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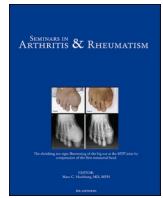


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Effectiveness of non-pharmacological interventions for fibromyalgia and quality of review methods: an overview of Cochrane Reviews

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A B S T R A C T

Background: Fibromyalgia syndrome (FMS) is defined as chronic widespread pain associated with sleep disorders, cognitive dysfunction, and somatic symptoms present for at least three months and cannot be better explained by another diagnosis.

Objectives: To examine efficacy and safety of non-pharmacological interventions for FMS in adults reported in Cochrane Reviews, and reporting quality of reviews. **Methods:** Systematic reviews of randomised controlled trials (RCTs) of non-pharmacological interventions for FMS were identified from the Cochrane Database of Systematic Reviews (CDSR 2022, Issue 3 and CDSR 2023 Issue 6). Methodological quality was assessed using the AMSTAR-2 tool and a set of methodological criteria critical for analgesic effects. The primary efficacy outcomes of interest were clinically relevant pain relief, improvement in health-related quality of life (HRQoL), acceptability, safety, and reduction of mobility difficulties as reported by study participants. No pooled analyses were planned. We assumed a clinically relevant improvement was a minimal clinically important difference (MCID) between interventions and controls of 15%, or a SMD of more than 0.2, or a MD of more than 0.5, on a 0 to 10 scale.

Results: Ten Cochrane reviews were eligible, reporting 181 randomized or quasi-randomized trials (11,917 participants, average trial size 66 participants). The reviews examined exercise training, acupuncture, transcutaneous electrical nerve stimulation, and psychological therapies.

One review was rated moderate according to AMSTAR 2, seven were rated low and two were rated critically low. All reviews met most of the additional methodological quality criteria. All reviews included studies with patient-reported outcomes for pain.

We found low certainty evidence of clinically relevant positive effects of aerobic and mixed exercise training and for cognitive behavioural therapies (CBTs) at reducing mobility difficulties and for mixed exercise training and CBTs for improving HRQoL at the end of the intervention. Number needed to treat for an additional beneficial outcome (NNTB) values for a MCID of 15% ranged between 4 and 9. We found low certainty evidence that was clinically relevant for mixed exercise and CBTs for reducing mobility difficulties at an average follow up of 24 weeks. We found low certainty evidence of clinically relevant positive effects of mixed exercise on HRQoL at an average follow up of 24 weeks. NNTB values for a MCID of 15% ranged from 5 to 11. The certainty of evidence of the acceptability (measured by dropouts) of the different non-pharmacological interventions ranged from very low to moderate and the dropout rate for any reason did not differ across the interventions or the controls, except for biofeedback and movement therapies. All the systematic reviews stated that the reporting of adverse events was inconsistent in the studies analysed (very low certainty evidence).

Authors' conclusions: There is low certainty evidence of clinically relevant reduction of mobility difficulties and of improvement of HRQoL among individuals with FMS by aerobic and mixed exercise training and by CBTs at the end of the intervention. There is low certainty evidence that CBTs and mixed exercise training reduces mobility difficulties post-treatment and that mixed exercise training improves HRQoL at follow-up by clinically meaningful scores.

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Background

This is an overview of Cochrane Reviews of non-pharmacological interventions used to relieve symptoms associated with fibromyalgia syndrome (FMS). Cochrane Reviews are undertaken according to standard guidance which should facilitate reliable overviews and are informed by criteria for what constitutes reliable evidence in chronic pain in general [1], and in FMS in particular [2]. Most non-Cochrane systematic reviews in pain and anaesthesia provide low or very confidence in results due to inadequate reporting quality; most Cochrane reviews, by contrast, provide moderate or high confidence [3]. This is the rationale for examining only Cochrane reviews. Unfortunately, RCTs included in reviews are often (predominantly) of high risk of bias [3,4]. These factors, alone and especially together, suggest a high degree of caution is important when assessing the impact of interventions for a condition as complex and difficult as FMS.

In the International Classification of Diseases (ICD-11), FMS is coded under chronic widespread pain (CWP; Code MG30.01) [5]. We use the ICD-11 preferred term 'fibromyalgia syndrome' in this overview. FMS is defined as a form of CWP (pain in at least 4 of 5 body regions or in at least 3 or 4 body quadrants) associated with sleep disorders, cognitive dysfunction, and somatic symptoms, and symptoms must have been present at a similar level for at least three months and cannot be better explained by another diagnosis [5,6].

FMS is common. A 2013 review gives a global mean prevalence for FMS of 2.7% (range 0.4% to 9.3%) and a mean prevalence of 3.1% in the Americas, 2.5% in Europe, and 1.7% in Asia [7]. FMS is more common in women, with a female-to-male ratio of 3:1 (4.2%:1.4%). Estimates of prevalence in specific populations vary greatly but have been reported to be as high as 9% in female textile workers in Turkey, 10% in metalworkers in Brazil, and 59% in individuals with repetitive strain injury [7]. Determining the incidence of FMS is problematic. A US large insurance claims database study found that the US age-adjusted rate for 'new' FMS was 6.88 cases per 1000 person-years for men and 11.28 cases per 1000 person-years for women between 1997 and 2002 [8].

The clinical presentation of people with FMS is heterogenous. FMS can be associated with mental disorders (mainly anxiety and depressive disorders) and other chronic secondary pain syndromes such as inflammatory rheumatic diseases and osteoarthritis [9]. Most people with FMS in secondary and tertiary medical care report high disability levels and poor health-related quality of life (HRQoL), along with extensive use of medical care [10].

FMS symptoms are difficult to treat effectively, and only a minority of individuals experience a clinically relevant benefit from any one intervention [10]. Recent clinical guidelines recommend a stepwise graduated approach depending on the key symptoms and the extent of disability [11,12], starting with education, defining realistic goals for treatment (improvement of daily functioning), and non-pharmacological interventions such as exercise and psychological therapies. A multidisciplinary approach combining pharmacological therapies with non-pharmacological (i.e., physical or cognitive interventions) interventions is recommended for people with FMS who do not respond sufficiently to these interventions [11,12]. Recent guidelines prefer non-pharmacological interventions over medications as first-line care [11,12], because the former have more ubiquitous clinically relevant effects on FMS symptom domains (pain, sleep disturbance, fatigue, affective symptoms (depression/anxiety), functional deficit, and cognitive impairment) and fewer side effects [13]. Guidelines note that the potential reduction of FMS symptoms by pharmacological therapies are limited to the time of treatment [14], whereas positive effects (although declining over time) are seen for non-pharmacological therapies such as cognitive-behavioural therapies [15] and multicomponent treatments [16]. The precise number and types of non-pharmacological therapies that might be used to treat FMS is unknown. Surveys of people with FMS have found they use multiple non-pharmacological interventions [17,18].

Although many non-pharmacological interventions are used for FMS and there are published Cochrane Reviews of many of these interventions, the overall picture of which interventions work best, their safety profiles and their acceptability has not yet been established. The potential limitations of the available Cochrane Reviews, which might impact their reliability and the strength we can attach to their results, have also not been systematically assessed.

Most primary studies of people with FMS have reported the outcomes (e.g., pain intensity, HRQoL) as mean values. However, the standards used to assess evidence in chronic pain trials have changed substantially in the last 10 years. The most important change is the move from using average pain scores, or average change in pain scores, to the number of people who have a substantial (by at least 50%) or a moderate (by at least 30%) decrease in pain and who continue in treatment, ideally in trials of 8 to 12 weeks or longer. In addition, expert panels suggest using responder criteria for FMS-associated symptoms other than pain such as sleep problems, fatigue or reduced HRQoL and using combined responder criteria (e.g., predefined reduction of pain and sleep problems and global impression of improvement) [2]. This overview assesses if Cochrane Reviews have analysed responders' outcomes described in these ways. Many non-pharmacological trials have not systematically assessed adverse events [19] and this overview also assesses if Cochrane Reviews have analysed adverse events.

Objectives

Our primary objectives were to summarise the evidence on the efficacy, acceptability, and safety of non-pharmacological interventions for FMS in adults. Our secondary objectives were to explore the degree of variability in methods across Cochrane Reviews, in relation to inclusion/exclusion criteria, outcomes, comparisons, and the methods of assessment of adverse events. We also examined the quality of the eligible Cochrane Reviews.

Methods

The protocol was developed in collaboration with Cochrane Neuro-muscular Diseases and Cochrane Musculoskeletal groups [20]. The overview is reported according to the PRIOR statement [21] (see Appendix A). Protocol changes and further methods details are in Appendix B.

Eligibility criteria

We included any Cochrane Review (with or without meta-analysis) of randomised controlled trials (RCTs) and quasi-RCTs of non-pharmacological interventions for adults (aged 18 years and older) with a diagnosis of FMS using one of the established criteria [22–26]. We only included reviews with a range of medical conditions if data for FMS had been reported separately. We excluded reviews of non-pharmacological interventions for FMS in children and adolescents, and reviews with mixed populations if outcomes were not reported separately for adults.

In the absence of an internationally accepted definition and classification of non-pharmacological interventions, we use a definition from [27], which defined non-pharmacological interventions as therapies that do not involve taking medicine or any other active substance. Any non-pharmacological therapies were eligible for this overview.

Eligible comparisons were placebo (sham) control, treatment as usual, attention or waiting-list control, or any different active treatment. Reviews which reported any, or no, outcomes were eligible. We planned to calculate outcomes, if possible, in cases where the review had not already calculated them.

The choice of outcomes is discussed in Appendix B. Details of the outcomes extracted from the eligible Cochrane Reviews are specified in Table 1. We extracted outcomes assessed at the end of therapy and at the

Table 1
Outcomes assessed in the overview.

Primary outcomes	Details/examples
Participant-reported clinically relevant pain relief	For example, pain relief of 30% or more; percentage of participants with a minimal clinically important difference of 15 points on a 100-point continuous pain scale.
Participant-reported disability (mobility difficulties)/physical function:	We preferred analyses of composite measures over analyses of single-item scales. We preferred analyses of number of responders over analyses of mean scores.
Participant-reported clinically relevant improvement of health-related quality of life.	We preferred analyses of disease-specific instruments (e.g., the Fibromyalgia Impact Questionnaire (FIQ)) over generic instruments. We preferred responder analysis (dichotomous outcomes, e.g., improvement of FIQ total score of 20% or more, or a relative difference of 15% over mean scores) over analyses of mean scores.
Safety	Participants experiencing any serious adverse event. Serious adverse events typically include any unwanted medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an ‘important medical event’ that may jeopardise the person, or may require an intervention to prevent one of the above characteristics or consequences.
Acceptability	Number of participants dropping out of the study for any reason.
Secondary outcomes	Details
Participant-reported sleep problems	We preferred analyses of composite measures over analyses of single-item scales.
Participant-reported fatigue	We preferred analyses of number of responders over analyses of mean scores.
Participant-reported mean pain intensity	We preferred analyses of change from baseline scores over analyses of intensity at the end of the study.
Participant-reported depression	We preferred analyses of composite measures. We preferred analyses of number of responders over analyses of mean scores

longest follow-up analysed by the Cochrane Review.

Search, selection process, quality assessments

We searched the most recent issue of the Cochrane Database of Systematic Reviews (via the Cochrane Library) on 30 September 2022 and 15 June 2023, with no date limits (see Appendix B).

Two overview authors independently screened reviews against the eligibility criteria (RAM, JB, WH). If a review had been updated, we used the most recent version.

Two authors independently performed assessments of methodological quality (EF, WH), extracted data (RB, JB, WH), analysed data if required (JB, WH), assessed how the review authors had used the GRADE criteria (EF, WH), and made their own GRADE assessments based on the information provided (EF, WH). Some of the overview authors were also authors of eligible Cochrane Reviews; final assessment decisions were made by overview authors who did not have a conflict of interest with that review. All overview authors agreed on final assessments.

We extracted data (details in Table 2) from the included reviews

Table 2
Data extraction and risk of bias/validity checks.

Data extraction elements	Details
Databases searched and relevant search strategies	
Inclusion and exclusion criteria	For both the systematic reviews and the randomized controlled trials
Details of study settings	
Number of included studies and participants	
Study populations	Baseline demographic and clinical measures
Interventions	Type, frequency, length, and intensity of intervention
Patient-reported outcomes	
Summary results	For at least one desired outcome
Any additional methodological information considered important	
Risk of bias assessments made within the systematic reviews	
Systematic review quality assessment	
AMSTAR-2	Shea BJ, Reeves BC, Wells GA, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. <i>BMJ</i> 2017; 358: j4008.
Additional validity check elements	Details
Did the review use defined diagnostic criteria for fibromyalgia?	
Did the review include only studies in which patients made their own assessment of pain?	Professionals’ and patients’ assessment of pain often differ, with professionals significantly underestimating patients’ pain[28].
Did the review use studies with defined minimum pain intensity of moderate or severe pain as an inclusion criterion?	Mild pain can reduce the sensitivity of trials to demonstrate an analgesic effect[1].
Did the review examine study size as a confounding factor in any analysis of efficacy?	Systematic reviews have been criticised for being overconfident about results with inadequate data[29]; there is increasing evidence of the importance of small trial size, both because of random chance and as an important source of bias[30]
Did the review examine susceptibility to publication bias?	For each review, susceptibility to publication bias was calculated based on the number of participants in studies with zero effect (Relative Risk = 1) that would be needed to give an NNTB too high to be clinically relevant[31]. In such a case, we used as a cut-off for clinical relevance of NNTB values of 10 and 20 for the outcome of participant-reported pain relief of 30% or greater, or 50% or greater. We planned to use this method because statistical tests for the presence of publication bias have been shown to be unhelpful[32].
Did the review examine or comment upon imputation methods for missing data as a potential source of bias?	
Did the review analyse the inclusion and exclusion criteria of the studies and discuss the utility of the study results to people with FMS in routine clinical care?	
Did the review perform subgroup analysis according to the type of control group?	

Key: NNTB: number needed to treat for an additional beneficial outcome

employing a piloted data extraction form. We only revisited the original study reports to gather information if specific data were missing from the Cochrane Review. We did not explore the reviews for study overlap because the interventions were so different. For example, we did not anticipate any overlap between a review of acupuncture and a review of aerobic exercise trials.

Data management

Details of the data extracted, and data management, are provided in the protocol [20] and Appendix B. The systematic reviews all explored different interventions, and thus no discrepant data were identified across the systematic reviews.

Assessment of methodological quality of included reviews

We assessed included reviews against the AMSTAR-2 criteria [33] to provide context about whether and to what extent the reviews' methods may have affected the overview's comprehensiveness and results. We conducted additional checks of potentially critical factors in the evaluation of efficacy [34] (see Table 2 and Appendix C). To assess the risk of bias due to missing results in a review, we collected data on any imputation methods used for missing data.

Data synthesis

We summarised the eligible outcome data reported in the Cochrane Reviews and where outcomes were not reported, we calculated them from the data provided where possible.

Summary of findings and assessment of the certainty of the evidence

We used GRADE to assess the certainty of the evidence related to the key outcomes (Appendix A) [35]. Two overview authors independently rated the certainty of the evidence for each outcome, blinded to any GRADE evaluation in the original reviews. The two assessments for each review were compared. We took account of how the Cochrane Review authors had used the GRADE criteria and noted where the overall rating for a particular outcome needed to be adjusted as recommended by GRADE [35]. In circumstances where no data were reported for an outcome, we reported the certainty of evidence as very low [36].

We used the following descriptors for levels of evidence [37] and we note that "substantially different" in this context implies a large enough difference that it might affect a decision:

- High: this research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different is low.
- Moderate: this research provides a good indication of the likely effect. The likelihood that the effect will be substantially different is moderate.
- Low: this research provides some indication of the likely effect. The likelihood that it will be substantially different is high.
- Very low: this research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different is very high.

We used the amount and certainty of evidence to report results in a hierarchical way, as previously reported in overviews of Cochrane Reviews on pharmacological treatments of chronic pain [38,39]:

- Non-pharmacological interventions for which Cochrane Reviews found no information (very low certainty evidence).
- Non-pharmacological interventions for which Cochrane Reviews found inadequate information: fewer than 200 participants in comparisons (very low certainty evidence).

- Non-pharmacological interventions for which Cochrane Reviews found evidence of effect, but where results were potentially subject to publication bias. We considered the number of additional participants needed in studies with zero effect (relative benefit of one) required to change the number needed to treat for an additional beneficial outcome (NNTB) for at least 50% maximum pain relief to an unacceptably high level (in this case the arbitrary NNTB of 10) [31]. Where this number is less than 400 (equivalent to four studies with 100 participants per comparison, or 50 participants per group), we considered the results to be susceptible to publication bias and therefore unreliable (low certainty evidence).
- Non-pharmacological interventions for which Cochrane Reviews found no evidence of effect or evidence of no effect: more than 200 participants in comparisons, but where there was no statistically significant difference from placebo (moderate or high certainty evidence).
- Non-pharmacological interventions for which Cochrane Reviews found evidence of a clinically relevant effect, where results were reliable and not subject to potential publication bias (high certainty evidence).

We created summary of findings tables for the primary outcomes and some secondary outcomes, where data permitted and we considered it was appropriate (Appendix D). Explorations of heterogeneity in the results of the reviews are described in the protocol [20].

Results

The search of the Cochrane Library identified 40 possible Cochrane reviews for inclusion (September 30 2022). The most recent search (15 June 2023) identified 39 Cochrane reviews, all of which had been identified by the earlier search. We excluded 29 reviews (see Appendix E).

Description of included reviews

We included ten Cochrane reviews, all authored by the Cochrane Musculoskeletal Group (Table 3) and published between 2013 and 2019; only one was published after 2017. Six of the reviews investigated different types of exercise: aquatic exercise [40]; aerobic exercise [41]; whole body vibration [42]; mixed exercise [43]; resistance training [44] and flexibility training [45]. Two reviews investigated different types of therapies using electrophysical agents; a review of acupuncture [46] and a review of TENS [47]. One review focused on cognitive-behavioural therapies (CBTs) [48]. One review assessed 'mind-body' therapies [49]. The latter review classified guided imagery as relaxation therapy. However, guided imagery aims to promote changes in subjective experience, alterations in perception, sensation, emotion, thought or behaviour by imagination [50], therefore, we did not analyse relaxation therapy. We also decided not to analyse "psychological therapies" in that review because different types of psychological treatments with different types of action were pooled [49].

Reviews included between four and 61 RCTs (total 181 RCTs in all reviews). The number of participants in reviews ranged from 150 to 4234 (total = 11,917), and the average number of patients per included trial ranged from 37 to 88 (overall average 66 participants per trial). The mean age of the participants ranged from 41 to 57 years. Women formed the majority in all the reviews (89% to 100% of the participants). There were various control groups; no treatment, treatment as usual, attention placebo, waiting list, sham placebo, other active therapy) (see Table 3). Study overlap across the reviews was not investigated since the reviews explored different interventions.

Methodological quality of included reviews

AMSTAR-2 confidence levels depend on meeting all seven critical

Table 3
Details of included Cochrane Reviews

Review (reference)	Non-pharmacological intervention category and specific intervention	Intervention details	Control	Number/type of studies	Total number of participants	Mean age of participants (years)	Percentage female (%)	Date of last search
Bidonde 2014 [40]	Exercise Aquatic exercise	Supervised group setting Time: average of 17 weeks (range 4 to 32 weeks) Frequency: 2/ week Volume: Average 35 minutes Temperature of the water: Cool 27-32°C Temperate: 33 to 35°C Warm >35°C	Balneotherapy, education-relaxation, sedentary recreational activities	RCTs: 16	881	44 to 51	98	Oct 2013
Bidonde 2017a [41]	Exercise Aerobic exercise	Time: 6 to 24 weeks Frequency: 2 per week Average: 35 minutes	Treatment as usual, wait list, daily activities including physical activity as usual	RCTs: 13	839	41	89	June 2016
Bidonde 2017b [42]	Exercise Whole body vibration	Frequency: 2 per week Time: 6 to 12 weeks Volume: NR	Sham whole body vibration	RCTs: 4	150	57	100	Dec 2016
Bidonde 2019 [43]	Exercise Mixed exercise	Duration: 14 weeks (4 to 26 weeks) Sessions per week: mean 3.1 [1] [7] Intensity: aerobic 40-50% to 85% HRmax Volume: 45 to 180 minutes per session	Wait list, non-exercise (e.g. biofeedback)	RCTs: 29	2088	51	98	Dec 2017
Busch 2013 [44]	Exercise Resistance training	30-60 minutes/ week for 12-26 weeks Frequency: 2 to 3 sessions/week Intensity: moderate- to high-intensity	Untreated control group	RCTs: 5	241	NR	91	March 2013
Kim 2019 [45]	Exercise Flexibility training	Frequency: 1 to 3/ week Time: median 10 [5] [54] weeks Volume: median 10 [6] [60]	Untreated control group	RCTs: 12	743	48.6	100% female: 7 trials Gender NR: 4 trials	Dec 2017
Deare 2013 [46]	Electrophysical Acupuncture	Mean duration: 1 month Frequency: 2 sessions per week Volume (needle retention time): 20 to 30 minutes per session	Sham acupuncture	RCTs: 9 Quasi RCTs: 1	395	NR	93	Jan 2022
Johnson 2017 [47]	Electrophysical TENS	Time and frequency: 30 minutes, 7 days, 21 days, 42 days High (n=5) and low frequency TENS (n=1) Combination of high and low (n=2) Strong intensity (n=6), constant tingling (n=1),	Sham TENS	RCTs: 7 Quasi RCTs: 1	315	18 to 75	95	Jan 2017

(continued on next page)

Table 3 (continued)

Review (reference)	Non-pharmacological intervention category and specific intervention	Intervention details	Control	Number/ type of studies	Total number of participants	Mean age of participants (years)	Percentage female (%)	Date of last search
Bernardy 2013 [48]	Psychological Cognitive behavioural therapies	pleasant tingling (n=1) Sessions: median 10[6] ¹⁰ [60] Total hours: median 18[3] ¹⁰ ₁₀₂	Wait list, attention controls, active controls, treatment as usual	RCTs: 23	2031 (including 86 children)	47.5 (including 86 children)	96%	Aug 2013
Theadom 2015 [49]	Mind-body therapies Biofeedback (n=5), mindfulness (n=3), movement therapy (3 tai chi studies, 3 Yoga studies, 3 Qi-Gong studies, 1 dance therapy study and 1 Pilates study), psychological therapies (2 emotional freedom interventions, 1 study using the Resserquier approach, 1 study using the written emotional disclosure paradigm, 1 study using Acceptance Commitment Therapy (ACT), 1 study using psychodynamic psychotherapy, 17 studies of cognitive behaviour therapy and 11 studies based on psychoeducation; relaxation (3 studies using the guided imagery approach); 4 studies were unclassified but were deemed to meet the inclusion criteria for a mind-body intervention including music therapy, hypnosis and multi-component interventions.	Length of treatment: 1 day to 25 weeks. Average treatment duration: 17 hours.	Treatment as usual, attention control	RCTs: 61	4234	NR in the review. Age mentioned in characteristics of included studies table as 'mean age'.	100% female: 54.1% of studies	Oct 2013

Key: HRmax – maximum heart rate; NR – not reported; RCT – randomized controlled trial; TENS – transcutaneous electrical stimulation

domains in the 16-point assessment. Most of the included reviews met almost all of these, but the impact of publication bias (small study results) was not met by 7/10, and the consideration of risk of bias when interpreting the results of a review was not met by 2/10. As a result, AMSTAR-2 confidence in the evidence tended to be low. It was moderate in one review [48], low in seven reviews [40–43,46,47,49] and critically low in two reviews [44,45] (see Appendix C). In one review, which did not perform quantitative synthesis due to a lack of data, a full PICO could not be defined [47].

Reviews generally reported few included RCTs to have low risk of bias for all items scored. For example, only 7/120 RCTS in nine reviews were without any reported risk of bias, but one review [49] reported that 28/61 RCTs had no risks of bias.

All reviews met five or more of nine additional methodological criteria (see Appendix D). All reviews stated that they included studies with FMS established according to diagnostic criteria but six did not explicitly mention the diagnostic used [40–45]. All reviews included studies with patient-reported outcomes of pain although this was not a predefined criterion for inclusion in the individual reviews, but no review required for inclusion that studies had established pain intensity at baseline should be at least moderate or reported participants' pain intensity at baseline. All reviews used predefined criteria of a minimal clinically important difference (MCID) between study groups (15%) for outcomes.

Appendix C shows the comparisons of the GRADE assessments conducted by the Cochrane Review authors and those conducted by the authors of this overview for pain outcomes. GRADE assessments were the same in seven reviews. One did not perform a GRADE rating for pain as the outcome was not measured [42]. There were discrepancies in the GRADE rating in two reviews [46,49] due to different interpretations of the GRADE assessment.

Effects of interventions

Reviews of non-pharmacological interventions were classified into one of three groups, depending on the amount of data used for analysis and level of effect on primary outcomes:

- those that found evidence of no effect (low certainty evidence);
- those that found insufficient information (fewer than 200 participants in comparisons; very low certainty evidence);
- those that found evidence of a clinically relevant effect on some primary or secondary outcomes, where results were reliable and not subject to potential publication bias.

The effects of interventions on primary and secondary outcomes at end of therapy and at the end of follow-up are detailed in Appendix D along with the summary of findings tables.

There was low certainty evidence of no effect for acupuncture (studies with manual acupuncture and electroacupuncture combined versus sham acupuncture for pain; 3 RCTs with 200 participants) [46].

There was very low certainty insufficient evidence (fewer than 200 participants in comparisons) for benefits from flexibility training [45], biofeedback [49], movement therapies [49], resistance training [44], TENS [47] and whole body vibration [42]. There were fewer than 200 participants in comparisons for all outcomes of acupuncture [46] except pain.

There was high certainty evidence of a clinically relevant effect on some primary or secondary outcomes, where results were reliable and not subject to potential publication bias for aerobic exercise training [41], aquatic exercise training [40], mixed exercise training [43] and CBT [48], at intervention end. Mobility difficulties were reduced by aerobic exercise training (NNTB 5 for MCID; 95% CI 3 to 13) and by

CBTs (NNTB for MCID 7; 95% CI 4 to 26) [41,48]. HRQoL was improved by aerobic exercise training (NNTB for MCID 6; 95% CI 4 to 14) and by CBT (NNTB for MCID 9; 95% CI 6 to 27) [41,48]. According to the predefined categories, the effect sizes were small and met the criteria of the predefined clinically relevant benefit. Mixed exercise training improved HRQoL and reduced mobility difficulties [43]. The effect size for HRQoL was small and for mobility difficulties was moderate. Both effect sizes met the criteria of the predefined clinically relevant benefit.

We found high certainty evidence for some effects on secondary outcomes at the end of the intervention. Pain was reduced by aerobic exercise training (NNTB for MCID 4; 95% CI 2 to 15), by aquatic exercise training (NNTB for MCID 5; 95% CI 3 to 8) and by CBT (NNTB for MCID 7; 95% CI 5 to 19) [40,41,48]. CBT reduced fatigue (NNTB for MCID 9; 95% CI 5 to 109) and depression (NNTB for MCID 6; 95% CI 4 to 12) [48]. According to the predefined categories, the effect sizes were small and met the criteria of the predefined clinically relevant benefit. Pain and fatigue were reduced by mixed exercise training [43]. The effect size for pain was small and for fatigue was moderate. Both effect sizes met the criteria of the predefined clinically relevant benefit.

There was some high certainty evidence for effects on primary outcomes at latest follow-up. Mobility difficulties were reduced by CBTs (NNTB for MCID 4; 95% CI 3 to 12) [48]. According to the predefined categories, the effect size was moderate and met the criteria of the predefined clinically relevant benefit. Mobility difficulties were reduced and HRQoL was improved by mixed exercise training [43]. The effect sizes for both outcomes were moderate and met the criteria of the predefined clinically relevant benefit.

We found some high certainty evidence for small effects on secondary outcomes at latest follow-up. CBT reduced fatigue (NNTB for MCID 5; 95% CI 3 to 14), pain (NNTB for MCID 10; 95% CI 6 to 24) and depression (NNTB for MCID 11; 95% CI 6 to 43) [48]. According to the predefined categories, the effect sizes were small but met the criteria of the predefined clinically relevant benefit.

The dropout rate for any reason did not differ across any of the non-pharmacological interventions reviewed or controls. The review authors rated the certainty of evidence for high adherence as moderate for aerobic and mixed exercise training [41,43] and mindfulness [49], low for aquatic exercise [40], CBT [48] and resistance training [44], and very low for biofeedback [49], movement therapies [49] and whole body vibration [42]. The reviews of acupuncture and TENS did not assess dropouts [46,47] and the flexibility review made no GRADE rating for this outcome [45].

All included reviews stated that the reporting of adverse events, including serious adverse events, was inconsistent in the studies analysed (see Appendix D), but the few studies that reported adverse events within the reviews, reported low rates. Therefore, we rated the certainty of evidence on adverse events to be very low.

Discussion

Cochrane reviews have a special place in the assessment of the clinical efficacy of interventions, because they concentrate on methodological issues designed to reduce the impact of bias. For pain-related topics, most forms of bias tend to increase, often significantly, estimates of treatment effects. There is good evidence for this for trials that are not randomised, not blind, that are small, and where imputation methods used may be inappropriate [51–55]. But significant treatment effects can also be hidden by inappropriate methods, for example, by trying to estimate efficacy where baseline pain is low [56] or different analytical strategies [57]. Inadequate methods used in many systematic reviews in pain and anaesthesia limit confidence in their results; Cochrane reviews typically provide moderate or high confidence [3].

This overview of Cochrane reviews of non-pharmacological interventions for FMS examined 10 reviews published between 2013 and 2019. One provided medium confidence, but nine provided low or critically low confidence. The common cause was failure to meet the

generic 2017 AMSTAR-2 requirement to discuss the impact of possible publication bias and/or considering risk of bias when interpreting or discussing the results. Additional methodological issues more specific to pain were met commonly, though minimum pain intensity or reported pain intensity at baseline.

Deficiencies that limit confidence probably reflect the fact that these reviews were published before the publication of the AMSTAR-2 criteria in September 2017. The methodological requirements of a high quality and trustworthy review become increasingly more stringent, as our knowledge of factors detracting from confidence increase. For example, fabrication is now known to be an important issue that can have major effects on review results, some with relevance to FMS [58], and some Cochrane review groups, and journals have begun to introduce assessments of potential fabrication.

Beyond systematic review methods, attention is increasingly focussed on the RCTs included within reviews. Most RCTs included in Cochrane reviews have high or unknown risks of bias and are usually small in size, and questions arise about how much weight can be given to assessments of efficacy based on them [4,59]. When results from small studies with methodological issues are compared with those from single large and high quality RCTs in meta-analyses, they are often found to overestimate treatment effects [60]. For example, a very large randomised trial of paracetamol (acetaminophen) for low back pain (1650 patient trial) showed it to be no more effective than placebo [61]

This is the context against which the results of the Cochrane non-pharmacological systematic reviews need to be viewed. They provide low certainty evidence of clinically relevant effects of aerobic exercise training and CBT on mobility difficulties and pain intensity, and of aquatic and mixed exercise training on pain intensity at the end of treatment. There was also low certainty evidence of clinically relevant positive effects of mixed exercise training on fatigue and CBT on depression, at the end of treatment. The NNTB values calculated for these outcomes ranged between 4 and 9. The findings, taken at face value, imply that aerobic, aquatic and mixed exercise training and CBTs can reduce some key symptoms of FMS in at most 2 out of 10 persons with FMS more than control interventions at the end of treatment.

There was low certainty evidence of clinically relevant positive effects of CBT on depression, mobility difficulties, fatigue and pain intensity at an average follow up of 24 weeks. NNTB values for these outcomes ranged from 5 to 11, implying that some key symptoms of FMS would be reduced by at best 2 out of 10 persons with FMS more than with control interventions at long-term follow-up. There was low certainty evidence of clinically relevant effects of mixed exercise training on mobility difficulties and HRQoL at an average follow up of 26 weeks. In contrast to pharmacological therapies (Moore et al., forthcoming), there is low quality evidence of sustained positive effects of CBTs and mixed exercise training on some key domains of FMS at follow-up assessment after the end of the intervention.

The demographics of almost all the trials included in the Cochrane Reviews reflected those of clinical samples of people with FMS, comprising predominantly women in their fifth and sixth decades of life, but the preponderance of Caucasians in most studies means that the findings are not globally representative.

Currently, Cochrane reviews cover only some of the possible non-pharmacological interventions that are likely to be used by people with FMS [17,18]. A recent systematic review of RCTs of non-pharmacological interventions for individual symptoms of FMS included education, multidisciplinary treatment, balneotherapy, massage, manual therapy, electrotherapy, laser therapy, transcranial direct current stimulation, magnetotherapy, music therapy, nutrition and weight loss compared to different types of controls [62]. Other non-pharmacological interventions for FMS have been reviewed, including exergame training [63], dance therapy [64], and guided imagery / hypnosis [50]. Given the focus of this overview, we are unable to comment on the effectiveness of those interventions or their implications for clinical practice.

Because FMS is a difficult clinical condition without any dominating effective therapy, it is difficult to comment on how results of clinical research can be used in clinical practice. The results of this overview suggest that caution and wisdom are needed. Whether these findings support recommendations of evidence- and consensus based guidelines that non-pharmacological therapies should be preferred in the long-term management of FMS is an interesting point beyond the scope of this paper [11,12].

The implication for future systematic reviews, both within and outside Cochrane, is that attention to a host of details is required to produce evidence of which we can be confident. Beyond that, the fact that few available RCTs are without some high or unknown risk of bias might give us pause. Do we continue to produce research of low confidence and trust, or do we find ways to conduct large, high quality RCTs that would best support patients and their professional carers?

Agreements and disagreements with other studies or reviews

Exercise

Comparison of the exercise reviews with other systematic non-Cochrane reviews on exercise is hampered by the different types of exercise interventions studied, different control groups studied and outcomes assessed.

Galvão-Moreira 2021 analysed 10 RCTs (508 participants) that compared swimming pool-based exercise versus land-based or no physical exercise. Pool-based exercise was superior to the control interventions at the end of treatment in reducing pain and improving HRQoL. There was no GRADE assessment of the certainty of evidence [65].

Couto 2022 analysed 18 RCTs (1154 participants) that compared aerobic exercise training, resistance training, or stretching performed out of water, compared to different types of control interventions. All exercise interventions were superior to control interventions at the end of therapy in reducing pain and improving HRQoL [66]. The GRADE certainty of evidence for both outcomes was very low.

Kundakci 2022 analysed exercise interventions (mixed exercise: 11 RCTs, 487 participants; aerobic exercise: 9 RCTs, 568 participants; resistance training: 4 RCTs, 221 participants; flexibility: 2 RCTs, 98 participants) [62]. Aerobic, mixed, and strengthening exercises improved HRQoL compared to usual care at the end of the intervention. Aerobic, mixed, and strengthening exercises were effective at relieving pain and depression at the end of the intervention. Strengthening exercises were effective at improving fatigue, whereas aerobic exercise, flexibility, and resistance trainings were effective at improving sleep, at the end of the intervention. There was no GRADE rating of the certainty of evidence.

Acupuncture

Zhang 2019 analysed eight studies (528 participants) of acupuncture compared to sham acupuncture [67] and found acupuncture was superior in reducing pain at the end of the intervention. The GRADE certainty of evidence was rated as moderate. The review included four studies published after the included Cochrane Review search [46]. Kundakci 2022 analysed eight acupuncture RCTs (518 participants) of which six (340 participants) had sham acupuncture as a comparator and two studies (178 participants) had a "usual care" comparator [62]. Acupuncture was more effective than sham acupuncture and usual care for improving HRQoL and reducing pain and fatigue, but not more effective for sleep problems. There was no GRADE rating of the certainty of evidence. Therefore, acupuncture might need to be re-evaluated by Cochrane reviewers as new evidence seems to be available which might change the conclusions of Deare 2013.

TENS

Salazar 2017 analysed nine RCTs (180 participants) that investigated TENS alone or TENS combined with other therapies (e.g. exercise, hydrotherapy, superficial warmth therapy) [68]. Only one comparison was with placebo TENS. Five studies that investigated TENS, with or without another type of therapy, showed no statistically significant pain relief compared to controls. The GRADE certainty of evidence was low. As the Cochrane Review authors noted, robust conclusions about the effectiveness of TENS for FMS are still not possible [47].

Psychological therapies

Comparisons of systematic reviews of psychological therapies are difficult because the reviews use different classification criteria for psychological therapies. In this overview we included the 2013 Cochrane Review of CBTs [48]. This has been updated in 2018 (Bernardy 2018) and published outside the Cochrane Library. The update included seven new studies (546 participants) [15,48]. In the update, acceptance and commitment therapy was classified as a type of CBT and studies with mindfulness-based stress reduction were excluded [15]. In another recent non-Cochrane review (Haugmark 2019) created a separate category of psychological therapies combining mindfulness- and acceptance-based interventions [69].

In Bernardy 2018, all CBTs pooled together were superior to control interventions (wait list, attention control, treatment as usual, other active non-pharmacological therapies pooled together) in attaining pain relief of 50% or greater, in achieving a 20% or greater improvement of HRQoL and in reducing negative mood, mobility difficulties and fatigue at the end of the intervention and at long-term follow-up [15]. There was no difference in efficacy between traditional CBTs, operant therapies and acceptance and commitment therapies (ACT) at the end of the intervention. Only traditional CBTs and ACT could be analysed at long-term follow-up. Operant therapy was superior to traditional CBTs in achieving an improvement of HRQoL of 20% or greater and in reducing in mobility difficulties and negative mood and in attaining pain relief of 30% or greater. The GRADE certainty of evidence for the outcomes ranged from moderate to high.

Haugmark 2019 analysed nine studies (750 participants) of mindfulness-based stress reduction, mindfulness-based cognitive therapy and ACT [69]. These interventions were superior to control interventions (no intervention, wait list control, treatment as usual, or active interventions pooled together) at the end of the intervention in reducing pain, sleep problems and depression, and in improving HRQoL. The GRADE certainty of evidence was very low.

Kundakci 2022 analysed 29 trials (2447 participants) comparing CBTs and mindfulness interventions to "usual care" [62]. The interventions were superior to usual care in reducing pain, sleep problems and depression and improving HRQoL at the end of the intervention. There was no GRADE certainty of evidence rating.

Taken together, these recent reviews confirm the conclusion of the Cochrane review that CBTs (including acceptance and mindfulness-based interventions) can relieve some key symptoms of FMS at the end of follow-up and in the long-term after the end of the intervention [48].

Limitations of this overview

There are several limitations in our overview. As with any review, an outcome could have been reported in the original paper that was not picked up by the Cochrane Review. We did not check the data extraction of the original studies. The overview included only Cochrane Reviews, although we have compared the findings of our overview with other reviews of the same interventions, this overview does not include all the available non-pharmacological interventions.

Although overview authors were also authors of some of the reviews,

we ensured, the data extraction and quality assessment of those reviews were performed by overview authors not involved in the original reviews, but with all authors able to comment. Procedures to minimise bias were discussed with Cochrane editorial teams at the protocol stage. We are aware of no other biases in the overview process.

Implications for practice

Non-pharmacological therapies are aimed at multidimensional targets of FMS. Some types of exercise (aerobic, aquatic and mixed exercise training) and CBTs, including ACT, can have positive effects on multiple domains of symptoms (pain, fatigue, psychological distress) of some people with FMS and can reduce mobility difficulties at the end of the intervention and at follow-up up to an average of 24 weeks after the end of the interventions. These findings support the recommendations of evidence- and consensus based guidelines that non-pharmacological therapies should be preferred in the long-term management of FMS [11,12]. FMS symptoms persist in nearly all patients during their lifetimes. Different types of exercise and types of psychological techniques, such as mindfulness, acceptance and commitment and stress reduction, can be used as self-management by people with FMS after instruction by health care professionals.

Implications for research

Implications for randomized controlled trials

The GRADE rating of the certainty of evidence for pain was low to very low in nine reviews and moderate in one review. Some Cochrane authors have argued there should be a halt on trial registration, until the quality and focus of studies with psychological therapies in chronic pain radically improve, because of a significant threat of research waste [70].

Future randomized clinical trials of non-pharmacological interventions delivered by health care professionals (e.g. physiotherapy, psychological therapies) should improve the implementation of the intervention and provide clearer reporting of blinding status, particularly of trial personnel who can be easily blinded such data managers, the data safety and monitoring committee, statisticians and conclusion makers [71].

The systematic reviews included in this overview could only analyse reported means and standard deviations for pain and HRQoL because responder rates for pain relief were not reported by most of the studies analysed. However, the relevance of average results to the experience of individual participants is problematic [1]. Studies should collect, analyse and report responder rates (e.g. 30% or greater symptom relief or 20% or greater improvement in HRQoL) according to suggested responder definitions for FMS clinical trials [2].

Adverse events in trials of non-pharmacological interventions for FMS should be monitored and reported. Adverse events should be included in any formal ethical consideration of planned research and should be a requirement for publication of trials or evaluation reports [72].

Implications for systematic reviews

Where data are available, systematic reviews should collect and report baseline pain relief and HRQoL scores in the section "Characteristics of included studies". Based on these data, responder rates can be calculated by validated imputation methods by scores at baseline and at the end of the intervention [73], if these outcomes were not reported by the studies themselves.

The representativeness of the study populations with regards to somatic and psychiatric comorbidities should be critically discussed.

The availability of the non-pharmacological intervention reviewed in routine clinical care should be critically discussed.

Meta-regression analyses should be performed to find the optimal duration and intensity of non-pharmacological interventions.

Network meta-analyses of non-pharmacological interventions might

guide people with FMS and their care givers to select the most effective and safest intervention.

Some Cochrane Reviews included in this overview need to be updated, because new studies have been published.

Authors' conclusions

There is low certainty evidence from Cochrane Reviews that aerobic and mixed exercise training and cognitive CBT can have positive effects on multiple symptoms (pain, fatigue, depression) of some people with FMS and can reduce mobility difficulties and improve health-related quality of life. The certainty of evidence for the benefit of acupuncture and of other therapies (e.g., dance therapy, exergame, non-invasive brain stimulation) remains to be determined in terms of Cochrane Reviews or reviews of equal quality. There is sparse evidence about adverse events.

Contributions of authors

WH, RAM, and JB drafted the overview. All authors had input into the overview development and agreed on the final version. JB and WH are the guarantors.

Declaration of Competing Interest

WH is a specialist in general internal medicine, psychosomatic medicine, and pain medicine who treats people with FMS. He is a member of the medical board of the German Fibromyalgia Association and the European Network of Fibromyalgia Associations. He is affiliated with the German Pain Society and is the head of the steering committee of the guideline on FMS of the Association of the Scientific Medical Societies in Germany. He is a member of the steering committee of the European League Against Rheumatism (EULAR) update recommendations on the management of fibromyalgia. He receives royalties from Hypnos Publishers for a CD with medical hypnosis for FMS. He has published systematic reviews and opinions on fibromyalgia pharmacological and non-pharmacological treatment. WH was a member of the Cochrane Pain, palliative and Supportive Care (PaPaS) Editorial Board, but was not involved in the editorial process.

EF: was a member of the PaPaS Editorial Board, but was not involved in the editorial process.

SP: is a specialist in rheumatology and pain medicine who treats people with FMS. He is a member of the steering committee of the European League Against Rheumatism (EULAR) update recommendations on the management of fibromyalgia. SP has published opinions on fibromyalgia treatment, and is affiliated to the Société Française d'Etude et de Traitement de la Douleur (French Society on Pain; SFTED), which has published recommendations on the treatment of fibromyalgia.

RAM: in 2021 RAM received an honorarium from Biogen for advice relating to the possible future design of randomised trials in diabetic neuropathy.

Data availability

Materials used in the overview of reviews are available from WH upon reasonable request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152248.

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