

Effectiveness of multicomponent treatment in patients with fibromyalgia: Protocol for a systematic review and meta-analysis

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Protocol

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Abstract

Background

The purpose of this protocol is to provide new and clear data on the systematic review with meta-analysis with the current Cochrane methodology to compare the effectiveness of multicomponent treatment versus other interventions for patients with fibromyalgia.

Methods

This protocol conforms to Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and the recommendations of the Cochrane Collaboration Handbook. An electronic search will be conducted in MEDLINE, EMBASE, Web of Science, Cochrane CENTRAL, LILACS, CINAHL, and PEDro, from the inception until January 2021. There will be no language restrictions. The Cochrane Collaboration tool for assessing the risk of bias (RoB2) will be used. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) scale will be used to evaluate the strength of the evidence. The DerSimonian and Laird random effects of Mantel-Haenszel fixed effects methods will be used, depending on the heterogeneity. To compute a pooled estimate of mean difference (MD) or standardized mean difference (SMD), and respective 95% confidence intervals (CI) for pain intensity, physical function, pain catastrophizing, kinesiophobia, quality of life, sleep quality, and level of depression.

Discussion

This systematic review will synthesize evidence on the effectiveness of multicomponent treatment in patients with fibromyalgia. This systematic review could add important evidence in the treatment of FM that could improve the clinical practice and the making of decisions and actions in this field. The novel statistical analysis will try to show the effects of multicomponent treatment by type and dose of exercise in patients with FM. The results will be disseminated by publication in a peer-reviewed journal. Ethics approval will not be needed because the data used for this systematic review will be obtained from individual trials and there will be no concerns about privacy.

PROSPERO systematic review registration number:

CRD42020142082

1. Background

According to the evidence, fibromyalgia (FM) is a chronic disease that includes musculoskeletal pain, fatigue, and cognitive problems.[1, 2] The prevalence of FM in the general population has been established to range from 2–6.6% worldwide with more frequency among women.[3, 4] This clinical condition can affect

the patients' quality of life and cause high health care costs as patients often need cost-effective treatment options.[5–7]

Currently, different evidence-based approaches have been published to give patients and physicians an orientation on multidisciplinary treatment options for FM.[8, 9] Previous systematic reviews have shown that the effect of pharmacological treatments, including pregabalin, amitriptyline, and milnacipran are controversial and produce only moderate effects on patients with FM.[10–13] Moreover, other studies indicate that multidisciplinary treatments such as multicomponent treatment have positive results on FM symptoms in the short-term, for pain intensity, fatigue, depressive symptoms, and physical function, [14, 15] specifically when including exercise and cognitive behavioral therapy.[16–18] However, the multifactorial nature of FM, its wide variety of symptoms and different types of multicomponent treatment could interfere with treatment success.[14, 19]

A recent overview of guidelines [20, 21] has shown inconsistent results for multicomponent treatments in the management of FM. Thus, it is difficult to establish which type and dose of physical exercise or specific multicomponent treatment therapy combination is more clinically useful for FM patients. The recent guidelines of the European League Against Rheumatism [22] concluded that the recommendation of multidisciplinary interventions has a “low to moderate effect” in pain relief and the improvement of fatigue. However, it has been suggested that further studies with a clearer methodology should be implemented to optimize results in patients with FM.

Additionally, the results of previous clinical trials on the effect of multicomponent treatment on the different symptoms of FM have been inconsistent; therefore, there is a necessity for a systematic review to present a clear and transparent procedure for systematically reviewing, evaluating, and summarizing existing evidence. [21, 23] To date, there has been no systematic review that included a novel methodology to study the effectiveness of multicomponent treatment in the medium and long-term for patients with FM. Therefore, the aim of this protocol systematic review study will be to establish new, clear data and a novel methodology for conducting a systematic review and meta-analysis to determine the effectiveness of multicomponent treatment compared to other interventions in patients with FM.

1.1 Objective

This protocol study aims to establish a transparent, clear and current methodology to conduct a systematic review and meta-analysis aimed to determine the effectiveness of multicomponent treatment compared to other interventions such as; pharmacological treatment, drugs therapy, and other different types of physical exercise in the physical function, pain catastrophizing, kinesiophobia, quality of life, sleep quality, and level of depression of patients with FM.

2. Methods And Analysis

This systematic review protocol has been registered in the PROSPERO database (registration number: CRD42020142082). It will be conducted according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [24] and The Cochrane Handbook for

Systematic Reviews of Interventions. [25] The financial support for the investigation was provided by the Universidad de las Américas funding.

2.1 Inclusion and exclusion criteria

The study will include research defined by the following characteristics; type of study (randomized clinical trials and controlled clinical trials); type of participants (subjects older than 18 years of age with a medical diagnosis of FM based on American College of Rheumatology); [26] type of intervention (multicomponent treatment that could include any physical exercise, cognitive behavioral therapy, and/or education); type of comparison (other interventions such as pharmacological treatment, drug therapy, wait and see, placebo, and other different types of physical exercise or complementary therapy). Finally, this review will include studies in which the outcome of interest is pain intensity, physical function, pain catastrophizing, kinesiophobia, quality of life, sleep quality, and level of depression. We will exclude studies with the following characteristics: studies reporting pre-post analysis without comparison group; studies involving subjects with other pathologies and conditions such as chronic fatigue syndrome, myalgic encephalomyelitis, and chronic cancer pain; and studies involving subjects with metabolic disorder and/or uncontrolled comorbidities.

2.2 Main outcomes

The primary outcome: pain intensity and physical function.

The secondary outcome: pain catastrophizing, kinesiophobia, quality of life, sleep quality, and level of depression.

2.3 Search strategy

Relevant studies of multicomponent treatment for FM will be obtained through an extensive computerized search from the following bibliographic databases: MEDLINE (via PubMed), EMBASE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Latin American and the Caribbean Literature in Health Sciences (LILACS), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Physiotherapy Evidence Database (PEDro), from inception until January 2021. The literature search procedure will be complemented by manually searching the references of the identified articles to detect additional studies of interest. The combinations of the following keywords: “fibromyalgia”, “multicomponent treatment”, “multimodal therapy”, “multidisciplinary approach”, “randomized clinical trial”, “controlled clinical trial”, “pain intensity”, “fibromyalgia impact”, “catastrophizing”, “kinesiophobia”, “quality of life”, “sleep quality”, and “depression” will be combined in the search. (See Table 1)

Table 1
Search strategy

Number	Search terms
1	Fibromyalgia
2	Multicomponent treatment
3	Multimodal therapy
4	Multidisciplinary approach
5	#2 OR #3 OR #4
6	#1 AND #5
7	Randomized clinical trial
8	Randomized controlled trial
9	#7 OR #8
10	Humans
11	Animals
12	#10 NOT # 11
13	#11 AND #15 AND #18

2.4 Selection and analysis of trials

After the search is performed, two reviewers will independently screen the titles and abstracts retrieved. The full text of manuscripts selected for inclusion will be examined, and the inclusion and exclusion criteria will be applied (Fig. 1). The reviewers will not be blinded to authors, institutions, or journals. Disagreements between reviewers will be solved by consensus or through the participation of a third reviewer. The reviewers will independently extract the following information from the included studies: author and year of publication, design of the trial, country, type of intervention (multicomponent treatment and other interventions), intervention characteristics (dose, length, and setting), population characteristics, number of participants, age of participants, outcomes studied, and results. In addition, information reported about clinical significance/relevance (i.e., effect size, minimal clinically important difference) of the results will also be included (Table 2). Any disagreement between reviewers will be resolved by consensus. Finally, study authors will be asked to supply any missing data.

Table 2
 Characteristics of the trials included in the systematic review and meta-analyses

Reference	Design	Country	Population	Intervention	control	Results/Follow-up
Authors	RCTs, CCTs	Countries where the trial was conducted	Patients with fibromyalgia	Type, dose and characteristics	Type, dose and characteristics	ΔX : SD:
/years						P-Value
RCTs = randomized clinical trial, CCTs = controlled trial, x = mean; SD = standard deviation, Δx = mean difference.						

2.5 Evaluation of the risk of bias (RoB)

Two reviewers will independently assess the risk of bias according to the Cochrane Collaboration Handbook recommendations. [25] Disagreements will be solved by consensus or through the participation of a third reviewer. The randomized clinical trials will be assessed using the Cochrane Collaboration tool for assessing the risk of bias (RoB2). [27] This tool assesses the risk of bias according to six domains: bias arising from the randomization process, bias due to deviations from intended interventions, the bias due to missing outcome data, the bias in the measurement of the outcome, the bias in the selection of the reported result, and overall bias. Overall bias will be considered as “low risk of bias” if the paper has been classified as ‘low risk’ in all domains, “some concerns” if there is at least one domain with a rating of ‘some concern’, and “high risk of bias” if there is at least one domain with a ‘high risk’, or several domains with some concerns’ that could affect the validity of the results. The agreement rate between reviewers will be calculated using kappa statistics.

2.6 Grading the quality of evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool will be used to assess the quality of the evidence and make recommendations. [28, 29] Each outcome could obtain a high, moderate, low, or very low evidence value, depending on the study design, risk of bias, inconsistency, indirect evidence, imprecision, and publication bias.

2.7 Data analysis

Descriptive analyses will be conducted for those studies which present insufficient data for overall pooling, and narrative synthesis will be performed following the Cochrane Collaboration guidelines. [25] The DerSimonian and Laird random effects or the Mantel-Haenszel fixed effects methods will be used, [30] depending on the heterogeneity, to compute a pooled estimate of mean difference (MD) or standardized mean difference (SMD), and respective 95% confidence intervals (CI) outcomes measures. The heterogeneity of results across studies will be evaluated using the I² statistic, which will be considered as: might not be important (0–40%), may represent moderate (30–60%), may represent substantial (50–90%) and considerable (75–100%) heterogeneity. [25] Also, the corresponding *p*-values will be considered. Publication

bias will be evaluated through a visual inspection of funnel plots, as well as by using the method proposed by Egger. [31] The meta-analysis will be performed using the RevMan 5.3 program. The synthesis and quality of evidence for each outcome will be performed by GRADE profiler (GRADEpro) to import the data from Review Manager 5.3 (RevMan 5.3) to create a 'summary of findings' table. This approach entails the downgrading of evidence from high to moderate to low and very low quality based on certain criteria. Downgrading the evidence one level: (1) for study limitation if the majority of studies (> 50%) was rated as high risk of bias; (2) for inconsistency, if heterogeneity was greater than the accepted low level ($I^2 > 40\%$); (3) for indirectness, if the MT treatment session does not correspond to what is used in clinical practice; (4) for imprecision, if meta-analysis had a small sample size ($n < 300$).

2.8. Analysis by subgroups

If possible, subgroup analysis will be performed based on the type of intervention, as this is a characteristic that can modify the results for the different outcomes, including: type of multicomponent treatment and comparators, such as; physical exercise, education, and drug therapy. Additionally, if possible, subgroup analyses will be performed based on dose or intensity of exercise used.

2.9 Ethics and dissemination

This systematic review will synthesize the evidence on the effectiveness of multicomponent treatment in patients with FM. The results will be disseminated by publication in a peer-reviewed journal. Ethics approval will not be needed because the data used for this systematic review will be obtained from individual trials contributing primary data for meta-analyses. There will be no concerns about the privacy of patients because all data will be fully anonymized prior to being imported into our database.

3. Discussion

FM is one of the most common musculoskeletal disorders of unknown cause involving adults, especially women. [32] A multidisciplinary approach is recommended for the treatment of FM. [21, 22] However, pharmacotherapy is prescribed as first-line treatment of FM and its efficacy remains controversial. [10–13, 33] Recent clinical trials comparing MT versus pharmacotherapy and other interventions in patients with FM have been published, however, the inconsistent results have made it difficult to draw conclusions from the new available evidence. [15, 34–37]

This protocol aims to provide a new and clear data analysis that overcomes the limitations existing in previous systematic reviews and meta-analyses, which only assess the effect of multicomponent treatment on FM, without considering the type of exercise or the dose/intensity of the intervention used. [9, 10, 14, 20] To our knowledge, this will be the first systematic review that will be conducted and reported according to the current highest methodological standard, to identify methodological and clinical aspects to consider for health making decisions of medical and physiotherapist professionals in health care of FM patients. Therefore, it is beneficial to perform a systematic review and meta-analysis, including the new clinical trials to determine the magnitude of change in the main FM symptoms, to improve the estimations, and to rate the quality of evidence with GRADE for the systematic review.

The pharmacotherapy remains being used as the most common treatment to manage FM condition. Thus, due to the low compliance of patients to recommendations on physical activity or healthy lifestyle recommendations, physicians trend to medicalize the disease. [38] However, the 50% of patients with FM do not improve significantly with pharmacological treatment. [36, 39]

Three significant concerns exist in this topic that should be considered. First, there are several mixed clinical trials, where the effects of physical exercise with education and other interventions (e.g., cognitive behavioral therapy, medical education, stretching exercise) could be a source of heterogeneity. Second, we may be able to find studies where unsupervised exercise is prescribed. No special consideration will be made in the analysis, only the type and intensity of the prescribed exercise or other interventions will be taken into account. However, the lack of direct supervision could threaten the validity of the data. Third, the controlled clinical trial can be affected by selection bias and allocation concealment, so the homogeneity of the basal characteristics of the intervention and control groups are not ensured.

Potential limitations are those common to the systematic reviews, which are; (1) bias due to publication and information of clinical trials; (2) although we will search seven databases and include manual references search, we could miss articles relevant to our search; (3) it is possible to have a high degree of clinical and statistical heterogeneity among the included studies, potential sources of heterogeneity could be different doses and types of intervention, and different scales used to measure the outcome; (4) the analyses, reporting methods and findings of the included studies could be a source of bias in grading the quality of evidence.

This systematic review could add important evidence in the treatment of FM that could improve the clinical practice and the making of decisions and actions in this field. The novel statistical analysis will try to show the effects of multicomponent treatment by type and dose of exercise in patients with FM. This approach and the quality of the evidence performed with the GRADE system will provide the strongest evidence to date on the effect of multicomponent treatment on the treatment of FM symptoms.

Strengths And Limitations

- This systematic review could add important evidence in the treatment of FM for improve the clinical practice and making decisions.
- This review provide the evidence performed with the GRADE system to rating the quality of evidence of multicomponent treatment in FM.
- Different dose and type of intervention could be a source of different results and heterogeneity between studies and may limit the quality of the evidence this meta-analysis and systematic review.
- We will search seven databases and manual references, however, we could miss clinical trials relevant to our research.

Abbreviations

FM

Fibromyalgia

MD

Mean difference

SMD

Standard mean difference

CI

Confidence interval

PRISMA-P

Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

RoB

Risk of Bias

Declarations

Ethical Approval and Consent to participate: Not applicable.

Consent to publication: Not applicable.

Availability of supporting data: Not applicable.

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Figures

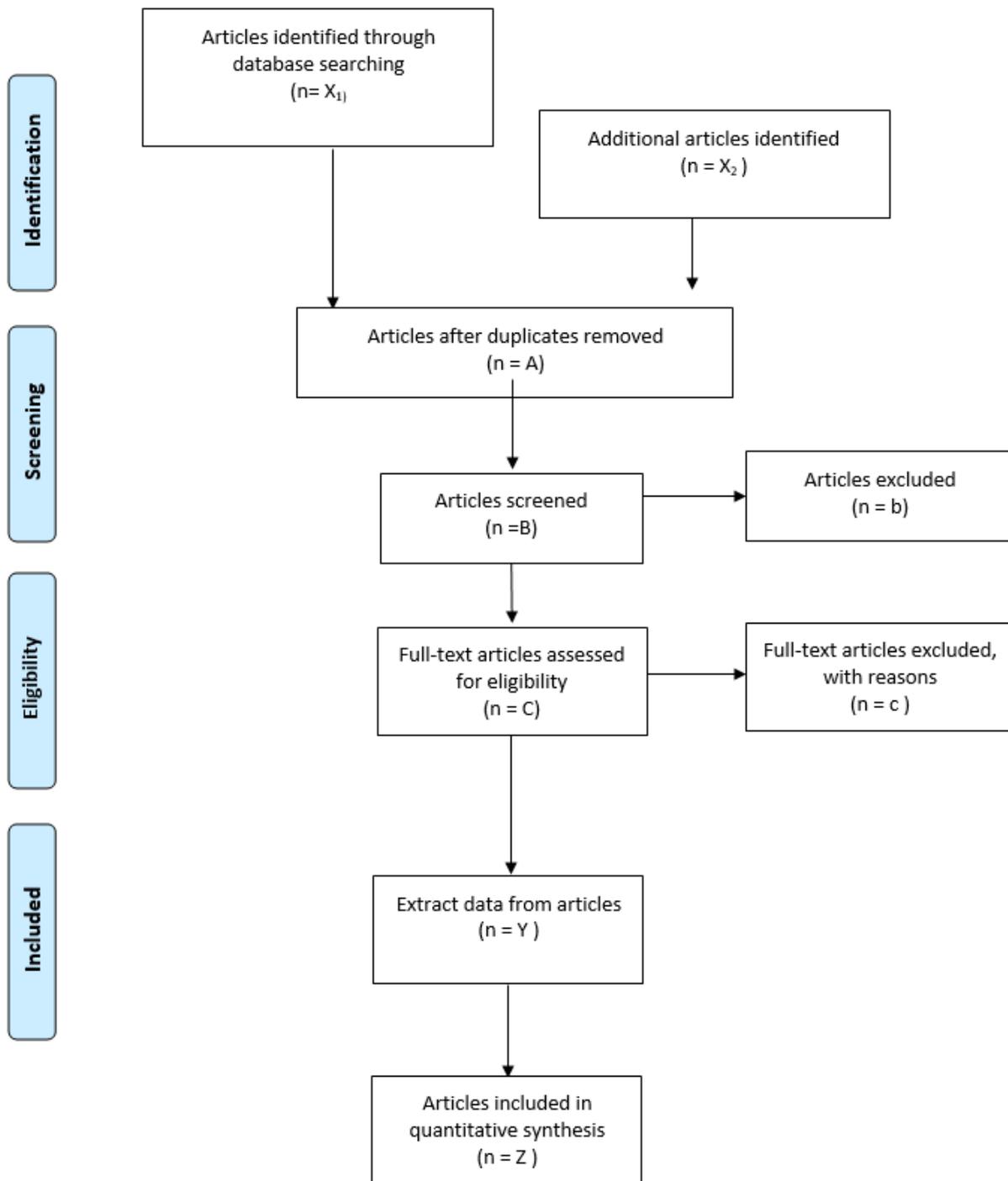


Figure 1

After the search is performed, two reviewers will independently screen the titles and abstracts retrieved. The full text of manuscripts selected for inclusion will be examined, and the inclusion and exclusion criteria will be applied (Figure 1).

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