, Elliott, Suh, & Cutler, 1992).
2. Alternative variance data occurred as interquartile-range (IQR), which was handled by conversion by the formula: IQR/1.35 (Julian PT Higgins, 2022).

3. Point estimates occurred as median instead of mean, handled by directly interpreting the median as mean (Michiels et al., 2005).

In addition, the authors of two included trials were contacted due to missing data. The first of these articles (Rodrigues, 2020), a parallel analysis to a RCT not referenced to, did not report baseline participant pain. The second article did not report SDs or alternative variance data for calculating SD in the 8-week follow-up assessment. Unfortunately, neither author replied to my e-mails.

Approximately 1 week after the data-extraction, data was checked again to reduce the risk of reporting-errors. This inspection was repeated several times after.

3.9 Assessment of risk of bias within studies

Certain aspects of the methodological validity of a randomized controlled trial have the potential to influence its reflection of truth. For example, trials that lack group allocation concealment has been shown to exaggerate the reported treatment effect (Pildal et al., 2007). The Physiotherapy Evidence Database´ checklist (PEDro) is a valid measure of the methodological quality of clinical trials (de Morton, 2009). Thus, the PEDro 11-point checklist was used to score each included trial to determine their validity. Only one reviewer assessed risk of bias within studies in this review.

3.10 Planned methods of analysis

The trials were subgrouped according to adherence to the WALT treatment recommendations (Therapy). WALT recommends using a minimum of 2 joules/point with an irradiation time of 30-600 seconds with 904 nm wavelength laser. They also recommend using a minimum of 4 joules/point with an irradiation time of 20-300 seconds with a 780-860 nm wavelength laser. Trials were classified as adhering to WALT if following the guidelines both related to joules/point, irradiation duration, and wavelength.

All the meta-analyses were performed utilizing a random effects model, due to the diverse nature between the individual trials. This model, in contrast to a fixed effects model which assumes all variation in effect stems from the participants, assumes that small variations exist from experiment to experiment as well (DerSimonian & Kacker, 2007). The influence of heterogeneity was assessed with I^2 statistics, where values was interpreted as follows: 25% =

low, 50% = moderate, 75% = high (Higgins, Thompson, Deeks, & Altman, 2003). The synthetization of pain results was done using the Hedges´g standardized mean difference (SMD) method. The SMDs was interpreted in accordance with the Cochrane handbook, where 0.2, 0.5, and 0.8 indicate a small, moderate, and large effect, respectively (Julian Higgins, 2021). As pain scores reported on VAS and NPRS highly correlates, they were regarded identical.

4. RESULTS

4.1 Study selection

The 10 most recent trials fitting the eligibility criteria were identified for inclusion in this review. A total of 1748 trials were obtained from the search in PubMed (726) and Embase (1022). 1336 remained after removal of duplicates. Of these, 1253 records were rejected because it was clear from reading the titles and abstracts that these records did not meet the inclusion criteria. Among the 83 remaining articles, four studies were discarded from not being available online in full text. 60 records sorted by publication date (most recent first) was thoroughly assessed in full-text before identifying 10 eligible trials. During this process of reading full-text studies, one study failed to report output power, interpreted as “not LLLT”. One study failed to report participant age, interpreted as “different age group”. One study used LLLT on the ear (auriculotherapy), which is not the TMJ, nor masticatory muscles, whilst another used LLLT on acupoints spread across the whole body. One study compared active LLLT + placebo drugs with placebo LLLT + active drugs, which did not qualify as a valid placebo comparator. For a complete overview of the study selection process with reasons for exclusion, see Figure 1 and Table II below.

Figure 1: Flow diagram of the study selection process. Retrieved from PRISMA Statement: (Page et al., 2021)

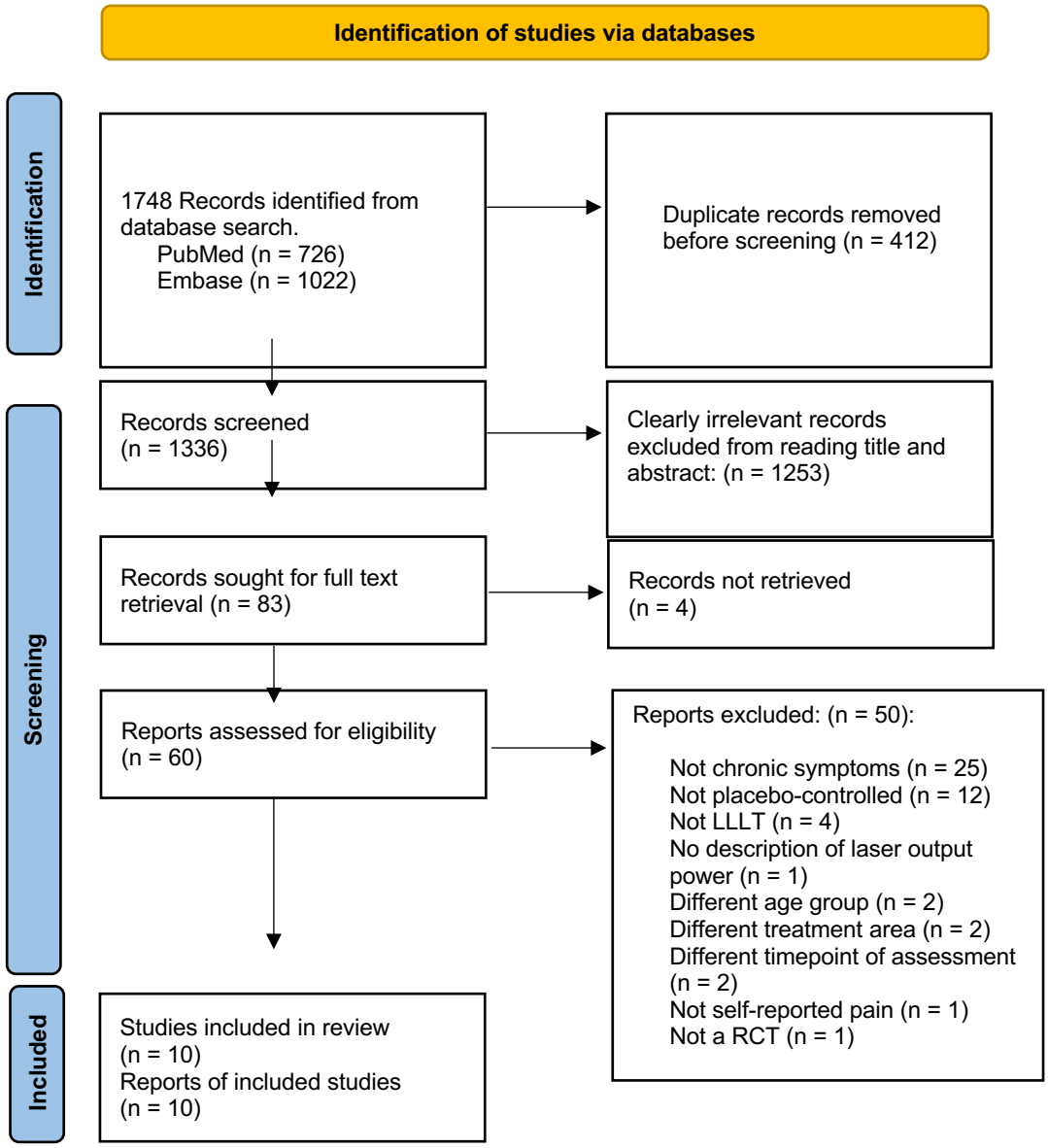

Table II: Table of excluded trials

First author	Reason for exclusion
Ferreira, 2013	Treatment applied to acupoints in the whole body
Uemoto, 2013	Not chronic pain
Ahrari,2014	Not chronic pain
Demirkol, 2014	Not chronic pain
Madani, 2014	Not chronic pain
Pereira, 2014	Not placebo-controlled
Fornaini, 2015	Not chronic pain
Leal de Godoy, 2015	Not the correct age group
Panhoca, 2015	Not placebo-controlled
Cavalcanti, 2016	Not chronic pain
De Carli, 2016	Not placebo-controlled
Khalighi, 2016	Not properly placebo-controlled
Machado, 2016	Not self-reported pain
Molina-Torres, 2016	Not placebo-controlled
Costa, 2017	Not chronic pain
Demirkol, 2017	Not chronic pain
Hosgor, 2017	Not placebo-controlled
Rezazadeh, 2017	Not placebo-controlled
Seifi, 2017	Not chronic pain
Shobha, 2017	Not chronic pain
F. T. Brochado, 2018	Not placebo-controlled
H. M. Elgohary,, 2018	Not placebo-controlled
Manfredini 2018	Not LLLT
Pihut 2018	Not LLLT (no description of laser output power)
Sveshtarov 2018	Not chronic symptoms
Altindis 2019	Not chronic symptoms
Barbosa 2019	Not LLLT
Khairnar 2019	Not placebo-controlled
Mansourian 2019	Not placebo-controlled
Rodrigues 2019	Treatment area not TMJ or masticatory muscles
Abbasgholizadeh, 2020	Not chronic pain
Azangoo Khiavi, 2020	Not chronic pain
Brignardello-Petersen, 2020	Different timepoint of assessment
Brignardello-Petersen, 2020	Not chronic pain
Chellappa, 2020	Participant age not reported
De Oliveira Chami, 2020	Not chronic pain
Herpich, 2020	Not chronic pain
Maracci, 2020	Not chronic pain

Nadershah, 2020	Not chronic pain
Tunc, 2020	Not chronic pain
Yamaner, 2020	Not chronic pain
Aisaiti, 2021	Not chronic pain
El Zawahry, 2021	Not LLLT
Eraslan, 2021	Not chronic pain
Fetai, 2021	Not LLLT
Magri, 2021	Different timepoint of assessment
Shousha, 2021	Not chronic pain
Tanhan, 2021	Not chronic pain
Yanik, 2021	Not a RCT
Khalighi, 2022	Not placebo-controlled

4.2 Characteristics of included studies

4.2.1 Population:

The included trials involved 423 participants for which the mean age was 33.3 years varying between 27.7-49.9 years in the intervention groups and 32.5 years varying between 25.6-46.6 years in the control groups (data from 10 trials). The mean percentage of women was 86.6%, varying between 70-100% (data from 9 trials). 7/10 trials did not report body mass index of the participants. The mean baseline pain was 61.2 mm, varying between 40.4-80.0 mm (9 trials), reported on VAS in 8 trials and NPRS in 1 trial. Eight studies diagnosed their subjects according to the Research Diagnostic Criteria for Temporomandibular Disorder (RDC/TMD) or to the revised version DC/TMD (Schiffman et al., 2014). In one of the two remaining trials (Nambi, 2022) patients with healed unilateral cervicofacial burns were diagnosed 6 months post injury with temporomandibular joint- and orofacial pain, but the term “TMD” was not used. The mean duration of TMJ- and orofacial pain was at least 3 months in all the included trials. For further details, see Table III.

Table III: Characteristics of the included trials

First author	Intervention group at baseline	Control group at baseline	Intervention vs. Control programme	Outcome scales, week of reassessment (timepoint for meta-analysis in bold)
Nambi, 2022	N: 18 Women: - Age: 31.3 ± 2.1 BMI: 23.2 ± 1.4 NPRS pain: 70.1 mm ± 0.6	N: 18 Women: - Age: 30.5 ± 2.6 BMI: 22.9 ± 1.5 NPRS pain: 60.9 mm ± 0.5	4 weeks of regular physiotherapy care + LLLT vs. 4 weeks of regular physiotherapy care + sham LLLT	Pain: NPRS Week of assessment: 0, **4, 8,** 26
Del Vecchio, 2021	N: 30 Women: 86.6% Age: 39.04 ± 15.28 BMI: - VAS pain: 65.52 mm ± 17.44	N: 30 Women: 83.3% Age: 42.45 ± 12.52 BMI: - VAS pain: 74.48 mm ± 13.25	1 week of LLLT vs. 1 week of sham LLLT	Pain: VAS Week of assessment: 0**, 1**
Benli, 2021	N: 31 Women: 80% Age: 49.93 ± 6.23 BMI: 26,8 VAS pain: 80 mm ± 15	N: 30 Women: 86.7% Age: 46.6 ± 6.85 BMI: 26,4 VAS pain: 80 mm ± 15	4 weeks of LLLT vs. (4 weeks is assumed but duration is not mentioned) of sham LLLT	Pain: VAS Week of assessment: 0, **4, 8**
Rodrigues, 2020	N: 34 Women: 100% Age: 31.94 ± 9.57 (in total, all groups) BMI: - VAS pain: Not reported	N: 33 Women: 100% Age: 31.94 ± 9.57 (in total, all groups) BMI: - VAS pain: Not reported	4 weeks of LLLT vs. 4 weeks of sham LLLT	Pain: VAS Week of assessment: 0, **4, 8**
Monteiro, 2020	N: 22 Women: 77.3% Age: 29,1 ± 11 BMI: - VAS pain: 40.59 mm ± 20.36	N: 20 Women: 75% Age: 25.6 ± 8 BMI: - VAS pain: 40.45 mm ± 20.6	4 weeks of LLLT vs. 4 weeks of sham LLLT	Pain: VAS Week of assessment: 0, **8**

Magri, 2018	N: 20 Women: 100% Age: 32.7 mm (5.4) BMI: - VAS pain: 50.2	N: 21 Women: 100% Age: 29.8 mm (4.3) BMI: - VAS pain: 40.7	4 weeks of LLLT vs. 4 weeks of sham LLLT	Pain: VAS Week of assessment: 0, **4, 8**	

First author	**Intervention group 1 ($8J/cm^2$) at baseline**	**Intervention group 2 ($60J/cm^2$) at baseline**	**Intervention group 3 ($105J/cm^2$) at baseline**	**Placebo at baseline**	**Intervention vs. Control programme**	**Outcome scales, week of reassessment**
Borges, 2018	N: 11 Women: 100% Age: 35.82 ± 13.77 BMI: 23.2 ± 1.4 VAS pain: 70.1 mm ± 0.6	N: 11 Women: 90% Age: 27.73 ± 9.75 BMI: 23.2 ± 1.4 VAS pain: 70.1 mm ± 0.6	N: 11 Women: 78% Age: 34.82 ± 15.28 BMI: 23.2 ± 1.4 VAS pain: 70.1 mm ± 0.6	N: 11 Women: 90.9% Age: 29.45 ± 12.45 BMI: 23.2 ± 1.4 VAS pain: 70.1 mm ± 0.6	3 weeks of LLLT ($8J/cm^2$) vs. 3 weeks of LLLT ($60J/cm^2$) vs. 3 weeks of LLLT ($105J/cm^2$) vs. sham LLLT	Pain: VAS Week of assessment: 0, **3**

First author	**Intervention group 1 at baseline**	**Intervention group 2 at baseline**	**Control group at baseline**	**Intervention vs. Control programme**	**Outcome scales, week of reassessment**
Sancakli, 2015	N: 10 Women: 70% Age: 30.80 ± 9,81 BMI: - VAS pain: 62.65 mm ± 10.42	N: 10 Women: 70% Age: 29.33 ± 8.59 BMI: - VAS pain: 58.38 mm ± 7.25	N: 10 Women: 70% Age: 31.94 ± 12.20 BMI: - VAS pain: 53.31 mm ± 8.79	4 weeks of LLLT (greatest pain points in masseter and temporalis) vs. 4 weeks of LLLT (6 pre-defined points in masseter and temporalis) vs. 4 weeks of sham LLLT	Pain: VAS Week of assessment: 0, **4**

First author	**Intervention group 1 at baseline**	**Control group at baseline**	**Intervention vs. Control programme**	**Outcome scales, week of reassessment**
De Moraes Maia, 2014	N: 12 Women: 90.5 % in total, both groups Age: 27.76 ± 10.44 in total, both groups BMI: - VAS pain: 80mm (70-90) median and interquartile-range	N: 9 Women: 90.5 % in total, both groups Age: 27.76 ±10.44 in total, both groups BMI: - VAS pain: 60mm (50-80) Median and interquartile-range	4 weeks of LLLT vs. 4 weeks of sham LLLT	Pain: VAS Week of assessment: **4, 8**

De Carli, 2013	N: 11 Women: 90.6% (in total, all groups) Age: 34 BMI: - VAS pain: 48mm	N: 10 Women: 90.6% (in total, all groups) Age: 29.4 BMI: - VAS pain: 41.3mm	10 days of LLLT + piroxicam vs. 10 days of sham LLLT + piroxicam	Pain: VAS Week of assessment: 0, 1, **2, 6**

The values for age, BMI, NPRS and VAS are means and standard deviations (SD) unless stated otherwise. N, number; BMI, body mass index; NPRS, numeric pain rating scale; mm, millimeter; LLLT, low level laser therapy; VAS, visual analogue scale; j/cm^{2,} joules/square centimeters.

4.2.2 Intervention:

The mean LLLT period duration was 3.4 weeks, varying between 1 and 4 weeks. LLLT was used as an adjunct to regular physiotherapy care in one study, and to drugs (piroxicam) in one study. Treated area varied between studies. Del Vecchio, 2021 and Borges, 2018 treated only the TMJ, Sancakli, 2015 and De moraes Maia, 2014 treated only masticatory muscles while Nambi, 2022; Rodrigues, 2020; Monteiro, 2020; Magri, 2018 and De Carli, 2014 treated both. One study used a laser with a wavelength of 635 nm which is shorter than the minimal recommended wavelength of 780 nm (Therapy). Eight studies used a laser device within the recommended wavelength of 780-860nm while one study used a device with 905nm which is also recommended. One study treated three intervention groups with LLLT; each with a different dose. One study treated two intervention groups with LLLT; one where the most painful muscle spots were irradiated and one where three predetermined points per related muscle were irradiated. In one study the patients treated themselves (after one introductory treatment by a therapist) at home, twice daily with the LLLT device for only 1 week.

Three trials (Nambi,2022; Monteiro, 2020 and Borges 2018 60J/cm^2) followed the WALT treatment recommendations for both joules/point and irradiation time. Monteiro used a 635 nm wavelength laser which is in the red, visible spectrum and is not included in the WALT guidelines. Therefore, nine trials were categorized as “not recommended” (Del Vecchio, 2021; Benli, 2021; Monteiro, 2020; Rodrigues, 2020; Magri, 2018; Borges 2018 8J/cm^2; Borges, 2018 105J/cm^2; Sancakli, 2015; De Moraes Maia 2014 and De Carli 2013). For further intervention details, see Table IV.

Table IV: Laser therapy variables of the included trials

First author	Treated area	Wavelength (nm)	Joules per treatment spot	Mean output power (mW)	Seconds per treated spot	Number of spots treated	Sessions/ sessions per week	Dose recommended by WALT
Nambi, 2022 TMJ + Muslces	Phase 1: Temporomandibular joint region Phase 2: Masseter and temporalis muscles	905	Phase 1: 6 Phase 2: 1.5 = 3.75	25	Phase 1: 240 Phase 2: 60	Phase 1: 1 Phase 2: 4	12/3	Joules per spot: Yes Seconds: Yes
Del Vecchio, 2021 TMJ	Temporomanidbular joint	808	40	250	480	1	14/14	Joules per spot: Yes Seconds: No
Benli, 2021 Muscles	Masseter- and anterior temporalis muscles	808	1.9	100	19	5 per muscle=10	8/2	Joules per spot: No Seconds: No
Rodrigues, 2020 TMJ + Muslces	Temporomandbular joint, masseter and temporalis muscles	780	TMJ: 3 Muscles: 1.2 = 2.1	60	TMJ: 50 Muscles: 20	TMJ: 5 Facial muscles: 4	8/2	Joules per spot: No Seconds: Yes
Monteiro, 2020 TMJ + Muslces	The laser beam was applied over the sensitive points where the pain was reported by the participants as recorded in the diagnostic questionnaire, which involved the TMJ, mandible and masticatory muscles	635	4	200mW	20	Depending of painful points at palpation (average of 4 points per side)	4/1	Joules per spot: Yes Seconds: Yes Wavelength: No

Magri, 2018 TMJ + Muslces	TMJ, temporalis and masseter muscles	780	TMJ: 0.3 Muscles: 0.2	TMJ: 30 Muscles: 20	10	TMJ: 4 Temporalis: 3 Masseter: 3	8/2	Joules per spot: No Seconds: No
Borges 2018 Intervention group 1 (8J/cm2) TMJ	4 application points for each temporomandibular joint. The application points were in the preauricular region and in the external acoustic meatus	830	0.96	30	32	Four for each side	10/3	Joules per spot: No Seconds: Yes
Borges 2018 Intervention group 2 (60J/cm2)	4 application points for each temporomandibular joint. The application points were in the preauricular region and in the external acoustic meatus	830	7.2	30	240	Four for each side	10/3	Joules per spot: Yes Seconds: Yes
Borges 2018 Intervention group 3 (105J/cm)	4 application points for each temporomandibular joint. The application points were in the preauricular region and in the external acoustic meatus	830	12.64	30	420	Four for each side	10/3	Joules per spot: Yes Seconds: No
Sancakli, 2015 LLLT group 1 Muscles	The greatest points of pain in the related muscle (masseter and/ or temporalis)	820	3	300	10	?	12/3	Joules per spot: No Seconds: No
Sancakli, 2015 LLLT group 2	In the same manner to three predetermined points on the	820	3	300	10	6	12/3	Joules per spot: No Yes

	masseter muscle (superior, middle, and inferior points) and three points on the temporalis muscle (anterior, middle, and posterior points)							Seconds: No
De Moraes Maia, 2014 **Muscles**	At the trigger points of the anterior temporal and masseter muscles, five points were applied on each muscle, four forming a cross and one a central point	808	1.9	100	19	10	8/2	Joules per spot: No Seconds: No
De Carli, 2013 **TMJ** + **Muslces**	Directly on the skin at 10 points on each side: joint capsule (lateral, posterior, superior, anterior, inferior), masseter (origin, insertion) and temporal (anterior, middle, posterior)	808	2.8	100	28	10	4/2	Joules per spot: No Seconds: Yes

TMJ, temporomandibular joint; nm, nanometer; mW, milliwatt; WALT, Word Association for Laser Therapy.

4.2.3 Outcome:

Whether pain intensity assessments reflected "present time", mean/or worst pain experienced in the last couple of days, last week, at rest or during activity etc., was in the majority of trials not adequately reported. Three trials assessed pain felt at the present time of assessment (Benli, 2021; Rodrigues, 2020 and De Moraes Maia, 2014). The remaining trials did not provide further details other than that self-reported pain intensity was measured with VAS/NPRS. Rodrigues, 2020 aimed to assess if TMD symptom severity correlated with the analgesic effect from LLLT and placebo, and so reported the VAS scores separately for three severity-graded groups. For this review, the mean results between all three groups were combined. Magri 2018 aimed to differentiate between responders and non-responder to active

and placebo LLLT, and therefore subgrouped subjects according to anxiety levels, salivary cortisol, use of oral contraceptives and premenstrual period. As this subgroup analysis is irrelevant to this review, only the total VAS scores were extracted. For an overview of all assessment timepoints, see Table III.

4.3 Risk of bias within studies

Table V: Summary table of PEDro scores of all included trials by the author of this review. Official PEDro score of one included trial.

Study ID	1	2	3	4	5	6	7	8	9	10	11	Total	Quality
Nambi, 2022 My score	+	+	+	+	+	-	+	+	+	+	+	9/10	High
Offical PEDro score													
Del Vecchio, 2021	-	+	-	+	+	+	+	+	+	+	+	9/10	High
Offical PEDro score													
Benli, 2021	+	+	-	+	+	-	-	+	+	+	+	7/10	High
Offical PEDro score													
Monteiro, 2020	+	+	+	+	+	-	+	+	-	+	+	8/10	High
Offical PEDro score													
Rodrigues, 2020	-	+	+	-	+	+	-	+	-	+	-	6/10	Moderate
Offical PEDro score													

Magri, 2018	+	+	+	+	+	+	+	-	-	+	+	8/10	High
Offical PEDro score													
Borges, 2018	-	+	-	+	+	+	+	+	-	+	+	8/10	High
Offical PEDro score	+	+	-	+	+	-	+	+	-	+	+	7/10	High
Sancakli, 2015	+	+	-	+	+	+	+	-	+	-	+	7/10	High
Offical PEDro score													
De Moraes Maia, 2014	+	+	-	-	-	-	-	-	-	-	+	2/10	Low
Offical PEDro score													
De Carli, 2013	+	+	-	+	+	+	+	-	-	+	+	7/10	High

Item number explanation:

1. Eligibility criteria not specified
2. Random allocation
3. Concealed allocation
4. Groups similar at baseline
5. Subject blinding
6. Therapist blinding
7. Assessor blinding
8. Less than 15% dropout
9. Intention-to-treat analysis
10. Between-group statistical comparisons
11. Point measures and variability data

Eight of the included trials (80%) were rated to be of high methodological quality, one to be of moderate- and one of low methodological quality. All trials featured sufficient randomization, while adequate allocation concealment only occurred in four trials (40%). Eight trials (80%) had groups that were similar at baseline. The subjects were blinded in nine trials (90%), therapist blinded in six trials (60%) and assessors blinded in seven (70%) trials. Measures of outcomes were available from more than 85% of participants in six (60%) trials. Intention-to- treat analysis was applied in four (40%) trials. Between-group statistical comparisons were present in eight (80%) trials. Point-measures and measures of variability were present in nine (90%) trials. In the trial in which this point was not achieved, variance data was the missing data item. The lack of allocation concealment and intention-to-treat analysis were the two most frequent methodological inadequacies. Because the author of this thesis was alone in the task of judging the risk of bias, the official scorings in the PEDro database was sought for comparison. Only one of the included trials in this thesis was available in the PEDro database, of which disagreed with my judgement on just a single relevant point (therapist blinding).

Table VI: Support for risk of bias judgments.

Nambi, 2022		**Score: 9/10**
Type of bias:	**Judgment**	**Support for judgment**
Eligibility criteria were specified	Yes	Page 406.
Subjects were randomly allocated to groups	Yes	Quote: "*…by two block randomization method and allocated through sealed envelopes*."
Allocation was concealed	Yes	Quote: "*allocated through sealed envelopes*."
The groups were similar at baseline	Yes	Table 1 and 2
There was blinding of all subjects	Yes	Page 407
There was blinding of all therapists	No	Quote: "*Due to the design and settings of the study, it was not possible to blind the treating therapist"*
There was blinding of all assessors	Yes	Page 407
Measures of at least one key outcome obtained >85% of the participants	Yes	Figure 1
Intention to treat	Yes	Quote: "*All the participants completed the four weeks of treatment"*
The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Table 3
The study provides both point measures and measures of variability for at least one key outcome	Yes	Table 2

Del Vecchio, 2021		**Score: 9/10**
Type of bias:	**Judgment**	**Support for judgment**
Eligibility criteria were specified	No	The source of subjects is not described.
Subjects were randomly allocated to groups	Yes	"*The web Research Randomizer® free resource for researchers was used for randomization*"
Allocation was concealed	Unclear	Not enough information to make a qualified judgement
The groups were similar at baseline	Yes	Table 2, 3 and 4
There was blinding of all subjects	Yes	"*In both groups, SG and PG, neither the patients nor the examiner knew whether the device was effective or not*"
There was blinding of all therapists	Yes	The therapists were the subjects themselves, delivering the LLLT to themselves at home
There was blinding of all assessors	Yes	"*In both groups, SG and PG, neither the patients nor the examiner knew whether the device was effective or not*"
Measures of at least one key outcome obtained >85% of the participants	Yes	Figure 2
Intention to treat	Yes	Figure 2
The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Table 6
The study provides both point measures and measures of variability for at least one key outcome	Yes	Table 4

Benli, 2021		**Score: 7/10**
Type of bias:	**Judgment**	**Support for judgment**
Eligibility criteria were specified	Yes	Page 2
Subjects were randomly allocated to groups	Yes	Quote: "*Group allocation was based on a single-blind rando- mized controlled trial, and the random sampling method was conducted by using a web-based number generator*"
Allocation was concealed	Unclear	Not enough information to make a qualified judgement
The groups were similar at baseline	Yes	Figure 2
There was blinding of all subjects	Yes	Quote: "*The limitations of the present study are a short span for follow-up, the predominance of female samples, one- way therapy application, single blinding…"*
There was blinding of all therapists	No	Quote: "*The limitations of the present study are a short span for follow-up, the predominance of female samples, one- way therapy application, single blinding*"
There was blinding of all assessors	No	Quote: "*The limitations of the present study are a short span for follow-up, the predominance of female samples, one- way therapy application, single blinding*"
Measures of at least one key outcome obtained >85% of the participants	Yes	Figure 1
Intention to treat	Yes	Figure 1
The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Table 2
The study provides both point measures and measures of variability for at least one key outcome	Yes	Page 5

Monteiro, 2020		**Score: 8/10**
Type of bias:	**Judgment**	**Support for judgment**
Eligibility criteria were specified	Yes	Page 281
Subjects were randomly allocated to groups	Yes	Quote: «Patients were randomly divided into two groups, an intervention laser group (n = 22) and the placebo group (n = 20 for analysis), using a lottery method performed during the diagnostic visit. For randomization, each patient selected a sealed envelope having a card corresponding to one of the possible groups and indicated by a code letter. The code was blinded to the patient and to the clinical evaluaton»
Allocation was concealed	Yes	Quote: "For randomization, each patient selected a sealed envelope having a card corresponding to one of the possible groups and indicated by a code letter. »
The groups were similar at baseline	Yes	Table 2
There was blinding of all subjects	Yes	Quote: "For randomization, each patient selected a sealed envelope having a card corresponding to one of the possible groups and indicated by a code letter. The code was blinded to the patient and to the clinical evaluator. »
There was blinding of all therapists	No	Not reported
There was blinding of all assessors	Yes	Quote: «*For randomization, each patient selected a sealed envelope having a card corresponding to one of the possible groups and indicated by a code letter. The code was blinded to the patient and to the clinical evaluator*."
Measures of at least one key outcome obtained >85% of the participants	Yes	Figure 1
Intention to treat	Unclear	Not enough information to make a qualified judgement
The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Table 3
The study provides both point measures and measures of variability for at least one key outcome	Yes	Table 3

Rodrigues, 2020		**Score: 6/10**
Type of bias:	**Judgment**	**Support for judgment**
Eligibility criteria were specified	No	Source of participants not mentioned.
Subjects were randomly allocated to groups	Yes	Quote: "*Women who fulfilled the criteria described above were randomly selected by lottery method to receive active laser or placebo"*
Allocation was concealed	Yes	Quote: "*The lottery was performed after the initial assessment of the patients; a total of 67 slips (33 indicating tip A and 34 indicating tip B) were placed in an envelope and ran- domly selected for each patient, to avoid directing patients to specific groups*."
The groups were similar at baseline	Unclear	Not enough information to make a qualified judgement
There was blinding of all subjects	Yes	Quote: "*The nomination of laser tips A and B was necessary for the study blinding. Researchers and patients were given access to informa- tion on laser and placebo tips only after completion of the study (double-blind)."*
There was blinding of all therapists	Yes	Quote: "*The nomination of laser tips A and B was necessary for the study blinding. Researchers and patients were given access to informa- tion on laser and placebo tips only after completion of the study (double-blind)."*
There was blinding of all assessors	Unclear	Not enough information to make a qualified judgment
Measures of at least one key outcome obtained >85% of the participants	Yes	Figure 1
Intention to treat	No	Figure 1
The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Figure 4
The study provides both point measures and measures of variability for at least one key outcome	No	No reported measure of variability

Magri, 2018		**Score: 8/10**
Type of bias:	**Judgment**	**Support for judgment**
Eligibility criteria were specified	Yes	Page 386
Subjects were randomly allocated to groups	Yes	Quote: "*The randomization was made by lottery method (simple) after the initial assessment"*
Allocation was concealed	Yes	Quote: "*papers written tip A and B were placed in an envelope and were randomly selected for each patient to void directing patients to specific groups*."
The groups were similar at baseline	Yes	Table 1
There was blinding of all subjects	Yes	Quote: "*Researchers and patients were given access to information on the laser/placebo tips only after the completion of the study (double blind)."*
There was blinding of all therapists	Yes	Quote: "*Researchers and patients were given access to information on the laser/placebo tips only after the completion of the study (double blind)."*
There was blinding of all assessors	Yes	Quote: "*The person responsible for setting the device was not involved in the data collection or analysis"*
Measures of at least one key outcome obtained >85% of the participants	No	Table 1
Intention to treat	No	Table 1 lists dropouts; ITT is not mentioned in the article.
The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Figure 1
The study provides both point measures and measures of variability for at least one key outcome	Yes	Figure 1

Borges, 2018		**Score: 8/10**
Type of bias:	**Judgment**	**Support for judgment**
Eligibility criteria were specified	Unclear	Source of subjects and exclusion criteria is listed but no criteria for inclusion; which is not a clear picture.
Subjects were randomly allocated to groups	Yes	Quote: "*The subjects were randomized by an independent research- er through a list of random numbers, assigned into 8, 60, and 105 J/cm^2 group, and placebo group.* "
Allocation was concealed	Unclear	Not enough information to make a qualified judgement.
The groups were similar at baseline	Yes	Table 3, and "results and discussion".
There was blinding of all subjects	Yes	«*The subjects were randomized by an independent research- er through a list of random numbers, assigned into 8, 60, and 105 J/cm^2 group, and placebo group. «* *«The placebo group received the application of laser therapy with the equipment turned on, but with zero intensity for 15 s at each point"*
There was blinding of all therapists	Yes	«*The subjects were randomized by an independent research- er through a list of random numbers, assigned into 8, 60, and 105 J/cm^2 group, and placebo group. «* *«The placebo group received the application of laser therapy with the equipment turned on, but with zero intensity for 15 s at each point"*
There was blinding of all assessors	Yes	«*The subjects were randomized by an independent research- er through a list of random numbers, assigned into 8, 60, and 105 J/cm^2 group, and placebo group. «* *«The placebo group received the application of laser therapy with the equipment turned on, but with zero intensity for 15 s at each point"* *"In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind"* (PEDro, 1999)
Measures of at least one key outcome obtained >85% of the participants	Yes	Figure 1
Intention to treat	Unclear	The report does not explicitly state that all subjects received treatment or control conditions as allocated.
The results of between-group statistical	Yes	Figure 3

comparisons are reported for at least one key outcome		
The study provides both point measures and measures of variability for at least one key outcome	Yes	"Results and discussion": mean and standard deviations

Sancakli, 2015		**Score: 7/10**
Type of bias:	**Judgment**	**Support for judgment**
Eligibility criteria were specified	Yes	Page 2
Subjects were randomly allocated to groups	Yes	Quote: "The randomizations of the patients were done with the help of a computer program»
Allocation was concealed	Unclear	Not enough information to make a qualified judgement
The groups were similar at baseline	Yes	Table 5
There was blinding of all subjects	yes	Quote*: "Patients were unaware of their group assignments."*
There was blinding of all therapists	Yes	Quote: "*In the PG, the laser device was switched on, but not programmed.* "
There was blinding of all assessors	Yes	"An experienced prosthodontist who was blinded to the applied treatment evaluated the patients twice»:
Measures of at least one key outcome obtained >85% of the participants	Unclear	The report does not explicitly state *both* the number of subjects initially allocated to groups *and* the number of subjects from whom key outcome measures were obtained (PEDro, 1999)
Intention to treat	Yes	Quote: *Sixty-two of 814 examined patients with TMD of muscular origin fulfilled the inclusion criteria, and 33 of these patients agreed to participate in the study. Three enrolled patients did not attend appointments regularly and were excluded from the study. The study sample thus comprised 30 patients with TMD of muscular origin (21 women, 9 men; mean age, 39.2 ± 2.8 years) allocated to the three study groups (n = 10 per group).*
The results of between-group statistical comparisons are reported for at least one key outcome	No	No inter-group statisctical comparions was made, only intra-group analyses.

The study provides both point measures and measures of variability for at least one key outcome	Yes	Table 5: Mean and standard deviations.

de Moraes Maia, 2014		**Score: 2/10**
Type of bias:	**Judgment**	**Support for judgment**
Eligibility criteria were specified	Yes	Page 30
Subjects were randomly allocated to groups	Yes	Quote: "*Of the subjects 108 were evaluated, of which only 26 were able to participate in the study. These were randomly divided into two groups: laser group (n 0 14) and placebo group (n 0 12). »*
Allocation was concealed	Unclear	Not enough information to make a qualified judgement
The groups were similar at baseline	Unclear	No table of participant characteristics reported.
There was blinding of all subjects	Unclear	Not enough information to make a qualified judgement
There was blinding of all therapists	Unclear	Not enough information to make a qualified judgement
There was blinding of all assessors	Unclear	Not enough information to make a qualified judgement
Measures of at least one key outcome obtained >85% of the participants	No	Figure 1. Number of participants analyzed not reported.
Intention to treat	No	Figure 1
The results of between-group statistical comparisons are reported for at least one key outcome	No	Inter-group statistical comparisons of outcome measures are not reported.
The study provides both point measures and measures of variability for at least one key outcome	Yes	Figure 2,3,4 and 5

De Carli, 2013		**Score: 7/10**
Type of bias:	**Judgment**	**Support for judgment**
Eligibility criteria were specified	Yes	Page 172
Subjects were randomly allocated to groups	Yes	Quote: "*The method of randomisation used was the computerised random numbers that was generated using the web site 'www.randomization.com' by one of the non-treating authors (A.L.W.)»*
Allocation was concealed	Unclear	Not enough information to make a qualified judgement
The groups were similar at baseline	Yes	Table 1
There was blinding of all subjects	Yes	Quote: "*patients and research therapists were unaware of which treatment the subjects received during both the intervention and follow-up phases."*
There was blinding of all therapists	Yes	Quote: "*patients and research therapists were unaware of which treatment the subjects received during both the intervention and follow-up phases".*
There was blinding of all assessors	Yes	Quote: "*Assessments of the partici- pants (days 1, 3, 8, 10 and 30) were conducted by an independent investigator who was unaware of the participants' group allocation "*
Measures of at least one key outcome obtained >85% of the participants	Unclear	Six patients dropped out during treatment and were eliminated from the study. Of which groups, is not reported.
Intention to treat	Unclear	Not enough information to make a qualified judgement
The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Table 3 and 4
The study provides both point measures and measures of variability for at least one key outcome	Yes	Table 3 and 4

4.4 Results of individual studies

Benli, 2021 and De Mores Maia, 2014 reported their point estimates and variance data as median ± IQR. From this, mean ± SD was converted by the methods explained in chapter 3.8. The follow-up 8-week assessment was only displayed graphically, and lacked IQR. Thus, the IQR was imputed from baseline values. The medians were extracted from graph by the use of a ruler. Rodrigues, 2020 did not report any variance data. Thus, SD was imputed from the mean SD from the intervention groups and control groups respectively of the other trials with similar assessment timepoints. Further details are reported in attachment 3; Result table of individual studies.

4.5 Synthesis of results

The pooled study results are presented with forest plots in accordance with Prisma's recommendations (Liberati et al., 2009a). I as a single reviewer performed the meta-analyses, using the software "Review Manager 5.4". Because most trials lacked transparency in pain assessment reporting, direct comparison is not necessarily feasible. To accommodate, standardized mean difference was chosen as the effect measure for the meta-analyses (Liberati et al., 2009b).

4.5.1 Overall pain results – LLLT versus placebo control

Data suitable for a meta-analysis of an immediate pain change was obtainable from nine trials, and for a meta-analysis of pain-change at follow-up 1-8 weeks after treatment from seven trials.

Overall, pain results immediately after therapy favored LLLT over placebo, but the difference was only borderline significant (SMD = -0.63 (95%CI -1.26 to 0.01), I^2 = 85%, n = 338) (Figure 2).

At follow-up 1-8 weeks after completed treatment, pain results significantly favored LLLT over placebo (SMD = -1.51 (95% CI -2.56 to -0.47), I^2 = 92%, n = 279) (Figure 2).

In total, overall pain results significantly favored LLLT over placebo (SMD = -0.92 (95% CI -1.47 to -0.37), I^2 = 89%, n = 617) (Figure 2).

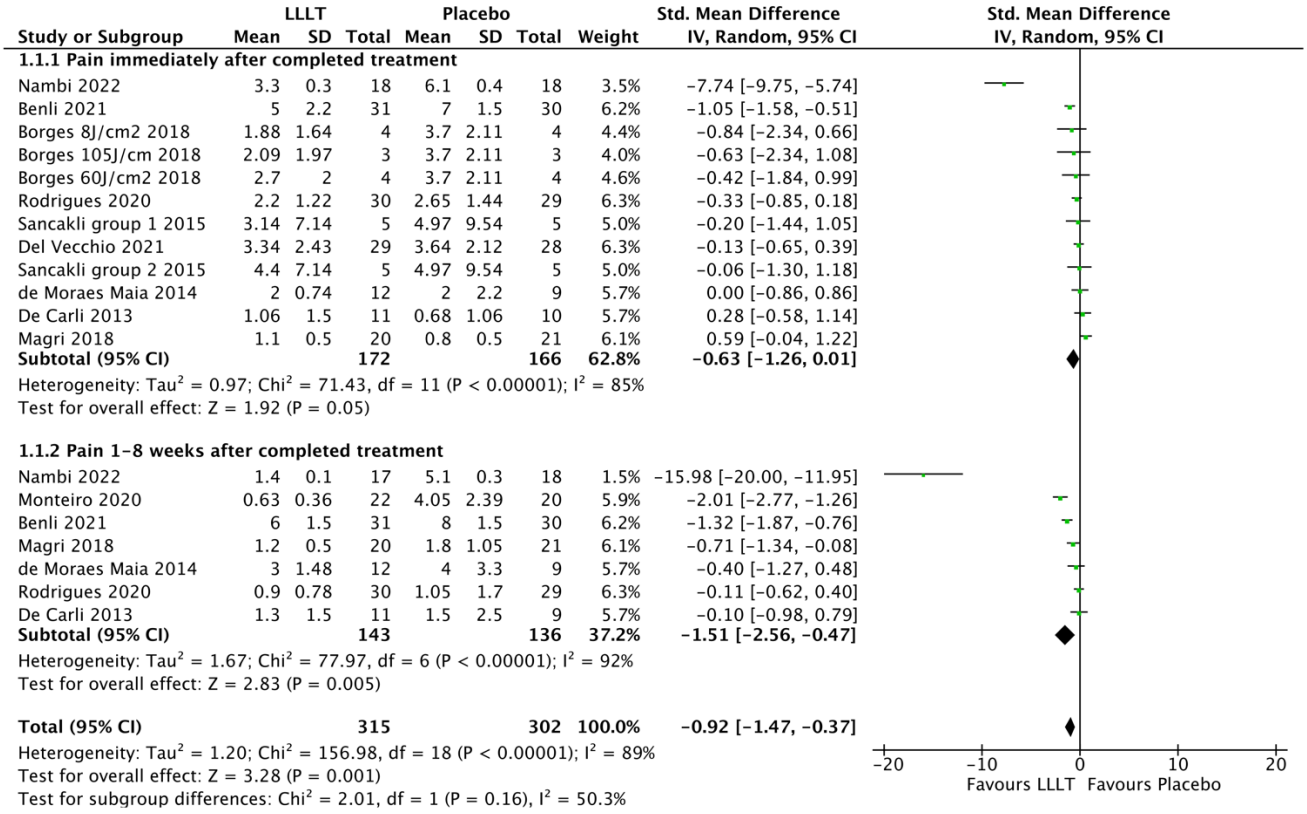

Figure 2: Overall pain results immediately after completed treatment and last timepoint of assessment 1-8 weeks after completed treatment – LLLT vs. Placebo.

4.5.2 Pain results for subgroups by irradiated area – LLLT versus placebo control

Data suitable for a meta-analysis of the first assessment post-therapy were available from two trials irradiating the TMJ, three trials irradiating masticatory muscles and from five trials irradiating both.

For the TMJ, pain results for the first assessment post-therapy favored LLLT over placebo, but not significantly (SMD = -0.26 (95% CI -0.70 to 0.19) I^2 = 0%, n = 79) (Figure 3).

For masticatory muscles, pain results for first assessment post-therapy favored LLLT over placebo, but not significantly (SMD = -0.45 (95% CI -1.07 to 0.17) I^2 = 47%, n = 102) (Figure 3).

For both the TMJ and masticatory muscles, pain results for first assessment post therapy significantly favored LLLT over placebo (SMD = -1.55 (95% CI -3.10 to -0.00) I^2 = 95%, n = 199) (Figure 3).

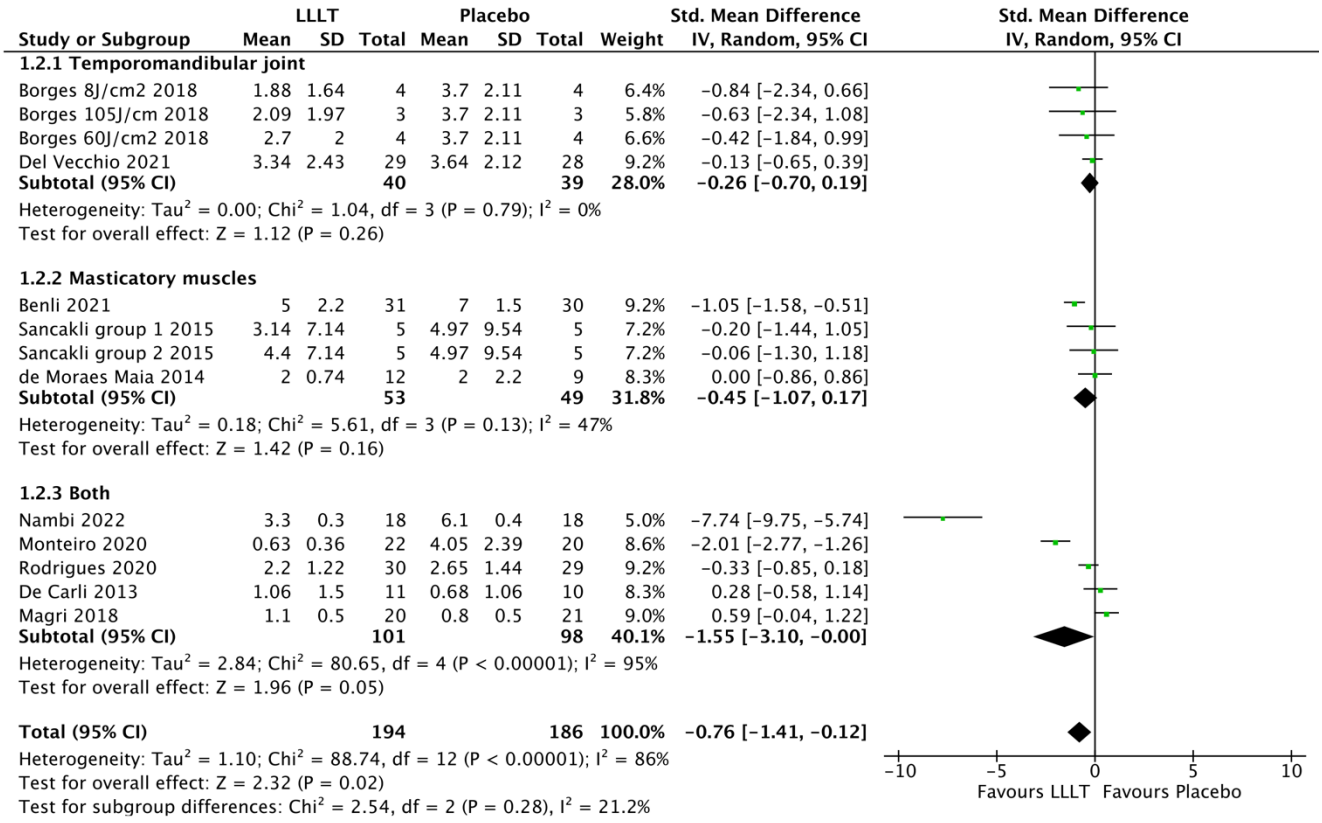

Figure 3 Pain results subgrouped by treatment area; first timepoint of assessment after completed therapy.

4.5.3 Pain results for subgroups by WALT-adherence – LLLT versus placebo control

The subgroup by WALT adherence analysis was formed on the first timepoint of assessment after completed therapy.

The pain results from two trials using recommended laser doses showed that LLLT lowered pain compared to placebo, but not significantly (SMD = -4.05 (95% CI -11.22 to 3.13) I^2 = 97%, n = 44) (Figure 4).

The pain results from nine trials using a non-recommended laser dose favored LLLT over placebo, but not significantly (SMD = -0.39 (95% CI -0.86 to 0.08) I^2 = 73%, n = 336) (Figure 4).

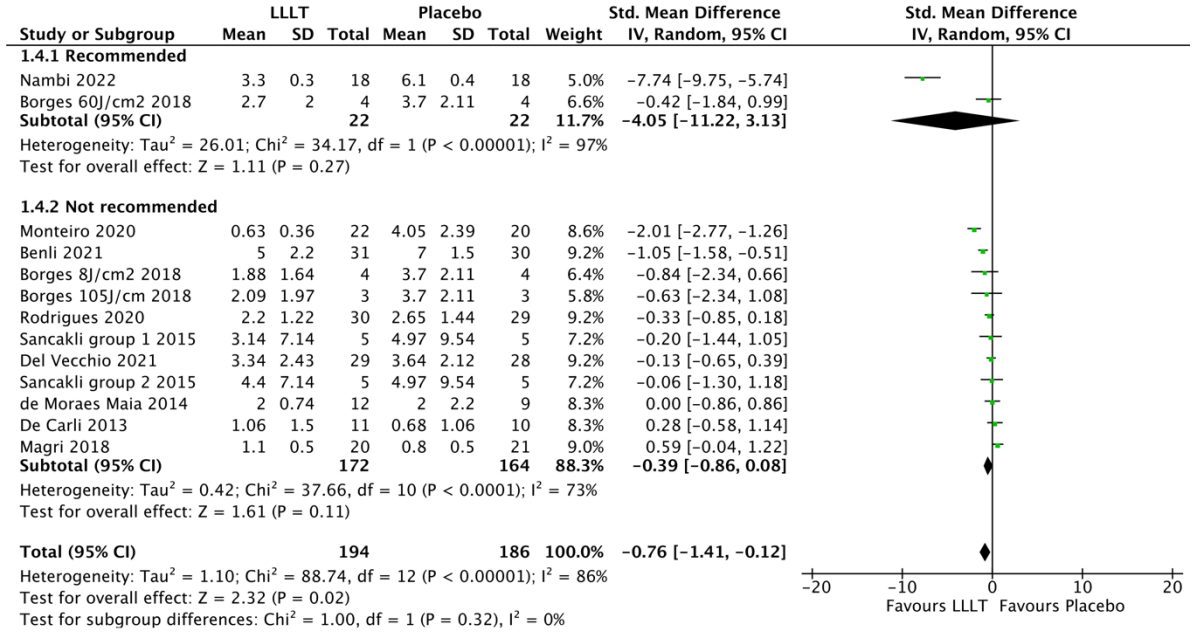

Figure 4 Pain results subgrouped by WALT adherence; first timepoint of assessment after completed therapy.

4.5.4 Between-study risk of bias

Studies with smaller samples sometimes leads to exaggerated treatment results. When heterogeneity is present, a random effects model distributes weigh to each trial more equally than a fixed effects model (Cochrane). As heterogeneity was present in the meta-analysis for overall pain results (85% and 92% respectively), a sensitivity analysis was performed to compare effect sizes when switching to a fixed effects model (Figure 5). The total effect size changed from large (SMD = -0.92 (95% CI -1.47 to -0.37) in the random effects model to moderate (SMD = -0.55 (95% CI -0.72 to -0.37) in the fixed effects model.

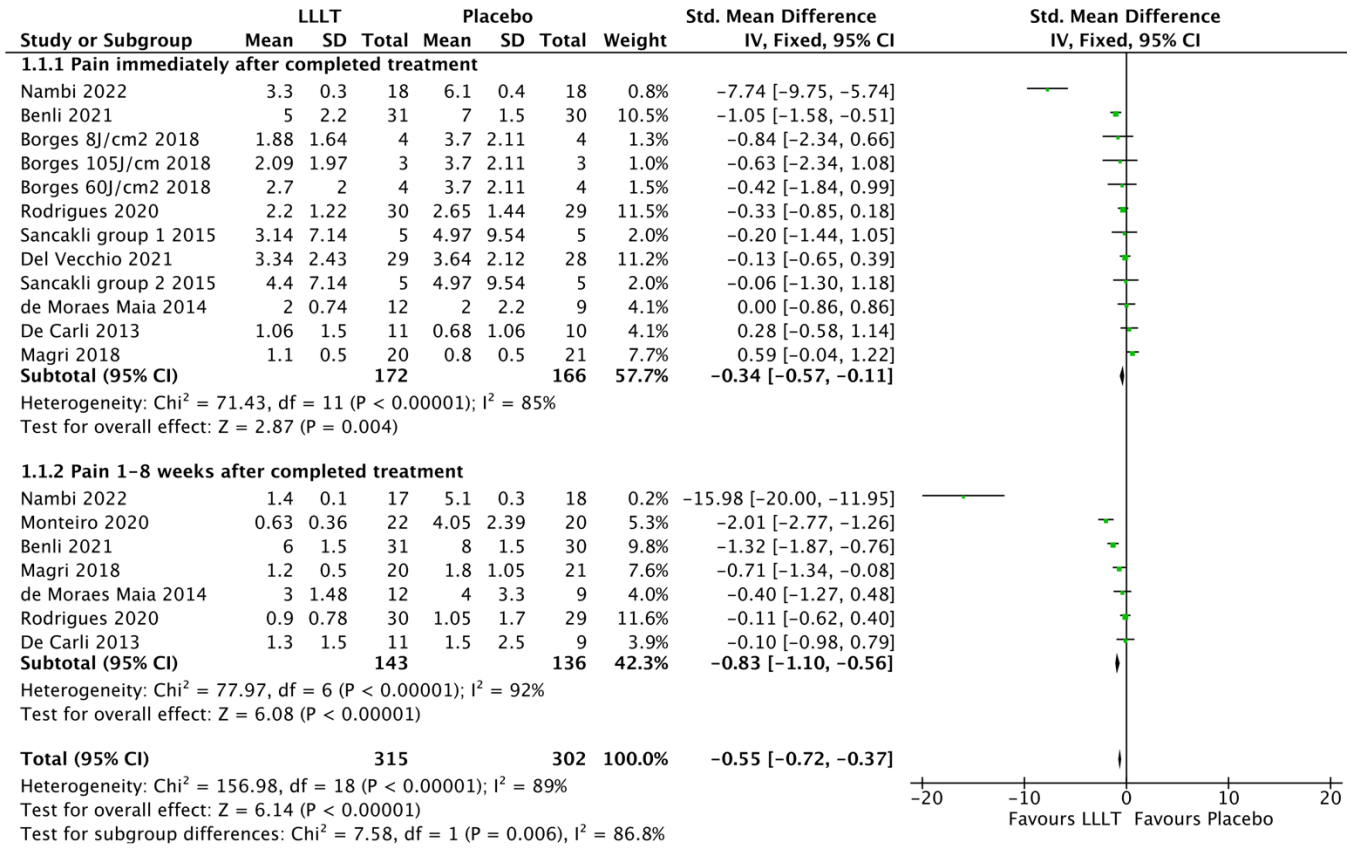

Figure 5 Fixed effects model of overall pain results immediately after completed treatment and last timepoint of assessment 1-8 weeks after completed treatment – LLLT vs. Placebo.

4.5.5 Sensitivity analysis with removal of outlier

After removing Nambi, 2022, the total SMD of overall pain results decreased from a large (SMD = -0.92) to small effect (SMD = -0.44 (95% CI -0.77 to -0.11), still being statistically significant. The total heterogeneity decreased from 89% to 68% which is a drop from high to moderate (Figure 6).

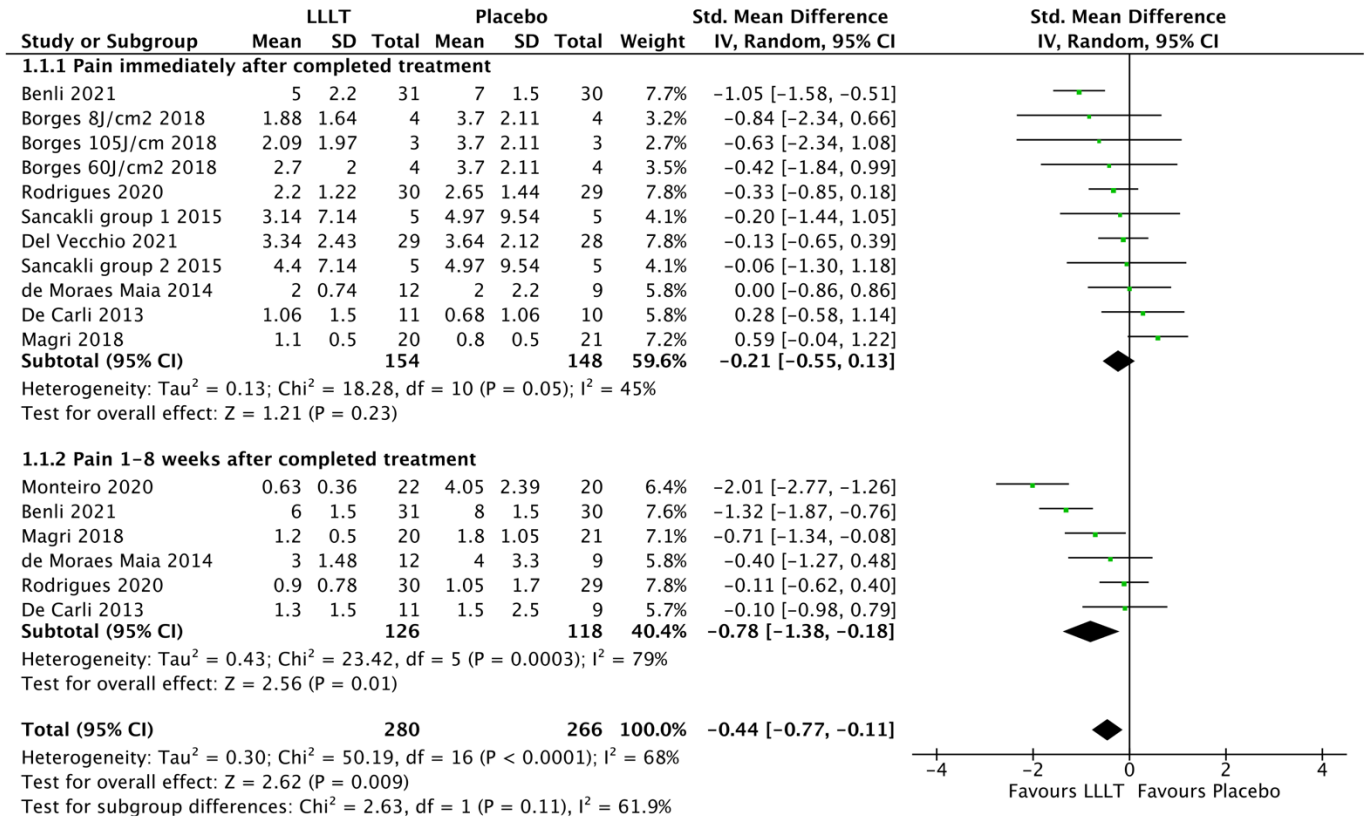

Figure 6 Sensitivity analysis of overall pain results where the outlier Nambi, 2022 is removed. Assessments immediately after completed treatment and last timepoint of follow-up 1-8 weeks after completed treatment – LLLT vs. Placebo.

5. DISCUSSION

5.1 Main findings

This review investigated whether LLLT reduces pain in people suffering from chronic TMD. My meta-analysis of patient-reported, overall pain results showed that pain was significantly reduced by LLLT compared with placebo when results for immediately post therapy and follow-up 1-8 weeks later were pooled together. Moreover, the pooled SMD of 0.92 is considered a large effect (Andrade, 2022).

However, looking further into this meta-analysis, the reduction in pain scaled with time, and was greater at follow-up with a highly statistically significant, large effect size of 1.51 compared to a moderate effect size of 0.63 immediately after completed treatment, which was only borderline statistically significant. This is an interesting finding, being as a reduction in inflammation plays a key role in LLLT´s analgesic effect, which would lead one to expect lower pain levels around the time of antiphlogistic outcome. A possible explanation could be the statistical phenomenon "regression to the mean", as the closer the assessment of pain is to an extreme of an individuals across-time distribution, the greater is the chance of the next assessment being less extreme (Whitney & Von Korff, 1992). Patient enrollment in a study evaluating pain is likely done when the pain level is at such an extreme, which would only make it natural to subside with time. Even still, it would appear that LLLT may induce a longer-lasting effect than certain painkiller drugs. For example, the analgesic induction from the commonly prescribed anti-inflammatory drug tiaprofenic acid, does not provide benefits beyond a week after discontinuation, leaving the patient likely to soon experience re-exacerbation (Scott et al., 2000).

5.2 Dose subgroups

This review also aimed to unveil the optimal energy density and irradiation duration for treating pain in temporomandibular disorders. Therefore, trials were subgrouped using the WALT treatment recommendations (Therapy). Both the recommended and non-recommended laser doses favored LLLT over placebo control in reducing pain first assessment after treatment. The non-recommended doses showed a small difference while the recommended doses showed a notably vaster difference. The magnitude of the difference between subgroups suggests that WALT´s doses are superior in reducing TMD patients´ pain. Moreover, only two of the omitted trials adhered to the recommended joules, irradiation

duration and wavelength concurrently. This resulted in considerable heterogeneity between recommended trials, arguably caused by Nambi,2022´s extreme effect size, discussed further in chapter 5.3.

Monteiro, 2020, despite applying a 635 nm red wavelength laser, still utilized WALT´s recommended joules and irradiation duration, concurrently having the largest SMD score in the non-recommended subgroup. 635 nanometer, even though not recommended by WALT, is still classified as low-level laser and has proven effective in trials (Walker, 1983); (Bliddal, Hellesen, Ditlevsen, Asselberghs, & Lyager, 1987), even performing better than the more commonly used 820 nm laser, penetrating deeper into tissue (Brosseau et al., 2003). It certainly is possible that WALT´s doses are what ranks Monteiro, 2020 above all the other trials in this subgroup. Nevertheless, this hypothesizing is without possibilities for affirmation based on the properties of this review. Whether joules per spot and irradiation duration are more critical variables than the wavelength being in the infra-red rather than the red spectrum, is a topic for future research.

Subgrouping trials using the WALT recommendations was conducted because no other systematic review to date concerning TMD has currently done this before. There does however exist evidence that suggests WALT´s doses are superior in treating some common musculoskeletal pathologies.

Stausholm et al. performed a systematic review on knee-osteoarthritis, investigating a dose-response relationship based on joules per treatment spot (Martin Bjørn Stausholm et al., 2019). 12 trials with recommended doses vs. 7 with non-recommended doses were compared, revealing a significant dose-response relationship in favor of WALT. Only the recommended doses offered clinically relevant pain reduction and was above the threshold of minimal clinically important improvement (MCII).

Naterstad et al. performed a similar review investigating lower-extremity tendinopathy (Naterstad et al., 2022). Seven recommended trials were compared to one non-recommended and two trials with unknown doses. Also here, the recommended doses produced superior, clinically relevant results.

The dose subgroup analysis of this review is congruent with the evidence of these reviews, being that a dose-response relationship with LLLT seems to be of clinical significance in alleviating pain both for arthrogenous and tendinous diseases. TMD conditions often involve both arthrogenous and myogenous pathology, making a comparison biologically rational. However, my data material is insufficient, and the results less precise, making conclusions more speculative. Even still, drawing biologically rational parallels between these pathological conditions similar to another, suggests that more solid evidence could be produced by subgrouping vaster quantities of RCTs in a dose meta-analysis.

5.3 Exploring statistical heterogeneity

Even though the size of the overall effect is large and statistically significant, individual studies differ substantially in terms of point estimates and confidence intervals. According to the Cochrane handbook, 89% heterogeneity is considered substantial (Jacqueline Chandler, 2022). Variation in clinical and methodological variables is to be expected when bringing together studies for statistical comparison. When intervention effects differ more than random error would likely constitute alone, statistical heterogeneity presents. Nambi, 2022 constitutes an effect size exceeding the effect sizes of all the other studies combined, both after completed treatment and at follow-up respectively. Why this large discrepancy manifests is immediately not obvious. Nambi, 2022 scores high on PEDro, has an average intervention duration and a moderate number of participants, diminishing the risk for small-study bias. The only identified methodological insufficiency was therapist blinding, which also lacked in 50% of the trials. One factor for consideration is that the subjects were treated for post-traumatic TMD symptoms after healing from a cervicofacial burn. As LLLT has shown regenerative properties in several bodily tissues including skin ulcers (Kazemikhoo et al., 2018) some unidentified, proliferative mechanism may be at play here. Furthermore, patients were not classified with the DC/TMD protocol.

Exploring sources for heterogeneity is often more suggestive rather than conclusive, due to large variety in study characteristics. The Cochrane handbook postulates several strategies for addressing this issue (Jonathan J Deeks, 2022b). The risk for extraction errors is higher when only one author is responsible for this task. To accommodate, the data was checked repetitively. No errors relating to specific numbers/decimals or data units were identified. After excluding Nambi, 2022 in a sensitivity analysis (Figure 7), the statistical heterogeneity

dropped by 21%, reducing the I^2 stat-score from high to moderate. Also worth noting is that Nambi, 2022 due to a very wide confidence interval has the lowest weight of all trials, not contributing much to the statistical significance. Although Nambi, 2022 solely increases the total effect size from small to large, it does not conflict with the great majority of trial results, as most trials favored LLLT over placebo.

5.4 Small study bias

Larger studies tend to hold higher validity due to more resources being invested, also decreasing the risk of publication bias. Smaller studies tend to be more vulnerable to methodological flaws in general and are in many ways more perceptive to different types of bias. Because of this, smaller studies have the tendency to present with exaggerated treatment effect estimates (Sterne, Egger, & Smith, 2001). The median trial size in this review was not particularly small, but some of the included trials were. The choice of utilizing a random effects model for my meta-analysis was based on the rationale that suspected variability between results would inevitably stem from differences in study context and settings in addition to actual difference between intervention effects. Unfortunately, the random effect model is known for exacerbating the effect of bias in smaller studies (Cochrane). In my sensitivity analysis (Figure 5) where I switched from a random to fixed effects model, the SMD score decreased from large to moderate, suggesting the "small study effect" may have had a moderate influence on the total effect size. That said, while studies are sorted by effect size in the forest plot, it does not appear to the examining eye that study size follows effect size to any particular degree (Figure 4). Looking at the first assessment after completed treatment, Nambi,2022; Monteiro,2020 and Benli,2021, comprise the greatest effects while all being relatively large in size, while De Carli,2013 and de Moraes Maia,2014, the two smallest studies in the sample, account for two out of three studies that favor placebo over LLLT**.**

5.5 Risk of Bias within studies

The included trials had low to high methodological quality, but the mean PEDro score was high (7.1), with only two trials deviating from a high score.
Thus, it did not appear that the statistical heterogeneity could be explained by risk of bias.

5.6 Subgroups by irradiated area

According to the Research Diagnostic Criteria for Temporomandibular Disorders, TMD presents in three phenotypes; myogenous, and arthrogenous with and without disc-displacement (Dworkin, 2010). As the pathophysiological processes may differ, as so could one expect the need for different treatment considerations. Not many RCTs seems to have explored this. In 1997, Conti et al. found improvement in pain only for myogenous patients (Conti, 1997), while Kulekcioglu et al. found similar positive effects for myogenous and arthrogenous patients. (Kulekcioglu, Sivrioglu, Ozcan, & Parlak, 2003)

The subgroup analysis by treatment area showed no dramatic difference in effect between targeting the temporomandibular joint vs. masticatory muscles. The magnitude of the difference does not convincingly suggest that LLLT works better for one location over the other. Peculiarly, the "combined areas" group showed a much larger effect than the other groups. Some caution must be held in making inferences from this. Subgroup analyses, even though comparing controlled trials where the subjects have been randomized intra-study, does not contain an additional randomization process between trials being compared. Therefore, the interpretation of the results can be said to be merely observational in nature, being as vulnerable for potential confounders and biases as any other observational study (Jonathan J Deeks, 2022a). This subgroup also contained considerable heterogeneity. Whether treatment area impacted the overall heterogeneity is possible, but a more comprehensive analysis involving more studies is needed to make conclusions. Therapists applying laser on the muscles may also mistakenly have hit the joint due to close proximity of the structures, a potential source of bias that cannot be excluded.

(Hanna et al., 2021) provided the most extensive systematic review to date on the topic of PBMT for TMD, conducting a literature search from 2005-2021, omitting 43 RCTs. In spite of merging and analyzing massive amounts of data and creating clinical- and research guidelines from a substantial variety of sources, a subgroup analysis on treatment area was not conducted. This question thus requires further investigation for future research.

5.7 Considering external research

Five systematic reviews of RCTs investigating PBMT for TMD was identified. All performed meta-analyses with VAS as outcome. Conclusions trough time have been inconsistent.

Petrucci et al. concluded from six RCTs that LLLT compared to placebo disclosed no statistically significant difference in alleviating pain (Petrucci, Sgolastra, Gatto, Mattei, & Monaco, 2011). Chang et al. found a modest difference in favor of LLLT compared to placebo from seven RCTs, though some of the included trials was only single-blinded (Chang et al., 2014). Chen et al. concluded from 14 trials that LLLT don't perform better than placebo in decreasing chronic pain (J. Chen, Huang, Ge, & Gao, 2015). Xu et al. performed a meta-analysis of 31 studies comparing LLLT to placebo-control, finding that LLLT potently reduced pain (Xu et al., 2018). Additionally, Xu et al. conducted a dose subgroup analysis which did not favor either high (>50 J/cm2) or low doses (≤50 J/cm2) over another.
Hanna et al. meta-analyzed 30 trials for pain reduction, comparing PBMT to placebo, pharmaceutical treatment, cognitive therapy, physiotherapy, occlusal splint, needle therapy and electric therapy. This resulted in a statistically significant decrease in pain, favoring PBMT. As heterogeneity was high, high-risk studies selected from a risk-of-bias analysis was removed from the analysis. This left 16 high quality studies for comparison, which with low heterogeneity significantly favored PBMT over control (Hanna et al., 2021).

As punctuated, inter-review agreement has not been consistent across time. Still, three out of five reviews concluded that LLLT is better than control. The two most recent reviews, appraising 30 trials each, which is more than twice the quantity of the former reviews, both concluded that LLLT is superior to control for reducing pain in people suffering from TMD.

5.8 Clinical considerations

Statistical significance is a measure of confidence to the certainty of our results validity. But a statistically significant result does not demonstrate that a treatment is effective enough to be clinically relevant.

The minimal clinically important difference (MCID) is defined as "*the smallest difference in score in the domain of interest which patients perceive beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient´s health care management*" (Calixtre, Oliveira, Alburquerque-Sendín, & Armijo-Olivo, 2020).
Calixtre et al. reports that women with TMD experienced a large improvement of their general health status if their VAS-score descended by 1.2cm for maximum pain, 1.9cm for current pain and 0.9cm for minimum pain (mean value = 1.3cm) (Calixtre et al., 2020). As

discussed in this review, how VAS was measured was generally underreported by the authors of the included trials. Cohen´s D scores reflects inter-group differences between interventions and are not comparable to MCID, as baseline pain is not considered. Therefore, from each trial included in the overall meta-analysis at follow up, I manually calculated the change scores. Every single trial was above the threshold of MCID reported by Calixtre and colleagues (1.3cm):

Table VII: Overall pain change at follow-up; Change scores from baseline to follow-up, intervention groups.

Study	**Change score from baseline to follow-up**
Nambi, 2022	5.7cm
Benli, 2021	2cm
Rodrigues, 2020	(Baseline pain not reported)
Monteiro, 2018	3.96cm
Magri, 2018	4cm
De Moraes Maia, 2014	5cm
De Carli, 2013	3.5cm

Table VIII: Overall pain change at follow-up; Change scores from baseline to follow-up, placebo groups.

Study	**Change score from baseline to follow-up**
Nambi, 2022	0.9cm
Benli, 2021	0cm
Rodrigues, 2020	(Baseline pain not reported)
Monteiro, 2018	0.4cm
Magri, 2018	2.9cm
De Moraes Maia, 2014	2cm
De Carli, 2013	2.63cm

5.9 Strengths and limitations of this study

This is a systematic review synthesizing data exclusively from RCTs, the gold standard for establishing cause-effect relationships (Svartdal, 2018). See chapter 3.2 for an abbreviation of why this provides more valid conclusions than observational designs.
Systematic reviews of intervention effects should be presented properly so that they provide clinical value for healthcare professionals aiming to make evidence-based decisions. PRISMA has bestowed precision and transparency in reporting of this review´s content. Furthermore, the Cochrane handbook has guided every step in the scientific process; planning the project, searching for and omitting trials, collecting data, assessing risk of bias, conducting statistical procedures and interpreting the results (Jacqueline Chandler, 2022). Reporting bias was prevented by prospectively registering a study protocol in PROSPERO.

A primary strength of the meta-analysis is the ability to quantitively summarize the individual results of a wide range of studies into a single manageable number. This provides increased result precision and transferability to a wider context (external validity), as these two qualities scale with increased study quantity and size (Smedslund, 2013). While a single RCT is restricted to a relatively homogenous sample of patients in a narrow context, the meta-analysis contains insights into how the effect fluctuates between types of patients and non-identical contexts. Herein lies also a potential pitfall with concern to generalization. A meta-analysis reflects the mean value of several mean values; distancing itself further and further away from the individual patient and each specific context. Without sufficient homogeneity between studies, assuming utility for any certain group of patients can be a mistake.

Substantial heterogeneity between trials manifested in the overall meta-analysis. Mostly this stemmed from differences in effect sizes but some trials also pointed in opposing direction of the SMD. A strength of this study was the effort to explain heterogeneity by the conduction of several sensitivity- and subgroup analyses. Though this ruled out some potential biases to a certain degree, ultimately the heterogeneity still threatened the overall validity of this study. The use of a funnel plot with linear regression lacks sensitivity in meta-analyses of less than 20 trials (Sterne et al., 2001), and was thus not performed in this review. Comparing the random effects analysis to a fixed effects model was done, but lacks the precision of a funnel plot.

TMD is a multidimensional disease which often involves mechano-functional and psychosocial impairments (Hanna et al., 2021). This study only considered self-reported pain, without secondary outcomes like masticatory- or daily function, psychological status or quality of life. Moreover, self-reported pain reflects a subjective experience of great complexity; and some would argue it does not provide the same objectivity as an evaluation trough the means of for example pain pressure threshold (PPT) (Sancakli et al., 2015). However, pain intensity has proven to be the most predictive outcome for improvement of the general health status of patients with TMD (Calixtre et al., 2020).

It was also increasingly apparent trough the study selection process that most published trials on the topic have not specified “chronic pain” in the eligibility criteria. This consequently may have caused the problem with inadequate number of trials for the dose subgroup analysis. It may be natural for study conductors to infer that TMD is in fact a chronic re-occurring issue, which in hindsight seems appropriate to consider when aspiring literature saturation for a systematic review on this topic.

Relevant trials may also have been missed because placebo was the only chosen comparator, excluding trials that compare LLLT to conservative interventions and wait-and-see approaches. By contrast, some of my eligibility criteria has welcomed a broader spectrum of trials. For example, the use of the DC/TMD diagnostic tool was not mandatory for inclusion. Rather, merely listing TMD symptoms was deemed adequate. Whether this lack of standardized patient screening affected heterogeneity, was not analyzed, and could pose a risk to validity. Neither was a lower threshold for PEDro-score demanded for inclusion in this review, and thus studies of diverse methodological quality were potentially eligible. Advantageous as that may be for literature saturation, ideally a subgroup analysis to uncover if methodological quality influenced the results should be conducted, and is a shortcoming of this review.

Another limitation is that no extra efforts was done to retrieve relevant trials other than searching in MEDLINE and Embase. As written in the Cochrane handbook, many reasons exist as to why reports may not have been published at all, or in full text, or indexed properly in the major electronic databases (Cochrane, 2022). Handsearching medical journals, conference papers, and reference lists of RCTs and systematic reviews, would be natural in a greater context where eligibility criteria is not restricted to the ten latest published, most

suitable trials. Furthermore, some of the retrieved abstracts deemed eligible were not possible to retrieve in full text, and as a result of the restricted scope of this thesis, the authors were not contacted. Neither were unpublished trials sought after, of which are often smaller studies with low power not showing statistically significant results. This poses a risk for asymmetry towards artificially positive results in my meta-analysis (Nair, 2019).

The Cochrane group states that systematic reviews should be undertaken by a team, preferably involving experienced authors and experts in the field (Toby J Lasserson, 2019). To publish a review under Cochranes banner, at least two researchers are expected to independently select eligible trials, perform data extraction and appraise the quality of evidence. I as a single reviewer performed every task alone. Potential flaws from this involves overlooking eligible studies, selecting incompatible studies, data extraction errors concerning numbers and units, and poor judgement in the assessment of risk of bias. Compensational aims to compare my appraisals to PEDro´s official scores failed, as only one of the assessed studies was identified in the PEDro database. Nevertheless, extracted data was checked repetitively, at multiple points in time. My supervisor was also available for consultations when presented with procedural difficulties.

Stated limitations poses some threats to the credibility of this systematic review. Experience and insights, both methodologically and thematically, is arguably advantageous in conducting high quality science.

Conflicts of interest influencing selection and assessment of studies and results, may potentially arrive from the author being a physiotherapist. The author of this study has no affiliations with the World Association for Laser Therapy.

6. CONCLUSIONS

The results indicate that LLLT can reduce TMD pain. The statistical heterogeneity was high, but it was caused by a single trial with a relatively small sample size. More trials with WALT´s recommended doses are needed in the search for a possible dose-response relationship.

6.1 Implications for practice

Based on this study, LLLT can be recommended as an effective option for clinicians treating TMD patients. Recommended joules, irradiation duration and wavelength were only applied in two trials, prohibiting a comprehensive investigation of the optimal dosages. Since the trials adhering to WALT´s recommendations showed a larger effect, the author of this review suggests clinicians adhere to WALT´s recommendations until more robust analyses are published.

6.2 Implications for research

Future trials should adhere to WALT´s guidelines for best results. Researchers conducting systematic reviews are encouraged to explore the dose-response relationship further, with comprehensive search strategies that cover all relevant trials. Therefore, “chronic pain” should not be an eligibility criterion. In addition to self-reported pain, objective measures like PPT and relevant outcomes like function, psychological status and quality of life should be considered.

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Attachments:

Attachment 1: PRISMA 27-item checklist

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	Front page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	11
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	14
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	15
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	15
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	16
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	16
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	16
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	16
Study risk of bias	11	Specify the methods used to assess risk of bias in the included studies,	17

Section and Topic	Item #	Checklist item	Reported on page #
assessment		including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	18
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	18
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	17
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	18
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	18
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	18
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	43
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	42
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	x
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	18
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	x
Study characteristics	17	Cite each included study and present its characteristics.	20
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	27
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	38

Section and Topic	Item #	Checklist item	Reported on page #
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	46
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	39
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	46
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	43
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	47
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	46
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	44
	23b	Discuss any limitations of the evidence included in the review.	51
	23c	Discuss any limitations of the review processes used.	52
	23d	Discuss implications of the results for practice, policy, and future research.	54
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	x
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	12
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	12
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	x
Competing interests	26	Declare any competing interests of review authors.	54
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	62

Attachment 2: PubMed search strategy. Last updated 3 June 2022.

Search number	Query	Sort By	Filters	Search Details	Results	Time
28	((((((((((((Low-Level Light Therapy[MeSH Terms]) OR (LLLT[Title/Abstract])) OR (low level[Title/Abstract])) OR (low power[Title/Abstract])) OR (laser therap*[Title/Abstract])) OR (laser acupuncture[Title/Abstract])) OR (HeNe[Title/Abstract])) OR (632 nm[Title/Abstract])) OR (Ga-Al-As[Title/Abstract])) OR (820 nm[Title/Abstract])) OR (830 nm[Title/Abstract])) OR (850 nm[Title/Abstract])) OR (GaAs[Title/Abstract])) OR (904 nm[Title/Abstract])) AND ((((((((((Temporomandibular Joint Disorders[MeSH Terms]) OR (temporomandibular[Title/Abstract])) OR (TMJ disorder*[Title/Abstract])) OR (TM disorder*[Title/Abstract])) OR (TM pain[Title/Abstract])) OR (TMJ pain[Title/Abstract])) OR (TMD[Title/Abstract])) OR (myofascial pain[Title/Abstract])) OR (craniomandibular disorder*[Title/Abstract])) OR (mandibular dysfunction*[Title/Abstract])) OR (osteoarthr*[Title/Abstract]))			("low level light therapy"[MeSH Terms] OR "LLLT"[Title/Abstract] OR "low level"[Title/Abstract] OR "low power"[Title/Abstract] OR "laser therap*"[Title/Abstract] OR "laser acupuncture"[Title/Abstract] OR "HeNe"[Title/Abstract] OR "632 nm"[Title/Abstract] OR "Ga-Al-As"[Title/Abstract] OR "820 nm"[Title/Abstract] OR "830 nm"[Title/Abstract] OR "850 nm"[Title/Abstract] OR "GaAs"[Title/Abstract] OR "904 nm"[Title/Abstract]) AND ("temporomandibular joint disorders"[MeSH Terms] OR "temporomandibular"[Title/Abstract] OR "tmj disorder*"[Title/Abstract] OR "tm disorder*"[Title/Abstract] OR "tm pain"[Title/Abstract] OR "tmj pain"[Title/Abstract] OR "TMD"[Title/Abstract] OR "myofascial pain"[Title/Abstract] OR "craniomandibular disorder*"[Title/Abstract] OR "mandibular dysfunction*"[Title/Abstract] OR "osteoarthr*"[Title/Abstract])	726	06:22:29
27	((((((((((Temporomandibular Joint Disorders[MeSH Terms]) OR (temporomandibular[Title/Abstract])) OR (TMJ disorder*[Title/Abstract])) OR (TM disorder*[Title/Abstract])) OR (TM pain[Title/Abstract])) OR (TMJ pain[Title/Abstract])) OR (TMD[Title/Abstract])) OR (myofascial pain[Title/Abstract])) OR (craniomandibular disorder*[Title/Abstract])) OR (mandibular dysfunction*[Title/Abstract])) OR (osteoarthr*[Title/Abstract])			"temporomandibular joint disorders"[MeSH Terms] OR "temporomandibular"[Title/Abstract] OR "tmj disorder*"[Title/Abstract] OR "tm disorder*"[Title/Abstract] OR "tm pain"[Title/Abstract] OR "tmj pain"[Title/Abstract] OR "TMD"[Title/Abstract] OR "myofascial pain"[Title/Abstract] OR "craniomandibular disorder*"[Title/Abstract] OR "mandibular dysfunction*"[Title/Abstract] OR "osteoarthr*"[Title/Abstract]	119,228	06:16:30
26	osteoarthr*[Title/Abstract]			"osteoarthr*"[Title/Abstract]	87,211	06:14:56
25	mandibular dysfunction*[Title/Abstract]			"mandibular dysfunction*"[Title/Abstract]	301	06:14:19
24	craniomandibular disorder*[Title/Abstract]			"craniomandibular disorder*"[Title/Abstract]	455	06:13:59
23	myofascial pain[Title/Abstract]			"myofascial pain"[Title/Abstract]	2,517	06:13:33
22	TMD[Title/Abstract]			"TMD"[Title/Abstract]	7,607	06:13:04

21	TMJ pain[Title/Abstract]			"tmj pain"[Title/Abstract]	720	06:12:49
20	TM pain[Title/Abstract]			"tm pain"[Title/Abstract]	7	06:12:33
19	TM disorder*[Title/Abstract]			"tm disorder*"[Title/Abstract]	58	06:12:16
18	TMJ disorder*[Title/Abstract]			"tmj disorder*"[Title/Abstract]	721	06:12:02
17	temporomandibular[Title/Abstract]			"temporomandibular"[Title/Abstract]	23,187	06:11:28
16	Temporomandibular Joint Disorders[MeSH Terms]			"temporomandibular joint disorders"[MeSH Terms]	18,307	06:10:28
15	((((((((((((Low-Level Light Therapy[MeSH Terms]) OR (LLLT[Title/Abstract])) OR (low level[Title/Abstract])) OR (low power[Title/Abstract])) OR (laser therap*[Title/Abstract])) OR (laser acupuncture[Title/Abstract])) OR (HeNe[Title/Abstract])) OR (632 nm[Title/Abstract])) OR (Ga-Al-As[Title/Abstract])) OR (820 nm[Title/Abstract])) OR (830 nm[Title/Abstract])) OR (850 nm[Title/Abstract])) OR (GaAs[Title/Abstract])) OR (904 nm[Title/Abstract])			"low level light therapy"[MeSH Terms] OR "LLLT"[Title/Abstract] OR "low level"[Title/Abstract] OR "low power"[Title/Abstract] OR "laser therap*"[Title/Abstract] OR "laser acupuncture"[Title/Abstract] OR "HeNe"[Title/Abstract] OR "632 nm"[Title/Abstract] OR "Ga-Al-As"[Title/Abstract] OR "820 nm"[Title/Abstract] OR "830 nm"[Title/Abstract] OR "850 nm"[Title/Abstract] OR "GaAs"[Title/Abstract] OR "904 nm"[Title/Abstract]	103,124	06:05:27
14	904 nm[Title/Abstract]			"904 nm"[Title/Abstract]	221	06:02:57
13	GaAs[Title/Abstract]			"GaAs"[Title/Abstract]	7,563	06:02:19
12	850 nm[Title/Abstract]			"850 nm"[Title/Abstract]	1,183	06:02:07
11	830 nm[Title/Abstract]			"830 nm"[Title/Abstract]	980	06:01:48
10	820 nm[Title/Abstract]			"820 nm"[Title/Abstract]	480	06:01:25
9	Ga-Al-As[Title/Abstract]			"Ga-Al-As"[Title/Abstract]	167	06:01:06
8	632 nm[Title/Abstract]			"632 nm"[Title/Abstract]	233	06:00:53
7	HeNe[Title/Abstract]			"HeNe"[Title/Abstract]	1,811	06:00:36
6	laser acupuncture[Title/Abstract]			"laser acupuncture"[Title/Abstract]	349	06:00:25
5	laser therap*[Title/Abstract]			"laser therap*"[Title/Abstract]	10,560	05:59:59
4	low power[Title/Abstract]			"low power"[Title/Abstract]	11,309	05:59:27
3	low level[Title/Abstract]			"low level"[Title/Abstract]	69,450	05:58:56
2	LLLT[Title/Abstract]			"LLLT"[Title/Abstract]	2,113	05:58:35
1	Low-Level Light Therapy[MeSH Terms]			"low level light therapy"[MeSH Terms]	6,817	05:55:59

Attachment 3: Result table of individual studies.

Results for pain intensity; mean final scores (M), standard deviations (SD) of means, number of participants at the time of assessment. Presented in centimeters. I, Intervention group; C, Control group.

First author, **Number of participants**	**Results intervention group** **(mean ± SD)**	**Results control group** **(mean ± SD)**
Nambi, 2022 **I:** 4 weeks: 18 8 weeks: 17 **C:** 4 weeks:18 8 weeks: 18	4 weeks: **3.3 ± 0.3** 8 weeks: **1.4 ± 0.1**	4 weeks: **6.1 ± 0.4** 8 weeks: **5.1 ± 0.3**
Del Vecchio, 2021 **I:** 1 weeks: 29 **C:** 1 weeks: 28	1 week: **3.34 ± 2.43**	1 week: **3.64 ± 2.12**
Benli, 2021 **I**: 4 weeks: 31 8 weeks: 31 **C:** 4 weeks: 30 8 weeks: 30	Below are means (directly converted from medians) ± SD estimated from interquartile range. The median values were measured with a ruler from Figure 3 (Benli, 2021). As no IQR is reported for the 8-week mark, SD is imputed from baseline IQR. 4 weeks: **5 ± 2.2** 8 weeks: **6 ± 1.5**	Below are means (directly converted from medians) ± SD estimated from interquartile range. The median values were measured with a ruler from Figure 3 (Benli, 2021). As no IQR is reported for the 8-week mark, SD is imputed from baseline IQR. 4 weeks: **7 ± 1.5** 8 weeks: **8 ± 1.5**
Rodrigues, 2020 **I:** 4 weeks: 30 8 weeks: 30 **C:** 4 weeks: 29 8 weeks: 29	Mean values for the 3 sub-groups: 4 weeks: **2.2 ± 1.22** 8 weeks: **0.9 ± 0.78** *SD is imputed from the mean SD from the intervention-groups of the other included trials that has similar timepoints of assessment.	Mean values for the 3 sub-groups: 4 weeks: **2.65 ± 1.44** 8 weeks. **1.05 ± 1.7** * SD is imputed from the mean SD from the control- groups of the other included trials that has similar timepoints of assessment.

Monteiro, 2020 **I:** 22 **C:** 20	8 weeks: **0.63 ± 0.36**	8 weeks: **4.05 ± 2.39**
Magri, 2018 **I**: 20 **C**: 21	4 weeks: **1.1 ± 0.5** 8 weeks: **1.2 ± 0.5**	4 weeks: **0.8 ± 0.5** 8 weeks: **1.8 ± 1.05**
Borges 2018 **I 1:** (8J/cm2): 11 **I 2:** (60J/cm2): 11 **I 3:** (105J/cm): 11 **C:** 11	Intervention group 1 (8J/cm2): 3 weeks: **1.88 ± 1.64** Intervention group 2 (60J/cm2): 3 weeks: **2.70 ± 2.00** Intervention group 3 (105J/cm): 3 weeks: **2.09 ± 1.97**	3 weeks: **3.7 ± 2.11**
Sancakli, 2015 **I 1:** 10 **I 2**: 10 **C:** 10	LLLT group 1: 4 weeks: **3.14 ± 7.14** LLLT group 2: 4 weeks: **4.40 ± 7.14**	4 weeks: **4.97 ± 9.54**
De Moraes Maia, 2014 **I:** 12 **C:** 9	Below are means (directly converted from medians) ± SD estimated from interquartile range. Week 4: **2 ± 0.74** Week 8: **3 ± 1.48**	Below are means (directly converted from medians) ± SD estimated from interquartile range. Week 4: **2 ± 2.2** Week 8: **4 ± 3.3**
De Carli, 2013 **I:** 11 **C:** Week 2: 10 Week 6: 9	Week 2: **1.06 ± 1.5** Week 6: **1.3 ± 1.5**	Week 2: **0.68 ± 1.06** Week 6: **1.5 ± 2.5**

Attachment 4: PROSPERO protocol

Systematic review

This record cannot be edited because it has been marked as out of scope

1. * Review title.

Give the title of the review in English

Efficacy of low-level laser therapy on pain and disability in temporomandibular disorders: Systematic review and meta-analysis of randomized controlled trials

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

01/05/2022

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/03/2024

5. * Stage of review at time of this submission.

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Martin Bjørn Stausholm

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Stausholm

7. * Named contact email.

Give the electronic email address of the named contact.

m.b.stausholm@gmail.com

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

Bøgevej 3, Kalundborg, Denmark

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+45 93888792

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be

completed as 'None' if the review is not affiliated to any organisation.

University of Bergen.

Organisation web address:

https://www.uib.no/en

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Mr Fabian Lillebostad. University of Bergen
Professor Jan Magnus Bjordal. University of Bergen
Dr Martin Bjørn Stausholm. University of Bergen

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

University of Bergen.

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

What is the effectiveness of low-level laser therapy on patient-reported pain and disability in persons with temporomandibular disorders?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

The databases PubMed, Embase, and Cumulated Index to Nursing and Allied Health Literature will be searched. In addition, reference lists from the included trial articles and systematic review articles on the topic will be screened, citation searches will be performed, and experts in the field will be asked to provide additional published and unpublished trial articles.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Temporomandibular disorder refers to a group of conditions involving the orofacial region divided into those affecting the masticatory muscles and those affecting the temporomandibular joint.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Humans diagnosed with temporomandibular disorders.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Low-level laser therapy.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Placebo low-level laser therapy or other conservative treatment.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Randomized controlled trials.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Patient-reported pain. This outcome will be assessed at two time-points:- Immediately after completed laser therapy.

- First time-point of assessment 1-12 weeks after completed laser therapy.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Patient-reported pain will be meta-analyzed using the Standardized Mean Difference (SMD) method.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

Patient-reported disability. This outcome will be assessed at two time-points:

• Immediately after completed laser therapy.

• First time-point of assessment 1-12 weeks after completed laser therapy.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Patient-reported disability will be meta-analyzed using the SMD method.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Two reviewers will independent scrutinize the titles and abstracts of the publications identified by the search,

and any article will be retrieved in full-text if it is judged possible eligible by at least one reviewer. The same two reviewers will evaluate the full texts of all potentially eligible articles and make a careful decision whether to include or exclude each article, with close attention to the eligibility criteria. Study selection disagreements will be resolved by discussion.

One reviewer will extract the data and another reviewer will check this work for correctness. Data-extraction disagreements will be resolved by discussion. Extraction of the following data will be mandatory:

• Number of participants randomized to laser and control groups, type and duration of interventions, selected outcome measurement scales, and time-points of assessments.

• Participants gender and baseline age, duration of pain, and pain intensity.

• Laser-specific application information, that is, wavelength, energy density per treated spot, number of spots treated, mean power density per treated spot, treatment time per spot, treatment location, total number of sessions, and number of sessions per week.

• Effect estimates for pain and disability.

• Adverse events of any type.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Two reviewers will independently judge the risk of bias of the trials with the Physiotherapy Evidence Database 1-10 point risk of bias tool. Risk of bias disagreements will be resolved by discussion.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

A random effects model meta-analysis will be applied using the DerSimonian & Laird method. When standard deviations (SD) are not available, they will be estimated from other variance data in the following prioritized order: (1) standard errors, (2) 95% confidence intervals, (3) p-values, (4) interquartile ranges, (5) medians of correlations, (6) graphs, or (7) other methods. The SMD will be adjusted to Hedges g, using a correction factor, and clinically interpreted as originally proposed by Cohen; a SMD of 0.2 is considered small, a SMD of ~0.5 is considered moderate and a SMD of 0.8 is considered large. Heterogeneity will be

calculated as the I^2 statistics measuring the proportion of variation (i.e., inconsistency) in the combined estimates. The levels of inconsistency will be categorized as low (25%), moderate (50%), and high (75%).

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

The trials will be subgrouped using the World Association for Laser Therapy treatment recommendations for laser dose and irradiation time per treatment spot. The recommended dose per spot with red/infrared continuous laser is minimum 4 joules over 20-300 seconds. The recommended dose per spot with super-pulsed laser is minimum 2 joules over 30-600 seconds.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
Yes

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention

No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental

No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
Yes

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
Yes

Palliative care
No

Perioperative care

No

Physiotherapy

Yes

Pregnancy and childbirth

No

Public health (including social determinants of health)

No

Rehabilitation

Yes

Respiratory disorders

No

Service delivery

No

Skin disorders

No

Social care

No

Surgery

No

Tropical Medicine

No

Urological

No

Wounds, injuries and accidents

No

Violence and abuse

No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Denmark

Norway

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

low-level laser therapy; photobiomodulation therapy; temporomandibular disorder; systematic review; meta-analysis

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.