Review Article

Efficacy of Pharmacological & Non Pharmacological Treatments for Fibromyalgia: A Systematic Literature Review and Meta-analysis

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Background: The management of fibromyalgia (FM) poses a complex challenge due to its multifaceted and often severely debilitating symptoms. This study delves into the effectiveness of pharmacological and non-pharmacological interventions in tackling the intricate nature of FM symptoms.

Methodology: We conducted a comprehensive search using e-databases (PubMed and Embase), from inception to 16th March 2023. Randomized controlled trials (RCTs) that evaluated the efficacy of pharmacological and non-pharmacological treatments for FM with primary outcomes impact of fibromyalgia on a person's daily life, Pain, Depression and health related Quality of Life. For data synthesis, we calculated the standardized mean differences (SMD) accompanied by 95% confidence intervals (CI) were included. To combine the findings from the included studies, we performed a meta-analysis using the Der-Simonian and Laird method.

Results: This study comprised 27 RCTs encompassing 2390 participants, allocated to three interventions categories. A meta-analysis utilizing the Visual analogue scale (VAS) score, Fibromyalgia impact questionnaire (FIQ) scores, Tender point count (TPC) indicated a non-significant effect size, therapy over treatment as usual (TAU), with a SMD of 0.02 (95% CI: -0.57 to 0.54), -0.31 (CI: -0.64 to 0.02), -0.17 (95% CI: -0.55 to 0.21) respectively. The SF-36 score demonstrated that the intervention group had a higher score than the TAU group, with an SMD of -0.15 (95% CI: -0.18 to 0.48). The Beck's Depression Inventory (BDI) score meta-analysis showed an SMD of 0.79 (95% CI: -1.14 to 2.72) in the intervention group compared to the TAU group.

Conclusion: The approach that combines both pharmacological and non-pharmacological interventions shows potential for achieving the most favourable outcomes.

Introduction

Fibromyalgia (FM) is a chronic condition, which is characterized by widespread and multifocal pain, exhibiting fluctuations in both its spatial distribution and intensity across the course of the illness. Patients suffering from FM exhibit augmented sensitivity towards various stimuli, including thermal and mechanical pressure, as well as ischemic pressure. Such stimuli evoke pain responses in patients even when applied at levels of intensity that are non-painful for healthy individuals.[1] Ranking as the third most common chronic condition[2,3,] FM's prevalence varies from 0.5% to 5% in the general population and up to 15.7% in clinical settings.[4] While more common among older adults, its precise origins remain elusive. Hypotheses suggest a blend of genetic predisposition, stressful life events, and both peripheral (inflammatory) and central (cognitive-emotional) mechanisms contributing to pain perception development, referred to as "nociplastic pain." In recent years, research has linked FM pathogenesis to factors like inflammation, immunity, endocrine function, genetics, and psychosocial

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elements. Diagnosis by rheumatologists usually involves considering a patient's history of body-wide pain lasting at least three months and the elicitation of pain through digital pressure in at least 11 out of 18 specific tender points.[5] The Fibromyalgia Impact Questionnaire (FIQ) is a validated assessment tool designed to measure the overall impact of fibromyalgia on a patient's life, encompassing aspects like pain, functioning, fatigue, and psychological well-being.[6] The Visual Analog Scale (VAS) is a self-reporting tool that employs a 10-point scale to quantify the intensity of pain experienced by individuals, aiding in tracking pain fluctuations over time.[7] The Tender Point Count (TPC) involves the manual palpation of specific tender points on the body, aiding in the diagnosis of fibromyalgia by identifying localized pain and tenderness.[8] These tools are crucial in clinical settings to comprehensively evaluate fibromyalgia symptoms, monitor progress, and tailor treatment strategies.

The management of FM is currently very challenging due to its multiple etiological factors and the lack of a straightforward cure. The primary focus of treatment is symptoms relief and enhancing affected individuals' quality of life, given the substantial impact these symptoms can have on overall well-being.[9] Regrettably, the efficacy of interventions has been limited, as only a minority of patients report substantial clinical improvements from these therapies. Commonly recommended medications, such as antidepressants, anticonvulsants, and opioids, exhibit restricted efficacy, leading to a mere 10% to 25% reduction in pain intensity and a 50% reduction in specific symptoms[10] Conversely, non-pharmacological approaches like cognitive-behavioural therapy, exercise, and relaxation techniques show promise in mitigating FM symptoms. These strategies are viewed as safe, non-invasive, and cost-effective alternatives to pharmacological treatments. However, concerns persist regarding their effectiveness, safety, and potential adverse effects associated with prolonged usage.[11]

While both non-pharmacological and pharmacological interventions have been explored for FM treatment, their comparative effectiveness remains a point of contention. Furthermore, consensus on the optimal treatment approach is lacking.[12] The objective of this meta-analysis review is to offer a comprehensive and updated overview of the existing evidence regarding the effectiveness and safety of these interventions. Such insights can significantly inform clinical decision-making and provide guidance for future research endeavours.

Methods

Search Strategy and Study Selection

This systematic review (SR) and meta-analysis (MA) was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[13] The study participants followed the American College of Rheumatology preliminary diagnostic criteria for fibromyalgia classification and definition of FM and measurement of symptom severity.[14] The study employed the PICOS framework (Population, Intervention, Comparator, Outcome, Study Design)[15] as a criterion for including relevant studies. It integrated Randomized Clinical Trials (RCTs) that involved patients aged 18 years or older with FM. The inclusion encompassed studies where patients were designated to receive either pharmacological or non-pharmacological interventions, which were compared with placebo, alternative therapy, treatment as usual (TAU), or no intervention. No restrictions were placed on publication dates, Studies published in English language only were included. The study excluded the trials with a crossover design, surgical treatments, non-randomized RCTs, reviews, editorials, case reports, conference abstracts and studies that did not meet the intended outcomes. The protocol was pre-registered in Prospective Register of Systematic Reviews (PROSPERO) registration no - CRD42022378125.

In order to identify pertinent studies, a systematic preliminary search was conducted on PubMed and EMBASE, commencing from inception till 16th March 2023. In addition, a manual search was conducted on Google Scholar and the reference lists of the articles that met the pre-determined criteria for inclusion and exclusion, with the objective of discovering additional studies that may be of relevance. The key search terms were as follows, "FM" and "non-pharmacological" and "pharmacological" treatments, such as cognitive behaviour therapy, manual therapy, manipulation therapy, exercise, Pregabalin, duloxetine, milnacipran, amitriptyline, and gabapentin. The search terms were adjusted to align with the glossary of each database searched. Duplicate records were identified and eliminated using the Endnote software. A comprehensive search strategy has been provided in tables S3.

Data extraction, and Quality Assessment

The two authors (S.K.B and K.C) conducted an autonomous data screening and extraction process. Any discrepancies encountered were resolved through discussion with a third author, DB. The

screening process began by evaluating the titles and abstracts of the retrieved citations based on pre-determined eligibility criteria. Subsequently, they meticulously scrutinized the full text of the potentially relevant citations for suitability. A standardized excel sheet were utilised to extract all the necessary study data, including variables such as publication year, country, participant demographics, baseline characteristics, intervention details, reported outcomes, and any other relevant information mentioned in the included studies.

The methodological quality of each included RCT was critically appraised using the revised Cochrane Risk-of-Bias-2 (ROB-2) tool.[16] Two independent reviewers (S.K.B and K.C) performed the assessment and resolved any disagreements through discussion. The ROB2 tool assesses five domains of bias: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each domain has been assigned a score of low, moderate to high.

Primary and Secondary Outcomes

The management of FM focuses on alleviating the prominent symptoms associated with the condition, such as chronic widespread pain, fatigue, insomnia, and cognitive impairment. Effective treatment approaches are tailored to suit the specific needs of each patient and incorporate a combination of nonpharmacological and pharmacological interventions. The primary outcomes of interest were FM Impact Questionnaire (FIQ), Visual Analog Scale (VAS), and the Tender Point Count (TDC). As secondary outcomes, we analysed additional objective and subjective measures of efficacy like Beck's Depression Inventory (BDI) score and Quality of Life using the 36-Item Short Form Survey (SF-36). For outcomes that are reported at multiple time intervals, the longest time point available is taken. Standardized mean difference (SMD), 95% confidence intervals (CI), and P-values were calculated for outcome analysis.

Statistical analysis

To account for the anticipated heterogeneity in methodology and clinical features across the encompassed studies and to achieve the highest level of generalizability in the meta-analytic assessments, a random-effects model was employed. Since all efficacy outcomes represent continuous data, the standardized mean difference (SMD) or Cohen's d was used to determine the effect size, along with 95% confidence intervals (CI). Data analysis was done by using the "meta" and "dmetar" package of RStudio (R Foundation). Standardised mean difference (Cohen's d) was used to measure the effect size (ES) as the data were continuous. All analyses were based on the random-effects model using the Der-Simonian and Laird method. The I2 statistic was utilized to evaluate the heterogeneity present among the studies. An I2 value of 0% to 40% suggested that the heterogeneity may not have significant implications, whereas an I2 value of 30% to 60% indicated moderate heterogeneity. A value of 50% to 90% signified substantial heterogeneity, and an I2 value of 75% to 100% represented considerable heterogeneity.[17] The effects of the various types of intervention like pharmacological, non-pharmacological and multicomponent therapy (MCT) were pooled and analysed. Since the population in the included studies is predominantly female, and the data is relatively homogeneous, coupled with a low sample size, it was not imperative to conduct a subgroup analysis.

Results

Search Results and Study Characteristics

A total of 791 articles were identified through the searches conducted, three additional articles were discovered by scrutinizing the references of the papers that surfaced during the screening process. After removing 385 duplicates, 406 articles were subjected for screening based on title/abstract. Out of these, 357 articles were excluded as they did not meet the inclusion exclusion criteria, finally 27 articles were included in our study according to inclusion criteria 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45 (Fig: S1). The analysis includes a total of 2390 patients, randomly assigned across three categories of intervention: Five pharmacological interventions (6 studies), 19 non-pharmacological interventions (20 studies), and MCT (4 studies). The non-pharmacological interventions employed in the study included strengthening exercises, aerobic exercises, Stanger bath therapy and spa therapy, Whole body vibration, Mud Bath therapy, Aquatic Respiratory therapy, Basic Body Awareness Therapy, Exercise Therapy, Psychological Support, and Nature Exposure and Motivational Interviewing. Pharmacological interventions, such as Pyridostigmine, creatinine, Growth hormone (Nutropin), Pregabalin, Opioid and Paroxetine were utilized. MCT incorporated both pharmacological and non-pharmacological treatments. The studies were conducted across various countries, including Spain (6 studies), Brazil (4 studies), Denmark (1 studies), USA (6 studies), Turkey (6 studies), Italy (2) and

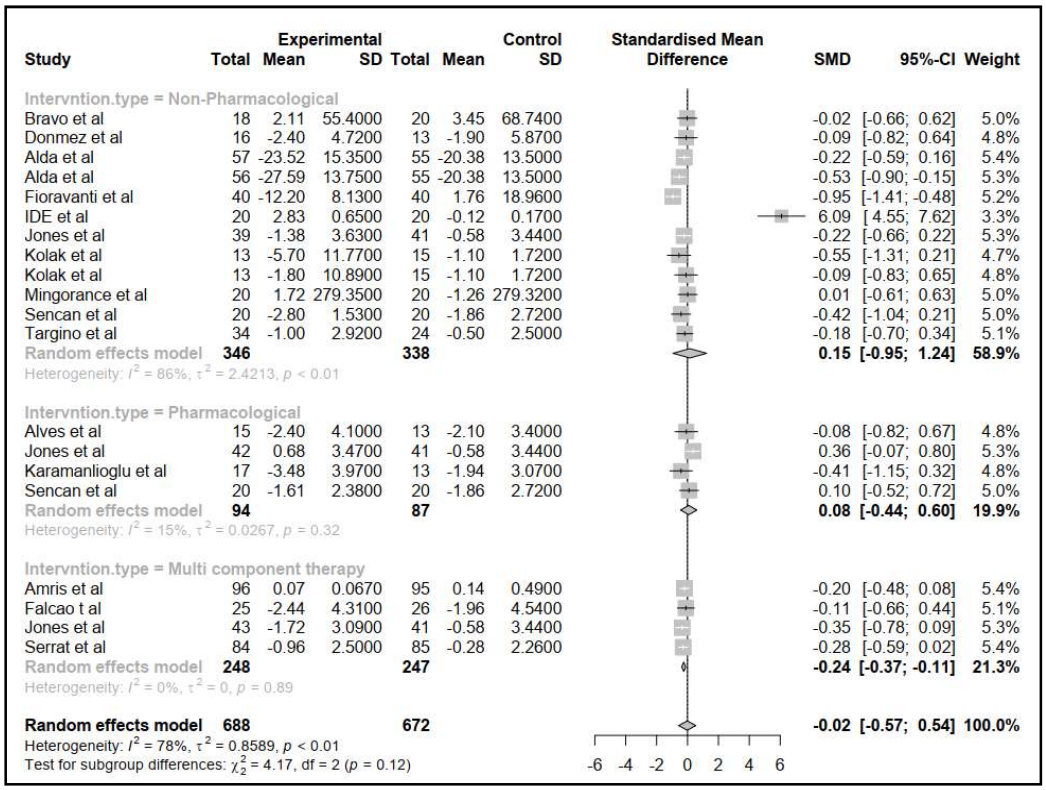

Figure 4: Forest plots for of VAS outcome

Sweden (1 studies), between 1998 and 2022. Among these, 25 studies were single centric while 2 were multicentric. The study included a predominantly female population, with 2097 participants (96.6%) and a mean age of 47.03 (SD = 8.8) years (Fig: S3). A baseline study characteristic of included RCTs were provided in Tables S1.

Risk of Bias

Overall, the risk of bias was deemed low for 12 studies, moderate for 11 studies, and high for four study. The majority of the studies had low risk of bias in the domains of randomization process, Deviations from the intended interventions, Missing outcome data, measurement of outcomes, and selection of reported results. However, two studies were judged to have high risk of bias in the domain of Measurement of the outcome, as measurement were made at a number of time points or using multiple scales. Overall, the ROB2 assessment suggests that the included studies have a generally low to moderate risk of bias (Fig S2).

Study Outcome

Efficacy Analysis

The efficacy analysis comprised of twenty-seven studies. Among the participants, 233 patients received pharmacological intervention while 1637 patients were given non-pharmacological interventions and MCT provided to 520 patients. The control group comprised of Placebo or patient receiving treatment as usual (TAU).

Visual Analogue Scale

The meta-analysis conducted on VAS comprised 18 RCTs [18, 19, 20, 22, 24, 25, 28, 29, 30, 32, 38, 39, 40, 41, 44,] wherein 16 interventions were categorized into three groups, namely non-pharmacological (nine interventions), pharmacological (four interventions) and MCT (four interventions). The collective sample size for the outcome assessment was 1360 participants, with the non-pharmacological group accounting for the majority of interventions (n=9) and the pharmacological group having 181 participants. The MCT group comprised four interventions, and a total of 495 participants were included in this category. Overall, the meta-analysis showed a small and non-significant effect size favouring pharmacotherapy over TAU with an SMD of 0.02 (95% CI: -0.57 to 0.54). The forest plot suggests that most of the individual studies are consistent with this overall finding, as the confidence intervals for each study's effect size overlap with the summary effect size. However, the meta-analysis also revealed significant heterogeneity among the studies, with an I2 value of 78%.

The subgroup analysis revealed that the non-pharmacological intervention was associated with a small effect size (SMD = 0.15; 95% CI: -0.95 to 1.24), indicating no significant difference compared to treatment as usual. The Pharmacological intervention was associated with a small effect size (SMD = 0.08; 95% CI: -0.44 to 0.60), indicating no significant difference compared to treatment as usual. However, the MCT had a moderate effect size (SMD = -0.24; 95% CI: -0.37 to -0.11), indicating a statistically significant improvement compared to treatment as usual.

FM Impact Questionnaire

The meta-analysis performed on FIQ consisted of 15 RCTs [18, 21, 23, 24, 26, 31, 32, 33, 35, 36, 37, 38, 42, 43, 44]

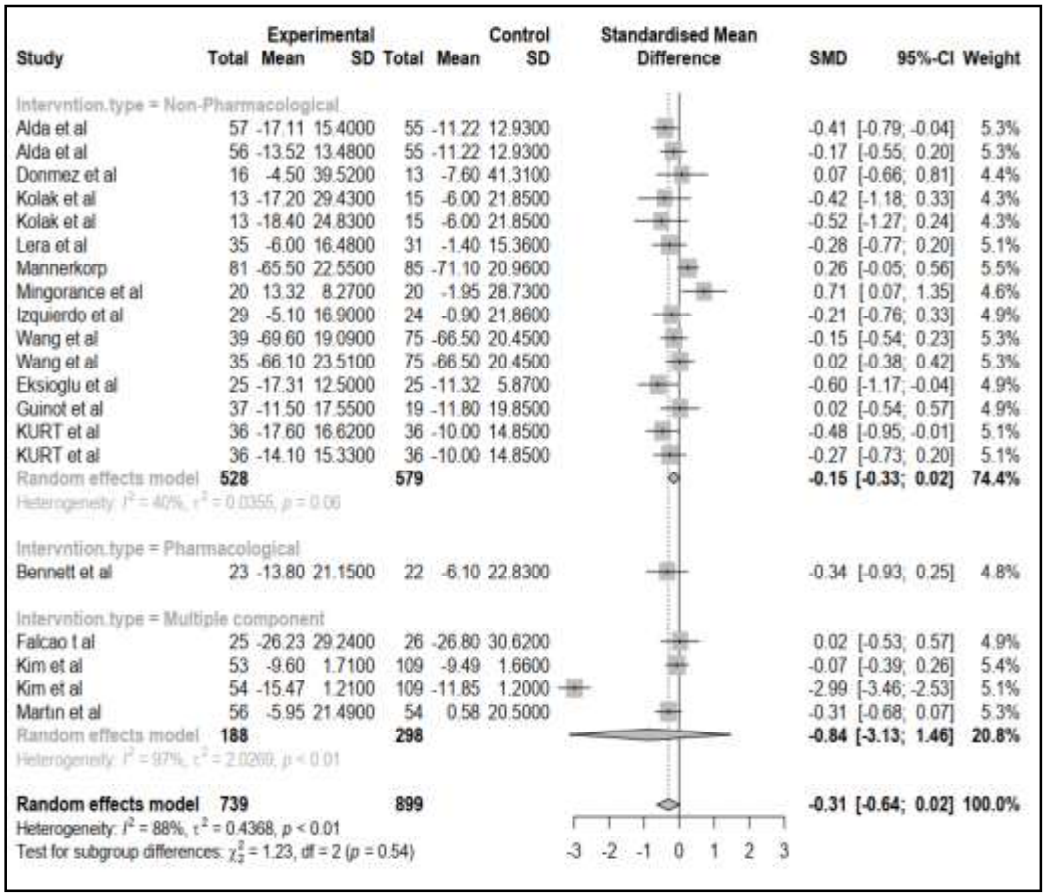

Figure 5: Forest plots for FIQ score outcome

involving 1638 participants. Out of the 15 studies, 11 evaluated non-pharmacological treatments, comprising 1107 participants. Only one study assessed pharmacological treatment, involving 45 participants, and three studies with four interventions assessed the FIQ score for MCT.

The forest plot displays the meta-analysis findings of the FIQ score, comparing the intervention group (Treatment) to the comparator group (Treatment as usual). The overall result of the meta-analysis revealed that SMD = -0.31 (CI: -0.64 to 0.02), indicating a statistically significant enhancement in the FIQ score for the intervention group compared to the treatment as usual group. Furthermore, the forest plot also demonstrates the findings of subgroup analyses based on the type of intervention. The Non-Pharmacological intervention subgroup revealed a statistically non-significant effect on the FIQ score SMD = -0.15 (CI: -0.33 to 0.02), while the Pharmacological intervention subgroup showed a statistically significant improvement in the FIQ score SMD = -0.34 (CI: -0.93 to 0.25). The MCT subgroup exhibited a large but statistically non-significant effect on the FIQ score SMD = -0.84 (CI: -3.13 to 1.46). (Figure 5).

Tender Point Count

The meta-analysis performed on TPC consisted of 7 RCTs [21, 23, 27, 29, 35, 42, 44] involving 535 participants, of which 6 studies evaluated non-pharmacological treatments, comprising 323 participants and two study assessed pharmacological treatment, involving 212 participants. The overall pooled estimate found to be, SMD = -0.17 (95% CI: -0.55 to 0.21). The subgroup analysis of the TPC score based on the type of intervention showed that the non-pharmacological group had a pooled effect size of SMD = -0.11 (95% CI: -0.69 to 0.47). On the other hand, the pharmacological group had a pooled effect size of SMD = -0.28 (95% CI: -1.37 to 0.82). The forest plot also shows that there is moderate heterogeneity among the studies, with an I2 = 64%, and the p-value for heterogeneity is less than 0.01, indicating that the heterogeneity is significant (Figure 6).

Secondary outcome

The health status and depression of patients with FM was evaluated as a secondary outcome using the Short Form-36 [27, 32, 36, 40, 41, 43] and BDI score [22, 24, 26, 32, 34, 43, 44]. A total of 607 and 463 patients were included in the meta-analysis for each outcome, respectively, across six studies. The pharmacological intervention was compared to the usual treatment. The meta-analysis indicates that the SF36 score in the intervention group was SMD= -0.15 (95% CI: -0.18 to 0.48) higher than in the treatment as usual group, with an I^2 value of 48%. Overall, the findings suggest a non-significant difference in SF36 score between the intervention and treatment as usual groups (Figure 7).

While for the other outcome meta-analysis showed that the intervention group had a BDI score of SMD = 0.79 (95% CI -1.14 to 2.72) compared to the treatment as usual group. The subgroup analysis based on intervention type revealed that MCT had an effect size of SMD = 0.01 (95% CI -0.54 to

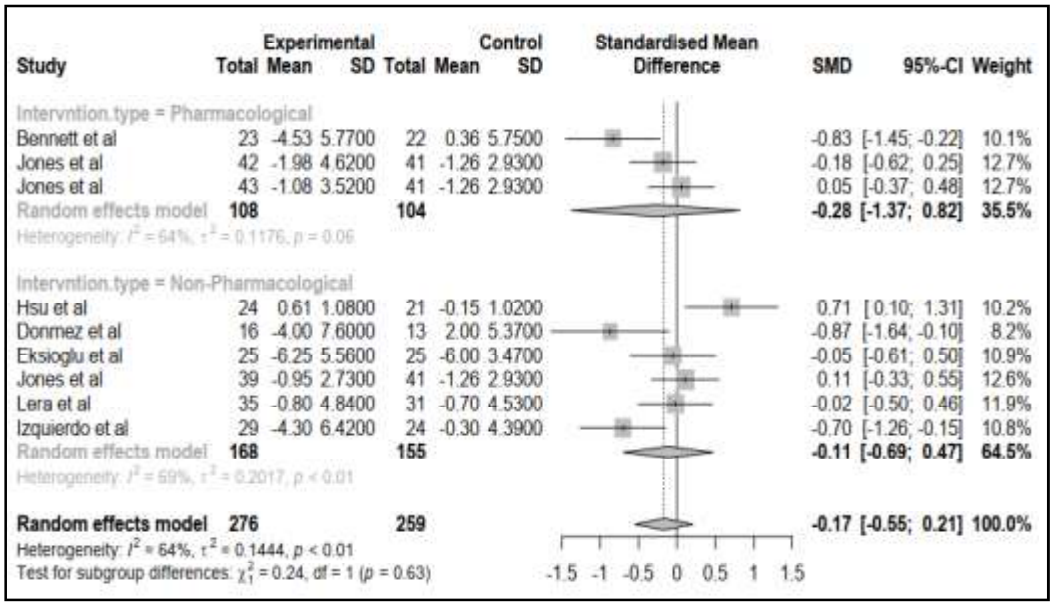

Figure 6: Forest plots for TPC outcome

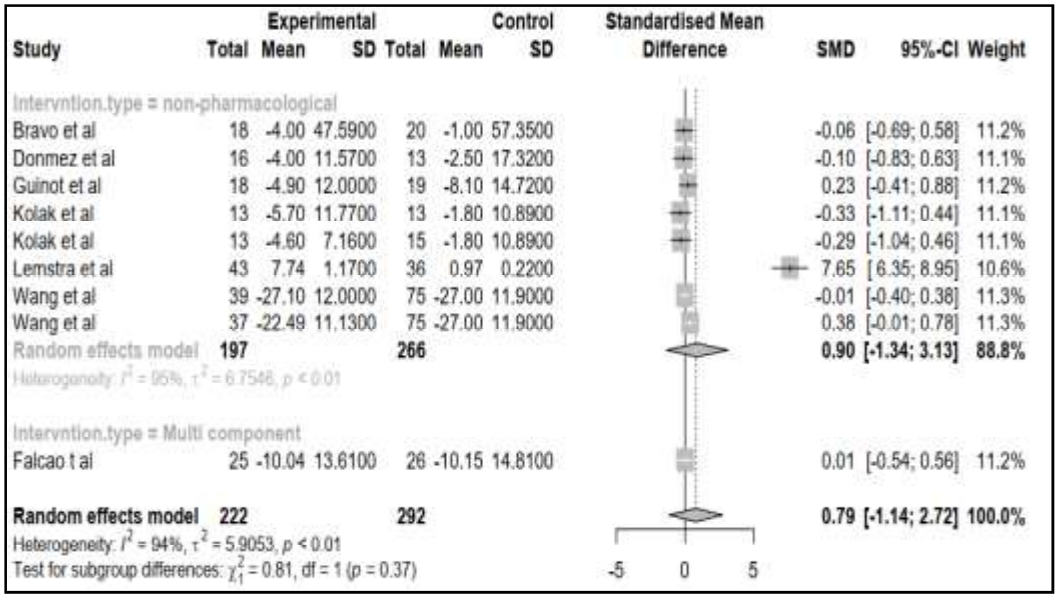

Figure 7: Forest plots for meta-analysis of SF-36

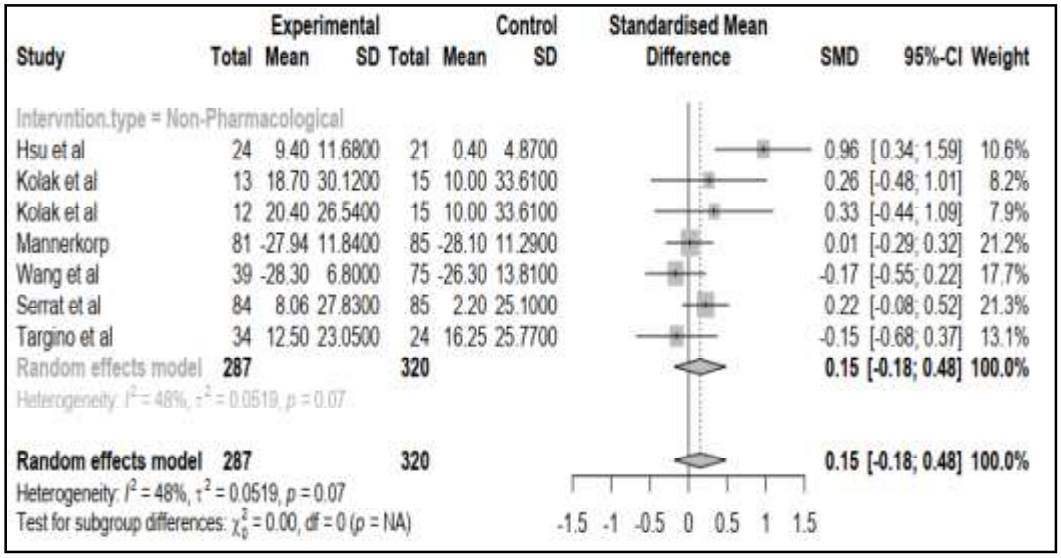

Figure 8: Forest plots for meta-analysis of BDI score

0.56), while pharmacological therapy had an effect size of SMD = -0.90 (95% CI, -1.34 to 3.13), both compared to treatment as usual (Figure 8).

Figure 8: Forest plots for meta-analysis of BDI score

Discussion

The current study evaluates both pharmacological and nonpharmacological interventions for FMS. The analysis was based on a pooled effect of 27 studies that involved 2390 patients which mainly address the symptomatic aspects of FMS reported by the patient. Only those trails were included who have assessed the effectiveness of pharmacotherapy or non-pharmacotherapy compared with TAU or Placebo. The prevalence of FMS shows a remarkable gender disparity, with women having a higher incidence than men. Thus, the current study focuses on evaluating the SMD of pain score VAS, FIQ score, and TPC, in addition assessing depression and quality of life. In a study conducted by Muhammad et al., it was observed that the ratio of female to male patients suffering from FMS was 9:1.[46] This finding is corroborated by a review conducted by Heidari et al., which estimated the total prevalence of FMS in

women to be 3.98%, while in men, it was found to be only 0.01%.[47] A similar result was observed in the present study, where 96.6% of the participants with FMS were female. The reasons for the higher prevalence of FMS in women remain uncertain. Additionally, women tend to exhibit more severe and unpredictable symptom progression compared to men. FMS predominantly occurs in adults aged between 40-50 years.[48] The study conducted herein has demonstrated that the mean age of individuals diagnosed with FMS is 47.03 (SD 8.8) years. The present study's results align with those of Walitt et al. investigation, which derived analogous findings via an interview-based survey. Our investigation discovered that the incidence of FM syndrome (FMS) was least prevalent among individuals aged 18-29, at a rate of 0.76% (0.05, 1.46), and rose to 2.41% (1.49, 3.33) among those aged 50-59 years. Moreover, there was no significant difference in the prevalence of FMS compared with older age groups. These results provide important insights into the age distribution of FMS and could inform the development of targeted interventions for this population.[49] Despite being recognized for several decades, the diagnosis of FMS remains difficult due to the absence of a definitive pathophysiological mechanism. The diagnostic and therapeutic procedures for FMS patients are protracted and intricate, encompassing multiple consultations with healthcare providers and a prolonged waiting period averaging two years prior to diagnosis.[50]

Current research has examined the effectiveness of various agents in the treatment of FMS. However, the use of pharmacological interventions alone is insufficient in treatment this condition. Despite the potential benefits of pharmacological interventions, non-pharmacological interventions have been shown to be equally effective in managing FMS symptoms. The results showed a non-significant improvement in the FIQ score with a SMD of 3.61 (CI: -0.79-8.01), p-value of 0.1, while the VAS score showed a significant improvement with a SMD of 1.41 (CI: 0.08-2.73), p-value of 0.003, in favour of the non-pharmacological intervention group. Among non-pharmacological interventions, MCT followed by aerobic exercise Low to moderate intensity endurance and strength training are strongly recommended. Chiropractic, laser therapy, magnetic field therapy, massage and transcranial magnetic stimulation are not recommended and CBT was most promising for reducing pain and improving quality of life. Of the non-pharmacological interventions, only exercise was evaluated in one large trial.[51] Pharmacological treatments show limited clinical evidence, and non-pharmacological interventions also lack substantial support. However, healthcare professionals concur that enhancing daily function and quality of life relies on crucial self-management strategies. Despite the scarcity of scientific evidence endorsing their effectiveness, self-management strategies can incorporate complementary and alternative medicine interventions.[52]

The present meta-analysis is subjected to several limitations. Firstly, the only few studies [53, 54, 55, 56] included trials that directly compared the efficacy of pharmacological therapy to non-pharmacological therapy, which limits the conclusions that can be drawn about the relative effectiveness of these treatments. Secondly, the majority of studies included in the analysis had small sample sizes, which may have reduced the quality of the pooled results. Finally, the predominantly female sample may limit the generalizability of the findings to male populations, as FM is a syndrome that affects women more frequently than men.

The main reason for the disparity in recommendations for pharmacological treatment of FMS is the lack of sufficient high-quality randomized control trials in the field. As a result, the guidelines have to rely on evidence of lower quality and expert consensus.[57] The use MCT (combination of aerobic exercise with at least one psychological therapy) with a duration of at least 24 h is strongly recommended for patients with severe forms of FM.[58]

Conclusion

In conclusion, the study highlights the limited evidence available about effective and clinically relevant treatments for FMS. A combination of pharmacological and non-pharmacological interventions may be most promising, but additional high-quality trials are needed to confirm the effectiveness of non-pharmacological interventions such as CBT, aerobic exercise, and MCT.

Supplementary file information

Tables S1 gives a comprehensive overview of key characteristics of included RCTs. Tables S2 outlines the exclusion of specific studies, elucidating the selection criteria with reasons. Tables S3 delineates the systematic review's search strategy, revealing the methods employed in identifying pertinent literature. Tables S4 Presents the PRISMA Checklist, which serves as a reference for assessing the adherence of the guidelines. Fig S1 shows PRISMA flow chart visually illustrates the study selection process. Fig S2 displays results from the Methodological Quality Assessment via RoB-2 and Fig S3 presents a gender-based distribution of FM in the study.

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Competing interests

Authors declare no conflict of interests

Availability of data

The data used to support the findings can be provided on relevant request.

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