Pain Physician 2020; 23:461-475 • ISSN 1533-3159

Systematic Review

Efficacy of Manual Therapy on Pain, Impact of Disease, and Quality of Life in the Treatment of Fibromyalgia: A Systematic Review

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Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 02-27-2020
Accepted for publication: 04-08-2020

Free full manuscript: www.painphysicianjournal.com

Background: Myofascial mobilization has been used as an intervention for patients with fibromyalgia (FM) for acting on ascending nociceptive pathways possibly involved in the central sensitization process, modulating the pain experience. However, there is still a gap in its efficacy compared with another hands-on approach because manual therapy has nonspecific effects, such as placebo.

Objectives: This systematic review aims to review the scientific literature for an overview of the efficacy of manual therapy in pain, disease impact, and quality of life in patients with FM compared with control or other treatments through randomized clinical trials.

Study Design: This study involved systematic review of published randomized controlled trials (RCTs).

Setting: This study examined all RCTs evaluating the effect of manual therapy on pain, impact of disease, and quality of life for patients with FM.

Methods: Systematic review. The research was performed in 9 databases: MEDLINE/PubMed, CINAHL, Web of Science, Scopus, ScienceDirect, Lilacs, SciELO, PEDro, and Cochrane. Searches were carried out from the end of the project until September 2019, with no language and year restrictions. Randomized controlled clinical trials that used the following outcome measures were included: Visual Analog Scale, Fibromyalgia Impact Questionnaire, and SF-36 Quality of Life Questionnaire. The risk of bias and quality of studies was assessed using the PEDro scale; the Cochrane risk-of-bias tool; and Grading of Recommendations Assessment, Development, and Evaluation System.

Results: Seven studies were included (368 patients). The quantitative analysis was performed on 4 studies because of the lack of data in the others. Myofascial release was the most used modality. The level of evidence ranged from very low to moderate, mainly because of the inconsistency and inaccuracy of results.

Limitations: The present systematic review presented limitations because of the heterogeneity of the included studies and only a short-term analysis of the intervention results. It was observed that other information, such as pressure, repetition, and/or sustaining manual therapy techniques, could be better described in future protocols, aiming at a better comparison between the techniques and their subsequent reproducibility.

Conclusions: Current evidence of manual therapy in patients with FM, based on a very low to moderate quality of evidence, was inconclusive and insufficient to support and recommend the use of manual therapy in this population. To date, only general osteopathic treatment has achieved clinically relevant pain improvement when compared with control.

Key words: Fibromyalgia, manual therapy, pain, quality of life, impact of disease, physiotherapy, manipulation techniques, mobilization

Pain Physician 2020: 23:461-475

Fibromyalgia (FM) is a rheumatic syndrome with an unknown etiology, which may be due to different pathophysiological disorders involving the processing of pain in the central nervous system (1,2). It is predominant in women between ages 30 and 55 years, with a prevalence ranging from 0.2% to 6.6% in the general population (3,4). Although individuals with FM may present a great variability of clinical conditions, regarding their symptoms and the presence of comorbidities (2,5), the main characteristic is the presence of chronic diffuse musculoskeletal pain, which may have a negative impact on their physical functioning and quality of life (6-9).

Because it is a chronic condition, FM treatment is of major importance because these patients make frequent and extensive use of health services, impacting on high personal and social costs (10,11). It is known that interdisciplinary treatment is recommended for this population, and as far as physiotherapy is concerned, a multimodal approach encompassing different resources during care has been recommended (9,12,13).

Among the range of physiotherapy techniques, manual therapy has been increasingly studied as a treatment for this population because it acts on ascending nociceptive pathways possibly involved in the process of central sensitization, improving pain through mechanical and neurophysiological mechanisms (12,14,15). Manual therapy is defined as "any techniques administered manually, using touch, by a trained practitioner for therapeutic purposes," and may include mobilization or manipulation of joints in varying directions and velocities, stretching, massage, and soft tissue manipulation techniques (16-18).

The use of manual therapy as physiotherapy management of patients with FM has already demonstrated an effect on improving the impact of its symptoms, mainly on pain and the quality of life (17,19-23). Systematic reviews to assess the efficacy of chiropractic techniques and different types of massage have indicated the positive effects of massage and myofascial release on FM symptoms, especially pain (24-26). However, in addition to presenting limitations in their evidence due to language restrictions (24,25), searches were concluded at least 5 years ago and new studies have since been published (24-26).

To our knowledge, no systematic review has yet been found that assesses the risk of bias, quality of evidence, and external validity of studies involving the efficacy of different manual therapy techniques in FM patients to verify whether there are other more effective approaches among the possibilities already studied.

Based on the foregoing, this systematic review aims to review the scientific literature regarding the efficacy of manual therapy on pain, impact of disease, and quality of life for patients with FM compared with control or other treatments through randomized controlled trials (RCTs).

Methods

This systematic review was structured along the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and was prospectively registered at PROSPERO (CRD42018107818).

Selection Criteria

To verify the eligible articles, the following steps were followed: searching for titles found in each cross-referencing of all databases, exclusion of repeated titles, exclusion of titles with irrelevant contents, and exclusion of titles by reading the abstract according to the eligibility criteria. Afterward, the full texts of the possible articles were revised for inclusion.

The present systematic review included articles that met the following PICOS criteria: 1) patients: confirmed diagnosis of FM according to the established criteria of the American College of Rheumatology (ACR) from 1990, 2010, and 2016 (6,7,27). 2) Intervention: manual therapy, alone or combined with exercise, manual therapy performed by a therapist, which includes spinal or joint manipulation or mobilization (with or without thrust), massage, craniosacral therapy, osteopathy, chiropractic, and myofascial release techniques. 3) Comparison: sham treatment, no treatment (control), active therapies (e.g., exercise) or other physiotherapy interventions. For studies that performed manual intervention combined with exercise, we included those in which the comparison was exercise or exercise combined with sham manual therapy. 4) Outcomes: pain, FM impact, and quality of life. 5) Study: RCTs. Studies were excluded if they involved adolescents (aged < 18 years); pregnant women; patients with other associated rheumatic diseases; severe decompensated comorbidities (cancer, thyroid disease, and diabetes); presence of cardiac, renal, or hepatic insufficiency; arterial or peripheral venous insufficiency.

Studies were excluded that did not detail the component of manual therapy used or that used the following techniques: stretching, techniques based on traditional Chinese medicine, use of instruments to per-

form therapy, energy therapies that do not involve direct touch, or nonrandomized studies. Studies in which the full article was published with only partial results were also excluded.

Study Selection and Search Strategy

The study was conducted by 2 independent reviewers in the following databases: MEDLINE/PubMed, CINAHL, Web of Science, Scopus, ScienceDirect, Lilacs, SciELO, PEDro, and Cochrane. Searches were carried out from the end of the project until September 2019, with no language and year restrictions. The databases were accessed through CAPES Journals by both reviewers.

Only RCTs that presented pain, FM impact and/ or quality of life as outcomes were included. The measures of the selected outcomes were: the visual analog scale (VAS) for the pain outcome, the FM impact questionnaire (FIQ) and the revised FM impact questionnaire for the FM impact outcome, and the SF-36 (short form) quality of life questionnaire for the quality of life outcome. These instruments were chosen because they are the most used for this population, which evaluate the most important clinical aspects related their symptoms (27–31). The FIQ is the main questionnaire, once it is a specific instrument to evaluate the impact of FM (28).

For the search strategies in English, the following MeSH entry terms and keywords were used for MEDLINE/PubMed, Web of Science, Scopus, ScienceDirect, PEDro, and Cochrane databases: for the population (fibromyalgia), for the intervention (musculoskeletal manipulations, chiropractic, myofascial release, soft-tissue techniques, connective tissue release, massage-myofascial release, osteopathy, joint manipulation, spinal manipulation, joint mobilization, and connective tissue massage) and for outcomes (pain and quality of life) (Fig. 1).

For CINAHL database, as it contains its own descriptors, the following words were used: for the population (fibromyalgia), for the intervention (musculoskeletal manipulations, myofascial release manual therapy, joint manipulation, and spinal manipulation) and for outcomes (pain and quality of life) (Fig. 1).

For the search strategies in Portuguese, the following DeCS entry terms and keywords were used for Lilacs and SciELO databases: for the population (fibromialgia), for the intervention (manipulações musculoesqueléticas, quiroprática, manipulação miofascial, liberação miofascial, liberação tecido conjuntivo, massagem de liberação miofascial, osteopatia, manipulação articular, manipulação vertebral e mobilização articular) and for outcomes (dor e qualidade de vida) (Fig. 2).

The Boolean operator "AND" was used to combine terms between population, intervention, and outcome, totaling 22 crosses in MEDLINE/PubMed, Web of Science Scopus, ScienceDirect, PEDro, and Cochrane; 20 crosses in Lilacs and SciELO; and 10 crosses in CINAHL. Baseline delimitations were not used to access a larger number of studies. Additional potential articles were searched manually from the reference lists of identified articles.

This systematic review was structured along the guidelines of PRISMA (Preferred Reporting Items for

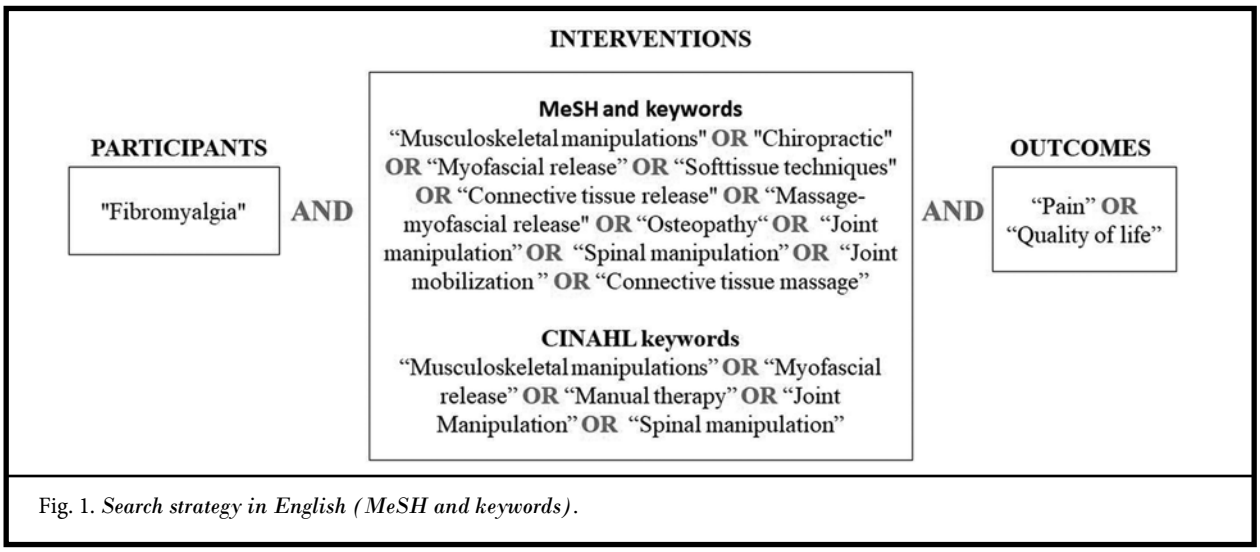

Fig. 1. *Search strategy in English (MeSH and keywords).*

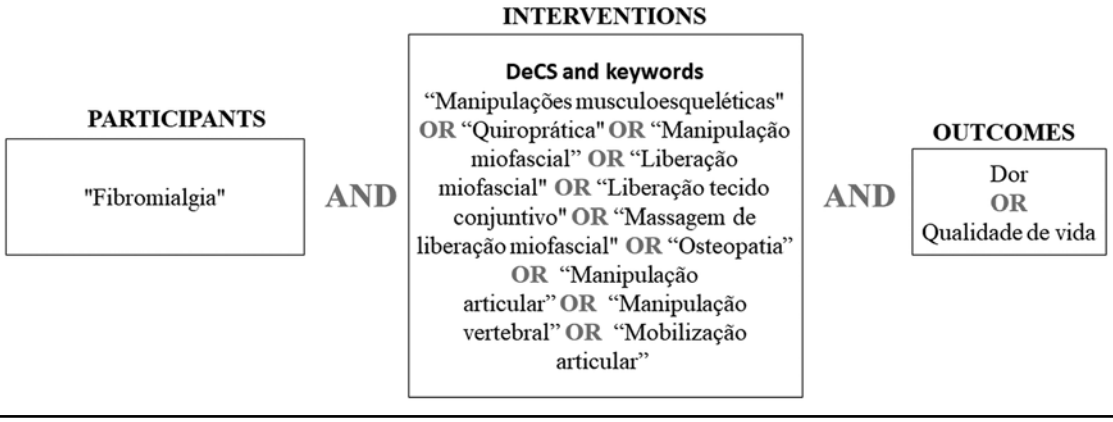

Fig. 2. *Search strategy in Portuguese (DeCS and keywords).*

Systematic Reviews and Meta-Analyses) and was prospectively registered at PROSPERO (CRD42018107818).

Data Extraction

Data were extracted from included studies according to the following parameters: author/year, number of patients, intervention (manual therapy modality), comparison, frequency, duration, side effects, results, and conclusions. There were no differences between reviewers.

For included articles that did not present the necessary data in their results to calculate the treatment effect (mean and standard deviation), the corresponding authors were contacted through the e-mail address provided in the article to request them.

Methodological Quality Appraisal

Three independent reviewers assessed the bias categories of each study, followed by a discussion of discrepancies to reach consensus. The quality evaluation of the study was performed using the PEDro scale of 11 items (32-34) and the Cochrane risk-of-bias tool recorded in the Systematic Review Data Repository (35,36). Studies with a PEDro score of 6 or more were considered to define adequate trial quality (33,35,37-39), whereas for the Cochrane tool, the risk of bias in each section (random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete of outcome data, selective reporting, other bias) was indicated as low (2 points), uncertain (1 point), or high (0 point) (35,40). Besides that, the Grading of Recommendations Assessment, Development, and Evaluation System (GRADE) was used to determine the quality of evidence (41-43). The assessment is subjective and it was based on the methodological guidelines GRADE System—manual for grading the quality of evidence and recommendation strength for health decision-making (44).

Analysis Strategy and Effect of Treatment

The studies were analyzed by subgroups according to the mode of manual therapy used: myofascial release, myofascial release combined with exercise, and general osteopathic treatment.

To analyze the effect of treatment, all variables were continuous, and thus the mean difference and estimated confidence interval (95%) were calculated. The minimum important difference (MID) was considered an improvement of 2 points on the Visual Analog Scale (VAS) (45), and a 14% decrease in the total score on the Fibromyalgia Impact Questionnaire (FIQ) (46).

Results

Study Selection and Characteristics of Included Studies

In total, 609 articles were analyzed by title, after exclusion of repeated titles (n = 608). Of these, 565 were excluded by titles with irrelevant contents, such as other subjects, study design, population, and intervention, and 21 were excluded after reading the abstract (Fig. 3). Twenty-three full studies were analyzed for eligibility (17,19-21,23,47-64), of which 16 were excluded because of the study design (21,52-54,57,59), other

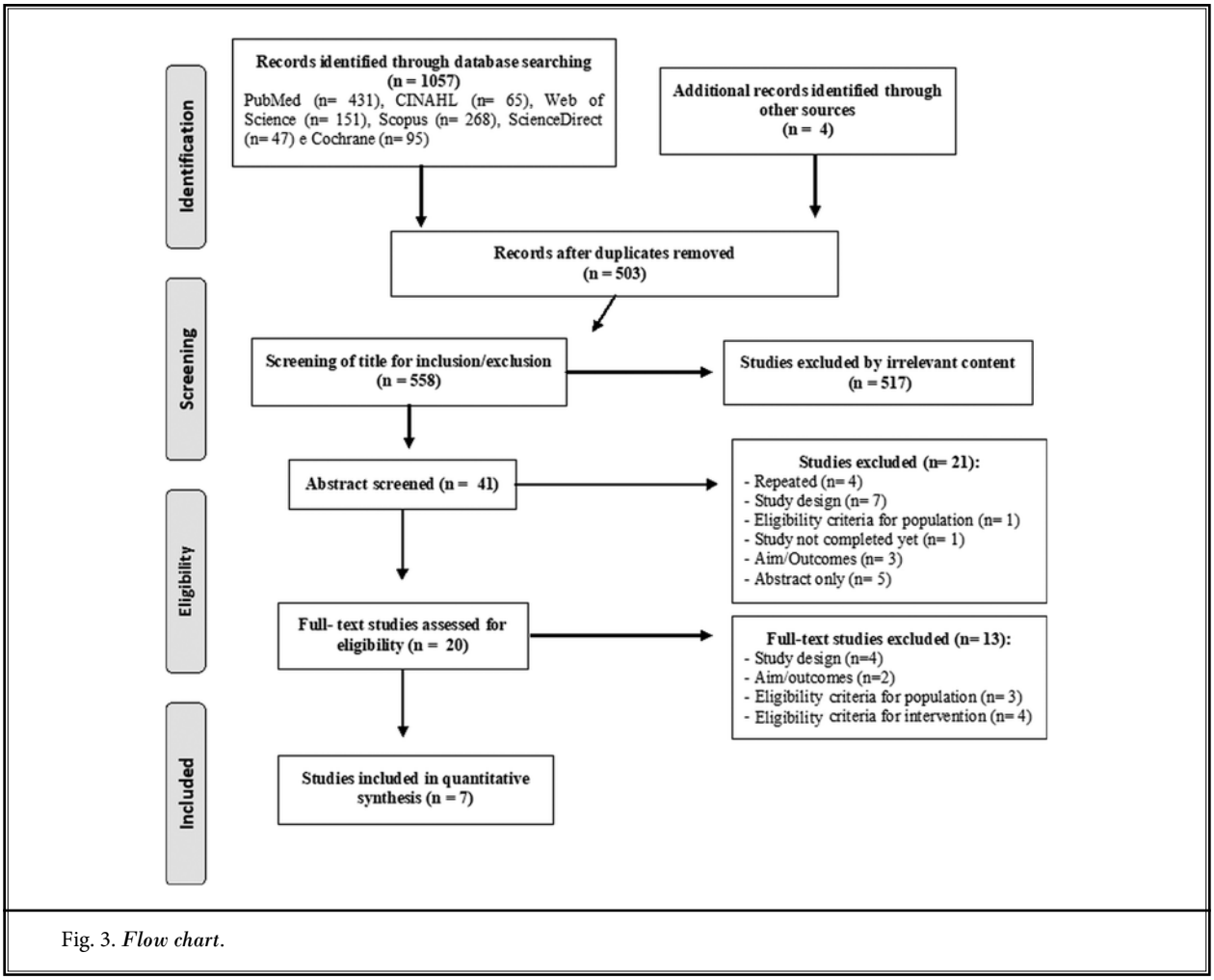

Fig. 3. *Flow chart*.

outcomes (23,66), did not meet the eligibility criteria for the population (19,50,61), and for the intervention (49,51,55,60). Seven studies involving 368 patients were included in the qualitative and quantitative analysis (17,19,47,48,62-64). It has been noted that even more recent articles still use the 1990 diagnostic criteria, of all studies, only 1 used the 2010 criteria (63).

The characteristics of the studies, such as year, place, sample (number of patients, gender, and average age), assessed outcomes, intervention (protocol, duration, number of sessions, and weekly frequency), results/conclusion, and PEDro score, are presented in Table 1.

With regard to the mode of manual therapy, myofascial release in its isolated form (19,48,63,64), combined with the thrust maneuver (17) and exercise (62), was the most common technique. Osteopathy was also used in a study through general osteopathic treatment, which involves joint and soft tissue techniques (47).

The number of sessions performed ranged from 4 to 20, with a duration of 5 to 90 minutes and a frequency of 1 to 5 times per week (17,20,47,48,62-64). All included studies used VAS to assess the outcome pain. Most studies used the FIQ to assess the impact of FM (17,47,48,62-64), and 3 studies used the SF-36 Quality of Life Questionnaire (SF-36) (20,62,63).

Risk of Bias

The risk of bias summary, analyzed through the Cochrane risk-of-bias tool, is presented in Fig. 4. With this tool, only one study received a low risk of bias in all evaluated items (63). One study presented a high risk of bias in the allocation concealment because it is a method of alternation; incomplete outcome be-

Table 1. *Characteristics and PEDro score of the included studies.*

Author, year	Place	Sample	Assessed outcomes	Intervention	Results/Conclusion	PEDro score
EKICI, 2009 (64)	Turkey	Groups: - EG 1: n= 25 F mean age= 36.96 - EG 2: n= 25 ↺ mean age= 38.84	Pain: Visual Analogue Scale Impact of FM: FM Impact Questionnaire	EG 1: myofascial release of the lumbosacral, lower thoracic, scapular, interscapular and cervical-occipital areas. Duration 5 – 20 minutes. Number of sessions: 15. Frequency: 5 per week. EG 2: manual lymphatic drainage of the trunk with light, rhythmic movements without causing pain, following the direction of the flow of the lymphatic vessels. Regions: abdominal, central lymphatic stimulation, neck and head, stimulation of bilateral axillary, inguinal and cervical lymph nodes Duration: 45 minutes. Number of sessions: 15. Frequency: 5 per week.	EG 1: improvement of pain (P <.05) and FM impact (P <.05), except in the subscales of functional capacity and missing work. EG 2: improvement of pain (P <.05) and FM impact (P <.05). Comparison between groups: difference in the improvement of fatigue (P =.006), anxiety (P =.006) and of the total FIQ score (P =.010) of EG 2 compared to EG 1.	6
CASTRO-SÁNCHEZ , 2011 (20)	Spain	Groups: - EG: n= 28 F, 2 M mean age = 49.32 - CG: n= 28 F, 1 M mean age = 46.29	Pain: Visual Analogue Scale Quality of life: Quality of life questionnaire SF-36 (short form)	EG: Myofascial release on the 18 tender points. Mobilized regions: massage-myofascial release in temporal muscle insertion, release of cerebellum sickle by frontal elevation, release of tentorium cerebelli by temporal synchronization, assisted release of cervical fascia, release of the anterior thoracic portion, release of the pectoral region, decompression lumbosacral, gluteal fascia release, flexion of the flexors of the wrist and fingers, and release of the quadriceps fascia. Duration: 90 minutes. Number of sessions: 20. Frequency: 1 per week. CG: sham magnetotherapy applied to the cervical (15 min.) and lumbar (15 min.) regions. Duration: 30 minutes. Number of sessions: 20. Frequency: 1 per week.	EG: improvement of pain (P < .043) and of the domains of physical functioning (P < .007), role physical (P < .039), bodily pain (P < .043) and social functioning (P < .048) of quality of life immediately after 20 sessions. Improvement of pain (P <.043) and physical functioning (P < .01) after one month of treatment. No significant differences were encountered after 6 months of treatment. CG: no significant improvement. Comparison between groups: difference between EG x CG in improvement of pain (P < .043), physical functioning (P = .012), role physical (P = .026), bodily pain (P = .040) and social functioning (P = .028), immediately after 20 sessions After 1 month of intervention, there was a significant difference in pain (P <.043) and physical functioning scores (P = .049), role physical (P = .047) and bodily pain (P = .046). EG x CG. No significant differences were encountered after 6 months.	6
CASTRO-SÁNCHEZ, 2014 (17)	Spain	Groups: - EG: n= 24 F, 21 M mean age = 54 - CG: n= 24 F, 20 M mean age = 53	Pain: Visual Analogue Scale Impact of FM: FM Impact Questionnaire	EG: manual therapy protocol: Suboccipital release, pectoral region release, diaphragmatic release, lumbosacral decompression, psoas fascia release, thoracic manipulation in prone position (thrust). Duration: 45 minutes. Number of sessions: 5. Frequency: 1 per week. CG: no treatment, continued with normal activities.	Comparison between groups: Difference between the EG and CG in pain (P =.038) and FM impact (P <0.001).	7

Table 1 (cont.). *Characteristics and PEDro score of the included studies.*

Author, year	Place	Sample	Assessed outcomes	Intervention	Results/Conclusion	PEDro score
CELENAY, 2017 (62)	Turkey	Groups: - EG: n= 20 F mean age = 42.5 - CG: n= 20 F mean age = 39.9	Pain: Visual Analogue Scale Impact of FM: FM Impact Questionnaire Quality of life: Quality of life questionnaire SF-36 (short form)	EG: exercise + connective tissue massage - Exercises: guidelines for initial postural education and warm-up (10'), aerobic and strengthening (40') and relaxation (10') exercises. Duration: 60 minutes. Number of sessions: 12. Frequency: twice per week, for 6 weeks. - Connective tissue massage: Lower thoracic, scapular and interscapular and cervical regions. Duration: 5-20 minutes. Number of sessions: 12. Frequency: 2 per week. CG: Exercises: guidelines for initial postural education and warm-up (10'), aerobic and strengthening (40') and relaxation (10') exercises. Duration: 60 minutes. Number of sessions: 12. Frequency: 2 per week, for 6 weeks.	EG: improvement of pain ($P < 0.001$), FM impact and quality of life ($P < 0.05$). CG: significant improvement of pain ($P < 0.001$), the subscales of FM impact ($P < 0.05$), except physical functioning and depression, as well as the domains of physical functioning ($P = .006$), role physical ($P = .038$), bodily pain ($P = .004$), and functional impairment , role emotional ($P = .006$), vitality ($P = .005$) and general health ($P = .020$) of quality of life. Comparison between groups: pain ($P = .010$) and the domain of function limitations due to physical health ($P = .030$) quality of life improved in the EG compared to the CG.	6
EKICI, 2017 (48)	Turkey	Groups: - EG 1: n= 15 F mean age = 37.13 - EG 2: n= 21 F mean age = 36.86	Pain: Visual Analogue Scale Impact of FM: FM Impact Questionnaire	EG 1: Pilates Method. Protocol: warm-up (10 '), exercises (40') and cooling down (10'). Number of repetitions increased gradually from 5 to 10 repetitions, as well as the difficulty level of the exercises. Duration: 60 minutes. Number of sessions: 12. Frequency: 3 per week. EG 2: Myofascial release of the following regions: lumbosacral, lower thoracic, scapular, interscapular and cervical-occipital areas Duration: 5 – 20 minutes. Number of sessions: 12. Frequency: 3 per week.	EG 1: improvement of pain ($P = .001$) and of the subscales of FM impact, except in physical functioning capacity and missing work ($P < 0.05$). EG 2: improvement of pain ($P = .001$) and the FM impact ($P < 0.05$). Comparison between groups: significant difference between EG 1 and EG 2 in the subscale of anxiety ($P = .019$) of FM impact.	5
ALBERS, 2018 (47)	Germany	Groups: - EG: n= 16 F mean age = 55.4 - CG: n= 14 F mean age = 53.8	Pain: Visual Analogue Scale Impact of FM: FM Impact Questionnaire	EG: global osteopathic treatment (GOT): Slow mobilization of soft and articular tissues through wide, smooth, rhythmic, continuous movements. Duration: 45 minutes. Number of sessions: 10 Frequency: sessions spread over a period of 12 weeks. CG: no treatment. Only performed assessments in the same intervals as the other groups.	EG: improvement of pain ($P = 0.000$) and FM impact ($P = 0.023$). Comparison between groups: Significant difference in pain between EG and CG ($P = 0.004$).	6

Table 1 (cont.). *Characteristics and PEDro score of the included studies.*

Author, year	Place	Sample	Assessed outcomes	Intervention	Results/Conclusion	PEDro score
CASTRO-SANCHEZ , 2018 (63)	Spain	Groups: - EG 1: n= 28 F, 4 M mean age = 46.79 - EG 2: n= 30 F, 2 M mean age= 47.37	Pain: Visual Analogue Scale Impact of FM: FM Impact Questionnaire Quality of life: Quality of life questionnaire SF-36 (short form)	EG 1: myofascial release of the following regions: release of the deep fascia in the temporal region, suboccipital release, compression-decompression of the temporomandibular joint, global release of the cervicodorsal fascia, release of the pectoral region, diaphragmatic release. Duration: not informed. Number of sessions: 4. Frequency: 1 per week. EG 2: dry needling in active or latent myofascial trigger points with depth of 5 to 15 mm of the following muscles: occipitofrontalis, splenius of the head, sternocleidomastoid, scalene, trapezius, supraspinatus, infraspinatus and multifidus. Insertions were performed using the Hong fast-in and fast-out technique. Hypoxia was produced by compression (by 15") on all active or latent needled trigger points. Duration: not informed. Number of sessions: 4. Frequency: 1 per week.	EG 1: Improvement of pain (P <0.05); of the domains of physical functioning (P = .009) and bodily pain (P = .011) quality of life (P = .001), missing work (P = .004), ability to work (P = .012), pain (P = .015) and stiffness (P = .008) of the FM impact. EG 2: Improvement of pain, in all domains of quality of life and FM impact (P <0.05). Comparison between groups: Significant difference between EG 2 x EG 1 in pain (P <0.001), in the domains of role physical (P =.003), bodily pain (P <0.001), vitality (P =.049) and social functioning of the quality of life, and in the subscales of functional capacity (P =.021), number of days feeling well (P <0.001), missing work (P <0.001), ability to work (P <0.001), pain (P <0.001), fatigue (P <0.001), nonrestorative sleep (P <0.001), stiffness (P <0.001), anxiety (P =.006) and in the total score (P <0.001) of the FM impact.	8

Abbreviations: CG, control group; EG, experimental group.

cause it presented a considerable number of losses without clear reason; and in the item of other biases for presenting a difference between groups at baseline in one of the analyzed outcomes (48). Another study also presented a high risk of bias in the allocation concealment because it is a method of alternation (64). The remaining studies presented uncertain risks in random sequence generation (20,47,48,64), allocation concealment (17,20,47,62), evaluator blindness (20,47), and incomplete outcome (62,64) due to a lack of the necessary information to judge them.

Effect of Interventions and Level of Evidence (GRADE)

The included studies were analyzed according to the mode of manual therapy, however, because they presented great heterogeneity, mainly in relation to the comparison, it was not possible to generate a meta-analysis.

Three studies did not present the means and standard deviations of the outcomes analyzed, and did not respond to our e-mail contact requesting them, therefore it was not possible to calculate the effect of the intervention and the level of evidence by GRADE (17,62,63). The differences in means and confidence intervals estimated from the studies that provided the data are presented in Table 2.

Myofascial Release Vs Lymphatic Drainage

The low level of evidence suggested a higher pain intensity and FM impact in myofascial release compared with lymphatic drainage (Table 3) (64).

Myofascial Release Vs Sham Magnetotherapy

A very low level of evidence suggested a decrease in the score of role physical, role emotional, mental health, and pain (SF-36), and an increased vitality score in myofascial release compared with sham magnetotherapy; and a low level of evidence suggested a decreased pain intensity (VAS), physical functioning, general health, and social aspects (SF-36) in myofascial release compared with sham magnetotherapy (Table 4) (20).

Myofascial Release Vs Pilates

Very low level of evidence suggested a higher pain intensity and FM impact in myofascial release compared with Pilates (Table 5) (48).

General Osteopathic Treatment Vs Control

A moderate level of evidence suggested a reduced pain intensity, and a very low level of evidence suggested an reduction in the impact of FM in general osteopathic treatment compared with control (Table 6) (47).

Discussion

The results of the present systematic review were inconclusive with regard to the efficacy of manual therapy on pain, the impact of FM, and the quality of life of patients with FM, because of the heterogeneity of the included studies and the methodological quality, which ranged from very low to moderate.

It should be noted that the limitations concerning the level of evidence found were due to imprecise and inconsistent results, owing to an overlap of the confidence intervals and differences in intervention (mainly the dosage), and high or uncertain risk of bias (mainly random sequence generation, allocation concealment, and incomplete outcomes).

A previous systematic review concluded that myofascial release is more effective in treating chronic musculoskeletal pain, including FM, than sham procedures (65). However, through the quantitative analysis of the present systematic review, in contrast to what was presented in the study car-

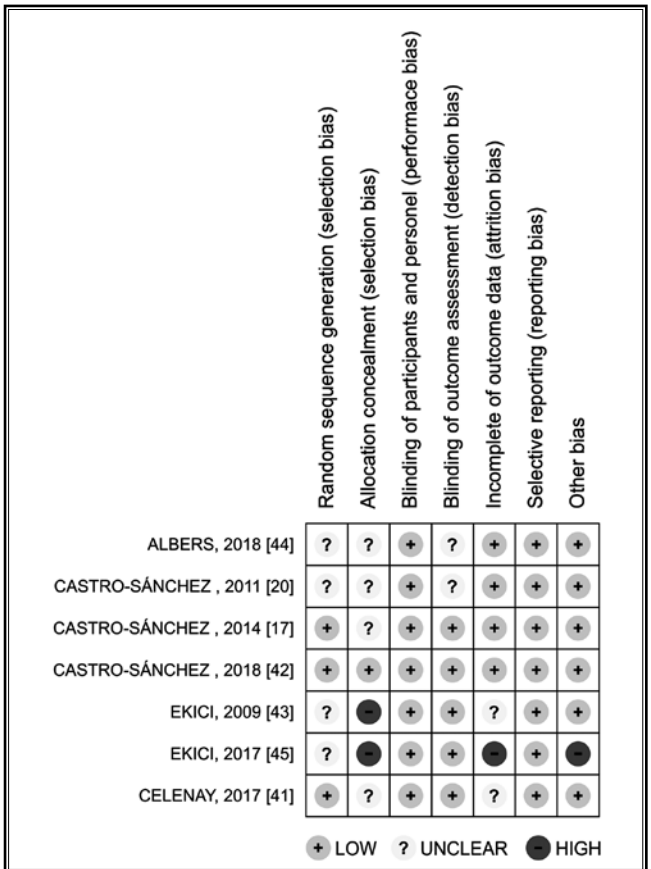

Fig. 4. *Summary of risk of bias of the included studies through the Cochrane risk-of-bias tool.*

Table 2. *Difference of mean values and estimated confidence interval.*

Study	Outcome (score range)	Difference of Mean Values (EG-CG)	Estimated Confidence Interval (95%)
Ekici et al 2009 (64)	VAS (0–10)	1.09	2.05 to 0.14
	FIQ (0–100)	9.67	16.02 to 3.31
Castro-Sánchez et al 2011 (20)	VAS (0–10)	–1.09	–0.27 to –1.92
	SF-36: Physical functioning (0–100)	–4.31	–0.39 to –8.22
	SF-36: Role physical (0–100)	–3.41	0.10 to –6.92
	SF-36: Bodily pain (0–100)	–3.60	1.62 to –8.84
	SF-36: General health (0–100)	–4.64	–1.60 to –7.69
	SF-36: Vitality (0–100)	3.53	8.12 to –1.04
	SF-36: Role social (0–100)	–4.48	–0.45 to –8.50
	SF-36: Role emotional (0–100)	–1.32	4.08 to –6.72
	SF-36: Mental health (0–100)	–3.75	1.96 to –9.46
Ekici et al 2017 (48)	VAS (0–10)	0.37	1.58 to –0.82
	FIQ (0–100)	6.55	14.32 to –1.20
Albers et al 2018 (47)	VAS (0–10)	–2.3	–0.72 to –3.87
	FIQ (0–100)	–11.69	2.6 to –26

Abbreviations: EG-CG, mean difference of experimental group in relation to control group.

Table 3. *Level of evidence by GRADE for myofascial release compared with lymphatic drainage for FM.*

Outcomes	Potential Absolute Effects* (95% CI)		Number of Patients (studies)	Certainty of the Evidence (GRADE)
	Risk with Lymphatic Drainage	Risk with Myofascial Release		
Pain assessed with: VAS Scale of 0–10	The mean intensity of pain was 1.49 points	The mean intensity of pain in the intervention group was 1.09 points more (2.05 more to 0.14 more)	50 (1 RCT)	⊕⊕◯◯ LOW
Impact of FM (physical and mental symptoms) assessed with FIQ Scale of 0–100	The mean impact of FM (physical and mental symptoms) was 18.88 points	The mean impact of FM (physical and mental symptoms) in the intervention group was 9.67 points more (16.02 more to 3.31 more)	50 (1 RCT)	⊕⊕◯◯ LOW
*The risk in the intervention group (and the CI of 95%) is based on the risk assumed by the comparison group and the relative effect of the intervention CI of 95%. CI, confidence interval.				
GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.				

Table 4. *Level of evidence by GRADE for myofascial release compared with sham magnetotherapy.*

Outcomes	Potential Absolute Effects* (95% CI)		Number of Patients (studies)	Certainty of the Evidence (GRADE)
	Risk with Sham Magnetotherapy	Risk of Myofascial Release		
Pain assessed with VAS scale of 0–10	The mean pain was 7 points	A mean pain of the intervention group was 1.09 points less (0.27 less to 1.92 less)	59 (1 RCT)	⊕⊕◯◯ LOW
Quality of life: physical functioning assessed with SF-36 scale of 0–100	The mean quality of life physical functioning was 51.03 points	The mean quality of life physical functioning in the intervention group was 4.31 points less (0.39 less to 8.22 less)	59 (1 RCT)	⊕⊕◯◯ LOW
Quality of life: role physical assessed with SF-36 scale of 0–100	The mean quality of life role physical was 26.32 points	The mean quality of life role physical in the intervention group was 3.41 points less (0.1 higher to 6.92 less)	59 (1 RCT)	⊕◯◯◯ VERY LOW
Quality of life: general health assessed with SF-36 scale of 0–100	The mean quality of life general health was 69.85 points	A mean quality of life general health in the intervention group was 4.64 points less (1.6 less to 7.69 less)	59 (1 RCT)	⊕⊕◯◯ LOW
Quality of life: vitality assessed with SF-36 scale of 0–100	The mean quality of life vitality was 59.99 points	The mean quality of life vitality was in the intervention group was 3.53 points more (8.12 more to 1.04 less)	59 (1 RCT)	⊕◯◯◯ VERY LOW
Quality of life: social functioning assessed with SF-36 scale of 0–100	The mean quality of life social functioning was 64.03 points	The mean quality of life social functioning in the intervention group was 4.48 points less (0.45 less to 8.5 less)	59 (1 RCT)	⊕⊕◯◯ LOW
Quality of life: role emotional assessed with SF-36 scale of 0–100	The mean quality of life role emotional was 47.74 points	The mean quality of life role emotional in the intervention group was 1.32 points less (4.08 higher to 6.72 less)	59 (1 RCT)	⊕◯◯◯ VERY LOW
Quality of life: mental health assessed with SF-36 scale of 0–100	The mean quality of life mental health was 82.02 points	The mean quality of life mental health in the intervention group was 3.75 points less (1.96 higher to 9.46 less)	59 (1 RCT)	⊕◯◯◯ VERY LOW
Quality of life: bodily pain assessed with SF-36 scale of 0–100	The mean quality of life bodily pain was 77.54 points	The mean quality of life bodily pain in the intervention group was 3.6 points less (1.62 higher to 8.84 less)	59 (1 RCT)	⊕◯◯◯ VERY LOW
*The risk in the intervention group (and the CI of 95%) is based on the risk assumed by the comparison group and the relative effect of the intervention (and its CI of 95%). CI, confidence interval.				
GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.				

Table 5. *Level of evidence by GRADE for myofascial release compared with Pilates.*

Outcomes	Potential Absolute Effects* (95% CI)		Number of Patients (studies)	Certainty of the Evidence (GRADE)
	Risk with Pilates	Risk of Myofascial Release		
Pain assessed with VAS scale of 0–10	The mean pain was 2.15 points	The mean pain in the intervention group was 0.37 points more (1.58 more to 0.82 less)	36 (1 RCT)	⊕◯◯◯ VERY LOW
Impact of FM assessed with FIQ scale of 0–100	The mean impact of FM was 22.12 points	The mean impact of FM in the intervention group was 6.55 points more (14.32 more to 1.2 less)	36 (1 RCT)	⊕◯◯◯ VERY LOW
*The risk of the intervention group (and the CI of 95%) is based on the risk assumed by the comparison group and the relative effect of the intervention (and the CI of 95%). CI, confidence interval.				
GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.				

Table 6. *Level of evidence by GRADE for general osteopathic treatment compared with the control.*

Outcomes	Potential Absolute Effects* (95% CI)		Number of Patients (studies)	Certainty of the Evidence (GRADE)
	Risk with Control	Risk of General Osteopathic Treatment		
Pain assessed with VAS scale of 0–10	The mean pain was 6.6 points	The mean pain in the intervention group was 2.3 points less (0.72 less to 3.87 less)	(1 RCT)	⊕⊕⊕◯ MODERATE
Impact of FM assessed with FIQ scale of 0–100	The mean impact of FM was 51.8 points	The mean impact of FM in the intervention group was 11.69 points less (2.6 higher to 26 less)	(1 RCT)	⊕◯◯◯ VERY LOW
*The risk of the intervention group (and the CI of 95%) is based on the risk assumed by the comparison group and the relative effect of the intervention (and the CI of 95%). CI, confidence interval.				
GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.				

ried out by Castro-Sánchez et al (20), a worsening was observed in the group submitted to 20 once-weekly 90-minute sessions of myofascial release on restrictions at the sites of the 18 painful points reported by the ACR regarding physical functioning, role physical, general health, social functioning, role emotional, mental health, and bodily pain on the SF-36 when compared with 20 once-weekly 30-minute sessions of sham magnetotherapy (very low to low level of evidence) because in the SF-36 interpretation, the higher the score, the better the quality of life (31,66). In contrast, myofascial release demonstrated an improvement in pain and vitality on the SF-36 when compared with sham magnetotherapy (20).

Ekici et al (48) reported an improvement in pain and the impact of FM after 12 sessions of 60-minute 3 times per week of Pilates compared with 12 sessions of 5- to 20-minute 3 times per week of myofascial release. However, in addition to the interventions involving different physiological effects and presenting considerable discrepancy in treatment time, their study presented a very low level of evidence. For the outcome of pain (VAS), the baseline groups presented a statistically significant and clinically relevant difference (>2 points),

causing bias in the estimation of the effect of intervention on this outcome.

Although a systematic review with prior meta-analysis (2015) suggested moderate evidence that myofascial release has an effect on pain reduction in patients with FM (26), according to a later review (2018), the significant improvement of studies included in the meta-analysis did not reach the MID, from 1.5 to 2 points on the numerical scale, and therefore it was not possible to generate a confirmation (65). The MID between the mean values of the VAS was achieved only in the study conducted by Albers et al (47), which involved joint and soft tissue techniques through general osteopathic treatment.

The study by Albers et al (47) indicated that 10 sessions of 45 minutes within a time period of 12 weeks of general osteopathic treatment reduced pain (moderate level of evidence) and the impact of FM (very low level of evidence) compared with control.

It is known that touch therapy has nonspecific effects, much like placebo and patient expectation, making it important to compare the proposed intervention with a hands-on component (67,68). In the present review, only one study compared 2 interventions with manual therapy (64).

Ekici et al (64) compared myofascial release with another hands-on therapy, lymphatic drainage. A low level of evidence suggested that 15 sessions of 45-minute, 5 times per week of lymphatic drainage reduced pain and the impact of FM when compared with 15 sessions of 5- to 20-minute, 5 times per week of myofascial release (64). However, an important factor that may have influenced the results is the discrepancy between the doses of the interventions. It is important to compare similar interventions in terms of number of sessions, duration, and frequency to minimize the influence of the placebo effect.

From the studies included in the present review, which did not provide the necessary data, and thus did not generate the quantitative analysis nor the level of evidence through GRADE, a significant improvement of pain and the impact of FM was observed after 5 once-weekly sessions of 45 minutes of combined myofascial release and thrust when compared with control (17), as well as significant improvement in pain and of the role physical domain on the SF-36 after 12 twice-weekly sessions of 5 to 20 minutes of myofascial release combined with exercise when compared with exercise alone (62).

Castro-Sánchez et al (63), however, discovered that for the improvement of pain, FM impact, and the domains of role physical, bodily pain, vitality, and role social on the SF-36 questionnaire, 4 dry-needling sessions were superior to 4 sessions of myofascial release. However, they did not provide data on the aforementioned outcomes in the baseline, and thereby did not enable verification of comparability between the groups.

In relation to the safety of manual therapy, none of the included studies reported significant adverse events.

The present systematic review presented limitations because of the heterogeneity of the included studies and only a short-term analysis of the intervention results. It was observed that other information, such as pressure, repetition, and/or sustaining manual therapy techniques, could be better described in future protocols, aiming at a better comparison between the techniques and their subsequent reproducibility.

Given the earlier mentioned, current evidence of manual therapy in patients with FM, based on a very low to moderate quality of evidence, was inconclusive and insufficient to support and recommend the use of manual therapy in this population. Concerning pain, only the general osteopathic treatment achieved a clinically important effect when compared with control.

Furthermore, although the study that performed the most myofascial release sessions (20 sessions of 90 minutes) reported an improvement in pain, this was not clinically relevant and demonstrated a worsening of some SF-36 domains compared with sham magnetotherapy, making it important to investigate the influence of repeated manual interventions. However, smaller amounts of release performed in associated with a joint technique or exercise seems to have a positive effect on FM symptoms, especially on pain modulation.

Thus the verification of a possible dose-response relationship of applying manual therapy also seems relevant, given the wide variation between the application dosage (number of sessions, duration, and weekly frequency) and response to the intervention studied so far.

Conclusions

Future clinical trials should use the new criteria for FM established by the ACR to better select their sample, be more homogeneous in relation to the comparison, with a larger sample and longer follow-up, to control selection biases and cointerventions for a higher level of evidence and be included in meta-analysis and generate more conclusive results.

Author Contributions

NS was the lead author and participated in absolutely all phases of the study and writing of the article. MS was one of the reviewers and participated in the search phase. GA was one of the reviewers and participated in the search phase and analysis (study quality and quality of evidence) of the included articles. MM was one of the reviewers and participated in the analysis (study quality and quality of evidence) of the articles and cooriented the study. GS was the study advisor. All authors read and approved the final manuscript.

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