Systematic Review

Low-Level Laser Therapy for Fibromyalgia: A Systematic Review and Meta-Analysis

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Background: Fibromyalgia is a chronic disorder characterized by widespread pain and tenderness. Low-level laser therapy (LLLT), an emerging nonpharmacological treatment, has been used for relieving musculoskeletal or neuropathic pain.

Objective: The objective of this review and meta-analysis was to determine the efficacy of LLLT on patients with fibromyalgia.

Study Design: This study involved systematic review and quantitative meta-analysis of published randomized controlled trials (RCTs).

Setting: This study examined all RCTs evaluating the effect of LLLT on fibromyalgia.

Methods: We performed a systematic review and meta-analysis of RCTs evaluating the effect of LLLT on patients with fibromyalgia. PubMed, EMBASE, and the Cochrane Library were searched for articles published before August 2018. RCTs meeting our selection criteria were included. The methodological quality of the RCTs was evaluated according to the Cochrane risk-for-bias method. Review Manager version 5.3 was used to perform the meta-analysis. The primary outcomes were the total scores on the Fibromyalgia Impact Questionnaire (FIQ), pain severity, and 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.

Results: We identified 9 RCTs that included 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.

Limitations: There were some limitations in this review, mostly because of the low-to-middle methodological quality of the selected studies; for example, there was no clear allocation process and only patients were blinded in most studies. In addition, one study used per-protocol analysis with a 20% loss to follow-up. On the other hand, the differences in laser types, energy sources, exposure times, and associated medication status in these studies may have resulted in some heterogeneity.

Conclusions: Our results provided the most up-to-date and relevant evidence regarding the effects of LLLT in fibromyalgia. LLLT is an effective, safe, and well-tolerated treatment for fibromyalgia.

Key words: Low-level laser therapy, fibromyalgia, meta-analysis, FIQ, pain, tender points, exercise

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Fibromyalgia is a chronic disorder characterized by widespread pain and tenderness. Patients with fibromyalgia often suffer from fatigue, sleep disturbance, and memory problems (1). Neurological complaints such as paresthesia, blurred vision, numbness, and weakness are also commonly seen (1,2). Its estimated prevalence is 2.1% to 5.3% in the general population, with women experiencing more severe symptoms. This syndrome typically occurs in middle-aged adults, but it can develop in any age group, including childhood, adolescence, as well as in the elderly (1). Although the cause of fibromyalgia is uncertain, central nervous system sensitization is considered to be its major pathogenesis. External factors such as infection, trauma, and stress may precipitate it (1,2). No curative treatment for fibromyalgia is available thus far. A combination of pharmacological and nonpharmacological treatments is generally recommended for adequate symptom relief (1). The US Food and Drug Administration approved duloxetine (Cymbalta), milnacipran (Savella), and pregabalin (Lyrica) for treating fibromyalgia. Duloxetine and milnacipran help control pain levels by changing some of the brain neurotransmitters (serotonin and norepinephrine), whereas pregabalin blocks the overactivated neurons involved in pain transmission. Physical exercise and cognitive behavior therapy are the nonpharmacological options with stronger evidence of efficacy in fibromyalgia (3,4). Other interventional approaches with lower levels of evidence include occipital nerve stimulation, lidocaine infusion, and hyperbaric oxygen therapy (4).

Low-level laser therapy (LLLT) is an emerging, noninvasive alternative treatment with some efficacy in relieving musculoskeletal or neuropathic pain and improving the quality of life (5-10). The mechanism is believed to involve photochemical reactions, which alter cell membrane permeability, increase messenger RNA buildup, and lead to cell proliferation. The light emitted during LLLT reacts with cytochrome c oxidase, a respiratory enzyme in mitochondria, and increases adenosine triphosphate (ATP) production and reduces reactive oxygen species levels; this helps reduce cell inflammation and death (11). Some randomized controlled trials (RCTs) have investigated the efficacy of LLLT for fibromyalgia. However, the results have been inconsistent, with small sample sizes. Therefore, we conducted a comprehensive systematic review and meta-analysis of the effectiveness of LLLT in fibromyalgia, aiming to contribute to evidence-based decision-making regarding the use of LLLT in fibromyalgia. On the other hand, since exercise therapies or physical therapies have been proven to be beneficial to patients with fibromyalgia, we also used meta-analysis to compare the effectiveness of a standardized exercise program plus LLLT with a standardized exercise program alone.

Methods

Selection Criteria

We reviewed RCTs evaluating the efficacy of LLLT for fibromyalgia. We included trials that (a) compared the results of LLLT and placebo laser therapy in patients with fibromyalgia; (b) described the inclusion and exclusion criteria for patient selection; and (c) reported power, wavelength, and laser exposure duration. We excluded trials that used a class IV laser because laser class ≤ IIIB is considered therapeutic, whereas a class IV laser causes tissue destruction. Furthermore, trials with laser treatment focusing only on one joint or a specific region of the body were excluded.

Search Strategy and Study Selection

We searched PubMed, EMBASE, and the Cochrane Library for studies on fibromyalgia. The following MeSH terms and Boolean operator were used: fibromyalgia AND (laser OR low-level laser OR photobiomodulation OR phototherapy). The "Related Articles" option in PubMed was used to broaden the search. We applied no language restrictions. The final search was performed in August 2018. We selected studies on the basis of the titles and abstracts meeting the selection criteria. The systematic review described here was accepted by PROSPERO, the online international prospective register of systematic reviews of the National Institute for Health Research (CRD42017079531).

Data Extraction

Two authors (SWY and CHH) independently selected RCTs and extracted the relevant details: number, age, and gender of participants; inclusion and exclusion criteria; laser strategies; and outcome parameters. The individually-recorded information of both reviewers was compared, and a third reviewer (YCK) resolved any discrepancies.

Methodological Quality Appraisal

The 3 aforementioned reviewers independently evaluated the methodological quality of the RCTs according to the Cochrane risk-for-bias method (12).

Several domains were evaluated: allocation generation and concealment; blinding of patients, personnel, and outcome assessor; incomplete outcome data (intention-to-treat or per-protocol); and loss to follow-up rate.

Outcome Assessment

To logically and clearly perform the meta-analysis, the outcome assessment comprised 2 sections. One section pooled data from RCTs comparing LLLT with placebo to evaluate the benefits of LLLT. The other section pooled data from RCTs comparing LLLT plus standardized exercise with standardized exercise alone in order to investigate whether applying the additional laser to exercise therapies provides more benefits than exercise alone.

In each section, we evaluated 3 primary outcomes, namely improvement in the total Fibromyalgia Impact Questionnaire [FIQ] scores (13), severity of pain, and number of tender points; and 4 secondary outcomes, namely improvement in fatigue, stiffness, anxiety, and depression. The improvement in pain severity was assessed by extracting the score of the subitem "pain" from FIQ (0-10), using a 5-point Likert scale (0 = none, 1= mild, 2 = moderate, 3 = severe, and 4 = extreme), or by using a visual analog scale (VAS) in cm. As for the definition of tender points, points that were reported by patients as being painful were regarded as tender points; additional tender points were more rigorously defined if patients felt pain at pressure less than or equal to 2.6 kgf/cm^2 while subject to an increasing pressure of 0.1 kgf/s via placement of an apparatus perpendicular to the point to be evaluated (14). Improvements in fatigue, stiffness, anxiety, and depression were assessed using the subitem score of "fatigue" on the FIQ (0-10) or on the Likert scoring system for grading, "stiffness" on the FIQ and "morning stiffness" on the Likert scoring system, "anxiety" on the FIQ, and "depression" on the FIQ, respectively. In some cases, depression was assessed by a psychiatrist according to the Hamilton Depression Rating Scale (HDRS) (15,16), DSM-IV criteria (17), or the Beck Depression Inventory (18).

Statistical Analysis

We used RevMan 5.3 (The Nordic Cochrane Center for The Cochrane Collaboration, Copenhagen, Denmark) to perform the meta-analysis of the RCTs according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines (19). The standardized mean difference (SMD) was calculated as the effect size for continuous outcomes. The accuracy of the result was reported as a 95% confidence interval (CI). $P < 0.05$ was considered significant. When necessary, the means and standard deviations of pretreatment-posttreatment changes were estimated according to the reported pretreatment and posttreatment data (20). Due to possible heterogeneity between each study, the DerSimonian and Laird random-effects model was used for calculating a pooled estimate of the mean difference (21). The I-square test was performed to assess the heterogeneity among these trials.

Results

Study Selection and Characteristics of Included Studies

Figure 1 illustrates a flowchart of the study selection process. We initially identified 305 potential trials but excluded 105 duplicates and 97 ineligible articles after screening their titles and abstracts. Subsequently, 103 additional reports were excluded as follows: 55 were on different topics, 14 used different comparisons, 14 were review articles, 6 were systematic reviews, 3 were protocols, 1 was a cohort study, and 1 was a case study. Finally, the remaining 9 RCTs were further analyzed.

The characteristics of these eligible studies (14,22-29) are summarized in Table 1. These 9 RCTs were published between 2002 and 2018, with sample sizes of 20 to 80 patients. The mean participant age ranged from 29 to 52 years; however, an earlier trial in 2002 by Gür et al (29) did not offer any information on age. Most RCTs only included women, except that the trial by Gür et al (28) enrolled some male patients and the trial by Ruaro et al (24) enrolled one man in the placebo group. All patients had been diagnosed with fibromyalgia. For patient diagnosis, 6 RCTs (14,22,24,27-29) used the American College of Rheumatology's diagnostic criteria (30), one (23) used the American Rheumatology Society's criteria, and the diagnostic criteria were not mentioned in 2 RCTs (25,26). Patients continued their usual pharmacological therapy in one RCT (22), whereas 3 RCTs did not mention whether the patients were taking medication concurrently (24-26), some of the patients in one RCT continued their regular medication for fibromyalgia (14), and the remaining 4 claimed that no patients took analgesic, anti-inflammatory medications or central nervous system drugs during the study period.

Regarding laser parameters, 6 RCTs (23,24,26-29) used GaAlAs or Ga-AS laser, one (25) used Girlase, one RCT employed a 9-diode cluster device containing mul-

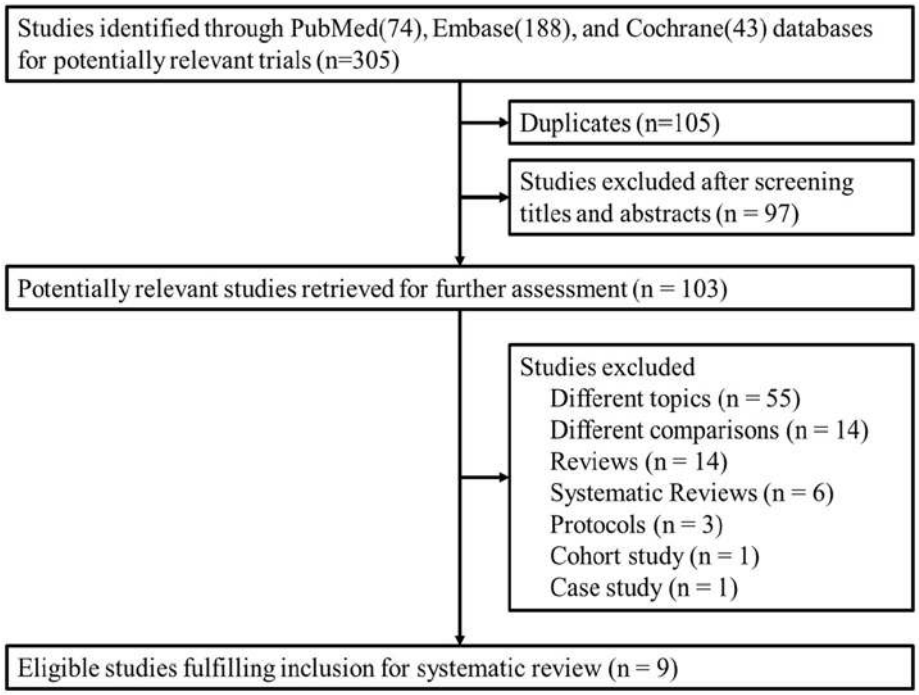

Fig. 1. *Flow chart of the process of study selection.*

tiple light sources (LLLT and light-emitting diode [LED]) (22), and the latest RCT used a DMC® Photon Laser III device (14). Therefore, we performed a subgroup analysis to differentiate the efficacy of monowavelength LLLT vs an LLLT/LED combination. Laser wavelength ranged from 640 to 950 nm and power from approximately 0.9 to 1000 MW. The follow-up period of the 8 RCTs ranged from 2 to 10 weeks; one RCT further followed for 6 months. Five studies (24,25,27-29) involving 173 patients evaluated the effectiveness of LLLT by comparing with placebo laser. Three RCTs compared LLLT plus stretching exercise with stretching exercise alone (14,23,26). One RCT designated patients into 4 groups: control group, phototherapy group, stretching and aerobic exercise training group, and phototherapy plus stretching and aerobic exercise training group (22).

Study Quality

As shown in Table 2, the methodological quality of 9 RCTs was assessed (14,22-29). Five RCTs (14,22,24,28,29) reported acceptable methods of randomization, but none described allocation concealment methods. Eight RCTs (14,22-25,27-29) reported patient blinding by applying placebo or sham laser treatment; the remaining RCT (26) did not provide any relevant blinding information. Three RCTs by Armagan et al (27), da Silva et al (22) and Germano (14) blinded outcome assessors; da Silva et al also blinded the phototherapy programmer. Eight RCTs used an intention-to-treat analysis without loss to follow-up. However, 20% of the patients withdrew from one RCT (26) without reporting the reason, so per-protocol analysis was used for that study. One RCT reported higher variability of emitted power and energy dose of laser (26).

Comparison of LLLT and Placebo LLLT

Primary Outcome (FIQ Score, Pain, and Number of Tender Points)

The meta-analysis showed significant improvement in FIQ score after monowavelength LLLT than that after placebo laser treatment (pooled SMD: 1.16; 95% CI, 0.64-1.69; I^2 = 47%; Fig. 2). The severity of pain was also significantly reduced in the monowavelength LLLT group (pooled SMD: 1.18; 95% CI, 0.82-1.54, I^2 = 0%; Fig. 3) compared with the placebo groups. A significant decrease in the number of tender points after monowavelength LLLT was also noted (SMD: 1.01; 95%

Table 1. *Characteristics of the selected RCTs*.

Study	Inclusion Criteria	No. of Patients	Age (yrs)	Intervention	Outcomes
Germano (14), 2018 (Brazil)	Diagnosed with FM by ACR criteria	I: 11 (0%) C: 11 (0%)	I: 39.73 ± 5.25 C: 40.36 ± 7.24	I: functional exercise program (40 to 60 min/session) associated with active phototherapy (808 nm, 100 mW, continuous, 4 J, and 142.85 J/cm^2 on 17 tender points immediately after exercise, 40 s/site 3 times/wk) x 8 wks C: functional exercise program (40 to 60 min/session) associated with placebo phototherapy (3 times/wk) x 8 wks	FIQ, VAS, no. of tender points, Beck Depression Inventory, pain threshold, functional performance, muscle performance (flexibility, strength)
da Silva (22), 2018 (Brazil)	Diagnosed as FM by ACR criteria on FIQ for > 5 yrs, ≥ 35 y/o women	I: 20 (0% [a]) C1: 20 (0%) C2: 20 (0%) C3: 20 (0%)	Overall: 40 ± 2	I: Phototherapy (a cluster with 9 diodes-1 super-pulsed infrared 905 nm, 4 LED of 640 nm, 4 LED of 875 nm, 39.3 J & 5 min/point x 10 sites) x 10 wks C1: Placebo phototherapy x 10 wks C2: Phototherapy + exercise[b] x 10 wks C3: Placebo phototherapy + exercise[b] x 10 wks	FIQ, VAS, fatigue, body stiffness, no. of tender points, depression, anxiety, SF-36; (10 wks)[e]
Vayvay (23), 2016 (Turkey)	Diagnosed with FM by ARS criteria, ≥18 y/o, continuous chronic pain ≥ 6 mos	I: 15 (0%) C1: 15 (0%) C2: 15 (0%)[c]	I: 36.4 ± 8.3 C1: 38 ± 8.4 C2: 38 ± 9.9 [c]	I: Ga-AS Laser (850 nm; 40 mW; 2 J/cm^2; 50-60 Hz, 3 min/painful point on back and head) + exercise x 3 wks C1: Placebo laser + exercise[d] x 3 wks C2: Kinesiotape on the back for 3 wks + exercise[d] x 3 wks	FIQ, VAS, SF-36, Beck Depression Inventory Anxiety Level (3 wks)
Ruaro (24), 2014 (Brazil)	Diagnosed with FM by ACR criteria	I: 10 (0%) C: 10 (10%)	I: 39.4 (34-45) C: 43.4 (33-55)	I: GaAlAs laser (670 nm, 20 mW, 4 J/cm^2 on 18 tender points, 3 times/wk) x 4 wks C: Placebo laser x 4 wks	FIQ, McGill Pain Questionnaire, VAS (4 wks)
Fernández (25), 2011 (Spain)	Diagnosis of FM for 3-10 yrs, 36-61 y/o woman	I: 16 (0%) C: 15 (0%)	I: 51.6 ± 6.18 C: 52.4 ± 5.88	I: Girlase E1.1010 (905 + 10 nm, 0.70 mJ/drive, 1000 mW boost of the drives, pulsed, 1 min/frequency x 6 on 7 points) x 8 wks C: Placebo laser x 8 wks	CRD (FIQ), Generalized pain, fatigue (8 wks)
Matsutani (26), 2007 (Brazil)	Diagnosed as FM for 25-60 y/o, exclude neoplasia	I: 10 (0%) C: 10 (0%)	I: 44 (28-60) C: 45 (31-57)	I: GaAlAs laser (830 nm, 3 J/m^2, average 30 mW, continuous) + exercise[d] 1 h BIW x 5 wks C: Placebo laser + exercise[d] 1 h BIW x 5 wks	FIQ, VAS, SF-36 (5 wks)
Amargan (27), 2006 (Turkey)	Diagnosed with FM by ACR criteria	I: 16 (10%) C: 16 (0%)	I: 38.9 ± 4.9 C: 37.6 ± 5.9	I: GaAlAs laser (830 nm, 50 mW, continuous, 1 min & 2 J/tender point), 5 days/wk x 2 wks C: Placebo laser 5 days/wk x 2 wks	FIQ, no. of tender points, morning stiffness, VSGI (2 wks)
Gür (28), 2002 (Turkey)	Diagnosed with FM by ACR criteria; exclude major clinical conditions other than FM	I: 25 (20%) C1: 25 (24%) C2: 25 (16%)[c]	I: 30.4 ± 6.9 C1: 28.5 ± 6.3 C2: 30.1 ± 8.7[c]	I: Ga-As laser (904 nm, average 11.2 mW, 2 J/cm^2, 2.8 kHz) 3 min/tender point every afternoon x 2 wks (except weekend) C1: Placebo laser x 2 wks C2: Amitriptyline 10 mg at bedtime x 8 wks[c]	FIQ, depression (HDRS, DSM-IV), pain, no. of tender points, morning stiffness, sleep disturbance, fatigue (2 wks/6 mos)
Gür (29), 2002 (earlier published) (Turkey)	Diagnosed with FM by ACR criteria; exclude major clinical conditions other than FM	I: 20 (0%) C: 20 (0%)	Not mentioned	I: Ga-As laser (904 nm, average 11.2 mW, 2 J/cm^2, 2.8 kHz) 3 min/tender point every afternoon x 2 wks (except weekends) C: Placebo laser x 2 wks	Pain, morning stiffness, no. of tender points, sleep disturbance, fatigue (2 wks)

Abbreviations: ACR, American College of Rheumatology; ARS, American Rheumatology Society; C, Control group; CRD, Cuaderno de recogida de datos; FIQ, Fibromyalgia Impact Questionnaire; FM, Fibromyalgia; HDRS, Hamilton Depression Rating Scale; I, Intervention group; LED, light-emitting diode; SF-36, 36-item Short-Form Health Survey; VAS, Visual Analog Scale of pain; VSGI, global improvement as reported on a verbal scale. Age was presented as mean ± SD or mean (range). [a] (): % men; [b] stretching and aerobic exercise; [c] not included for our analysis; [d] stretching; [e] (): duration of outcome follow-up

Table 2. *Methodological quality assessment of the selected RCTs.*

Study	Allocation Generation	Allocation Concealment	Blinding	Data Analysis	Loss to Follow-up	Patient Gender	Other Relevant Remarks
Germano (14), 2018	Adequate	Unclear	Patients, evaluators	ITT	0%	Only women	Some patients continued regular medications for fibromyalgia in 2 groups
da Silva (22), 2018	Adequate	Unclear	Patients, phototherapy programmer, and outcome assessor	ITT	0%	Only women	Age distribution not reported; unknown pharmacological therapy for fibromyalgia in 2 groups
Vayvay (23), 2016	Unclear	Unclear	Patients	ITT	0%	Only women	-
Ruaro (24), 2014	Adequate	Unclear	Patients	ITT	0%	Only women, with one man in the placebo group	Unknown pharmacological therapy for fibromyalgia in 2 groups
Fernández (25), 2011	Unclear	Unclear	Patients	ITT	0%	Only women	Unknown pharmacological therapy for fibromyalgia in 2 groups
Matsutani (26), 2007	Unclear	Unclear	Unclear	PP	20%	Only women	Unclear reasons for, and unknown distribution of, loss of follow-up; may have high variability of emitted power and energy dose; unknown pharmacological therapy for fibromyalgia in 2 groups
Armagan (27), 2006	Unclear	Unclear	Patients and evaluators	ITT	0%	Only women	-
Gür (28), 2002	Adequate	Unclear	Patients	ITT	0%	-	-
Gür (29), 2002 (earlier published)	Adequate	Unclear	Patients	ITT	0%	Only women	Age distribution not reported

Abbreviations: ITT, intention to treat; PP, per-protocol; RCT, randomized controlled trial.

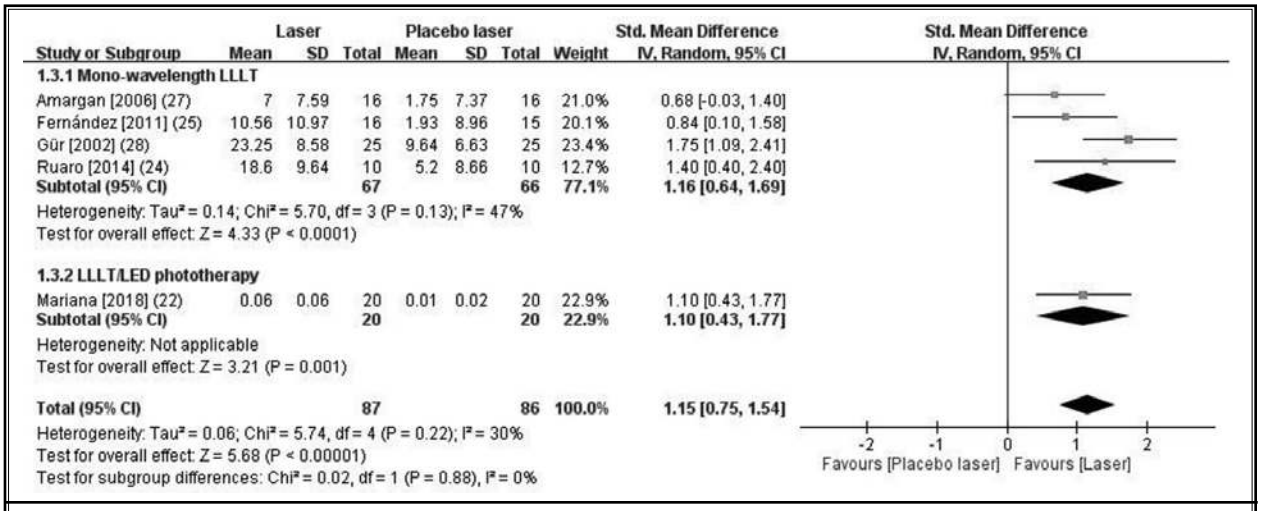

Fig. 2. *Forest plot of changes in FIQ score after LLLT or placebo laser treatment.*

CI, 0.49-1.52; I^2 = 49%; Fig. 4). As for the combined LLLT/LED phototherapy, the only RCT evaluating efficacy showed significant improvement in FIQ, pain, and number of tender points compared with the placebo group. The effect of combined LLLT/LED phototherapy on pain relief and reduction in the number of tender points seemed to be more obvious than monowavelength LLLT (Figs. 3 and 4).

Secondary Outcomes (Fatigue, Stiffness, Depression, and Anxiety)

In the monowavelength LLLT group, our analysis showed significant improvements in the severity of fatigue (pooled SMD: 1.4; 95% CI, 0.96-1.8), stiffness (pooled SMD: 0.92, 95% CI: 0.36-1.48), depression (pooled SMD: 1.46, 95% CI: 0.93-2.00), and anxiety (pooled SMD: 1.46, 95% CI, 0.45-2.47). On the other hand, the only one RCT evaluating the efficacy of the combined LLLT/LED phototherapy demonstrated significant improvement in the severity of fatigue, stiffness, and anxiety, but not depression, when compared with those in the placebo laser group.

Comparison of LLLT Plus Exercise and Placebo Laser Treatment Plus Exercise

Three RCTs evaluated the efficacy of monowavelength LLLT with exercise (14,23,26). There was no significant difference between the monowavelength

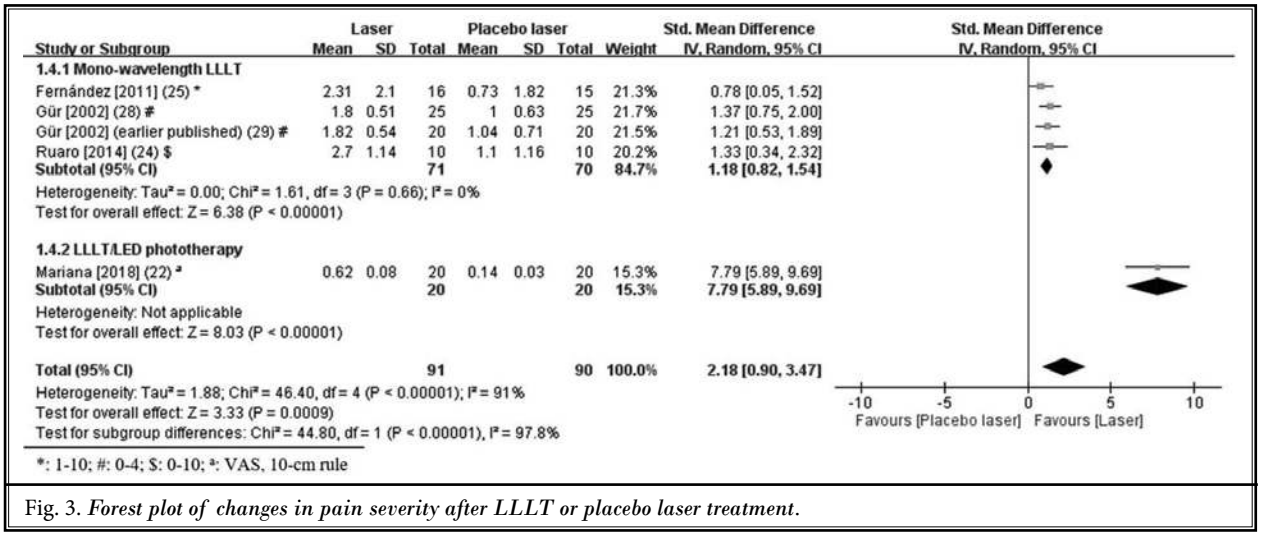

Fig. 3. *Forest plot of changes in pain severity after LLLT or placebo laser treatment.*

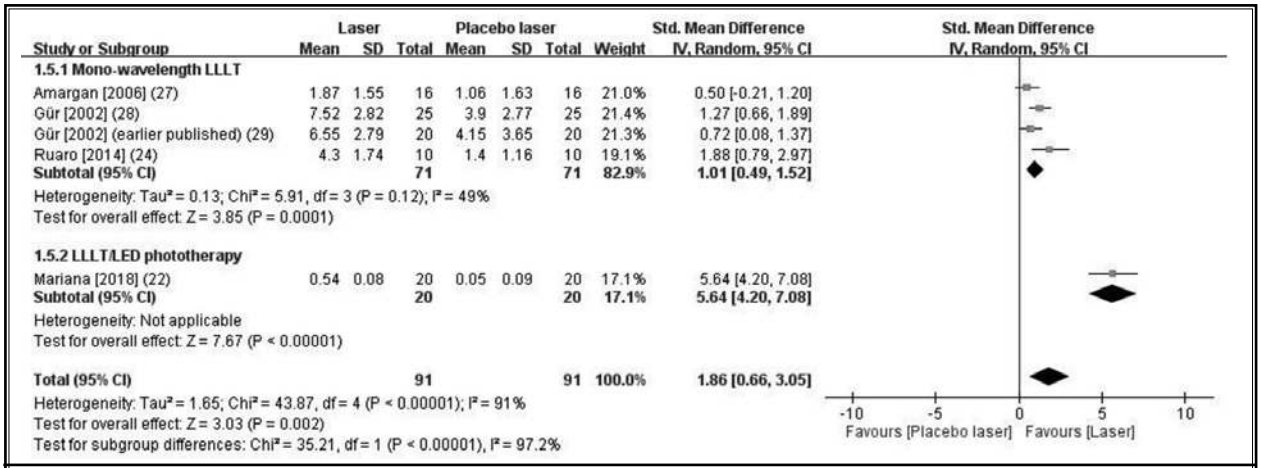

Fig. 4. *Forest plot of changes in number of tender points after LLLT or placebo laser treatment.*

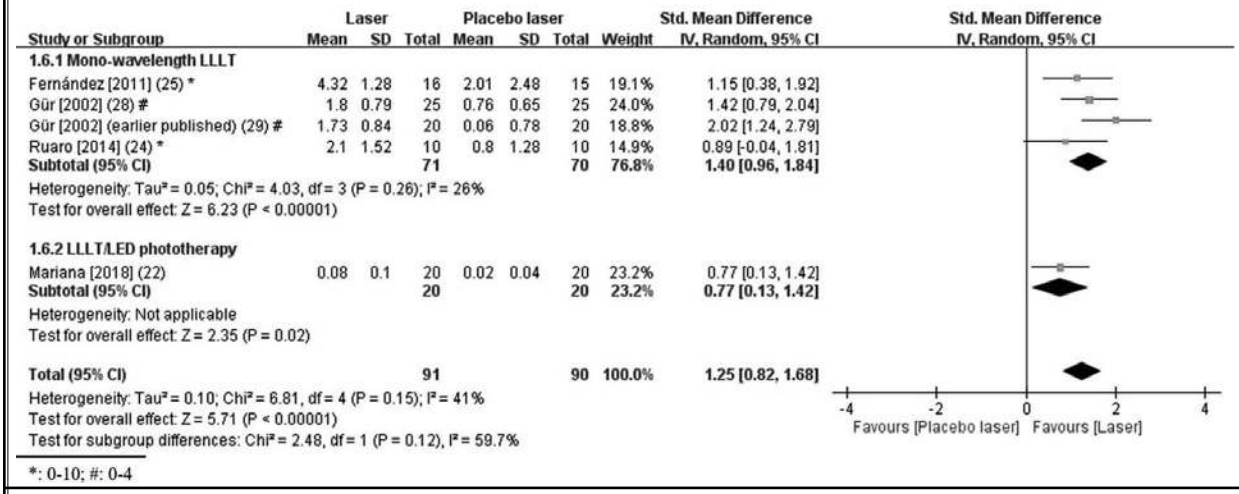

Fig. 5. *Forest plot of changes in severity of fatigue after LLLT or placebo laser treatment.*

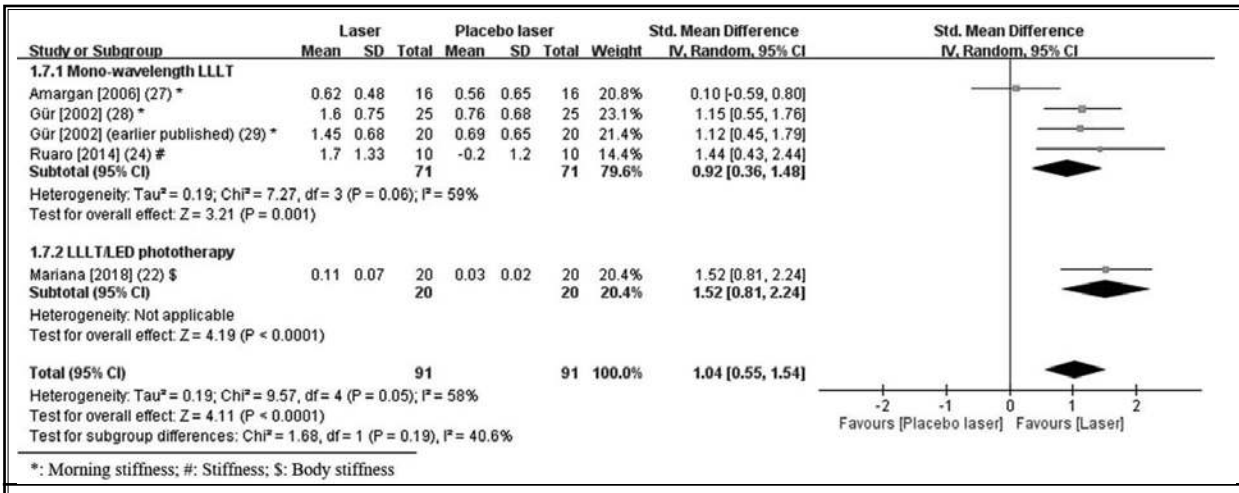

Fig. 6. *Forest plot of changes in severity of stiffness difference after LLLT or placebo laser treatment.*

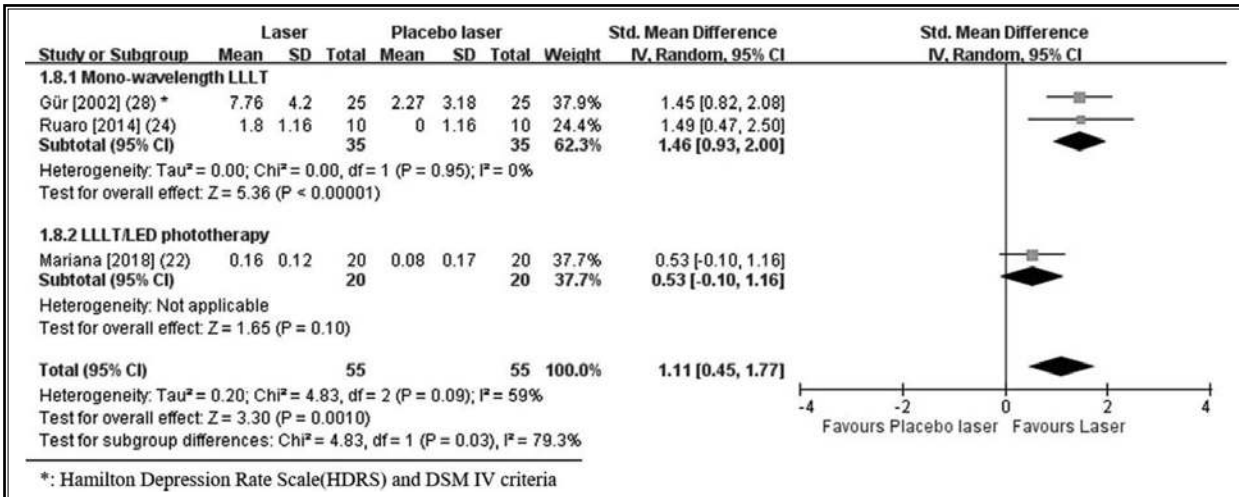

Fig. 7. *Forest plot of changes in severity of depression after LLLT or placebo laser treatment.*

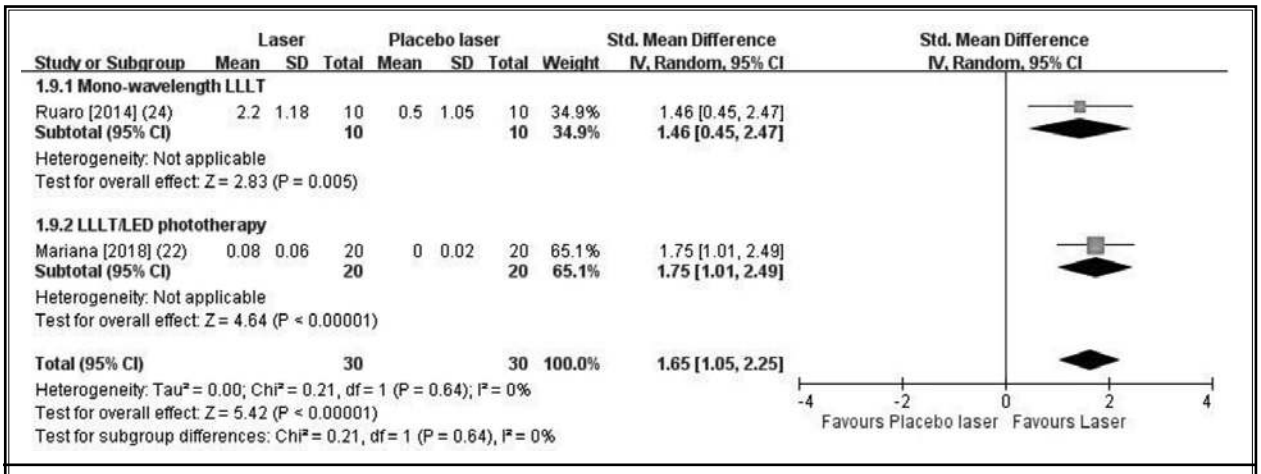

Fig. 8. *Forest plot of changes in severity of anxiety after LLLT or placebo laser treatment.*

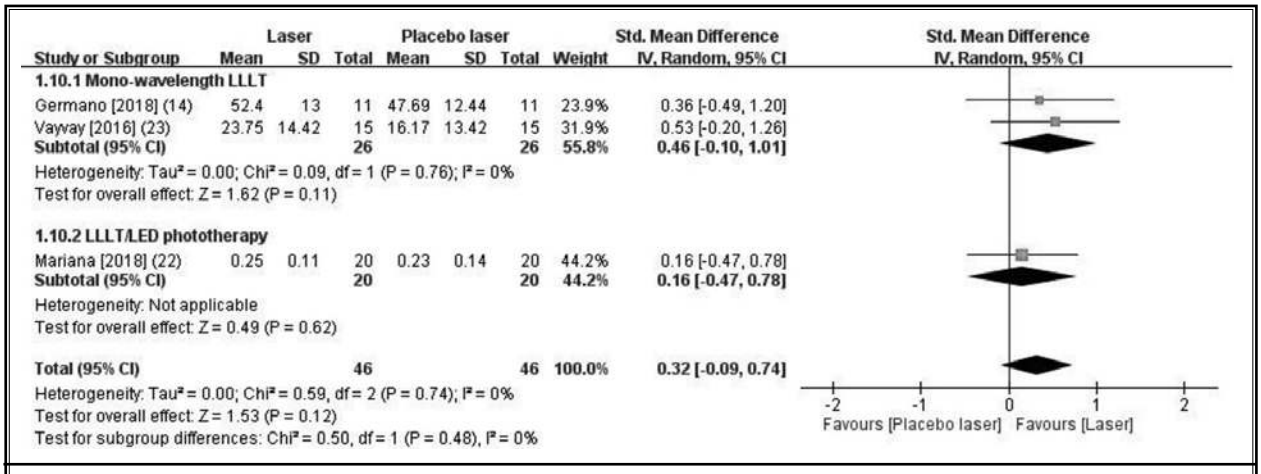

Fig. 9. *Forest plot of changes in FIQ scores between LLLT with exercise and exercise alone.*

LLLT plus standardized exercise program and exercise program alone in the primary outcomes of FIQ score (pooled SMD: 0.34; 95% CI, -0.17 to 0.85; I^2 = 14%; Fig. 9), pain (pooled SMD: 0.46; 95% CI, -0.10 to 1.01; I^2 = 0%; Fig. 10) and number of tender points (pooled SMD: 0.59; 95% CI, -0.26 to 1.45; Fig. 11) and secondary outcomes of fatigue, stiffness, anxiety, or depression (SMD: -0.16; 95% CI, -1.04 to 0.72; SMD: 0.08; 95% CI, -0.79 to 0.96; SMD: 0.09; 95% CI, -0.80 to 0.98; I^2 = 70%; SMD: -0.38; 95% CI, 1.27-0.50, respectively; Figs. 12-15).

Compared with standardized exercise alone, LLLT/LED combination phototherapy plus exercise program, as reported in only one RCT, provided significant additional benefit in relieving the primary outcome of the severity of pain and number of tender points (SMD: 5.20; 95% CI, 3.85-6.55 and SMD: 7.02; 95% CI, 5.29-8.76, respectively) and the secondary outcome of fatigue (SMD: 1.35; 95% CI, 0.65-2.04), but it not decrease in FIQ score, severity of stiffness, or psychiatric symptoms (Figs. 9-15) (22).

Side Effects

Four RCTs (22,24,27,29) reported no side effects of LLLT in patients with fibromyalgia, consistent with previous studies (6,10,31). However, the remaining RCTs did not report on side effects (14,23,25,26,28).

Discussion

LLLT has been introduced as a noninvasive, therapeutic intervention for pain in several musculoskeletal disorders. Some mechanisms, such as increased nociceptive threshold, endorphin production, and downstream

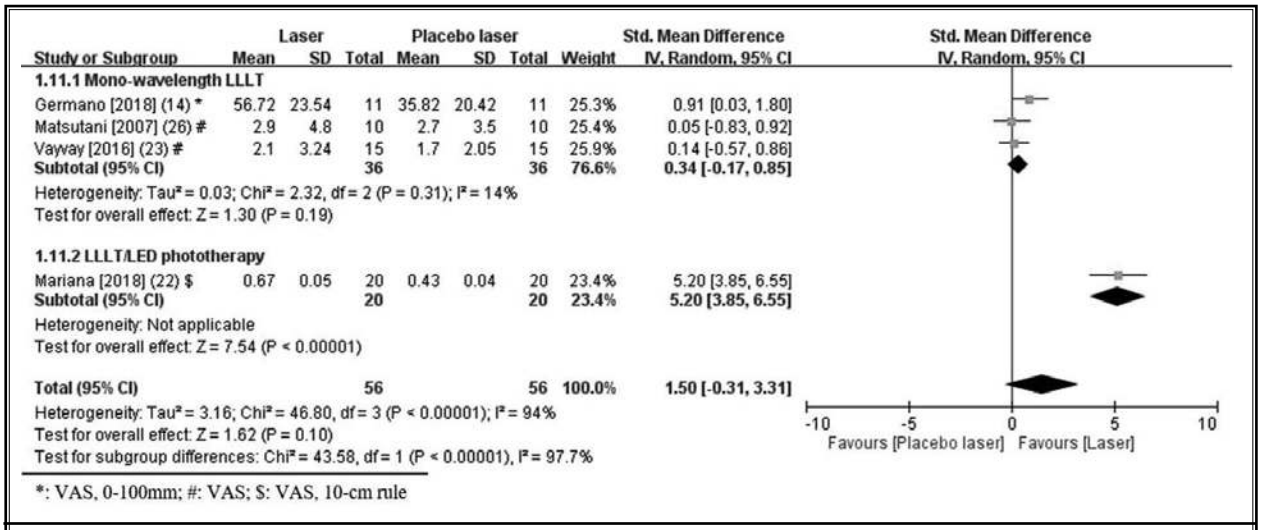

Fig. 10. *Forest plot of changes in severity of pain between LLLT with exercise and exercise alone.*

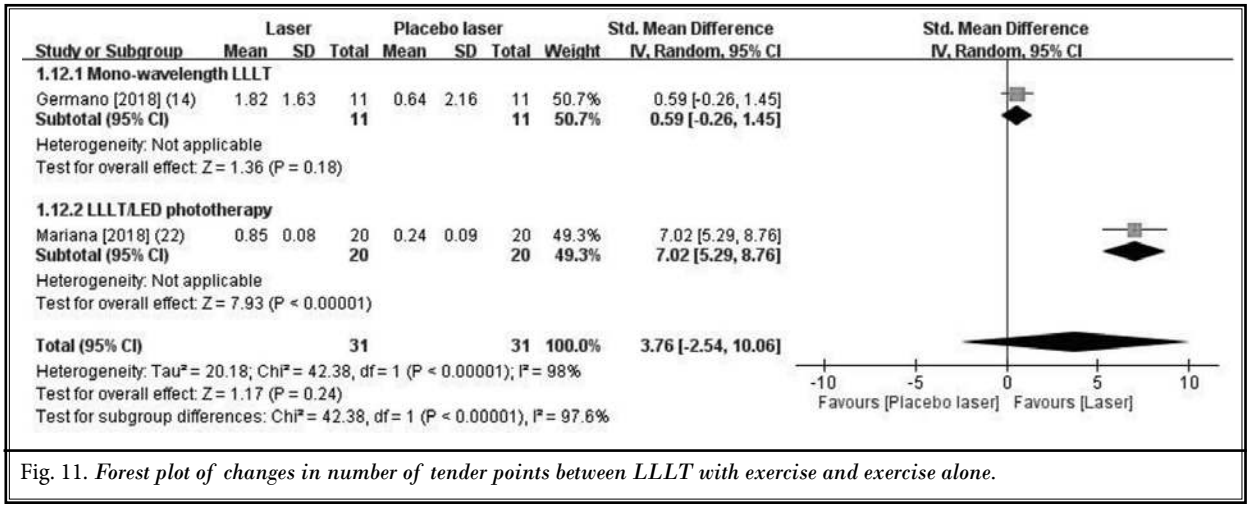

Fig. 11. *Forest plot of changes in number of tender points between LLLT with exercise and exercise alone.*

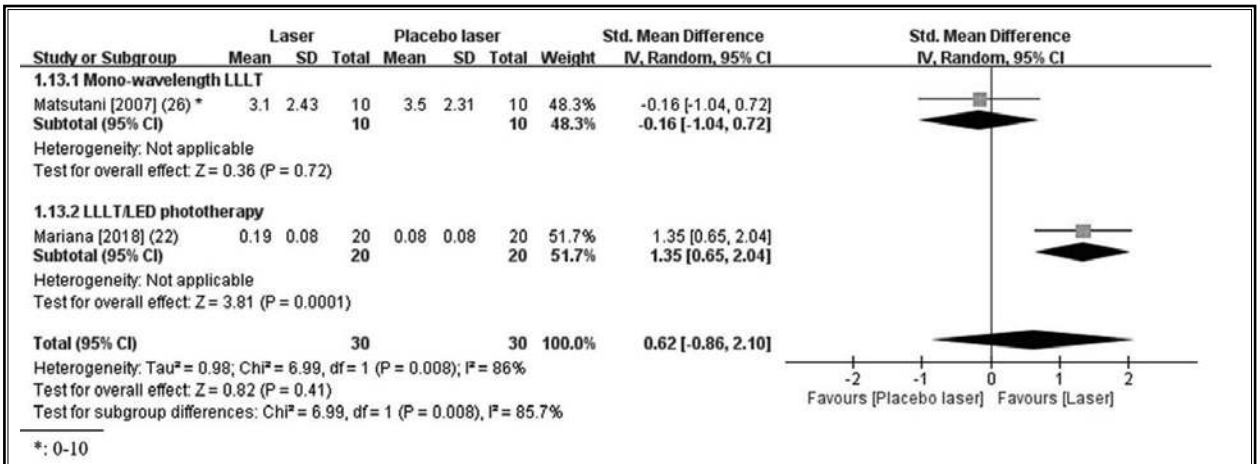

Fig. 12. *Forest plot of changes in severity of fatigue between LLLT with exercise and exercise alone.*

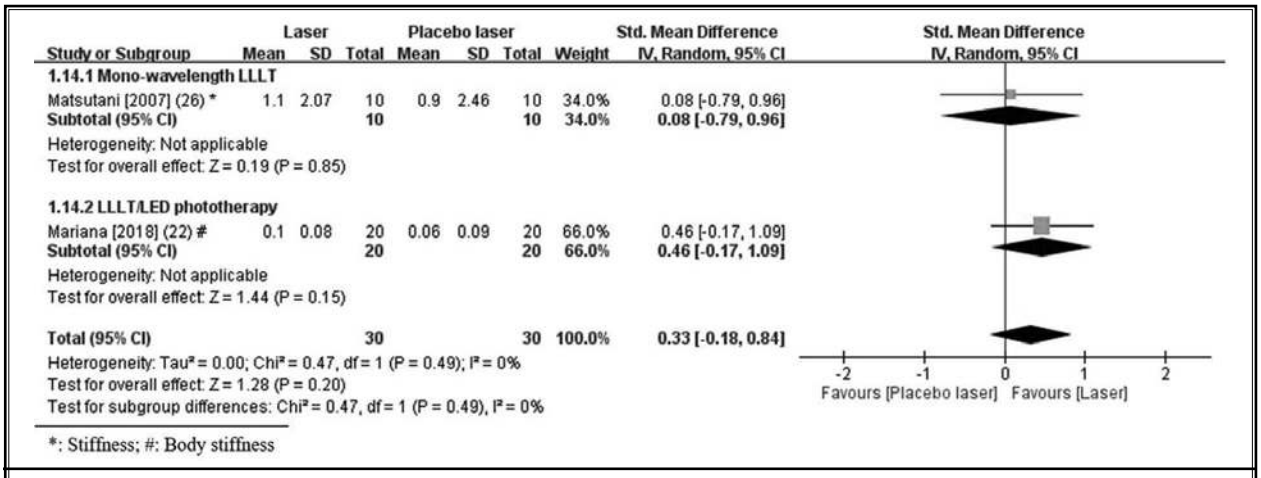

Fig. 13. *Forest plot of stiffness between laser with physical activity and physical activity only.*

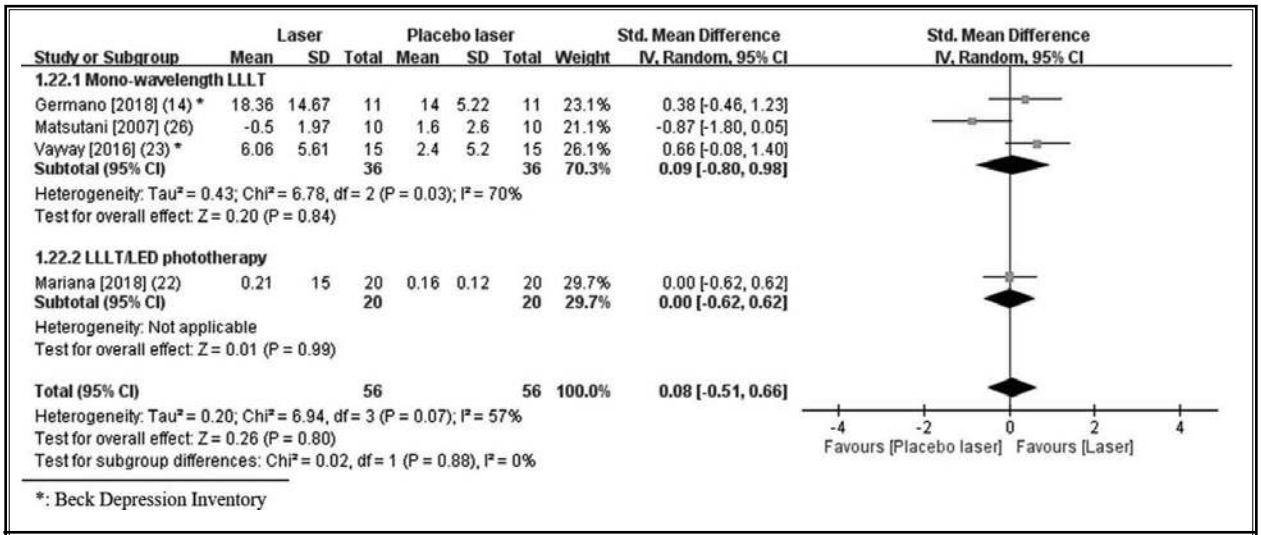

Fig. 14. *Forest plot of depression between laser with physical activity and physical activity only.*

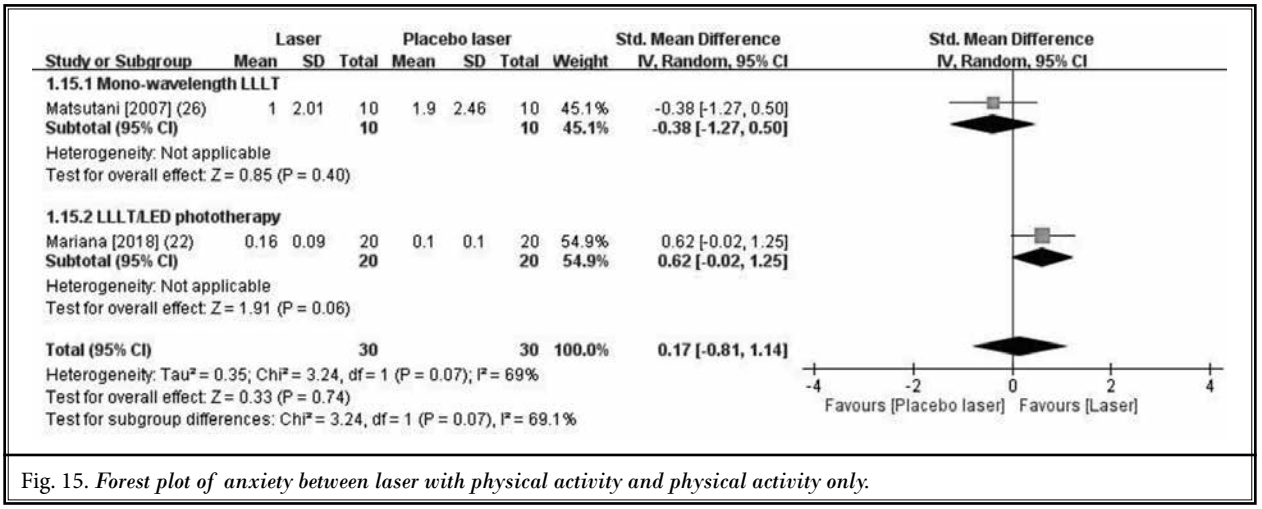

Fig. 15. *Forest plot of anxiety between laser with physical activity and physical activity only.*

opioid receptors, have been postulated to explain the analgesic effect of phototherapy (32). Other hypotheses include anti-inflammation due to a decrease in prostaglandin-2 and cyclooxygenase-2 levels (28,32), proliferation and neovascularization of connective tissue cells (33,34), and increase in blood flow and promotion of healing by increase in the levels of nitric oxide, a powerful vasodilator (32). A recent systematic review and meta-analysis of 18 studies suggested that LLLT effectively reduces pain in adult patients with musculoskeletal disorders; however, patients with fibromyalgia were not included in this meta-analysis (7). Furthermore, studies have indicated the beneficial role of LLLT/LED combination in the treatment of nonspecific knee pain (35) as well as masseter and temporalis muscle pain in women with temporomandibular disorder (36).

Pain is the main symptom in patients with fibromyalgia. Some RCTs have investigated the effect of LLLT on fibromyalgia, but by using small sample sizes. Our study is the first systematic review and meta-analysis including 9 RCTs involving 325 patients to specifically evaluate the efficacy of LLLT in fibromyalgia. Our results demonstrated that LLLT provided significant improvement in FIQ score, pain severity, number of tender points, fatigue, stiffness, depression, and anxiety compared to placebo. However, when compared with pure exercise therapy, LLLT with exercise therapy did not show more benefits. On the other hand, the single RCT using LLLT/LED showed significant improvement in the above-mentioned outcomes, except for depression, when compared to placebo. When compared with patients with fibromyalgia who received exercise therapy, combined LLLT/LED phototherapy and exercise therapy had additional benefits in reducing the severity of pain, number of tender points, and fatigue.

However, this review still has some limitations, mostly because of the low-to-middle methodological quality of the selected studies (Table 2). First, most studies did not report the allocation process clearly and only blinded the patients; neither phototherapy programmer nor outcome assessor were blinded. Considering that nearly all outcomes were subjective parameters, the above shortcomings may introduce allocation bias, performance bias, and detection bias. Second, one study used per-protocol analysis because of a 20% loss to follow-up without reporting the reasons for, or the distribution of, the loss to follow-up (26); this may have introduced attrition bias. Third, although LLLT was used in all trials, the differences in laser types, energy sources, and exposure times used in the studies may have resulted in some heterogeneity. Fourth, although patients with fibromyalgia did not take associated medications in most RCTs, patients in one trial maintained their usual pharmacological therapies (22), another trial included some patients continuing their regular medications (14), and the other 3 RCTs did not mention whether the participants were under concurrent medication (24-26); therefore, we could not clarify the separate roles of medication or phototherapy in fibromyalgia. Finally, long-term follow-up up to 6 months was only conducted in one RCT (27).

In spite of the limitations, our study is the largest systematic review and meta-analysis to evaluate the efficacy of LLLT in patients with fibromyalgia, and it has provided the most relevant available evidence on LLLT for fibromyalgia. In conclusion, our data indicate that LLLT is an emerging, noninvasive, well-tolerated treatment for fibromyalgia to relieve discomfort, particularly in patients who do not exercise regularly.

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