



## Laser therapy in the treatment of chronic multi-site pain: a systematic review

### *O uso da terapia laser no tratamento da dor crônica difusa: uma revisão sistemática*

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#### ABSTRACT

Laser therapies are noninvasive techniques with painless, safe, and low-cost therapeutic procedures for chronic pain. No systematic review has evaluated the effects of laser in the treatment of multi-site chronic pain. **Objective:** To evaluate the effects of laser in the treatment of generalized multi-site chronic pain. **Methods:** This pioneering study presents a PRISMA systematic review protocol designed to up-to-date the current literature on Laser Therapy in patients with chronic multi-site pain from all founded etiologies. This protocol was registered on the PROSPERO website before data extraction (registration n. CRD42019152345). **Results:** About 1391 articles met the inclusion criteria and 15 studies were selected for the data extraction. We found 12 studies in patients with fibromyalgia, 01 study about myofascial pain syndrome, 01 study about rheumatoid arthritis and 01 study about diabetic sensorimotor polyneuropathy. Homogeneity was not found in the Laser protocols, clinical conditions studied, the evaluation methods, or in the controlled groups but together studies suggested that Laser could have benefits in the treatment of pain severity, quality of life, fatigue, stiffness, depression, and anxiety compared to placebo and other therapies for fibromyalgia and for pain at Rheumatoid Arthritis and Diabetic Polyneuropathy. **Conclusion:** Laser therapy plus the standardized exercise or amitriptyline provided no extra advantage in the relief of symptoms at fibromyalgia. For TMD myofascial pain no benefits were founded. Studies showed numerous different points and locations of light application but none of the selected studies used spinal stimulation as the Laser application site.

**Keywords:** Laser Therapy, Phototherapy, Chronic Pain, Rehabilitation

#### RESUMO

As terapias a laser são técnicas não invasivas, indolores, seguras e de baixo custo e de utilidade no tratamento da dor crônica. Nenhuma revisão sistemática avaliou os efeitos do laser no tratamento da dor crônica em múltiplos locais simultâneos. **Objetivo:** Avaliar os efeitos do laser no tratamento da dor crônica multifocal generalizada. **Métodos:** Revisão sistemática PRISMA sobre o uso do laser em pacientes com dor crônica multifocal de diversas etiologias. Este protocolo foi registrado no site PROSPERO antes da extração dos dados (registro nº. CRD42019152345). **Resultados:** 1.391 artigos atenderam aos critérios de inclusão e 15 estudos foram selecionados para a extração de dados, sendo 12 estudos em pacientes com fibromialgia, 01 estudo sobre síndrome dolorosa miofascial, 01 estudo sobre artrite reumatoide e 01 estudo sobre polineuropatia sensorio-motora diabética. Não foi encontrada homogeneidade nos protocolos do laser, nos métodos de avaliação ou nos grupos controlados, mas em conjunto os estudos sugeriram que o laser poderia ter benefícios no tratamento da intensidade da dor, qualidade de vida, fadiga, rigidez, depressão e ansiedade em comparação com placebo e outras terapias para fibromialgia e para dor na artrite reumatóide e polineuropatia diabética. A terapia a laser mais o exercício padronizado ou amitriptilina não proporcionou nenhuma vantagem extra no alívio dos sintomas da fibromialgia. Para dor miofascial DTM, nenhum benefício foi encontrado. **Conclusão:** Os estudos mostraram vários pontos e locais diferentes de aplicação de luz, mas nenhum dos estudos selecionados usou a estimulação espinal como local de aplicação do laser.

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**Palavras-chaves:** Terapia a Laser, Fototerapia, Dor Crônica, Reabilitação

## INTRODUCTION

The latest data from the Global Burden Disease (GBD) analysis point to the growth of chronic pain patients in the last decade, one of the most prevalent causes of chronic disease and disability in the world.<sup>1</sup> Costs associated with chronic pain include costs with assistive technology devices, medication, surgery, and losses related to working difficulties and insertion in the supply chain.<sup>2</sup>

Chronic pain treatment involves pain management and also functional rehabilitation. Since the years 1990 chronic widespread pain (CWP) is defined as pain lasting longer than 3 months, with pain being on the left and right sides of the body, above and below the waist, and on the axial skeleton. Recently the Manchester criteria requires also pain to be found in two locations of two contralateral limbs and also in the axial skeleton.<sup>3,4</sup>

Recent reviews suggested that widespread or multi-site pain adversely affects the quality of life, mobility, and physical function.<sup>5,6</sup> The management comprises a range of different intervention strategies including drug therapy and non-medical interventions. Although protective factors such as exercise, a healthy diet, and aerobic functional training can alleviate symptoms in generalized chronic pain, many other factors involved in its pathophysiology are not modifiable.

Physical disability due to pain and functional loss reduce the quality of life and increase the risk of increased morbidity, and although there is a wide range of devices and medications available that can alleviate pain and improve quality of life, there is no single pharmaceutical product that can eliminate widespread, extremely disabling pain. Future research should be directed to the discovery of early diagnosis tools, biomarkers of diagnosis, evolution, response to treatment and especially for the development of therapies that can reduce the presence of pain, considered the main cause of functional loss in these patients.

However, despite the knowledge of the molecular pathophysiology of acute pain, there is still little knowledge about the pathophysiology of pain chronicity in these patients. Classically, the possible causes of acute pain in myoarticular disease are known to be related to local inflammation, capsular fibrosis, contracture, and extraarticular muscle weakness.

Recent studies show, however, that neuropathic hyperalgesia is responsible for much of the maintenance of reported pain chronicity. Unlike acute pain, in which the pathophysiology is relatively well known, chronic pain has peripheral and central neurological mechanisms of the perpetuation of pain, often not compatible with the magnitude of the tissue injury and presenting with poor clinical control. In this sense, a better understanding of the complex mechanisms involved in pain generation, modulation, amplification, and perpetuation plays an important role in determining the best therapies to be used to treat pain in patients with chronic pain, especially in widespread pain.

The laser (light amplification by stimulated emission of radiation) is an electromagnetic and non-ionizing radiation that does not cause damage to health and has the advantages of the short duration of application (30 seconds to 2 minutes), being painless and harmless to the skin as it avoids infections, as well as providing treatment possibilities for children, adults,

elderlies, psychiatric patients among others. Photobiomodulation (PBM) uses light sources to reduce inflammation and relief pain.

The low-intensity light-emitting diode (LED) seems to provide important analgesic effects in pain control. Previous studies indicated that photobiomodulation (PBM) and LED therapy are noninvasive techniques with a painless, safe, and low-cost therapeutic procedures for chronic pain.<sup>7</sup> Under this scenario, Laser-therapies seem to provide important analgesic effects in multi-site widespread pain control by the multidisciplinary team. Laser devices are practical, allowing safe and efficient home use, increasing patient compliance with treatment.

Among the causes of generalized chronic pain, it's important to highlight fibromyalgia, polymyalgia rheumatica, endocrine and metabolic diseases, celiac disease, Lyme disease, peripheral polyneuropathies, and medication-induced pain conditions. During the last years, a large number of randomized controlled trials (RCTs) have been published and these have been summarized in systematic reviews mainly concerning Laser therapies for acute pain treatment. But no systematic review has evaluated the effects of laser in the treatment of generalized multi-site chronic pain of all etiologies.

Based on these premises, this study presents a systematic review aiming to investigate the clinical efficacy of the use of Biophotonics in the treatment of generalized multi-site chronic pain. This pioneering study presents a PRISMA review designed to up-to-date the current literature on laser therapy in patients with chronic widespread pain from all founded etiologies.

## OBJECTIVE

The present PRISMA systematic review aimed to evaluate the current literature regarding the effect of laser therapies use in the treatment of chronic generalized multi-site pain from different etiologies.<sup>8</sup> Are laser therapies effective for the treatment of chronic widespread multi-site pain?

## METHOD

### Ethics and registration

We design a protocol research by local ethical requirements and also based on recommendations in Helsinki (1964), as amended in Tokyo (1975), Venice (1983) and Hong Kong (1989) and accordingly with international standards of ethics in research and publication. This protocol was properly registered on the PROSPERO website before data extraction (registration nº. CRD42019152345).

A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)<sup>8</sup> statement searching for human studies, eighteen years old plus, limit our search to English, French, Spanish, Portuguese or Italian language follow the P.I.C.O. strategy terms where P= chronic widespread pain, I= Laser Therapies C= sham Therapy, control no treatment group or other treatment, and O= clinical/symptoms and/or laboratory amelioration.

MEDLINE/PubMed, EMBASE, LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde [Latin American &

Caribbean Health Sciences Literature]) via Biblioteca Virtual em Saúde [Virtual Healthcare Library] (BVS), PEDro, and open Gray electronic (available at <http://www.opengray.eu/>) database were searched to identify relevant articles. Additionally, to locate any potential unidentified study, the search strategy includes a manual search of bibliographies and reference lists of the included studies.

### Search Strategy

This study is a systematic literature review, performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.<sup>8</sup> In January 2020 we search Embase, Medline, Central PubMed, PEDro, Lilacs, and Open Gray database for studies published in humans over eighteen years of age.

We added the studies written in English, Portuguese, Spanish, Italian, and French. For the search terms, we included the MeSH terms and PICO strategy where P= patient, I= intervention, C= comparison, and O= outcome, with the following key-words: (photo\* OR laser\* OR Photodynamic OR laser OR PDT OR Phototherapy OR Light-emitting Diode OR LED OR LLLT OR laser OR low-level laser OR phototherapy OR photobiomodulation OR Biophotomodulation OR photodynamics OR cold laser) AND (diffuse OR generalized OR widespread OR global OR total OR fibromyalgia) AND (chronic) AND (pain OR pain\*).

Two authors conducted independent systematic electronic searches of Databases. The terms used at all databases and the search strategy for each one are described in Chart 1.

**Chart 1.** The terms used at all databases and the search strategy for each database

Database	Search Strategy
PUBMED/Medline	(photo* OR laser* OR Photodynamic OR laser OR PDT OR Phototherapy OR Light emitting Diode OR LED OR LLLT OR laser OR low level laser OR phototherapy OR photobiomodulation OR Biophotomodulation OR photodynamics OR cold laser) AND (diffuse OR generalized OR widespread OR global OR total OR fibromyalgia) AND (chronic) AND (pain OR pain*)
EMBASE	Laser AND pain AND chronic
LILACS	Laser AND Pain
Open Gray	Laser AND pain
PEDro	Laser AND pain

### Condition Being Study / Population

Chronic widespread pain (CWP) or generalized multi-site pain is defined as pain, from any etiologies, lasting longer than 3 months, with pain being on the left and right sides of the body, above and below the waist, and on the axial skeleton, for no minimum 03 different point painful locations.

### Intervention

The term "laser" stands for light amplification by stimulated emission of radiation. Ordinary light, such as that from a light bulb, has many wavelengths and spreads in all directions. Laser light, on the other hand, has a specific wavelength. It is focused

in a narrow beam and creates a very high-intensity light.

This powerful beam of light may be used to cut through steel or to shape diamonds. Because lasers can focus very accurately on tiny areas, they can also be used for very precise surgical work or for cutting through tissue (in place of a scalpel). Laser therapy or photobiomodulation is a therapeutic modality for a range of pathologies, including cancer, tissue repair or pain. In this study, we will only look for studies in which the laser was used with analgesia or anti-inflammatory effects.

### Inclusion Criteria of Studies

English, Portuguese, Spanish, French and Italian-language studies of randomized and quasi-randomized clinical trials in humans over eighteen years of age about the use of laser therapies in the treatment of chronic multi-site pain from any etiologies, compared to no treatment control group, sham control group or other therapy.

Studies that evaluated the effects of laser on chronic multi-site pain patients (more than 3 different pain locations) were included since our interest is to evaluate the effects of laser on chronic pain patients with pain at more than one different site. No restriction of the gender of patients, occurrence of disease, etiology of pain, stage of disease, or drug users.

Systematic reviews and meta-analyses in which the outcomes were similar to those proposed by this review were also included. Studies using laser therapy in combination with other therapies were included and these data reported. Case reports, case group studies or other studies were excluded.

### Exclusion Criteria of Studies

1. In vitro reports and animal models.
2. Papers due to Laser therapy outcomes in other fields (outside of chronic pain).
3. Studies done with extracted parts of the human body.
4. Studies about pain less than 3 months long.
5. Studies with the pediatric population
6. Studies with split-mouth or split-body randomization
7. Epidemiological reports, non-randomized or no controlled trials, case reports, published protocols without results, case group studies, scientific reports, unpublished data, conference papers, historic reviews, letters to the editor, and non-systematic reviews.
8. Studies evaluating the treatment of localized pain.
9. Studies evaluating the treatment of chronic pain or its complications with techniques other than laser therapy.

### Main outcome

1. Laboratory cure or amelioration: defined as a decrease values test of samples defined by the author, after completion of therapy for patients with a definitive diagnosis of widespread pain. The lab results should be examined at the end of treatment to document a fall in values count.

2. Clinical cure or amelioration: defined as continued amelioration or absence of signs or symptoms.

3. Adverse events: in general defined by the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice<sup>9</sup> as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient

hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. We will consider all other adverse events as non-serious. Within adverse events, we will describe the reported outcomes. Also, we will describe other adverse events related to therapeutic regime administered such as photosensitivity, staining of radiated area, eosinophilia, pain, burning sensation, or rashes.

4. Recurrence of clinical or signs and symptoms of sequela.

5. Time to recovery: defined as the time to achieve clinical or laboratory cure.

### Comparator(s)/control

Controlled no treatment Group or Sham laser therapy or Other treatment comparators. In vivo studies evaluating the efficacy of Laser Therapy compared to other therapy are also included.

### Screening and selection of articles

The review follows the recommendations and items of the PRISMA guideline for systematic review and meta-analysis. These terms act as index topics, including several other synonyms or similar terms. These articles were analyzed by their title and summary, evaluating eligibility according to the inclusion criteria established. Duplicate or non-compliant items were excluded. Finally, the references of the selected articles were reviewed. Those that meet eligibility criteria and are not already included in the first selection were added.

Articles were sorted by title and abstract by a couple of independent reviewers. The eligibility of the articles was confirmed using a tab with the criteria described above. The information collected was confronted between the reviewers in parallel with the third evaluation in discordant cases. The review itself is performed to reject articles that did not meet the inclusion criteria. The data found are reviewed by two investigators. Any disagreement between reviewers was solved via debate although in specific cases of disagreement that is not resolved with discussion, opinion of a senior commentator (C.R.B.) was required.

Hand searching of reference lists of original and reviewed articles that were found to be relevant were also performed. In a second step, full-text copies of all remaining articles are obtained and further meticulous assessment is performed by reviewers to determine whether or not they were eligible for this study based on the specific inclusion and exclusion criteria cited above and proven for agreement.

Finally, the references of the selected full-text articles are reviewed. The data found in the articles are reported in a chart by two investigators. Any disagreement between reviewers was solved via debate although in specific cases of disagreement that is not resolved with discussion, opinion of a senior commentator (C.R.B.) was required.

### Analysis of the studies

The quality evaluation of the studies is carried out according to the PRISMA guidelines by two independent reviewers in parallel with the third evaluation in discordant cases. The studies were evaluated concerning the risk of bias and quality

of study by the tools of Cochrane (Risk of Bias Tool - ROB 2.0 tool).<sup>10</sup>

The minimum criteria analyze are: study blindness, presence of control group, randomization, report of a calculation of sample size, report of losses occurred during the study, use of validated instruments for assessment and diagnosis, clear description of statistical methods used to objectively clinical analysis, and description of minimum longitudinal follow-up, notification of selective outcome (if the study protocol analyzed was previously recorded in database).

### Data Collection, Extraction

The main objective of the analysis is to determine the efficacy of laser treatment in patients with widespread pain from any etiologies. A standard spreadsheet of data extracted includes:

1. Author (with reference) and year of publication;
2. Type of study and its design with parameters as blindness, randomization, allocation;
3. A clear statement of objectives;
4. Previous protocol register;
5. Report of a calculation of sample size;
6. Report of losses occurred during the study;
7. Description of minimum longitudinal follow-up;
8. Notification of selective outcome (if the study protocol analyzed was previously recorded in the database);
9. Sample size, age, and gender of patients;
10. Clinical assessment method and use of validated instruments for assessment and diagnosis;
11. Time of onset of symptoms;
12. Clinical condition and etiology of pain treated;
13. Local of Laser application;
14. Type of intervention and treatment groups;
15. Technical parameters of laser therapy (light source, peak wavelength, the diameter of optical fiber, power output, energy fluence, irradiation period);
16. Objectives measurement of amelioration;
17. A clear description of statistical methods used to objectively clinical analysis;
18. Related adverse effects;
19. Clinical effects, results, and outcomes;
20. Laboratory effects, results, and outcomes;
21. Associated prior comorbidities reported in patients;
22. Conclusions and limitations.

### Strategy for data synthesis

A qualitative descriptive analysis of the collected data is done. We planned an individual participant data description and a narrative synthesis. Synthesis provided of the findings from the included studies, structured around the positive or negative results of laser therapy reported the type of intervention, type of clinical conditions treated and study design.

### Associated risks

This study presents the risks of selection errors, selection biases (inclusion and exclusion), and there are no direct risks to the research subjects.

**RESULTS**

Upon the first searches, the researchers found 831 relevant studies that were related to the theme at PubMed, 160 relevant studies related to the theme at PEDro, 335 studies at LILACS, and 592 studies at EMBASE. After the excluded duplications, only 1391 articles met the inclusion criteria.

After a reading of the title and the abstract, only 40 were selected for a complete reading. After the complete reading, only 15 studies were selected for the data extraction (PRISMA Flow in Figure 1). Finally, 13 randomized clinical trials accounted for a total of 760 patients and 02 systematic reviews were included for final results. In all of the 15 studies, the research question or objective was clearly stated – and all of them specified and defined the included population.

In relation to the etiology of pain, we found 12 studies in patients with fibromyalgia, 01 study about patients with diffuse multi-site pain due to myofascial pain syndrome, 01 study about patients with diffuse multi-site pain due to rheumatoid arthritis and 01 study about patients with diffuse multi-site pain due to diabetic sensorimotor polyneuropathy. We did not find studies on CWP patients from other etiologies.

The studies used parametric tests for the normal distribution data, non-parametric tests for the non-normal distribution data, and multivariate analyses for comparisons between the groups. The risk of bias summary of the authors' judgments for the included RCT can be viewed in Chart 2.

Studies using several different Laser protocols were found, with the irradiation times and light characteristics, present a great variation also founded in the studies. In relation to the side effects of laser mild pain and/or a burning sensation during the irradiation were reported by some patients but no studies reported no other side effects or complications when using laser. The evaluation moments also varied greatly and the mean follow-up time was from 05 week varying from three weeks to six months. Eleven studies found statistical differences between the groups for one or more of the outcomes evaluated when accounting for favorable Laser results.

Although homogeneity was not found in the laser protocols in the clinical conditions studied, the evaluation methods, and even in the groups that were used for comparisons with the Laser group, all together of these studies suggested that Laser could have benefits in the treatment of the painful conditions studied. This data and the limitations of these choices will be discussed below in the discussion section.

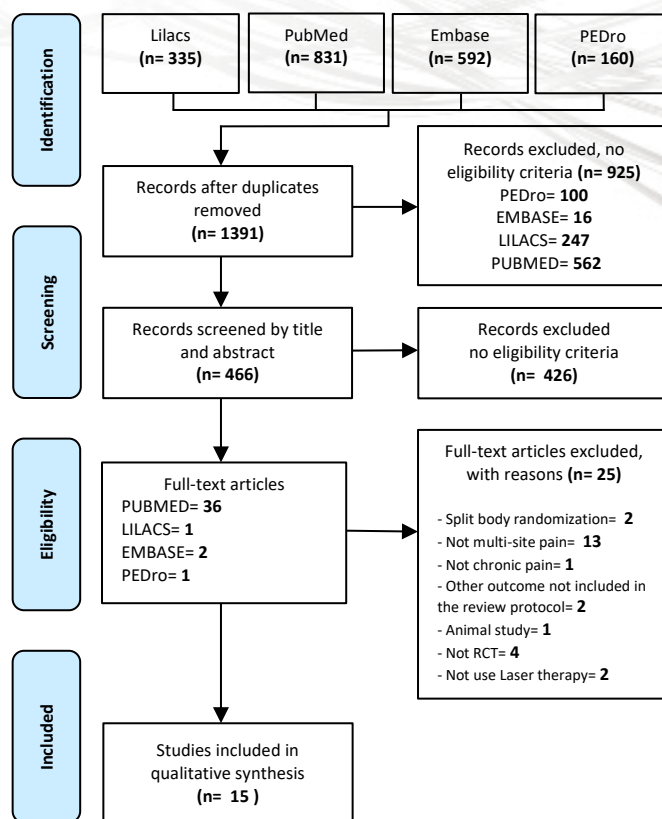
**Qualitative Analysis**

**Clinical trials**

**About Fibromyalgia**

In 2018, Germano Maciel et al.<sup>11</sup> aims to investigate the effects of low-level laser therapy (LLLT) combined with a functional exercise program on the treatment of Fibromyalgia.

A double-blind and placebo-controlled randomized clinical trial composed of 22 women divided into two groups: placebo group (functional exercise program associated with placebo phototherapy n= 11) and laser group (same exercise program



**Figure 1.** Flow Diagram

**Chart 2.** The risk of bias summary of the authors' judgments for the included RCT

Study /Year	Randomization	Allocation	Blinding	Loss to Follow-up
Armagan et al. <sup>11</sup> 2006	unclear	Unclear	Double Blinded	Zero
Garcia et al. <sup>12</sup> 2011	Unclear	Unclear	Patients Blinded	Zero
Germano Maciel et al. <sup>13</sup> 2018	Low Risk	Unclear	Patients Blinded	Zero
Gur et al. <sup>14</sup> 2002	Low Risk	Unclear	Patients Blinded	Zero
Gur et al. <sup>15</sup> 2002	Low Risk	Unclear	Patients Blinded	Zero
Matsutani et al. <sup>16</sup> 2007	Unclear	Unclear	Patients Blinded	Maximum 20%
Magri et al. <sup>17</sup> 2017	Unclear	Unclear	Double Blinded	Maximum 7.5%
Panton et al. <sup>18</sup> 2013	High Risk	Unclear	Double Blinded	Maximum 7.3%
Ruaro et al. <sup>19</sup> 2014	Low Risk	Unclear	Patients Blinded	Zero
Silva et al. <sup>20</sup> 2018	Low Risk	Unclear	Double Blinded	Zero
Vayvay et al. <sup>21</sup> 2016	Unclear	Unclear	Patients Blinded	Zero
Walker et al. <sup>22</sup> 1987	Unclear	Unclear	Patients Blinded	Zero
Zinman et al. <sup>23</sup> 2004	Unclear	Unclear	Patients Blinded	Zero

associated with active phototherapy; n= 11).

Each session lasted from 40 to 60 min and was performed three times a week for 8 weeks. Phototherapy (808 nm, 100 mW, 4 J, and 142.85 J/cm<sup>2</sup> per point) was bilaterally applied to different points of the quadriceps (8), hamstrings (6), and

triceps sural muscles (3) immediately after each exercise session.

Pre and post-intervention evaluations regarding pain (sites, intensity, and threshold), functional performance (balance, functional tests), muscle performance (flexibility and isokinetic variables), depression, and quality of life were conducted. A reduction in pain and improvement in functional and muscular performance, depression, and quality of life were observed in both groups ( $p < 0.05$ ); however, with no significant differences between them ( $p > 0.05$ ). In conclusion, the benefic effects of functional exercise were not improved by combination with LLLT.

In 2018, Silva et al.<sup>20</sup> the role of phototherapy and exercise training (EXT) as well as the combined treatment in general symptoms, pain, and quality of life in women suffering from fibromyalgia (FM). A total of 160 women were enrolled and measures were carried out in two sets: it was sought to identify the acute effect for a single phototherapy and EXT session (Set 1); long-term effect (10 weeks) of the interventions (Set 2).

Phototherapy irradiation was performed at 11 locations in their bodies, employing a cluster with nine diodes (one super-pulsed infrared 905 nm, four light-emitting diodes [LEDs] of 640 nm, and four LEDs of 875 nm, 39.3 J per location).

Algometry and VAS instrument was applied to evaluate pain. The FM symptoms were evaluated with the Fibromyalgia Impact Questionnaire (FIQ) and Research Diagnostic Criteria (RDC) instruments. Quality of life was assessed through the SF-36 survey.

Set 1: pain threshold was improved with the phototherapy, and EXT improved the pain threshold for temporomandibular joint (right and left body side) and occipital site (right body side).

Set 2: there was improved pain threshold in several tender points with the phototherapy and EXT. There was an overlap of therapies to reduce the tender point numbers, anxiety, depression, fatigue, sleep, and difficulty sleeping on FIQ/RDC scores. Moreover, quality of life was improved with both therapies. The phototherapy and EXT improved the pain threshold in FM women. A more substantial effect was noticed for the combined therapy, in which pain relief was accomplished by improving VAS and FIQ scores as well as quality of life.

Vayvay et al.<sup>21</sup> investigate the effects of Laser and taping applications on pain, flexibility, anxiety, depression, functional status and quality of life in patients with fibromyalgia syndrome. Forty-five female patients with fibromyalgia syndrome were included to the study and randomly allocated into three treatment groups; Laser ( $n = 15$ ), placebo Laser ( $n = 15$ ), and taping applications ( $n = 15$ ). Visual analogue scale for pain intensity, trunk flexibility, Fibromyalgia Impact Questionnaire for functional status, Short Form 36 Questionnaire for quality of life and health status, and Beck Depression Inventory for anxiety level were evaluated before and after three weeks interventions.

There were decreased pain severity inactivity ( $p = 0.028$ ), anxiety level ( $p = 0.01$ ) and improved general health status, quality of life ( $p = 0.01$ ) found at Laser group, whereas there were increased trunk flexibility, flexion ( $p = 0.03$ ), extension ( $p = 0.02$ ) found at taping group. After interventions, there were decreased pain severity for whole groups at night for Laser

group ( $p = 0.04$ ), placebo Laser group ( $p = 0.001$ ), taping group ( $p = 0.01$ ) and improved functional status found for Laser group ( $p = 0.001$ ), placebo Laser group ( $p = 0.001$ ), taping group ( $p = 0.01$ ).

Ruaro et al.<sup>19</sup> evaluate the effects of LLLT in patients in a placebo-controlled, randomized clinical trial carried out with 20 patients divided randomly into either an LLLT group ( $n = 10$ ) or a placebo group ( $n = 10$ ). The LLLT group was treated with a GaAlAs laser (670 nm, 4 J/cm<sup>2</sup> on 18 tender points) three times a week over 4 weeks. Before and after treatment, patients were evaluated with the Fibromyalgia Impact Questionnaire (FIQ), McGill Pain Questionnaire, and visual analog scale (VAS).

Data from the FIQ and McGill questionnaire for the treated and control groups were analyzed by paired t-tests, and Wilcoxon tests were used to analyze data from the VAS. After LLLT or sham treatment, the number of tender points was significantly reduced in both groups (LLLT,  $p < 0.0001$ ; placebo,  $p = 0.0001$ ). However, all other fibromyalgia symptoms showed significant improvements after LLLT compared to placebo (FIQ,  $p = 0.0003$ ; McGill,  $p = 0.0078$ ; and VAS,  $p = 0.0020$ ). LLLT provided relief from fibromyalgia symptoms in patients and should be further investigated as a therapeutic tool for management in fibromyalgia.

Panton et al.<sup>18</sup> evaluated the effects of Class IV laser therapy on pain, Fibromyalgia (FM) impact, and physical function in women diagnosed with FM in a double-blind, randomized control trial. Thirty-eight (38) women (52 – 11 years; mean – standard deviation) with FM were randomly assigned to one of two treatment groups, laser heat therapy (LHT;  $n = 20$ ) or sham heat therapy (SHT;  $n = 18$ ). Both groups received treatment twice a week for 4 weeks.

Treatment consisted of application of LHT or SHT over seven tender points located across the neck, shoulders, and back. Treatment was blinded to women and was administered by a chiropractic physician for 7 minutes. Participants were evaluated before and after treatment for number and sensitivity of tender points, completed the FM Impact Questionnaire (FIQ) and the pain question of the FIQ, and were measured for function using the continuous scale physical functional performance (CS-PFP) test. Data were evaluated using repeated-measures analysis of variance with significance accepted at  $p \leq 0.05$ .

There were significant interactions for pain measured by the FIQ (LHT: 7.1 – 2.3 to 6.2 – 2.1 units; SHT: 5.8 – 1.3 to 6.1 – 1.4 units) and for upper body flexibility measured by the CS-PFP (LHT: 71 – 17 to 78 – 12 units; SHT: 77 – 12 to 77 – 11 units) with the LHT improving significantly compared to SHT. There was a time effect for the measure of FM impact measured by the FIQ, indicating that FM impact significantly improved from pre- to post-treatment in LHT (63 – 20 to 57 – 18 units), while no change was observed in the SHT (57 – 11 to 55 – 12 units) showing evidence that LHT may be a beneficial modality for women with FM in order to improve pain and upper body range of motion, ultimately reducing the impact of FM.

García et al.<sup>12</sup> evaluated the benefits of a program of treatment by laser on the improvement of symptoms associated with fibromyalgia. A total of 31 participants took part in the study, randomized into two groups: intervention with laser and placebo. The intervention consisted of the individual application of six frequencies on seven anatomical

zones of the body showed statistically significant differences for “weariness” and “difficulty sleeping” variables. In the rest of the variables, we did not find any statistical significance. One of the conclusions from the present study is the need for development of new research to verify the influence in the improvement of symptoms associated with fibromyalgia.

Matsutani et al.<sup>16</sup> assess the efficiency of a treatment composed of muscle stretching exercises, associated or not to laser therapy at tender points, for patients with fibromyalgia (FM), in view of bettering their quality of life. Twenty patients were randomly assigned to two groups: one submitted to laser therapy and stretching (LSG, n= 10), and the other only to stretching exercises (SG, n= 10). The visual analog scale of pain (VAS) and dolorimetry at tender points were used to assess pain; life quality was evaluated by means of the Fibromyalgia Impact Questionnaire (FIQ) and the 36-item Short-Form Health Survey (SF-36). After the treatment program, both in LSG and SG were detected pain reduction, higher pain threshold at tender points (all  $p < 0.01$ ), lower mean FIQ scores, and higher SF-36 mean scores (all  $p < 0.05$ ). No significant differences were found between both groups.

In 2006, Armagan et al.<sup>11</sup> investigate the efficacy of low-level laser therapy (LLLT) in fibromyalgia patients. Thirty-four fibromyalgia patients were randomly assigned to LLLT (n= 16) and placebo laser groups (n= 16). Outcome measures included the number of tender points (NTP), Fibromyalgia Impact Questionnaire (FIQ), morning stiffness, global improvement as reported on a verbal scale (VSGI), and total myalgia score.

Clinical evaluations were performed before, immediately after, and six months after the treatment showing significant improvement in the number of tender points and morning stiffness in the placebo group ( $p < 0.05$ ) plus improvement in scores of FIQ, VSGI, and total myalgia in the active laser group ( $p < 0.05$ ). The clinical evaluations performed after six months demonstrated improvements in the clinical parameters only in the LLLT group ( $p < 0.05$ ).

In 2002, Gur et al.<sup>14</sup> examine the effectiveness of low power laser (LPL) and low-dose amitriptyline therapy on clinical symptoms and quality of life (QOL) in patients with fibromyalgia (FM). Seventy-five patients with FM were randomly allocated to active gallium-arsenide (Ga-As) laser (25 patients), placebo laser (25 patients), and amitriptyline therapy (25 patients).

All groups were evaluated for the improvement in pain, the number of tender points, skinfold tenderness, morning stiffness, sleep disturbance, muscular spasm, and fatigue. Depression was evaluated by a psychiatrist according to the Hamilton Depression Rate Scale and DSM IV criteria.

The quality of life of the FM patients was assessed according to the Fibromyalgia Impact Questionnaire (FIQ). In the laser group, patients were treated for 3 min at each tender point daily for 2 weeks, except weekends, at each point with approximately 2 J/cm<sup>2</sup> using a Ga-As laser. The same unit was used for the placebo treatment, for which no laser beam was emitted. Patients in the amitriptyline group took 10mg daily at bedtime throughout the 8 weeks.

Significant improvements were indicated in all clinical parameters in the laser group ( $P= 0.001$ ) and significant improvements were indicated in all clinical parameters except fatigue in the amitriptyline line group ( $P= 0.000$ ), whereas

significant improvements were indicated in pain ( $P= 0.000$ ), tender point number ( $P= 0.001$ ), muscle spasm ( $P= 0.000$ ), morning stiffness ( $P= 0.002$ ), and FIQ score ( $P= 0.042$ ) in the placebo group.

A significant difference was observed in clinical parameters such as pain intensity ( $P= 0.000$ ) and fatigue ( $P= 0.000$ ) in favor of the laser group over the other groups, and a significant difference was observed in morning stiffness ( $P= 0.001$ ), FIQ ( $P= 0.003$ ), and depression score ( $P= 0.000$ ) after therapy.

A significant difference was observed in morning stiffness ( $P= 0.001$ ), FIQ ( $P= 0.003$ ), and depression ( $P= 0.000$ ) in the amitriptyline group compared to the placebo group after therapy. Additionally, a significant difference was observed in the depression score ( $P= 0.000$ ) in the amitriptyline group in comparison to the laser group after therapy.

Our study suggests that both amitriptyline and laser therapies are effective on clinical symptoms and QOL in fibromyalgia and that Ga-As laser therapy is a safe and effective treatment in cases with FM. Additionally, the present study suggests that the Ga-As laser therapy can be used as a monotherapy or as a supplementary treatment to other therapeutic procedures in FM.

At 2002, Gurt et al.<sup>15</sup> evaluate the efficacy of low-energy laser therapy in 40 female patients with fibromyalgia. Patients with fibromyalgia were randomly allocated to active (Ga-As) laser or placebo laser treatment daily for two weeks except weekends.

Both the laser and placebo laser groups were evaluated for the improvement in pain, number of tender points, skinfold tenderness, stiffness, sleep disturbance, fatigue, and muscular spasm. In both groups, significant improvements were achieved in all parameters ( $p < 0.05$ ) except sleep disturbance, fatigue and skinfold tenderness in the placebo laser group ( $p > 0.05$ ). It was found that there was no significant difference between the two groups with respect to all parameters before therapy whereas a significant difference was observed in parameters like pain, muscle spasm, morning stiffness and tender point numbers in favor of laser group after therapy ( $p < 0.05$ ).

None of the participants reported any side effects. The study suggests that laser therapy is effective on pain, muscle spasm, morning stiffness, and total tender point number in fibromyalgia and suggests that this therapy method is a safe and effective way of treatment in the cases with fibromyalgia.

### About Rheumatoid Arthritis

At 1987, Walker et al.<sup>22</sup> evaluated 34 patients with Rheumatoid Arthritis using transcutaneous low-power helium-neon laser (1MW, 632.5 nm, 20 Hz) over painful joints. Control group (34 patients) received treatment by a placebo Laser apparatus for 10 weeks. Subjects in the experimental group exhibited a highly reduction in pain intensity. The low-power laser may represent an adjunct in the management of the pain of rheumatoid arthritis.

### About Myofascial Syndrome

Magri et al.<sup>17</sup> analyze the effect of LLLT on pain intensity (visual analogue scale, VAS), in orofacial and corporal points (pressure pain threshold, PPT), and on Short Form-McGill Pain

Questionnaire (SF-MPQ) indexes of women with myofascial pain (a subtype of muscle temporomandibular disorders - TMD).

Ninety-one women (18–60 years) were included in the study, among which 61 were diagnosed with myofascial pain (Research Diagnostic Criteria for Temporomandibular Disorder—Ia and Ib) and were divided into laser (n= 31) and placebo group (n= 30), and 30 were controls. The LLLT was applied at pre-established points, twice a week, eight sessions (780 nm; masseter and anterior temporal= 5 J/cm<sup>2</sup>, 20 mW, 10 s; TMJ area= 7.5 J/cm<sup>2</sup>, 30 mW, 10 s). Pain intensity, and the SF-MPQ indexes were measured at the baseline, during laser sessions, and 30 days after treatment.

For intra-group comparisons, the Friedman test was performed, and for inter-group, the Mann-Whitney test. Increased pain sensitivity was found in women with myofascial pain when compared to controls ( $p < 0.05$ ). There was a reduction in pain intensity for both groups after LLLT. The LLLT did not change the PPT for any group ( $p > 0.05$ ).

Active laser and placebo reduced the indexes of sensory, total pain, and VAS, maintaining the results after 30 days; there was a reduction in the affective pain rating index for both groups, with no maintenance after 30 days for placebo, and the present pain intensity decreased in the laser group and did not change in the placebo after LLLT. In conclusion, the LLLT active or placebo are effective in reducing the overall subjective perception of myofascial pain (VAS and SF-MPQ indexes); however, they have no effect in reducing the pain sensitivity in orofacial and corporal points (PPT increase).

#### About Diabetic Sensorimotor Polyneuropathy (DSP)

At 2004, Zinman et al.<sup>23</sup> determine whether Laser relieves the pain of DSP in a randomized, double-masked, sham therapy–controlled clinical trial in 50 patients with painful DSP diagnosed with the Toronto Clinical Neuropathy Score. All patients received sham therapy over a 2-week baseline period and were then randomized to receive biweekly sessions of either sham or LILT for 4 weeks.

The primary efficacy parameter was the difference in the weekly mean pain scores on a visual analog scale (VAS). Both groups noted a decrease in weekly mean pain scores during sham treatment. After the 4-week intervention, the LILT group had an additional reduction in weekly mean pain scores of 1.0 0.4 compared with 0.0 0.4 for the sham group ( $P = 0.07$ ). LILT had no effect on the Toronto Clinical Neuropathy Score, nerve conduction studies, sympathetic skin response, or quantitative sensory testing.

#### Systematic Reviews

At 2019, Yeh et al.<sup>24</sup> evaluated the effect of LLLT on patients with fibromyalgia. PubMed, EMBASE, and the Cochrane Library were searched. The primary outcomes were the total scores on the Fibromyalgia Impact Questionnaire (FIQ), pain severity, and the number of tender points. The secondary outcomes were changes in fatigue, stiffness, anxiety, and depression.

Standardized mean difference (SMD), 95% confidence intervals (CI), and P values were calculated for outcome analysis identifying 9 RCTs complaining 325 fibromyalgia patients undergoing LLLT or placebo laser treatment with or

without an exercise program.

The meta-analysis showed that patients receiving LLLT demonstrated significantly greater improvement in their FIQ scores (SMD: 1.16; 95% CI, 0.64-1.69), pain severity (SMD: 1.18; 95% CI, 0.82-1.54), number of tender points (SMD: 1.01; 95% CI, 0.49-1.52), fatigue (SMD: 1.4; 95% CI, 0.96-1.84), stiffness (SMD: 0.92; 95% CI, 0.36-1.48), depression (SMD: 1.46; 95% CI, 0.93-2.00), and anxiety (SMD: 1.46; 95% CI, 0.45-2.47) than those receiving placebo laser.

Furthermore, when compared with the standardized exercise program alone, LLLT plus the standardized exercise program provided no extra advantage in the relief of symptoms. On the other hand, the results of the only RCT using combined LLLT/LED phototherapy showed significant improvement in most outcomes except for depression when compared to placebo.

When compared with pure exercise therapy, combined LLLT/LED phototherapy plus exercise therapy had additional benefits in reducing the severity of pain, number of tender points, and fatigue. The author concluded that LLLT is effective, safe and well-tolerated treatment for fibromyalgia.

At 2010, Ricci et al.<sup>25</sup> investigate the scientific evidence relating to electrothermal and phototherapeutic methods for the treatment of fibromyalgia syndrome (FMS) in Pubmed, Medline, Lilacs, Scielo, ISI Web of Knowledge, PEDro and Cochrane Collaboration databases.

Randomized controlled clinical trials published after 2000 years in English, Portuguese and Spanish were selected. The methodological quality of the studies was assessed using the Jadad scale.

Seven studies were reviewed in full, and about 4 studies identified laser interventions. The intervention methods and their duration varied widely, and there was no mention of the parameters used in the phototherapeutic methods with variability and limitations on the generalization of the results, adverse reactions and doses of the FMS treatment.

#### DISCUSSION

This pioneering study presents a PRISMA review designed to up-to-date the current literature on laser therapy in the treatment of generalized multi-site chronic pain and found positive results.

Chronic pain is one of the most prevalent causes of chronic disease and disability in the world. Treatment options for chronic pain include assistive technology devices, medication, surgery, multidisciplinary approach among others. Chronic pain treatment involves pain management and also functional rehabilitation for residual disabilities.

For this reason, it is important that health teams are vigilant in the assessment of a patient presenting with chronic pain syndrome, and that a differential diagnosis is established before immediately assigning a diagnosis of chronic pain or start treatment.

In the assessment of a person presenting with multi-site chronic pain the total clinical context must always be addressed because other conditions might require a completely different treatment strategy. The treatment and follow-up of patients with chronic pain requires a lot of effort from the multidisciplinary team. Since the symptoms are permanent,



affect the quality of life, independence and functionality, it is essential that the therapeutic resources available to the interdisciplinary follow-up team are efficient, reinforce the patients' adherence to therapies and provide improvement of symptoms in a safe, inexpensive and in a home and ecological environment.

The first cold laser was US Food and Drug Administration (FDA) - approved for treating pain in 2001, and low-level laser therapy (LLLT), also known as cold laser therapy, has been used in the USA since only 2002. Laser therapy has been introduced as a noninvasive, therapeutic intervention for chronic pain in several musculoskeletal disorders.

Laser therapy involves a simple, non-invasive, "point-and-shoot" technique that can be performed by technicians, allied health professionals, and physicians. Some mechanisms, such as increased nociceptive threshold, endorphin production, and downstream opioid receptors, have been postulated to explain the analgesic effect of phototherapy.<sup>26</sup>

Cellular chromophores are presumed to be the receptor sites responsible for the beneficial effects of the laser light beam, including both cytochrome c oxidase (with absorption peaks in the near-infrared range) and photoactive porphyrins.<sup>27-30</sup> Mitochondria are also thought to be a site for the therapeutic effects of infrared light, leading to increased ATP production, modulation of reactive oxygen species, and induction of transcription factors.

These effects lead to increased cell proliferation and migration by fibroblasts; reduction in the levels of cytokines, growth factors, and inflammatory mediators; and increased tissue oxygenation, leading to enhanced control of the inflammatory process, reduced pain, and improved wound healing. Other hypotheses include anti-inflammation due to a decrease in prostaglandin-2 and cyclooxygenase-2 levels, proliferation and neovascularization of connective tissue cells, and increase in blood flow and promotion of healing by increase in the levels of nitric oxide, a powerful vasodilator.<sup>27-29</sup>

Recent systematic reviews and meta-analysis suggested that LLLT effectively reduces pain in adult patients with musculoskeletal disorders. Furthermore, studies have indicated the beneficial role of LLLT/ LED combination in the treatment of lumbar pain, nonspecific knee pain, cervical pain as well as masseter and temporalis muscle pain in women with temporomandibular disorder. However, patients with multi-site pain were not included in many reviews or meta-analysis.

Our study is the first systematic review including 13 RCTs involving 760 patients plus 2 Systematic Reviews to specifically evaluate the efficacy of laser Therapies in chronic generalized multi-site pain. The results demonstrated that laser therapies provided significant improvement in pain severity, number of painful points, fatigue, stiffness, depression, and anxiety compared to placebo and other therapies for fibromyalgia and for pain at Rheumatoid Arthritis and Diabetic Polyneuropathy.

About fibromyalgia LLLT evaluated by FIQ or SF-36 demonstrating significant differences compared with the control group for 03 studies ( $p=0.01$ ). The 3 studies that found positive results are the studies with the best scientific methodology with placebo controlled groups and a larger sample size, which suggests that the use of laser can be promising in improving the quality of life of fibromyalgia patients.

Only two studies compared laser therapies with the standardized exercise program alone and no additional benefits were founded. And only one study compared laser therapy with Amitriptyline, with no additional benefits for Laser Group. But for both results no long term follow up was imposed, to determine other effects or if it depends on number of sessions. For TMD myofascial pain and for other outcomes different from pain at diabetic sensorimotor polyneuropathy no benefits were founded.

It's interesting to note that studies selected from this review treat generalized or multifocal chronic pain using numerous different points and locations of light application. In this sense, it is important to identify all possible etiological diagnoses found in the various generalized chronic pain syndromes, assessing whether the response and the location of the laser application depend on the etiological diagnosis.

It is interesting to note that although several studies related to chronic pain already demonstrate the importance of central sensitization mechanisms and paravertebral stimulation / block as a therapeutic tool,<sup>31,32,33</sup> none of the selected studies used spinal stimulation as the laser application site.

Laser devices are practical, allowing safe and efficient home use and increasing patient compliance with treatment. But future studies need to better elucidate whether laser therapy can provide additional benefits for the use of physical exercise or the use of tricyclic antidepressants, the gold standard therapies of choice currently in the treatment of fibromyalgia and other multi-site chronic pain. Moreover need to better define the best points for laser application as well as to compare the responses at the chosen points with applications in the dorsal ganglion root, currently seen as a crucial place for the treatment of chronic pain.

This review still has some limitations, mostly because of the low-to-middle methodological quality of the selected studies (Chart 2). In addition, our review excluded articles published in languages other than English, Portuguese, Italian and French, which could have influenced the results. Most studies did not report the allocation and the blinded process clearly. The differences in laser types, energy sources, exposure times, outcomes and control group therapies used in the studies may have resulted in some heterogeneity.

Moreover patients maintained their usual regular pharmacological therapies so we could not clarify the separate roles of medication or laser therapy. Finally, long-term follow-up of up to 6 months was only conducted in Armagan et al.<sup>18</sup> study but to the best of our knowledge, in spite of the limitations, the present PRISMA Systematic Review Protocol is pioneering in investigating the efficacy of laser therapies in patients with multi-site chronic pain and it has provided the most relevant available evidence on laser therapies for this situation.

## CONCLUSION

Our data indicate that laser therapy is an emerging, non-invasive, well-tolerated treatment for multi-site chronic pain. More up-to-date information on chronic multi-site pain treatment and efficacy of laser therapy for pain treatment can elucidate the patterns of disease involvement, as well as the best plans for early intervention, prevention, and rehabilitation

that can provide greater independence, autonomy, and quality of life for these patients.

Laser therapies are effective, safe, and well-tolerated treatment for chronic pain. Moreover further studies needed to investigate the use of laser therapy at paravertebral stimulation points as a central desensitization tool for chronic multi-site pain and clarify if compared with exercises or tricyclic antidepressant, laser therapy could to provide extra advantage in the relieved symptoms at chronic multi-site pain.

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