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Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia
A Systematic Review and Meta-analysis

Rodrigo Oliveira Mascarenhas, MSc; Mateus Bastos Souza, BAppSc; Murilo Xavier Oliveira, PhD; Ana Cristina Lacerda, PhD; Vanessa Amaral Mendonça, PhD; Nicholas Henschke, PhD; Vinícius Cunha Oliveira, PhD

IMPORTANCE Fibromyalgia is a chronic condition that results in a significant burden to individuals and society.

OBJECTIVE To investigate the effectiveness of therapies for reducing pain and improving quality of life (QOL) in people with fibromyalgia.

DATA SOURCES Searches were performed in the MEDLINE, Cochrane, Embase, AMED, PsycInfo, and PEDro databases without language or date restrictions on December 11, 2018, and updated on July 15, 2020.

STUDY SELECTION All published randomized or quasi-randomized clinical trials that investigated therapies for individuals with fibromyalgia were screened for inclusion.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data and assessed risk of bias using the 0 to 10 PEDro scale. Effect sizes for specific therapies were pooled using random-effects models. The quality of evidence was assessed using the Grading of Recommendations Assessment (GRADE) approach.

MAIN OUTCOMES AND MEASURES Pain intensity measured by the visual analog scale, numerical rating scales, and other valid instruments and QOL measured by the Fibromyalgia Impact Questionnaire.

RESULTS A total of 224 trials including 29 962 participants were included. High-quality evidence was found in favor of cognitive behavioral therapy (weighted mean difference [WMD], −0.9; 95% CI, −1.4 to −0.3) for pain in the short term and was found in favor of central nervous system depressants (WMD, −1.2 [95% CI, −1.6 to −0.8]) and antidepressants (WMD, −0.5 [95% CI, −0.7 to −0.4]) for pain in the medium term. There was also high-quality evidence in favor of antidepressants (WMD, −6.8 [95% CI, −8.5 to −5.2]) for QOL in the short term and in favor of central nervous system depressants (WMD, −8.7 [95% CI, −11.3 to −6.0]) and antidepressants (WMD, −3.5 [95% CI, −4.5 to −2.5]) in the medium term. However, these associations were small and did not exceed the minimum clinically important change (2 points on an 11-point scale for pain and 14 points on a 101-point scale for QOL). Evidence for long-term outcomes of interventions was lacking.

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis suggests that most of the currently available therapies for the management of fibromyalgia are not supported by high-quality evidence. Some therapies may reduce pain and improve QOL in the short to medium term, although the effect size of the associations might not be clinically important to patients.

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Supplemental content

Author Affiliations: Department of Physiotherapy, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, Brazil (Mascarenhas); Postgraduate Program in Rehabilitation and Functional Performance, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, Brazil (Souza, M. X. Oliveira, Lacerda, Mendonça, V. C. Oliveira); Institute for Musculoskeletal Health, The University of Sydney School of Public Health, Sydney, New South Wales, Australia (Henschke).

Corresponding Author: Vinícius Cunha Oliveira, PhD, Postgraduate Program in Rehabilitation and Functional Performance, Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM), Campus JK–Rodovia MGT 367, Km 583, No. 5000, Alto da Jacuba, Diamantina, MG 39100-000, Brazil (vcunhaoliveira@gmail.com).

Fibromyalgia is a chronic condition of unknown cause characterized by generalized body pain, fatigue, sleep disturbance, impaired cognition, and anxiety.[1] The prevalence ranges from 0.2% to 6.6% in the general population,[2] and the condition causes disability with high direct costs (eg, costs of drug therapy and health care) and indirect costs (eg, productivity loss).[3-5] The diagnostic criteria for fibromyalgia have changed in recent years.[1,6-8] Despite differences in the characteristics of patients diagnosed using the newer version of the diagnostic criteria,[9] to our knowledge, no systematic review has investigated the association of the diagnostic criteria with the estimated effect sizes of therapies used to treat this population.

There are many therapies available for fibromyalgia, including exercise,[10] electrotherapy,[11] pharmacologic therapies,[12] psychological therapies,[13] and complementary and alternative treatments.[14] Many systematic reviews have reported the outcomes of these therapies for patients with fibromyalgia; however, the methods adopted by some reviews might have compromised the effect estimates presented. These methods include the use of control groups that received some kind of active intervention,[10,11,14] language restrictions on the selection of the studies,[15] inclusion of nonrandomized clinical trials,[16] and not evaluating the strength of the evidence supporting the estimated effect sizes.[17] In addition, the evaluation of the effectiveness of some therapies is in need of updating,[13,18] as new trials have been recently published.[19,20]

This systematic review with meta-analysis was conducted following the guidance of the Cochrane Handbook[21] with the aim to investigate the short-, medium-, and long-term effectiveness of therapies for reducing pain and improving the quality of life (QOL) in patients with fibromyalgia. We explored whether the risk of bias of studies or the diagnostic criteria are associated with the estimated effect sizes. In addition, we investigated the strength of the evidence supporting the effect size estimates using the Grading of Recommendations Assessment (GRADE) approach[22,23] and discuss its clinical relevance.

Key Points

Question What is the association of therapies with reduced pain and improved quality of life in patients with fibromyalgia?

Findings In this systematic review, the effectiveness of most therapies for fibromyalgia was not supported. Strong evidence supported only cognitive behavioral therapy for pain, as well as antidepressants and central nervous system depressants for pain and quality of life, but these associations were small.

Meaning Some therapies may be associated with small reductions in pain and improvements in quality of life in people with fibromyalgia; however, current evidence is lacking for most therapies.

Methods

Searches and Inclusion Criteria

This systematic review of randomized or quasi-randomized clinical trials followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline checklist[24] and the Cochrane Handbook recommendations.[21] The protocol was prospectively registered in PROSPERO (CRD42019117326).

Search strategies were conducted in the MEDLINE, Cochrane, Embase, AMED, PsycInfo, and PEDro databases without language or date restrictions on December 11, 2018, and updated on July 15, 2020. The search terms were related to "randomized controlled trials" and "fibromyalgia." No specific term related to "therapies" was used to increase the sensitivity of our search and avoid exclusions of possible relevant therapies of which we were not aware. The detailed search strategy is provided in the eAppendix in the Supplement. In addition to the electronic search, the reference lists of relevant systematic reviews were screened for potentially relevant trials.

Published randomized or quasi-randomized clinical trials were included if participants had received a diagnosis of fibromyalgia according to any of the American College of Rheumatology (ACR) definition criteria.[1,6-8] Trials were eligible if they included people with fibromyalgia regardless of age or sex, from any health care setting receiving any therapy. Trials comparing these therapies with a control group (ie, no intervention, waiting list, placebo, or sham) were included. Trials investigating surgical therapies were not considered in our review because these are rarely offered for the management of fibromyalgia. Comparisons with control groups that received any form of active intervention were excluded. We anticipated that a high number of interventions would be included; thus, we restricted our analysis to 2 outcomes: pain and QOL measured with the Fibromyalgia Impact Questionnaire (FIQ).[25] This choice was based on pain being the most characteristic symptom of this health condition[6] and the FIQ being an instrument that captures other commonly reported symptoms in this population (ie, fatigue, stiffness, anxiety, and depression).[25]

For pain, we analyzed data from the visual analog scale (VAS). When the VAS was not available, we used numerical rating scales (NRSs) and other valid instruments (described in eTable 1 in the Supplement).

Selection of Trials

After the electronic searches, the retrieved references were exported to an Endnote file, and duplicates were removed. Two independent reviewers (R.O.M. and M.B.S.) screened titles and abstracts and assessed potential full texts. Full texts fulfilling the eligibility criteria were included in the review. Discrepancies between reviewers were resolved by a third reviewer (V.C.O.).

Data Extraction

Two independent reviewers (R.O.M. and M.B.S) extracted study characteristics and outcome data from the included trials, and any discrepancies were resolved by a third reviewer (V.C.O.). Data extracted included the type of study, source of participants, types of therapy and comparator, outcomes, and time

points. For the outcomes of interest, mean (SD) values and sample sizes of groups were extracted for short-, medium-, and long-term outcomes. A short-term outcome was considered any time point from randomization to 3 months, a medium-term outcome was defined as more than 3 months and less than 12 months, and long-term outcomes were follow-up of at least 12 months after randomization. If more than 1 time point was available within the same period, the point closest to the end of the intervention was extracted and analyzed. When trials evaluated more than 1 similar therapy with control or more than 1 form of sham or placebo, we combined outcome data following Cochrane Handbook recommendations.[21] For trials that evaluated different types of therapies, each trial group was extracted and pooled separately. In trials for which SDs were not available, they were imputed following recommended methods[21,26] (eMethods in the Supplement). Data that were considered to have skewed distribution were excluded from the quantitative analysis as recommended by the Cochrane Handbook.[21]

Risk-of-Bias Assessment

Two independent reviewers (M.X.O. and V.A.M.) assessed the methodological quality of included trials using the 0 to 10 PEDro scale (https://www.pedro.org.au/), where 0 indicates high risk of bias and 10 indicates low risk of bias.[27,28] A third reviewer (V.C.O.) resolved discrepancies between reviewers. When they were available, we extracted scores for trials directly from the PEDro database.

Statistical Analysis

Data from trials that investigated the same type of therapy were pooled in independent meta-analyses. When different modes of the same treatment were assessed (ie, ≥2 drugs of the same class or different modalities of exercise), data were pooled based on what had been done in previously published systematic reviews.[29-31] Weighted mean differences (WMDs) and 95% CIs were presented for each specific therapy in forest plots. When pooling of more than 1 trial was not possible, we presented the mean difference and 95% CI. The overall outcome was evaluated by the *z* test, all *P* values were from 2-sided tests, and results were deemed statistically significant at $P < .05$. The clinical importance of therapies was interpreted by comparing the estimated effect sizes and 95% CI in association with the minimal clinically important difference (MCID) of the outcome of interest.[32] For pain, we considered the MCID of 2 points on an 11-point pain rating scale,[33] and for QOL, we used the MCID of 14 points on the 101-point FIQ scale.[34] All analyses were conducted using Comprehensive Meta-analysis software, version 2.2.04 (Biostat), and meta-analysis was conducted using a random-effects model (DerSimonian and Laird method).

Two independent reviewers (R.O.M. and M.B.S.) also assessed the strength of the current evidence for each therapy using the GRADE method.[22,23] According to the 4-level GRADE system, evidence may range from high to very low quality, with lower levels indicating that future high-quality trials are likely to change estimated outcomes. In the present review, evidence began at high quality and was downgraded by 1 point for each of the following issues: publication bias when it was present in analysis of at least 10 trials,[35] imprecision when fewer than 400 participants were included in the meta-analysis,[36] risk of bias when more than 25% of the participants in a meta-analysis were from trials with a high risk of bias (ie, PEDro score <6 of 10),[37] and inconsistency of results when the I^2 statistic was greater than 50% or when pooling was not possible.[21] To evaluate publication bias, we conducted a visual inspection of funnel plots and used the Egger test, adopting an $\alpha = 0.1$[38] (eFigure 1 in the Supplement). Between-reviewer discrepancies were resolved by a third reviewer (V.C.O.). We conducted sensitivity analyses to investigate whether poor methodological quality and the definition criteria were associated with the estimated outcomes. The first was done by removing trials from the meta-analysis with a PEDro score lower than 6. The second was done by performing a different meta-analysis including only trials that used the ACR 2010 or later updated definition criteria.[1,7,8] Metaregression was not possible because of the small number of trials.[21]

Deviations From the Protocol

Our original plan was to pool data from different instruments using the standardized mean difference; however, it was noticed that many of the included trials reported data as change from baseline and not postintervention scores at the data extraction stage. Because the Cochrane Handbook advises against pooling change and postintervention data using the standardized mean difference,[21] we modified our analysis by converting data to a similar scale and pooling it using WMDs when possible.

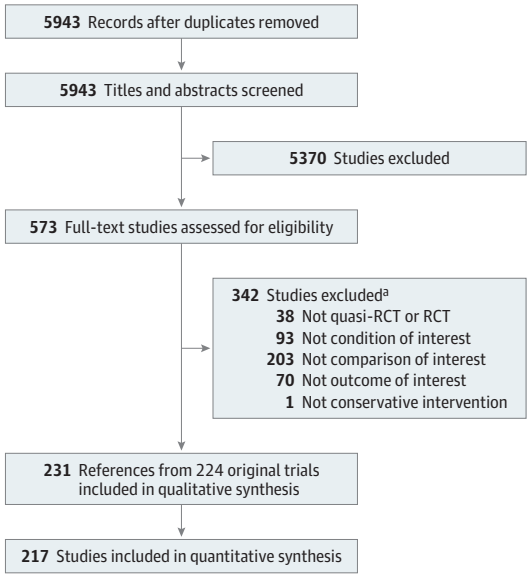
Results

The flow of studies through the review is summarized in **Figure 1**. The initial searches identified 5943 records, from which 573 potential full texts were assessed. A total of 231 published references of 224 original trials including 29 962 participants were included in the review. Seven original trials were reported in 2 different publications each.[39-52] Eleven trials (including 1203 participants) were not included in the quantitative analysis because outcome data were not reported and imputations were not possible[53-60] or data indicated a skewed distribution.[61-63]

Study Characteristics

The trials included in the quantitative analysis investigated 65 different therapies, including single nonpharmacologic treatments (n = 36), combinations of 2 or more nonpharmacologic treatments (n = 8), pharmacologic treatments (n = 17), a combination of 2 or more pharmacologic treatments (n = 3), or a combination of pharmacologic and nonpharmacologic therapy (n = 1). Study characteristics are reported in eTable 1 in the Supplement. From the trials that reported the sex of the participants (188 of 224 trials), most participants were women (20 421 of 21 473 [95.1%]). The sample size of the included trials ranged from 13 to 1293 participants. Only 34 of the included trials (15.2%) used the ACR 2010 or later updated diagnostic criteria for inclusion of the participants. Trials were con-

Figure 1. Flow of Studies Through the Review



RCT indicates randomized clinical trial.

[a] Articles could be excluded for more than 1 reason.

ducted across 5 continents (Africa, North America, Asia, Australia, and Europe), although only 1 trial was from Africa. The outcomes of both pain and QOL were investigated in 125 of the included trials (55.8%), 70 of the trials (31.3%) investigated pain only, and 29 trials (12.9%) investigated QOL only. Of the trials included in the meta-analysis, 181 reported data for pain (eg, VAS, NRS, Brief Pain Inventory, and McGill Pain Questionnaire), and 149 reported data for QOL (ie, FIQ). Short-term outcomes for pain were investigated in 137 trials, medium-term outcomes for pain were investigated in 50 trials, and long-term outcomes for pain were investigated in 1 trial; short-term outcomes for QOL were investigated in 106 trials, medium-term outcomes for QOL were investigated in 50 trials, and long-term outcomes for QOL were investigated in 1 trial.

Risk of Bias

The median score on the 0 to 10 PEDro scale for the included trials was 7. Of the 224 original trials, 56 (25.0%) were considered at high risk of bias (PEDro score <6) (eTable 2 in the Supplement). The main reasons for risk of bias were not blinding of the therapists (162 trials [72.3%]), not performing concealed allocation (119 trials [53.1%]), not performing an intention-to-treat analysis (114 trials [50.9%]), and withdrawal rates higher than 15% (112 trials [50.0%]).

Summary of the Evidence

Figure 2 and **Figure 3** summarize the high- and moderate-quality evidence for pain and QOL in the short and medium term. The estimated outcomes are presented as WMD for data on an 11-point scale for pain and a 101-point scale for QOL. Although some of the outcomes estimated with high to moderate quality of evidence were statistically significant, the 95% CI of our estimates indicate that only transcutaneous electrical nerve stimulation, magnetic field therapy, acupuncture, transcranial direct current stimulation, manual therapy, and transcranial magnetic stimulation in the short term and massage or myofascial release in the medium term may reach the MCID of 2 points in an 11-point pain rating scale for patients with fibromyalgia. For pain in the short term, we found high-quality evidence in favor of cognitive behavioral therapy (CBT; WMD, −0.9 [95% CI, −1.4 to −0.3]; 14 trials with 905 participants) and no evidence in favor of antiemetics (WMD, −0.9 [95% CI, −2.0 to 0.2]; 2 trials with 456 participants). For pain in the medium term, we found high-quality evidence in favor of central nervous system depressants (WMD, −1.2 [95% CI, −1.6 to −0.8]; 2 trials with 1121 participants) and antidepressants (WMD, −0.5 [95% CI, −0.7 to −0.4]; 12 trials with 7424 participants).

For the outcomes estimated with a high to moderate quality of evidence, only the effect estimates for acupuncture, magnetic field therapy, transcranial direct current stimulation, balneotherapy, and manual therapy in the short term reach values higher than the reported MCID of 14 points on the 101-point FIQ scale; however, these estimates are imprecise and the 95% CIs indicate that they may not be clinically important. For QOL in the short term, we found high-quality evidence in favor of antidepressants (WMD, −6.8 [95% CI, −8.5 to −5.2]; 12 trials with 2478 participants). For QOL in the medium term, we found high-quality evidence in favor of central nervous system depressants (WMD, −8.7 [95% CI, −11.3 to −6.0]; 3 trials with 1135 participants) and antidepressants (WMD, −3.5 [95% CI, −4.5 to −2.5]; 11 trials with 8171 participants). Forest plots of meta-analysis rated as high and moderate quality of evidence are available in eFigure 2 in the Supplement.

We did not find any high- or moderate-quality evidence supporting any therapy for pain or QOL in people with fibromyalgia in the long term. The main reason for downgrading the quality of evidence was imprecision (120 of 137 comparisons), followed by inconsistency (90 of 137), risk of bias (41 of 137), and publication bias (3 of 137). A summary of low- and very-low-quality evidence is presented in eFigures 3 and 4 in the Supplement.

Sensitivity Analysis

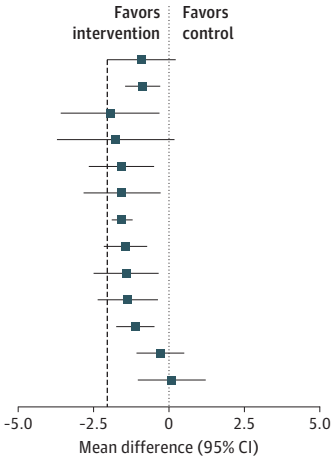
Here we present the association of risk of bias and the fibromyalgia definition criteria with the effect estimates supported by high-quality evidence. The detailed analysis for all interventions is presented in eTables 3 and 4 in the Supplement. Risk of bias was associated only with the estimated outcome of acupuncture for pain in the short term that changed from significant (WMD, −1.5 [95% CI, −2.8 to −0.3]) to nonsignificant (WMD, −1.2 [95% CI, −2.5 to 0.2]) when 1 trial with a high risk of bias was removed from the pooling.[64] Because of this result, we downgraded the evidence supporting acupuncture for pain in the short term from high to moderate.

The analysis of the association of the definition criteria with effect estimates was limited by the small number of trials that used the ACR 2010 or later updated criteria (only 34 trials were included in the quantitative analysis). As previously described, a small number of trials (11 of 215) measured pain with instruments other than the NRS or VAS that could not be

Figure 2. Summary of High- and Moderate-Quality Evidence Meta-analysis on Treatment of Pain in Fibromyalgia

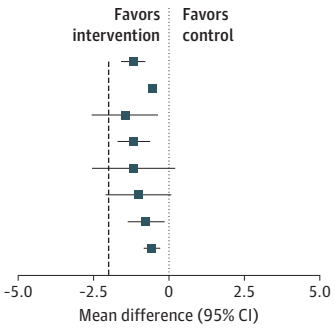
A Short-term outcomes

Intervention	Trials, No.	Participants, No.	I^2	Mean difference (95% CI)	GRADE
Antiemetics	2	456	0	-0.9 (-2.0 to 0.2)	High
CBT	14	905	0	-0.9 (-1.4 to -0.3)	High
TENS	2	238	0	-1.9 (-3.5 to -0.3)	Moderate[a]
Hyperbaric oxygen therapy	2	83	0	-1.8 (-3.7 to 0.2)	Moderate[a]
Magnetic field therapy	5	260	1	-1.6 (-2.6 to -0.5)	Moderate[a]
Acupuncture	5	400	0	-1.5 (-2.8 to -0.3)	Moderate[b]
Exercises	13	624	0	-1.5 (-1.9 to -1.2)	Moderate[c]
tDCS	7	284	0	-1.4 (-2.1 to -0.8)	Moderate[a]
Manual therapy	2	138	0	-1.4 (-2.4 to -0.4)	Moderate[a]
TMS	12	437	0	-1.4 (-2.3 to -0.4)	Moderate[d]
Nutritional supplements	7	338	0	-1.1 (-1.7 to -0.5)	Moderate[a]
Analgesics	2	141	0	-0.3 (-1.0 to 0.5)	Moderate[a]
EEG neurofeedback	2	90	0	0.1 (-1.0 to 1.2)	Moderate[a]



B Medium-term outcomes

Intervention	Trials, No.	Participants, No.	I^2	Mean difference (95% CI)	GRADE
CNS depressants	2	1121	0	-1.2 (-1.6 to -0.8)	High
Antidepressants	12	7424	0	-0.5 (-0.7 to -0.4)	High
Massage or myofacial release therapy	2	102	0	-1.5 (-2.5 to -0.4)	Moderate[a]
Exercises	13	963	0	-1.2 (-1.7 to -0.6)	Moderate[c]
Nutritional supplements	2	58	0	-1.2 (-2.5 to 0.2)	Moderate[a]
Magnetic field therapy	2	105	0	-1.0 (-2.1 to 0.1)	Moderate[a]
CBT	2	159	0	-0.8 (-1.4 to -0.2)	Moderate[a]
Anticonvulsants	4	2726	0	-0.6 (-0.8 to -0.3)	Moderate[c]



A, Short-term outcomes. B, Medium-term outcomes. Dashed line indicates the minimum clinically important difference. CBT indicates cognitive behavioral therapy; CNS, central nervous system; EEG, electroencephalography; GRADE, Grading of Recommendations Assessment; tDCS, transcranial direct current stimulation; TENS, transcutaneous electrical nerve stimulation; and TMS, transcranial magnetic stimulation.

[a] Downgraded owing to imprecision: less than 400 participants included in the meta-analysis.

[b] Downgraded owing to inconsistency: I^2 statistic was higher than 50% or pooling was not possible.

[c] Downgraded owing to risk of bias: more than 25% of the participants in the meta-analysis were from trials with a high risk of bias (ie, PEDro score <6 of 10).

[d] Downgraded owing to publication bias based on visual inspection of funnel plots and using the Egger test adopting an α = 0.1.

combined. A separate quantitative analysis was conducted for these data that resulted in estimates of low- to very-low-quality evidence (data presented together with the sensitivity analyses in eTables 3 and 4 in the Supplement).

Discussion

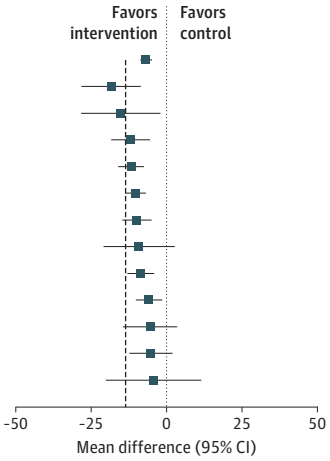
This systematic review with meta-analysis investigated the effect sizes of therapies for pain reduction and QOL improvement in people with fibromyalgia. We found high-quality evidence, which means that the estimated outcomes are unlikely to change with further trials, supporting the use of CBT for pain in the short term, central nervous system depressants and antidepressants for pain in the medium term, antidepressants for QOL in the short term, and antidepressants and central nervous system depressants for QOL in the medium term. Moreover, we found high-quality evidence that antiemetics were no better than placebo for pain in the short term. More important, our results indicate small effect sizes that may not be clinically important for antidepressants and central nervous system depressants for pain or QOL (ie, 95% CIs do not reach the MCID of 2 points in an 11-point pain rating scale or 14 points on the 101-point FIQ scale).

Our review involved the analysis of numerous interventions; therefore, we opted to combine several antidepressants in the same analysis to give an overall estimate of antidepressants. We found a small and nonclinically important association for antidepressants and pain reduction in the medium term and for QOL in the short and medium term. This approach increased the precision of our estimates but had a potential limitation of increasing heterogeneity in our meta-analysis. Our results showed substantial heterogeneity (I^2 > 50%) only for antidepressants when investigating pain in the short term, and the quality of the evidence was downgraded owing to inconsistency. In a previous systematic re-

Figure 3. Summary of High- and Moderate-Quality Evidence Meta-analysis on Quality of Life in Fibromyalgia

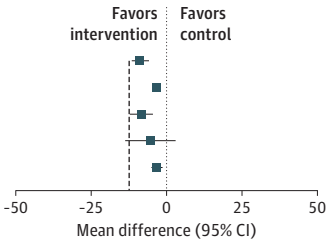
A Short-term outcomes

Intervention	Trials, No.	Participants, No.	I^2	Mean difference (95% CI)	GRADE
Antidepressants	12	2478	0	-6.8 (-8.5 to -5.2)	High
Acupuncture	3	284	0	-18.3 (-27.9 to -8.6)	Moderate[a]
Magnetic field therapy	3	171	4.4	-15.2 (-28.1 to -2.3)	Moderate[a]
tDCS	4	197	1.5	-11.9 (-18.1 to -5.6)	Moderate[a]
Balneotherapy	4	216	0	-11.7 (-15.7 to -7.7)	Moderate[a]
Exercises	16	723	2.5	-10.3 (-13.4 to -7.2)	Moderate[b]
Manual therapy	2	138	0	-9.8 (-14.5 to -5.2)	Moderate[a]
Exercises and whole-body vibration	2	62	0	-9.1 (-20.6 to 2.4)	Moderate[a]
TMS	8	220	0	-8.5 (-12.7 to -4.3)	Moderate[a]
CBT	17	1231	0	-5.8 (-9.9 to -1.6)	Moderate[b]
Analgesics	2	141	0	-5.4 (-14.2 to 3.3)	Moderate[a]
Vibratory stimulation therapy	2	123	0	-5.2 (-12.2 to 1.7)	Moderate[a]
CBT and exercises	2	175	0	-4.3 (-19.8 to 11.3)	Moderate[a]



B Medium-term outcomes

Intervention	Trials, No.	Participants, No.	I^2	Mean difference (95% CI)	GRADE
CNS depressants	3	1135	0	-8.7 (-11.3 to -6.0)	High
Antidepressants	11	8171	0	-3.5 (-4.5 to -2.5)	High
Exercises	15	943	1.5	-10.3 (-13.9 to -6.8)	Moderate[b]
Growth hormone	2	170	0	-5.3 (-13.5 to 2.8)	Moderate[a]
Anticonvulsants	4	2723	0	-3.1 (-4.6 to -1.6)	Moderate[b]



A, Short-term outcomes. B, Medium-term outcomes. Dashed line indicates the minimum clinically important difference. CBT indicates cognitive behavioral therapy; CNS, central nervous system; GRADE, Grading of Recommendations Assessment; tDCS, transcranial direct current stimulation; and TMS, transcranial magnetic stimulation.

[a] Downgraded owing to imprecision: less than 400 participants included in the meta-analysis.

[b] Downgraded owing to risk of bias: more than 25% of the participants in the meta-analysis were from trials with a high risk of bias (ie, PEDro score <6 of 10).

view, antidepressant drugs that we pooled in our review were assessed separately.[65] That systematic review found different associations of each of these drugs with pain reduction. Although citalopram was not associated with pain reduction, the other drugs had associations with pain reduction that ranged from large (amitriptyline) to small (duloxetine and milnacipran).[65] The exploration of potential heterogeneity by type of antidepressants was not within the scope of our review, and our study was underpowered to conduct this analysis by the inclusion of small numbers of trials for some classes of antidepressants.

A previous systematic review provided moderate-quality evidence for a modest effect size of CBT in the treatment of pain and disability in people with fibromyalgia.[13] Our results are in accordance with these results, and we also found a significant association between CBT and pain reduction in both the short and medium term that, despite being statistically significant, was not clinically important. However, in contrast to this previous review, our current findings are supported by high- to moderate-quality evidence. These differences might be partially explained by differences in inclusion criteria (eg, we did not include trials with usual care or other active therapy as a comparison group) and data analysis (eg, pooling data separately by time points). The inclusion criteria may have led to the lower between-study heterogeneity observed in our estimates compared with the previous reviews that downgraded evidence owing to inconsistency.

Exercise therapy is strongly recommended in clinical guidelines for the management of fibromyalgia,[66-69] and previous systematic reviews exploring its effectiveness found evidence supporting different modalities of exercise (ie, aerobic, strengthening exercise, and aquatic exercise).[70-73] In our review, we combined all exercise modalities into 1 unique category of intervention. This decision had the potential to increase the heterogeneity of our estimates, but our analysis showed low levels of heterogeneity across studies (I^2 values available in Figure 2 and Figure 3). This consistency has also been observed in previous explorations by direct comparisons between aerobic vs strengthening exercise for QOL[72] and land vs aquatic exercise for pain and QOL.[73] Our effect estimates are similar to those shown in a previous study of mixed exercise training[71] that found moderate-quality evidence of a positive association of exercises with pain reduction and QOL improvement. The evidence supporting exercise was downgraded owing to risk of bias (pain and QOL at short and medium term); thus, further high-quality trials may increase our

certainty with respect to the effectiveness of exercises in fibromyalgia.

In our review, we included trials that adopted the different versions of ACR diagnostic criteria for inclusion of participants. The 2010 ACR criteria and its updated versions were conceptualized to consider common fibromyalgia symptoms other than pain (eg, sleep disturbance, fatigue, and morning stiffness).[74] Therefore, we believe that the choice of the diagnostic criteria for eligibility of participants in trials may be associated with the estimates of the association of therapies with the outcomes investigated in our review (ie, pain intensity and QOL measured with FIQ). Although this exploration was not possible in our review owing to the inclusion of a small number of trials that adopted the ACR 2010 or later criteria, we suggest that authors of future trials and systematic reviews should consider this as an important factor to be explored and provide complete data on the diagnostic criteria for included participants.

Strengths and Limitations

This systematic review has some strengths, including that it was conducted with strong methodological rigor following the recommendations of the Cochrane Handbook.[21] It updates and synthesizes all available evidence on the effectiveness of therapies (65 different interventions) for pain and QOL in people with fibromyalgia. The simultaneous analysis of different therapies adopting a single methodological strategy, estimating the effect sizes on critical outcomes for patients, assessing the certainty of evidence for each effect estimate, and discussing the clinical relevance of the effect sizes across therapies allows patients and clinicians to (indirectly) compare the evidence for the effectiveness of different therapies and facilitates informed decision-making.

However, this review has some potential limitations. Despite the high-quality evidence for the effectiveness of some therapies for pain and QOL (ie, antidepressants, CBT, and central nervous system depressants), clinical decision-making needs to consider the evaluation of other important outcomes not evaluated here (ie, costs, adverse events, and dropout rates). In our funnel plot analysis, we found evidence for asymmetry, indicating small trials favoring intervention (ie, antidepressants for pain in the short term) or control (ie, transcranial magnetic stimulation for pain in the short term). To minimize this issue, we admitted uncertainty in this evidence by downgrading it owing to publication bias. We incorporated multiple methods to impute missing data and contacted authors when imputation was not possible. Despite this, data from 11 trials could not be included in our meta-analysis. By admitting the inclusion of quasi-randomized clinical trials in our eligibility criteria, we could have biased our estimates. Such a bias could have been investigated by conduction of sensitivity analysis, but this was not necessary because none of the included trials had this randomization issue.

Conclusions

Clinicians should be aware that current evidence for most of the available therapies for the management of fibromyalgia is limited to small trials of low methodological quality. We found high certainty only for the effectiveness of CBT for pain and antidepressants for QOL in the short term and that antidepressants and central nervous system depressants are effective for both pain and QOL in the medium term. However, the effect sizes of these interventions alone might not be clinically meaningful. In addition, the current evidence is lacking for the long-term associations of therapies with outcomes in this chronic health condition. Clinicians and patients should choose therapies by considering other important outcomes in addition to those presented in this review, such as adverse effects, out-of-pocket costs, and patient preferences.

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Acquisition, analysis, or interpretation of data: All authors.
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