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Extended Research Article

Effects of pharmacological and non-pharmacological interventions for the management of sleep problems in people with fibromyalgia: a multi-methods evidence synthesis

Mari Imamura[1], Clare Robertson[1], Jemma Hudson[1], Daniel Whibley[2,3], Lorna Aucott[1], Katie Gillies[1], Marcus Beasley[3], Martin J Stevens[3], Paul Manson[1], Debra Dulake[4], Abhishek Abhishek[5], Nicole KY Tang[6], Gary J Macfarlane[3] and Miriam Brazzelli[1*]

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Abstract

Background: Fibromyalgia is a chronic condition characterised by widespread musculoskeletal pain. Sleep problems are reported by 92% of people living with fibromyalgia.

Objectives: To evaluate the effectiveness and safety of interventions for the management of fibromyalgia-related sleep problems; explore the experiences of people with fibromyalgia-related sleep problems and examine the content of patient-reported outcome measures for 'sleep quality'.

Methods: We conducted: (1) a network meta-analysis of randomised controlled trials to compare the effectiveness of pharmacological and non-pharmacological interventions; (2) a systematic thematic synthesis of qualitative evidence; (3) a content analysis of existing patient-reported outcome measures validated in people with fibromyalgia. Major electronic databases were searched in November 2021.

Results: One hundred and sixty-eight studies were included in the effectiveness synthesis. The network meta-analysis assessing sleep quality included 35 treatment categories from 65 studies (8247 participants). Most studies were at high overall risk of bias. There is some evidence that compared with placebo or sham treatments, some forms of exercise [i.e. land-based aerobic exercise training in combination with flexibility training (standardised mean difference −4.69, credible interval −8.14 to −1.28) and aquatic-based aerobic exercise training (standardised mean difference −2.63, credible interval −4.74 to −0.58)] may improve sleep. There is also a suggestion that land-based strengthening exercise, psychological and behavioural therapies with a focus on sleep, electrotherapy, weight loss, dental splints, antipsychotics and tricyclics may have a modest effect on sleep, but credible intervals are wide. For other interventions, there is no clear evidence of beneficial effects on sleep. Our certainty of current evidence was predominantly low to very low. The thematic synthesis highlighted the bidirectional relationship between sleep and pain. Twenty-one sleep domains were identified across five patient-reported outcome measures. The domain most frequently identified was sleep maintenance. The Pittsburgh Sleep Quality Index was the most comprehensive tool (15 domains), followed by the Medical Outcomes Study Sleep Scale (11 domains).

Limitations: Quantitative studies varied considerably in terms of characteristics of interventions, control treatments and type of outcome measures. In the network, most interventions were compared with placebo, sham treatment or usual care and not with another active treatment. In general, studies were small, unblinded and of short duration (median 12 weeks). For the qualitative synthesis and patient-reported outcome measures analysis, it is unclear whether study participants are adequately representative of the wider population of fibromyalgia patients due to poor reporting of demographic data.

Conclusions: Some forms of exercise may be effective for managing sleep problems in people with fibromyalgia. However, heterogeneity, imprecision and low quality of the current evidence base preclude any firm conclusions. Qualitative data indicate that poor sleep is a common, profoundly disabling problem for people with fibromyalgia that negatively affects their other symptoms (e.g. pain), health and well-being. While we found heterogeneity among the item content of the patient-reported outcome measures, all capture constructs associated with sleep quality and, conceptually, are similar enough to be combined in a synthesis.

Future work: High-quality research is needed to investigate which interventions are more likely to be effective for treating fibromyalgia-related sleep problems. Future studies must be designed in collaboration with fibromyalgia patients and include an appropriate comparator treatment. Pre-registration of study protocols is essential.

Study registration: This study is registered as PROSPERO CRD42021296922.

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Supplementary materials can be found on the NIHR Journals Library report page (https://doi.org/10.3310/GTBR7561).

Supplementary materials have been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

ACR	American College of Rheumatology
ACT	acceptance and commitment therapy
AE	adverse event
AP	antipsychotics
BMI	body mass index
CASP	Critical Appraisal Skills Programme
CBT	cognitive–behavioural therapy
CINeMA	Confidence In Network Meta-Analysis
CNS	central nervous system
CNS depressants	central nervous system depressants
COS	core outcome set
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
DLPFC	dorsolateral prefrontal cortex
Electro T	electrotherapy
Ex	exercise
FIQ	Fibromyalgia Impact Questionnaire
FMSD	Fibromyalgia Sleep Diary
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADE-CERQual	Grading of Recommendations Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative research
ICF	International Classification of Functioning, Disability and Health
JSS	Jenkins Sleep Scale
LD	land-based (exercise)
Manual T	manual therapy
MCID	minimal clinically important difference
MCS	mental component summary
Mind–body Ex	mind–body exercise
MOS-SS	Medical Outcomes Study Sleep Scale
NMA	network meta-analysis
Non-MSM practice	non-mainstream practice
NR	not reported
NRS	numerical rating scale
OIC	operculo-insular cortex
PBO/Sham	placebo or sham treatment
PCS	physical component summary
PICOS	participants, interventions, comparisons, outcomes, study design
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMs	patient-reported outcome measures
PSQI	Pittsburgh Sleep Quality Index
PT/BT	psychological or behavioural therapy
PT/BT gen	generic psychological or behavioural therapy
PT/BT sleep	psychological or behavioural therapy tailored to sleep problem
RCT	randomised controlled trial
RoB2	a revised Cochrane risk-of-bias tool for randomised trials
rTMS	repetitive transcranial magnetic stimulation
SAE	serious adverse event
SERM	selective oestrogen receptor modulator
SF-36	36-Item Short Form Survey

SMT	Symptom Management Theory	tDCS	transcranial direct-current stimulation
SQ-NRS	Sleep Quality Numeric Rating Scale	TeCA	tetracyclic antidepressant
SRI	serotonin reuptake inhibitor	TENS	transcutaneous electrical nerve stimulation
SSRI	selective serotonin reuptake inhibitor	Tx	treatment
SUCRA	surface under the cumulative ranking curve	UC	usual care
SXB	sodium oxybate	VAS	visual analogue scale
TAU	treatment as usual	WHO	World Health Organization

Plain language summary

It is common for people with fibromyalgia to experience sleep problems. However, it is unclear which treatments work best.

We brought together results from studies that have looked at the effects of medical and non-medical treatments for sleep problems experienced by people with fibromyalgia. We compared treatments using a technique called network meta-analysis, which allows three or more treatments to be compared to each other. We also collected information about the experiences of people with fibromyalgia in coping with their sleep problems and the tools (questionnaires and rating scales) that are currently used to gather information on sleep quality from people with fibromyalgia.

We found 168 studies evaluating a wide range of treatments. Of these, 65 studies (8247 patients) investigated 35 different treatments. Some types of exercise performed on land or in water may improve sleep in the short term. However, most studies were small and poorly conducted (e.g. the choice of alternative treatments used for comparisons was often not appropriate). People with fibromyalgia described poor sleep quality as a major problem that had negative consequences on their symptoms (especially pain), health and well-being. We found that the questionnaires that are currently used to assess sleep quality in people with fibromyalgia are similar enough to allow us to sensibly compare findings from different studies that have used different questionnaires.

Overall, the current evidence is patchy and difficult to trust; we cannot know for sure which treatments should be recommended for fibromyalgia-related sleep problems. We need more well-conducted studies to inform clinical practice and aid patients' self-management. It is crucial to involve patients in the design of future studies, especially during the development of questionnaires used to assess sleep to make sure they contain questions that matter to patients and reflect the experiences of the diverse fibromyalgia community.

Scientific summary

Background and objectives

Fibromyalgia is a long-term condition characterised by chronic widespread musculoskeletal pain, sleep disturbance, fatigue, cognitive dysfunction and low mood. It affects 1.7 million adults in the UK, adversely impacting their daily functioning and health-related quality of life. While there is no cure for fibromyalgia, a range of treatments are offered to alleviate symptoms. Sleep disturbances are reported as one of the most common symptoms by 92% of those living with fibromyalgia. Nevertheless, fibromyalgia-related sleep problems are poorly managed in the NHS, with people continuing to seek help for improving their sleep for many years after their initial diagnosis. The manifestation of sleep problems in fibromyalgia is diverse and can include difficulty with sleep onset, frequent awakenings, feeling unrefreshed on waking, and a perception of poor sleep quality. The 2015 European guidelines for the management of fibromyalgia considered sleep as one of the key outcomes of interest but the evidence for managing sleep problems was graded as 'weak' due to paucity of published evidence at that time.

The overarching aim of this project was to assess the current quantitative and qualitative evidence on interventions for treating fibromyalgia-related sleep problems and provide useful information to help patients' self-management, aid clinical decision-making and guide future research.

Objectives

The specific objectives were:

- To undertake a comprehensive quantitative evidence synthesis to assess the clinical effectiveness and adverse effects of both pharmacological and non-pharmacological treatments for the management of fibromyalgia-related sleep problems.
- To update and enhance the findings of a previously published qualitative evidence synthesis exploring the experiences and expectations of people who receive treatments for fibromyalgia-related sleep problems.
- To examine the content of existing patient-reported outcome measures (PROMs) related to sleep in people with fibromyalgia and compare them in terms of consistency and relevance for patients.

Methods

Data sources

We developed comprehensive search strategies to identify reports of randomised controlled trials (RCTs) assessing sleep outcomes in people with fibromyalgia. We searched Ovid MEDLINE, EMBASE, PyscInfo, and AMED, EBSCO CINAHL, Clarivate Science Citation Index, and the Cochrane Controlled Trials Register (CENTRAL) in November 2021.

We also updated the search strategies reported in the Climent-Sanz *et al*. qualitative synthesis published in 2020 (from 3 January 2020 to 5 November 2021) and in their PROMs analysis (from 6 March 2020 to 5 November 2021). We also repeated their searches adding relevant text terms to identify studies conducted in children (these searches covered all years up to 17 November 2021). Databases searched were PubMed, Scopus, Web of Science and CINAHL.

Inclusion criteria

To be eligible for inclusion, studies had to evaluate pharmacological and/or non-pharmacological interventions for managing fibromyalgia symptoms in adults and children, regardless of whether they were targeted to improve sleep or used for fibromyalgia pain management with a potential effect on sleep. The primary effectiveness outcome of interest was 'sleep quality' based on a validated PROM in fibromyalgia. Secondary outcomes included quality of life and sleep efficiency and duration.

Studies, conducted in any relevant setting, were eligible for inclusion in the qualitative synthesis if they reported data on the experiences of people with fibromyalgia-related sleep problems and the way they managed their symptoms.

Studies reporting sleep measures validated in people with fibromyalgia were eligible for inclusion in our PROMs analysis. When possible, for studies that included PROMs originally developed in non-fibromyalgia patients, we consulted the original development study to inform our analysis.

Data extraction and risk-of-bias assessment

Two review authors screened the citations identified by the search strategies and assessed full-text papers of all potentially relevant studies. Data and qualitative findings were extracted by one reviewer and checked by a second. Disagreement was resolved by discussion or referred to a third review author. A risk-of-bias assessment of included RCTs was conducted using the Cochrane Risk of Bias tool. We used the CINeMA approach based on the Grading of Recommendations Assessment, Development and Evaluation framework to evaluate the certainty of the evidence included in the network meta-analysis (NMA) assessing sleep quality. We appraised qualitative studies using the Critical Appraisals Skills Programme tool.

Data synthesis

Data from quantitative studies that assessed relevant sleep outcomes using validated PROMs were analysed using random-effects pairwise and NMAs. Where appropriate, standardised mean differences (SMDs) or mean differences were estimated for continuous outcomes. Common and serious adverse-effect outcomes and other sleep-related outcomes assessed using non-validated PROMs (e.g. visual analogue and numerical rating scales) were tabulated and summarised narratively.

For qualitative studies, we conducted a deductive analysis by mapping the extracted data to the analytical themes of the 'symptom experience' and 'symptom management' components of the Symptom Management Theory (SMT) conceptual framework used in the Climent-Sanz *et al*. meta-synthesis. Any data that did not fit into the existing analysis were captured as a new theme. We applied Grading of Recommendations Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative research to the findings of the thematic synthesis.

For each identified PROM, we analysed the individual verbatim items using an inductive content approach. All items were examined and systematically categorised into conceptual health domains according to the aspect they aimed to capture; however, where appropriate, items were coded to more than one domain. Domains were generated inductively from the identified individual items and were informed by terms and definitions contained in the Sleep Foundation Dictionary and the World Health Organization International Classification of Functioning, Disability and Health.

Results

Results of the quantitative evidence synthesis

The quantitative evidence synthesis included a total of 90 RCTs assessing sleep quality using PROMs validated in fibromyalgia patients, and a further 78 RCTs assessing other sleep-related outcome measures. Quantitative studies using PROMs evaluated 45 active treatment categories; the majority involved non-pharmacological interventions (n = 34) with the remainder pharmacological interventions (n = 11). Across studies, the most common treatment categories were land-based mind–body exercise (e.g. Tai Chi) performed in 13 studies, generic psychological and behavioural therapies, which did not focus specifically on sleep (e.g. cognitive–behavioural therapy for pain), in 10 studies and gabapentinoids (e.g. pregabalin) in 8 studies. Most other intervention categories were assessed only in a few or single trials. Most active interventions were compared with placebo/sham treatment or usual care (UC), while only 25 studies compared an active intervention with another. The majority of included studies were judged at high risk of bias in at least one risk-of-bias domain, often because of inadequate reporting of the randomisation process, missing outcome data, and, for most studies assessing non-pharmacological interventions, lack of blinding in the measurement of outcome.

The NMA, which combined evidence from direct and indirect treatment comparisons, included a total of 65 studies that assessed 'sleep quality' using a PROM validated in fibromyalgia. The results suggest that when compared with placebo

or sham treatment (PBO/Sham) (number of study participants = 2087), there was evidence of a beneficial effect on sleep for land-based aerobic training in combination with flexibility training [*n* = 32; SMD −4.69, credible interval (CrI) −8.14 to −1.28] and aquatic-based aerobic exercise training (*n* = 59; SMD −2.63, CrI −4.74 to −0.58). There was also a suggestion of a modest effect on sleep for land-based strengthening exercise training (*n* = 56, SMD −0.95, CrI −3.89 to 2.04), sleep-focused psychological and behavioural therapies (*n* = 94, SMD −0.89, CrI −2.39 to 0.61), weight loss (*n* = 41, SMD −1.15, CrI −3.55 to 1.27), electrotherapy (*n* = 20, SMD −0.98, CrI −3.28 to 1.34), dental splints (*n* = 29, SMD −1.62, CrI −4.862 to 1.65), tricyclics (*n* = 43, SMD −1.26, CrI −4.47 to 1.93) and antipsychotics (AP) (*n* = 53, SMD −1.28, CrI −3.56 to 0.97). However, CrIs were wide and the certainty of the evidence was low to very low.

For most of the remaining non-pharmacological and pharmacological interventions, there was no clear evidence of an improvement in sleep compared with PBO/Sham.

Improvements in quality of life were observed for some types of exercise training, psychological and behavioural therapies, and some pharmacological interventions. However, we observed only a modest overlap between interventions that improved sleep quality and those that improved quality of life. In general, non-pharmacological treatments under investigation were reported to be reasonably well tolerated and adverse events (AEs) were usually reported to be of mild or moderate severity (e.g. stiffness, fatigue). Higher rates of AEs were recorded after pharmacological treatments, with the most reported events being dizziness, drowsiness, headache and dry mouth.

The 78 trials evaluating sleep outcomes using non-PROM tools involved a total of 5911 randomised participants (5804 adults and 107 adolescents). The reporting of outcomes in these studies was not uniform across studies and, apart from two assessment tools, there was no common sleep outcome assessed by more than one study. We were not able to draw any firm conclusion about the treatment effects of these studies.

Results of the qualitative synthesis and the patient-reported outcome measures analysis

We identified nine reports of eight new qualitative studies to add to the Climent-Sanz *et al*. meta-synthesis. In total, 26 reports of 25 studies were included in our qualitative synthesis. Our findings were mapped onto the two pre-established global themes: *The experience of poor sleep quality in fibromyalgia* and *Management strategies for poor sleep quality in fibromyalgia*. The global themes correspond to the 'symptom experience' and 'symptom management strategies' components of the SMT. The first of these global themes comprised themes relating to how people with fibromyalgia evaluate their poor sleep quality and their response to poor sleep quality. The second global theme comprised themes relating to the management strategies used to encourage sleep and how people manage the consequences of a sleepless night. Eleven subthemes were identified. Most studies were of good methodological quality, and we have moderate confidence in most of the review findings poor sleep was described as one of the worst symptoms of fibromyalgia. Our analysis confirmed the previous findings regarding the bidirectional relationship between poor sleep and pain. Insufficient sleep was reported to increase pain and fatigue, with a consequent negative impact on activities of daily living. Poor sleep was also described as having a negative impact on cognitive functioning, mental health and fibromyalgia symptom 'flare-ups'. Strategies to manage the consequences of a sleepless night included trying to rest and relax during the day. Interventions to encourage sleep included mind–body interventions, multidisciplinary group-based interventions and taking medication. Participants described how the effectiveness of interventions lessened over time and some felt that medication caused unpleasant side effects.

The PROMs search update identified one new eligible report. Combined with the studies identified by the Climent-Sanz *et al*. search, eight reports of five eligible PROMs studies were included in our analysis. The eligible PROMs were: the Fibromyalgia Sleep Diary (FMSD), the Jenkins Sleep Scale, the Medical Outcomes Study Sleep Scale (MOS-SS), the Pittsburgh Sleep Quality Index (PSQI) and the Sleep Quality-Numeric Rating Scale (SQ-NRS). The number of items varied across PROMs and ranged from 1 to 24 items with a total of 43 individual items (median = 8) across the 5 PROMs. However, one of the questions contained in the FMSD was considered to measure two domains: sleep maintenance and degree of sleep disturbance. Therefore, the domains are represented by 44 items. Our synthesis identified 21 relevant sleep domains. The domain most frequently identified across PROMs was *sleep maintenance*, with six (13.6% of total items) items measuring this concept. The PSQI with 15 of the 21 identified domains is considered

the most comprehensive tool, followed by the MOS-SS with 11 domains. The SQ-NRS contains only one item and is the least comprehensive tool.

Limitations

The quantitative evidence synthesis was hampered by the limitations of the current evidence base, notably a wide range of diverse interventions assessed mainly by small, short-term, unblinded trials. Most interventions were compared with placebo, sham treatment or UC rather than with another active intervention. While pharmacological interventions were usually assessed against placebo, often non-pharmacological interventions failed to include a proper sham treatment with appropriate control strategies. Sleep quality was not measured consistently across quantitative studies and several different PROMs were used. Apart from sleep quality, there were few other sleep outcome measures shared by the included studies, making treatment comparisons challenging. Quantitative studies varied considerably in terms of study protocols and characteristics of interventions. Components of interventions and adherence were not consistently reported across studies. We found evidence of some inconsistency across the networks assessing sleep quality and quality of life using the Fibromyalgia Impact Questionnaire. Most of the quantitative studies focused on middle-aged women living in high-income countries, making it difficult to generalise our findings to the wider fibromyalgia community.

Regarding the synthesis of qualitative evidence and the PROMs analysis, because of the poor reporting of sociodemographic data, it proved difficult to ascertain whether the participants enrolled in the qualitative studies are fully representative of the wider fibromyalgia community. We did not identify any studies that reported qualitative data or evaluated PROMs for children with fibromyalgia-related sleep problems and it is uncertain whether the identified PROMs capture and measure sleep outcomes that are most relevant for children with fibromyalgia.

Conclusions

Implications for health care and future research

Poor sleep is a common and disabling problem for people with fibromyalgia. There is a suggestion that some forms of exercise training, psychological and behavioural therapies and some medications may be effective in treating fibromyalgia-related sleep problems and/or improving people's quality of life. However, any suggestion about the benefits of specific interventions should be tempered by the limitations of the current evidence base, which is too patchy, heterogeneous, and generally of poor quality.

There is a need to improve the quality and reliability of current evidence. Future research should focus on high-quality, adequately powered studies, with longer-term follow-ups to investigate the effects of interventions for treating sleep problems in people with fibromyalgia and assess whether beneficial effects are retained over time. Future studies should include an appropriate comparator treatment, detailed information on the characteristics of the interventions and their components, including compliance with treatment, and a representative sample of fibromyalgia patients. Conversely, further unblinded, small, two-arm studies comparing non-pharmacological interventions versus UC (including waiting list) should be avoided because of the inadequacy of their design.

Future studies should be designed in collaboration with people who have lived experience of fibromyalgia symptoms. Future PROMs development should be conducted in accordance with the principles of initiatives such as the National Institute for Health and Care Research INnovations in Clinical trial design and delivery for the UnDEr-served framework to ensure they are truly representative of the wider fibromyalgia community and include items that matter most to a broad cross-section of patients.

Study registration

This study is registered as PROSPERO CRD42021296922.

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Chapter 1 Background and research question

Description of underlying health problem

Fibromyalgia is a complex and heterogeneous condition.[1] Symptoms are commonly multiple, tend to fluctuate and cannot be easily classified within known medical diagnostic categories.[2] There are no imaging modalities of clinical laboratory investigations to confirm or refute the presence of fibromyalgia. Several classifications and diagnostic criteria have been proposed over the years. The 2016 revision of the 2010–1 criteria of the American College of Rheumatology (ACR) and the ACTTION-APS Pain Taxonomy diagnostic criteria are widely used for establishing a diagnosis of fibromyalgia.[3,4] Fibromyalgia is usually diagnosed based on the presence of key elements such as widespread musculoskeletal pain, fatigue, non-refreshing sleep, cognitive complaints (e.g. trouble thinking, brain fog) and low mood.

Fibromyalgia affects 1.7 million adults in the UK, adversely impacting their daily functioning and health-related quality of life.[5,6] Sleep disturbance is reported as one of the most common symptoms by 92% of those living with fibromyalgia.[7,8] Nevertheless, fibromyalgia-related sleep problems are poorly managed in the NHS, with people continuing to seek help for improving their sleep for many years after their initial fibromyalgia diagnosis.[6]

The manifestation of sleep disturbances in fibromyalgia can be diverse and includes self-report of difficulty with sleep onset, frequent awakenings, feeling unrefreshed on waking and, overall, a perception of poor sleep quality. A meta-analysis of polysomnographic studies corroborates these reports, with evidence of shorter sleep duration, less time in deep sleep, lower sleep efficiency and more time spent awake after sleep onset in people with fibromyalgia, compared with controls.[9] In terms of neurophysiology, these sleep disturbances are marked by reduced sleep spindles (12–14 Hz oscillations, a hallmark of sleep) during shallow sleep (N2 stage), intrusion of alpha activities (8–13 Hz oscillations, a marker of wakeful relaxation) during deep sleep (N3 stage) and increased rates of cyclical alternating pattern, which is a structural polysomnographic marker of sleep regulation instability. Although a unique signature of sleep disturbances specific to fibromyalgia is yet to be identified, there is an expert consensus backed by epidemiological data that alterations to normal sleep are a driver of pathological pain processing and central sensitisation, generating pain and cognitive–emotive symptoms that mimic those of fibromyalgia.[10] Specific sleep disorders are highly prevalent among those with fibromyalgia; over 50% of people with a fibromyalgia diagnosis meet a clinical threshold or diagnostic criteria for chronic insomnia disorder, over 40% have been estimated to have comorbid restless leg syndrome and over a quarter exceed the clinical threshold for a diagnosis of obstructive sleep apnoea.[11–13]

Impact of health problem

Fibromyalgia has been shown to affect 2–3% of people in studies worldwide,[14] although in the UK, and using more recent classification criteria, the prevalence was approximately 5%.[15] Fatigue is one of the most disabling symptoms experienced by people with fibromyalgia. A study conducted in the USA reported that three-quarters of people with fibromyalgia showed clinically important levels of fatigue, which did not meaningfully improve over time, and that symptoms were strongly related to sleep disturbance.[16,17]

The toll of the problem on individuals is immense; our patient representative (DD) maintains that ‘sleep disturbance is torturous, being mentally, physically and emotionally exhausting at every level’. In addition to negative impacts on the individual, fibromyalgia-related sleep disturbances have also important health-economic consequences, with an estimated 150,000 general practitioner (GP) consultations per year in the UK.[6] Fibromyalgia-related sleep disturbances are also associated with greater utilisation of ambulatory care services, increased drug prescriptions, including those not necessarily targeting sleep disturbances (e.g. muscle relaxants, antidepressants), and a higher risk of drug dependency and undesirable side effects (e.g. related to antidepressants, anticonvulsants and opioid use).[18–20]

Decision problem

The 2015 European guidelines for the management of fibromyalgia considered sleep as one of the key outcomes of interest.[1] Although general recommendations were made for managing sleep disturbances, these were graded as 'weak' due to paucity of published evidence at that time. Additionally, sleep management was not the primary focus of the guidelines. Evidence reviews have recently informed National Institute of Health and Care Excellence (NICE) draft guidelines for the management of chronic pain; however, these cluster together a wide range of conditions (including osteoarthritis, mechanical back pain, fibromyalgia), and do not have a specific focus on sleep management.[21] Given the increased number of published randomised controlled trials (RCTs) in this clinical area, there is a scope to conduct network meta-analyses of direct and indirect evidence to evaluate the comparative effectiveness of different interventions for the management of sleep problems in fibromyalgia.[22,23] The results of the network meta-analysis (NMA) could be further enhanced by incorporating findings from a synthesis of qualitative evidence regarding the acceptability of different interventions from a patient perspective. A critical evaluation of measures used in trials to evaluate intervention performance is also essential to determine whether the outcomes that matter most to patients are being considered.

Research into interventions for managing sleep problems in people with fibromyalgia is still a top priority of the James Lind Alliance Priority Setting Partnerships initiative.[24] The importance of this is amplified by a compelling body of literature demonstrating associations between sleep disturbances and exacerbation of other fibromyalgia symptoms. Disturbed sleep is an adverse prognostic factor, with evidence of dose-dependent relationships with pain intensity, worse physical and cognitive functioning, low mood, anxiety, catastrophising, low self-efficacy and poor quality of life.[25] Sleep problems have also been implicated in the development of depression among those with persistent pain.[26] The potential of sleep as a particularly salient management target is bolstered by large-scale population-based cohort studies identifying sleep disturbance as an independent factor that increases the risk of developing fibromyalgia by two- to fourfold, with a follow-up period of up to 12 years.[27,28] Conversely, and perhaps more importantly, having restorative sleep has been found to prospectively predict successful resolution of chronic widespread pain.[29]

Description of interventions under assessment

Broadly, the interventions for management of fibromyalgia can be divided into pharmacological and non-pharmacological interventions. Pharmacological interventions may include:[30]

- Simple and opioid analgesics – for example paracetamol +/– opioids, tramadol (opioid with serotonin and norepinephrine reuptake inhibitor activity)
- Tricyclic antidepressants – for example amitriptyline, cyclobenzaprine (5-HT2 receptor blocker)
- Selective serotonin reuptake inhibitors (SSRIs) – for example citalopram, escitalopram, fluoxetine, paroxetine
- Serotonin reuptake inhibitors (SRIs) – for example duloxetine, es-reboxetine, milnacipran
- Gabapentinoid – gabapentin, pregabalin
- *N*-methyl-D-aspartate receptor antagonists – ketamine, memantine
- Cannabinoids – dronabinol, nabilone.

Non-pharmacological intervention may be classified as:[31]

- Exercise – this includes aerobic exercise, flexibility exercises, strengthening exercises, Mind–body exercise (mind–body Ex) (e.g. Tai Chi), or mixed exercise. Exercise could take place in water or on land.
- Psychological and behavioural interventions such as cognitive–behavioural therapy (CBT); mindfulness; acceptance and commitment therapy (ACT) and attachment-based compassion therapy.
- Relaxation or meditation, such as relaxation, meditation, hypnosis, guided imagery.
- Balneotherapy – defined as aquatic therapy that uses a natural thermal mineral water. This includes all aquatic interventions that involved adopting a static position in water with different minerals or in sea water.
- Manual therapy (Manual T) such as massage, physical therapy (e.g. mobilisation).

- Electrical therapy such as electrotherapy (Electro T), specifically neuromuscular electric stimulation, transcutaneous electrical nerve stimulation (TENS), laser therapy, and neuromodulation, such as transcranial direct-current stimulation (tDCS).[32]
- Complementary and non-mainstream interventions such as traditional acupuncture, magnetotherapy, homeopathy, cupping therapy, hyperbaric oxygen therapy, cryotherapy, whole body vibration.
- Dietary/nutrition interventions, such as nutritional supplements.
- Education.

Population and relevant subgroups

People of any age living with fibromyalgia.

Setting/context

Any relevant clinical setting (e.g. primary care, secondary care, community care).

Overall aim and objectives of this assessment

The overarching aim is to provide useful information to help patients' self-management, aid clinical decision-making and guide future research by assessing the existing quantitative and qualitative evidence on interventions that may be used for the management of fibromyalgia-related sleep problems.

Specific objectives

- To undertake a comprehensive evidence synthesis to assess the clinical effectiveness and adverse effects of pharmacological and non-pharmacological treatments for the management of fibromyalgia-related sleep problems (quantitative evidence synthesis).
- To update and enhance a previously published qualitative evidence synthesis[33] to ascertain the experiences and expectations of people who receive treatments for fibromyalgia-related sleep problems (qualitative evidence synthesis).
- To examine item content of existing patient-reported outcome measures (PROMs) related to sleep in people with fibromyalgia to assess heterogeneity and patient relevance (PROMs analysis).
- To provide an overview of current quantitative and qualitative evidence including evidence on PROMs.

Chapter 2 Quantitative evidence synthesis

Methods

Protocol and registration

We followed recommendations from the Cochrane Handbook for Systematic Reviews of Interventions.[34] and pre-specified our methods in a research protocol (PROSPERO database registration number: CRD42021296922).

Search methods for identification of studies

Sensitive search strategies were designed by an information scientist using database subject headings and text word terms to identify reports of RCTs in fibromyalgia patients with sleep as an outcome. The Cochrane Highly Sensitive Search Strategy for identifying RCTs was used in MEDLINE and adapted for other electronic databases. There were no date or language restrictions in the search. The databases searched were Ovid MEDLINE, EMBASE, PyscInfo, and AMED (Allied and Complementary Medicine), EBSCO CINAHL, Clarivate Science Citation Index and the Cochrane Controlled Trials Register (CENTRAL). The searches were conducted on 1 November 2021. Reference lists of systematic reviews and included studies were checked to identify additional potentially relevant reports. Full details of the search strategies are reported in *Appendix 1*.

To allow studies that evaluated all potential interventions to be included in the review, a broad list of keywords was developed. This was guided by studies identified in a previous systematic review of non-pharmacological interventions for the management of fibromyalgia.[31] We focused on studies that mentioned relevant sleep outcomes in the titles or abstracts of the study publication with or without numerical data. Studies were not deemed suitable for inclusion if they did not mention sleep outcomes in their titles or abstracts. Outcome data from multiple publications from the same research were linked as a single study. However, we excluded publications reporting secondary or post hoc analysis of the same outcome data of already included studies.

Inclusion and exclusion criteria

The key eligibility criteria for the quantitative evidence review are summarised using a participants, interventions, comparisons,outcomes, study design (PICOS) framework in *Table 1*.

Types of studies

Parallel-group, crossover and cluster RCTs assessing the effectiveness of any intervention for the management of fibromyalgia-related sleep problems were eligible for inclusion. We excluded quasi- or non-randomised studies, single-arm studies and observational studies. We included studies, published in full, regardless of the language used in the publication.

Types of setting

We included studies conducted in any relevant clinical setting, for example primary care, secondary care or community care.

TABLE 1 Summary of eligibility criteria for quantitative systematic review based on the PICOS framework

Population	Intervention	Comparison	Outcome	Study design
Adults and children with fibromyalgia	Pharmacological and non-pharmacological interventions for treating sleep problems	Another treatment or no treatment	Sleep-related outcomes (e.g. sleep quality and duration); disease-specific quality of life; adverse events	RCT design

Types of population (participants)

We included people of any age (both adults and children) with fibromyalgia. Regarding the age limits used to differentiate between adults and children, we accepted those reported by the authors of the identified studies. Studies in which only a subset of participants had fibromyalgia were considered for inclusion, if data were available separately for the relevant subset.

Types of interventions

We included any pharmacological or non-pharmacological intervention for the management of sleep disturbances in fibromyalgia.

Pharmacological treatments included antipsychotic (AP; e.g. quetiapine), anticonvulsant (e.g. gabapentin, pregabalin), antidepressant (e.g. amitriptyline) and hormonal (e.g. melatonin) medications. We considered eligible pharmacological treatments regardless of their dose or routes of administration. Examples of non-pharmacological interventions included exercise (e.g. aerobic, strengthening, stretching/flexibility, aquatic exercise, Tai Chi, yoga), psychological or behavioural therapy (PT/BT) (e.g. CBT), patient education, dietary and lifestyle modifications, as well as complementary and non-mainstream therapies (e.g. acupuncture).

We included interventions regardless of whether they were targeted to improve sleep or used for fibromyalgia pain management with a potential effect on sleep. Interventions that focused primarily on the management of comorbid autoimmune inflammatory conditions in people with fibromyalgia were excluded; these include, for example, disease-modifying antirheumatic drugs for rheumatoid arthritis that could treat symptoms of rheumatoid arthritis and improve the quality of sleep of coexisting fibromyalgia.

Eligible interventions included discrete interventions or multicomponent interventions, which comprise a combination of different interventions that may be delivered concurrently or sequentially. Interventions could be delivered one-to-one, in a group, in person or remotely.

Types of comparators

We investigated comparisons of active (experimental) interventions with usual care (UC), placebo or no treatment (including wait list), or with another active intervention. We excluded comparisons of two or more regimens of the same treatment (e.g. varying doses of the same drug), if placebo or another intervention group was not considered.

Types of outcomes

In consultation with clinical experts and patient partners, we decided to include the following outcomes measured at the end of the designated intervention period, or at the first assessment point after the end of the intervention.

Primary outcomes:

- sleep quality (patient's experience of sleep and perceived sleep quality)
- adverse events (AEs).

Secondary outcomes:

- sleep efficiency (%; calculated as total sleep time / total time in bed × 100%)
- duration of sleep/total sleep time
- disease-specific quality of life.

Outcome data were considered suitable for inclusion irrespective of whether they were reported as primary or secondary end points in the published studies. For the sleep quality outcome, our primary focus was on the five PROMs

on sleep quality, validated in people with fibromyalgia, that we identified as part of the update of a recently published systematic review.[35] These measures included: Pittsburgh Sleep Quality Index (PSQI),[36] Medical Outcomes Study Sleep Scale (MOS-SS),[37] Jenkins Sleep Scale (JSS),[38] Fibromyalgia Sleep Diary (FMSD)[39] and Sleep Quality Numeric Rating Scale (SQ-NRS).[40] Numerical rating scales (NRSs) or visual analogue scales (VASs) broadly measuring sleep quality were also included.

In the absence of an accepted quality-of-life tool specific to fibromyalgia, we used the Fibromyalgia Impact Questionnaire (FIQ)[41] and the 36-Item Short Form Survey (SF-36) physical and mental health components as a proxy for disease-specific measures.[42]

We recorded information on AEs reported in at least 10% of participants of included studies as well as serious adverse events (SAEs); we accepted the categorisation of events reported by the authors of the included studies.

Selection of studies

Two review authors (CR and MI) independently screened a sample of 100 titles and abstracts at the beginning of the study-selection process and compared the results to ensure consistency. The remaining citations were divided into two segments and the abstracts screened by the same two review authors, where one author screened for any studies that could clearly be excluded, with the second author deciding on all studies that were labelled unsure and 10% of the studies marked as excluded. All potentially relevant articles were retrieved in full and divided between the same two review authors. One review author assessed all full-text articles for inclusion, with the second author checking all studies that were labelled unsure and 10% of the studies that were not considered suitable for inclusion. Any discrepancy or inconsistency was resolved by discussion between reviewers.

Data extraction

Data extraction forms were developed and piloted by the same two review authors with input from our patient and public involvement (PPI) collaborator (DD). Information on setting, characteristics of participants, characteristics of interventions and outcome measures were recorded. The two review authors independently extracted data from 10% of the included studies to ensure consistency and accuracy. The remaining studies were divided between the two reviewers and single data extraction was undertaken, with one review author checking the data extracted by the other review author for consistency. Any discrepancy between the review authors was resolved by discussion or consultation with a third review author (MB).

Quality assessment of included studies

The risk of bias of each included study was assessed using the revised Cochrane risk-of-bias tool (RoB2).[43] To implement RoB2 assessments, we used the Excel tool available at the Risk of Bias tools website (www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). The assessment addressed the following domains:

- bias arising from the randomisation process
- bias due to deviations from intended interventions
- bias due to missing outcome data
- bias in measurement of the outcome
- bias in selection of the reported result
- overall risk of bias.

We judged each domain as 'low risk', 'some concerns' or 'high risk'. Two review authors (CR and MI) independently assessed the first 10% of included studies to ensure consistency. During this process, we developed a document on decision-making rules with instructions on how to answer the signalling questions of the RoB2 tool. The remaining studies were then divided between the two reviewers for single assessment. Any uncertainties or disagreements arising during risk-of-bias assessment were resolved by discussion between the two review authors. While double assessment is generally recommended, the proposed approach was adopted to improve the efficiency of the systematic review process and ensure the timely completion of the project.

Quantitative synthesis and network meta-analysis

For sleep quality, there were several different outcomes identified: PSQI, MOS-SS, JSS, FMSD, SQ-NRS as well as single-item VAS/NRS measuring a similar sleep quality construct to that of the SQ-NRS. We decided to pool these outcomes together to form an overarching 'Sleep' outcome. However, we also performed analysis on each individual outcome as well as performing a sensitivity analysis of combining SQ-NRS and VAS. Where a study reported more than one sleep quality outcome, we specified a hierarchy based on the most reported outcome across included studies. The adopted hierarchical order was as follows: PSQI, MOS-SS, JSS, FMSD, SQ-NRS and VAS/NRS. A mixture of 'change from baseline' and 'final score' was reported; therefore, we converted the final score to 'change from baseline' when baseline values were available. For imputation of the change from baseline standard deviation (SD), we used a correlation coefficient as per the recommendation of the Cochrane Handbook for Systematic Reviews of Intervention.[34] As we had no available data to calculate the correlation coefficient, we chose a 0.5 value and decided to perform a sensitivity analysis assuming a correlation coefficient of 0.8 to assess whether the results changed. The effect size calculated was the standardised mean difference (SMD), which divides the difference in mean between interventions by the estimated pooled between-person SD for that trial. However, due to some studies having small sample sizes we used the Hedges (adjusted) G method.[44] Effect sizes reported were either SMD for the 'Sleep' outcome and mean differences (MDs) for the remaining outcomes along with 95% confidence intervals (CIs) or credible intervals (CrIs).

Whenever possible, we performed a pairwise and NMA of all included outcome variables. For each pairwise meta-analysis, a random-effects model was used to compare the direct evidence, with heterogeneity being assessed by I^2 statistic. This analysis was performed in Stata version 17.[45]

For each relevant outcome, a NMA was performed to combine both direct and indirect evidence using a Bayesian framework, according to guidance from the NICE Decision Support Unit in the UK and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for network meta-analyses. Random-effects models with a normal likelihood were used as all our outcomes were continuous. Convergence was assessed using history, autocorrelation and Brooks-Gelman Rubin plots. Consistency was evaluated by examining the agreement between direct and indirect evidence in all closed loops. To explore the presence of inconsistency for any treatment contrast in the network, we performed a node-splitting analysis. We also estimated the ranking probabilities of the different interventions using the surface under the cumulative ranking (SUCRA) curve, which is a numeric presentation of the likelihood that an intervention is successful, as well as presented rankograms. The network diagrams and the node-splitting analysis were performed in Stata 17[45] using the network command, while all remaining analysis was done using the WinBUGS (MRC Biostatistics Unit, Cambridge, UK).[46]

Assessment of the certainty of the evidence

We used the Confidence In Network Meta-Analysis (CINeMA) approach,[47] which is broadly based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework,[48] to evaluate the certainty of evidence from the NMA on sleep quality outcome. The CINeMA framework considers six domains that may affect the level of confidence in NMA findings: (1) within-study bias, (2) reporting bias, (3) indirectness, (4) imprecision, (5) heterogeneity and (6) incoherence. For each relative treatment effect derived from the NMA, the level of concern was assessed as 'no concerns', 'some concerns' or 'major concerns'. The final judgements across domains were summarised into four confidence ratings: 'high', 'moderate', 'low' or 'very low'. As we had no available data to define the minimal clinically important difference (MCID) for the sleep quality outcome, we chose a 0.5 value for SMD, based on benchmarks for 'medium' effect size suggested by Cohen (1988).[49]

Results

Quantity of the evidence

The database search identified 4113 records of published studies. Of these, 377 records were retrieved for full-text assessment. After exclusion of 209 studies, we selected 168 studies for inclusion. *Figure 1* shows the flow diagram of the selection process. A list of included studies is presented in *Report Supplementary Material 1*. A full list of studies excluded after evaluation of the full-text publications, alongside the main reasons for exclusion, is presented in *Report Supplementary Material 2*.

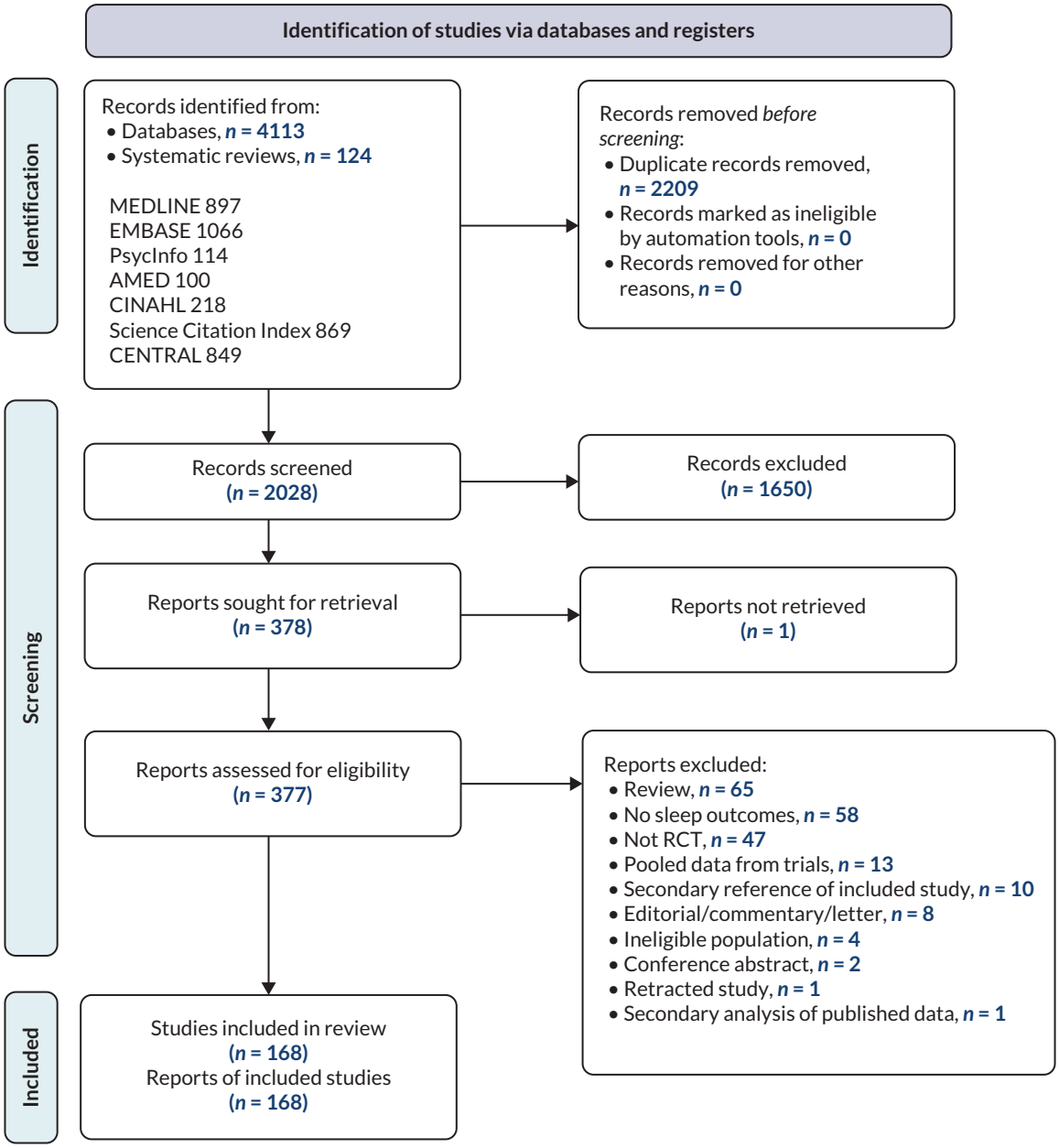

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram for identification of the quantitative studies. Reproduced with permission from Page *et al.*[50] For more information, visit: www.prisma-statement.org/.

Of the 168 included studies, 90 assessed sleep quality using one of the PROMs validated in people with fibromyalgia (i.e. PSQI, MOS-SS, JSS, FMSD and SQ-NRS), 68 assessed sleep quality using other measures (e.g. VAS) and 10 assessed sleep efficiency and sleep duration.

The 90 studies assessing sleep quality using PROMs validated with people with fibromyalgia were eligible for the NMA, while results from the remaining 78 studies were synthesised narratively.

Description of studies

Studies eligible for the network meta-analysis

We describe the 90 studies considered for NMA below. Additional information is provided in *Table 2* (baseline demographic characteristics of study participants), *Report Supplementary Material 3* (list of interventions) and *Appendix 2*, *Table 18* (inclusion and exclusion criteria, details of the intervention and baseline characteristics of study participants).

Study design

Eighty-five studies were parallel RCTs, while five were randomised crossover trials.[113,115,117,128,138] Publication years ranged from 1992[114] to 2021.[51,72,75,76,86,100,107,112] Most studies were published in English; two in Spanish,[66,92] and one each in German,[118] Korean[100] and French.[130]

Participants

All 90 studies evaluated adult populations living with fibromyalgia, including a total of 12,082 participants. The number of participants per study ranged from 13[58] to 884,[129] with a median of 70. Most participants across studies (94% overall) were women, with the reported mean or median age of each study group ranging from 35.1[82] to 57.7.[70] Twenty-seven studies were conducted in Spain,[52,56,58,60,63,64,66,68,75,78,79,87,88,90–95,97,99,103,108,119,130] 20 in the USA,[70,71,81,83,85,89,101,106,113,121,124,126–128,131,133,134,136,139,140] 5 in Canada[55,61,107,116,125] and 4 in Brazil.[69,80,86,120] A few studies were conducted in a single European country (France,[51,59,72,104] Italy,[84,115,117,140] Germany,[57,62,118] UK,[96,102,105] Sweden,[98,110] Norway[112] and Switzerland[114]) as well as Turkey,[82,109] Egypt,[65,73] Iran,[77] Israel,[74] China,[54] Japan,[123] Korea,[100,111] Taiwan[76] and Thailand.[135] One study each was conducted in multiple countries in Europe,[129] Europe and the USA,[132] Europe, Asia (India, Korea), Australia and the Americas (Canada, Mexico, Venezuela),[137] and Asia (India, Taiwan), Canada and USA.[122]

Thirty-four studies (38%) reported baseline body mass index (BMI) for each study group. Reported mean or median BMI ranged from 20.5[79] to 33.9,[89] with 9 studies having a mean BMI of 30 or higher (classified obese) in at least one of the study groups.[65,80,81,83,85,89,95,136,140] Among the 30 studies (33%) which recorded information on ethnicity,[52,54,56,69,74,81,83,85,89,96,99,101,103,106,116,121,122,124,131–134,136,137,139,140] the predominant majority of participants were 'white' or 'Caucasian', except for 2 studies (evaluating Tai Chi in the USA) which included people from 'diverse' backgrounds of whom just over half were 'white'. The educational attainment of participants was described in 35 studies.[51,54,56,57,60–63,65,67,72,73,76,81–83,85,87–90,93,96–101,103,106,109,112,113,120,138] While definition of schooling varied, making comparison across studies difficult, one study focused specifically on patients with 'low education levels',[103] and nine studies had more than half of the recruited participants with basic or primary education.[56,57,60,65,67,82,90,96,103] The other studies reported that the majority (50% or higher) of participants completed high school or higher education (e.g. college, university)[51,54,61–63,72,76,83,85,87–89,93,97,98,100,101,112,138] or had an average duration of education longer than 10 years.[106,109,113,120] Further information on the demographic characteristics of participants is presented in *Table 2*.

Twenty-four studies (27%) described the baseline clinical characteristics of participants.[51–54,58,59,62,69,74,76,78,81,89,91,100,101,105,107,115,118–120,136,138] Although the type of comorbidities varied across studies, the number of participants with comorbidities was fairly balanced between treatment groups within each study. Common comorbidities (reported in > 50% of participants from these 24 studies) included psychological trauma or prolonged stress,[51] depression,[51] mood disorder, anxiety disorder, irritable bowel syndrome,[51] back pain,[52] osteoarthritis, shortness of breath, temporomandibular dysfunction and headache or migraine. Symptom severity (pain or fibromyalgia) was reported in 38 studies using various outcome measures, with the most common outcome measures used being pain VAS or NRSs.[51,53,54,56,58,59,68,69,71,72,77,80,81,83–85,92,95,104,108,114,115,117–122,124,125,128,131–133,135,137,139,140] In most studies pain severity was rated to be moderate or high. Participants' baseline characteristics are summarised in *Appendix 2*.

Interventions

The 90 included studies assessed a total of 97 active treatments, either alone or in combination. Most were non-pharmacological treatments (76 non-pharmacological treatments and 21 pharmacological treatments). These treatments were grouped into 45 categories according to their characteristics and mode of action (34 non-pharmacological and 11 pharmacological) (see *Report Supplementary Material 3*).

Exercise interventions were classified into four categories according to the American College of Sports Medicine recommendation[141] and a previous systematic review of exercise training for treating osteoarthritis.[142] These categories include: (1) aerobic exercise (e.g. cycling, dancing, walking, running, swimming); (2) muscle strengthening or resistance

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
Non-pharmacological interventions								
Studies reporting PSQI outcome								
UC vs. balneotherapy	Maindet 2021[51] Ref ID 704	24 (Tx 3w; Ax at 24w)	UC	108 F92% M8%	49.2 (8.8)	27.7 (5.8)	NR	< Baccalaureate: 31.5%; high school diploma (baccalaureate): 30.6%; university degree or higher: 38.0%
			Spa therapy	110 F90% M10%	50.4 (8.9)	26.6 (6.6)	NR	< Baccalaureate: 31.8%; high school diploma (baccalaureate): 25.5%; university degree or higher: 42.7%
UC vs. Flex/skill LD	Ceca 2020[52] Ref ID 2297	20	Wait list	33 F95% M5%	57.4 (4.5)	NR	White: 100%	NR
			Self-myofascial conditioning programme	33 F87% M13%	50.6 (7.1)	NR	White: 100%	NR
UC vs. Manual T	Castro-Sánchez 2014[53] Ref ID 237	5	No treatment	44 F55% M45%	53 (7)	NR	NR	NR
			Manual T	45 F53% M47%	54 (8)	NR	NR	NR
UC vs. Mind–body Ex LD	Jiao 2019[54] Ref ID 215	12	Wait list (stable usual therapy)	31 F87% M13%	53.5 (0.6)	26.3 (3.3)	Chinese: 100%	< 9 grade: 10%; high school: 23%; college: 61%; postgraduate: 6%
			Ba-Duan-Jin	31 F84% M16%	48.9 (10.2)	23.4 (2.4)	Chinese: 100%	< 9 grade: 10%; high school: 26%; college: 55%; postgraduate: 10%

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m^2, mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
UC vs. Mind–body Ex LD	Lynch 2012[55] Ref ID 327	8	Control (wait list/UC)	47 F98% M2%	52.1 (8.6)	NR	NR	NR
			Qigong	53 F94% M6%	52.8 (8.9)	NR	NR	NR
UC vs. Mx Exercise AQ	Munguía-Izquierdo 2008[56] Ref ID 199	16	Control	25 F100%	46 (8)	27 (4)	White: 100%	Highest education (%) elementary school 63; high school 29; college/university 8;
			Aquatic exercise	35 F100%	50 (7)	27 (4)	White: 100%	Highest education (%) elementary school 56; high school 32; college/university 12
UC vs. PBO/Sham vs. Non-MSM practice	Lauche 2016[57] Ref ID 217	18 days	UC	46 F100%	56.8 (7.7)	28.2 (5.4)	NR	< High school: 69.6%; high school: 13.0%; university degree: 17.4%
			Sham cupping	48 F98% M2%	56.3 (8.7)	27.2 (4.7)	NR	< High school: 33 (68.8); high school: 8 (16.7); university degree: 7 (14.6)
			Cupping therapy	47 F98% M2%	54.35 (10.6)	29.4 (7.3)	NR	< High school: 35 (74.5); high school: 10 (21.3); university degree: 2 (4.3)
UC vs. Nutrition	San Mauro Martin 2019[58] Ref ID 651	4	No supplement	7 F100%	51.7 (7.5)	27.0 (6.7)	NR	NR
			Turmeric-based food supplement	6 F100%	51.2 (9.4)	28.1 (4.5)	NR	NR
UC vs. PBO/Sham vs. Nutrition	Barmaki 2019[59] Ref ID 268	24	No supplementary treatment	31 F100%	47.8 (9.0)	25.58 (5.25)	NR	NR

continued

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
			Food supplement (as placebo)	33 F100%	47.4 (8.6)	25.54 (5.14)	NR	NR
			Phytotherapy treatment (Fib-19-01)	36 F100%	49.6 (9.4)	27.23 (6.02)	NR	NR
UC vs. PT/BT gen	Amutio 2018[60] Ref ID 1397	7	Wait list	19 F100%	51.8 (10.2) whole pop	NR	NR	No formal education: 8%; primary-school education: 62%; intermediate studies education: 16%; 14% had a higher education (whole pop)
			Mindfulness treatment	20 F100%		NR	NR	
UC vs. PT/BT gen	Simister 2018[61] Ref ID 265	8	TAU	34	39.7 (9.36) whole pop	NR	NR	87% of the sample had at least a high school education and 59% had education beyond the high school level (whole pop)
			Online ACT + TAU	33 (F95% M5% whole pop)		NR	NR	
UC vs. PBO/Sham vs. PT/BT gen	Schmidt 2011[62] Ref ID 349	8	Wait list	59 F100%	52.3 (10.9)	NR	NR	no school completed: 1.7%; 9 years: 30.5%; 11 years/GCSE: 25.4%; A-level/college entry: 42.4%; missing data: 0
			Active control (muscle relaxation and stretching)	59 F100%	51.9 (9.2)	NR	NR	no school completed: 0; 9 years: 28.6%; 11 years/GCSE: 39.3%; A-level/college entry: 30.4%; missing data: 1.8%

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
			Mindfulness-based stress reduction	59 F100%	53.4 (8.7)	NR	NR	No school completed: 1.9%; 9 years: 34.0%; 11 years/GCSE: 41.5%; A-level/college entry: 20.8%; missing data: 1.9%
UC vs. PT/BT gen vs. PT/BT sleep	Lami 2018[63] Ref ID 458	10 (Tx 9w; Ax at 10w)	Usual medical care (UMC)	42 F100%	51.4 (9.4)	NR	NR	Basic education: 26.8%; high school: 34.2%; professional instruction: 17.1%; university studies: 22%
			CBT-P (CBT for pain)	42 F100%	49.4 (6.4)	NR	NR	Basic education: 29.4%; high school: 44.1%; professional instruction: 20.6%; university studies: 5.9%
			CBT-IP (CBT for insomnia and pain)	42 F100%	49.7 (8.4)	NR	NR	Basic education: 31.5%; high school: 21.1%; professional instruction: 7.9%; university studies: 39.5%
UC vs. relaxation/medication	Onieva-Zafra 2019[64] Ref ID 689	Unclear (8w?)	Control	27? F96% M4%	51.3 (6.5)	NR	NR	NR
			Guided imagery	29? F97% M3% (study enrolled 60 in total)	53.6 (5.8)	NR	NR	NR
UC vs. weight loss	Senna 2012[65] Ref ID 345	24	No weight loss	43 F90% M10%	46.3 (14.4)	32.8 (1.4)	NR	Education > high school: 59.5%
			Dietary weight loss	43 F90% M10%	44.8 (13.6)	32.3 (1.4)	NR	Education > high school: 58.5%

continued

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
PBO/Sham vs. aerobic LD + relaxation/meditation	Arcos-Carmona 2011[66] Ref ID 358	10	Sham magnet therapy	28 F100% M0%	44.4 (9.25) whole pop	NR	NR	NR
			Aerobic exercise + progressive relaxation technique	28 F100% M0%		NR	NR	NR
PBO/Sham vs. Manual T	Castro-Sanchez 2011[67] Ref ID 711	20	(Sham) magnotherapy	32 F96% M4%	46.3 (12.3)	NR	NR	No school: 65.5%; primary school: 24.1%; secondary school: 3.4%; university: 6.9%
			Massage-myofascial release therapy	32 F94% M6%	49.3 (11.6)	NR	NR	No school: 73.3%; primary school: 13.3%; secondary school: 10%; university: 3.3%
PBO/Sham vs. Manual T	Nadal-Nicolás 2020[68] Ref ID 2308	4	Placebo (sham ultrasound)	15 F100%	53 (6) whole pop	28.7 (4.1)	NR	NR
			Manual T	15 F100%	--	28.4 (4.3)	NR	NR
PBO/Sham vs. Mind–body Ex AQ	Ide 2008[69] Ref ID 493	4	Control (supervised recreational activities)	20 F100%	45.5 (8.7)	NR	White: 95%	NR
			Aquatic respiratory exercise-based programme	20 F100%	46.6 (9.8)	NR	White: 95%	NR
PBO/Sham vs. Mind–body Ex LD	Liu 2012[70] Ref ID 110	6	Sham (specially developed sham Qigong exercise)	6 Gender NR	57.5 (range 45–70)	NR	NR	NR
			Qigong	8 Gender NR	55.7 (range 20–70)	NR	NR	NR

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m^2, mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
PBO/Sham vs. Mind–body Ex LD	Sarmento 2020[71] Ref ID 409	10	Sham Qigong	14 F100% M0%	56.1 (12.3)	NR	NR	NR
			Qigong	14 F100% M0%	42.6 (10.7)	NR	NR	NR
PBO/Sham + multicomponent therapy (MT) vs. neuromodulation + MT (aerobic LD + flex/ skill AQ + relaxation/ medication + education)	Guinot 2021[72] Ref ID 2313	12	Sham rTMS + MT	19 F79% M21%	42.8 (8.8)	25.1 (4.5)	NR	College: 63.2%; high school: 36.8%
			rTMS + MT [aerobic training (land-based) + pool-based therapy (balance and posture work) + relaxation + education]	20 F100%	46.5 (10.4)	26.7 (4.8)	NR	College: 50.0%; high school: 50.0%
PBO/Sham + multimodal vs. Manual T + multimodal (PT/ BT gen + Flex/skill LD)	Moustafa 2015[73] Ref ID 346	12	Control (multimodal programme, plus manual contact similar to manipulative therapy)	60 F45% M55%	51.4 (7)	NR	NR	Primary school: 23.5%; secondary school: 28.5%; advanced technical college: 21.5%; university diploma: 21.5%; other: 5%
			Upper cervical manipulative therapy + multimodal programme (consisting of CBT and stretching exercise)	60 F42% M58%	53.5 (8)	NR	NR	Primary school: 20%; secondary school: 32%; advanced technical college: 25%; university diploma: 18%; other: 5%
PBO/Sham vs. neuromodulation	Goldway 2019[74] Ref ID 227	5	Sham neurofeedback	12 F78% M22%	35.9 (10.6)	--	--	--
			Amygdala electrical-fingerprint (Amyg-EFP) neurofeedback	31 F96% M4%	35.5 (12.6)	--	--	--

continued

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
PBO/Sham vs. neuromodulation	Samartin-Veiga 2021[75] Ref ID 1787	Unclear (Tx 3w, Ax at 4w?)	Sham tDCS	30 F100% M0%	50.67 (8.88)	NR	NR	NR
			M1-tDCS (classic)	34 F100% M0%	49.38 (8.83)	NR	NR	NR
			DLPFC-tDCS (classic)	33 F100% M0%	50.55 (8.89)	NR	NR	NR
			OIC-tDCS (novel)	33 F100% M0%	50.21 (8.20)	NR	NR	NR
PBO/Sham vs. neuromodulation	Wu 2021[76] Ref ID 2311	8	Telephone support (control)	20 F70% M30%	42.2 (10.9)	23.8 (5.1)	NR	≤ High school: 30.0%; college: 55.0%; ≥ graduate school: 15.0%
			Neurofeedback	60 F95% M5%	48.6 (13.5)	21.9 (3.9)	NR	≤ High school: 26.7%; college: 65.0%; ≥ graduate school: 8.3%
PBO/Sham + SSRI vs. nutrition + SSRI	Mirzaei 2018[77] Ref ID 1967	8	Placebo + trazodone	37 Gender NR	41 (10.3)	NR	NR	NR
			Vitamin D + trazodone	37 Gender NR	42.1 (10.8)	NR	NR	NR
PBO/Sham vs. Non-MSM practice	Mataran-Penarrocha 2011[78] Ref ID 659	25	Placebo (sham ultrasound treatment)	52 F98% M2%	52.3 (11.0)	NR	NR	NR
			Craniosacral therapy	52 F95% M5%	48.2 (13.3)	NR	NR	NR
Aerobic LD vs. aerobic LD + Flex/skill LD	Gómez-Hernández 2020[79] Ref ID 603	12	Control (stationary cycling)	32 F100% M0%	54.6 (8.5)	20.5 (1.7)	NR	NR
			Flexibility	32 F100% M0%	54.0 (5.0)	21.0 (1.9)	NR	NR

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
Aerobic AQ vs. Mind–body Ex LD	de Medeiros 2020[80] Ref ID 209	12	Aquatic aerobic exercise	21 F100%	50.7 (9.7)	30.4 (5.2)	NR	NR
			Mat pilates	24 F100%	45.5 (10.6)	27.8 (4.7)	NR	NR
Aerobic LD vs. Mind–body Ex LD vs. Mind–body Ex LD vs. Mind–body Ex LD vs. Mind–body Ex LD	Wang 2018[81] Ref ID 276	24	Aerobic exercise 2 × 24 (twice weekly for 24w)	75 F96% M4%	50.9 (12.5)	30.0 (6.8)	White: 60.0%	High school or higher education: 96.0%
		12	Tai Chi 1 × 12 (once weekly for 12w)	39 F85% M15%	53.0 (12.6)	30.6 (6.4)	White: 71.8%	High school or higher education: 97.4%
		12	Tai Chi 2 × 12 (twice weekly for 12w)	37 F81% M19%	52.1 (10.3)	30.4 (6.8)	White: 54.1%	High school or higher education: 94.6%
		24	Tai Chi 1 × 24 (once weekly for 24w)	39 F97% M3%	50.8 (11.8)	29.9 (6.4)	White: 61.5%	High school or higher education: 92.1%
		24	Tai Chi 2 × 24 (twice weekly for 24w)	36 F100%	52.1 (13.3)	29.3 (7.4)	White: 58.3%	High school or higher education: 97.2%
Balneotherapy vs. balneotherapy + Mx Exercise AQ vs. Mx Exercise AQ	Kurt 2016[82] Ref ID 687	3	Balneotherapy	40 F100%	38.1 (10.9)	NR	NR	Illiterate: 16.2%; primary – secondary: 43.2%; high school: 29.7%; university: 10.8%
			Balneotherapy + exercise	40 F100%	35.1 (11.6)	NR	NR	Illiterate: 13.9%; primary – secondary: 55.6%; high school: 27.8%; university: 2.8%
			Exercise	40 F100%	41.9 (12.8)	NR	NR	Illiterate: 16.7%; primary – secondary: 47.2%; high school: 27.8%; University: 8.3%

continued

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
Education vs. Mind–body Ex LD	Jones 2012[83] Ref ID 210	12	Education	50 F94% M6%	54.8	30.1	White: 95.3%	Some college or higher: 80.9%
			Tai Chi	51 F92% M8%	53.3	30.9	White: 98.0%	Some college or higher: 88.2%
Education vs. Mind–body Ex LD	Maddali Bongi 2016[84] Ref ID 153	16	Control (FMS educational lesson)	25? Gender NR	54.3 (10.6)	NR	NR	NR
			Tai Ji Quan	25? Gender NR	50.4 (13.7)	NR	NR	NR
Education vs. Mind–body Ex LD	Mist 2012[85] Ref ID 641	12	Education	50 F94% M6%	54.8	30.1	White: 95.3%	Some college or higher: 80.9%
			Tai Chi	51 F92% M8%	53.3	30.9	White: 98.0%	Some college or higher: 88.2%
Education vs. Mx Exercise AQ	Fonseca 2021[86] Ref ID 271	11	Health education	19 F100%	54.5 (11.2)	29.4 (5.1)	NR	NR
			Aquatic physiotherapy	27 F100%	53.8 (10.4)	27.2 (5.9)	NR	NR
Education vs. PT/BT sleep	Martínez 2014[87] Ref ID 118	6	Sleep hygiene educational programme	32 F100%	48.66 (7.27)	NR	NR	(*n* = 29) Basic education 38.1%; high school 14.3%; professional instruction 28.6%; university studies 19.0%
			CBT-I	32 F100%	46.53 (6.31)	NR	NR	(*n* = 30) Basic education 21.7%; high school 34.8%; professional instruction 17.4%; university studies 26.1%

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m^2, mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
Education vs. PT/BT sleep	Miró 2011[88] Ref ID 2540	6	Sleep hygiene	22 F100%	50.2 (6.1)	NR	NR	(*n* = 15) Basic education: 30%; high school: 16.7%; professional instruction: 18.0%; university studies: 25.3%
			CBT-I	22 F100%	43.9 (6.1)	NR	NR	(*n* = 16) Basic education: 32.5%; high school: 21.3%; professional instruction: 14.5%; university studies: 32.8%
Education + Flex/skill LD vs. Mind–body Ex LD	Wang 2010[89] Ref ID 245	12	Control (wellness education and stretching)	33 F88% M12%	50.5 (10.5)	31.5 (7.4)	White: 52%	High-school or higher education: 91%
			Tai Chi	33 F85% M15%	49.7 (11.8)	33.9 (8.9)	White: 61%	High-school or higher education: 94%
Electro T vs. occlusal SS	Molina-Torres 2016[90] Ref ID 341	12	Laser therapy	29 F93% M7%	51.0 (8.3)	NR	NR	Primary studies: 63.0%; higher education: 37.0%
			Occlusal stabilisation splint	29 F97% M3%	51.8 (7.8)	NR	NR	Primary studies: 67.9%; higher education: 32.1%
Flex/skill AQ vs. Mind–body Ex AQ	Calandre 2009[91] Ref ID 243	6	Stretching in pool	39 F87% M13%	51 (8.0)	NR	NR	NR
			Tai Chi in pool	42 F93% M7%	49 (8.4)	NR	NR	NR
Flex/skill LD vs. Aerobic AQ	López-Rodríguez 2013[92] Ref ID 248	12	Stretching	38 F100%	54.8 (7.5) whole pop	NR	NR	NR
			Aquatic Bio-dance	38 F100%		NR	NR	NR

continued

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
Manual T vs. Non-MSM practice	Castro Sánchez 2019[93] Ref ID 238	4	Myofascial release	32 F88% M12%	46.8 (7.2)	NR	NR	No studies: 9.4%; school level: 43.7%; bachelor level: 40.6%; university level: 6.3%
			Dry needling	32 F94% M6%	47.4 (5.0)	NR	NR	No studies: 15.6%; school level: 31.3%; bachelor level: 37.5%; university level: 15.6%
Nutrition vs. nutrition	Martínez-Rodríguez 2020[94] Ref ID 213	16	Control (Mediterranean diet)	11 F100%	50 (5)	28.6 (5.1)	NR	NR
			Tryptophan- and magnesium-enriched Mediterranean diet	11 F100%	48 (4)	28.2 (3.7)	NR	NR
Nutrition vs. nutrition	Slim 2017[95] Ref ID 1811	24	Gluten-free diet	35 F100%	52 (36–66) median (range)	27.0 (5.85)	NR	NR
			Hypocaloric diet	40 F95% M5%	53 (32–65) median (range)	30.2 (5.29)	NR	NR
PT/BT gen vs. PT/BT gen	Van Gordon 2017[96] Ref ID 198	8	CBT	74 F84% M16%	47.3 (9.8)	NR	White British: 71.6%; White non-British: 9.5%; Asian: 9.5%; Black Caribbean: 9.5%	School leaver: 59.5%; vocational: 25.7%; university: 14.9%
			Meditation awareness training (mindfulness-based intervention)	74 F82% M18%	46.4 (9.1)	NR	White British: 77.0%; White non-British: 9.5%; Asian: 8.1%; Black Caribbean: 5.3%	School leaver: 55.4%; vocational: 25.7%; university: 18.9%

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
PT/BT gen vs. PT/BT sleep	Prados 2020[97] Ref ID 2269	9	CBT for pain	19 F100%	51.2 (5.3)	27.8 (3.0)	NR	Non-compulsory secondary or higher education: 60.0%
			CBT for pain and insomnia combined	20 F100%	49.0 (9.5)	26.4 (5.6)	NR	Non-compulsory secondary or higher education: 82.4%
Relaxation/medication vs. strengthening LD	Ericsson 2016[98] Ref ID 326	15	Relaxation (active control)	63 F100%	52.1 (9.8)	28.7 (5.3)	NR	≤ 9 years: 24%; 10–12 years: 35%; > 12 years: 41%
			Resistance exercise	67 F100%	50.8 (9.1)	27.4 (5.3)	NR	≤ 9 years: 12%; 10–12 years: 51%; > 12 years: 37%;
Studies reporting Medical Outcome Study Sleep Scale (MOS-SS) outcome								
UC vs. multidisciplinary (PT/BT gen + Mx Exercise LD + Mx Exercise AQ)	Castel 2013[99] Ref ID 376	Unclear (possibly 12w)	Pharmacological treatment	74 F100%	48.8 (7.2)	28.8 (5.8)	98% of the total sample were Caucasian	NR but the inclusion criteria included between 3 and 8 years of schooling
			Multidisciplinary [including CBT + physical therapy (aerobic capacity, muscular strengthening, and flexibility, as part of hydro-kinesiotherapy and kinesiotherapy in a gymnasium)] + pharmacological treatment	81 F100%	49.0 (6.8)	27.6 (4.8)		
UC vs. PT/BT gen	Kong 2021[100] Ref ID 716	8	Control	30 F97% M3%	≤ 39 years: 13%; 40–49 years: 13%; 50–59 years: 37%; ≥ 60 years: 37%	NR	NR	≤ Middle: 33.3%; ≤ high: 23.3%; ≥ college: 43.3%

continued

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
			CBT	30 F93% M7%	≤ 39 years: 23%; 40–49 years: 13%; 50–59 years: 37%; ≥ 60 years: 27%	NR	NR	≤ Middle: 30.0%; ≤ high: 36.7%; ≥ college: 33.3%
UC vs. PT/BT gen	Williams 2010[101] Ref ID 273	24	Standard care	59 F95% M5%	50.8 (10.6)	29.3 (5.2)	White: 96.6%, other: 3.4%	Postgraduate degree: 11.9%; college degree: 33.9%; some college: 37.3%; high school or less: 16.9%
			Web-enhanced behavioural self-management programme + standard care	59 F95% M5%	50.2 (12.3)	28.0 (5.3)	White: 58/59 (98.3%), other: 1/59 (1.7%)	Postgraduate degree: 11.9%; college degree: 25.4%; some college: 42.4%; high school or less: 20.3%
UC vs. PT/BT gen vs. UC vs. PT/BT gen	Racine 2019[102] Ref ID 296	10	Delayed operant learning	36 Gender NR	NR	NR	NR	NR
			Immediate operant learning	54 Gender NR	NR	NR	NR	NR
			Delayed energy conservation	35 Gender NR	NR	NR	NR	NR
			Immediate energy conservation	53 Gender NR	NR	NR	NR	NR

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m^2, mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
UC vs. PT/BT gen vs. PT/BT gen + relaxation/medication	Castel 2012[103] Ref ID 281	14	Pharmacological treatment (standard care)	30 F100%	48.7 (6.5)	NR	White: 100%	Formal education status. Low: 60%; middle: 33.3%; high: 6.7%
			CBT	34 F94% M6%	50.0 (7.6)	NR	White: 100%	Formal education status. Low: 58.8%; middle: 32.4%; high: 8.8%
			CBT + hypnosis	29 F97% M3%	50.2 (6.2)	NR	White: 100%	Formal education status. Low: 44.8%; middle: 51.7%; high: 3.4%
UC vs. relaxation/medication	Picard 2013[104] Ref ID 275	12 (Tx duration unclear; Ax at 12w)	Wait list	31 F100%	49.3 (8.5)	NR	NR	NR
			Self-hypnosis	31 F100%	48.1 (9.3)	NR	NR	NR
UC vs. PBO/Sham vs. relaxation/medication	Amirova 2017[105] Ref ID 583	4	UC	58 F91% M9%	49.0 (10.1)	NR	NR	NR
			Attention control	66 F95% M5%	50.5 (10.8)	NR	NR	NR
			Mitchell method relaxation technique online	67 F94% M6%	48.1 (11.1)	NR	NR	NR
PBO/Sham vs. neuromodulation	Nelson 2010[106] Ref ID 331	Unclear (22 sessions)	Sham LENS	21 F100%	52.0 (11.4)	NR	Non-Hispanic White: 88.2%	Mean (SD) years: 16.1 (3.1)
			Low energy neurofeedback system (LENS)	21 F94% M6%	51.6 (8.6)	NR	Non-Hispanic White: 88.2%	Mean (SD) years: 15.8 (2.9)
Studies reporting JSS outcome								
UC vs. hyperbaric oxygen therapy	Curtis 2021[107] Ref ID 2323	12 (Ax at end of waiting period)	Wait list	9 F100%	51.8 (14.5)	25.0 (4.2)	NR	NR
		8 (Ax immediately after the 8-w Tx period)	Hyperbaric oxygen therapy	9 F78% M22%	45.7 (14.2)	24.9 (5.3)	NR	NR

continued

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m^2, mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
PBO/Sham vs. Electro T	Udina-Corte 2020[108] Ref ID 2309	4	Sham NAE	19 F100%	52 (8)	NR	NR	NR
			Neuro-adaptive electrostimulation (NAE)	23 F100%	52 (9)	NR	NR	NR
Flex/skill LD vs. Flex/skill LD + Manual T	Toprak Celenay[109] 2020 Ref ID 333	6	Spinal stabilisation exercise	21 F100%	44.0 (10.0)	27.4 (7.1) median (IQR)	NR	Median (IQR) years: 12.0 (11.0)
			Spinal stabilisation exercise + kinesio taping	21 F100%	38.0 (24.0)	24.8 (4.6) median (IQR)	NR	Median (IQR) years: 12.0 (4.0)
Studies reporting VAS/NRS on sleep quality								
UC vs. Mind–body Ex LD	Haak 2008[110] Ref ID 1609	7	Waiting list control	28 F100%	53.4 (8.0)	NR	NR	NR
			Qigong	29 F100%	54.0 (9.4)	NR	NR	NR
UC vs. Mind–body Ex LD	Wong 2018[111] Ref ID 220	12	Control	19 F100%	51 (2)	22.2 (0.6)	NR	NR
			Tai Chi	18 F100%	51 (2)	23.1 (0.5)	NR	NR
UC vs. PT/BT gen	Haugmark 2021[112] Ref ID 2302	12	TAU	85 F95% M5%	41 (24, 51)	NR	NR	Primary/middle school (1–10 years): 14%; upper secondary school/vocational 10–12 years: 38%; bachelor/university > 12 years: 48%

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m^2, mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
			Multicomponent programme [Norwegian mindfulness-based and acceptance-based programme, the Vitality Training Programme (VTP), and physical activity counselling]	85 F92% M8%	44 (26, 52)	NR	NR	Primary/middle school (1–10 years): 9%; upper secondary school/ vocational 10–12 years: 42%; bachelor/university > 12 years: 47%
PBO/Sham vs. nutrition	Merchant 2001[113] Ref ID 470	12 (Tx 12w, wash-out 4w, then Tx 12w)	Placebo (tablet and liquid) Dietary supplementation with chlorella extract (tablet and liquid)	43 F95% M5% (crossover trial)	46.6 (8.6)	NR	NR	Mean (SD) years: 14.0 (2.2)
PBO/Sham vs. Non-MSM practice	Deluze 1992[114] Ref ID 218	3	Sham electroacupuncture	34 F62% M38%	49.0 (2.0)	NR	NR	NR
			Electroacupuncture	36 F92% M8%	46.8 (2.3)	NR	NR	NR
Mind–body Ex LD vs. Mind–body Ex LD	Maddali Bongi[115] 2012 Ref ID 154	7	Qui Gong Rességuier method	38 Gender NR (crossover trial)	57.30 (11.5)	NR	NR	NR
Pharmacological interventions								
Studies reporting PSQI outcome								
PBO/Sham vs. AP	Potvin 2012[116] Ref ID 230	12	Placebo + current medication	26 F100%	49.1 (8.7)	NR	Caucasian: 100%	NR
			Quetiapine extended-release as add-on to current medication	25 F100%	50.0 (11.7)	NR	Caucasian: 100%	NR

continued

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m^2, mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
PBO/Sham vs. antioxidant	Di Pierro 2017[117] Ref ID 202	12	Control (CoQ10-free supplement)	10 (crossover trial first phase only) F100%	53.6 (7.8)	NR	NR	NR
			Coenzyme Q10 (CoQ10)	12 (crossover trial first phase only) F100%	52.5 (10.4)	NR	NR	NR
PBO/Sham vs. CNS depressant	Reuter 2017[118] Ref ID 310	15	Placebo	12 F100%	53.8 (6.9)	NR	NR	NR
			Oral gamma-hydroxybutyrate	13 F100%	55.2 (4.9)	NR	NR	NR
Tricyclics vs. AP	Calandre 2014[119] Ref ID 253	16	Amitriptyline as monotherapy	45 F96% M4%	50.6 (8.2)	NR	NR	NR
			Quetiapine extended-release as monotherapy	45 F100%	49.7 (7.9)	NR	NR	NR
Tricyclics + PBO/Sham vs. endogenous hormone + PBO/ Sham vs. endogenous hormone + tricyclics	de Zanette 2014[120] Ref ID 370	6	Amitriptyline + placebo	21 F100%	49.8 (8.9)	27.6 (3.9)	NR	Mean (SD) years: 10.9 (5.1)
			Melatonin + placebo	21 F100%	47.4 (7.8)	27.2 (4.0)	NR	Mean (SD) years: 11.3 (3.8)
			Melatonin + amitriptyline	21 F100%	49.7 (7.2)	27.6 (4.6)	NR	Mean (SD) years: 8.2 (5.6)
Studies reporting Medical Outcome Study Sleep Scale (MOS-SS) outcome								
PBO/Sham vs. gabapentinoids	Arnold 2007[121] Ref ID 377	12	Placebo	75 F87% M13%	47.3 (11.8)	NR	White: 97.3%; African American: 1.3%; Asian: 0%; other: 1.3%	NR

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m^2, mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
			Gabapentin 1200–2400 mg/day	75 F93% M7%	49.2 (10.6)	NR	White: 97.3%; African American: 1.3%; Asian: 1.3%; other: 0	NR
PBO/Sham vs. gabapentinoids	Arnold 2014[122] Ref ID 146	13	Placebo	58 F90% M10%	49.3 (12.7)	NR	White: 89.7%; black: 5.2%; Asian: 5.2%; other: 0	NR
			Pregabalin 165 mg	63 F92% M8%	50.3 (12.1)	NR	White: 90.5%; black: 4.8%; Asian: 4.8%; other: 0	NR
PBO/Sham vs. gabapentinoids	Ohta 2012[123] Ref ID 222	15	Placebo	250 F88% M12%	46.7 (12.6)	NR	NR	NR
			Pregabalin 300 or 450 mg	251 F90% M10%	47.9 (12.0)	NR	NR	NR
PBO/Sham vs. gabapentinoids vs. gabapentinoids vs. gabapentinoids	Arnold 2008[124,a] Ref ID 368	14	Placebo	184 F92% M8%	49 (11.4)	NR	White: 91.8%; black: 3.8%; other: 4.3%	NR
			Pregabalin 300 mg/day	183 F95% M5%	49.1 (11.2)	NR	White: 89.6%; black: 4.9%; other: 5.5%	NR
			Pregabalin 450 mg/day	190 F96% M4%	50.8 (11.8)	NR	White: 90.0%; black: 6.3%; other: 3.7%	NR
			Pregabalin 600 mg/day	188 F95% M5%	50.9 (11.1)	NR	White: 92.6%; black: 2.7%; other: 4.8%	NR

continued

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
PBO/Sham vs. gabapentinoids vs. gabapentinoids vs. gabapentinoids	Crofford 2005[124,a] Ref ID 260	8	Placebo	131 F91% M9%	49.7 (10.7)	NR	White: 95.4%	NR
			Pregabalin 150 mg/day	132 F96% M4%	48.0 (10.4)	NR	White: 93.2%	NR
			Pregabalin 300 mg/day	134 F90% M10%	47.7 (10.1)	NR	White: 91.8%	NR
			Pregabalin 450 mg/day	132 F90% M10%	48.9 (11.3)	NR	White: 92.4%	NR
PBO/Sham vs. gabapentinoids vs. gabapentinoids vs. gabapentinoids	Mease 2008[124,a] Ref ID 2539	13	Placebo	190 F96% M4%	48.6 (11.3)	30	Caucasian: 87.9%; black: 5.3%; Hispanic: 6.3%; other: 0.5%	NR
			Pregabalin 300 mg/day	185 F94% M6%	50.1 (10.4)	31.4	Caucasian: 91.4%; black: 5.4%; Hispanic: 92.7%; other: 90.5%	NR
			Pregabalin 450 mg/day	183 F92% M8%	47.7 (10.8)	30.2	Caucasian: 92.3%; black: 3.8%; Hispanic: 3.8%; other: 0%	NR
			Pregabalin 600 mg/day	190 F95% M5%	48.7 (11.2)	30.5	Caucasian: 89.5%; black: 4.2%; Hispanic: 4.7%; other: 1.6%	NR

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
PBO/Sham vs. gabapentinoids vs. SRI vs. gabapentinoids + SRI	Gilron 2016[125] Ref ID 157	6	Placebo Pregabalin Duloxetine Pregabalin + duloxetine	41 F88% M12% (crossover trial)	56 (20–71) median (range)	NR	Caucasian: 98%	NR
PBO/Sham vs. iron replacement	Boomershine 2018[126] Ref ID 626	5 days	Placebo	40 F100%	43.9 (10.8)	NR	White: 75%; black: 17.5%; Hispanic: 5.0%; Asian: 0; other: 2.5%	NR
			Ferric carboxymaltose	41 F98% M2%	41.2 (11.1)	NR	White: 80.5%; black: 17.1%; Hispanic: 0; Asian: 2.4%; other: 0	NR
PBO/Sham vs. SRI	Arnold 2010[127] Ref ID 350	8	Placebo	133 F90% M10%	50.1 (range 20–84)	NR	White: 89.5%; black: 6.0%; Asian: 0; other: 4.5%	NR
			Es-reboxetine	134 F89% M11%	49.2 (range 21–79)	NR	White: 87.3%; black: 4.5%; Asian: 0.7%; other: 7.5%	NR
PBO/Sham vs. SRI	Ahmed 2016[128] Ref ID 223	5	Placebo Milnacipran	19 'Predominantly women and white' (89.5%) (crossover trial)	49.2 (range 28–72)	NR	NR	NR

continued

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
PBO/Sham vs. SRI	Branco 2010[129] Ref ID 1522	16	Placebo	449 F94% M6%	49.2 (10.3)	26.7 (5.0)	NR	NR
			Milnacipran 200 mg/day	435 F95% M5%	48.3 (9.3)	26.7 (5.4)	NR	NR
Ultrasound T + Manual T vs. SSRI	González-Viejo[130] 2005 Ref ID 279	24 (Tx 3w; Ax at 24w)	Ultrasonography plus physical therapy	34 F100%	46.8 (8.4)	NR	NR	NR
		24 (Tx 24w)	Sertraline, 50 mg/24 hours	36 F100%	45.2 (7.2)	NR	NR	NR
Studies reporting JSS outcome								
PBO/Sham vs. CNS depressant	Moldofsky 2010[131] Ref ID 147	8	Placebo	66	46.5 (11.3) whole pop	NR	Caucasian: 92% of whole pop	NR
			SXB 4.5 g	62				
			SXB 6 g	67 (F94 M6% whole pop)				
PBO/Sham vs. CNS depressant	Spaeth 2012[132] Ref ID 122	14	Placebo	188 F89% M11%	46.8 (9.7)	27.4 (4.7)	White: 92.0%; black: 5.3%; other: 2.7%	NR
			SXB 4.5 g	195 F90% M10%	46.6 (10.8)	27.4 (4.3)	White: 93.3%; black: 5.6%; other: 1.0%	NR
			SXB 6 g	190 F89% M11%	46.4 (11.4)	28.0 (4.8)	White: 88.9%; black: 9.5%; other: 1.6%	NR
PBO/Sham vs. CNS depressant	Russell 2011[133] Ref ID 228	14	Placebo	183 F91% M9%	46.5 (11.4)	28.9 (5.1)	White: 91.3%; black: 4.4%; other: 4.4%	NR

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m^2, mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
			SXB 4.5 g	182 F91% M9%	47.0 (11.8)	28.1 (4.6)	White: 90.1%; black: 7.1%; other: 2.7%	NR
			SXB 6 g	183 F91% M9%	47.5 (10.6)	28.4 (4.6)	White: 91.3%; black: 6.6%; other: 2.2%	NR
PBO/Sham vs. SRI	Vitton 2004[134,135] Ref ID 328	12	Placebo	28 (F96–98% whole pop)	Range 46.2 to 48.0, whole pop	NR	Caucasian: 79% to 89% of whole pop	NR
			Milnacipran 25 mg QD (single daily dose)	46		NR		NR
			Milnacipran 12.5 mg BID (two divided doses)	51		NR		NR
PBO/Sham vs. TeCAs vs. TeCAs	Yeephu 2013[135] Ref ID 340	13	Placebo	13 F100% M0%	47.4 (10.5)	22.6 (3.4)	NR	NR
			Mirtazapine 15 mg	13 F100% M0%	42.7 (12.6)	22.0 (2.5)	NR	NR
			Mirtazapine 30 mg	14 F100% M0%	43.9 (9.4)	22.1 (3.2)	NR	NR
Studies reporting FMSD outcome								
PBO/Sham vs. ASP0819	Arnold 2020[136] Ref ID 2315	8	Placebo	95 F95% M5%	49.8 (12.5)	32.2 (6.2)	White: 77.7%; black or African American: 17.0%; Asian: 1.1%; American Indian or Alaskan Native: 3.2%; Native Hawaiian or other Pacific Islander: 1.1%; other: 0%	NR

continued

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
							not Hispanic or Latino: 86.2%; Hispanic or Latino: 13.8%	
			ASP0819	91 F98% M2%	48.7 (12.1)	31.8 (6.6)	White: 86.7%; black or African American: 11.1%; Asian: 0%; American Indian or Alaskan Native: 0%; Native Hawaiian or other Pacific Islander: 1.1%; other: 1.1%; not Hispanic or Latino: 88.9%; Hispanic or Latino: 11.1%	NR
Studies reporting SQ-NRS outcome								
PBO/Sham vs. gapapentinoids vs. gapapentinoids vs. gapapentinoids	Pauer 2011[137] Ref ID 148	14	Placebo	184 F91% M9%	48.1 (11.3)	NR	White: 76.6%; black: 0%; Hispanic: 13.0%; other: 10.3%	NR
			Pregabalin 300 mg/day	184 F90% M10%	48.4 (10.8)	NR	White: 77.7%; black: 0.5%; Hispanic: 11.4%; other: 10.3%	NR

TABLE 2 Characteristics of studies reporting PROMs of sleep quality included in the NMA (ordered by intervention category comparison) (*continued*)

Intervention category comparison	Study ID (author, year, reference ID)	Duration of treatment (Tx) or first assessment (Ax), if later (weeks)	Intervention	Number randomised and gender [female (F), male (M), %]	Age, years, mean (SD)	BMI kg/m², mean (SD)	Ethnicity, *n* (%)	Education status, *n* (%)
			Pregabalin 450 mg/day	182 F92% M8%	48.0 (11.3)	NR	White: 74.7%; black: 0%; Hispanic: 13.2%; other: 12.1%	NR
			Pregabalin 600 mg/day	186 F90% M10%	49.6 (11.3)	NR	White: 74.7%; black: 0%; Hispanic: 12.4%; other: 12.9%	NR
Studies reporting VAS/NRS on sleep quality								
PBO/Sham vs. endogenous hormones	Mameli 2014[138] Ref ID 292	3	Placebo Oxytocin	14 F100% (crossover trial)	51.9 (7.8)	NR	NR	Junior: 21.4%; secondary: 35.7%; high: 42.9%

AQ, aquatic or pool-based; Ax, assessment; BID, twice daily; CNS depressants, central nervous system depressants; DLPFC, dorsolateral prefrontal cortex; Flex/skill, flexibility/neuromotor skills exercise; FMS, fibromyalgia syndrome; GCSE, General Certificate of Secondary Education; LD, land-based; Mx Exercise, mix (aerobic and anaerobic) exercise; Non-MSM practice, non-mainstream practice; NR, not reported; OIC, operculo-insular cortex; PBO/Sham, placebo or sham treatment; PT/BT gen, generic psychological or behavioural therapy; PT/BT sleep, psychological or behavioural therapy, sleep-focused; QD, once daily; Ref ID, reference ID; rTMS, repetitive transcranial magnetic stimulation; SERM, selective oestrogen receptor modulators; SXB, sodium oxybate; TAU, treatment as usual; TCA, tricyclics or tricyclic antidepressant; TeCAs, tetracyclic antidepressants; Tx, treatment; w, weeks.
a This study also reports SQ-NRS outcome.

exercise (e.g. lifting hand-held weights, push-ups, squats); (3) flexibility (e.g. stretching) and neuro-motor skills training to improve balance and coordination (e.g. wobble board) and (4) Mind–body Ex that combines body movement, mental focus and controlled breathing (e.g. yoga, Tai Chi, qigong). Stretching or relaxation as part of a warm-up or cool-down component of exercise training was not classified as a distinct intervention. Exercise training was categorised as mixed exercise when it included both aerobic and anaerobic exercise. A further distinction was made for exercise training between aquatic, pool-based exercise training and land-based (exercise) (LD) training. Psychological and behavioural therapies, as well as patient education, were considered as a distinct intervention only if they were based on specific theories or delivery plans (e.g. delivered using specific instructions or programmes). A distinction was also made between interventions tailored to sleep problems (e.g. CBT for insomnia) and generic interventions with no specific focus on sleep problems (e.g. CBT for pain), and between balneotherapy and hydrotherapy, with the latter meaning water-based exercise training.

The most frequently used comparator treatment was placebo/sham treatment (39 studies) or UC (26 studies). Only 25 studies compared an active treatment with another active treatment. For the definitions of placebo and sham treatments, we accepted those provided by the authors of the included studies. We also included 'attention control' (typically for behavioural therapy) as placebo/sham treatment to indicate certain procedures designed to increase attention or treatment contact without providing any active therapeutic elements. Typically, pharmacological treatments were compared with placebo, while non-pharmacological treatments with sham and attention-control treatments. While in some studies appropriate sham procedures were used (e.g. sham device for neuromodulation, sham cupping therapy, sham Qigong), not all sham treatments were appropriately designed as they did not mimic closely the features of the active interventions (e.g. Manual T compared with sham ultrasound). Some of the attention-control treatments were also not clearly defined in the included studies (e.g. 'telephone support' as control for active neurofeedback treatment) and it could not be easily established whether the intended control programme did not comprise any active therapeutic elements (see *Appendix 2*). Within the definition of 'usual care' we included 'standard treatment', 'treatment as usual' (TAU) and 'wait list' control as reported by studies' authors. It is worth noting that a wide variety of medical and non-medical interventions were categorised as 'standard treatment' or 'TAU' in the included studies. Concomitant treatments (e.g. routine medication) were permitted in most studies and were generally balanced between intervention groups. Information on adherence and compliance to the study treatment was not universally and consistently reported across studies and even when reported could not be easily incorporated into the analysis, as results were not presented separately for 'responders' and 'non-responders', for example, to allow us to assess its impact on outcomes.

The characteristics of the included interventions are summarised in *Table 2* with further details provided in *Appendix 2*.

Outcomes

Sleep quality outcome was reported using PSQI in 53 studies,[51–98,116–120] MOS-SS in 17 studies,[99–106,121–123,125–130] SQ-NRS in 1 study,[137] both MOS-SS and SQ-NRS in 3 studies,[124,139,140] JSS in 8 studies[107–109,131–135] and FMSD in 1 study.[136]

In addition, when sleep quality was evaluated on a NRS or VAS, using a single item, we considered it as a proxy for SQ-NRS and included it in the NMA. Seven studies met this description.[110–115,138] Rating scales that did not explicitly measure 'sleep quality' or were based on multiple items were considered to be measuring different constructs from SQ-NRS and were not treated as its proxy measure.

In the studies focusing on non-pharmacological interventions (65 studies), the duration of interventions ranged from 2.6[57] to 25 weeks,[78] with a median of 10 weeks. Studies focusing on pharmacological interventions (25 studies) lasted from 5 days[126] to 6 months,[130] with a median of 12 weeks.

Studies not eligible for the network meta-analysis

Seventy-eight studies reported sleep-related outcomes other than PROMs of sleep quality eligible for the NMA. *Appendix 3*, *Table 19* presents a summary of characteristics of these 78 studies.

Study designs

Of the 78 studies, 71 were parallel RCTs and 7 were randomised crossover trials.[143–149] Most studies were published in English, with two published in Turkish,[150,151] and one study each published in Spanish,[152] German[153] and Italian.[154]

Participants

The 78 included studies involved a total of 5911 participants. One study comprised an adolescent population (*n* = 107), aged 12–17 years,[155] while all other studies were composed of adults (total number of participants = 5804), with mean or median age of study group ranging from 28.5[156] to 60.3 years.[157] Study sample size ranged from 10[148] to 530,[158] with a median of 53.5. Across studies the vast majority of participants were women (96%).

Interventions

The 78 included studies assessed 119 different active treatments, either alone or in combination. These treatments were grouped into 45 active treatment categories (26 non-pharmacological, 19 pharmacological). Interventions and corresponding intervention categories evaluated in these studies were broadly similar to those of the studies included in the NMA. New treatment categories for non-pharmacological interventions included phototherapy and botox cervical infiltration. There were also six new pharmacological intervention categories that were not included in the NMA: serotonin receptor antagonist and dopamine receptor agonist (e.g. terguride), opioid antagonist (e.g. naltrexone), selective oestrogen receptor modulators (SERMs; e.g. raloxifene), cannabinoid (e.g. nabilone), orexin antagonists (e.g. suvorexant) and acetylcholine esterase inhibitor (e.g. pyridostigmine).

The most frequently used comparator treatment was placebo or sham treatment (PBO/Sham) (36 studies) or UC (20 studies). Twenty-two studies compared an active treatment with another active treatment.

In the studies focusing on non-pharmacological interventions (57 studies), the duration of interventions ranged from 0.7[159] to 25 weeks,[160] with a median of 8 weeks. Studies focusing on pharmacological interventions (21 studies) lasted from 1.3[148] to 26 weeks,[161] with a median of 12 weeks.

Outcome

Self-reported sleep quality was reported using a variety of measures: 29 studies used VAS or NRS,[144,151,155,156,162–186] 26 studies used a questionnaire,[143,146,149,150,154,187–207] and 13 studies used a sleep subscale of a non-sleep-specific measure such as the FIQ.[152,158,160,161,208–216] Ten studies that did not assess sleep quality outcome reported sleep efficiency or sleep duration.[23,153,157,159,217–219]

Risk of bias in studies eligible for the network meta-analysis

A summary of the results of the RoB2 for the studies contributing to the NMA is shown in *Figure 2*. The risk-of-bias judgements for each study are presented in *Appendix 4*, *Figure 10*.

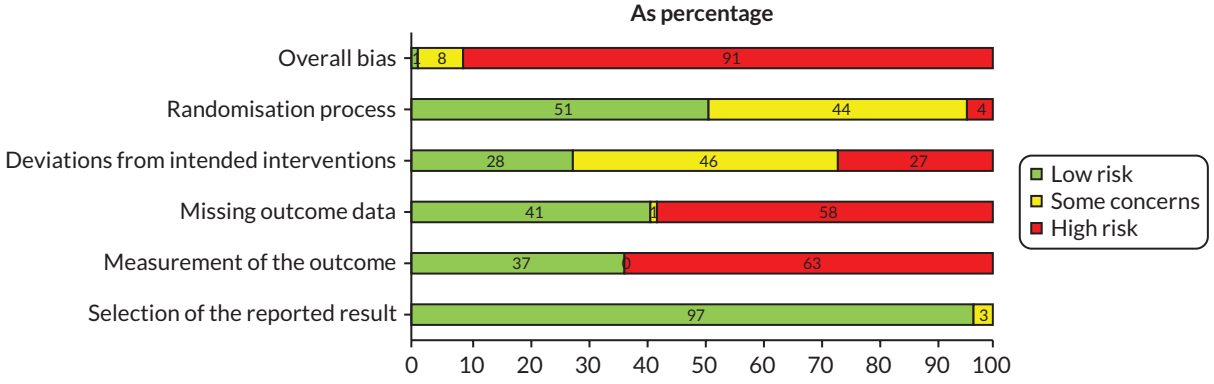

FIGURE 2 Summary of risk-of-bias assessment of the included studies (RoB2). Reproduced with permission from Hudson *et al.*[220] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

Randomisation process

Around half of the included studies (46 studies) reported an appropriate method for random-sequence generation and allocation concealment and we rated them as being at low risk.[51,53–58,60–62,67,73,76,80,81,85,87–91,93,95,96,98,101,102,105,107,112,114,115,117,119,122–124,125–128,131–133,139] We judged 42 studies as having 'some concerns', as they failed to report sufficient detail to provide assurance of an adequate method of allocation concealment (19 studies)[52,59,63,68,72,74,77,79,83,86,94,97,99,100,108,109,111,120,138] or of both allocation concealment and sequence generation (23 studies).[64–66,70,75,78,82,84,92,103,104,106,110,113,116,118,121,129,130,134,135,137,140] Two studies were judged to be at high risk due to a suboptimal method of allocation concealment,[69] or because information on allocation concealment was insufficient and there was a baseline imbalance in age across treatment arms which could have influenced sleep quality outcome.[71]

Deviations from the intended interventions

As expected, for most of the non-pharmacological interventions, blinding of participants and personnel was not feasible due to the nature of the interventions and blinding of investigators and assessment staff (e.g. statisticians) was not consistently reported across studies.

Nineteen placebo-controlled pharmacological trials[72,75,77,116,120–122,124,127,129,132–140] and one UC-controlled non-pharmacological trial[53] were rated as being at low risk as they implemented blinding of participants and personnel and adopted an intention-to-treat analysis approach.

There were four studies with blinding of participants and personnel that we rated as having 'some concerns' because they documented an inappropriate method of analysis (e.g. completer or per-protocol analysis).[123,125,126,131]

Similarly, 36 studies that did not implement blinding procedures were rated as having 'some concerns'.[51,54,56,57,59–62,65,73,76,79–81,83–86,89–91,93,94,96,98–101,103–105,107,110,112,117,119] These studies either documented an appropriate method of analysis or documented an inappropriate method of analysis but provided no specific reasons to believe that this would have a substantial impact on the results.

Nine studies with blinding[71,74,78,106,108,113,114,118,128] and 21 studies without blinding[52,55,58,63,64,66–70,82,87,88,92,95,97,102,109,111,115,130] were judged to be at high risk of bias because they documented an inappropriate method of analysis and failed to provide sufficient information to ensure that its impact on the results would be minimal.

Missing outcome data

There were 53 studies with high levels of missing data (10% of participants or greater) that did not provide reasons for missing data, had differential dropout, or reported reasons for missingness related to treatment efficacy.[51,52,54–56,58,63,67,69,74,76,78,81,87,88,91,92,94,95,98,100–102,104–106,108,109,111–116,118,119,121–124,127–129,131–137,139,140] We rated these studies as high risk. The remaining 36 studies permitted a judgement of low risk for this risk domain.

Measurement of the outcome

Given that our primary outcome (sleep quality) is a participant-reported outcome, we judged 33 studies with blinding of participants to be at low risk of bias[53,71,72,74,75,77,78,106,108,113,114,116,118,120–129,131–140] and 57 studies with no blinding of participants to be at high risk of bias.[51,52,54–70,73,76,79–105,107,109–112,115,117,119,130]

Selection of the reported results

For most studies the study protocol was not available and therefore we assessed whether outcome measures and analyses reported in the methods section of the published article were comparable to those reported in the *Results* section. Three studies were rated as having 'some concerns', since they provided limited information on their analysis plan.[88,100,130] The remaining studies were judged to be at low risk of bias.

Overall risk of bias

Overall, the majority of the included studies were judged to be at high risk of bias in at least one domain and were given an overall judgement of high risk of bias. Seven studies were given an overall judgement of 'some concerns'[72,75,77,120,125,126,138] and one study an overall judgement of low risk.[53]

Effectiveness outcomes – studies eligible for the network meta-analysis

Sleep outcome

Results for the sleep outcome are presented below and in *Report Supplementary Material 4*. The sensitivity analysis, where we assume a higher correlation for calculating SD for those studies that did not provide a change from baseline score, showed similar results and are available on request.

Of the 90 studies that reported a sleep outcome, we were able to include 65 studies (total number of participants = 8247, total number of assessed intervention categories = 35) in the NMA (see *Appendix 5*, *Table 20* for the number of participants according to the type of intervention). Studies were excluded from the network if they did not provide enough data (13 studies),[64,66,67,77,78,91,93,101,113,132,135,139,140] if they were disconnected from the main network (4 studies),[72,73,77,120] evaluated an intervention and a comparator that belong to the same category (5 studies),[94–96,104,115] or did not clarify whether the outcome was an index or a subscale of a validated scale (2 studies).[126,130] In addition, one study was removed from the network because of data outliers (the mean and SD were considerably different).[103] The studies excluded from the NMA are summarised in *Report Supplementary Material 5*. The network comprises 39 studies providing PSQI outcome data, 13 providing MOS-SS data, 6 JSS data, 3 VAS data, 2 SQ-NRS and 1 study each providing FMSD and NRS data. *Figure 3* shows the network plot for eligible comparisons for sleep quality. Most interventions were compared to either placebo/sham or UC. Of the 35 interventions, the majority were non-pharmacological. In the case of cross-over trials, we only used data from the first phase prior to the cross over.

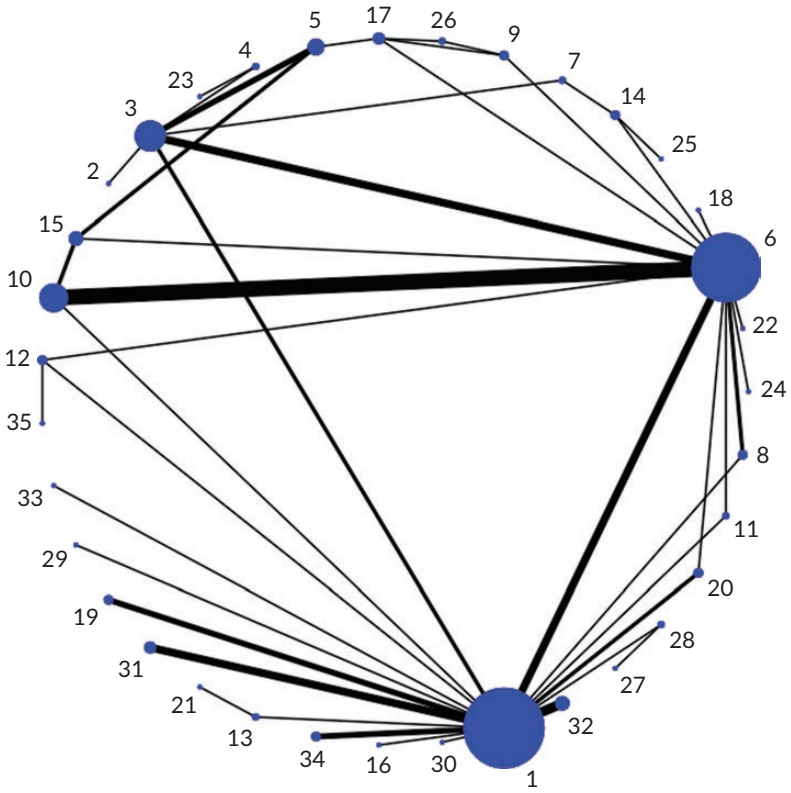

FIGURE 3 Network diagram for sleep outcome. 1, placebo/sham; 2, education + flexibility exercise LD; 3, Mind–body Ex LD; 4, aerobic exercise LD; 5, education; 6, UC; 7, aerobic exercise AQ; 8, nutrition; 9, balneotherapy; 10, generic psychological or behavioural therapy; 11, Manual T; 12, relaxation; 13, Electro T; 14, flexibility exercise LD; 15, psychological or behavioural therapy, sleep-focused; 16, Mind–body Ex AQ; 17, mixed exercise AQ; 18, weight loss; 19, neuromodulation; 20, non-mainstream practice; 21 dental splint; 22, hyperbaric oxygen therapy; 23, aerobic exercise LD + flexibility exercise LD; 24, multidisciplinary; 25, flexibility exercise LD + Manual T; 26, balneotherapy + mixed exercise AQ; 27, tricyclics; 28, AP; 29, endogenous hormones; 30, antioxidant; 31, SRI; 32, gabapentinoid; 33, analgesic; 34, central nervous system depressants; 35 strengthening exercise LD. AQ, aquatic; LD, land-based. Note: circle size represents the number of randomised participants; line width represents the number of direct comparisons. Reproduced with permission from Hudson *et al.*[220] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

Table 3 shows the results of the direct and indirect comparisons for the included interventions versus placebo/sham (see *Report Supplementary Material 1* for all other comparisons; pairwise comparisons are available on request). Compared with PBO/Sham (*n* = 2087), there was evidence of a beneficial effect on sleep for aquatic-based aerobic exercise training (*n* = 59, SMD −2.63, 95% CrI −4.74 to −0.58) and land-based aerobic exercise training in combination with flexibility exercise training (*n* = 32; SMD −4.69, CrI −8.14 to −1.28). We also found a positive effect for hyperbaric oxygen therapy (*n* = 9; SMD −4.51, CrI −7.44 to −1.56) but it is worth noting that it was derived from indirect evidence and based on the assessment of only nine participants in the intervention group. Compared with PBO/Sham, there was a suggestion of a modest effect on sleep for land-based strengthening exercise training (*n* = 56, SMD −0.95, CrI −3.89 to 2.04), psychological or behavioural therapy with a focus on sleep (PT/BT sleep; *n* = 94, SMD −0.89, CrI −2.39 to 0.61), weight loss (*n* = 41, SMD −1.15, CrI −3.55 to 1.27), Electro T (*n* = 20, SMD −0.98, CrI −3.28 to 1.34), dental splint (*n* = 29, SMD −1.62, CrI −4.862 to 1.65), tricyclics (*n* = 43, SMD −1.26, CrI −4.47 to 1.93) and AP (*n* = 53, SMD −1.28, CrI −3.56 to 0.97); however, this could not be confirmed with certainty because of the width of the CrIs. For most of the other pharmacological and non-pharmacological interventions, there was no clear evidence of an improvement in sleep quality. In addition, there was evidence that sleep outcome did not improve in participants randomised to aquatic Mind–body Ex training (*n* = 75, SMD 4.26, CrI 1.76 to 6.76) compared with those who received PBO/Sham. There was evidence of inconsistency between direct and indirect evidence for UC and aquatic-based aerobic exercise compared to land-based Mind–body Ex, land-based flexibility exercise compared to UC and land-based flexibility exercise compared to aquatic-based aerobic exercise (see *Appendix 6*, *Table 21*).

Quality-of-life outcomes

Fibromyalgia Impact Questionnaire

Of the 56 studies that used the FIQ to assess quality of life, 52 (total number of participants = 7127, total number of interventions = 35) were included in the NMA while 4 studies were excluded as they did not form part of the network.

TABLE 3 Results for direct comparison and NMA compared to placebo/sham for sleep outcome

	Direct evidence			NMA		
Treatment	**Number of trials**	**MD**	**95% CI**	**SMD**	**95% CrI**	**Grade**
Education + flexibility exercise LD	–			0.61	(−1.90 to 3.15)	Very low[a,b,c]
Mind–body Ex LD	2	−1.01	(−1.76 to −0.26)	−0.20	(−1.27 to 0.89)	Low[a,d]
Aerobic exercise LD	–			−0.14	(−2.63 to 2.30)	Very low[a,b,c]
Education	–			0.08	(−1.32 to 1.47)	Very low[a,b,c]
UC	4	0.20	(−0.04 to 0.44)	−0.17	(−1.07 to 0.72)	Low[a,e]
Aerobic exercise AQ	–			**−2.63**	**(−4.74 to −0.58)**	Low[a,c]
Nutrition	1	0.26	(−0.32 to 0.83)	−0.16	(−1.81 to 1.49)	Low[a,b]
Balneotherapy	–			−0.60	(−2.55 to 1.35)	Very low[a,c,d]
PT/BT generic	1	−0.01	(−0.47 to 0.45)	−0.44	(−1.57 to 0.66)	Low[a,d]
Manual T	1	−0.31	(−1.13 to 0.51)	−0.52	(−2.18 to 1.15)	Low[a,d]
Relaxation	1	−0.39	(−0.81 to 0.03)	−0.62	(−2.57 to 1.34)	Low[a,d]
Electro T	1	−0.98	(−1.67 to −0.29)	−0.98	(−3.28 to 1.34)	Very low[a,c,d]
Flexibility exercise LD	–			0.49	(−1.56 to 2.56)	Very low[a,b,c]

TABLE 3 Results for direct comparison and NMA compared to placebo/sham for sleep outcome (*continued*)

	Direct evidence			NMA		
Treatment	**Number of trials**	**MD**	**95% CI**	**SMD**	**95% CrI**	**Grade**
PT/BT sleep	–			−0.89	(−2.39 to 0.61)	Very low[a,c,e]
Mind–body Ex AQ	1	4.25	(3.00 to 5.49)	4.26	(1.76 to 6.76)	Low[a,c]
Mixed exercise AQ	–			−0.19	(−1.91 to 1.52)	Very low[a,b,c]
Weight loss	–			−1.15	(−3.55 to 1.27)	Very low[a,c,d]
Neuromodulation	3	−0.32	(−0.63 to −0.02)	−0.25	(−1.55 to 1.05)	Very low[a,c,d]
Non-mainstream practice	2	−0.98	(−1.38 to −0.58)	−1.15	(−2.66 to 0.33)	Moderate[a]
Dental splint	–			−1.62	(−4.86 to 1.65)	Low[a,c]
Hyperbaric oxygen therapy	–			**−4.51**	**(−7.44 to −1.56)**	Low[a,c]
Aerobic exercise LD + flexibility exercise LD	–			**−4.69**	**(−8.14 to −1.28)**	Low[a,c]
Multidisciplinary	–			1.79	(−0.61 to 4.20)	Low[a,c]
Flexibility exercise LD + Manual T	–			0.78	(−2.30 to 3.83)	Very low[a,b,c]
Balneotherapy + mixed exercise AQ	–			0.38	(−2.19 to 2.89)	Very low[a,b,c]
Strengthening exercise LD	–			−0.95	(−3.89 to 2.04)	Very low[a,b,c]
Tricyclics	–			−1.26	(−4.47 to 1.93)	Very low[a,c,d]
AP	1	−1.29	(−1.95 to −0.63)	−1.28	(−3.56 to 0.97)	Low[a,c]
Endogenous hormones	1	0.25	(−0.50 to 0.99)	0.24	(−2.06 to 2.53)	Low[b,c]
Antioxidant	1	−0.29	(−1.13 to 0.55)	−0.29	(−2.61 to 2.06)	Very low[a,b,c]
SRI	4	−0.01	(−0.12 to 0.10)	−0.02	(−1.13 to 1.10)	Very low[a,b,c]
Gabapentinoid	5	−0.28	(−0.37 to −0.19)	−0.42	(−1.41 to 0.56)	Very low[a,c,d]
Analgesic	1	−0.25	(−0.54 to 0.04)	−0.24	(−2.46 to 1.94)	Very low[a,b,c]
CNS depressants	3	−0.44	(−0.59 to −0.28)	−0.19	(−1.50 to 1.13)	Very low[a,c,d]

AQ, aquatic; CNS, central nervous system; LD, land-based; PT/BT generic, generic psychological or behavioural therapy; SMD, standardised mean difference.
a Downgraded by one level due to major concerns on within-study bias.
b Downgraded by one level due to major concerns on imprecision.
c Downgraded by one level due to major concerns on incoherence.
d Downgraded by one level due to some concerns on both imprecision and heterogeneity.
e Downgraded by one level due to major concerns on heterogeneity.

Notes
Between study SD 1.1 (95% CrI 0.8 to 1.5). Negative values indicate better outcomes while positive values indicate worse outcomes. Values in bold indicate significant NMA results.

Results are presented below and in *Report Supplementary Material 3*. *Appendix 5*, *Table 20* shows the total number of participants for each intervention. *Figure 4* shows the network plot for FIQ. Within the network many interventions were never directly compared. Placebo/sham and UC were the most common comparators.

The results of the direct and indirect comparisons for the included interventions compared with placebo/sham (*n* = 2263) are shown in *Table 4* (see *Report Supplementary Material 6* for all other comparisons; pairwise comparisons are available on request). Improvements in quality of life assessed using the FIQ were observed for participants undertaking land-based aerobic in combination with mixed flexibility exercise training (*n* = 32, MD −19.91, CrI −34.89 to −4.94), multidisciplinary training (*n* = 81, MD −17.31, CrI −28.38 to −6.29), land-based Mind–body Ex training (*n* = 420, MD −16.18, CrI −22.72 to −9.73), generic psychological or behavioural therapy (PT/BT generic) with relaxation (*n* = 29, MD −12.07, CrI −20.75 to −3.35), psychological or behavioural therapy targeted to sleep (PT/BT sleep-focused) (*n* = 77, MD −11.68, CrI −20.34 to −3.11) and generic PT/BT (*n* = 145, MD −6.23, CrI −12.02 to −0.62). Regarding pharmacological interventions, positive effects were observed for 97 participants receiving antioxidants (*n* = 12, MD −17.75, CrI −34.91 to −0.61), iron replacement (*n* = 38, MD −15.10, CrI −30.41 to −0.06), SRIs (SRI) (*n* = 573) (MD −9.85, CrI −15.80 to −3.80) and central nervous system (CNS) depressants (*n* = 881, MD −8.83, CrI −14.77 to −2.74). In general, magnitude of effects varied across interventions. A large positive effect was also observed after hyperbaric oxygen therapy (*n* = 9, MD −26.29, CrI −37.56 to −15.15); however, as explained before, we are not certain of the reliability of this estimate because it was derived from the assessment of a very small sample of patients (nine patients in the intervention group). Compared with placebo/sham treatments, there was no clear evidence that interventions such as education in combination with land-based flexibility exercise training (*n* = 33), aquatic flexibility exercise training (*n* = 39), UC (*n* = 551), relaxation (*n* = 67), land-based flexibility exercise training (*n* = 57), aquatic Mind–body Ex training (*n* = 60), mixed aquatic exercise training (*n* = 89) and neuromodulation (*n* = 76) had an effect on participants' quality

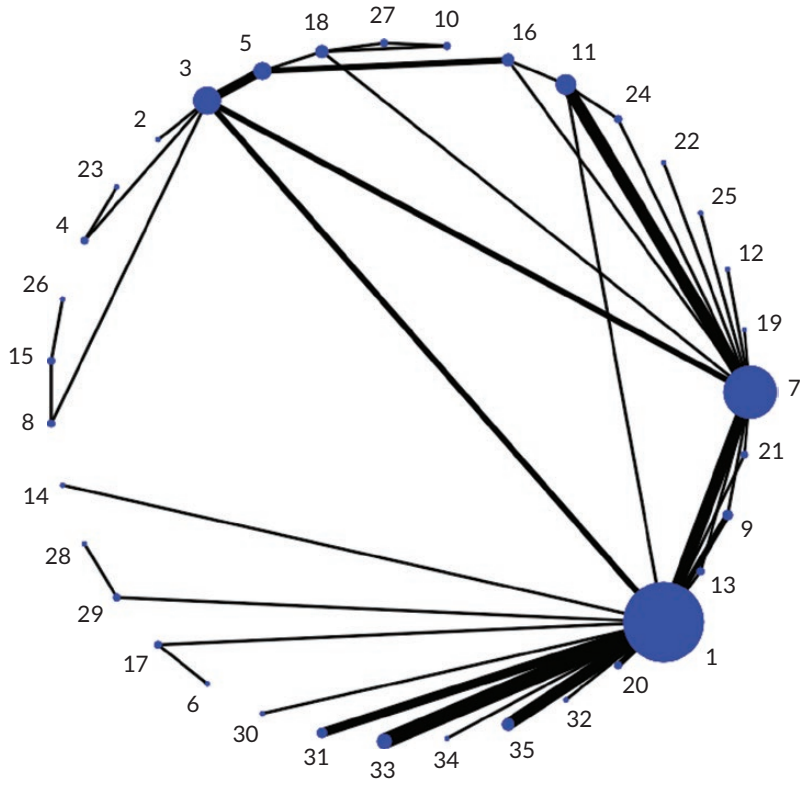

FIGURE 4 Network diagram for fibromyalgia impact questionnaire. 1, placebo/sham; 2, education + flexibility exercise LD; 3, Mind–body Ex LD; 4, aerobic exercise LD; 5, education; 6, flexibility exercise AQ; 7, UC; 8, aerobic exercise AQ; 9, nutrition; 10, balneotherapy; 11, PT/BT generic; 12, Manual T; 13, relaxation; 14, Electro T; 15, flexibility exercise LD; 16, PT/BT sleep-focused; 17, Mind–body Ex AQ; 18, mixed exercise AQ; 19, weight loss; 20, neuromodulation; 21, non-mainstream practice; 22, hperbaric oxygen therapy; 23, aerobic exercise LD + flexibility exercise LD; 24, PT/BT generic + relaxation; 25, multidisciplinary; 26, flexibility exercise LD + Manual T; 27, balneotherapy + mixed exercise AQ; 28, tricyclics; 29, antioxidant; 30, SRI; 31, iron replacement; 32, gabapentinoid; 33, analgesic; 34, AP; 35, central nervous system depressants. AQ, aquatic; LD, land-based; PT/BT, psychological or behavioural therapy. Note: circle size represents the number of randomised participants; line width represents the number of direct comparisons.

TABLE 4 Results for direct comparison and NMA compared to placebo/sham for FIQ outcome

	Direct evidence			NMA	
Treatment	**Number of trials**	**MD**	**95% CI**	**MD**	**95% CrI**
Education + flexibility exercise LD	–			2.14	(−11.61 to 15.64)
Mind–body Ex LD	2	−19.49	(−29.14 to −9.84)	**−16.18**	**(−22.72 to −9.73)**
Aerobic exercise LD	–			−9.23	(−21.46 to 3.07)
Education	–			−4.79	(−12.87 to 3.21)
Flexibility exercise AQ	–			5.58	(−8.00 to 19.30)
UC	4	0.23	(−0.48 to 0.93)	0.79	(−3.72 to 5.15)
Aerobic exercise AQ	–			−8.92	(−23.46 to 5.59)
Nutrition	2	−5.77	(−12.34 to 0.80)	−5.06	(−12.99 to 2.86)
Balneotherapy	–			−5.58	(−18.68 to 7.68)
PT/BT generic	1	−0.18	(−0.93 to 0.57)	**−6.23**	**(−12.02 to −0.62)**
Manual T	–			−9.22	(−20.18 to 1.81)
Relaxation	1	0.07	(−7.25 to 7.39)	1.80	(−7.29 to 10.91)
Electro T	1	−9.30	(−18.26 to −0.34)	−9.16	(−21.59 to 2.98)
Flexibility exercise LD	–			5.07	(−12.93 to 23.41)
PT/BT sleep	–			**−11.68**	**(−20.34 to −3.11)**
Mind–body Ex AQ	1	2.05	(1.70 to 2.40)	2.02	(−6.29 to 10.45)
Mixed exercise AQ	–			1.51	(−7.50 to 10.66)
Weight loss	–			−3.75	(−13.74 to 6.21)
Neuromodulation	2	0.10	(−11.50 to 11.71)	0.37	(−8.82 to 9.53)
Non-mainstream practice	1	−5.10	(−12.30 to 2.10)	−6.20	(−15.49 to 3.18)
Hyperbaric oxygen therapy	–			**−26.29**	**(−37.56 to −15.15)**
Aerobic exercise LD + flexibility exercise LD	–			**−19.91**	**(−34.89 to −4.94)**
PT/BT generic + relaxation	–			**−12.07**	**(−20.75 to −3.35)**
Multidisciplinary	–			**−17.31**	**(−28.38 to −6.29)**
Flexibility exercise LD + Manual T	–			−0.32	(−26.12 to 25.78)
Balneotherapy + mixed exercise AQ	–			−5.75	(−18.97 to 7.71)
Tricyclics	–			−10.63	(−27.49 to 6.09)
AP	1	−6.80	(−16.31 to 2.71)	−6.63	(−19.43 to 6.12)
Antioxidant	1	−18.20	(−33.15 to −3.25)	**−17.75**	**(−34.91 to −0.61)**
SRI	3	−10.16	(−14.84 to −5.47)	**−9.85**	**(−15.80 to −3.80)**
Iron replacement	1	−15.30	(−27.94 to −2.66)	**−15.10**	**(−30.41 to −0.06)**
Gabapentinoid	5	−3.63	(−6.37 to −0.90)	−3.86	(−8.18 to 0.40)
Analgesic	1	−3.27	(−3.78 to −2.76)	−3.29	(−11.68 to 5.19)
CNS depressants	4	−9.44	(−12.38 to −6.51)	**−8.83**	**(−14.77 to −2.74)**

AQ, aquatic; LD, land-based; MD, mean difference.

Notes

Values in bold indicate significant NMA results. Higher scores indicate a worse outcome. Between-study SD 4.3 (95% CrI 3.0 to 5.0).

of life (although the width of the CrIs indicates considerable uncertainty). It is worth noting that for some intervention comparisons (generic PT/BT therapy compared with placebo/sham, and sleep-focused PT/BT compared with education or UC), the node-splitting analysis showed significant disagreement (inconsistency) between direct and indirect estimates. See *Appendix 6*, *Table 22* for further details.

36-Item short form survey mental component summary score

Of the 17 studies that reported SF-36 mental component summary (MCS) scores, 15 (*n* = 359, 13 interventions) were included in the analysis while 2 were excluded as they did not form any link in the network. Results are presented below and in *Report Supplementary Material 7*. *Appendix 5*, *Table 20* shows the number of participants included in each intervention. *Figure 5* shows the network for SF-36 MCS score; placebo/sham and UC were the most common comparators.

The direct and indirect comparisons for the included interventions compared with placebo/sham (*n* = 1167) are shown in *Table 5* (see *Report Supplementary Material 7* for all other comparisons; pairwise comparisons are available on request). Land-based Mind–body Ex (*n* = 281, MD 7.27, 1,11 to 13.94) and education (*n* = 22, MD 10.31, CrI 2.06 to 19.35) were associated with an improvement in SF-36 MCS score compared with placebo/sham. In contrast, there was evidence that SF-36 MCS scores were worse after nutrition (*n* = 36) than after placebo/sham (*n* = 1167, MD −7.96, CrI −14.83 to −1.11) but no clear evidence that SF-36 MCS scores were worse after UC and Electro T than after placebo/sham. The remaining interventions showed no clear evidence of a positive effect when compared with placebo/sham. There was no need to check the inconsistency between direct and indirect estimates, as the only two closed loops in the network were from a three-arm trial with direct comparisons between arms.

36-Item short form survey physical component summary score

Of the 17 studies that reported SF-36 physical component summary (PCS) scores, 16 (total number of participants = 401, total number of interventions = 13) were included in the analysis and one was excluded as it did form any link. Results

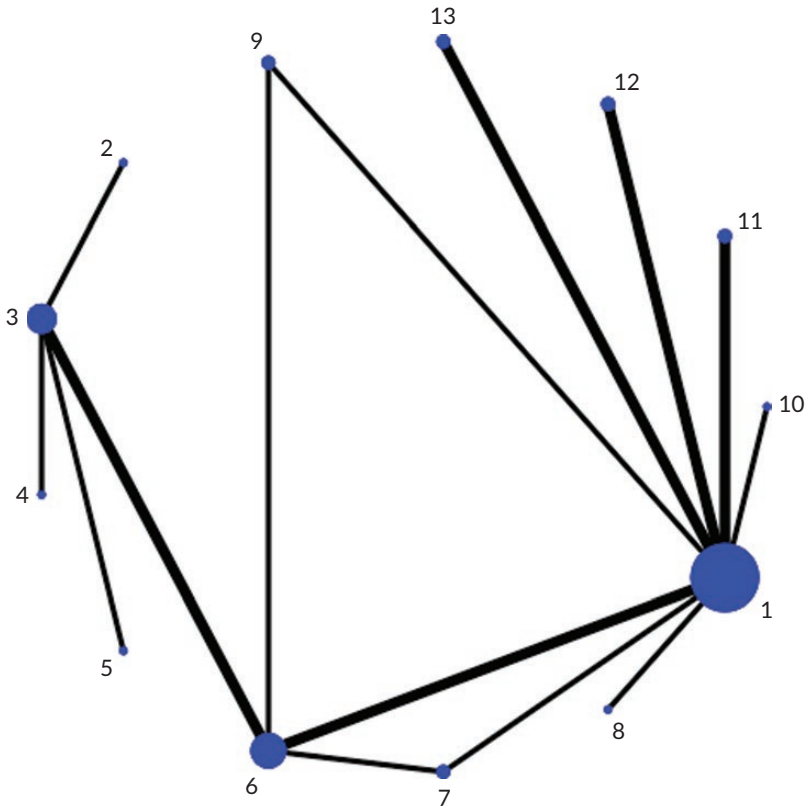

FIGURE 5 Network diagram for 36-item short form survey MCS score. 1, placebo/sham; 2, education + flexibility exercise LD; 3, Mind–body Ex LD; 4, aerobic exercise LD; 5, education; 6, UC; 7, nutrition; 8, electro T; 9, non-mainstream practice; 10, antioxidant; 11, SRI; 12, gabapentinoid; 13, CNS depressants. LD, land-based. Note: circle size represents the number of randomised participants; line width represents the number of direct comparisons.

TABLE 5 Results for direct comparison and NMA compared to placebo/sham for SF-36 MCS score

	Direct evidence			NMA	
Treatment	**Number of trials**	**MD**	**95% CI**	**MD**	**95% CrI**
Education + flexibility exercise LD	–			1.27	(−7.30 to 10.30)
Mind–body Ex LD	–			**7.27**	**(1.11 to 13.94)**
Aerobic exercise LD	–			4.23	(−3.49 to 12.33)
Education	–			**10.32**	**(2.06 to 19.35)**
UC	2	−0.39	(−5.34 to 4.57)	−0.46	(−5.22 to 4.36)
Nutrition	1	−7.79	(−16.17 to 0.59)	−7.96	(−14.83 to −1.11)
Electro T	1	−0.80	(−3.77 to 2.17)	−0.78	(−5.26 to 3.62)
Non-mainstream practice	1	3.70	(−1.91 to 9.31)	3.84	(−1.68 to 9.22)
Antioxidant	1	7.20	(−0.83 to 15.23)	7.27	(−1.68 to 15.62)
SRI	2	1.68	(0.60 to 2.75)	1.79	(−0.84 to 4.62)
Gabapentinoid	2	0.82	(−1.12 to 2.77)	0.87	(−2.22 to 4.11)
CNS depressants	2	0.98	(−0.89 to 2.84)	1.09	(−1.80 to 4.22)

LD, land-based; MD, mean difference.

Notes
Values in bold indicate significant NMA results. Negative values indicate worse outcomes while positive values indicate better outcomes. Between-study SD 1.0 (95% CrI 0.0 to 3.9).
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are presented below and in *Report Supplementary Material 8*. *Appendix 5*, *Table 20* shows the number of participants included in each intervention. *Figure 6* shows the network plot for SF-36 PCS score; placebo/sham and UC were the most common comparators.

The direct and indirect comparisons for the included interventions compared with placebo/sham are shown in *Table 6* (see *Report Supplementary Material 8* for all other comparisons; pairwise comparisons are available on request). Compared with placebo/sham (n = 1355), a better SF-36 PCS score was recorded after land-based Mind–body Ex training (n = 281) (MD 7.61, 3.56 to 13.06), land-based aerobic exercise training (n = 75, MD 6.17, CrI 1.05 to 12.81) and use of CNS depressants (n = 874, MD 2.93, CrI 1.10 to 4.79). There was insufficient evidence that Electro T (n = 20) had a positive effect on the SF-36 PCS score compared with placebo/sham (MD −0.82, CrI −4.13 to 3.97) and there was no clear evidence that the effects of the remaining interventions were different from those of placebo/sham. There was no need to check for the presence of inconsistency between direct and indirect estimates as the only two closed loops in the network were from a single three-arm trial.

Sleep duration and efficiency

Sleep duration was reported in two studies (total number of participants = 363, total number of interventions = 3). Results are presented below and in *Report Supplementary Material 6*. *Figure 7* shows the network. There was insufficient evidence that gabapentinoid (n = 169) increased sleep duration compared to placebo/sham (n = 179) (MD 7.40, CrI −9.84 to 24.74), while SRI (n = 15) appeared to be detrimental to sleep duration compared to placebo/sham (n = 179) (MD −24.40, CrI −59.81 to 21.96) (see *Report Supplementary Material 9*, for further details).

Insufficient data meant that we were only able to perform a pairwise meta-analysis for sleep efficiency. Results are available on request.

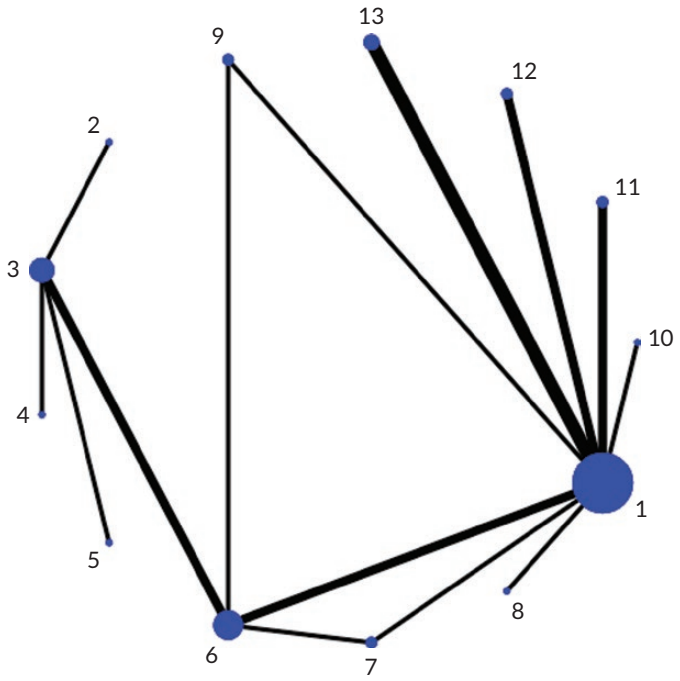

FIGURE 6 Network diagram for 36-item short form survey PCS score. 1, placebo/sham; 2, education + flexibility exercise LD; 3, Mind–body Ex LD; 4, aerobic exercise LD; 5, education; 6, UC; 7, nutrition; 8, electro T; 9, non-mainstream practice; 10, antioxidant; 11, SRI; 12, gabapentinoid; 13, CNS depressants. LD, land-based. Note: circle size represents the number of randomised participants; line width represents the number of direct comparisons.

TABLE 6 Results for direct comparison and NMA compared to placebo/sham for SF-36 PCS score

	Direct evidence			NMA	
Treatment	**Number of trials**	**MD**	**95% CI**	**MD**	**95% CrI**
Education + flexibility exercise LD	–			0.59	(−5.42 to 7.95)
Mind–body Ex LD	–			**7.61**	**(3.56 to 13.06)**
Aerobic exercise LD	–			**6.17**	**(1.05 to 12.81)**
Education	–			3.29	(−3.10 to 11.04)
UC	2	0.62	(−2.68 to 3.91)	0.68	(−2.48 to 3.87)
Nutrition	1	0.83	(−4.71 to 6.37)	0.82	(−4.02 to 5.43)
Electro T	1	−0.10	(−3.23 to 3.03)	−0.08	(−4.13 to 3.97)
Non-mainstream practice	1	1.60	(−2.60 to 5.80)	1.73	(−2.45 to 5.75)
Antioxidant	1	5.10	(0.17 to 10.03)	5.00	(−0.43 to 10.80)
SRI	2	1.59	(0.13 to 3.06)	1.50	(−0.45 to 3.79)
Gabapentinoid	2	0.12	(−1.27 to 1.51)	0.10	(−2.32 to 2.51)
CNS depressants	3	2.95	(1.90 to 4.01)	**2.93**	**(1.10 to 4.79)**

LD, land-based; MD, mean difference.

Notes
Negative values indicate a worse outcome while positive values indicate a better outcome. Values in bold indicate significant NMA results. Between-study SD 0.7 (95% CrI 0.0 to 2.5).

Ranking of interventions

Surface under the cumulative ranking curve and rank of the interventions for sleep (see *Report Supplementary Material 4*), FIQ (see *Report Supplementary Material 6*), SF-36 MCS score (see *Report Supplementary Material 7*), SF-36 PCS score (see *Report Supplementary Material 8*) and sleep duration (see *Report Supplementary Material 6*) are summarised in *Report Supplementary Material 10*. For both sleep and FIQ, hyperbaric oxygen therapy and land-based aerobic + flexibility exercise training were ranked as the top two (these were not evaluated for SF-36). However, it is important to note that SUCRA does not consider the magnitude of differences in effects between interventions, as well as the body and quality of evidence that contributes to each treatment comparison. Moreover, between the five considered outcomes, we observed some inconsistencies. For example, antioxidant and land-based Mind–body Ex were ranked low for sleep but not for FIQ.

Non-pharmacological interventions: sensitivity analyses

We conducted sensitivity analyses by removing pharmacological interventions from the main analyses. These sensitivity analyses were only relevant for the following outcomes: sleep (see *Report Supplementary Material 1*), FIQ (see *Report Supplementary Material 3*) and SF-36 MCS and PCS score (see *Report Supplementary Materials 4* and *5*). Apart from only minor differences, the results of the sensitivity analyses were similar to those of the main analyses that combined pharmacological and non-pharmacological interventions. For the ranking of the non-pharmacological interventions (see *Report Supplementary Material 7*), there were some minor changes.

Adverse events

For the studies eligible for the inclusion of the NMA on sleep, data for common AEs reported by ≥ 10% of participants and SAEs are reported in *Tables 7* and *8*. Overall, the AE data were reported by two studies which assessed non-pharmacological interventions,[75,77] and 18 studies which assessed pharmacological interventions.[116,118–124,126,129,132,133,135–137,139,140,207] Due to the presence of heterogeneity across included studies, AEs are summarised narratively and not combined in a meta-analysis.

Common adverse events in non-pharmacological studies

Two non-pharmacological studies reported common AE data. The first of these studies, conducted by Samartin-Veiga and colleagues (2021), compared three types of active tDCS treatment [M1, dorsolateral prefrontal cortex (DLPFC) and operculo-insular cortex (OIC)] with sham treatment.[75] Apart from burning, which was experienced by an equal proportion of participants in the sham and tDCS arms (28% in each treatment arm), more people experienced tickling and itching in the sham arm than in the three combined tDCS treatment arms: 56% versus 43% and 52% versus 46%, respectively. In the study by Mirzaei and colleagues (2018), more people experience dizziness in the vitamin D 50,000

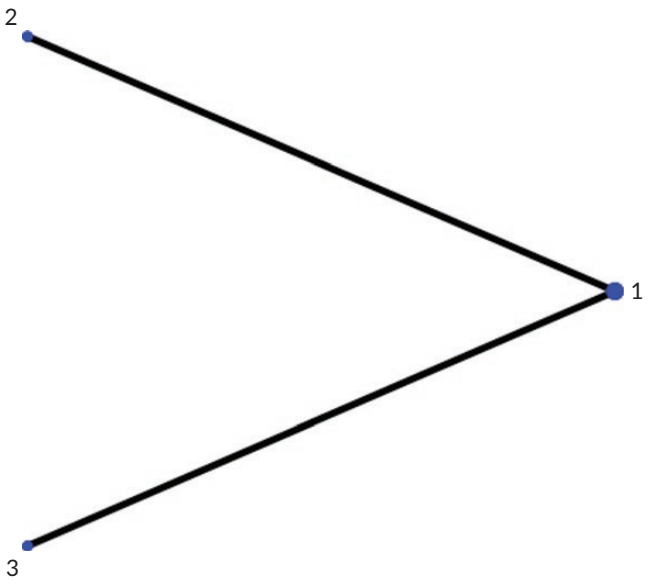

FIGURE 7 Network diagram for sleep duration. 1, placebo; 2, SRI; 3, gabapentinoid.

TABLE 7 Common AEs reported by ≥ 10 % of the participants in studies eligible for the NMA on sleep

	Intervention category 1	Intervention category 2	Intervention category 3	Intervention category 4	Outcome at the end of intervention period or at first assessment if later	Intervention 1 *n*/*N* (%)	Intervention 2 *n*/*N* (%)	Intervention 3 *n*/*N* (%)	Intervention 4 *n*/*N* (%)
Non-pharmacological intervention									
Samartin-Veiga 2021[75] Ref ID 1787	PBO/Sham	Neuromodulation (M1-tDCS)	Neuromodulation (DLPFC-tDCS)	Neuromodulation (OIC-tDCS)	Tickling – AE attributed to tDCS	14/25 (56)	35/82 (43)	–	–
					Itching – AE attributed to tDCS	13/25 (52)	38/82 (46)	–	–
					Burning – AE attributed to tDCS	7/25 (28)	23/82 (28)	–	–
Mirzaei 2018[77] Ref ID 1967	PBO/ Sham + SSRI	Vitamin D + SSRI	–	–	Dizziness	1/37 (3)	5/37 (14)	–	–
Pharmacological intervention									
Potvin 2012[116] Ref ID 230	PBO/Sham	AP	–	–	Dry mouth	NR	14/20 (70)	–	–
					Headache/migraine	12/24 (50)	13/20 (65)	–	–
					Dizziness	9/24 (38)	8/20 (40)	–	–
					Constipation	7/24 (29)	7/20 (35)	–	–
					Somnolence	11/24 (46)	16/20 (80)	–	–
					Nausea	11/24 (46)	NR	–	–
					Agitated sleep	9/24 (28)	NR	–	–
					Mood change	8/24 (33)	NR	–	–
					Fatigue	7/24 (29)	NR	–	–
					Irritability	7/24 (29)	NR	–	–
Arnold 2020[136] Ref ID 2315	PBO/Sham	Analgesic (ASP0819)	–	–	Headache – TEAE	11/94 (12)	12/90 (13)	–	–

TABLE 7 Common AEs reported by ≥ 10 % of the participants in studies eligible for the NMA on sleep (*continued*)

	Intervention category 1	Intervention category 2	Intervention category 3	Intervention category 4	Outcome at the end of intervention period or at first assessment if later	Intervention 1 *n*/*N* (%)	Intervention 2 *n*/*N* (%)	Intervention 3 *n*/*N* (%)	Intervention 4 *n*/*N* (%)
Reuter 2010[118] Ref ID 310	PBO/Sham	CNS depressant	–	–	Headache	7/12 (58)	4/11 (36)	–	–
					Grippal infection	6/12 (50)	2/11 (18)	–	–
					Sweating	0/12 (0)	4/11 (36)	–	–
Russell 2011[133] Ref ID 228	PBO/Sham	CNS depressant (SXB 4.5 g)	CNS depressant (SXB 6 g)	–	Headache	20/183 (11)	27/182 (15)	42/183 (23)	–
					Nausea	10/183 (5)	26/182 (14)	39/183 (21)	–
					Dizziness	5/183 (3)	24/182 (13)	31/183 (17)	–
					Vomiting	7/183 (4)	8/182 (4)	19/183 (10)	–
Spaeth 2012[132] Ref ID 122	PBO/Sham	CNS depressant (SXB 4.5 g)	CNS depressant (SXB 6 g)	–	Nausea	16/188 (9)	37/194 (19)	40/189 (21)	–
					Dizziness	3/188 (2)	23/194 (12)	25/189 (13)	–
Arnold 2007[121] Ref ID 377	PBO/Sham		–	–	Headache – TEAE	16/75 (21)	20/75 (27)	–	–
					Dizziness – TEAE	7/75 (9)	19/75 (25)	–	–
					Sedation – TEAE	3/75 (4)	18/75 (24)	–	–
					Nausea – TEAE	16/75 (21)	16/75 (21)	–	–
					Somnolence – TEAE	6/75 (8)	14/75 (19)	–	–
					Oedema – TEAE	6/75 (8)	12/75 (16)	–	–
					Light headedness – TEAE	1/75 (1)	11/75 (15)	–	–
					Insomnia – TEAE	6/75 (8)	9/75 (12)	–	–
					Diarrhoea – TEAE	5/75 (7)	8/75 (11)	–	–
					Pharyngitis – TEAE	11/75 (15)	7/75 (9)	–	–
					Cold virus – TEAE	11/75 (15)	5/75 (7)	–	–

continued

TABLE 7 Common AEs reported by ≥ 10 % of the participants in studies eligible for the NMA on sleep (*continued*)

	Intervention category 1	Intervention category 2	Intervention category 3	Intervention category 4	Outcome at the end of intervention period or at first assessment if later	Intervention 1 *n*/*N* (%)	Intervention 2 *n*/*N* (%)	Intervention 3 *n*/*N* (%)	Intervention 4 *n*/*N* (%)
Arnold 2008[122] Ref ID 368	PBO/Sham	Gabapentinoid (300 mg/day)	Gabapentinoid (450 mg/day)	Gabapentinoid (600 mg/day)	Dizziness – TEAE	14/184 (8)	51/183 (28)	71/190 (37)	79/188 (42)
					Somnolence – TEAE	7/184 (4)	23/183 (13)	37/190 (19)	41/188 (22)
					Weight increased – TEAE	4/184 (2)	22/183 (12)	24/190 (13)	26/188 (14)
					Headache – TEAE	19/184 (10)	14/183 (8)	24/190 (13)	14/188 (7)
					Peripheral oedema – TEAE	5/184 (3)	12/183 (7)	12/190 (6)	23/188 (12)
					Vision blurred – TEAE	1/184 (0.5)	7/183 (4)	13/190 (7)	22/188 (12)
					Constipation – TEAE	7/184 (4)	5/183 (3)	14/190 (7)	19/188 (10)
Arnold 2014[122] Ref ID 146	PBO/Sham	Gabapentinoid	–	–	Dizziness	12/58 (21)	13/63 (21)	–	–
					Somnolence	6/58 (10)	6/63 (10)	–	–
					Peripheral oedema	5/58 (9)	11/63 (17)	–	–
					Dry mouth	6/58 (10)	3/63 (5)	–	–
					Insomnia	1/58 (2)	7/63 (11)	–	–
Crofford 2005[139] Ref ID 260	PBO/Sham	Gabapentinoid (150 mg/day)	Gabapentinoid (300 mg/day)	Gabapentinoid (450 mg/day)	Dizziness	14/131 (11)	30/132 (23)	42/134 (31)	65/132 (49)
					Somnolence	6/131 (5)	21/132 (16)	37/134 (28)	37/132 (28)
					Headache – TEAE	25/131 (19)	16/132 (12)	20/134 (15)	17/132 (13)
					Dry mouth – TEAE	2/131 (2)	9/132 (7)	8/134 (6)	17/132 (13)
					Peripheral oedema – TEAE	1/131 (1)	7/132 (5)	9/134 (7)	14/132 (11)
					Infection – TEAE	22/131 (17)	11/132 (8)	13/134 (10)	13/132 (10)
Mease 2008[140] Ref ID 2539	PBO/Sham	Gabapentinoid (300 mg/day)	Gabapentinoid (450 mg/day)	Gabapentinoid (600 mg/day)	Dizziness – TEAE	16/190 (8)	60/185 (32)	80/183 (44)	88/190 (46)
					Somnolence – TEAE	10/190 (5)	39/185 (21)	44/183 (24)	53/190 (28)
					Weight gain – TEAE	5/190 (3)	15/185 (8)	16/183 (9)	26/190 (14)
					Dry mouth – TEAE	4/190 (2)	14/185 (8)	19/183 (10)	20/190 (11)
					Nausea – TEAE	11/190 (6)	9/185 (5)	8/183 (4)	20/190 (11)

TABLE 7 Common AEs reported by ≥ 10 % of the participants in studies eligible for the NMA on sleep (*continued*)

	Intervention category 1	Intervention category 2	Intervention category 3	Intervention category 4	Outcome at the end of intervention period or at first assessment if later	Intervention 1 *n*/*N* (%)	Intervention 2 *n*/*N* (%)	Intervention 3 *n*/*N* (%)	Intervention 4 *n*/*N* (%)
Ohta 2012[123] Ref ID 222	PBO/Sham	Gabapentinoid	–	–	Somnolence	45/248 (18)	116/250 (46)	–	–
					Dizziness	15/248 (6)	74/250 (30)	–	–
					Nasopharyngitis	45/248 (18)	45/250 (18)	–	–
					Increased weight	9/248 (4)	39/250 (16)	–	–
					Constipation	17/248 (7)	36/250 (14)	–	–
Pauer 2011[137] Ref ID 148	PBO/Sham	Gabapentinoid (300 mg/day)	Gabapentinoid (450 mg/day)	Gabapentinoid (600 mg/day)	Dizziness	28/184 (15)	68/184 (37)	76/182 (42)	93/186 (50)
					Somnolence	11/184 (6)	37/184 (21)	24/182 (13)	34/186 (18)
					Peripheral oedema	7/184 (4)	19/184 (10)	15/182 (8)	27/186 (15)
					Weight increase	6/184 (3)	24/184 (13)	24/182 (13)	24/186 (13)
					Dry mouth	4/184 (2)	16/184 (9)	20/182 (11)	20/186 (11)
					Fatigue	15/184 (8)	14/184 (8)	26/182 (14)	17/186 (9)
					Headache	30/184 (16)	27/184 (15)	25/182 (14)	16/186 (9)
					Nausea	20/184 (11)	22/184 (12)	6/182 (3)	12/186 (6)
Zhang 2021[207] Ref ID 2316	PBO/Sham	Gabapentinoid	–	–	Dizziness	30/164 (18)	71/170 (42)	–	–
					Somnolence	13/164 (8)	30/170 (18)	–	–
Boomershine 2018[126] Ref ID 626	PBO/Sham	Iron replacement	–	–	Flushing – TEAE	0/40 (0)	6/41 (15)	–	–
Branco 2010[129] Ref ID 1522	PBO/Sham	SRI	–	–	Nausea	50/446 (11)	112/431 (26)	–	–
					Hyperhidrosis	13/446 (3)	102/431 (24)	–	–
					Headache	55/446 (12)	73/431 (17)	–	–
					Constipation	10/446 (2)	54/431 (13)	–	–
					Dizziness	34/446 (8)	44/431 (10)	–	–

continued

TABLE 7 Common AEs reported by ≥ 10 % of the participants in studies eligible for the NMA on sleep (*continued*)

	Intervention category 1	Intervention category 2	Intervention category 3	Intervention category 4	Outcome at the end of intervention period or at first assessment if later	Intervention 1 *n*/*N* (%)	Intervention 2 *n*/*N* (%)	Intervention 3 *n*/*N* (%)	Intervention 4 *n*/*N* (%)
Yeephu 2013[135] Ref ID 340	PBO/Sham	TeCAs (15 mg)	TeCAs (30 mg)	–	Somnolence	9/13 (69)	9/13 (69)	12/14 (86)	–
					Increased appetite	3/13 (23)	9/13 (69)	12/14 (86)	–
					Dry mouth	8/13 (62)	12/13 (92)	10/14 (71)	–
					Weight gain	1/13 (8)	3/13 (23)	9/14 (64)	–
					Fatigue	7/13 (54)	5/13 (38)	8/14 (57)	–
					Dizziness	6/13 (46)	6/13 (46)	6/14 (43)	–
					Postural hypotension	5/13 (38)	3/13 (23)	3/14 (21)	–
					Flu-like symptoms	3/13 (23)	4/13 (31)	3/14 (21)	–
					Palpitation	3/13 (23)	2/13 (15)	3/14 (21)	–
					Constipation	4/13 (31)	7/13 (54)	2/14 (14)	–
Calandre 2014[119] Ref ID 253	Tricyclics	AP	–	–	Dry mouth	28/45 (62)	14/45 (31)	–	–
					Nausea/vomiting	8/45 (18)	6/45 (13)	–	–
					Constipation	13/45 (29)	8/45 (18)	–	–
					Increased appetite	6/45 (13)	3/45 (7)	–	–
					Increased weight	7/45 (16)	5/45 (11)	–	–
					Dizziness	12/45 (27)	17/45 (38)	–	–
					Somnolence	13/45 (29)	15/45 (33)	–	–
					Anxiety	4/45 (9)	8/45 (18)	–	–
					Nightmares	7/45 (16)	4/45 (9)	–	–
					Hypoesthesia	1/45 (2)	5/45 (11)	–	–
					Headache	11/45 (24)	4/45 (9)	–	–
					Palpitations	8/45 (18)	2/45 (4)	–	–
					Tachycardia	6/45 (13)	2/45 (4)	–	–
					Tinnitus	5/45 (11)	0/45 (0)	–	–

TABLE 7 Common AEs reported by ≥ 10 % of the participants in studies eligible for the NMA on sleep (*continued*)

	Intervention category 1	Intervention category 2	Intervention category 3	Intervention category 4	Outcome at the end of intervention period or at first assessment if later	Intervention 1 *n*/*N* (%)	Intervention 2 *n*/*N* (%)	Intervention 3 *n*/*N* (%)	Intervention 4 *n*/*N* (%)
de Zanette 2014[120] Ref ID 370	Tricyclics + PBO/ Sham	Endogenous hormone + PBO/ Sham	Endogenous hormone + tricyclics	–	Minor side effects (nausea, mild dizziness, weight gain, dry mouth and mild headache)	8/21 (38)	5/21 (24)	3/21 (14)	–
					Major side effects (severe dizziness, vivid nightmares, crippling drowsiness, severe headache, behavioural changes and pain worsening)	5/21 (24)	5/21 (24)	6/21 (29)	–

AE, adverse event; NR, not reported; SXB, sodium oxybate; TEAE, treatment-emergent adverse event; TeCAs, tetracyclic antidepressants; w, weeks.

TABLE 8 Serious AEs reported in studies eligible for the NMA on sleep

	Intervention category 1	Intervention category 2	Intervention category 3	Intervention category 4	Outcome at the end of intervention period or at first assessment if later	Intervention 1 *n*/*N* (%)	Intervention 2 *n*/*N* (%)	Intervention 3 *n*/*N* (%)	Intervention 4 *n*/*N* (%)
Non-pharmacological intervention									
Lauche 2016[57] Ref ID 217	UC	PBO/Sham	Non-MSM practice (cupping therapy)		Serious AE (1 with a torn meniscus; 1 with persistent pain after spinal operation; 1 had the flu)	0/46 (0)	3/48 (6)	0/47 (0)	–
Maindet 2021[51] Ref ID 704	UC	Balneotherapy	–	–	Serious AE (In the intervention group 11 patients reported 13 SAEs, and in the control group 14 patients reported 20 SAEs. In the intervention group, 6 were fibromyalgia-related, 3 related to another pathology, 2 were trauma-related, and 2 were surgery-related. In the control group, 8 SAEs were fibromyalgia-related, 5 were surgery-related, 4 related to another pathology and 3 were trauma-related)	14/108 (13)	11/110 (10)	–	–
Pharmacological interventions									
Russell 2011[133] Ref ID 228	PBO/Sham	CNS depressant (SXB 4.5 g)	CNS depressant (SXB 6 g)	–	Serious AE related to medication (sleep paralysis)	0/183 (0)	0/182 (0)	1/183 (0.5)	–
Zhang 2021[207] Ref ID 2316	PBO/Sham	Gabapentinoid	–	–	Serious AE (life-threatening, resulted in hospitalisation/incapacity or death); 2 were considered to be treatment-related (atrial tachycardia in a 71-year-old female that was not resolved by end of study; cerebral haemorrhage in a 55-year-old female that resolved without sequelae)	9/164 (5)	0/170 (0)	–	–
Arnold 2014[122] Ref ID 146	PBO/Sham	Gabapentinoid	–	–	Serious AE (vertigo, breast cancer; both considered unrelated to study drug)	0/58 (0)	2/63 (3)	–	–

TABLE 8 Serious AEs reported in studies eligible for the NMA on sleep (*continued*)

	Intervention category 1	Intervention category 2	Intervention category 3	Intervention category 4	Outcome at the end of intervention period or at first assessment if later	Intervention 1 *n*/*N* (%)	Intervention 2 *n*/*N* (%)	Intervention 3 *n*/*N* (%)	Intervention 4 *n*/*N* (%)
Pauer 2011[137] Ref ID 148	PBO/Sham	Gabapentinoid (300 mg/day)	Gabapentinoid (450 mg/day)	Gabapentinoid (600 mg/day)	Serious AE (only 1 SAE, an incidence of chest pain in a patient in the 450 mg/day pregabalin group, was considered by the investigator to be related to treatment and the patient was withdrawn from the study)	4/184 (2)	2/184 (1)	8/182 (4)	4/186 (2)
Ohta 2012[123] Ref ID 222	PBO/Sham	Gabapentinoid	–	–	Serious AE [1 from the placebo group (abnormal liver function test result) and 3 from the pregabalin group (breast cancer, viral gastroenteritis and musculoskeletal stiffness)]	1/248 (0.4)	3/250 (1)	–	–

AE, adverse event; Non-MSM practice, non-mainstream practice; Ref ID, reference ID; SXB, sodium oxybate.

IU (plus trazodone 25 mg) treatment arm than in the placebo (plus trazodone 25 mg) treatment arm: 14% versus 3% respectively.[77]

Common adverse events pharmacological studies

Eighteen pharmacological studies reported common AEs. A meaningful comparison across studies proved challenging as most studies assessed different doses of individual pharmacological therapies and included different control treatments. Eight studies compared either gabapentinoid versus placebo or different dose regimes.[121–124,137,139,140,207] Three studies compared CNS depressants [gamma-hydroxybutyric acid 25 mg/kg body weight[118] and sodium oxybate (SXB) 4.5 g and 6 g][132,133] with placebo. AP treatments were assessed in two studies: one assessed quetiapine versus placebo[116] and another quetiapine versus amitriptyline.[119] One study each compared the following treatments with placebo: analgesic (ASP0819):[136] iron replacement (ferric carboxymaltose 15 mg/kg up to 750 mg),[126] SRIs (milnacipran 200 mg/day)[129] and tetracyclic antidepressants (TeCAs) (mirtazapine 15 mg/day and 30 mg/day).[135] One study compared 10 mg melatonin alone or in combination with a tricyclic (amitriptyline 25 mg) with a tricyclic (amitriptyline 25 mg) alone.[120]

In general, a greater incidence of AEs was observed in participants receiving active treatments than PBO/Shams. Higher doses of active treatment were usually associated with higher numbers of people reporting an AE. In the original studies, the reporting of the AEs did not always specify whether they related to study treatment. Common AEs that were frequently reported across trials that evaluated gabapentinoid treatment included dizziness, drowsiness (somnolence), headache, weight gain, dry mouth and peripheral oedema. CNS depressants were often associated with headache, sweating, nausea and dizziness, and AP treatments with dry mouth, somnolence and dizziness. Frequently reported common AEs associated with the other active treatments included dry mouth, increased appetite, somnolence, dizziness, nausea, headache, hyperhidrosis, flushing and constipation.

Adverse events that were reported by a high proportion of participants included somnolence and dry mouth. The study conducted by Potvin and colleagues reported that 80% and 70% of the participants experienced somnolence and dry month, respectively, after AP treatment, while 46% of the participants receiving placebo manifested somnolence.[116] Similarly, in the study conducted by Yeephu and colleagues (2013) somnolence, increased appetite and dry mouth were reported by 86%, 86% and 71% of the participants treated with 30 mg/day mirtazapine, respectively.[135] In the placebo and 15 mg/day mirtazapine arms of this trial, somnolence was reported by 69% of participant in both arms, increased appetite was reported by 23% of participants receiving placebo and by 69% of participants treated with 15 mg/day mirtazapine, and dry mouth was reported by 62% of participants receiving placebo and by 92% of those treated with 15 mg/day mirtazapine.

Serious adverse events in non-pharmacological studies

Two non-pharmacological studies reported SAE data. These include three SAEs (one torn meniscus; one persistent pain after spinal operation; one flu episode) associated with the sham arm in the trial conducted by Lauche and colleagues (2016); no SAEs were reported in the other two treatment arms (UC and cupping therapy).[57] In the study conducted by Maindet and colleagues (2021), slightly more SAEs were reported in the UC arm [14/108 (13%)] than in the balneotherapy treatment arm [11/110 (10%)].[51] None of the SAEs were reported as being related to treatment by the study authors.

Serious adverse events in pharmacological studies

Five pharmacological studies reported SAEs.[122,123,133,137,207] Five studies compared gabapentinoids with placebo and one study CNS depressants with placebo. In the study conducted by Pauer and colleagues, incidence of chest pain and subsequent withdrawal of a participant who received 450 mg/day pregabalin was considered to be related to study treatment.[137] Other SAEs reported by participants treated with gabapentinoids included breast cancer,[122,123] vertigo,[122] viral gastroenteritis[123] and musculoskeletal stiffness.[123]

The study conducted by Zhang and colleagues (2021) documented one episode of atrial tachycardia and one case of cerebral haemorrhage in participants receiving placebo.[207] The authors report that atrial tachycardia occurred in a 71-year-old female that was not resolved by end of the study and cerebral haemorrhage occurred in a 55-year-old female that was resolved without residual symptoms. The authors did not report any further information about these SAEs.

Russell and colleagues (2011) recorded an episode of treatment-related sleep paralysis, which lasted 30 minutes and occurred 45 minutes after the participant's first exposure to the CNS depressant SXB (2.25 g).[133]

In brief, the type and frequency of both common and SAEs are in line with the known safety profiles of the active treatments reported by the included pharmacological studies.

Effectiveness outcomes – studies not eligible for the network meta-analysis

Sleep outcome

Results for sleep-related outcomes from the 78 studies not included in the meta-analysis are summarised narratively and presented in *Report Supplementary Material 11*.

Self-reported sleep quality was reported using a variety of measures: 29 studies used VAS or NRS,[144,151,155,156,162–186] 26 studies used a questionnaire[143,146,149,150,154,187–197,199,201–207,221] and 13 studies used a sleep subscale of a non-sleep-specific measure such as FIQ.[152,158,160,161,208–216]

Only nine of the VAS or NRS included a measure of 'sleep quality',[151,155,165,172,173,176,180,182,186] while most included measures related to sleep disturbance, sleep problem, sleep disorder, unrefreshed sleep or how pain affected sleep. The 24 studies reporting a VAS or NRS for non-pharmacological interventions all used different scales. Three of these studies comparing placebo/sham with PT/BT generic,[172] neuromodulation[165] and non-mainstream practice (non-MSM practice),[183] respectively, reported a statistically significant *p*-value (< 0.05), although it is not clear whether the differences were clinically important. Of the five studies reporting a VAS or NRS for pharmacological interventions, the results in one study were reported to be statistically significant, possibly favouring SERMs over placebo/sham, although the scale used in this study was not fully described.[185]

Among the 26 studies reporting sleep quality outcome using a questionnaire, the Insomnia Severity Index (ISI) was used by five studies[149,150,195,201,202] and the Post-Sleep Inventory by three studies,[189,196,197] while all other questionnaires used were reported by a single study. Of the 19 studies using a questionnaire for non-pharmacological interventions, 10 studies reported a statistically significant effect compared with PBO/Sham favouring strength LD,[150] education (sleep hygiene),[187] PT/BT generic (e.g. CBT),[187,192,195,201] Electro T,[188,191] neuromodulation,[190] phototherapy + mixed exercise training[193] and non-MSM practice,[154] although the difference between treatment groups was relatively small. Of the seven studies with a questionnaire focusing on pharmacological interventions, three studies reported a statistically significant effect favouring gabapentinoid over placebo/sham,[207] tricyclics over SSRI,[204] and combined SSRI and gabapentinoid over combination of SRIs and gabapentinoid or tricyclics and gabapentinoid,[206] respectively, although details of the questionnaires used were not fully reported.

Of the 13 studies that used a sleep subscale of a non-sleep-specific measure, 6 showed a statistically significant effect compared with PBO/Sham favouring multicomponent therapy,[208] Electro T,[209] neuromodulation,[160] non-MSM practice,[210] SRIs[215] and acetylcholine esterase inhibitor (pyridostigmine).[161]

Ten studies assessed sleep efficiency or sleep duration.[23,153,157,159,217–219] Two of these studies reporting sleep duration by a self-reported measure (sleep log) showed a statistically significant effect favouring mixed aquatic exercise training + aquatic Manual T over Manual T alone[217] and Manual T over relaxation/meditation.[218] No suitable data (presented according to treatment periods) were available from three crossover trials that measured sleep efficiency or sleep duration after pharmacological interventions.[145,147,148]

Adverse events

For the studies not eligible for the inclusion in the NMA on sleep, common AEs (reported by ≥ 10% of participants) reported by 11 studies and SAEs reported by one study, are presented in *Report Supplementary Material 12*.

Common adverse events in non-pharmacological studies

Common AEs reported by ≥ 10% of participants were documented by three non-pharmacological studies,[160,195,211] comparing non-pharmacological interventions against UC, PBO/Sham. The active intervention categories included PT/BT generic (CBT),[195] neuromodulation [electroencephalography neuro-biofeedback,[211] and repetitive transcranial magnetic stimulation (rTMS)].[160] Compared with UC, more people receiving CBT experienced increased pain [4/70 (6%) vs. 9/70 (13%), respectively]. Compared with PBO/Sham, higher proportions of people treated with neuromodulation experienced AEs. Common AEs that were reported across studies included fatigue, tiredness, pain, sleep drowsiness or change in sleep patterns and stiffness or muscle spasms.

Common adverse events in pharmacological studies

Eight pharmacological studies reported common AEs. Seven studies focused on adults[147,185,186,204,214–216] and one study on adolescents aged 12 to 17 years.[155] The studies that enrolled an adult population compared the following active treatments with placebo or sham (single studies): gabapentinoids (pregabalin 300–450 mg/day),[147] opioid antagonist (naltrexone 4.5 mg/day),[186] serotonin receptor antagonist and dopamine receptor agonist (terguride 3 mg/day maximum),[216] SERMs (raloxifen, 60 mg every other day),[185] SRI [duloxetine 60 mg once daily (QD) or duloxetine 60 mg twice daily][215] and SSRI (citalopram 20–40 mg daily).[214] One study compared an SSRI (paroxetine 20 mg/day rising to 40 mg/day) with a tricyclic (amitriptyline 10 mg/day rising to 20 mg/day).[204] The study conducted among adolescents compared gabapentinoid treatment pregabalin (75–450 mg/day) with placebo.[155]

More people reported experiencing AEs in the active treatment arms than in the control arms. Frequently reported common AEs included nausea, headache, dizziness, dry mouth, constipation, diarrhoea and somnolence. In the study conducted by Capaci and Hepguler (2002) comparing paroxetine with amitriptyline, more participants in the amitriptyline arm experienced dry mouth, constipation and rash than those in the paroxetine arm.[204] AEs that occurred more frequently in the paroxetine arm included sleepiness, diarrhoea, nausea, dizziness and sexual dysfunction.

Serious adverse events

In general, few SAEs were reported by the authors of the individual studies. One study conducted by Arnold and colleagues (2016) comparing pregabalin (75–450 mg/day) with placebo in adolescents reported two SAEs, cholelithiasis and major depression, occurring in one participant treated with pregabalin.[155] No SAEs were reported among adolescents receiving placebo in this study.

In brief, the type and frequency of the common and SAEs are in line with the known safety profiles of the active treatments reported by the pharmacological studies.

Discussion

Summary of main results

This evidence synthesis included a total of 90 RCTs assessing sleep quality using PROMs validated for use in fibromyalgia patients, and a further 78 RCTs assessing other sleep-related outcome measures. To our knowledge, this evidence synthesis and NMA is the most comprehensive approach to assess the current evidence on pharmacological and non-pharmacological interventions for fibromyalgia-related sleep problems.

The 90 RCTs that provided sleep quality PROM data involved a total of 12,082 adult participants. Most studies were parallel-arm trials with a small sample size (median 70) and short follow-up (median 12 weeks). Five studies were crossover randomised trials. The included studies evaluated 45 active treatment categories (grouped by mode of action). The most commonly evaluated treatment categories were land-based Mind–body Ex training (e.g. Tai Chi) in 13 studies,[54,55,70,71,80,81,83–85,89,110,111,115] generic psychological and behavioural interventions, which were not targeted to address sleep problems (e.g. CBT, ACT, mindfulness) in 10 studies,[60–63,96,100–103,112] gabapentinoids (e.g. pregabalin) in 8 studies,[121–125,137,139,140] neuromodulation (e.g. tDCS) in 5 studies,[72,74–76,106] nutrition (e.g. food supplement) in 5 studies,[58,59,94,95,113] CNS depressants (e.g. SXB) in 4 studies,[118,131–134] SRIs (e.g. milnacipran) in 4 studies[127–129,134] and non-MSM practice (e.g. dry needling or electroacupuncture) in 4 in studies.[57,78,93,114] Most other intervention categories were assessed only in either a few or single trials.

Considering that the scope of this evidence synthesis was to assess the effects of current interventions for treating fibromyalgia-related sleep problems, we focused specifically on studies reporting sleep outcome data. We assessed study eligibility based on the description of any sleep outcome (defined either as primary or secondary outcome) in the title and abstract of citations identified by our search strategies regardless of whether it contained numerical results. Studies that did not mention sleep outcomes in their titles and abstracts were excluded. This allowed us to identify studies that had a prominent focus on fibromyalgia-related sleep problems but may have limited inclusion of studies that assessed other fibromyalgia symptoms which could interfere with sleep, or studies that did not find significant effects on sleep outcome. We conducted a check of a 10% random selection of the excluded studies and identified no studies that reported sleep outcome data that could have been included in the NMA. Due to resource constraints, a single review author carried out study selection, data extraction, and risk-of-bias assessment, which were subsequently checked by another review author.

The findings of our NMA, which included 65 studies assessing sleep using validated PROMs, show that, compared with PBO/Sham, some forms of exercise training such as land-based aerobic exercise training combined with flexibility exercise training, and aquatic aerobic exercise training may improve sleep, although our certainty in the current evidence, assessed using CINeMA, is generally low. For all other pharmacological and non-pharmacological interventions, there was only a modest positive effect on sleep compared with PBO/Sham (CrIs indicated uncertainty and the quality of evidence is low to very low). Notably, we did not observe a significant, beneficial effect of pharmacological interventions on sleep quality.

Furthermore, compared with PBO/Sham, some interventions positively affected participants' quality of life. Using the FIQ, an improvement in quality of life was observed among participants who undertook land-based aerobic and flexibility exercise training, multidisciplinary training, land-based Mind–body Ex training, either PT/BT generic or PT/BT tailored to sleep problems, generic PT/BT alongside relaxation, and pharmacological treatments including antioxidant, iron replacement, SRIs, and CNS depressants, although the magnitude of effect varied. An improvement in the SF-36 mental health component summary score was observed after land-based Mind–body Ex and education interventions, while an improvement in the SF-36 PCS score was observed after land-based Mind–body Ex training, land-based aerobic exercise training and use of CNS depressants.

In general, non-pharmacological treatments under investigation were reported to be reasonably well tolerated and AEs were usually reported to be of mild or moderate severity (e.g. stiffness, fatigue). For pharmacological treatments, commonly reported adverse effects included dizziness, somnolence, headache and dry mouth.

Strengths and limitations

To determine the impact of our findings on current clinical practice it is important to take into consideration the limitations of our NMAs. Overall, our analyses were hampered by the limitations of the current evidence base; specifically, the lack of head-to-head comparisons for active treatments. Most interventions were compared to either a placebo, sham or UC; however, the control treatments were often inadequate to test the study hypothesis (e.g. the choice of 'usual care/waiting list' as comparator treatment for hyperbaric oxygen therapy). We were also unable to include all studies identified by our search strategies in the NMA because some interventions were outliers or disconnected from other interventions in the network. Most of the studies that contributed to the network were small, with short-term follow-ups (around 3 months), and assessed a diverse range of interventions. The 90 studies that reported a PROM of sleep quality and were eligible for inclusion in the NMA assessed a total of 97 different active interventions. To make the NMA feasible, we grouped these active interventions into 45 categories. Specifically, among the 65 studies that contributed to the sleep quality NMA, 35 different treatment categories were considered but only a limited number of studies, usually of small sample size, were available for each treatment comparison. Most studies included fewer than 100 participants and some even fewer than 20 participants in the active treatment group. It is important to acknowledge that while interventions included in the same category were similar as we grouped them according to their characteristics and mode of action, inevitably they were not the same. It is also worth noting that many of the studies included in the NMA were conducted in the USA and Spain, with only three studies conducted in the UK.

While the diverse range of existing interventions may suggest that there is no one-size-fits-all approach for managing sleep problems in fibromyalgia, it hampers the possibility to reach any definite conclusion. The characteristics of exercise-based interventions varied considerably across studies in terms of intensity, frequency and duration, as well as description of the specific elements of the physical training/programme, making treatment comparisons very challenging and impossible to establish which exercise protocols or 'active ingredients' are more likely to be effective for the treatment of sleep problems in people with fibromyalgia. Moreover, there was variability in terms of mode of delivery, with some interventions delivered as 'group activity' and others at an individual level. We were also only able to analyse average treatment effects and not relevant clinical and demographic modifiers at the patient level (e.g. severity of disease, duration of illness, lifestyle, extent and nature of sleep disturbances, and level of physical activity before and during treatment). It is also worth noting that while pharmacological interventions were usually assessed against placebo, non-pharmacological interventions were compared with control interventions in very different ways in the included studies. Some of the included non-pharmacological studies failed to compare their active interventions to sham procedures that involved appropriate control strategies in terms of exposure time (frequency and duration) and 'attention' received by the therapist/instructor. Appropriate sham controls have been used in similar clinical areas and are considered particularly useful for studies with subjective or self-reported end points (e.g. improvement of symptoms) and when the risk of the sham procedures is low (e.g. less intensive, or generic physical activity/procedure).[222,223] Furthermore, the recent CoPPS Statement on the development, implementation and reporting of control interventions in efficacy trials of physical, psychological and self-management therapies recommends designing control interventions that are as similar as possible to the interventions under investigation, apart from the components whose effect the trials aim to study.[224] The use of inadequate controls (e.g. no intervention, UC) may result in an exaggeration of effect estimates or produce misleading results and often is methodologically inadequate to test the study hypothesis. Therefore, the diverse characteristics of both active and control interventions across included studies as well as the intrinsic limitations of the design of most studies included in the NMA (no adequate control treatments, small sample size, short duration) may explain differences with respect to the effects of interventions and the incoherence we observed between some direct and indirect estimates of effects.

Moreover, our primary outcome, sleep quality, was not measured consistently across included studies; several different PROMs were used (i.e. PSQI, MOS-SS, JSS, FMSD, SQ-NRS as well as single-item VAS/NRS measuring a similar sleep quality construct to that of the SQ-NRS). As there is no consensus on which is the best outcome measure to use in the field of fibromyalgia, we decided to combine studies irrespective of the way sleep quality was measured provided that a validated instrument was used. This again might have contributed to increasing heterogeneity and inconsistency in the network and limited the reliability of our findings. Furthermore, for some outcome measures that assessed sleep quality, the interpretation of results was complicated by the fact that we did not find reliable information on what can be considered a minimally important clinical difference.

According to CINeMA, for many comparisons included in our NMA, our certainty of the evidence was rated as low to very low. The level of certainty was downgraded primarily due to within-study bias, imprecision, heterogeneity and incoherence. For within-study bias, most studies were judged to be at an overall high risk of bias mostly due to an inadequate reporting of randomisation and allocation concealment methods as well as issues related to missing outcome data. For studies evaluating non-pharmacological treatments, blinding of participants and personnel is particularly challenging due to the nature of interventions. However, unblinded patients who undergo a specific procedure/treatment may have higher expectations about improvement while, in contrast, those who are aware of receiving no intervention, a different control intervention or UC may have much lower expectations or a nocebo response. These higher and lower expectations can influence outcome measurement, especially when symptoms are subjective, self-reported and susceptible to changes. The certainty level was downgraded for imprecision because of the low number of studies available for each comparison and their small sample size. Moreover, heterogeneity and incoherence across comparisons also yielded a downgrading in the level of certainty. Given our CINeMA findings, we were unable to conduct sensitivity analyses restricted to high-quality studies.

The SUCRA approach is the most common method for ranking NMA results and identifies the 'best' and 'worst' treatment in terms of the probability of success for each analysed outcome. However, given the low and very low quality of the evidence included in our NMA and the small amount of available evidence for most comparisons, the results of our SUCRA ranking may generate misleading and unreliable inferences and, therefore, we have little

confidence in them. Moreover, it is worth stressing that one limitation of the SUCRA approach is that it does not consider the magnitude and precision of effect estimates.

The 78 trials which evaluated sleep outcomes using non-PROM instruments or tools, and therefore were not included in the NMA, involved a total of 5911 randomised participants (5804 adults and 107 adolescents). The reporting of sleep outcomes was not consistent across studies and various scales and questionnaires were used. Apart from the Insomnia Severity Index (ISI) reported in five studies[149,150,195,201,202] and the Post Sleep Inventory reported in three studies,[189,196,197] no other common outcome measures were assessed in the remaining studies. These studies presented the same limitations as those included in the NMA and even though we summarised their results, we could not draw any firm inferences about treatment effects.

It is also worth noting that in the included studies most participants were middle-aged women from high-income countries. Information on ethnicity and level of education was often not reported (NR). Therefore, our findings cannot be generalised to all people with fibromyalgia and different settings.

In brief, regarding the effects of interventions for the management of sleep problems in people with fibromyalgia, the current evidence base is very fragmented, with many diverse interventions often assessed by small, individual trials generally of poor quality. The considerable heterogeneity in terms of study design, characteristics of interventions and exercise/practice protocols hampers the possibility to draw firm conclusions. There is an indication that some interventions may produce positive effects on sleep or on quality of life in people with fibromyalgia. The beneficial effects of physical activity on health and well-being are well known and it makes sense to encourage fibromyalgia patients to follow healthy lifestyle recommendations. However, the limitations of the current evidence base preclude any specific recommendation in terms of optimal interventions for managing sleep problems. It is difficult to fathom why land-based aerobic training in combination with flexibility training may be effective but land-based aerobic training alone or flexibility training alone is not; similarly, it is difficult to understand why aquatic-based aerobic exercise training may be effective, but aquatic Mind–body Ex training and aquatic mixed exercise are not. It is also difficult to figure out why some pharmacological interventions may improve quality of life but not sleep. Our original plan was to conduct a component NMA to disentangle the effect of each component of the interventions assessed by the included studies, but this proved impossible due to the lack of suitable data.

There are several published systematic reviews assessing different forms of exercise training and other non-pharmacological interventions for the management of fibromyalgia symptoms.[225–228] Although their primary focus is not on sleep problems, they all point out similar limitations to those we have observed here, including the heterogeneity among included studies in terms of protocols, the insufficient evidence to establish the effectiveness of one intervention compared with another, the lack of proper comparator treatments, the lack of appropriate statistical power in most studies and the low-to-moderate quality of the evidence base. A systematic review conducted by Kundakci *et al.* in 2022, which aimed to evaluate the effectiveness of non-pharmacological treatments for fibromyalgia, revealed that all types of exercise, except for flexibility exercises, helped ease pain. Both mind–body and strengthening exercises were found to be helpful in reducing fatigue, while aerobic and strengthening exercises were found to be useful in improving sleep.[31] However, the authors identified only a limited number of studies usually of small sample sizes for each form of exercise (10 for aerobic exercise, 9 for strengthening and 2 for flexibility) and found considerable heterogeneity and high risk of bias among included studies. They also acknowledged that outcome measures, intervention programmes and control interventions varied considerably across studies, which is in line with our results. Findings for other types of interventions were found to be less convincing.

Chapter 3 Synthesis of qualitative and mixed-methods evidence evaluating the experiences and expectations of people who are treated for fibromyalgia-related sleep problems

Introduction

Value of mixed-methods qualitative studies and quantitative evidence syntheses

Historically, healthcare assessment and guideline development have been dominated by evidence syntheses that use quantitative methods with numerical data pooling.[229,230] As health care has evolved towards a patient-centred model involving complex, multifactorial shared decision-making between clinicians, patients, and their families, it is important to consider the perspectives and experiences of patients in healthcare evaluations.[231] Qualitative studies provide an in-depth understanding of the lived experiences of patients from a wide range of demographic and contextual backgrounds, including how patients experience symptoms related to their conditions and how their condition affects their daily lives and the lives of their family and friends, and those involved in their care. Qualitative studies can also provide an understanding of the acceptability of interventions for patients and the barriers and facilitators for intervention access and effectiveness.[230]

By combining quantitative and qualitative evidence syntheses in healthcare evaluations, clinical and policy decision-makers can be better informed on the management of the healthcare condition beyond issues of clinical effectiveness, to provide an understanding of the feasibility of interventions and how their implementation might vary depending on context.[230]

Role for qualitative studies in fibromyalgia-related sleep problems

We originally planned to systematically review existing qualitative evidence relevant to addressing our research question. However, during the application stage of our proposal, we became aware of a recently published qualitative evidence synthesis conducted by Climent-Sanz *et al*. in 2020, which provided an exploration of how people diagnosed with fibromyalgia experience and manage poor sleep quality.[33] We therefore sought to update and extend, rather than replicate, the Climent-Sanz (2020) synthesis. The Climent-Sanz (2020) meta-synthesis findings indicated that poor sleep quality is a severe and disabling symptom associated with fibromyalgia and that prescribed treatments and self-management strategies are largely ineffective. Only studies that included adult participants and were published in English or Spanish languages were considered eligible for inclusion in the Climent-Sanz *et al*. synthesis. It is, therefore, unclear whether any relevant studies of the perspectives of children with fibromyalgia or studies of adults and children with fibromyalgia published in languages other than English and Spanish have been omitted from the Climent-Sanz *et al*. synthesis. Climent-Sanz *et al*. also did not report on the certainty of evidence in their synthesis. In this qualitative evidence synthesis, we sought to ascertain the experiences and expectations of people who receive treatments for fibromyalgia-related sleep problems by updating and extending the Climent-Sanz *et al*. synthesis to consider studies of both adults and children published in any language. We took the opportunity to identify and synthesise any newly published research into the Climent-Sanz (2020) synthesis. We also sought to apply the Grading of Recommendations Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative research tool (GRADE-CERQual) to our findings.[232]

Methods

Searching and identification of relevant studies

The search strategy of the Climent-Sanz *et al*. synthesis was developed following Peer Review of Electronic Search Strategies guideline recommendations,[233] combining medical subject heading (and their equivalent in other databases) and free-text terms such as 'fibromyalgia', 'sleep', 'sleep quality', 'qualitative research'.[33] We repeated the search strategies from the Climent-Sanz *et al*. synthesis from the date of their last search (3 January 2020) to 5 November 2021. The databases searched were PubMed, Scopus, Web of Science and CINAHL. Additionally, as the current synthesis includes children, who were excluded from the Climent-Sanz *et al*. synthesis, the searches were re-run with text words to identify studies in children for all dates; these searches were run on 17 November 2021.

We also screened the titles and abstracts generated from our literature searches for the quantitative evidence synthesis (reported in *Chapter 2*) and the PROMs analysis (reported in *Chapter 4*) and selected any articles that seemed potentially relevant for our qualitative synthesis.

New studies identified by our updated searches were incorporated into the existing findings following current recommendations for updating qualitative evidence syntheses. The approach we have taken follows the method described by France and colleagues (2016) as 'extending and renovating the original house' (i.e. adding to and revising the original Climent-Sanz (2020) meta-synthesis to incorporate findings from new articles).[234]

We followed the eligibility criteria outlined by the Climent-Sanz (2020) synthesis; however, we extended the inclusion criteria to include studies considering children and adults published in any language. Eligible study designs included qualitative or mixed-methods research exploring the experience and/or management of sleep problems in people diagnosed with fibromyalgia.

The key eligibility criteria are summarised using the SPICE framework in *Table 9*.

Study selection and data extraction

The citations identified by the updated searches were independently screened between four review authors (MBe, MS, CR and MI). Full-text copies of all potentially relevant studies were retrieved and assessed for eligibility. A 10% check of all screening citations was conducted to ensure consistency between review authors. Information on the main characteristics of each identified study (e.g. aims and methods, populations involved) was extracted into a data-extraction form designed for this assessment. Data from the newly identified studies were extracted from the results sections of the included reports by a single review author (MBe or MS) and checked by a second review author for 10% of the included studies (MBe or MS).

Qualitative analysis

The analysis was conducted by two review authors (MBe and MS), who first conducted a deductive analysis by mapping the extracted data to the existing analytical themes of the 'symptom experience' and 'symptom management' components of the Symptom Management Theory (SMT)[235] conceptual framework used in the Climent-Sanz (2020) synthesis.[33] Any data that did not fit into the existing analysis was captured as a new theme and discussed within the team as to 'fit' within the SMT. The SMT provides a multidimensional framework that can be used to evaluate the patient's experience of their symptoms. A symptom can be defined as the subjective experience reflecting changes in the biopsychosocial functioning, sensations or cognitions of the individual.[236] In the SMT, symptom experience is

TABLE 9 Eligibility criteria of the qualitative evidence synthesis based on the SPICE framework

Setting (Where?)	Perspective (For whom?)	Phenomenon of interest (What?)	Comparison (Compared with what?)	Evaluation (With what result?)
Any relevant setting	People with fibromyalgia	Sleep problems	Any, including compared with nothing	Experience and management of sleep problems

determined by three main components: the individual's perception of a symptom, their evaluation of the meaning of a symptom, and their response to that symptom. The relationship between these components is bidirectional; thus an individual's evaluation of a symptom may influence their perception of the intensity of a symptom, and consequently shape their symptom response.[236] We align with Climent-Sanz *et al.*'s position that the symptom-focused conceptual framework of the SMT is particularly useful for understanding patients' experiences of chronic health conditions like fibromyalgia, where the main treatment goals are the alleviation and management of symptoms rather than curative treatment.

The initial reading and coding of the findings were undertaken independently by the two reviewers, and any disagreements were resolved by consensus or arbitration by our patient partners.

Quality-assessment strategy

The Critical Appraisal Skills Programme (CASP) checklist for qualitative studies was used to assess the quality of each of the newly included studies.[237] To ensure consistency, two review authors (MBe and MS) independently double-assessed the risk of bias in the first 10% of the identified studies. Single assessment was performed by the same review authors for the remaining studies. Any disagreements were resolved by discussion between the two review authors. The CASP assessments for the individual studies included in the Climent-Sanz (2020) synthesis were obtained from the review authors and included in the overall assessment of study quality.

Confidence in the findings of the qualitative synthesis

To enhance the quality of the findings of the Climent-Sanz (2020)[33] qualitative evidence synthesis and to integrate them with the results of our quantitative synthesis, we applied the GRADE-CERQual tool to the findings of our updated synthesis.[232,238]

The GRADE-CERQual approach is based on four components: the methodological limitations of included studies, the coherence of the review findings and the adequacy of data contributing to the review findings, and the relevance of the included studies to the review question. Two review authors (MI and CR) made an overall GRADE-CERQual assessment of confidence based on each thematic finding of the synthesis. Judgements on the initial assumption were that all findings were 'high confidence' and a reasonable representation of the phenomenon of interest, and then downgraded accordingly if there were concerns regarding any of the GRADE-CERQual components.

Findings

Description of included studies

The literature search identified a total of 61 citations. Following title and abstract screening, 29 articles were retrieved for full-text assessment. Twenty studies were excluded because they failed to meet our pre-specified inclusion criteria. Reasons for exclusion were: no suitable data reported (n = 14), ineligible study design (n = 3), ineligible study population (n = 1), full-text report not available (n = 1), and one study was available as a conference abstract only. Nine reports from eight studies were included in this synthesis. One study was identified from our literature search for our PROMs analysis[239] and four studies were identified from our search for our quantitative evidence synthesis.[240–243] Four reports evaluated participants' perceptions of mind–body interventions for poor sleep quality in fibromyalgia pat ients.[240,241,243,244] The remaining studies included one study conducted by the same lead author as the original meta-synthesis and explored the experiences and management of poor sleep quality in people with fibromyalgia.[245] A further study explored the psychological functioning and psychosocial processes associated with living with fibromyalgia.[239] One study focused on the experiences of fibromyalgia patients during the first COVID-19 lockdown in France (the exact dates are not reported by the study authors but correspond to weeks in April–May 2020).[246] Two studies evaluated the experiences of fibromyalgia patients undergoing a 4- to 6-week non-pharmacological, multidisciplinary educational group intervention[247] and a 10-week community-based group intervention involving education, exercise and sleep management.[242]

It is important to highlight that two of these reports by Sawynok and colleagues (2013) and Sawynok and Lynch (2014)[240,241] are linked to a RCT included in our quantitative NMA, which compares the effectiveness of level 1 Chaoyi

Fanhuan Qigong (CFQ) with a wait-list control for improving sleep quality in fibromyalgia patients.[55] Participants from this trial were invited to participate in a further trial, described by the authors as an extension trial, in which level 2 CFQ (meditation) was added to the level 1 CFQ (movement) instruction. In the report by Sawynok and colleagues (2013), responses to a questionnaire, which invited open-ended comments on participants' experience of the interventions, were analysed for 20 participants who took part in the extension trial. The 2014 report also analysed free-text responses to questionnaire items for the subgroup who took part in the open-label extension trial (n = 20) and all participants who completed the RCT (n = 73). It is unclear whether the 20 participants in each of the trial extension studies were the same participants. For the purposes of our analyses, we have treated these studies as comprising data from the same participant sample. Curry and colleagues (2021) also evaluated qigong as part of a mixed-methods observational study that combined quantitative measures and qualitative comments arising from open-ended comments obtained via a survey questionnaire.[244] Finally, the study by Lazaridou and colleagues (2019) conducted semistructured telephone interviews with participants with fibromyalgia who had completed a non-randomised pilot study exploring the quantitative effects of yoga on sleep, pain and stress.[243]

A visual summary of the study screening process is provided as *Figure 8*. The bibliographic details of the included studies are provided in *Report Supplementary Material 13*.

The key characteristics of the included studies are summarised in *Table 10*. The studies included in the Climent-Sanz (2020) synthesis were published between 2000[248] and 2018.[249] The studies included in our synthesis were published between 2012[239] and 2021.[244–246] Collectively, the studies included across both syntheses were conducted in North America (eight studies in Canada[240–242,244,248,250–252] and six studies in the USA[243,253–257]) and Europe (five studies in England,[39,247,258–260] two studies in Sweden[239,261] and one study each in Finland,[262] France,[246] Northern Ireland[249] and Spain[245]). One study was conducted with participants from France, Germany and the USA.[263] All studies included only adult participants. In total, the studies reported data about the perspectives of 565 people with fibromyalgia. Of the included participants, 46 were men and 434 were women. The sex of the 11 participants included in the study by Teo and colleagues[242] and the 73 participants who completed the RCT in the study by Sawynok 2014[241] was NR. The sex of one participant included in the study by Curry and colleagues (2021)[244] was not given. The youngest and oldest reported mean ages of the participants were 41 years[248] and 61 years[255] respectively. Only eight studies[39,243,253,255,256,258,263,264] reported the participants' race or ethnicity. The majority (80.5%) of participants in these eight studies were described as white or Caucasian. Other demographic characteristics (e.g. marital status, employment status and educational attainment level) were often NR or were reported in formats that made it difficult to make quantitative comparisons between studies.

Quality-assessment results

The majority (84.6%) of studies had a high overall CASP score, with 10[243,246,247,249,252,254,259,261,263,264] scoring 10/10 for the CASP checklist items and 12[39,239,245,248,250,251,253,255,256,258,260,262] scoring 9/10. The study conducted by Curry and colleagues (2021) was considered poor quality, scoring 3/10 for the CASP checklist items.[244]

All studies provided a clear statement of aims and considered ethical issues, and the majority (88.5%) were considered valuable and relevant to address our research question. All studies were judged to have used appropriate recruitment strategies except for the studies conducted by Curry and colleagues (2021),[244] Teo and colleagues (2017)[242] and Theadom and Cropley (2010).[260] The recruitment strategies used in these studies were either unclear or considered only partially adequate. Three studies conducted by Curry and colleagues (2021),[244] Sawynok and colleagues (2013)[240] and Sawynok and Lynch (2014)[241] did not consider sleep as a primary outcome and, while providing some valuable data, had less relevance for this qualitative synthesis. The authors of these three studies did not justify or discuss the choice of their study design, whereas all the remaining studies were judged to have provided adequate justification and rationale for their chosen study design. These three studies were also the only studies that were judged to have failed to have sufficiently rigorous qualitative data analysis and the authors did not provide a clear statement of their findings. It was unclear whether study authors had adequately considered the relationship between the researcher and participants in over half (53.8%) of the studies, while two studies (7.7%), conducted by Curry and colleagues (2021)[244] and Arnold and colleagues (2008),[253] were considered to have failed to adequately consider this relationship.

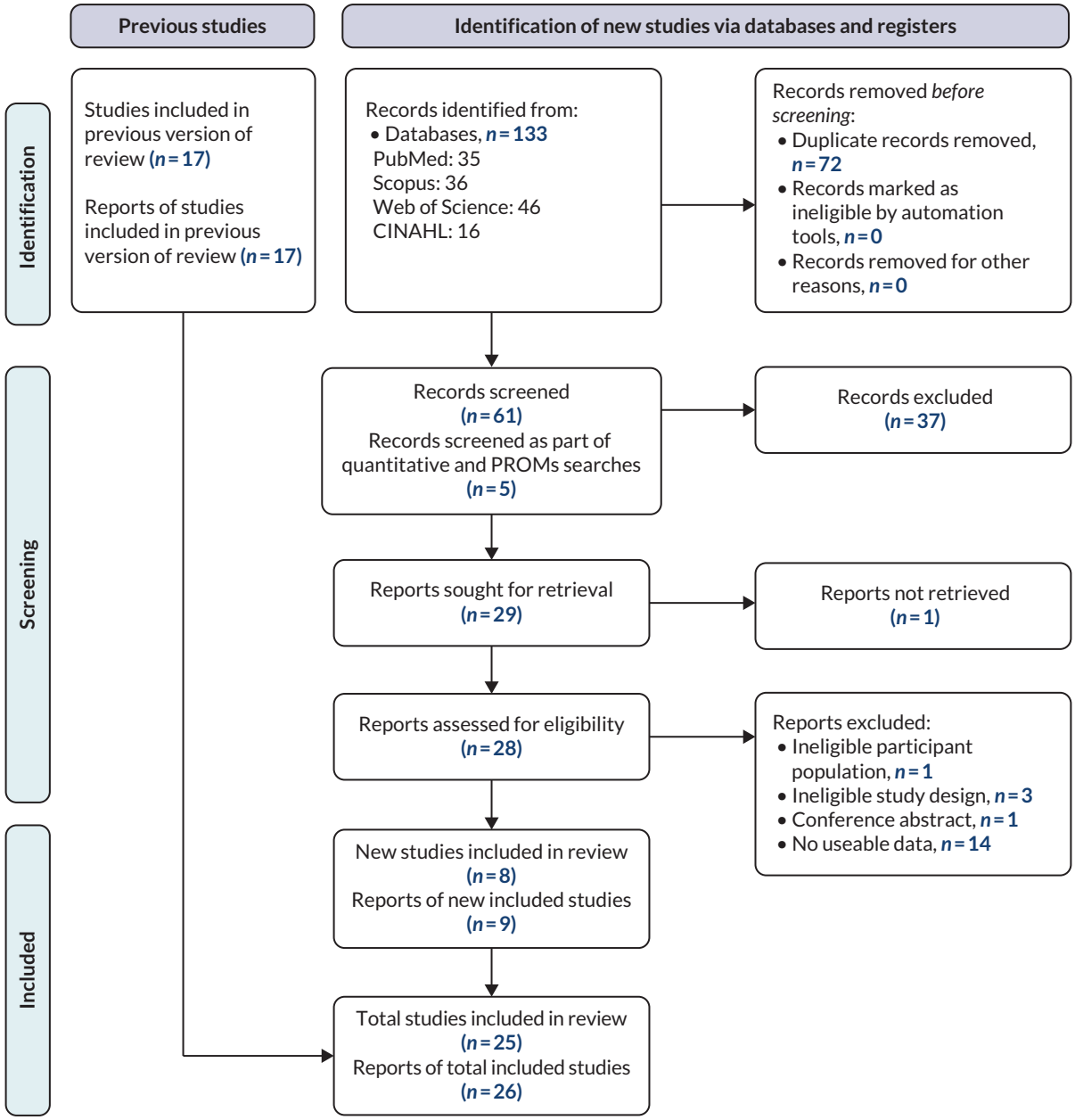

FIGURE 8 Preferred reporting items for systematic reviews and meta-analyses flow diagram for identification of the qualitative studies.[50]

Overall findings

As stated earlier, we adopted the SMT conceptual framework used in the Climent-Sanz (2020) synthesis.[33] Our findings are presented by the two pre-established global themes: *the experience of poor sleep quality in fibromyalgia* and *management strategies for poor sleep quality in fibromyalgia*. The global themes correspond to the 'symptom experience' and 'symptom management strategies' components of the SMT. The results are then presented by the four themes that were identified in the Climent-Sanz (2020) analysis and were mapped onto the SMT framework.[33] We amended the name of the theme *management strategies to favour sleep* to *management strategies to encourage sleep*. We took this decision to better reflect participants' experiences of medication-induced sleep. The presentation of findings for the global themes and themes in this report is as follows:

- The experience of poor sleep quality in fibromyalgia
    - evaluation of poor sleep quality
    - response to poor sleep quality.

TABLE 10 Main characteristics of the studies included in the qualitative evidence synthesis

Author year	Geographical location	Sample characteristics	Method for obtaining qualitative data	CASP checklist number of items fulfilled/ number of items
Studies identified from the updated searches				
Climent-Sanz 2021[245]	Spain	Number of participants = 21 Sex: male *n* = 0, female *n* = 21 Age (years), mean (range): 60 (44–75) Race/ethnicity: NR Sociodemographic status: Educational level, *n* (%): primary *n* = 7 (33.3%) secondary *n* = 12 (57.1%) tertiary *n* = 2 (9.5%) Employment status, *n* (%): full-time employment *n* = 5 (23.8%) part-time employment *n* = 2 (9.5%) retired *n* = 7 (33.3%) medically retired *n* = 6 (28.6%) on sick leave *n* = 1 (4.8%) Marital status, *n* (%): married: *n* = 12 (57.1%) divorced: *n* = 6 (28.6%) registered partner: *n* = 3 (14.3%)	In-depth semis-tructured personal interviews	9/10
Colas 2021[246]	France	Number of participants = 19 Sex: male *n* = 3; female *n* = 16 Age (years), mean (SD), range: 52 (9), 38 to 70 Race/ethnicity: NR Sociodemographic status: NR Marital status: NR	Semistructured interviews	10/10
Curry 2021[244]	Canada	Number of participants = 13 Sex: male *n* = 3, female *n* = 9, not given *n* = 1 Race/ethnicity: NR Age (years), mean (range): 52 (26–74) Sociodemographic status: NR Marital status: NR	Open-ended survey	3/10
Lazaridou 2019[243]	USA	Number of participants = 15 Sex: male *n* = 0, female *n* = 15 Age (years), mean (SD): 50 (14.3) Race/ethnicity, *n* (%): Caucasian *n* = 15 (100%) Sociodemographic status: Education, *n* (%): college degree or higher: 11 (73.3%) Marital status: NR	Semistructured interview and open-ended questions, using an interview guide, of 15–30 minutes by telephone	9/10
Pearson 2020[247]	England	Number of participants = 9 Sex: male *n* = 0; female *n* = 9 Age: NR Race/ethnicity: NR Sociodemographic status: NR Marital status: NR	Semistructured interviews	9/10
Sawynok 2013[240]	Canada	Number of participants = 20 Sex = male *n* = 0; female *n* = 20 Age: 53 years (unclear if mean or median) Race/ethnicity: NR Sociodemographic status: NR Marital status: NR	Qualitative ques-tionnaire that invited open-ended comments on experiences of interventions	5/10

continued

TABLE 10 Main characteristics of the studies included in the qualitative evidence synthesis (*continued*)

Author year	Geographical location	Sample characteristics	Method for obtaining qualitative data	CASP checklist number of items fulfilled/ number of items
Sawynok 2014[241]	Canada	Number of participants = 73 (RCT completers), 20 (extension trial) Sex: extension trial participants: male *n* = 0; female *n* = 20; RCT completers: NR Race/ethnicity: NR Age (years), mean: extension trial participants: 53, RCT completers: NR. The original trial average age was 52 years Sociodemographic status: NR Marital status: NR	Qualitative questionnaire that invited open-ended comments on experiences of interventions. Comments from the original RCT were considered as narratives for the extension trial subgroup (*n* = 20) and thematically, according to amount of practice, for all participants who completed the RCT (*n* = 73)	5/10
Teo 2017[242]	Canada	Number of participants = 11 Sex: NR Race/ethnicity: NR Age (years), mean (SD), range: 55.36 (11.87), 39–79 Sociodemographic status: Employment status, %: retired: 37% part-time employed: 27% on disability benefits: 18% unemployed: 9% full-time employment: 9% Marital status: NR	Semistructured interviews	8/10
Wentz 2012[239]	Sweden	Number of participants = 8 Sex: male *n* = 0; female *n* = 8 Age (years), mean (range): 56 (39–68) Race/ethnicity: NR Sociodemographic status: Education, years: mean 13.7 years (range 8–16) Employment, *n* (%): full-time *n* = 4 (50%) none *n* = 4 (50%) Marital status, *n* (%): married *n* = 5 (62.5%) divorced *n* = 2 (25%) widowed *n* = 1 (12.5%)	Semistructured in-depth interview	10/10
Studies identified by the Climent-Sanz (2020) search				
Arnold 2008[253]	USA	Number of participants = 48 Sex: male *n* = 0; female *n* = 48 Age (years), mean (SD): 51 (10) Race/ethnicity, *n* (%):	Focus groups	9/10

TABLE 10 Main characteristics of the studies included in the qualitative evidence synthesis (*continued*)

Author year	Geographical location	Sample characteristics	Method for obtaining qualitative data	CASP checklist number of items fulfilled/ number of items
		white: 45 (94%) African American: 1 (2%) Asian: 1 (2%) other: 1 (2%) Sociodemographic status: Work status, *n* (%)[a] full or part-time: 19 (40%); part-time due to FM: 4 (8%); not working due to FM: 5 (10%) applied/receiving disability: 8 (17%) looking for work: 1 (2%) full-time homemaker: 0 (0%) retired: 2 (4%) other: 9 (19%) Education: some high school: 2 (4%) high school diploma or General Equivalency Diploma: 4 (8%) some college: 12 (25%) certificate programme: 3 (6%) college or university degree (2–4-year): 10 (21%) graduate degree: 10 (21%) other: 7 (15%) Marital status, *n* (%): single: 6 (13%) significant other: 4 (8%) married: 28 (58%) widowed: 2 (4%) divorced: 7 (15%) other: 1 (2%)		
Crooks 2007[250]	Canada	Number of participants = 55 Sex: male *n* = 0; female *n* = 55 Age (years), mean (range): 57.7 (30–88) Race/ethnicity: NR Sociodemographic status: NR Education: NR Marital status: NR	Personal semistructured interviews	9/10
Cudney 2002[254]	USA	Number of participants = 10 Sex: male *n* = 0; female *n* = 10 Age (years), mean (range): 49 (38–55) Race/ethnicity: NR Sociodemographic status: NR Education: high-school graduate, *n* (%): 4 (40%) post-high-school education, *n* (%): 5 (50%) Marital status: NR	Unstructured, online support group	9/10
Cunningham 2006[251]	Canada	Number of participants = 8 Sex: male *n* = 1; female *n* = 7 Age (years), mean (range): NR (30–70) Race/ethnicity: NR Sociodemographic status: Employment status, *n* (%): occasional casual work: 1 (12.5%) unable to work and receiving disability benefits: 6 (75%) retired: 1 (12.5%) Education: NR Marital status: NR	Personal in-depth interviews	9/10

continued

TABLE 10 Main characteristics of the studies included in the qualitative evidence synthesis (*continued*)

Author year	Geographical location	Sample characteristics	Method for obtaining qualitative data	CASP checklist number of items fulfilled/ number of items
Humphrey 2010[263]	USA, Germany and France	Number of participants = 40 Sex: male *n* = 12; female *n* = 28 Age (years), mean (range): 48.7 (25–69) Race/ethnicity, *n* (%): Hispanic: 0 (0%) Caucasian: 25 (83.3%) African American: 2 (6.7%) Asian Oriental or Pacific Islander: 0 (0%) other: 2 (6.7%) Sociodemographic status: Currently in paid work (full or part-time) *n* (%): yes = 18 (45%); no = 22 (55%) Education, *n* (%): secondary school education or less: 6 (20%) vocational school or some college: 10 (33.3%) university/college degree: 11 (36.7%) post-graduate degree qualification: 3 (10%) Living status, *n* (%): live alone: 16 (40%) live with husband/wife/partner: 13 (32.5%) live with parents/family or friends: 9 (22.5%) Other: 2 (5%)	Open-ended interviews	10/10
Kengen Traska 2012[255]	USA	Number of participants = 8 Sex: male *n* = 0; female *n* = 8 Age (years), mean (range): 61 (54–81) Race/ethnicity, *n* (%): Caucasian: 8 (100%) Hispanic: 1 (12.5%) Sociodemographic status: NR Education: all participants had attended either a trade or technical school, community college, university or had a professional or graduate degree Marital status, *n* (%): married *n* = 5 (62.5%) divorced/separated/never married *n* = 3 (37.5%)	Group interview	9/10
Kleinman 2014[39]	England	Number of participants = 34 Sex: male *n* = 4; female *n* = 30 Age (years), mean (SD), range: 47.8 (11.9) 22–70 Race/ethnicity, *n* (%): white: 25 (73.5%) black or African American: 1 (2.9%) Asian: 2 (5.8%) Native Hawaiian or other Pacific Islander: 4 (11.7%) American Indian or Alaska Native: 1 (2.9%) other:[b] 6 (17.6%) Hispanic or Latino: 8 (23.5%) Sociodemographic status: Employment status,[c] *n* (%): employed, full-time; 7 (20.5%) employed, part-time: 9 (26.4%) homemaker: 2 (5.8%) student: 1 (2.9%) unemployed: 7 (20.5%)	Focus groups	9/10

TABLE 10 Main characteristics of the studies included in the qualitative evidence synthesis (*continued*)

Author year	Geographical location	Sample characteristics	Method for obtaining qualitative data	CASP checklist number of items fulfilled/ number of items
England	England	retired: 3 (8.8%) disabled: 9 (26.4%) other: 2 (2.8%) Unemployed or disabled due to fibromyalgia (*n*, %) Yes: 10 (62.5) No: 6 (37.5%) Education: NR Marital status: NR	England	England
Lempp 2009[258]	England	Number of participants = 12 Sex: male *n* = 1; female *n* = 11 Age (years), mean (range): 49 (20–69) Race/ethnicity *n* (%): black: 1 (8.3%) Black African: 1 (8.33%) Black British: 1 (8.3%) British/English/white 6 (50%) Lebanese: 1 (8.3%) New Zealand/British: 1 (8.3%) Peruvian: 1 (8.3%) Sociodemographic status: Employment status, *n* (%): full-time work 3 (25%) temporary employment 1 (8.3%) retired on medical grounds 1 (8.3%) retired 2 (16.7%) unemployed 5 (41.7%) Education: NR Marital status, *n* (%): married 5 (41.7%), married living apart 1 (8.3%); divorced 1 (8.3%); single 4 (33.3%); not specified 1 (8.3%)	Personal semistructured interviews	9/10
Martin 2009[256]	USA	Number of participants = 20 Sex: male *n* = 4; female *n* = 16 Age (years), mean (range): 50.3 (29–64) Race/ethnicity *n* (%): white: 13 (65%), black 7 (35%) Sociodemographic status: Employment status: employed full-time 5 (25%) employed part-time 1 (5%) unemployed 1 (5%) disabled 8 (40%) retired 3 (15%) other[d] 2 (10%) Education *n* (%): advanced degree: 3 (15%) college graduate: 2 (10%) associates degree: 2 (10%) some college: 9 (45%) high school degree or equivalent: 4 (20%) Marital status: NR	Personal structured interviews	9/10

continued

TABLE 10 Main characteristics of the studies included in the qualitative evidence synthesis (*continued*)

Author year	Geographical location	Sample characteristics	Method for obtaining qualitative data	CASP checklist number of items fulfilled/ number of items
Ramlee 2016[259]	England	Number of participants = 6 Sex: male *n* = 3; female *n* = 3 Age (years), mean (SD): 49 (11.6) Race/ethnicity: NR Sociodemographic status: Employment status: full-time employment: 1 (16.7%) on sick leave/medically retired/retired/not working: 5 (83.3%) Education: NR Marital status: NR	Personal semistructured interviews	10/10
Raymond 2000[248]	Canada	Number of participants = 7 Sex: male *n* = 1; female *n* = 6 Age (years), mean: 41 Race/ethnicity: NR Sociodemographic status: working full-time: 3 (42.9%) receiving financial assistance: 4 (57.1%) Education: NR Marital status: NR	Semistructured interviews	9/10
Russell 2018[249]	Northern Ireland	Number of participants = 14 Sex: male *n* = 2; female *n* = 12 Age (years): NR Race/ethnicity: NR Sociodemographic status: Employment status *n* (%): paid employment full-time: 3 (21.4%) paid employment part-time: 1 (7.1%) self-employed part-time: 1 (7.1%) volunteer worker: 1 (7.1%) currently on sick leave due to FM: 2 (14.3%) no longer working due to FM: 6 (42.9%) Education: NR Marital status: NR	Focus groups	10/10
Sallinen 2011[262]	Finland	Number of participants = 20 Sex: male *n* = 0; female *n* = 20 Age (years), mean (range): 54 (34–65) Race/ethnicity: NR Sociodemographic status: Employment status *n* (%): full-time work: 6 (30%) permanent disability pension: 7 (35%) part-time work or unemployed: 3 (15%) sick-listed: 3 (15%) retired because of old age: 1 (5%) Education: NR Marital status: NR	Narrative interview	9/10

TABLE 10 Main characteristics of the studies included in the qualitative evidence synthesis (*continued*)

Author year	Geographical location	Sample characteristics	Method for obtaining qualitative data	CASP checklist number of items fulfilled/ number of items
Söderberg 2002[261]	Sweden	Number of participants = 25 Sex: male *n* = 0; female *n* = 25 Age (years), mean (range): 46.8 (35–60) Race/ethnicity: NR Sociodemographic status: the majority of women were working part-time Education: the majority of women had vocational/ upper secondary school education Marital status: the majority of women were married	Personal narrative interviews	9/10
Sturge-Jacobs 2002[252]	Canada	Number of participants = 9 Sex: male *n* = 0; female *n* = 9 Age (years) mean (range): NR (30–56) Race/ethnicity: NR Sociodemographic status: NR Education: NR Marital status: NR	Personal unstructured interviews	10/10
Theadom 2010[260]	England	Number of participants = 16 Sex: male *n* = 2; female *n* = 14 Age (years), mean (range): 50.9 (21–61) Race/ethnicity: NR Sociodemographic status: Employment status: full time employment: 1 part-time employment: 5 retired: 5 no longer working due to ill-health: 5 Education: all participants had completed secondary education, with 31.25% attending college or university Marital status: NR	Semistructured interviews	9/10
Vincent 2015[264]	USA	Number of participants = 44 Sex: male *n* = 10; female *n* = 34 Age (years), mean (SD): 45 (14.6) Race/ethnicity (%): non-Hispanic White: 93% Sociodemographic status: NR Education: NR Marital status *n* (%): married 25 (57%) divorced 4 (9%) single 15 (34%)	Open-ended interview administered electronically	10/10

FM, fibromyalgia.
a Data presented are not mutually exclusive; patients may have reported more than one work status.
b Six participants selected other and described themselves as 'Mexican American', 'Russian Jew Spanish', 'Mexican', 'Hispanic/Portuguese', 'Hispanic' and 'Mexican'.
c Participants could select more than one response option.
d One participant reported employment status as disabled and retired and is therefore counted in the 'Other' category.

- Management strategies for poor sleep quality in fibromyalgia
    - management strategies to encourage sleep
    - managing the consequences of a sleepless night.

By a process of reciprocal translation, we compared and grouped subthemes that were identified in the nine additional reports according to their shared meaning and these are presented for each relevant theme as a narrative synthesis of our findings with illustrative quotations. Most findings from the new articles were confirmatory (reciprocal) of the subthemes identified by Climent-Sanz and colleagues (2020).[33] None were contradictory (refutational); however, we amended the name of one of the subthemes identified in the Climent-Sanz (2020) synthesis that is associated with the *evaluation of poor sleep quality* theme. We amended the subtheme name *perceived effects of poor sleep quality in other symptoms of fibromyalgia* to *relationship between poor sleep quality and other symptoms of fibromyalgia* to encompass the often-complex relationship between poor sleep quality and other fibromyalgia symptoms more fully. Furthermore, we identified a new subtheme concerning participants' experiences of interventions to improve sleep quality, which we named *experiences of interventions*. Many of the included studies did not report demographic data for specific participant quotations. The contribution of each paper to the themes and subthemes is presented in *Table 11*.

Global symptom management theory theme 1: experience of poor sleep quality in fibromyalgia

This global theme describes the participants' perceptions of poor sleep quality. Perceptions of good sleep quality and poor sleep quality are subjective and are likely to vary between and within individuals depending on how that person evaluates a good night's sleep.[265] For example, a good night's sleep for one person might be continuous sleep with no or infrequent awakenings, while for another person the total number of hours spent asleep might be more important. This global SMT theme is presented as two themes: the participants' evaluation of the meaning of their poor sleep quality and their response to poor sleep quality, which are presented in detail below with associated subthemes.

Theme 1: evaluation of poor sleep quality

In keeping with the approach taken by Climent-Sanz and colleagues (2020), and in accordance with the SMT, we conceptualised the evaluation of poor sleep quality as the meaning that a person attributes to their experience of poor sleep quality in terms of its effect, severity, temporality, cause and treatability. Three of the nine reports included in this update contributed findings to the evaluation of the poor sleep quality theme.[239,245,246] Thus, a total of 16 reports contributed findings to this theme.[39,239,245,246,250–252,253,256,258–264] The following subthemes were developed from analysis of participants' descriptions.

Subtheme 1: poor sleep quality is a severe symptom of fibromyalgia. Participants frequently described poor sleep quality as a significant aspect of living with fibromyalgia, with some participants describing it as the worst symptom they experience. Being unable to sleep properly was seen as a betrayal of the body, leading to a sense of helplessness and lack of control to the extent that being able to sleep well was seen as unachievable or a 'fantasy'.

> *Sleep, or lack of it, is the worst thing about this condition for me […]. It's just another way my body has betrayed me.*
>
> *Sturge-Jacobs, 2002*[252]

> *I would say that it would be like a fantasy to be able to sleep well, because I sleep very badly.*
>
> *Climent-Sanz, 2021*[245]

> *I don't feel like I can sleep. This is aging me; I can feel it.*
>
> *Cudney, 2002*[254]

Sleep disturbances and poor sleep maintenance were often mentioned as problems the participants experienced most often, and that the experience of being unable to stay asleep or waking frequently throughout the night would leave them feeling exhausted and frustrated. Others described problems with falling asleep or feeling unsatisfied with the quality of their sleep.

> *The problem is that I wake up, the problem is that when I sleep, I don't sleep. I am sleeping, but it is as if I am awake.*
>
> *Climent-Sanz, 2021*[245]

TABLE 11 Contribution of the included studies to the themes and subthemes

	Experience of poor sleep quality in fibromyalgia						Management strategies for poor sleep quality in fibromyalgia				
	Evaluation of poor sleep quality				Response to poor sleep quality		Management strategies to favour sleep			Managing the consequences of a sleepless night	
Author ID	Poor sleep quality is a severe symptom of FM	Relationship between poor sleep quality and other symptoms of FM	Beliefs about the temporality and cause of poor sleep quality	Meaning of good sleep quality	Feeling frustrated and like a failure	Fear of going to bed	Medication: from dependency to rejection	Experiences of interventions[a]	Self-management: behavioural adaptations	Medication: finding the balance between benefits and side effects	Resting and relaxing during the day
Studies identified from the updated searches											
Climent-Sanz 2021[245]	•	•	•	•	•	•	•		•		•
Colas 2021[246]	•						•				•
Curry 2021[244]								•			
Lazaridou 2019[243]								•			
Pearson 2020[247]							•	•	•		
Sawynok 2013[240]								•			
Sawynok 2014[241]								•			
Teo 2017[242]								•		•	
Wentz 2012[239]		•	•								
Studies identified by the Climent-Sanz (2020) search											
Arnold 2008[253]							•				•

continued

TABLE 11 Contribution of the included studies to the themes and sub-themes (*continued*)

	Experience of poor sleep quality in fibromyalgia						Management strategies for poor sleep quality in fibromyalgia				
	Evaluation of poor sleep quality				Response to poor sleep quality		Management strategies to favour sleep			Managing the consequences of a sleepless night	
Author ID	Poor sleep quality is a severe symptom of FM	Relationship between poor sleep quality and other symptoms of FM	Beliefs about the temporality and cause of poor sleep quality	Meaning of good sleep quality	Feeling frustrated and like a failure	Fear of going to bed	Medication: from dependency to rejection	Experiences of interventions[a]	Self-management: behavioural adaptations	Medication: finding the balance between benefits and side effects	Resting and relaxing during the day
Crooks 2007[250]		•									•
Cudney 2002[254]	•	•			•		•				•
Cunningham 2006[251]		•								•	
Humphrey 2010[263]		•									
Kengen Traska 2012[255]											•
Kleinman 2014[39]	•	•			•						
Lempp 2009[258]		•					•				
Martin 2009[256]		•									
Ramlee 2018[259]		•		•							
Raymond 2000[248]									•		

TABLE 11 Contribution of the included studies to the themes and sub-themes (*continued*)

	Experience of poor sleep quality in fibromyalgia						Management strategies for poor sleep quality in fibromyalgia				
	Evaluation of poor sleep quality				Response to poor sleep quality		Management strategies to favour sleep			Managing the consequences of a sleepless night	
Author ID	Poor sleep quality is a severe symptom of FM	Relationship between poor sleep quality and other symptoms of FM	Beliefs about the temporality and cause of poor sleep quality	Meaning of good sleep quality	Feeling frustrated and like a failure	Fear of going to bed	Medication: from dependency to rejection	Experiences of interventions[a]	Self-management: behavioural adaptations	Medication: finding the balance between benefits and side effects	Resting and relaxing during the day
Russell 2018[249]					•						
Sallinen 2011[261,262]			•				•				
Söderberg 2002[261]		•								•	•
Sturge-Jacobs 2002[252]	•					•			•		
Theadom 2010[260]	•	•	•		•	•	•		•		•
Vincent 2016[264]		•									

FM, fibromyalgia.
a New subtheme identified in the updated synthesis analysis.

Subtheme 2: relationship between poor sleep quality and other symptoms of fibromyalgia. As discussed earlier, this concept most closely resembles the concept described as 'perceived effects of poor sleep quality in other symptoms of fibromyalgia' described by Climent-Sanz and colleagues (2020).[33] Our rationale for the coding of this concept is that our interpretation of the participants' description of the relationship between poor sleep quality and other symptoms of fibromyalgia is complex and bidirectional, rather than a single directional impact of sleep problems on their other symptoms. We believe that this approach is in keeping with the bidirectional aspect of the SMT and the Climent-Sanz (2020) interpretation regarding poor sleep, pain and fatigue as a vicious circle in which insufficient sleep results in an increase in pain intensity the next day, which then leads to a state of fatigue that prevents sleep at night and impacts on activities of daily living. Conversely, some participants also felt that getting a good night's sleep increased their pain due to being physically immobile while they were asleep.

> *It's not just the pain and the fatigue, […] it's the non-restorative sleep […] it's a vicious circle because if you don't get enough sleep, you feel pain more acutely […] you're more tired and unable to sleep well.*
>
> *Cunningham, 2006*[251]

> *It is that you wake up in the morning already with fatigue that looks like you have been run over by a truck, and you cannot handle your life.*
>
> *Climent-Sanz, 2021*[245]

> *If I sleep really well at night, I'm in much worse shape in the morning as far as pain goes … I'm not in as much pain because I've been moving. But then I'm a lot more tired, so I'm not going to be doing all that much.*
>
> *Crooks, 2007*[250]

As identified by Climent-Sanz *et al*. (2020), we also found that participants described the negative impacts of poor sleep on their cognitive function, including impaired ability to think and perform cognitive tasks in the workplace. In one study identified by our updated search participants described how poor sleep quality negatively impacted their mental health by causing feelings of heightened anxiety, irritability and nervousness.[245] This was described as, in turn, impacting on participants' physical health and ability to manage their symptoms. Participants also described how not being able to predict whether they would be able to sleep at night caused them to have poorer mental health.

> *[I fear] that I will go a little crazy […] because not sleeping gives you a lot of problems, gives you a lot of anxiety, you do not live your life with peace of mind, you have a very bad temper.*
>
> *Climent-Sanz, 2021*[245]

> *[…] there is nothing constant, it may be normal one day, and another day I can feel very tired or very nervous. The next night, I may sleep, or I may not sleep again […]. It changes every night, there is nothing constant.*
>
> *Climent-Sanz, 2021*[245]

As described by Climent-Sanz and colleagues (2020), we also note that participants described how their poor sleep quality impacted family members, such as causing disruption to bedfellows. Participants also described how they missed out on spending time with their family due to having to take naps to cope with fatigue brought on by their poor sleep.

> *I don't hardly ever sleep with my husband any more, because I disturb his sleep so much of the time with my tossing and turning, trying to get comfortable, getting in and out of bed, because I can't get comfortable.*
>
> *Cudney, 2002*[254]

Subtheme 3: beliefs about the temporality and cause of poor sleep quality. Participants described different beliefs about the causes of their poor sleep quality, ranging from the impact of other symptoms such as pain and tinnitus, to hormonal causes, such as the menopause, and working night shifts. Having to go to the bathroom was also discussed as disturbing sleep. Participants also described the relationship between sleep quality and the sleep environment, such as external noise causing poor sleep quality. Behaviours such as the consumption of stimulants like caffeine and increased physical activity levels were mentioned as additional causes of poor sleep quality.

> *Sometimes because of the arms and hands, because of the pain. And other times I go to the bathroom.*
>
> *Climent-Sanz, 2021*[245]

> *When you are silent is when you hear them (the tinnitus) the most. Then this […] and of course, if you wake up at two and you have this, it is very difficult to go back to sleep.*
>
> *Climent-Sanz, 2021*[245]

> *[…] everything happened more or less when my period stopped, and so I said, 'This is menopause'. Sometimes you say, 'This must be caused by the menopause' […] you always look for the solution or attribute the problem to something else, yes.*
>
> *Climent-Sanz, 2021*[245]

Subtheme 4: meaning of good sleep quality. In keeping with the Climent-Sanz (2020) findings, we identified good sleep quality as the feeling of being rested or renewed upon waking, a feeling of disconnection or not being able to remember dreaming and having enough energy to perform daily activities. Waking with the absence of pain was also described as being related to good sleep quality.

> *Getting up in the morning and feeling rested, I do not care about the hours, at least open my eyes and say, 'I have slept, I feel rested, come on, let's start the day'.*
>
> *Climent-Sanz, 2021*[245]

> *That you do not remember what you have dreamed about, that you do not remember anything and get up and say: I feel so rested, I got up feeling so well!*
>
> *Climent-Sanz, 2021*[245]

> *That you can wake up without any pain, this would be good for me […] the best.*
>
> *Climent-Sanz, 2021*[245]

Theme 2: response to poor sleep quality

The second theme that was identified as relevant to the experience of poor sleep quality in fibromyalgia was the response to poor sleep quality. This is conceptualised within the SMT framework as a person's reaction to their symptom at the physiological, psychological and social level. For example, if a person perceives (psychological level) that their symptom is serious and may cause disruption to their lives (social level), then the perceived intensity (physiological level) of that symptom may be heightened.[236] In keeping with the Climent-Sanz (2020) findings, we did not identify reports of any social factors relating to the participants' responses to poor sleep quality. Only one of the additional studies conducted by Climent-Sanz and colleagues (2021)[245] contributed to the response to the poor sleep quality subtheme. Therefore, a total of six studies contributed to this subtheme.[39,245,249,252,254,260] The following subthemes were identified:

Subtheme 5: feeling frustrated and like a failure. In accordance with the Climent-Sanz (2020) findings, participants described how constantly waking up is the worst thing about having fibromyalgia and how this can cause desperation and loneliness, and feelings of frustration that they are unable to sleep well. Participants also noted that they experience feelings of failure due to the negative impact that poor sleep quality has on their ability to work and perform daily activities of living. Participants also stated that they felt resentful that they must plan their lives around their sleep problems, to the extent that they sometimes 'hate life'.

> *Sleep, or lack of it, is the worst thing about this condition for me.*
>
> *Sturge-Jacobs, 2002*[252]

> *The not sleeping and then not being able to function the next day when you need to perform at work […] when you're being paid and you're meant to work and you can't function, it's horrible, it's really horrible because you feel like a failure.*
>
> *Theadom, 2010*[260]

> *I'm not saying my life is so exciting but when it's, just now I think oh, I have to plan it round, oh can I have a lay in this weekend, can I do this, can I do that, I find that very hard to cope with.*
>
> *Theadom, 2010*[260]

Subtheme 6: Fear of going to bed. The participants expressed how the anticipation of not being able to sleep or having poor sleep, including experiencing nightmares, leads to feelings of being afraid of going to bed and being afraid of the bedroom.

> *It was torture for me to go to sleep because I knew that I would have nightmares, I would have aches that I could not sleep at all […]. Initially, before going to sleep, I was already worried about what was going to happen to me in the dream.*
>
> *Climent-Sanz, 2021*[245]

As described by Climent-Sanz and colleagues (2020), the fear of poor sleep quality has such an effect on the personal lives of some participants that they were reconsidering parenthood due to the fear that their sleep needs would be further negatively impacted to the extent that they would be unable to cope.

> *We're wanting to start a family, so that's kind of an issue regarding sleep, actually; yes, that's a massive issue, because we've been wanting to start a family for ages, we're not even doing that because I don't think I could have that sort of sleep deprivation.*
>
> *Theadom, 2010*[260]

Global symptom management theory theme 2: management strategies for poor sleep quality in fibromyalgia

Within the SMT, the goal of symptom management is to avert or delay negative outcomes by identifying management strategies in response to an assessment of symptom experiences from the individual's perspective.[236] The global theme *management strategies for poor sleep quality in fibromyalgia* describes the strategies employed by the participants to manage their symptom experiences in response to their experience of poor sleep. The global theme is presented under the two subthemes identified by Climent-Sanz and colleagues (2020) describing participants' management strategies to initiate and maintain sleep, and how they manage the consequences of a sleepless night.

Theme 3: management strategies to encourage sleep

We identified three new studies in the update that contributed to this theme.[245–247] When added to the seven studies from the Climent-Sanz (2020) synthesis,[248,252–254,258,260,262] a total of 10 studies contributed data to this theme. This theme is composed of three subthemes capturing 'medication: from dependency to rejection', 'experiences of interventions' and 'self-management: behavioural adaptations' as discussed below.

Subtheme 7: medication: from dependency to rejection. As with the Climent-Sanz (2020) synthesis, the participants often described using medication to assist them to fall asleep and maintain sleep. The participants described using medication indicated for insomnia and analgesia in response to sleep disturbances caused by pain to allow them to fall back asleep. Some participants felt that they benefitted from taking medication, although the importance of taking the 'right' medication that worked for them was highlighted as important. Medication was also discussed in terms of participants' dependency on medication to allow them to fall asleep and alleviate their anxiety about falling asleep. The contrast between 'normal' sleep and medicated sleep was also discussed, with participants stating that medicated sleep feels like they 'pass out for a while' rather than experience sleep, although this did allow participants to feel physically rested. Other participants felt that medication was either ineffective or gradually became less effective over time and some rejected the use of medication due to concerns about side effects.

> *Now I am already taking Zolpidem, I do not sleep, I pass out for a while […] I am rested, because with other medicines, with other drugs that I have taken, I could not sleep.*
>
> *Climent-Sanz, 2021*[245]

> *I think that if I take it, it hurts me even more. Not in terms of sleep, but I feel worse. […]. You are full of drugs, it is not you, you are a vegetable. […] they put you to sleep, but to sleep, you'd better die now.*
>
> *Climent-Sanz, 2021*[245]

> *You get used to the drugs and after a while they no longer work.*
>
> *Climent-Sanz, 2021*[245]

Subtheme 8: experiences of interventions. Four of the reports identified in our update evaluated mind–body interventions to improve sleep quality. These reports included qualitative data describing the participants' experiences of the interventions. Three reports evaluated the effects of different types of qigong.[240,241,244] Qigong is a form of traditional Chinese medicine involving body–mind exercises in the form of specific slow-flowing movements, breathing techniques and meditation.[266] As discussed earlier, participants in the two reports conducted by Sawynok and colleagues (2013)[240] and Sawynok and Lynch (2014)[241] evaluated participants' experiences of CFQ. Curry and colleagues (2021) report the results of two observational studies (RIM1 and RIM2) of qigong practice in a sample of chronic pain patients with various underlying health conditions.[244] We have analysed the comments reported by the 13 participants with fibromyalgia.

Some participants noted that they felt less pain when they practised qigong and that this had led to improved sleep quality. Improvements in sleep quality were described in terms of reduced time to sleep onset, longer sleep duration, fewer awakenings during the night, being able to fall back to sleep faster, more 'restorative' or 'restful' sleep and less need to sleep during the day. For these people, qigong allowed them to feel calmer and more relaxed. Participants reported that they had more energy and less extreme fatigue and generally felt that their overall health had improved but they noticed that symptoms quickly returned if they stopped practising qigong. Some participants felt that initial improvements lessened over time, while others did not notice any improvement in their sleep patterns or reported increased pain resulting in even greater sleep disturbance.

> *Qigong has given me my life back. When I started, was using a walker, couldn't sleep and was in terrible pain. Now feel peaceful; am walking, sleeping well; pain levels have come down considerably.*
>
> *Sawynok, 2013*[240]

> *[…] previously had days of extreme tiredness and slept 4 hours in afternoon, have not had to sleep during day since beginning qigong.*
>
> *Sawynok, 2014*[241]

> *Felt wonderful after beginning of study, qigong was great benefit. until 3 weeks ago, woke to find fatigue and exhaustion had returned, couldn't fall asleep.*
>
> *Sawynok, 2014*[241]

> *Overall pain has increased, interfering with sleep.*
>
> *Sawynok, 2013*[240]

Lazaridou and colleagues (2019) conducted a qualitative evaluation of group and daily individual home yoga in women with fibromyalgia.[243] Fifteen women participated in semistructured telephone interviews after completing a 6-week Satyananda yoga programme. The authors describe Satyananda yoga as a holistic approach to developing an individual's physical, mental, emotional, psychic and spiritual state of being. Participants reported experiencing reductions in their fibromyalgia symptoms, including pain and stress, and noticed positive impacts on mood, sleep and self-confidence. Participants reported that they fell asleep faster and felt that the quality of their sleep had improved. Participants also felt that they were more alert and had more stamina during the day.

> *When I practiced the yoga or meditation before bed I would sleep faster.*
>
> *Lazaridou, 2019*[243]

> *I sleep deeper; my sleep quality is better.*
>
> *Lazaridou, 2019*[243]

In addition to the studies of mind–body interventions, Pearson and colleagues (2020) evaluated the Fibromyalgia Self-Management Programme (FSMP), which is a non-pharmacological, multidisciplinary education group intervention developed by allied health professionals within the NHS.[247] The main aims of the FSMP are to provide condition-specific, patient-centred education and exercise advice and to support the development of core self-management skills through behaviour change. Patients described how they benefitted from the educational component of the intervention by understanding more about links between sleep and pain, such as the association between substance P (a modulator of pain perception) and melatonin. Participants also found the practical tips for managing their sleep through behavioural adaptations helpful, such as buying blackout curtains or changing their bed.

> *I mean I've been thinking about these things for a long time but the substance P and your melatonin and all of those sorts of things, which I was just aware of but you don't always relate it to yourself. So that's been very, very helpful.*
>
> *Pearson, 2020*[247]

Teo and colleagues (2017) conducted a feasibility study of 10-week multidisciplinary intervention involving group-based education sessions, exercise and sleep management in a small urban centre in southern British Columbia, Canada.[242] Some of the participants in this study benefitted from having an organised treatment plan that involved alterations to their sleep aid therapies, such as a reduction in their medication.

> *He cut my medicine in half, my night time medication in half […] which enabled me to sleep better. Instead of giving me a sleep aid, he cut mine in half, which was tremendous.*
>
> *Teo, 2017*[242]

Subtheme 9: self-management: behavioural adaptations. In keeping with the Climent-Sanz (2020) findings, participants described the importance of establishing regular sleep cycles or behavioural patterns that work for the individual. Strategies such as the use of earplugs, blackout curtains, buying a comfortable bed, eating at the same time of day, going to bed at the same time of night and keeping the bedroom solely as a space for sleeping were described by the participants. Some participants found it useful to try to rest during the day, while others preferred to try to physically tire themselves and avoid napping to improve sleep at night. These strategies were described as having mixed and changeable success depending on the individual person.

> *Well, you may have been advised to try not to eat too much or not to eat too much at night […] if you want to read, do it on the sofa, don't go to bed […]. Everyone is different. So, each one of us must have our own tactics.*
>
> *Climent-Sanz, 2021*[245]

> *There are days when one thing works for me but then the next day I am no longer doing well. There are periods when I feel better […]. A week goes by and gets terrible again.*
>
> *Climent-Sanz, 2021*[245]

As with the Climent-Sanz (2020) findings, opposing strategies were employed for dealing with awakenings during the night, with some participants preferring to get out of bed while others preferred to stay in bed to try to fall back to sleep. Delaying going to bed was also discussed as a strategy to avoid waking up. Some participants stated that, while they were aware of strategies for avoiding poor sleep quality, they did not always follow the advice they were given.

> *I don't go to sleep before one […] I don't want to go at eleven or twelve because then I would already be awake at three or four.*
>
> *Climent-Sanz, 2021*[245]

> *I play with the computer and they already told me that I shouldn't do it because this is bad for sleeping.*
>
> *Climent-Sanz, 2021*[245]

Theme 4: managing the consequences of a sleepless night

This theme describes how participants cope with the consequences of their poor sleep. We identified three new studies that contributed to this theme.[242,245,246] When added to the seven studies from the Climent-Sanz (2020) synthesis,[250,251,253–255,260,261] a total of 10 studies contributed data to this theme. The theme is composed of two subthemes that describe how participants find the balance between the benefits and side effects of medication and resting and relaxing during the day.

Subtheme 10: medication: finding the balance between benefits and side effects. This subtheme describes how participants viewed taking medication as a necessary consequence of their poor sleep, as distinct from their experiences of the effects that medication had on the quality of their sleep. The participants tended to be taking several medications for symptoms associated with fibromyalgia, including pain and depression, as well as sleep problems. For some participants, the consequences of taking medication were that they were able to manage their activities of daily living and medication allowed them to 'continue to have a life' but for some participants this was at the expense of experiencing side effects due to their treatment. For other participants, reducing their medication allowed them to experience better-quality sleep.

> *When I have been resting a while and I sleep when I've taken a painkiller […] and can sleep an hour and then it feels much better, then I can manage the afternoon.*
>
> *Soderberg, 2002*[261]

> *I'm trying to function, so I take the various medications […] in the hopes that while it causes other problems it will at least allow me to continue to have a life.*
>
> *Cunningham, 2006*[251]

Subtheme 11: resting and relaxing during the day. In keeping with the Climent-Sanz (2020) findings, participants described how they experienced daytime fatigue due to poor sleep and that relaxing or taking naps during the day were necessary coping strategies to deal with their fatigue. This theme is related to using rest and relaxation as a behavioural management strategy to encourage sleep, but here rest and relaxation were viewed as unavoidable consequences of having a poor night's sleep. Some participants noted that sleeping during the day was against the advice they had received from health professionals for achieving good-quality sleep at night, but they stated that they felt they knew what worked best for themselves and preferred to develop their own coping strategies rather than follow generic guidance. Others described being unable to cope without resting during the day and that they planned their daily activities, such as providing food for family members, around their nap times. As described earlier, napping meant that participants missed out on spending time with their family, but this was described as unavoidable due to their experience of extreme fatigue. Relaxation strategies included taking hot baths with Epsom salts or lavender oil and lying down in a quiet room.

> *I know they advise you not to go to bed […] but I can't physically not and I find it makes me feel better actually if I do, so for me it works better, so you I've learnt to do what suits me rather than what I'm told to do.*
>
> *Theadom, 2010*[260]

> *I have to lay down because if I don't, I can't stand it […] and sometimes I leave them food and go to lay down because my body can't stand it […] and when I see that my husband stays there, sometimes I say 'Wake up, I can't'.*
>
> *Climent-Sanz, 2021*[245]

Assessment of confidence in the findings of the qualitative synthesis

Our confidence in the findings of this qualitative evidence synthesis is based on our GRADE-CERQual assessment. The GRADE-CERQual ratings are presented in *Table 12*. We rated each domain as 'no or very minor concerns', 'minor concerns', 'moderate concerns' or 'serious concerns'. We rated most subthemes as moderate confidence. Findings were downgraded for 'relevance' because participant demographic data, including sociodemographic status, race and ethnicity, were poorly reported across studies. Findings for the *experiences of interventions* subtheme were also downgraded for 'methodological limitations' because three reports that contributed data to this subtheme were of overall poor methodological quality as assessed by the CASP checklist for qualitative studies. These included the studies

TABLE 12 Grading of recommendations assessment, development, and evaluation-confidence in the evidence from reviews of qualitative research evidence profile

	Summary of findings	Studies contributing to review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
Global theme 1: Experience of poor sleep quality in fibromyalgia							
Theme 1: Evaluation of poor sleep quality							
1	Poor sleep quality is a severe symptom of FM	Climent-Sanz 2021[245] Colas 2021[246] Cudney 2002[254] Kleinman 2014[39] Sturge-Jacobs 2002[252] Theadom 2010[260] Wentz 2012[239]	*No or very minor concerns* about methodological limitations	*No or very minor concerns* about coherence	*No or very minor concerns* about adequacy	*Moderate concerns* about relevance given the poor reporting of participant demographic data including sociodemographic status, race and ethnicity.	*Moderate confidence*: Some concerns regarding relevance
2	Relationship between poor sleep quality and other symptoms of FM	Climent-Sanz 2021[245] Crooks 2007[250] Cudney 2002[254] Cunningham 2006[251] Humphrey 2010[263] Kleinman 2014[39] Lempp 2009[258] Martin 2009[256] Ramlee 2018[259] Soderberg 2002[261] Theadom 2010[260] Vincent 2014[264] Wentz 2012[239]	*No or very minor concerns* about methodological limitations	*No or very minor concerns* about coherence	*No or very minor concerns* about adequacy	*Moderate concerns* about relevance given the poor reporting of participant demographic data including sociodemographic status, race and ethnicity.	*Moderate confidence*: some concerns regarding relevance
3	Beliefs about the temporality and cause of poor sleep quality	Climent-Sanz 2021[245] Sallinen 2011[262] Theadom 2010[260] Wentz 2012[239]	*No or very minor concerns* about methodological limitations	*No or very minor concerns* about coherence	*No or very minor concerns* about adequacy	*Moderate concerns* about relevance given the poor reporting of participant demographic data including sociodemographic status, race and ethnicity.	*Moderate confidence*: some concerns regarding relevance
4	Meaning of good sleep quality	Climent-Sanz 2021[245] Ramlee 2018[259]	*No or very minor concerns* about methodological limitations	*No or very minor concerns* about coherence	*No or very minor concerns* about adequacy	*Moderate concerns* about relevance given the poor reporting of participant demographic data including sociodemographic status, race and ethnicity.	*Moderate confidence*: some concerns regarding relevance

TABLE 12 GRADE-CERQual evidence profile (*continued*)

Summary of findings		Studies contributing to review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
Theme 2: Response to poor sleep quality							
5	Feeling frustrated and like a failure	Climent-Sanz 2021[245] Cudney 2002[254] Kleinman 2014[39] Russell 2018[249] Theadom 2010[260]	*No or very minor concerns* about methodological limitations	*No or very minor concerns* about coherence	*No or very minor concerns* about adequacy	*Moderate concerns* about relevance given the poor reporting of participant demographic data including sociodemographic status, race and ethnicity.	*Moderate confidence*: some concerns regarding relevance
6	Fear of going to bed	Climent-Sanz 2021[245] Sturge-Jacobs 2002[252] Theadom 2010[260]	*No or very minor concerns* about methodological limitations	*No or very minor concerns* about coherence	*No or very minor concerns* about adequacy	*Moderate concerns* about relevance given the poor reporting of participant demographic data including sociodemographic status, race and ethnicity.	*Moderate confidence*: some concerns regarding relevance
Global theme 2: Management strategies for poor sleep quality in fibromyalgia							
Theme 3: Management strategies to encourage sleep							
7	Medication: from dependency to rejection	Arnold 2008[253] Climent-Sanz 2021[245] Colas 2021[246] Cudney 2002[254] Lempp 2009[258] Pearson 2020[247] Sallinen 2011[262] Theadom 2010[260]	*No or very minor concerns* about methodological limitations	*No or very minor concerns* about coherence	*No or very minor concerns* about adequacy	*Moderate concerns* about relevance given the poor reporting of participant demographic data including sociodemographic status, race and ethnicity.	*Moderate confidence*: some concerns regarding relevance
8	Experiences of interventions	Curry 2021[244] Lazaridou 2019[243] Pearson 2020[247] Sawynok 2013[240] Sawynok 2014[241] Teo 2017[242]	*Moderate concerns* about methodological limitations. Three studies were assessed as overall poor methodological quality. These studies did not have an appropriate research design or appropriate data-collection methods, did not adequately consider the relationship between the researcher and participants, failed to have sufficiently rigorous data analyses and did not report clear statements of their findings.	*No or very minor concerns* about coherence	*No or very minor concerns* about adequacy	*Moderate concerns* about relevance given the poor reporting of participant demographic data including sociodemographic status, race and ethnicity.	*Low confidence*: some moderate concerns regarding methodological limitations and relevance

continued

TABLE 12 GRADE-CERQual evidence profile (*continued*)

Summary of findings		Studies contributing to review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
9	Self-management: behavioural adaptations	Climent-Sanz 2021[245] Pearson 2020[247] Raymond 2000[248] Sturge-Jacobs 2002[252] Theadom 2010[260]	*No or very minor concerns* about methodological limitations	*No or very minor concerns* about coherence	*No or very minor concerns* about adequacy	*Moderate concerns* about relevance given the poor reporting of participant demographic data including sociodemographic status, race and ethnicity.	*Moderate confidence*: some concerns regarding relevance
Theme 4: Managing the consequences of a sleepless night							
10	Medication: finding the balance between benefits and side effects	Cunningham 2006[251] Soderberg 2002[261] Teo 2017[242]	*No or very minor concerns* about methodological limitations	*No or very minor concerns* about coherence	*No or very minor concerns* about adequacy	*Moderate concerns* about relevance given the poor reporting of participant demographic data including sociodemographic status, race and ethnicity.	*Moderate confidence*: some concerns regarding relevance
11	Resting and relaxing during the day	Arnold 2008[253] Climent-Sanz 2021[245] Colas 2021[246] Crooks 2007[250] Cudney 2002[254] Kengen Traska 2012[255] Soderberg 2002[261] Theadom 2010[260]	*No or very minor concerns* about methodological limitations	*No or very minor concerns* about coherence	*No or very minor concerns* about adequacy	*Moderate concerns* about relevance given the poor reporting of participant demographic data including sociodemographic status, race and ethnicity.	*Moderate confidence*: some concerns regarding relevance

FM, fibromyalgia.

conducted by Curry and colleagues (2021),[244] Sawynok and colleagues (2013)[240] and Sawynok and Lynch (2014).[241] The methodological concerns for these studies were that the research design and data-collection methods were not appropriate, the relationship between the researcher and participants was not adequately considered, data analyses were not sufficiently rigorous, and the authors did not report clear statements of their findings.

Discussion

This update of an existing qualitative meta-synthesis integrates and summarises the findings of 9 newly identified studies with the 17 studies that were included in the original published synthesis conducted by Climent-Sanz and colleagues (2020).[33] Most studies were of good methodological quality. We have moderate confidence in the findings of our qualitative synthesis except for people's experiences of interventions, which we rated as low confidence. The resulting synthesis confirms the findings of the previous evidence synthesis that poor sleep is perceived as a severe symptom of fibromyalgia, with some participants describing poor sleep as one of the worst aspects of fibromyalgia. Participants also described how their sleep problems impacted on their family life, including being unable to share a bed with their partners and missing out on spending time with family members. Poor sleep maintenance and sleep disturbance were mentioned as the problems participants experienced most often. Our analysis also confirms that people with fibromyalgia perceive good-quality sleep in terms of having uninterrupted sleep, feeling rested or renewed upon waking, waking with an absence of fatigue and pain, and having enough energy to perform daily activities. This implies that good-quality sleep is perceived mainly in terms of sleep continuity and restorative sleep rather than the total duration of sleep; however, the meanings that people attribute to good-quality sleep are subjective and are likely to vary between individuals. As we will discuss in our PROMs analysis in *Chapter 4*, sleep quality is, therefore, a complex construct that is likely to require a multifactorial approach to its measurement or evaluation.

Our findings support the perception of a bidirectional relationship between pain and poor sleep described in the Climent-Sanz (2020) synthesis.[33] Our findings also support the complex interconnected relationship between poor sleep, pain and fatigue. Poor sleep is associated with increased pain intensity and fatigue, with pain and fatigue further impairing sleep. The relationship between poor sleep, pain and fatigue was expressed by participants as having the biggest effect on them due to the negative impact that pain and fatigue have on people's ability to perform activities of daily living, such as work demands and family commitments. This leads to feelings of frustration and resentment for some participants. While our data do not allow an interpretation of the direction of causality in the relationship between poor sleep and pain in fibromyalgia, there is evidence from studies of people with various chronic pain conditions and healthy controls that poor sleep is a more reliable predictor of pain than vice versa.[267] It is likely that a biopsychosocial model can be applied to the understanding of the bidirectional sleep–pain relationship.[268] Several central and autonomic nervous systems have been posited as the underlying physiological mechanisms involved in sleep and pain,[10,268,269] while psychological factors such as pain catastrophising have been suggested as mediators in the sleep–pain relationship. In the example of pain catastrophising, it is suggested that people with chronic pain tend to think about their pain in the time leading up to attempting to go to sleep more often than people who do not have chronic pain, and that these thoughts can impair sleep onset and maintenance.[270] Interestingly, several participants in our analysis described developing a fear of going to bed due to the anticipation of not being able to sleep or having poor sleep. This suggests that experiencing negative thought patterns around the time of going to sleep might be common in people with fibromyalgia and other chronic pain conditions. Similarly, several sociodemographic and socioeconomic factors, such as age, sex, education and income, as well as behavioural factors, such as physical activity, alcohol and smoking, have been associated with insufficient sleep.[271] Sleep efficiency has also been identified as a predictor of pain.[272] Again, it is not possible to make causal inferences, but this highlights how the relationship between sleep and pain is complex and may be mediated by several social and behavioural determinants of poor sleep.

Participants described the negative impacts that poor sleep has on their mental health, including impaired ability to perform cognitive tasks and heightened feelings of anxiety. As with the sleep–pain relationship, our data do not allow inferences about the causal direction between poor sleep and poor mental health. People with fibromyalgia are more likely to have higher levels of perceived stress and dysfunctional beliefs about sleep compared with healthy individuals.[273] Higher levels of stress and dysfunctional beliefs are associated with greater sleep disturbance, daytime dysfunction, and poorer sleep quality.[273] General mental health has also been identified as a risk factor for insufficient

sleep.[271] People with fibromyalgia may, therefore, benefit from stress management techniques and therapies that encourage the cognitive reframing of beliefs and attitudes towards sleep. Likewise, people with fibromyalgia may require workplace support to allow them to remain or re-enter the workforce due to the negative impacts that poor sleep has on cognition and fatigue.

Several beliefs about the temporality and causes of poor sleep were discussed by the participants. In addition to the beliefs described in the Climent-Sanz (2020)[33] synthesis regarding working patterns and other symptoms of fibromyalgia, we were able to identify hormonal factors, such as the menopause, and the quality of the sleep environment as important causal beliefs held by the participants. There is a recognised association between perimenopause and menopause and various sleep problems.[274–276] Similarly, our PROMs analysis (see *Chapter 4*) identified the sleep environment as a relevant domain in the measurement of sleep outcomes. It may therefore be important to consider the causal beliefs held by fibromyalgia patients as part of a holistic approach to shaping therapeutic options for poor sleep.

Our analysis confirms the Climent-Sanz (2020) findings that pharmacological treatment is often rejected by people with fibromyalgia due to side effects or a fear of developing medication dependency.[33] While some participants described benefitting from medication, at least in the short term, others described how they did not feel that the quality of their sleep had improved. Instead, medication allowed participants to fall asleep and maintain sleep, but they felt that they had passed out rather than experienced good-quality sleep. Again, this highlights the complexity and subjectivity associated with the concept of 'good-quality sleep'. That the benefits of medication appeared to lessen or disappear over time could indicate that caution should be applied to the long-term prescribing of pharmacological treatments for sleep problems in fibromyalgia patients. Our update also allowed the analysis of participants' experiences of mind–body and multidisciplinary interventions in relation to sleep problems, which was not captured by the original meta-synthesis.[33] As with pharmacological treatments, some participants felt that initial improvements lessened over time, while some experienced increased pain resulting in more sleep disturbance. Careful instruction may, therefore, be required when prescribing treatments that involve an element of physical activity to ensure avoidance of injury. That medication and other management strategies were viewed as being largely ineffective over time indicates that long-term management requires ongoing consideration.

While the participants recognised the principles of good sleep hygiene, they often described adopting maladaptive self-management behavioural adaptations and strategies to cope with poor sleep. While we agree with the authors of the Climent-Sanz (2020) synthesis that this could indicate that patients do not receive adequate information from health professionals to allow them to develop effective strategies for managing poor sleep, our updated findings reveal that individuals experience differing levels of success with various sleep-management strategies and that participants believe that they know what works best for them, even when this might contradict professional advice. This suggests that people with fibromyalgia may welcome flexible, individualised, tailored advice for developing strategies to manage poor sleep rather than a one-size-fits-all approach.

Strengths and limitations

We used established and scientifically rigorous methods for the conduct, quality assessment and reporting of our updated evidence synthesis. Our update confirms and extends the findings of the Climent-Sanz (2020)[33] synthesis with nine additional studies, four of which evaluated the experiences of people with fibromyalgia who have used mind–body interventions for managing their fibromyalgia symptoms. Two further studies evaluated the experiences of fibromyalgia patients who attended group-based interventions for symptom management. Our update also provides a critical appraisal of the certainty of findings, which was not previously reported in the Climent-Sanz (2020) synthesis.[33] While we have taken a systematic and rigorous methodological approach to this update of existing evidence, we acknowledge that qualitative interpretive approaches are subjective, and it is possible that different overall findings may have emerged had this update been conducted by other researchers. We broadened the inclusion criteria of the Climent-Sanz (2020)[33] synthesis to consider adult and child populations and removed all language restrictions from our literature search. Unfortunately, we did not identify any eligible studies conducted in children. It is a limitation that the experiences of children who have fibromyalgia-related sleep problems are not captured in this update. We also did not identify any eligible studies published in non-English or non-Spanish languages. Although we employed hand-searching of the reference lists of included studies, we did not systematically search the grey literature. It is, therefore, unclear

whether any relevant unpublished reports have been missed. Due to the limited reporting of participant demographic data by the authors of the included studies, it is unclear whether the study participants are representative of the wider population of fibromyalgia patients. Similarly, it was not possible to analyse data for diverse demographic groups, for example by race, ethnicity, or socioeconomic status, due to the way these data were reported by the study authors. We did not identify any eligible studies from low- or middle-income countries. It is therefore unclear whether people living with fibromyalgia in low resource settings have different experiences from people who live in high-income countries. Finally, one of the studies conducted by Colas and colleagues (2021) interviewed participants during the first COVID-19 national lockdown in France during April 2020 and May 2020.[246] It is unclear whether the participants' experiences of managing their fibromyalgia-related sleep problems were impacted differently during the lockdown period and the beginning of the COVID-19 pandemic, or to what extent they were impacted differently, than at any other point in time. It is, therefore, possible that the experiences of the participants in this study are less reflective of people living with fibromyalgia; however, we did not find any substantial differences in the findings for this study compared with the other studies included in our synthesis.

What this update adds to previous knowledge

By providing insights into people's experiences of mind–body interventions and complex multidisciplinary group-based interventions to improve sleep, the findings of this evidence synthesis validate, confirm and extend the original findings published in 2020 by Climent-Sanz *et al*.[33] Our updated synthesis also identified additional beliefs held by fibromyalgia patients about the causes of their poor sleep and highlighted the lack of data on the experiences of children and adolescents with fibromyalgia-related sleep problems and on adults from diverse and under-served groups. We also applied the GRADE-CERQual tool to the findings of our synthesis to provide an assessment of the confidence in the overall findings, which was not included in the original meta-synthesis. To assess the confidence in our overall findings, we applied the GRADE-CERQual tool to all qualitative studies, the newly identified studies and those included in the original meta-synthesis.

Chapter 4 Fibromyalgia-specific patient-reported outcome measures of sleep outcome measures

Introduction

Patient-reported outcomes are defined as outcomes that are reported directly by the patient and are often collected using questionnaires called patient-reported outcomes measures (PROMs).[277] PROMs provide a useful way to obtain standardised measurements of a patient's health status and/or quality of life and can be used to assess and compare treatment outcomes from the patient's perspective.[277] Generic PROMs have been developed for use across different health conditions, while disease-specific PROMs measure aspects of health that are relevant to a particular health condition.

Individual PROMs can be made up of numerous items and scales that should assess outcomes that matter to patients. However, the diversity of items and scales between different PROMs can result in the combining and aggregation of dissimilar items and scales that, on face value, appear to be measuring similar concepts or result in measuring different aspects of the outcome of interest. It is, therefore, important to establish whether items contained in PROMs are comparable across different measures to determine whether PROMs data can be meaningfully pooled. There are a variety of ways to measure PROMs depending on whether the intention is to allow generic or disease-specific comparisons and depending on differences in how PROMs developers have considered the relevant concepts of interest when developing question items.[278] For instance, of two PROMs that measure quality of life, one might have items that consider concepts such as pain, sleep quality, fatigue and return to normal activities, while the other might have items that consider pain and physical aspects such as the inability to undertake activities of daily living, but not sleep. Without conducting an item analysis, it would be difficult to establish their comparability. Variability in individual items included in these tools and how they contribute to the overall 'quality of life' assessment can raise questions about the legitimacy of combining these measures in meta-analyses. For example, an analysis of PROMs used in studies of radical treatments for oesophageal cancer identified 32 different health domains from 21 PROMs that included 116 scales and 32 single items.[279] The authors noted that 94 different verbatim names were used to describe the PROM scales and single items and, while many of these names were similar, content analysis showed that the component questions did not always measure comparable issues. Similarly, a synthesis of PROMs in colorectal cancer surgery identified 51 health domains from 50 PROMs that included over 900 question items.[278] The authors noted that none of the PROMs measured all 51 domains and found major heterogeneity of PROM measurement and variation in the assessed content. The findings from both these analyses highlight how the variation in measuring PROMs in clinical trials can hinder comparisons between studies.

Methods to determine the validity and methodological quality of outcome measurements have been developed through the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN), which aim to improve the selection of health measurement instruments.[280] Climent-Sanz and colleagues (2020) recently published a systematic review to identify and describe existing sleep outcome PROMs used in studies that recruited adults diagnosed with fibromyalgia.[35] The review identified seven reports of five PROMs: the FMSD,[39] the JSS,[281] the MOS-SS,[256,282,283] the PSQI[284] and the SQ-NRS.[40,256] With the exception of the FMSD, the PROMs were not developed with a fibromyalgia patient population and can be used to measure sleep outcomes in different health conditions. Climent-Sanz and colleagues (2020) assessed the five PROMs as valid and reliable tools for assessing sleep quality in the context of fibromyalgia, although none met the full COSMIN criteria.[35] While the review examined the psychometric properties of the PROMs, the items contained within the different measures were not compared to each other. It is, therefore, unclear if important sleep domains are missing and whether the PROMs are similar enough to be combined in evaluations of interventions to treat fibromyalgia-related sleep problems. We therefore sought to examine the item variability of PROMs of sleep outcomes for people with fibromyalgia. Since the Climent-Sanz (2020)[35] review focused exclusively on studies that assessed adults with fibromyalgia published in English or Spanish, we also updated and extended the scope of the review to identify any additional PROMs in adults and children without applying any language restriction.

Methods

Search methods for identification of studies

The search strategy of the Climent-Sanz *et al.* synthesis was developed based on the COSMIN 'search filters for finding studies on measurement properties' provided as an additional tool in the COSMIN website[285] and was performed on 6 March 2020. We repeated the Climent-Sanz *et al*. searches to identify relevant reports published from 6 March 2020 to 5 November 2021. Additionally, their searches were repeated with text terms to identify studies including children that were excluded from their original synthesis; these searches covered all years to 17 November 2021.

Inclusion criteria

Studies reporting sleep measures validated in people with fibromyalgia were eligible for inclusion in our review. All measures identified (as opposed to included) in the Climent-Sanz *et al*. synthesis were included in our PROMs analysis, as our purpose was to critique item coverage, not psychometric properties, which are already addressed by the existing evidence synthesis. A summary of eligibility criteria is shown in *Table 13*.

Where eligible studies included PROMs that were originally developed in a non-fibromyalgia patient population, we also consulted the original development study to inform our analysis where this was possible.

Exclusion criteria

Studies of sleep measures validated in people with clinical conditions other than fibromyalgia were excluded.

Study selection and data extraction

Literature search results were screened by two reviewers (CR, MI) to identify relevant studies reporting PROMs. To ensure consistency, the reviewers independently screened 10% of all citations identified by the search strategies and compared screening decisions at the beginning of the study selection process. To ensure accuracy, each reviewer checked the data extracted by the other review author for 10% of all included studies.

Data were extracted on:

- the name of the PROM(s)
- the reported PROMs scales
- individual verbatim items, and
- whether and how patients were involved in tool development.

Data analysis

The analysis was informed by previous research that has analysed PROMs into individual outcome domains.[286]

The individual verbatim items from each PROM were analysed by using an inductive content analysis approach. All PROM items were examined and systematically categorised into conceptual health domains according to the aspect which they aimed to capture; however, items were coded to more than one domain where appropriate.

TABLE 13 Eligibility criteria for the published COSMIN systematic review of PROMs measuring sleep outcomes in fibromyalgia

Type of studies	Type of participants
• Validation or cross-cultural adaptation studies. • Studies that report the item development of PROMs originally developed in the context of fibromyalgia.	• Validation or cross-cultural adaptation studies involving adult and child participants (as defined by the studies' authors) diagnosed with fibromyalgia.

Domains were generated inductively from the identified individual items and were informed by terms and definitions contained in the Sleep Foundation Dictionary[287] and the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF).[288] Domain mapping was conducted independently by the two review authors with assistance from a senior member of the research team (KG) with experience in PROM coding. Any disagreements were resolved through discussion or referred to another member of the team with research and/or clinical expertise in sleep (DW and NT) and our patient representative (DD) as appropriate. The patients' input in the item inception and development phases of the PROMs measures was also recorded. The PROM items and their associated domain categories were summarised narratively.

Results

Descriptive characteristics: included studies

Our updated literature searches identified 292 titles and abstracts. Following title and abstract screening, 19 reports were selected for full-text eligibility assessment. After full-text assessment, one report associated with a study already identified by the original search strategies developed by Climent-Sanz *et al.*[35] was considered eligible for inclusion. This report is a validation study of a Turkish version of the JSS.[289] Thus, the current evidence base in terms of PROMs consists of a total of eight reports related to five studies. We did not identify any new PROMs tools validated for sleep outcomes in people with fibromyalgia. All included reports are published in English and focus only on adult participants. A visual summary of the study screening process is provided as *Figure 9*. The bibliographic details of the included studies are provided in *Report Supplementary Material 13*.

Across both the Climent-Sanz (2020) review and our current review, the studies were published between 2009 and 2020 and were conducted in the USA,[39,40,256,281–283] Spain[284] and Turkey.[289] Three of the PROMs are associated with development studies that were conducted in non-fibromyalgia patient populations. The JSS was developed for use in the general population by Jenkins and colleagues (1988)[38] in a population of air traffic controllers[290,291] and cardiac surgery patients.[292,293] The JSS was validated with fibromyalgia patients in the included studies conducted by Crawford and colleagues (2010)[281] and Unal-Ulutatar and Ozsoy-Unubol (2020).[289] The MOS-SS was developed in individuals with chronic illnesses[37] and was subsequently validated with fibromyalgia patients in the studies by Cappelleri and colleagues (2009),[283] Martin and colleagues (2009)[256] and Sadosky and colleagues (2009).[281] The PSQI was developed with people with major depressive disorder and healthy controls.[36] The Spanish version of the PSQI was validated with fibromyalgia patients by Hita-Contreras and colleagues (2014).[284] A summary of the study and participant characteristics of the development studies is presented in *Appendix 7*, *Table 23*.

The baseline participant and study characteristics of the included studies are summarised in *Table 14*. The included studies report data for 3226 people with fibromyalgia. The two reports conducted by Cappelleri and colleagues (2009) detailing the evaluation of the MOS-SS[283] and the SQ-NRs[40] were both based on data from fibromyalgia participants recruited to two randomised, double-blind, placebo-controlled trials of pregabalin: studies 1056 (n = 748) and 1077 (n = 745). The report by Martin and colleagues (2009) evaluated both the MOS-SS and SQ-NRS; therefore, the same participant sample (n = 20) was used for both analyses in this report.[256] Across studies the majority (92.8%) of participants were middle-aged women; the youngest and oldest reported mean ages were 44.3 years[289] and 52.8 years,[284] respectively. Race and ethnicity were NR by three studies.[282,284,289] In the two studies that reported race and ethnicity, the majority of participants were white [2604/2878 (90.5%)]. The studies often did not report baseline socioeconomic data such as educational attainment level or employment status. Of the three studies that did report education, half of participants were educated to high-school/college level [120/239 (50.2%)].[256,284,289] Of the three studies that reported participant employment status most participants [180/288 (62.5%)] were unemployed or retired.[39,256,284]

Descriptive characteristics: patient-reported outcome measures from included studies

Information on the characteristics of the PROMs identified in the included studies is presented in *Table 15*. Only one study reported including patients in the conceptual item identification stage of the PROMs tool.[39] In this study, focus groups were conducted with 34 fibromyalgia patients who experienced sleep disturbance to inform the development of a conceptual framework for the FMSD. Cognitive interviews were then conducted with a further 15

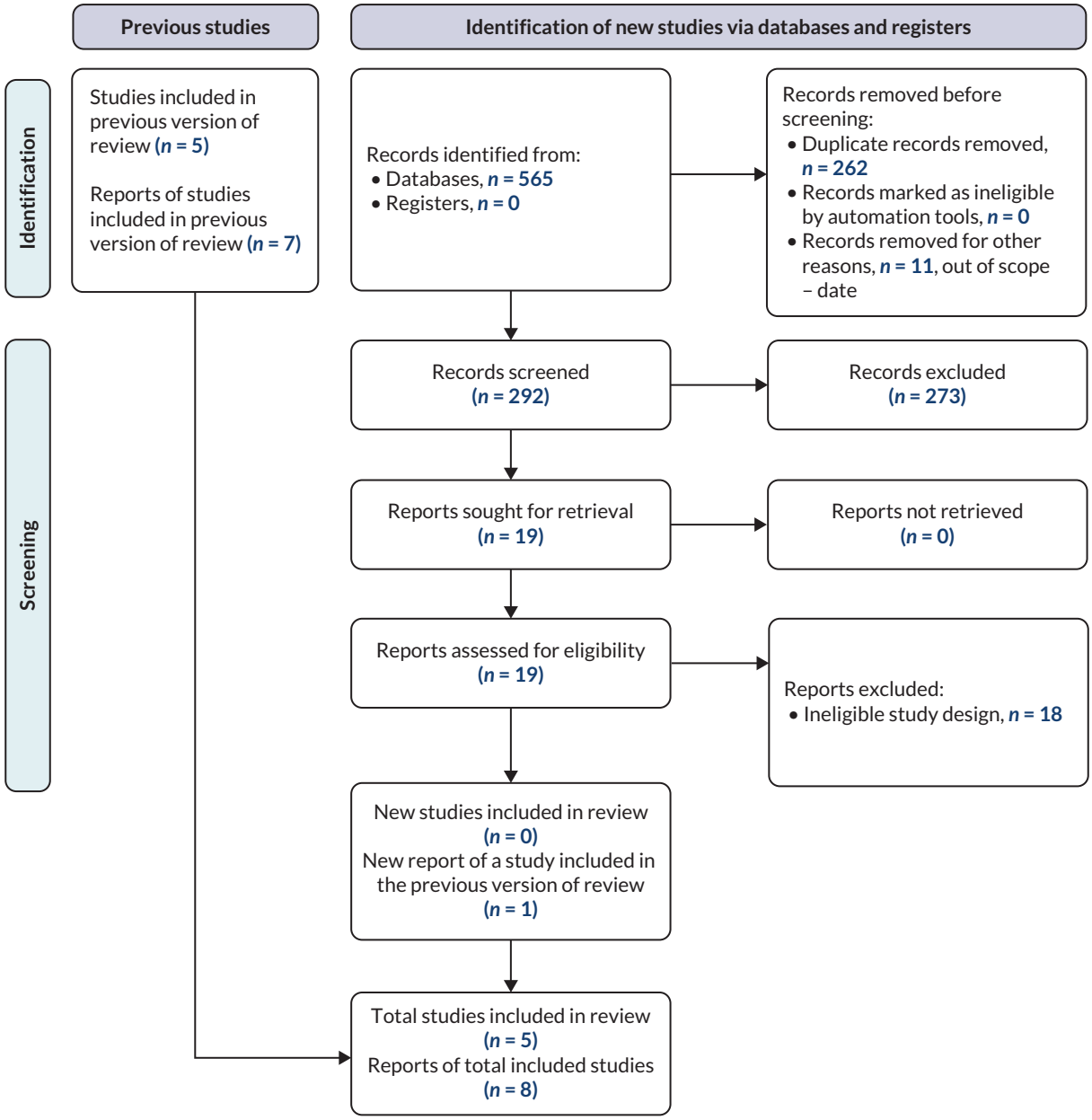

FIGURE 9 Preferred reporting items for systematic reviews and meta-analyses flow diagram for identification of the PROM studies.[50]

fibromyalgia patients to explore the content validity of the FMSD. Cognitive interviewing is a method that is used in the development of PROMs. Cognitive interviews are used to evaluate whether the tool sufficiently captures the concept of interest and checks whether participants' understanding of how to complete the PROM is as intended by the PROM developers, including the participants' interpretation of the meaning of the PROMs items, recall period and how to complete the response scales.[294] Cognitive interview results showed that the concepts were relevant to fibromyalgia patients and content was interpreted as intended.

In addition to the FMSD, two reports explored the content validity of two further PROMs for fibromyalgia patients: the MOS-SS[256] and the SQ-NRS.[256] For the MOS-SS, Martin and colleagues (2009) held qualitative cognitive debriefing with 20 adult fibromyalgia participants using a 'think-aloud' process.[256] In general, participants found the measure to be relevant to their sleep symptoms. However, participants indicated that several items in the MOS-SS could be re-worded, split, or deleted to improve relevance for fibromyalgia patients, and that some important concepts were not captured, such as 'trouble waking up' or 'getting out of bed, and other non-sleep specific symptoms or impacts of fibromyalgia'. The authors state that further research to address these modifications could improve the psychometric

TABLE 14 Main characteristics of the included PROMs studies

PROM, Country, Author ID	PROM general characteristics	Sample size	FM participant characteristics	Methods of the study
FMSD USA *Kleinman 201439*	The tool was created to measure sleep disturbance in FM patients	Total FM patients: *n* = 49 Focus group participants *n* = 34 Cognitive interview participants *n* = 15 The sample also included therapeutic area experts in FM *n* = 4	*Focus group* (*n* = 34) Age (years), mean (SD) range: 47.8 (11.9); 22–70 Gender, *n* (%): male: 4 (11.8%), female: 30 (88.2%) Race/ethnicity, *n* (%): white: 25 (73.5%) Hispanic or Latino: 8 (23.5%) black or African American: 1 (2.9%) Asian: 2 (5.8%) Native Hawaiian or other Pacific: 4 (11.7%) American Indian or Alaska Native: 1 (2.9%) other: 6 (17.6%) Marital status: NR Sociodemographic status: Employment status, *n* (%): employed, full-time: 7 (20.5%) employed, part-time: 9 (26.4%), homemaker: 2 (5.8%) student: 1 (2.9%) unemployed: 7 (20.5%) retired: 3 (8.8%) disabled: 9 (26.4%) other: 2 (2.8%) unemployed or disabled due to FM (*n*, %): yes 10 (62.5), no 6 (37.5%) *Cognitive interview participants* (*n* = 15) Age (years), mean (SD) range: 51.4 (10.1); 27–64 Gender, *n* (%): male: 1 (6.7%), female: 14 (93.3%) Race/ethnicity, *n* (%) white: 11 (73.3%) Hispanic or Latino: 0 (0%) black or African American: 3 (20.0%) Asian: 1 (6.7%) Native Hawaiian or other Pacific: 0 (0%) American Indian or Alaska Native: 0 (0%) other: 0 (0%) Marital status: NR Sociodemographic status: Employment status, *n* (%): employed, full-time: 4 (26.7%) employed, part-time: 1 (6.7%) homemaker: 1 (6.7%) student: 0 (0%) unemployed: 3 (20.0%) retired: 2 (13.3%) disabled: 6 (40.0%) other 0 (0%) unemployed or disabled due to FM (*n*, %): yes 7 (77.8%), no 2 (22.2%)	(1) A literature review identified key concepts associated with FM patients' experience of sleep and relevant PROMs; (2) Qualitative interviews with therapeutic experts; (3) Focus groups with FM patients; (4) Development of a conceptual framework and the FMSD and 5) Cognitive interviews with FM patients to explore the content validity of the FMSD.

TABLE 14 Main characteristics of the included PROMs studies (*continued*)

PROM, Country, Author ID	PROM general characteristics	Sample size	FM participant characteristics	Methods of the study
JSS USA Crawford 2010[281] JSS-TR Turkey Unal-Ulutatar 2020[289]	The tool assesses common sleep symptoms during the previous month.	Crawford 2010[281] Total *n* = 1316 One Phase 2 validation trial (*n* = 195) and two Phase 3, RCTs (*n* = 1121) in patients with fibromyalgia Unal-Ulutatar 2020[289] Total *n* = 81	*Crawford 2010*[281] *Phase 2 Validation trial (n = 195)* Age (years), mean (SD) (range): 46.5 (11.35) [20–83] Gender, *n* (%): male: 11 (5.6%) female: 184 (94.4%) Race/ethnicity, *n* (%): white/Caucasian: 180 (92.3%) black/African American: 11 (5.6%) Asian: 1 (0.5%) American Indian/Alaska Native: 0 (0%) other: 3 (1.5%)	*Crawford 2010*[281] Analysis began with the Phase 2 trial and was then followed by the two Phase 3 trials. The number of missing responses for each item over time, the. internal consistency reliability, test–retest reliability and responsiveness to change were evaluated. Construct validity was measured by examining correlations of the rescored JSS with other patient-reported outcome (PRO) scales: the Pain VAS, Fatigue VAS, FOSQ, SF–36, FIQ, and ESS. *Unal-Ulutatar 2020*[289] The JSS-TR was performed twice with a fortnightly interval. The intraclass correlation coefficient was used to evaluate test–retest reliability. The internal consistency was assessed by Cronbach's alpha coefficient. Convergent validity was measured via the correlation between the JSS-TR and PSQI, FIQ, FSS, EQ-5D-3 L and BDI.
			Marital status: NR Sociodemographic status: NR Time since first fibromyalgia symptoms (years), mean (SD) [range]: 10.6 (8.40) [0–41] Time since first fibromyalgia diagnosis (years), mean (SD) [range]: 6.0 (6.02) [0–41] *Trial 1 (n = 548)* Age (years), mean (SD) [range]: 47.0 (11.26) [18–79] Gender, *n* (%): male: 48 (8.8%); female: 500 (91.2%) Race/ethnicity, *n* (%): white/Caucasian: 498 (90.9%) black/African American: 33 (6.0%) Asian: 7 (1.3%) American Indian/Alaska Native: 6 (1.1%) other 4 (0.7%)	

continued

TABLE 14 Main characteristics of the included PROMs studies (*continued*)

PROM, Country, Author ID	PROM general characteristics	Sample size	FM participant characteristics	Methods of the study
			Marital status: NR Sociodemographic status: NR Time since first fibromyalgia symptoms (years), mean (SD) [range]: 9.7 (8.49) [0–47] Time since first fibromyalgia diagnosis (years), mean (SD) [range]: 5.9 (6.75) [0–39] *Trial 2 (n = 573)* Age, (years), Mean (SD) [range]: 46.6 (10.72) [19–80] Gender, *n* (%): M: 60 (10.5%); F: 513 (89.5%) Race/ethnicity, *n* (%): white/Caucasian: 524 (91.4%) black/African American: 39 (6.8%) Asian: 4 (0.7%) American Indian/Alaska Native: 3 (0.5%) other: 3 (0.5%)	
			Marital status: NR Sociodemographic status: NR Time since first fibromyalgia symptoms (years), mean (SD) [range]: 9.7 (8.75) [0–51] Time since first fibromyalgia diagnosis (years), mean (SD) [range]: 4.9 (5.61) [0–48] *Unal-Ulutatar 2020*[289] Age (years), mean (SD) minimum–maximum: 44.28 (10.6) 19–70 Gender, *n* (%): male; 10 (12.3%), female: 71 (87.7%) Race/ethnicity: NR	
			Marital status, *n* (%): married: 63 (77.8%) single: 18 (22.2%) Sociodemographic status: Education, *n* (%): primary-secondary school: 55 (67.9%) high school: 12 (14.8%) university: 14 (17.3%) Work status, *n* (%): employed: 24 (29.6%) unemployed: 55 (67.9%) retired: 2 (2.5%) Symptom duration (months), mean (SD) minimum-maximum: 47.88 (69.83) 3–480 Disease duration (months), mean (SD) minimum-maximum: 5.31 (12.89) 0–96	

TABLE 14 Main characteristics of the included PROMs studies (*continued*)

PROM, Country, Author ID	PROM general characteristics	Sample size	FM participant characteristics	Methods of the study
MOS-SS USA *Cappelleri 2009*[283] *Martin 2009*[256] *Sadosky 2009*[282]	The MOS-SS tool assesses sleep quality	*Cappelleri 2009*[283] *n* = 1493 FM patients were recruited from two RCTs (trial 1077 and trial 1056) comparing pregabalin vs. placebo *Martin 2009*[256] *n* = 20 *Sadosky 2009*[282] *n* = 129 Total *n* = 1642	*Cappelleri 2009*[283] *Trial 1056 (n = 748)* Age (years), mean (SD) 95% CI: 48.8 (10.9) 48.0 to 49.6 Gender, *n* (%): male: 42 (5.6), female: 706 (94.4) Race/ethnicity, *n* (%): white 675 (90.2%), black 35 (4.7%), other 38 (5.1%) Marital status: NR Sociodemographic status: NR Duration of FM prior to study start (months), mean (SD) 95% CI: 111.7 (95.0) 104.9 to 118.5 (*n* = 747) *Trial 1077 (n = 745)* Age (years), mean (SD) 95% CI: 50.1 (11.4) 49.3, 50.9 Gender, *n* (%): male: 41 (5.5), female: 704 (94.5) Race/ethnicity, *n* (%): white: 678 (91.0%), black: 33 (4.4%), Other: 34 (4.6%) Marital status: NR Sociodemographic status: NR Duration of FM prior to study start, (months) mean (SD) 95% CI: 120.2 (96.2) 113.3 to 127.1	*Cappelleri 2009*:[283] The MOS-SS was completed by FM patients at baseline and end of treatment The patients' scores were compared with scores obtained from a nationally representative sample in the USA. *Martin 2009*:[256] Twenty adults with FM were asked to complete each question using a 'think-aloud' process and answer follow-up probes from the interviewers related to the content, wording and comprehension of the item and gave feedback on their relevance to FM and suggest improvements. *Sadosky 2009*:[282] The MOS-SS was completed by FM patients with a current pain rating of > 2 on a 0–10 point NRS. All patients completed the 4-week and 1-week recall period versions of the MOS-SS. The test and retest of the 4- week recall version was separated by a time interval ranging between 1 and 3 days. The test–retest period of the 1-week recall version was 7 days.

continued

TABLE 14 Main characteristics of the included PROMs studies (*continued*)

PROM, Country, Author ID	PROM general characteristics	Sample size	FM participant characteristics	Methods of the study
			Martin 2009[256] Age (years), mean (range): 50.3 (29–64) Gender, *n* (%): male: 4 (20%) female: 16 (80%) Race/ethnicity, *n* (%): white: 13 (65%) black: 7 (35%) Marital status: NR Sociodemographic status: Education, *n* (%): advanced degree: 3 (15%) college graduate: 2 (10%) associates degree: 2 (10%) some college: 9 (45%) high-school degree or equivalent: 4 (20%) Employment status, *n* (%): employed full-time: 5 (25%) employed part-time: 1 (5%) unemployed: 1 (5%) disabled: 8 (40%) retired: 3 (15%) other: 2 (10%) Years since diagnosis of FM, mean (range): 8.9 (< 1–18) Average (SD) of reported pain level, 0–10-point scale where 0 indicates no pain and 10 indicates worst possible pain: 6.0 (1.6) *Sadosky 2009*[282] Age (years), mean (SD): 49.4 (11.0) Gender, %: male: 8.7%, female: 91.3% Race/ethnicity: NR Marital status: NR Sociodemographic status: NR Severity of FM, moderate, %: 88.1% ≥ 2 years since diagnosis, %: 88.3%	

TABLE 14 Main characteristics of the included PROMs studies (*continued*)

PROM, Country, Author ID	PROM general characteristics	Sample size	FM participant characteristics	Methods of the study
PSQI Spanish version Spain *Hita-Contreras 2014*[284]	The PSQI was developed to provide a reliable, valid and standardised measure of sleep quality; to discriminate between 'good' and 'poor' sleepers; and to provide a brief, clinically useful assessment of a variety of sleep disturbances that might affect sleep quality.	Total *n* = 138	Age (years), mean (SD): 52.83 (9.32) Gender, %: male: 0 (0%), female: 138 (100%) Race/ethnicity: NR Marital status: NR Sociodemographic status: Education *n* (%): primary education: 62 (44.9%) secondary education: 38 (27.5%) tertiary education: 14 (10.1%) Occupation *n* (%): retired: 58 (42.0%) working: 34 (24.6%) unemployed: 46 (33.3%) Years since FM was diagnosed, mean (SD) 8.27 (5.65) Years since fibromyalgia pain onset, mean (SD): 15.77 (9.76)	The English version of the PSQI was independently translated into Spanish by two bilingual experts. The Spanish version was then completed by 20 women with FM to verify their comprehension. The bilingual experts then compared the translated version with the original to check semantic and linguistic equivalence. The Spanish version was then completed by 96 participants. These results were compared with those obtained from the same participants two weeks earlier to evaluate test–retest reliability. Some of the Spanish PSQI items were modified because of cultural differences.
SQ-NRS USA *Cappelleri 2009*[40] *Martin 2009*[256]	The SQ-NRS was developed to allow a quick-to-complete daily record of the quality of sleep and to provide a generic approach to the global impact of sleep problems in patients with FM.	Total *n* = 1513 *Cappelleri 2009*:[40] *n* = 1493 FM patients recruited from two RCTs (trial 1077[124] and trial 1056[126]) comparing pregabalin vs. placebo *Martin 2009*:[256] *n* = 20 FM patients	See descriptions for the participants included in the MOS-SS validation studies conducted by Cappelleri 2009 and Martin 2009	*Cappelleri 2009*:[40] Test–retest reliability was evaluated by computing intraclass correlation coefficients. Responsiveness to treatment was evaluated by standardised effect sizes (difference between least squares mean changes in Sleep Quality scores in the two treatment groups divided by the SD of Sleep Quality scores across all patients at baseline). *Martin 2009*:[256] Twenty adults with FM were asked to complete each question using a 'think-aloud' process and answer follow-up probes from the interviewers related to the content, wording and comprehension of the item. Participants also provided feedback on, the item's relevance to FM and offered suggestions for improvement.

BDI, Beck Depression Inventory; EQ-5D, European Quality of Life Scale-5 Dimensions; FM, fibromyalgia; FSS, Fatigue Severity Scale; JSS-TR, JSS Turkish version.

performance of the MOS-SS for fibromyalgia patients. To our knowledge, the MOS-SS currently remains a generic instrument and has not been adapted for fibromyalgia patients. Martin and colleagues (2009) used the same method to explore the content validity of the SQ-NRS with the same sample of fibromyalgia patients.[256] The authors reported that most participants responded positively when asked how well the SQ-NRS captured the effect of fibromyalgia on their sleep. As with the MOS-SS, some participants stated that specific details regarding their sleep were not captured, such as the number of awakenings through the night, the ability to go to sleep, reasons for poor sleep quality and non-sleep-related fibromyalgia symptoms; however, the authors note that the brevity and ease of use of the SQ-NRS support its use in research and clinical practice.

The JSS was evaluated for construct validity, reliability and ability to detect a change in fibromyalgia patients.[281] The Spanish version of the PSQI concentrated on validating the translation of items with fibromyalgia patients.[284] It is unclear whether the authors also explored the content validity of the PSQI for fibromyalgia patients.

The total number of items varied across PROMs, ranging from 1 item in the SQ-NRS to 24 items in the PSQI. However, one of the items contained in the PSQI concerns information about whether the respondent shares a bed with a partner or has a roommate. Five additional items are answered by the bed partner or roommate rather than the patient. These six items are used for clinical information only and are not used for calculating the global PSQI score. The PSQI is the only one of the five tools to include questions addressing roommates. These six items were not included in our analysis. Our analysis, therefore, included a cumulative total of 43 individual items across the five PROMs (median = 8).

Two PROMs included 11-point NRS response options (the FMSD and SQ-NRS) and the remaining PROMs included a range of four- to six-point Likert scales and numerical response options. The PROMs varied in terms of their cut-offs to determine what constitutes significant sleep problems. Except for the five items directed at bed or roommates contained in the PSQI, all items were self-completed by the patient. The recall period of the PROMs ranged from 24 hours (FMSD and SQ-NRS) to 4 weeks (JSS, MOS-SS and PSQI). The MOS-SS was reported to take 3–5 minutes and the PSQI was reported to take 5–10 minutes for the participant to complete. The studies did not report the time taken to complete the remaining PROMs.

Item domain classification

Our review identified 21 relevant sleep domains representing the 43 items contained in the 5 PROMs. During analysis it was determined that question item 3 contained in the FMSD was considered to measure two domains: *sleep maintenance* and *degree of sleep disturbance*. The domains are, therefore, represented by 44 items. *Table 16* presents a summary of the domain labels, definitions and example items from the PROMs. The domains are conceptually distinguishable, but many are closely related. We often found it challenging to separate items measuring sleep maintenance and sleep disturbance as the items in these domains share a high degree of relatedness. It also important to note that we used the term *non-restorative sleep* as our domain name for coding question item 4 of the JSS: '*During the past month did you wake up after your normal amount of sleep feeling tired and worn out*?'. Our coding and definition for this domain were informed by current published literature and advice from our clinical expert (NT).[295] A summary table of the domain coding for each of the verbatim PROMs items is presented in *Report Supplementary Material 14*.

All PROMs (FMSD, JSS, MOS-SS and the PSQI) can be considered as being multi-dimensional (i.e. capturing more than one domain) based on their coded domains, apart from the SQ-NRS, which can be considered as being unidimensional (i.e. only capturing one domain) as this tool contains only one item: *sleep quality*. The PSQI is considered the most comprehensive tool as this includes 15 of the 21 identified domains, followed by the MOS-SS, which included 11 domains. *Table 17* presents
the domains identified across the included PROMs. We identified 12 items that reported measuring the broad concept of sleep disturbance across two PROMs tools (the MOS-SS and PSQI); however, these individual items measure seven different types of sleep disturbance, as presented in *Table 17*. Given that clinical treatments and patient management strategies might differ depending on the underlying causes of sleep disturbance, we chose to code these items as distinct domains according to the type of sleep disturbance being measured, rather than group the items under a broad sleep-disturbance domain. Two items from the FMSD and the MOS-SS were coded as measuring the *degree of sleep*

TABLE 15 Characteristics of the included PROMs

Tool, Country, Reference ID	Dimension (number of items)	Response options and scoring	Mode of administration	Tool recall period	Time to complete	Were patients/ participants involved in developing the tool items?	Content validity for FM patients explored?	Sample items
FMSD USA *Kleinman 2014*[39]	8 items	11-point numerical scale ranging from 0 to 10. Alternative response options included using the 'worst possible symptom and best possible symptom' as anchor points as well as 'no difficulty' and 'worst possible difficulty'.	Self-completion	Daily	NR	Yes Qualitative interviews with therapeutic area experts (n = 4) and focus groups with FM patients (n = 34) who experienced sleep disturbance were conducted to inform the development of a conceptual framework and the FMSD.	Yes	How difficult was it to fall asleep last night?
JSS *Jenkins 1988*[38] *Crawford 2010*[281] JSS-TR *Unal-Ulutatar 2020*[289]	4 items	Six-point Likert scale where 0 indicates no sleep problems and 5 indicates frequent sleep problems. The JSS is scored as the sum of the four items, resulting in a score from 0 to 20. Higher scores indicate greater sleep problems (0 indicates no sleep problems and 20 points indicates significant sleep problems).	Self-completion	4 weeks	NR	*Jenkins 1988*[38] Unclear *Crawford 2010*[281] No *Unal-Ulutatar 2020*[289] No	No	During the past month did you have trouble falling asleep?

continued

TABLE 15 Characteristics of the included PROMs (*continued*)

Tool, Country, Reference ID	Dimension (number of items)	Response options and scoring	Mode of administration	Tool recall period	Time to complete	Were patients/ participants involved in developing the tool items?	Content validity for FM patients explored?	Sample items
MOS-SS USA *Hays 1992*[37] *Cappelleri 2009*[283] *Martin 2009*[256] *Sadosky 2009*[282]	12 items with 6 sleep domains derived subscales. Answers are based on a retrospective assessment over the past 4 weeks There is a nine-item version of the MOS-SS, named Sleep Problems Index II and a 6-item version defined as the Sleep Problems Index I. Neither of the scales excludes any item from the original scale, but rather groups them in unique items so that the only difference is that these two scales are shorter.	One open numerical response option (item 2), one five-point Likert scale (item 1) and 10 six-point Likert scales (items 3 to 12). Quantity of sleep is scored as the average hours slept per night. The other scales and problems index are scored on a 0–100 possible range, except the 'quantity of sleep' item (ranges between 0 and 24) and the 'adequacy of sleep' item (ranges between 0 and 1). High scores indicate worse sleep problems, except for the 'sufficiency of sleep' and 'sleep quantity' items, where lower scores indicate worse sleep problems.	Self-completion	4 weeks	3–5 minutes	*Hays 1992*[37] Unclear The 12 MOS-SS items were identified based on two pilot studies that tested 17 items, but it is NR whether patients had any input to the development of the items beyond piloting the tool to assess whether the tool items could be scored separately and to identify the smallest number of items necessary to assess the independent sleep dimensions. *Cappelleri 2009*,[283] *Martin 2009*,[256] *Sadosky 2009*[282] No	Yes	How often during the past 4 weeks did you feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc.) while sleeping? - All of the time - Most of the time - A good bit of the time - Some of the time - A little of the time - None of the time

TABLE 15 Characteristics of the included PROMs (*continued*)

Tool, Country, Reference ID	Dimension (number of items)	Response options and scoring	Mode of administration	Tool recall period	Time to complete	Were patients/ participants involved in developing the tool items?	Content validity for FM patients explored?	Sample items
PSQI USA *Buysse 1989*[36] Spain *Hita-Contreras 2014*[284]	18 items, which combine to form 7 component scores to generate a global score that is used to determine cut-offs for good or poor sleep. Six additional questions rated by the bedpartner or roommate are used for clinical information only and are not tabulated in the scoring of the PSQI.	Mixture of four-point Likert scales and numerical coding of the following items: usual bedtime, number of minutes taken to fall asleep, usual getting up time and number of hours sleep per night. The 19 self-rated items are combined to form seven 'component' scores, each of which has a range of 0–3 points. A score of '0' indicates no difficulty, while a score of '3' indicates severe difficulty. The seven component scores are then added to give one 'global' score, with a range of 0–21 points, '0' indicating no difficulty and '21' indicating severe difficulties in all areas.	Self-completion	4 weeks	5–10 minutes	*Buysse 1989*[36] No Items in the PSQI were derived from three sources: clinical intuition and experience with sleep disorder patients; a review of previous sleep quality question-naires reported in the literature; and clinical experience with the instrument during 18 months of field testing. *Hita-Contreras 2014*[284] No Some of the translated Spanish PSQI items were modified because of cultural differences but the translations were conducted by two bilingual experts and not FM patients	*Hita-Contreras 2014*[284] No Some of the translated Spanish PSQI items were modified because of cultural differences, but content validity for FM not explored.	During the past month, how often have you had trouble sleeping because you… Cannot get to sleep within 30 minutes - Not during the past month - Less than once a week - Once or twice a week - Three or more times a week

continued

TABLE 15 Characteristics of the included PROMs (*continued*)

Tool, Country, Reference ID	Dimension (number of items)	Response options and scoring	Mode of administration	Tool recall period	Time to complete	Were patients/ participants involved in developing the tool items?	Content validity for FM patients explored?	Sample items
SQ-NRS USA *Cappelleri 2009*[40] *Martin 2009*[256]	1 item	11-point numeric scale ranging from 0 ('best possible sleep') to 10 ('worst possible sleep').	Self-completion	24 hours	NR	*Cappelleri 2009*[40] Unclear *Martin 2009*[256] No	Yes	Please complete the following question upon awakening. Select the number that best describes the quality of your sleep during the past 24 hours. (Circle one number only.) 0 1 2 3 4 5 6 7 8 9 10

FM, fibromyalgia; JSS-TR, JSS Turkish version.

disturbance, and this was considered as a further distinct domain associated with sleep disturbance. The most frequently reported domains across the PROMs were *sleep maintenance*, which consists of six items, representing 13.6% of the total number of items included in the domains across four PROMs, followed by *sleep quality*, consisting of five items (11.4%) across four PROMs, *sleep onset*, consisting of four items (9.1%) across three PROMs, and *daytime impairment*, consisting of four items (9.1%) across two PROMs. Two PSQI items that were categorised as measuring the domains *bedtime* (PSQI question item 1) and *wake-up time* (PSQI question item 3) are used in the PSQI tool in the calculation of time in bed and sleep efficiency. One further PSQI item (PSQI question item 4) – which was categorised as measuring sleep disturbance in our analysis – is also used in the calculation of sleep efficiency in the PSQI tool. As the individual PSQI question items do not capture time in bed or sleep efficiency in isolation, sleep efficiency and time in bed were not identified as distinct domains in our analysis. Other domains that were reported by only one PROM include: *non-restorative sleep* (one question item in the JSS), *sleep inertia* (one question item in the FMSD), *nap* (one question item in the MOS-SS) and *use of sleeping medication* (one question item in the PSQI).

Discussion

This systematic review of PROMs for people with fibromyalgia-related sleep problems is the first to systematically characterise the item content across these measures into individual outcome domains. It extends the findings of the Climent-Sanz (2020)[35] review to highlight the heterogeneity in domains measured across the sleep PROMs. Although we identified one additional relevant report, we did not identify any new sleep-related PROMs validated for use with fibromyalgia patients.

The identified PROMs varied in terms of the number of individual items and the domains covered by such items. None of the PROMs covered all 21 domains identified by our analysis. The most comprehensive identified PROM, in terms of the number of domains measured, is the PSQI, which captures 15 domains and includes the highest number of items across the five PROMs. Unsurprisingly, the least comprehensive PROM is the SQ-NRS as this is a single-item tool that only measures the *sleep quality* domain. Sleep quality is also measured by the PSQI and MOS-SS (one item each), and two items contained in the FMSD, but is not covered by the JSS. The SQ-NRS can, therefore, be considered to provide an overall assessment of sleep quality that is in keeping with most of the other PROMs but might lack the depth of the other tools. The *sleep maintenance* domain contained the highest number of items (six items) and is covered by all PROMs except the SQ-NRS; however, it should be noted that the dominance of the sleep maintenance domain is partly due to our decision to code items measuring the different underlying reasons for sleep disturbance as individual domains. Ten items across three PROMs (PSQI, MOS-SS and FMSD) measure different types of sleep disturbance and two further items contained in the MOS-SS and FMSD measure the degree of sleep disturbance. The large number of items associated with different types of sleep disturbance reflects the concentration of PSQI items measuring these domains. Just under half [8/18 (44.4%)] of the items contained in the PSQI measure different types of sleep disturbance. *Sleep maintenance* and *sleep disturbance* can be seen as interconnected and at times overlapping domains, as both capture concepts associated with the interruption of the state of being asleep or problems with sleep continuity. Sleep disturbance has a broader focus and could include sleep-disordered breathing, excessive limb movement, nightmare and nocturia. Interestingly, as discussed in *Chapter 3*, Climent-Sanz *et al.* noted that participants across the studies included in their qualitative meta-synthesis reported that the most common sleep problems associated with fibromyalgia were those related to the maintenance of sleep.[33] This was also associated with the feeling of being continuously sleep-deprived, and that constantly waking up is the worst thing about their health condition – aspects that would be captured by these existing PROMs.

Four tools included items measuring the domain *daytime impairment*. It should be noted that while we have chosen the term 'daytime' to correspond with the term used by the Sleep Foundation, we believe that this domain captures the negative effects of sleeping problems that occur during waking hours and could also measure impairment during the evening or nighttime, depending on the usual or desired waking hours of the respondent.

While we found heterogeneity among the item content of the PROMs, it is worth noting that our clinical expert and patient advisors (see *Acknowledgements* for further details) expressed the opinion that all identified PROMs capture constructs associated with sleep quality and, conceptually, are similar enough to be combined in a synthesis. This

TABLE 16 Domain definitions

WHO ICF category	Selected WHO ICF terms	Selected Sleep Foundation Dictionary terms	Definition of terms and domains[a]	Agreed domain name	Example PROMs item
b134 Sleep functions	*b1340 Amount of sleep* Mental functions involved in the time spent in the state of sleep in the diurnal cycle or circadian rhythm.	Sleep duration	The quantity of time that a person sleeps. Sleep duration may be measured for just one sleep period or over the course of a 24-hour day.	Sleep duration	PSQI Q4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.) This question item is used to calculate sleep efficiency in the PSQI PROM tool.
		Time in bed	The total amount of time that a person spends in bed regardless of whether or not they are sleeping during that time. This term is most often used in sleep studies to calculate sleep efficiency or to assess adherence to specific sleep rescheduling instructions during treatment.	Bedtime	PSQI Q1. During the past month, when have you usually gone to bed at night? This question item is used to calculate time in bed and sleep efficiency in the PSQI PROM tool.
				Wake-up time	PSQI Q3. During the past month, when have you usually gotten up in the morning? This question item is used by the authors in the calculation of time in bed and sleep efficiency.
		Sleep efficiency	The proportion of time during a sleep episode that is actually spent sleeping. It is calculated by dividing total sleep time by total time in bed × 100%.	N/A	N/A
	b1341 Onset of sleep Mental functions that produce the transition between wakefulness and sleep	Sleep onset	Falling asleep or initiating a sleep period.	Sleep onset	FMSD Q1. How difficult was it to fall asleep last night? [0–10 scale]

TABLE 16 Domain definitions (*continued*)

WHO ICF category	Selected WHO ICF terms	Selected Sleep Foundation Dictionary terms	Definition of terms and domains[a]	Agreed domain name	Example PROMs item
		Sleep latency	The amount of time from 'lights out', or bedtime, to actually falling asleep.	Sleep latency	PSQI Q2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night? Number of minutes
	b1342 Maintenance of sleep Mental functions that sustain the state of being asleep	Sleep maintenance	Staying asleep for the desired or planned amount of time after initially falling asleep.	Sleep maintenance	JSS Q3. During the past month did you have trouble staying asleep, including waking up far too early?
		Insufficient sleep	A condition in which the mind or body do not function properly because of short sleep duration or excessive sleep fragmentation.	Insufficient sleep	MOS-SS Q12. How often during the past 4 weeks did you get the amount of sleep you needed? • All of the time • Most of the time • A good bit of the time • Some of the time • A little of the time • None of the time
		Sleep disturbance	A disruption in sleep that causes arousal or awakening.	Degree of sleep disturbance	MOSS-SS Q3. How often during the past 4 weeks did you feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc.) while sleeping? • All of the time • Most of the time • A good bit of the time • Some of the time • A little of the time • None of the time

continued

TABLE 16 Domain definitions (*continued*)

WHO ICF category	Selected WHO ICF terms	Selected Sleep Foundation Dictionary terms	Definition of terms and domains[a]	Agreed domain name	Example PROMs item
		Bad dream	A dream period that involves negative or bothersome content but does not cause a person to wake up from the dream.	Sleep disturbance due to bad dream	PSQI Q5h. During the past month, how often have you had trouble sleeping because you … had bad dreams? • Not during the past month • Less than once a week • Once or twice a week • Three or more times a week“
		Nightmare	A dream with negative content that causes a person to wake up from sleep. Immediately after waking up, a person normally remembers the content of the nightmare.		
		Nocturia	Frequent urination at night. Most technical definitions consider nocturia to be awakening one or more times to urinate, but some studies focus on the effects of multiple bathroom trips.	Sleep disturbance due to toilet visit	PSQI Q5c. During the past month, how often have you had trouble sleeping because you … have to get up to use the bathroom? • Not during the past month • Less than once a week • Once or twice a week • Three or more times a week
		Sleep apnoea	A type of sleep disorder marked by disordered or abnormal breathing. The two main types are obstructive sleep apnoea and central sleep apnoea.	Sleep disturbance due to breathing problem or headache	MOS-SS Q5. How often during the past 4 weeks did you awaken short of breath or with a headache? • All of the time • Most of the time • A good bit of the time • Some of the time • A little of the time • None of the time

TABLE 16 Domain definitions (*continued*)

WHO ICF category	Selected WHO ICF terms	Selected Sleep Foundation Dictionary terms	Definition of terms and domains[a]	Agreed domain name	Example PROMs item
		Sleep environment	The setting where a person sleeps. Usually a bedroom, the sleep environment includes elements such as the mattress and bedding as well as ambient light, sound, smell and temperature.	Sleep disturbance due to sleep environment	PSQI Q5f. During the past month, how often have you had trouble sleeping because you … feel too cold? • Not during the past month • Less than once a week • Once or twice a week • Three or more times a week
		Snoring	An audible vibration of tissue at the back of the throat. When frequent, snoring may be known as chronic snoring or primary snoring.	Sleep disturbance due to coughing or snoring	PSQI Q5e. During the past month, how often have you had trouble sleeping because you … cough or snore loudly? • Not during the past month • Less than once a week • Once or twice a week • Three or more times a week
		No corresponding dictionary term	N/A	Sleep disturbance due to pain	PSQI Q5i. During the past month, how often have you had trouble sleeping because you … have pain? • Not during the past month • Less than once a week • Once or twice a week • Three or more times a week
		No corresponding dictionary term	N/A	Sleep disturbance due to other reason	PSQI Q5j. During the past month, how often have you had trouble sleeping because you … other reason(s), please describe: How often during the past month have you had trouble sleeping because of this? • Not during the past month • Less than once a week • Once or twice a week • Three or more times a week

continued

TABLE 16 Domain definitions (*continued*)

WHO ICF category	Selected WHO ICF terms	Selected Sleep Foundation Dictionary terms	Definition of terms and domains[a]	Agreed domain name	Example PROMs item
		Nap	A short sleep period, usually taken during the day, apart from a person's primary sleep period. A nap may also be referred to as a siesta, its name in Spanish.	Nap	MOS-SS Q11. How often during the past 4 weeks did you take naps (5 minutes or longer) during the day? • All of the time • Most of the time • A good bit of the time • Some of the time • A little of the time • None of the time
		Somnolence	The state of feeling sleepy or drowsy.		
		Sleep inertia	A drowsy or groggy feeling that occurs shortly after waking up from sleep.	Sleep inertia	FMSD Q7. How difficult was it to begin your day? [0–10 scale]
	b1343 Quality of sleep Mental functions that produce the natural sleep leading to optimal physical and mental rest and relaxation.	Sleep quality	An individual's satisfaction with their sleep, integrating aspects of sleep initiation, sleep maintenance, sleep quantity and feeling refreshed upon awakening. Sleep quality is not always defined in the same way and often relies on subjective assessments by individuals of how they slept.	Sleep quality	FMSD Q6. How rested were you when you woke up for the day? [0–10 scale]
		No corresponding dictionary term	The feeling that sleep is restless, light, or of poor quality even though the duration may appear normal.[296]	Non-restorative sleep	JSS Q4. During the past month did you wake up after your normal amount of sleep feeling tired and worn out?
	b1349 Sleep functions, unspecified	Sleep aid (use of)	A substance or medication used to try to improve sleep. Most sleep aids are either prescription drugs, over-the-counter medications, or dietary supplements. Other approaches, such as aromatherapy, may also be considered sleep aids.	Use of sleeping medication	PSQI Q7. During the past month, how often have you taken medicine (prescribed or 'over the counter') to help you sleep? • Not during the past month • Less than once a week • Once or twice a week • Three or more times a week
		Sedative (use of)	A substance or medication that induces drowsiness.		

TABLE 16 Domain definitions (*continued*)

WHO ICF category	Selected WHO ICF terms	Selected Sleep Foundation Dictionary terms	Definition of terms and domains[a]	Agreed domain name	Example PROMs item
b130 Energy and drive functions	*b1300 Energy level*	Fatigue	A feeling of a lack of mental or physical energy. Fatigue frequently overlaps with excessive daytime sleepiness, cognitive impairment and other symptoms of sleep problems.	Daytime impairment	MOS-SS Q6. How often during the past 4 weeks did you feel drowsy or sleepy during the day? • All of the time • Most of the time • A good bit of the time • Some of the time • A little of the time • None of the time
	b1301 Motivation	Cognitive impairment	Difficulty related to mental functions such as thinking, attention, reaction time, memory, learning and judgement.		
		Daytime impairment	Negative effects of sleeping problems that occur during waking hours. Daytime impairments can include cognitive deficits, physical problems, and emotional or mood disturbances.		

N/A, not applicable.
a Domain definitions are taken from the Sleep Foundation dictionary, with the exception of non-restorative sleep.
Sources: World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF)[288,297] and Sleep Foundation Dictionary.[287] Ohayon *et al.* 2005[296]

TABLE 17 Domains identified across relevant individual items from the included PROMs

Domain (*n* = 21)	Number of items in the domain	FMSD	JSS	MOS-SS	PSQI	SQ-NRS	Number of PROMs included in the domain
Sleep onset	4	2	1	1			3
Sleep latency	3			1	2		2
Bedtime	1				1		1
Wake up time	1				1		1
Sleep duration	2			1	1		2
Insufficient sleep	2	1		1			2
Sleep maintenance	6	2	2	1	1		4
Sleep disturbance due to bad dream	1				1		1
Sleep disturbance due to breathing problem or headache	2			1	1		2
Sleep disturbance due to coughing or snoring	2			1	1		2
Sleep disturbance due to pain	1				1		1
Sleep disturbance due to sleep environment	2				2		1
Sleep disturbance due to toilet visit	1				1		1
Sleep disturbance due to other reason(s)	1				1		1
Degree of sleep disturbance	2	1		1			2
Sleep quality	5	2		1	1	1	4
Non-restorative sleep	1		1				1
Sleep inertia	1	1					1
Nap	1			1			1
Daytime impairment	4			2	2		2
Use of sleeping medication	1				1		1
Total number of items	44	9[a]	4	12	18	1	N/A
Total number of domains included in PROM	N/A	6	3	11	15	1	N/A

N/A, not applicable.
a The FMSD contains eight items, but question item 3 was considered to measure two domains: sleep maintenance and degree of sleep disturbance.

Note
Darker shading indicates a higher number of items or PROMs included in the domain.

underlines our rationale for conducting separate network meta-analyses in our quantitative evidence synthesis, where we conducted an NMA that pooled data for all PROMs in our main 'sleep' outcome as well as performing analyses for each individual PROM (see *Chapter 2*).

It is noteworthy that we did not identify any studies that reported exploring the content validity of the JSS and PSQI items for use with fibromyalgia patients. Of the three PROMs that were explored for content validity, participants

indicated that both the MOS-SS and SQ-NRS missed items that are of relevance for fibromyalgia patients. Only the FMSD was developed with fibromyalgia patients, highlighting a lack of input from this patient group in the item development of the PROMs. This is not unexpected as the remaining PROMs did not include fibromyalgia patients during item conception. It should be noted that there is a possibility that the item coverage of the PROMs may be inadequate in terms of outcomes that matter to people who have fibromyalgia-related sleep problems. For example, our qualitative synthesis (reported in *Chapter 3*) demonstrated that aspects of the relationship between poor sleep quality and other symptoms of fibromyalgia, as well as feelings of frustration or failure, and fear of going to bed are highly relevant to fibromyalgia patients. It is our opinion that these concepts are not covered by the items contained in the five identified PROMs.

Due to the poor reporting of demographic data, such as race, ethnicity and sociodemographic status, it is unclear whether the participants in the validation studies are fully representative of the wider population of fibromyalgia patients. We did not identify any studies that evaluated the PROMs for children with fibromyalgia. It is, therefore, uncertain whether the identified PROMs measure sleep outcomes that are most relevant for children with fibromyalgia. Given our concerns about the inadequacy of item coverage in the existing PROMs for adults with fibromyalgia, and the lack of any such PROM for children, we recommend the development of separate core outcome sets (COSs) for measuring sleep outcomes in adults and children with fibromyalgia. Any future COS could then inform the development of new standardised PROMs for measuring sleep outcomes in children and adults with fibromyalgia. It is recommended that further evaluation of the current PROMs, and the development of any future PROMs, is conducted in accordance with guidance from recent relevant initiatives such as the National Institute for Health and Care Research INnovations in Clinical trial design and delivery for the UnDEr-served framework, published in 2020, to enhance the inclusion of diverse participant populations from historically underserved groups, and ensure that outcomes represent what is important and that they are measured in ways that are acceptable to the wider fibromyalgia patient community.[298]

Strengths and limitations

This systematic review of PROMs for people with fibromyalgia-related sleep problems extends the findings of the previously published review conducted by Climent-Sanz and colleagues (2020)[35] by characterising the item content of the PROMs and establishing their comparability. We conducted highly sensitive and comprehensive literature searches as part of our wider mixed-methods complex evidence synthesis to identify PROMs for assessing sleep outcomes that have been validated among fibromyalgia patients. While we employed hand-searching during our screening process, we did not conduct a systematic search of the grey literature. It is, therefore, possible that some relevant articles were not detected, although our clinical expert and patient advisors were unaware of any relevant missing reports. Other established sleep PROMs that have not currently been validated for the fibromyalgia patient group, such as the Insomnia Severity Index and the Sleep diary, were not eligible for inclusion in this review. Their exclusion does not indicate that these PROMs are unsuitable for use with fibromyalgia patients, and it is possible that these PROMs capture additional outcomes that are important to people with fibromyalgia. Scientifically rigorous methods were adopted to identify and code the relevant domains across the included PROMs. Content analysis was conducted by two reviewers, who worked independently before reaching a consensus agreement. While the analysis was informed by the WHO ICF category definitions and terms contained in the Sleep Foundation dictionary, along with advice based on the experiences and reflections of our clinical expert and patient advisors, the content analysis is a subjective qualitative interpretation of the PROMs items. Hence, we cannot exclude with certainty that the same analysis conducted by different researchers with different perspectives and lenses may produce different overall findings.

Chapter 5 Conclusions

Overview of quantitative and qualitative evidence and patient-reported outcome measures

We found only limited overlap between quantitative and qualitative studies in terms of management strategies for poor sleep quality in patients with fibromyalgia. While quantitative studies assessed a wide range of diverse pharmacological and non-pharmacological interventions, the qualitative studies focused on people's experience of using medications and undertaking Mind–body Ex training and multidisciplinary training to improve sleep quality. We did not identify other qualitative evidence on people's experience of other forms of exercise or non-pharmacological procedures to tackle fibromyalgia-related sleep problems. In general, qualitative studies reported that participants felt the need to take medications to address the poor quality of their sleep and to 'continue to have a life' but were also concerned about the occurrence of side effects. This observation is partly backed up by our synthesis of quantitative evidence, which shows that some pharmacological interventions (e.g. antioxidants, SRIs and CNS depressants) may have a positive effect on quality of life even though they do not seem to have a significant effect on sleep and are often associated with adverse effects such as dizziness, drowsiness, headache and dry mouth. Although the qualitative studies stressed the importance of taking the 'right' medication, the results of our quantitative synthesis did not provide reliable information on optimal pharmacological interventions for treating fibromyalgia-related sleep problems. In particular, we did not find that pharmacological interventions were superior to non-pharmacological interventions such as aerobic training in reducing sleep problems. Qualitative studies also revealed that participants who underwent Mind–body Ex training (e.g. qigong, yoga) experienced better sleep patterns (e.g. fell asleep faster) and sleep quality. These results are not consistent with the results of our NMA, which found that land-based Mind–body Ex training did not significantly improve sleep quality in people with fibromyalgia but showed some beneficial effects on their quality of life. It is also worth noting that in some qualitative and quantitative studies which focused on Mind–body Ex training, the choice of comparator treatment was questionable (e.g. waiting list). Therefore, it is challenging to know whether any positive effects experienced by some participants were a true consequence of the 'active component' of exercise training or the incidental result of participating in a new entertaining, structured activity. It is also worth noting that while qualitative studies reported that participants felt that the beneficial effects of exercise decreased over time, quantitative studies failed to provide information on the sustainability of treatment effects as they were often of short duration (3 months).

The findings of our qualitative synthesis also indicate that people with fibromyalgia welcome flexible and tailored advice for developing strategies to manage their sleep problems, as it is possible that certain interventions may work better for some but not for all. Our quantitative studies provided only aggregate data; therefore, analyses of relevant patient subgroups or at an individual level proved unfeasible.

Qualitative studies also reported that participants identified hormonal factors, such as menopause, and the quality of the sleep environment as important elements that could affect sleep. Our PROMs analysis also identified the characteristics of the sleep environment as a relevant domain in the measurement of sleep. Characteristics of the sleep environment were not considered in the quantitative studies. Providing choices and adapting interventions to the needs of fibromyalgia patients were also key implications of our qualitative data. Both qualitative and quantitative studies focused on adults, specifically on middle-aged women from high-income countries, making it difficult to generalise our findings to the wider fibromyalgia population.

While the characteristics of current validated PROMs for fibromyalgia vary, our analysis shows that the range of items included in each PROM captures constructs associated with sleep quality and may be considered conceptually similar. However, it is possible that outcomes which matter most to people with fibromyalgia-related sleep problems, as highlighted by our qualitative synthesis (i.e. the relationship between poor sleep and other fibromyalgia symptoms, feelings of failure and frustration and fear of going to bed), are not fully represented by the items included in the identified PROMs, which focus on items that measure primarily *sleep maintenance* and *sleep disturbance*. It is also questionable whether current PROMs measure sleep outcomes that are most relevant for children and adolescents with fibromyalgia as they have not been validated in these populations. In general, because of the lack of data on ethnicity

and socio–demographic factors, it is unclear whether the current PROMs validation studies are truly representative of the wider and diverse fibromyalgia patient population.

Implications for practice and further research

The current evidence indicates that poor sleep is a common and profoundly disabling problem for people with fibromyalgia, which has negative consequences on their general health and well-being and impacts on their ability to perform activities of daily living. There is a suggestion that some forms of exercise training, psychological and behavioural therapy and some pharmacological treatments may play a role in improving fibromyalgia-related sleep problems and/or patients' quality of life. However, the limitations of the current evidence base do not allow any reliable conclusions about optimal interventions for treating sleep problems in people with fibromyalgia. There is a clear need to improve the quality of existing evidence. Findings from our qualitative and quantitative syntheses also highlight the importance of involving people with fibromyalgia in future research.

- Future studies should be properly designed and include an adequate number of diverse patients to allow investigation of differences in patients' responses, an appropriate control treatment, and a detailed description of the characteristics of the intervention to allow a better understanding of their true effects. Specifically:
    - studies should have a clear research hypothesis and rationale
    - patient representatives should be actively involved in the design of fibromyalgia research
    - interventions should be compared with established therapies or adequate sham treatments to demonstrate their comparative efficacy and safety (e.g. sham treatment could include sub-effective low-intensity or generic, non-specific activity/practice); this would also permit the implementation of appropriate blinding procedures
    - information on the severity of the disease, duration of illness, extent and type of sleep disturbances, and level of physical activity before and during treatment should be recorded
    - patient populations should include all relevant age groups, including adolescents, and greater representation of historically (and currently) under-represented groups in fibromyalgia symptom management research, including people with different race/ethnic backgrounds, the elderly and men, to increase diversity and generalisability
    - adherence and compliance with study protocols should be monitored and reported (including separate results for responders and non-responders)
    - long-term follow-up assessments of primary outcomes to determine durability of effects, as well as maintenance of any behavioural changes (i.e. sustained participation in exercise activities) should be assessed
    - consensus on the MCID for sleep quality should be established to facilitate future research in this field.

- Any attempt to harmonise the choice of PROMs (i.e. questionnaires and assessment scales) and a future consensus on which is the most appropriate to use in the field of fibromyalgia would be more than welcome. The current use of a variety of different assessment tools makes comparisons between studies methodologically challenging, generates inconsistency in the way fibromyalgia symptoms are identified and described, and creates confusion for patients. The development of COS for measuring sleep outcomes in adults and children with fibromyalgia would be beneficial for informing the development of new standardised PROMs for measuring sleep outcomes in children and adults with fibromyalgia. In the future, it is crucial that people with fibromyalgia are involved in the conception and content validation of any tool measuring sleep, ensuring that PROMs cover what matters most to patients.
- Considering that fibromyalgia is a complex clinical condition for which there is not an established cure and given the variety of interventions that have been studied and proposed to help people to manage their symptoms more effectively, healthcare professionals should be invited to consider more holistic approaches to the treatment of sleep problems tailored to patients' individual needs.
- To increase transparency and research quality and reduce publication bias, a pre-registration or study protocol publication should be considered an essential requirement.
- Further unblinded studies comparing non-pharmacological interventions for the management of fibromyalgia-related sleep problems with no intervention or UC (including waiting list) are not needed. They are not designed to minimise the risks of comparing UC versus interventions that have anticipated benefits, and it is unlikely they may provide robust and reliable information on the effectiveness of these treatments.

- Experts in the field, in collaboration with patient representatives, should consider developing recommendations to help people with fibromyalgia to self-manage their sleep problems when high-level clinical evidence is lacking or not yet available.

Patient and public involvement

Public and patient involvement/engagement was undertaken throughout the project. The original research plan was developed in partnership with a woman who has considerable lived experience, having been diagnosed with fibromyalgia years ago and having suffered from sleep problems (DD). She supported the development of the funding application, and as a co-applicant was actively involved in all stages of the project. She steered this application from conception and ensured that the patient's voice was heard throughout. In particular, she explained that poor sleep quality is a major troublesome symptom among people with fibromyalgia and stressed the importance of assessing PROMs of sleep quality in people with a diagnosis of fibromyalgia. As a member of the project management team, she attended all team meetings, provided constant support and feedback, commented on draft versions of this report, proofread and approved its final version and contributed to the writing of the Plain language summary.

She also invited a male patient representative (MP) to contribute to our project and ensure a more 'inclusive and diverse representation'. Both patient partners (DD and MP) contributed to major project decisions including the choice of outcome measures and the categorisation of interventions. They also provided advice in terms of interpreting the findings, asking for information to be easily accessed by other patients to aid self-management, and making recommendations for dissemination activities.

They were inspiring and instrumental in shaping our dissemination plan, especially providing advice on how to disseminate our findings to patients and the public. They facilitated our communication with relevant charities and healthcare organisations in this clinical area such as Versus Arthritis and Fibromyalgia Action UK, which were actively involved in our project and are now helping disseminate our findings.

Furthermore, through their established links with relevant PPI, volunteer and social media groups we are planning to reach wider, diverse audiences. They will liaise with the Fibro Friends Support Group, the Nottingham University Hospitals NHS Trust PPI group and the Versus Arthritis PPI and volunteers' group. Contact with these groups will allow us to collect ideas/suggestions on the best ways to disseminate our findings and make them accessible and suitable for different audiences.

Under the leadership of our patient partners and in collaboration with representatives of Versus Arthritis and Fibromyalgia UK, we are planning to host a 'Meet the Team' event, which will be open to patients/public and academic researchers – encouraging involvement from both sides and showcasing what 'the project' looks like from both perspectives, offering an opportunity to discuss the project findings and collect views and experiences. This event will be advertised through academic and patient organisation channels and social media groups (e.g. the Nottingham University Hospitals NHS Trust PPI group and the Fibro Friends Support Group). Versus Arthritis will invite their Fellows and PhD students, along with their own patient/volunteering groups. We are hoping that this will provide a 'taster' of our research and open channels for sharing information, as well as create opportunities for future dissemination activities and for establishing fruitful relationships beyond the end of the project. This event will 'showcase' the symbiotic relationship between patients and researchers, showing the importance and utmost need for this: precisely, how it makes the process of research more relevant and, therefore, more applicable to the 'real world' that patients have to live in. The whole team has benefitted from this experience, not only for research reasons but for ongoing friendships and possible future research applications. Below is a statement from DD as she felt it was important to add how her involvement enhanced the research and how she felt about the whole experience.

> *Right from the very beginning, the team were friendly and open and asked for my opinion on all aspects of the proposed research. I was included and given the opportunity to provide feedback to all discussions; being asked to speak first was very empowering and encouraged me to open up and share 'real life' symptoms with the team. I raised the point of non-pharmacological outcomes being included because waiting times to see a consultant are at an all-time high.*

This means patients are having to self-manage their conditions for longer periods. Thus, any research that highlights which interventions 'work' best is regarded as a priority now. I really feel that I need to champion this research team and show other patients and the public what a 'gold standard' experience looks like. I hope that showing this aspect in our dissemination activities will encourage more people to become involved in research.

Equality, diversity and inclusion

This is an evidence synthesis and NMA. The scope of the project was defined by the NIHR Health Technology Assessment Programme, which is committed to promoting equality, diversity and inclusion principles in research.

Fibromyalgia is more common in women and adults; however, men are often underdiagnosed. Fibromyalgia symptoms including sleep problems can impact significantly on a person's ability to carry out normal day-to-day activities. Therefore, people with this condition may be considered under the disability position of the Equality Act (2010).

The team involved in this research project included people with a range of expertise and background.

Additional information

Contributions of authors

Mari Imamura (https://orcid.org/0000-0003-4871-0354) (Research Fellow) conducted both the quantitative and qualitative evidence syntheses and the patient-reported outcome measures (PROMs) analysis (screening of search results, data collection, risk-of-bias assessment, data extraction, description of included studies, interpretation and tabulation of findings), contributed to the development of the research protocol and drafted the initial version of this report.

Clare Robertson (https://orcid.org/0000-0001-6019-6795) (Research Fellow) conducted both the quantitative and qualitative evidence syntheses and the patient-reported outcome measures (PROMs) analysis (screening of search results, data collection, risk-of-bias assessment, data extraction, description of included studies, interpretation and tabulation of findings), contributed to the development of the research protocol and drafted the initial version of this report.

Jemma Hudson (https://orcid.org/0000-0002-6440-6419) (Medical Statistician) conducted all statistical analyses, interpreted the results of the quantitative synthesis and drafted the results section of the quantitative evidence synthesis.

Daniel Whibley (https://orcid.org/0000-0002-7131-7158) (Assistant Professor) contributed to the development of the research protocol, interpreted all results and analyses, and contributed to the writing-up.

Lorna Aucott (https://orcid.org/0000-0001-6277-7972) (Senior Medical Statistician) provided guidance and advice on the statistical analyses, interpreted the results of the quantitative synthesis and contributed to the writing-up..

Katie Gillies (https://orcid.org/0000-0001-7890-2854) (Professor of Health Services Research) contributed to the development of the research protocol, provided oversight of the synthesis of qualitative evidence and the PROMs analysis; interpreted their results and contributed to the writing-up.

Marcus Beasley (https://orcid.org/0000-0001-6045-386X) (Research Fellow) contributed to the synthesis of qualitative evidence (data extraction, data analysis and writing up).

Martin J Stevens (https://orcid.org/0000-0002-6142-5278) (Research Fellow) contributed to the synthesis of qualitative evidence (data extraction, data analysis and writing up).

Paul Manson (https://orcid.org/0000-0002-1405-1795) (Information Specialist) was responsible for developing and running all literature searches, obtaining full-text papers, building EndNote libraries, and compiling the reference list of this report.

Debra Dulake (https://orcid.org/0009-0003-4193-343X) (patient partner) was actively involved in all stages of the project, contributed to the development of the research protocol, interpreted the results, drafted the patient involvement section, chaired PPI meetings, and led the development of dissemination activities.

Abhishek Abhishek (https://orcid.org/0000-0003-0121-4919) (Professor of Rheumatology) contributed to the development of the research protocol, provided expert advice, and interpreted results.

Nicole KY Tang (https://orcid.org/0000-0001-7836-9965) (Professor of Clinical and Health Psychology) contributed to the development of the research protocol, provided expert advice, and interpreted results.

Gary J Macfarlane (https://orcid.org/0000-0003-2322-3314) (Professor of Epidemiology and Dean of Interdisciplinary Research and Impact) conceived the idea of the project, contributed to the development of the research protocol, provided expert advice, and interpreted results.

Miriam Brazzelli (https://orcid.org/0000-0002-7576-6751) (Professor of Health Services Research) was the principal investigator, conceived the idea of the project, had overall responsibility for the project, drafted the research protocol, interpreted results, and drafted and edited this report.

All authors provided comments on draft versions of this report and approved its final version.

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Data-sharing statement

This is an evidence synthesis and network-meta analysis; all quantitative data and main relevant qualitative data are presented in the text or contained within tables, figures and appendices. No new data, suitable for data sharing, have been created in the preparation of this synthesis. All queries should be submitted to the corresponding author for consideration. Access to full verbatim quotes extracted from the included qualitative studies may not be granted due to copyright issues.

Ethics statement

This is a synthesis of published or publicly available evidence and no primary research data were collected as part of this project. Ethics approval was not needed.

Information governance statement

There were no personal data involved in the preparation of this report.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GTBR7561.

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payments from UpToDate and Springer, and consulting fees from NGM Biopharmaceuticals, Limbic and Inflazome. Additionally, he occasionally receives fees for lectures, presentations, speakers' bureaus, manuscript writing, and educational events from Cadilla Pharmaceuticals and Janssen Pharmaceuticals. Abhishek Abhishek also participates on the NIHR HTA Prioritisation Committee B (In hospital) 2022–7. Miriam Brazzelli participates on the NIHR HTA Commissioning Committee 2023–8. Katie Gillies reports consulting fees from Boehringer & Ingelheim and participation on the NIHR HTA Clinical Evaluation and Trials Committee 2020–5. Lorna Aucott participates on the NIHR PHR – Research Funding Board 2017–23. Martin J Stevens reports research grants from European Alliance of Associations for Rheumatology (EULAR). Nicole KY Tang reports grants from NIHR, UKRI MRC and Midlands Engine and participation on the NIHR PGfAR Trial Steering Committee.

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Appendix 1 Search strategies

Ovid MEDLINE(R) and Epub Ahead of Print, In-process, In-Data-Review & Other Non-indexed Citations, Daily and Versions(R) < 1946 to 29 October 2021 >

1. Fibromyalgia/
2. (fibromyalg$ or fibrosit$ or FMS or muscular rheumatism).tw,kf.
3. (chronic adj2 widespread adj2 pain).tw,kf.
4. (chronic adj2 diffuse adj2 pain).tw,kf.
5. or/1-4
6. sleep/ or Sleep Wake Disorders/ or sleep deprivation/ or sleep hygiene/ or "Sleep Initiation and Maintenance Disorders"/
7. (sleep* or wakefulness or waking or awake$ or sleeplessness or insomni$).tw,kf.
8. 6 or 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. drug therapy.fs.
14. randomly.ab.
15. trial.ab.
16. groups.ab.
17. or/9-16
18. exp animals/ not humans/
19. 17 not 18
20. 5 and 8 and 19

Ovid EMBASE < 1974 to 2021 week 43 >

1. fibromyalgia/
2. (fibromyalgia or fibrositis).tw,kf.
3. (chronic adj2 widespread adj2 pain).tw,kf.
4. (chronic adj2 diffuse adj2 pain).tw,kf.
5. 1 or 2 or 3 or 4
6. sleep/ or sleep deprivation/ or sleep hygiene/ or exp sleep disorder/
7. (sleep* or wakefulness or waking or awake$ or sleeplessness or insomni$).tw,kf.
8. 6 or 7
9. Randomized controlled trial/
10. Controlled clinical study/
11. randomization/
12. double blind procedure/
13. random$.tw,kf.
14. placebo.ti,kf.
15. ((doubl* or singl*) adj blind).tw,kf.
16. (assigned or allocated).tw,kf.
17. (controlled adj7 (study or design or trial)).tw,kf.
18. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 5 and 8 and 18

APA PsycInfo < 1967 to October week 4 2021 >

1 fibromyalgia/
2 (fibromyalgia or fibrositis or FMS or muscular rheumatism).tw.
3 (chronic adj2 widespread adj2 pain).tw.
4 (chronic adj2 diffuse adj2 pain).tw.
5 1 or 2 or 3 or 4
6 Sleep/ or sleep wake disorders/ or sleep deprivation/ or sleepiness/
7 (sleep* or wakefulness or waking or awake$ or sleeplessness or insomni$).tw.
8 6 or 7
9 Randomized Controlled Trial/
10 randomized controlled trials/ or randomized clinical trials/
11 treatment effectiveness evaluation/
12 random$.tw.
13 placebo.tw.
14 ((doubl* or singl*) adj blind).tw.
15 (assigned or allocated).tw.
16 (controlled adj7 (study or design or trial)).tw.
17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18 5 and 8 and 17

AMED (Allied and Complementary Medicine) < 1985 to October 2021 >

1. fibromyalgia/
2. (fibromyalg$ or fibrosit$ or FMS or muscular rheumatism).tw,hw.
3. (chronic adj2 widespread adj2 pain).tw,hw.
4. (chronic adj2 diffuse adj2 pain).tw,hw.
5. or/1-4
6. sleep/ or Sleep disorders/
7. (sleep* or wakefulness or waking or awake$ or sleeplessness or insomni$).tw,hw.
8. 6 or 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. randomly.ab.
14. trial.ab.
15. groups.ab.
16. or/9-15
17. 5 and 8 and 16

CINAHL

S1 (MH “Fibromyalgia”)
S2 TX fibromyalg$ OR fibrosit$ OR FMS OR muscular rheumatism
S3 TX chronic N2 widespread N2 pain
S4 chronic N2 diffuse N2 pain
S5 s1 OR s2 OR s3 OR s4
S6 (MH “Sleep”) OR (MH “Sleep Disorders”) OR (MH “Sleep Deprivation”) OR (MH “Sleep Hygiene”)
S7 sleep* OR wakefulness OR waking OR awake$ OR sleeplessness OR insomni$
S8 S6 OR S7
S9 MH randomized controlled trials

S10 MH double-blind studies
S11 MH single-blind studies
S12 MH random assignment
S13 TI (randomised OR randomized)
S14 AB (random*)
S15 TI (trial)
S16 MH (placebos)
S17 PT (randomized controlled trial)
S18 AB (control W5 group)
S19 S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18
S20 S5 AND S8 AND S19

Web of Science Science Citation Index Expanded (SCI-EXPANDED), Conference Proceedings Citation Index – Science (CPCI-S)

1 fibromyalg* or fibrosit* or FMS or "muscular rheumatism" (Topic)
2 chronic NEAR/2 widespread NEAR/2 pain (Topic)
3 chronic NEAR/2 diffuse NEAR/2 pain (Topic)
4 #1 or #2 or #3
5 sleep* or wakefulness or waking or awake* or sleeplessness or insomni* (Topic)
6 (random* OR clinical) NEAR/3 (study OR trial) (Topic)
7 RCT or "double blind" or "single blind" or random* or trial (Topic)
8 #6 or #7
9 #4 and #5 and #8

CENTRAL

#1 MeSH descriptor: [Fibromyalgia] this term only
#2 fibromyalg* or fibrosit* or FMS or "muscular rheumatism"
#3 chronic NEAR/2 widespread NEAR/2 pain
#4 chronic NEAR/2 diffuse NEAR/2 pain
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Sleep] this term only
#7 MeSH descriptor: [Sleep Wake Disorders] this term only
#8 MeSH descriptor: [Sleep Deprivation] this term only
#9 MeSH descriptor: [Sleep Initiation and Maintenance Disorders] this term only
#10 sleep* or wakefulness or waking or awake* or sleeplessness or insomni*
#11 #6 or #7 or #8 or #9 or #10
#12 #5 and #11

Appendix 2 Characteristics of studies eligible for the network meta-analysis

TABLE 18 Characteristics of studies eligible for the NMA

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Ahmed 2016[130] Ref ID 223 **Country:** USA **Number of study centres:** 1 **Funding:** Forest Research Institute, Jersey City, NJ	**Intervention category:** PBO/Sham vs. SRI **Intervention:** Placebo vs. milnacipran **Inclusion criteria:** Males or females, aged ≥ 18 years meeting the ACR (1991) criteria for FM; along with clinically significant sleep disturbance, defined as complaint of maintaining sleep at least three times per week for at least 1 month and a sleep diary demonstrating sleep disturbance for at least 2 weeks prior to randomisation; comprehension and willingness to cooperate with the study procedures. **Exclusion criteria:** Unstable uncontrolled medical conditions; obstructive sleep apnoea with an apnoea–hypopnea index of ≥ 15 episodes per hour of sleep, and/or periodic limb movements associated with arousal (PLMAI) of ≥ 15 episodes per hour during the baseline PSG. Participants with a history of obstructive sleep apnoea controlled with nasal continuous positive airway pressure with demonstrated nightly compliance were allowed to participate in the study. Participants with psychiatric illnesses were accepted, but excluded if they were severely depressed or deemed to be at significant risk of suicide. Other exclusion criteria included uncontrolled glaucoma, participants unable to discontinue prohibited medications; females who were lactating or pregnant; a history of alcohol, narcotic, benzodiazepine, or other substance abuse within 1 year prior to the study; excessive caffeine use, defined as a consumption of more than 500 mg of caffeine or other xanthines; smoking more than one-half pack/day or alcohol use > 14 units/week; and history of allergy to milnacipran.	Placebo **Time and frequency of treatment session:** Treated with placebo for 5 weeks, followed by a 7-day washout period, and then crossed over to milnacipran. **Duration of treatment (weeks):** 5 **Follow-up:** None	Milnacipran **Time and frequency of treatment session:** Treatment was initiated with dose escalation for 7 days, with morning and evening doses of 12.5 mg milnacipran or matching placebo for 3 days, followed by 25 mg BID, on days 4 to 7. The maintenance dose of 50 mg given morning and evening was continued for the next 4 weeks. **Duration of treatment (weeks):** 5 **Follow-up:** None	**Number randomised** 19 (crossover trial) **Symptom severity** C: BPI mean severity score: 4.1 (0.6 SE) E: BPI mean severity score: 4.7 (0.4 SE) **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Amirova 2017[105] Ref ID 583 **Country:** UK **Number of study centres:** NR **Funding:** NR	**Intervention category:** UC vs. PBO/Sham vs. relaxation. **Intervention:** UC vs. attention control vs. Mitchell method relaxation technique (MMRT) online. **Inclusion criteria:** Aged between 18 and 80 years, with Internet access, and diagnosed with FM according to the ACR 1990 and 2010 criteria of widespread pain persistent for at least 3 months and tenderness at a minimum of 11 of the 18 tender points. **Exclusion criteria:** Participants reporting severe psychiatric comorbidities, life-threatening conditions, substance abuse, and pregnancy, as well as recipients of any non-pharmaceutical treatment.	C1: UC (waiting list control). Participants allocated to the waiting list group did not receive an active treatment and proceeded with UC. **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 4 **Follow-up:** 4 weeks (i.e. 8 weeks from randomisation) [no usable data] C2: Online Attention control. The attention control group were asked to listen to a relaxation audio recording. **Time and frequency of treatment session:** Self-application (online). Participants were asked to listen to the recording daily for 1 month. **Duration of treatment (weeks):** 4 **Follow-up:** 4 weeks (i.e. 8 weeks from randomisation)	E: Online Mitchell method relaxation technique (MMRT). Participants followed the guided MMRT audio recordings. **Time and frequency of treatment session:** Self-application (online). Participants were asked to practise the MMRT by listening to the audio recording every day for 1 month. **Duration of treatment (weeks):** 4 **Follow-up:** 4 weeks (i.e. 8 weeks from randomisation) [no usable data]	**Number randomised** C1: 58, C2: 66, E: 67 **Symptom severity** NR **Comorbidity** C1: restless leg syndrome: 13.8%; asthma: 9.1%; chronic fatigue syndrome: 1.7%; sleep apnoea: 6.9%; depression: 6.9%; other comorbidities: 67.2% C2: restless leg syndrome: 24.2%; asthma: 6.9%; chronic fatigue syndrome: 4.5%; sleep apnoea: 0; depression: 9.1%; other comorbidities: 54.5% E: restless leg syndrome: 17.9%; asthma: 9%; chronic fatigue syndrome: 3%; sleep apnoea: 6%; depression: 10.4%; other comorbidities: 68.7%

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Amutio 2018[60] Ref ID 1397 **Country:** Spain **Number of study centres:** NR **Funding:** NR	**Intervention category:** UC vs. PT/BT gen **Intervention:** Wait list vs. mindfulness treatment **Inclusion criteria:** Current diagnosis of FM (e.g. via a letter from a doctor or pain consultant), female, aged 18–70 years, and not currently undergoing mindfulness training and/or formal psychotherapy (stable prescription medication was permitted for both the intervention and control group). **Exclusion criteria:** NR	Wait list control Not described **Time and frequency of treatment session:** NR **Duration of treatment (weeks):** 7 **Follow-up:** 3 months after week 7	Mindfulness treatment **Time and frequency of treatment session:** 2-hour group sessions, once a week, for 7 weeks and 10–30 minutes individual daily breathing exercise at home **Duration of treatment (weeks):** 7 **Follow-up:** 3 months after week 7	**Number randomised** C: 19, E: 20 **Symptom severity** NR **Comorbidity** NR
Arcos-Carmona 2011[66] Ref ID 358 **Country:** Spain **Number of study centres:** NR **Funding:** NR	**Intervention category:** PBO/Sham vs. aerobic LD + relaxation/meditation **Intervention:** Sham magnet therapy vs. aerobic exercise + progressive relaxation technique **Inclusion criteria:** NR **Exclusion criteria:** NR	Sham magnet therapy **Time and frequency of treatment session:** twice a week **Duration of treatment (weeks):** 10 **Follow-up:** None	Aerobic exercise + progressive relaxation technique **Time and frequency of treatment session:** 30 minutes of aerobic exercises in the pool followed by the Jacobson progressive relaxation technique for 30 minutes twice weekly **Duration of treatment (weeks):** 10 **Follow-up:** None	**Number randomised** C: 28, E: 28 **Symptom severity** NR **Comorbidity** NR
Arnold 2007[121] Ref ID 377 **Country:** USA **Number of study centres:** 3 **Funding:** Supported by NIH grant N01-AR-2-2264 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (Dr. Arnold, Principal Investigator).	**Intervention category:** PBO/Sham vs. gabapentinoids **Intervention:** Placebo vs. gabapentin 1200–2400 mg/day **Inclusion criteria** Females or males aged ≥ 18 years and meeting the ACR criteria for FM. Patients with other rheumatic or medical disorders that contributed to the symptoms of fibromyalgia were excluded. Patients were required to score ≥ 4 on the average pain severity item of the Brief Pain Inventory (BPI) at screening and randomisation.	Matched placebo **Time and frequency of treatment session:** As gabapentin **Duration of treatment (weeks):** 12 **Follow-up:** None	Gabapentin 1200–2400 mg/d **Time and frequency of treatment session:** 300 mg once a day at bedtime for 1 week, 300 mg twice a day for 1 week, 300 mg twice a day and 600 mg once a day at bedtime for 2 weeks, 600 mg 3 times a day for 2 weeks, and 600 mg twice a day and 1200 mg once a day at bedtime (2400 mg/day) for the remainder of the study beginning at week 6. Patients were seen weekly for the first 2 weeks of the 12-week	**Number randomised** **C:** 75, E: 75 **Symptom severity** C: Brief Pain Inventory average pain severity score, range 0–10: 6.0 (1.5) E: Brief Pain Inventory average pain severity score, range 0–10: 5.7 (1.4) **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
			therapy phase; thereafter, study visits were at 2-week intervals. **Duration of treatment (weeks):** 12 **Follow-up:** None	
Dr. Arnold received consulting fees from Eli Lilly (more than $10,000) and from Pfizer, Cypress Bioscience, Wyeth Pharmaceuticals, Sanofi-Aventis, Boehringer Ingelheim, Sepracor, Forest Laboratories, Allergan, and Vivus (< $10,000 each). She also received research support from Eli Lilly, Pfizer, Cypress Bioscience, Wyeth Pharmaceuticals, Sanofi-Aventis, and Boehringer Ingelheim. Dr. Keck received consulting fees (< $10,000) from or is a member of the scientific advisory boards of Abbott, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmith-Kline, Eli Lilly, and Pfizer. He is a principal or coinvestigator on research studies sponsored by Abbott, the American Diabetes Association, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Glaxo-SmithKline, Eli Lilly, Janssen Pharmaceutica, the National Institute of Mental Health, the National Institute of Drug Abuse, Pfizer, the Stanley Medical Research Institute, and UCB.	**Exclusion criteria:** Pain from traumatic injury or structural or regional rheumatic disease; rheumatoid arthritis, inflammatory arthritis, or autoimmune disease; unstable medical or psychiatric illness; lifetime history of psychosis, hypomania or mania, epilepsy, or dementia; substance abuse in the last 6 months; serious risk of suicide; pregnancy or breastfeeding; unacceptable contraception in those of childbearing potential; patients who, in the opinion of the investigator, were treatment refractory; prior treatment with gabapentin or pregabalin; and treatment with an investigational drug within 30 days of screening. Concomitant medication exclusions included medications or herbal agents with CNS effects, except episodic use of sedating antihistamines (antidepressants required a 14-day washout period prior to beginning study medication except for fluoxetine, which required a 30-day washout period); analgesics, with the exception of acetaminophen or over-the-counter non-steroidal anti-inflammatory drugs; and unconventional or alternative therapies.			

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Arnold 2008[124] Ref ID 368 **Country:** USA **Number of study centres:** 84 **Funding:** Supported by Pfizer Global Research and Development (PGRD), Ann Arbor Laboratories, Ann Arbor, Michigan. Lesley M. Arnold received consulting fees from Eli Lilly and Company, Pfizer Inc, Cypress Biosciences Inc, Wyeth Pharmaceuticals, Sanofi-Aventis, Boehringer Ingelheim, Sepracor, Forest Laboratories Inc, Allergan, and Vivus Inc. Dr. Arnold received research support from Eli Lilly and Company, Pfizer Inc, Cypress Biosciences Inc, Wyeth Pharmaceuticals,	**Intervention category:** PBO/Sham vs. gabapentinoids vs. gabapentinoids vs. gabapentinoids **Intervention:** Placebo vs. pregabalin 300 mg/d vs. pregabalin 450 mg/d vs. pregabalin 600 mg/d **Inclusion criteria:** ≥ 18 years of age, male or female (non-pregnant and non-lactating), met the ACR criteria for fibromyalgia, and had a pain score of at least 40 mm on the 100-mm pain visual analogue scale (VAS) at screening (visit 1) and random assignment (visit 2). Patients had to complete a minimum of 4/7 daily entries in pain diaries during the 1-week, single-blinded run-in period, with average mean pain score ≥ 4.	Placebo **Time and frequency of treatment session:** BID **Duration of treatment (weeks):** 14 **Follow-up:** None	E1: Pregabalin 300 mg/day E2: Pregabalin 450 mg/day E3: Pregabalin 600 mg/day. **Time and frequency of treatment session** Given BID in equally divided doses: Pregabalin 300 mg/day, 150 mg BID; Pregabalin 450 mg/day, 225 mg BID; Pregabalin 600 mg/day, 300 mg BID. All pregabalin-treated patients started at 150 mg/day and titrated every 3–4 days, depending on what time of day patients began taking study medication; all patients received 300 mg/day by the end of the first week. Patients in the 450 mg/day and 600 mg/day groups continued escalating to their randomised dose of 450 mg/day or 600 mg/day at the end of week 2 (visit 3) and remained on their fixed dose of pregabalin for the remainder of the trial **Duration of treatment (weeks):** 14 **Follow-up:** None	**Number randomised** **C:** 184, E1: 183, E2: 190, E3: 188 **Symptom severity** C: Mean pain score 11-point NRS ranging from 0 (no pain) to 10 (worst possible pain): 6.6 (1.3) E1: Mean pain score 11-point NRS ranging from 0 (no pain) to 10 (worst possible pain): 6.7 (1.3) E2: Mean pain score 11-point NRS ranging from 0 (no pain) to 10 (worst possible pain): 6.6 (1.4) E3: Mean pain score 11-point NRS ranging from 0 (no pain) to 10 (worst possible pain): 6.7 (1.4) **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Sanofi-Aventis, Boehringer Ingelheim, Allergan, and Forest. Dr. Arnold is on the Speakers Bureau for Eli Lilly and Company and Pfizer Inc. I. Jon Russell has consulted for or conducted research studies for Pfizer, Autoimmune Technologies, LLC, Eli Lilly, LKB World, Orphan Medical/ Jazz Pharmaceuticals, Grunenthal GmbH, and Allergan. He is on speaker panels for Merck, Ortho-McNeil, and Pfizer. Erdal Diri receives research grants from Hoffman-La Roche Ltd/ Genentech Ltd, Pfizer, Pain Therapeutics, Proctor & Gamble Pharmaceuticals, and CORONA. He is a speaker and consultant for Pfizer, Amgen, Centecor, and Abbott. Rachel Duan, James Young, Susan Martin, Jeannette Barrett, and George Haig are employees of Pfizer Inc and own Pfizer stock. Uma Sharma is a consultant for Pfizer, Wyeth, Eisai, Analgesic Research, and Amgen. Editorial support was provided by Jillmarie Yanchick, PharmD, an employee of Pfizer Inc. Statistical support was provided by Ed Whalen, PhD, an employee of Pfizer Inc.	**Exclusion criteria:** Inflammatory rheumatic disease; active infections or untreated endocrine disorders or severe painful disorders that might confound the assessment of pain due to fibromyalgia; unstable medical or psychiatric disorders; history of illicit drug or alcohol abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, within the past 2 years; or previous pregabalin treatment at any time. Participants with pending worker's compensation, current receipt of disability, or past or pending litigation for monetary compensation related to fibromyalgia were also excluded. Prohibited medications included other concomitant medications taken for fibromyalgia (e.g. antidepressants, anticonvulsants, or other medications) as well as agents used to treat pain and insomnia.			

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Arnold 2010[129] Ref ID 350 **Country:** USA **Number of study centres:** 56 **Funding:** The study was sponsored by Pfizer Inc. Editorial support was funded by Pfizer Inc. and provided by Dr. Steven G. Burke at Complete Medical Communications, Glasgow, Scotland. Dr. Arnold has received grants/research support from Allergan, Boehringer Ingelheim, Cypress Biosciences Inc., Forest Laboratories Inc., Eli Lilly and Company, Pfizer Inc., Sanofi-Aventis, and Wyeth Pharmaceuticals. She has been a consultant for Allergan, AstraZeneca, Boehringer Ingelheim, Cypress	**Intervention category:** PBO/Sham vs. SRI **Intervention:** Placebo vs. es-reboxetine **Inclusion criteria:** Aged ≥ 18 years, met ACR criteria for fibromyalgia and had a score ≥ 40 mm on the 100-mm VAS (from 0 = no pain to 100 = worst possible pain) of the Short-Form McGill Pain Questionnaire (SF-MPQ) at screening were eligible for the study. **Exclusion criteria:** Other severe pain (e.g. diabetic neuropathy) that may have confounded assessment or self-evaluation of the pain associated with fibromyalgia; previous treatment with es-reboxetine; current treatment with reboxetine; any inflammatory musculoskeletal disorder; rheumatic disease; active infection; untreated endocrine disorder;	Placebo **Time and frequency of treatment session:** As esreboxetine **Duration of treatment (weeks):** 8 **Follow-up:** None	Es-reboxetine **Time and frequency of treatment session:** The initial es-reboxetine dosage was 2 mg/day for 2 weeks. At the end of each 2-week period, the dose could be increased by 2 mg/day to a maximum of 8 mg/day during the final 2-week period. A dose reduction of 2 mg/day could also be made at each visit. **Duration of treatment (weeks):** 8 **Follow-up:** None	**Number randomised** C: 133, E: 134 **Symptom severity** NR **Comorbidity** NR
Biosciences, Forest Laboratories, Eli Lilly and Company, Organon, Pfizer, sanofi-aventis, Sepracor, Takeda, Theravance, Inc., DCB,Vivus, Inc., and Wyeth. She has served on speakers' bureaus for Forest Laboratories, Eli Lilly and Company, and Pfizer. Drs. Chatamra, Hirsch, and Stoker were employees of Pfizer at the time of the study. They have indicated that they have no other conflicts of interest with regard to the content of this article.	Previous or current significant psychiatric disorder; severe depression (in the investigator's judgement); serious suicide risk; seizure disorder; uncontrolled narrow-angle glaucoma; recurrent syncope or evidence of low blood pressure; symptomatic postural hypotension; significant or unstable medical or psychological conditions; pregnancy, use of an unacceptable mode of contraception, or breastfeeding; or involvement in disability claims, civil litigation, or workman's compensation claims for fibromyalgia. Exclusions based on concomitant medications or treatments included tender-point injections and use of fluoxetine or opioids within 30 days before the study; use of thioridazine or inhibitors of cytochrome P450 3A4 within 14 days before the study; use of muscle relaxants,			

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
	antidepressants, anticonvulsants, oral steroids, mexiletine, dopamine agonists, long-acting benzodiazepines, acupuncture, or TENS within 7 days before the study; and use of diphenhydramine or melatonin within 1 day before the study. (1–30 days before visit 1); or ever taken thioridazine, vigabatrin, hydroxychloroquine and deferoxamine; patients with: estimated creatinine clearance < 60 ml/min (using Cockcroft–Gault equation); severe pain due to other conditions (e.g. diabetic peripheral neuropathy postherpetic neuralgia) that may confound assessment or self-evaluation of pain associated with fibromyalgia; widespread inflammatory musculoskeletal disorders, widespread rheumatic diseases (other than fibromyalgia), active infections, untreated endocrine disorders, somatoform disorder, or any other severe acute or chronic medical or psychiatric condition; laboratory abnormality (including erythrocyte sedimentation rate > 440 mm/h, abnormal antinuclear antibody ≥ 1:160 titre, or rheumatoid factor > 80 IU/ml) that may increase the risk associated with study participation or interfere with the interpretation of study results; alcohol or substance abuse or dependence within the previous year, severe depression or considered at risk of suicide or self-harm as assessed by the investigator or results of a risk assessment performed by a mental health professional; and pending disability claims or receiving monetary compensation pertinent to the patient's fibromyalgia or comorbid diseases.			

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Arnold 2014[122] Ref ID 146 **Country:** International: USA [30 centres], Canada [9 centres], India [7 centres], Taiwan [4 centres] **Number of study centres:** 50 **Funding:** The study was sponsored by Pfizer Inc. Declaration of financial/other relationships: L.M.A. disclosed that she received research support from Eli Lilly and Company, Pfizer, Forest, Theravance, Takeda, AstraZeneca, and Tonix; served as a consultant for Pfizer, Daiichi Sankyo, Theravance, Purdue, and Shire; and participated on a speakers' bureau for Pfizer. P.A. served as a member of an advisory board for Pfizer Canada and AstraZeneca, and as a speaker for Pfizer, Eli Lilly and Company Valeant, Purdue, and Janssen in Canada. C.H. received research funding from Meridien Research and has participated on a fibromyalgia advisory board for Pfizer. J.L.P., M.M., M.L.C., L.S., J.M.S., L.P., and A.G.C. are full-time employees of Pfizer Inc. and receive salary and other compensation, including stock options.	**Intervention category:** PBO/Sham vs. gabapentinoids **Intervention:** Placebo vs. pregabalin 165 mg **Inclusion criteria:** Men or women (nonpregnant, nonlactating) ≥ 18 years of age who met the ACR 1990 criteria for fibromyalgia who scored of ≥ 4 on the numeric rating scale (NRS; 0–10 with 10 = worst possible pain) for pain (1 week recall period) at screening (week -1), and at least four daily NRS pain diaries completed satisfactorily within the last 7 days before enrolment (week 0) with an average pain score ≥ 4 **Exclusion criteria:** Failed prior pregabalin treatment owing to lack of efficacy, experienced hypersensitivity or intolerance to pregabalin or other a2d ligands, participation in a previous pregabalin clinical study; concomitant use of prohibited medications (e.g. opioid analgesics, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, muscle relaxants, antidepressants, antiepileptics, steroids, benzodiazepines, antiparkinsonian agents, cannabinoids, mexiletine, dextromethorphan, tender-point injections) in the absence of appropriate washout periods	Matching placebo **Time and frequency of treatment session:** Once daily (QD) **Duration of treatment (weeks):** 13 **Follow-up:** None	Pregabalin **Time and frequency of treatment session:** 495 mg/day QD for 3 months (13 weeks) **Duration of treatment (weeks):** 13 **Follow-up:** None	**Number randomised** **C:** 58, E: 63 **Symptom severity** C: Daily pain score 11-point numeric rating scale from 0 (no pain) to 10 (worst possible pain) mean (SD): 6.8 (1.4) E: Daily pain score 11-point numeric rating scale from 0 (no pain) to 10 (worst possible pain) mean (SD): 6.8 (1.1) **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Arnold 2016[155] Ref ID 283 **Country:** USA, India, Taiwan, and the Czech Republic (authors are based in USA) **Number of study centres:** 36: 28 in the USA, 5 in India, 2 in Taiwan, and 1 in the Czech Republic. **Funding:** Sponsored by Pfizer. Medical writing support was provided by Joshua Fink, PhD, of Engage Scientific Solutions and funded by Pfizer.	**Intervention category:** PBO/Sham vs. gabapentinoids **Intervention:** Placebo vs. pregabalin **Inclusion criteria:** Aged between 12 and 17 years and met the Yunus and Masi criteria for FM and a score of ≥ 4 on the weekly pain NRS at screening and randomisation, ≥4 pain diary entries must have been completed for 7 days prior to randomisation, medications used for relief of pain associated with FM were to be discontinued prior to the trial; however, acetaminophen (up to 3 g/day) as rescue medication was permitted. **Exclusion criteria:** Pain due to conditions other than FM; systemic inflammatory musculo-skeletal disorders or rheumatic diseases other than FM; serious active infections; untreated endocrine disorders; prior participation in a clinical trial of pregabalin, or a history of failed treatment with pregabalin, taking pregabalin; unstable depressive disorders or at risk of suicide or self-harm; serious illness or abnormality that may have increased the risk associated with study participation or interfered with interpretation of study results; active malignancy or immunocompromised; or a history of illicit drug or alcohol abuse within the last 2 years.	Matched placebo **Time and frequency of treatment session:** BID **Duration of treatment (weeks):** 15 **Follow-up:** (6 months open-label phase not usable)	Pregabalin **Time and frequency of treatment session:** Administered orally BID. Subjects were started at 75 mg/day from the end of week 1 and escalated at each week over a 3-week period, based on investigator assessment of safety and tolerability, to an optimised dose of 75 mg/day, 150 mg/day, 300 mg/day, or 450 mg/day. **Duration of treatment (weeks):** 15 **Follow-up:** (6 months open-label phase not usable)	**Number randomised** **C:** 53, E: 54 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Arnold 2020[138] Ref ID 2315 **Country:** USA **Number of study centres:** 24 **Funding:** Astellas Pharma Global Development, Inc. provided funding for the trial and was involved in the development of the study protocol, and in data collection, analysis, and interpretation. Editorial and writing assistance, under the guidance of the authors, was provided by Patrick Tucker, PhD, and Elizabeth Hermans, PhD, of OPEN Health Medical Communications (Chicago, IL) and funded by the study sponsor.	**Intervention category:** PBO/Sham vs. ASP0819 **Intervention:** Placebo vs. ASP0819 **Inclusion criteria:** Male and female patients aged 18–80 years with a BMI of ≤ 45 kg/m^2 and met the ACR 1990 and 2010 FM diagnostic criteria at screening. Symptoms must have been present at a similar level for at least 3 months and patients must have been free of any other disorder that could have explained the pain. Patients must also have had a pain score ≥ 4 on FIQR pain item at screening, along with a mean daily average pain score of 4–9 (inclusive) on an 11-point (0–10) NRS during the baseline diary run-in period. They were also required to have met prespecified criteria for mean daily average pain scores. Patients had to agree to use only acetaminophen (up to 1000 mg per dose and not to exceed 3000 mg/day) as rescue medication for fibromyalgia pain during the study. Non-steroidal anti-inflammatory drugs were permitted (except for celecoxib) as needed for non-fibromyalgia pain, such as headache. **Exclusion criteria:** Receiving an investigational therapy within 28 days or 5 half-lives prior to screening; no meaningful improvement, from ≥ 2 prior treatments for fibromyalgia from at least two pharmacological classes; pain (including diabetic peripheral neuropathy, post-therapeutic neuralgia, traumatic injury, prior surgery, or complex regional pain syndrome) that would interfere with the assessment of fibromyalgia pain or that required excluded therapies; and/or infectious or inflammatory arthritis, autoimmune disease, or other widespread rheumatic diseases.	Placebo **Time and frequency of treatment session:** Three placebo tablets each given QD in the morning, with or without food, for 8 weeks **Duration of treatment (weeks):** 8 **Follow-up:** None	ASP0819 **Time and frequency of treatment session:** 15 mg (3 capsules of 5 mg) QD in the morning, with or without food, for 8 weeks. **Duration of treatment (weeks):** 8 **Follow-up:** None	**Number randomised** C: 95, **E:** 91 **Symptom severity** NR **Comorbidity** C: temporomandibular disorders: 20.2%; IBS: 18.1%; chronic tension type headache 18.1%; migraine 42.6%; chronic low back pain 37.2%; myalgic encephalomyelitis/CFS 9.6%; interstitial cystitis/painful bladder syndrome 3.2%; endometriosis (*n* for women only) 5.6%; vulvodynia (*n* for women only) 1.1%; alcohol use disorder 0; substance use disorder 2.1%; E: temporomandibular disorders 5.6%; IBS 25.6%; chronic tension type headache 18.9%; migraine 44.4%; chronic low back pain 42.2%; myalgic encephalomyelitis/CFS 12.2%; interstitial cystitis/painful bladder syndrome 2.2%; endometriosis (*n* for women only) 14.8%; vulvodynia (*n* for women only) 0 alcohol use disorder 0; substance use disorder 2.2%

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Barmaki 2019[59] Ref ID 268 **Country:** France **Number of study centres:** 9 **Funding:** Laboratoire de Rhumatologie Appliqué LABRHA SAS, Lyon, France	**Intervention category:** UC vs. PBO/Sham vs. Nutrition **Intervention:** No supplementary treatment (NoST) vs. food supplement (FS) vs. phytotherapy treatment (Fib-19-01) **Inclusion criteria:** Female, aged 30–65, with FM according to the 1990 ACR criteria and a FIQ score > 40; able to walk, with symptomatic treatment for FM and diet unchanged for at least 2 months. **Exclusion criteria:** Male sex, women with confirmed pregnancy or breast feeding, modifications of concurrent pharmacological treatment regimen over the last 2 months, any other active rheumatic disease or neurological condition that can interfere with pain assessment and any severe and progressive psychiatric, haematological, cardiovascular, broncho-pulmonary or endocrine disease. Patients who have been previously treated with Fib-19-01 were not allowed to participate. If child-bearing potential, a negative serum pregnancy test at screening and the use of contraception throughout the study were required. Anti-psychotic medications were not allowed.	C1: no supplement. No details given. **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 24 **Follow-up:** None C2: another food supplement (acting as a placebo) Consisted of magnesium 71 mg, valerian 65 mg, escholtzia (California poppy) 50 mg, white ginseng roots 83 mg, willow 50 mg, acerola 120 mg, sage 50 mg and L-tryptophan 220 mg. **Time and frequency of treatment session:** NR but assumed 1 capsule in the morning and 1 capsule at dinner for 24 weeks, as in the phytotherapy group **Duration of treatment (weeks):** 24 **Follow-up:** None	Nutrition (Fib-19-01) Morning pill: ginger extracts 50 mg, acerola 240 mg, vitamin C 120 mg, medowsweet 40 mg and royal jelly 40 mg. Evening pill: passiflora 80 mg, camomile 80 mg, meadowsweet 40 mg, quackgrass 100 mg and L-tyrosine 45 mg. **Time and frequency of treatment session:** One capsule 'morning' at breakfast and 1 capsule 'evening' at dinner **Duration of treatment (weeks):** 24 **Follow-up:** None	**Number randomised** C: 31, E1: 33, E2: 36 **Symptom severity** C: VAS pain, mean (SD) 7.6 (1.4) E1: VAS pain, mean (SD) 7.9 (1.7) E2: VAS pain, mean (SD) 7.5 (1.5) **Comorbidity** C: neuro and psychiatric: 22.6%; musculoskeletal: 22.6%; cardiovascular: 6.4%; endocrinology metabolism: 16.1%; gastrointestinal: 6.4%; bronchopulmonary: 9.7%; other: 12.9% E1: neuro and psychiatric: 24.2%; musculoskeletal: 18.2%; cardiovascular: 3.0%; endocrinology metabolism: 3.0%; gastrointestinal: 6.1%; bronchopulmonary: 12.1%; other: 12.1% E2: neuro and psychiatric: 19.4%; musculoskeletal: 22.2%; cardiovascular: 8.3%; endocrinology metabolism: 8.3%; gastrointestinal: 11.1%; bronchopulmonary: 8.3%; other: 11.1%

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Boomershine 2018[128] Ref ID 626 **Country:** USA **Number of study centres:** 1 **Funding:** Luitpold Pharmaceuticals, Inc.	**Intervention category:** PBO/Sham vs. iron replacement **Intervention:** Placebo vs. ferric carboxymaltose **Inclusion criteria:** Men and women aged ≥ 18 years with a FM diagnosis based on the 2011 ACR's criteria for diagnosing fibromyalgia, a baseline score ≥ 60 on the FIQR and stable dose(s) of fibromyalgia medications and narcotics ≥ 30 days before randomisation. **Exclusion criteria:** Parenteral iron use within 4 weeks before screening, an anticipated need for blood transfusion during the study, baseline ferritin level ≥ 0.05 µg/ml, baseline transferrin saturation ≥ 20%, haemoglobin above the upper limit of normal, known hypersensitivity reaction to any component of ferric carboxymaltose, and calcium or phosphorus concentrations outside the normal range, current infection other than viral upper respiratory tract infection, malignancy (unless skin cancer or cancer-free for ≥ 5 years), active inflammatory arthritis, pregnancy or lactation, severe peripheral vascular disease with significant skin changes, medication use for seizure disorders, history of iron-storage disorders, hepatitis with evidence of active disease, human immunodeficiency virus infection, and chronic alcohol or drug abuse within the preceding 6 months. Any patient who had an intervention for fibromyalgia (defined as the initiation of a new treatment or increase of a previously prescribed fibromyalgia treatment) was no longer eligible for efficacy evaluation starting at the time of the intervention but remained in the study for safety evaluation.	Placebo **Time and frequency of treatment session:** Blinded placebo doses (15 ml normal saline) IV push at 2 ml/min on the same schedule as the active intervention (1 dose on day 0 and 1 on day 5) **Duration of treatment (weeks):** 5 days **Follow-up:** 42 days/6 weeks from randomisation (37 days/5 weeks after treatment)	Ferric carboxymaltose **Time and frequency of treatment session:** Two 15 mg/kg (up to 750 mg) undiluted blinded doses of IV ferric carboxymaltose at 100 mg/min (1 dose on day 0 and 1 on day 5) **Duration of treatment (weeks):** 5 days **Follow-up:** 42 days/6 weeks from randomisation (37 days/5 weeks after treatment)	**Number randomised** C: 40, E: 41 **Symptom severity** NR **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Branco 2010[131] Ref ID 1522 **Country:** 13 European countries **Number of study centres:** 89 **Funding:** Supported by Pierre Fabre Médicament, Boulogne, France. Dr. Branco received grant support as an investigator and consultant for Pierre Fabre Médicament. Drs. Zachrisson and Perrot served as speakers and consultants for Pierre Fabre Médicament. Dr. Mainguy is an employee and shareholder of Pierre Fabre Médicament. Medical writing assistance provided by Prescott Medical Communications Group was supported by Pierre Fabre Médicament	**Intervention category:** PBO/Sham vs. SRI **Intervention:** Placebo vs. milnacipran 200 mg/day **Inclusion criteria:** Raw score ≥ 3 on the physical function component of the FIQ; willingness and ability to rate pain intensity using an electronic patient experience diary (PED) loaded with a VAS; and a baseline VAS pain intensity rating between 40 and 90 (0–100 scale). Patients had to use the PED device daily for a minimum of 21 weeks and to complete at least 10/14 morning reports during the 2-week baseline period. Patients also had to be willing to use a contraceptive (if female) and to discontinue medications and non-pharmacological treatments commonly used to treat FM. **Exclusion criteria:** Severe psychiatric illness including generalised anxiety disorder or current major depressive episode (assessed by the Mini-International Neuropsychiatric Interview) or BDI score > 25, alcohol/substance abuse; significant cardiovascular, respiratory, rheumatoid, rheumatic, hepatic, renal, or other medical condition; systemic infection; epilepsy; active cancer; severe sleep apnoea; unstable endocrine disease; active peptic ulcer or inflammatory bowel disease; prostatic enlargement or other genitourinary disorders (in male patients); pregnancy or breastfeeding; and history or behaviour that would prohibit study compliance.	Placebo **Time and frequency of treatment session:** BID sham dosing **Duration of treatment (weeks):** 16 **Follow-up:** None	Milnacipran 200 mg/day (100 mg BID) **Time and frequency of treatment session:** The 4-week dose escalation schedule was as follows: 25 mg QD (evening dose, days 1 and 2); 25 mg BID (days 3–7); 50 mg BID (days 8–14); 50 mg (morning dose) and 100 mg (evening dose, days 15–21); and 100 mg BID (days 22–28). **Duration of treatment (weeks):** 16 **Follow-up:** None	**Number randomised** **C:** 449, E: 435 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Calandre 2009[91] Ref ID 243 **Country:** Spain **Number of study centres:** 1 **Funding:** NR	**Intervention category:** Flex/skill AQ vs. Mind–body Ex AQ **Intervention:** Stretching in pool vs. Tai Chi in pool **inclusion criteria:** Aged ≥ 18 years, had a diagnosis of fibromyalgia according to the ACR 1990 criteria and provided written informed consent to participate. **Exclusion criteria:** Patients who had never attended a swimming pool, those with any concomitant disease susceptible to worsen with warm water exercise, such as coronary disease, severe chronic respiratory disease, known allergy to chlorine, etc.	Stretching in pool **Time and frequency of treatment session:** 60 minutes, 3 times a week during 6 weeks **Duration of treatment (weeks):** 6 **Follow-up:** 4 and 12 weeks after termination (1 and 3 months FU)	Tai Chi in pool **Time and frequency of treatment session:** 60 minutes, 3 times a week during 6 weeks **Duration of treatment (weeks):** 6 **Follow-up:** 4 and 12 weeks after termination (1 and 3 months FU)	**Number randomised** **C:** 39, **E:** 42 **Symptom severity** NR **Comorbidity** C: temporomandibular dysfunction 89.7%; tension-type headache 82.0%; migraine 53.8%; irritable bowel syndrome 61.5%; chronic fatigue syndrome 17.9%; thyroid disease 17.9%; rheumatoid arthritis 23.1% E: temporomandibular dysfunction 88.1%; tension-type headache 71.4%; migraine 73.8%; irritable bowel syndrome 83.3%; chronic fatigue syndrome 33.3%; thyroid disease 19.0%; rheumatoid arthritis 19.0%
Calandre 2014[119] Ref ID 253 **Country:** Spain **Number of study centres:** 1 **Funding:** Partial funding was provided by AstraZeneca, as an investigator-sponsored study. Dr. Rico-Villademoros served as a freelance consultant for AstraZeneca Farmacéutica Spain.	**Intervention category:** Tricyclics vs. AP **Intervention:** amitriptyline as monotherapy vs. quetiapine extended-release (XR) as monotherapy **Inclusion criteria:** Female and male patients aged 18–70 years who met the ACR 1990 diagnostic criteria by scoring a minimum of 40 on the FIQ total score and a minimum of 4 on the average pain severity item in the Brief Pain Inventory (BPI).	Amitriptyline as monotherapy **Time and frequency of treatment session:** Amitriptyline (10–75 mg daily), administered as a single daily dose at bedtime. Dose adjustments were performed according to the efficacy and tolerability of each drug at 7- to 14-day intervals, with stepwise increases of 10–15 mg of amitriptyline. **Duration of treatment (weeks):** 16 **Follow-up:** None	Quetiapine extended-release (XR) as monotherapy **Time and frequency of treatment session:** Quetiapine extended-release (XR) (50–300 mg daily), administered as a single daily dose at bedtime. Dose adjustments were performed according to the efficacy and tolerability of each drug at 7- to 14-day intervals, with stepwise increases of 50 mg of quetiapine. **Duration of treatment (weeks):** 16 **Follow-up:** None	**Number randomised** C: 45, E: 45 **Symptom severity** C: BPI severity: 7.32 (1.6); BPI interference: 7.68 (1.4) E: BPI severity: 7.25 (1.5); BPI interference: 7.46 (1.6) **Comorbidity** C: major depressive disorder 2/45 (4%) E: major depressive disorder 3/45 (7%)

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
	Exclusion criteria: Pregnancy, lactation, and women of childbearing age not using a valid contraception method; any DSM-IV-R Axis I psychiatric disorder other than major depression; major severe depression as evidenced by a Beck Depression Inventory (BDI) score of ≥ 30; substance and/or alcohol dependence; current clinically relevant cardiovascular, cerebrovascular, renal, hepatic, or respiratory disease or any other serious physical illness; uncontrolled diabetes mellitus; unwillingness to discontinue drugs prescribed for fibromyalgia; patients who had received quetiapine or amitriptyline within 1 year of randomisation; and patients who had a ≥ 20% change in the FIQ total score at randomisation compared with the value determined at the screening visit.			
Castel 2012[103] Ref ID 281 **Country:** Spain **Number of study centres:** NR **Funding:** NR	**Intervention category:** UC vs. PT/BT gen vs. PT/BT gen + relaxation **Intervention:** Pharmacological treatment (standard care) vs. CBT vs. CBT + hypnosis **Inclusion criteria:** Aged 18–65 years with a FM diagnosis according to the ACR diagnostic criteria. **Exclusion criteria:** ≥ 1 additional severe chronic medical pain conditions (e.g. sciatica and complex regional pain syndrome), significant suicidal ideation, severe psychopathology (e.g. psychosis), or moderate-to-severe cognitive impairment.	Standard pharmacological care Conventional pharmacological treatments, including analgesics, antidepressants, anticonvulsants, and myorelaxants, as appropriate. **Time and frequency of treatment session:** Dose regimen NR **Duration of treatment (weeks):** 14 **Follow-up:** 3 and 6 months	E1: CBT + standard pharmacological care **Time and frequency of treatment session:** 14 weekly, 120-minutes CBT treatment sessions **Duration of treatment (weeks):** 14 **Follow-up:** 3 and 6 months E2: CBT + hypnosis + standard pharmacological care **Time and frequency of treatment session:** 14 weekly, 120-minutes CBT treatment sessions **Duration of treatment (weeks):** 14 **Follow-up:** 3 and 6 months	**Number randomised** C: 30, E1: 34, E2: 29 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Castel 2013[99] Ref ID 376 **Country:** Spain **Number of study centres:** NR **Funding:** Supported by the Foundation Marato´ TV3 (grant 070910)	**Intervention category:** UC vs. multidisciplinary (PT/BT gen + Mx Exercise LD + Mx Exercise AQ) **Intervention:** Pharmacological treatment vs. multidisciplinary (including CBT + physical therapy [aerobic capacity, muscular strengthening, and flexibility, as part of hydrokinesiotherapy and kinesiotherapy in a gymnasium]) + pharmacological treatment **Inclusion criteria:** Female with a diagnosis of FM based on ACR 1990 diagnostic criteria and aged between 18 and 60 years with 3–8 years of schooling.	Control: conventional pharmacological treatment including analgesics, antidepressants (tricyclics, selective SRIs, and dual reuptake inhibitors), benzodiazepine, and nonbenzodiazepine hypnotics. **Time and frequency of treatment session:** N/A. Dosage regimen not specified. **Duration of treatment (weeks):** Unclear but assumed to be 12 weeks **Follow-up:** 3, 6 and 12 months after the intervention	Multidisciplinary treatment (adapted for fibromyalgia patients with low educational levels) + pharmacological treatment 1. Pharmacological treatment. Same conventional pharmacological treatment as in the control group. 2. Multidisciplinary programme consisting of CBT and physical therapy, performed in a group format (8 patients per group). **Time and frequency of treatment session:** 1 hour of CBT and 1 hour of physical therapy, '24 sessions at a frequency of 2 days per week'. Assumed this is over 12 weeks.	**Number randomised** C: 74, E: 81 **Symptom severity** NR **Comorbidity** NR
	Exclusion criteria: Another severe chronic pain pathology (e.g. sciatica or complex regional pain syndrome), having been diagnosed with inflammatory rheumatic disease, being physically unable to perform the exercises, an open wound, a skin disease, being under psychiatric and/or psychological treatment within the past 3 years, significant suicidal ideation, cognitive or sensorial deterioration that impedes an adequate follow-up to the treatment, or a pending legal resolution for disability.		**Duration of treatment (weeks):** Unclear but assumed to be 12 weeks **Follow-up:** 3, 6 and 12 months after the intervention	

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Castro Sánchez 2019[93] Ref ID 238 **Country:** Spain **Number of study centres:** NR **Funding:** NR	**Intervention category:** Manual T vs. non-MSM practice **Intervention:** Myofascial release vs. dry needling **Inclusion criteria:** Diagnosed with FM, manifesting chronic widespread musculoskeletal pain symptoms, aged 18–60 years, limitation in activities of daily living due to pain (at least 1 day in the previous month), and agreed to attend evening therapy sessions. **Exclusion criteria:** Change in the pharmacological therapy during the period of the study, presence of cardiac, renal or hepatic insufficiency, severe physical disability, comorbid condition (e.g. inflammatory disease), fever after infection, hypotension, skin alterations, psychiatric illness, or previous history of surgery.	Myofascial release **Time and frequency of treatment session:** 1 hour once weekly for 4 weeks **Duration of treatment (weeks):** 4 **Follow-up:** None	Dry needling **Time and frequency of treatment session:** Once weekly for 4 weeks **Duration of treatment (weeks):** 4 **Follow-up:** None	**Number randomised** C: 32, **E:** 32 **Symptom severity** NR **Comorbidity** NR
Castro-Sanchez 2011[67] Ref ID 711 **Country:** Spain **Number of study centres:** NR **Funding:** NR	**Intervention category:** PBO/Sham vs. Manual T **Intervention:** (Sham) magnotherapy vs. massage-myofascial release therapy **Inclusion criteria:** FM diagnosis, aged 18–65 years, no regular physical activity, and agreement to attend evening therapy sessions. **Exclusion criteria:** No agreement to study participation, receipt of other non-pharmacological therapies, presence of cardiac, renal or hepatic insufficiency, cardiovascular event during the previous year, and presence of peripheral arterial or venous insufficiency, physical or psychological disease, infection, fever, hypotension, respiratory alterations limiting treatment application, skin integrity alterations, and failure to comply with prescribed pharmaceutical therapy	Sham magnotherapy **Time and frequency of treatment session:** 30-minute session once weekly **Duration of treatment (weeks):** 20 **Follow-up:** (baseline) and immediately after the 20-week intervention and again at 1 and 6 months. Assessments at 20, 24, and 46 weeks from randomisation	Magnotherapy **Time and frequency of treatment session:** once weekly 90-minute session **Duration of treatment (weeks):** 20 **Follow-up:** Assessed immediately after the 20-week intervention and again at 1 month and 6 months. Assessments at 20, 24, and 46 weeks from randomisation	**Number randomised** C: 32, E: 32 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Castro-Sánchez 2014[53] Ref ID 237 **Country:** Spain **Number of study centres:** NR **Funding:** NR	**Intervention category:** UC vs. Manual T **Intervention:** No treatment vs. Manual T **Inclusion criteria:** FM diagnosis, aged from 18–70 years, no regular physical activity, limitation of usual activities due to pain on at least 1 day in the previous 30 days, and agreement to attend evening therapy sessions. **Exclusion criteria:** receipt of any non-pharmacological therapies, presence of cardiac, renal or hepatic insufficiency, severe physical disability, comorbid condition (e.g. interstitial cystitis, inflammatory disease), infection, fever, hypotension, respiratory alterations limiting treatment application, skin alterations, psychiatric illness, previous history of surgery, and failure to comply with prescribed pharmacological therapy.	No treatment (patients continued with usual activities and did not receive advice and education). **Time and frequency of treatment session:** Tender points were evaluated once weekly **Duration of treatment (weeks):** 5 **Follow-up:** None	Manual T **Time and frequency of treatment session:** One 45-minute session once weekly. **Duration of treatment (weeks):** 5 **Follow-up:** None	**Number randomised** C: 44, E: 45 **Symptom severity** C: McGill Pain Rating Index, mean (SD): 40.4 (9.2); McGill Present Pain Intensity (scale of 1–5), mean (SD): 2.2 (0.8); Pain VAS (0: no pain, 10: worst pain), mean (SD): 7.7 (1.7) E: McGill Pain Rating Index, mean (SD): 39.9 (9.0); McGill Present Pain Intensity (scale of 1–5), mean (SD): 2.4 (0.9); Pain VAS (0: no pain, 10: worst pain), mean (SD): 8.0 (1.24) **Comorbidity** None (comorbidities were an exclusion criterion)
Ceca 2020[52] Ref ID 2297 **Country:** Spain **Number of study centres:** 3 **Funding:** NR	**Intervention category:** UC vs. Flex/skill LD **Intervention:** Wait list vs. self-myofascial conditioning programme **Inclusion criteria:** Over 18 years of age with a diagnosis of FM and gave signed informed consent **Exclusion criteria:** Heart, kidney or liver failure; respiratory problems that could limit participation; a cardiovascular event in the previous year; having participated in any other exercise activity in the 3 months prior to the intervention; refusing to participate in the proposed intervention programme and refusing to sign the informed consent or being considered outliers (with scores higher than the mean plus two SDs).	Wait list (participants did not receive any treatment) **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 20 **Follow-up:** None	Self-myofascial conditioning programme **Time and frequency of treatment session:** Two 50-minute sessions per week (total 40 sessions) **Duration of treatment (weeks):** 20 **Follow-up:** None	**Number randomised** C: 33, E: 33 **Symptom severity** NR **Comorbidity** C: back pain: 55%; depression: 70%; insomnia: 35%; osteoarthritis: 50%; brain injury/cognitive impairment: 9.5%; chronic fatigue: 20%; anxiety: 55%; hypothyroidism: 15%; osteoporosis: 5%; irritable colon: 0 E: back pain: 60.9%; depression: 69.6%; insomnia: 13%; osteoarthritis: 34.8%; brain injury/cognitive impairment: 13%; chronic fatigue: 34.8%; anxiety: 39.1%; hypothyroidism: 13%; osteoporosis: 13%; irritable colon: 17.4%

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Crofford 2005[125] Ref ID 260 **Country:** USA **Number of study centres:** 40 **Funding:** Supported by Pfizer Global Research and Development, Ann Arbor, Michigan. Dr. Crofford received consulting fees of < $10,000 from Cypress Bioscience, Eli Lilly & Co., Orphan Pharmaceuticals, Pfizer, and Wyeth.	**Intervention category:** PBO/Sham vs. gabapentinoids vs. gabapentinoids vs. gabapentinoids **Intervention:** Placebo vs. pregabalin 150 mg/day vs. pregabalin 300 mg/day vs. pregabalin 450 mg/day **Inclusion criteria:** Men or women age ≥ 18 years who met the ACR criteria for the diagnosis of FM with a score of ≥ 40 mm on the 100-mm VAS of the Short-Form McGill Pain Questionnaire (SF-MPQ) at screening and randomisation and a mean score of ≥ 4 on a 0–10 pain rating scale, based on at least 4 daily pain diary entries, during the week before randomisation	Placebo **Time and frequency of treatment session:** Administered 3 times daily in equal doses **Duration of treatment (weeks):** 8 **Follow-up:** None	E1: Pregabalin 150 mg/day, E2: Pregabalin 300 mg/day, E3: Pregabalin 450 mg/day **Time and frequency of treatment session:** E2 and E1: the study medication was administered at the appropriate dose 3 times daily in equal doses; E3: the study medication was administered at a dose of 300 mg/day for the first 3 days followed by 450 mg/day thereafter. **Duration of treatment (weeks):** 8 **Follow-up:** None	**Number randomised** **C:** 131, E1: 132, E2: 134, E3: 132 **Symptom severity** C: Pain Score (based on 11-point scale: 0 = no pain, 10 = worst pain): 6.9 (1.2) E1: Pain Score (based on 11-point scale: 0 = no pain, 10 = worst pain): 6.9 (1.5) E2: Pain Score (based on 11-point scale: 0 = no pain, 10 = worst pain): 7.3 (1.2)
Dr. Rowbotham received consulting fees of < $10,000 from Eli Lilly & Co. and Xenoport, owns stock in Xenoport and Neuromolecular, and was a coinvestigator on a study of gabapentin funded by Pfizer. Dr. Mease received consulting fees of < $10,000 from Pfizer, Cypress Bioscience, Eli Lilly & Co., and Pierre Fabre and owns stock in Cypress Bioscience. Dr. Dworkin served on the advisory board or as a consultant for fees of < $10,000 for Abbott Laboratories, Alpharma, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Elan Pharmaceuticals, Eli Lilly & Co., GlaxoSmithKline,	**Exclusion criteria:** Inflammatory rheumatic disease or other severe painful disorders that might confound assessment of FM pain, clinically significant or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise participation in the study, a calculated creatinine clearance rate of ≤ 60 ml/minute, failed response to previous treatment with gabapentin at dosages ≥ 1200 mg/day for pain associated with FM, pregnancy or breastfeeding. Women of child-bearing potential were advised to use contraception reliably. Patients who were receiving disability, applying for disability, or engaged in litigation related to FM were excluded from the study.			E3: Pain Score (based on 11-point scale: 0 = no pain, 10 = worst pain): 7.0 (1.3) **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Johnson & Johnson, Merck KGaA, NeurogesX, Inc., Ortho-McNeil Pharmaceutical, and UCB Pharma; has received consulting fees of more than $10,000 from Pfizer, Allergan, Novartis, Epicept, and Endo; and owns stock in NeurogesX, Inc. Ms Corbin, Mr. Young, Ms LaMoreaux, Ms Martin and Dr. Sharma own stock in Pfizer.				
Curtis 2021[107] Ref ID 2323 **Country:** Canada **Number of study centres:** 1 **Funding:** The Department of Anesthesia and Pain Management, University Health Network, Toronto, Ontario, Canada	**Intervention category:** UC vs. HBOT **Intervention:** Wait list vs. HBOT **Inclusion criteria:** Diagnosed with severe FM according to the ACR (2010) guidelines, aged > 18 years, and had a score ≥ 60 on the Revised Fibromyalgia Impact Questionnaire (FIQR) during the baseline assessment. **Exclusion criteria:** A recent positive pregnancy test or planning to become pregnant during the study period; claustrophobia; seizure disorder; active asthma; chronic sinusitis; chronic or acute otitis media; current treatment with bleomycin, cisplatin, doxorubicin, or disulfiram; or participation in a concurrent investigative drug or device trial within the prior 30-day period.	Wait list No further detail **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 12 (assessment at the end of waiting period) **Follow-up:** None	HBOT **Time and frequency of treatment session:** 90 minutes, QD, five times per week for 8 consecutive weeks (40 treatments total) **Duration of treatment (weeks):** 8 (assessment immediately after the 8-week treatment) **Follow-up:** None	**Number randomised** C: 9, E: 9 **Symptom severity** NR **Comorbidity** C: headache: 62.5%; irritable bowel syndrome: 50.0%; pelvic pain: 50.0%; temporomandibular pain: 62.5% E: headache: 88.9%; irritable bowel syndrome: 22.2%; pelvic pain: 55.6%; temporomandibular pain: 55.6%
de Medeiros 2020[80] Ref ID 209 **Country:** Brazil **Number of study centres:** NR **Funding:** Partly financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Master's degree scholarship, Finance Code 001	**Intervention category:** Aerobic AQ vs. Mind–body Ex LD **Intervention:** Aquatic aerobic exercise (AAEG) vs. mat pilates (MPG) **Inclusion criteria:** Women diagnosed with FM according to the ACR 2010 criteria, aged between 18 and 60 years with pain between 3 and 8 on the Pain VAS. **Exclusion criteria:** Uncontrolled hypertension, decompensated cardiorespiratory disease,	1. Aquatic aerobic exercise group (AAEG). **Time and frequency of treatment session:** 40 minutes, twice a week, for 12 weeks **Duration of treatment (weeks):** 12 **Follow-up:** None	Mat pilates group (MPG) **Time and frequency of treatment session:** 50 minutes, twice a week, for 12 weeks **Duration of treatment (weeks):** 12 **Follow-up:** None	**Number randomised** C: 21, E: 24 **Symptom severity** C: Mean (SD) VAS pain (0 = no pain, 10 = worst pain): 7.5 (1.8) E: Mean (SD) VAS pain (0 = no pain, 10 = worst pain): 7.5 (1.6) **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
	history of exercise-induced syncope or arrhythmias, decompensated diabetes, severe psychiatric illness, history of regular exercise (at least twice a week) in the last 6 months or any another condition that made the patient unable to perform physical exercises were excluded.			
de Zanette 2014[120] Ref ID 370 **Country:** Brazil **Number of study centres:** NR	**Intervention category:** Tricyclics + PBO/Sham vs. Endogenous hormone + PBO/Sham vs. endogenous hormone + tricyclics **Intervention:** Amitriptyline + placebo vs. melatonin + placebo vs. sleep hormone + amitriptyline	Amitriptyline 25 mg + placebo **Time and frequency of treatment session:** Amitriptyline (25 mg) + placebo QD at bedtime **Duration of treatment (weeks):** 6 **Follow-up:** None	E1: Melatonin (10 mg) tablets + placebo **Time and frequency of treatment session:** Melatonin (10 mg) tablets + placebo QD at bedtime **Duration of treatment (weeks):** 6 **Follow-up:** None	**Number randomised** C: 21, E1: 21, E2: 21 **Symptom severity** C: Global pain VAS: 62.9 (14.3) E1: Global pain VAS: 64.9 (15.4)
Funding: Supported by grants and material support from the following Brazilian agencies: Committee for the Development of Higher Education Personnel – CAPES -PNPD/CAPES (grants to Rafael Vercelino; Deitos A; I.C.C. de Souza; (G. Laste MEC/MCTI/CAPES/ CNPq/FAPs No 71/2013); J.R. Rozisky International Cooperation Program – CAPES (023/11) and material support; National Council for Scientific and Technological Development – CNPq (grants to Dr. I.L.S. Torres, Dr. W. Caumo); Postgraduate Program in Medical Sciences	**Inclusion criteria A**ged ≥ 18 years with FM according to ACR criteria and refractory to their current treatment. Patients had to have a score of at least 50 mm on the 0–100 mm VAS (0 indicated 'no pain' and 100 indicated 'worst possible pain') in the week prior to randomisation and completed at least 4/7 pain diaries. Patients were allowed to remain on analgesic medications, including drugs for which they were refractory, and these medications could not be adjusted during the study. Patients could enrol with or without a history of major depressive disorder, but it could not be the main reason for their functional impairment or study enrolment.		E2: Amitriptyline (25 mg) + melatonin (10 mg) **Time and frequency of treatment session:** Amitriptyline (25 mg) + melatonin (10 mg) QD at bedtime **Duration of treatment (weeks):** 6 **Follow-up:** None	E2: Global pain VAS: 69.6 (10.9) **Comorbidity** C: psychiatric disease (SCID-I): 76%; depression: 38%; anxiety: 52% E1: psychiatric disease (SCID-I): 71%; depression: 62%; anxiety: 57% E2: psychiatric disease (SCID-I): 65%; depression: 55%; anxiety: 25%

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
at the School of Medicine of the Federal University of Rio Grande do Sul (material support); Postgraduate Research Group at the Hospital de Clínicas de Porto Alegre (material support); Foundation for Support of Research at Rio Grande do Sul (FAPERGS) (grant to Schwertner A).				
	Exclusion criteria: Inflammatory rheumatic disease, autoimmune disease or other painful disorders that might confound the assessment of fibromyalgia pain or a history of substance abuse, pregnancy, breastfeeding, a history of neurological or oncological disease, ischaemic heart disease, kidney or hepatic insufficiency.			
Deluze 1992[114] Ref ID 218 **Country:** Switzerland **Number of study centres:** NR **Funding:** NR	**Intervention category:** PBO/Sham vs. non-MSM practice **Intervention:** Sham vs. electroacupuncture **Inclusion criteria:** Adult patients with fibromyalgia as defined by ACR criteria **Exclusion criteria:** Severe concomitant disease, treatment with morphine-like drugs or anticoagulants, peripheral neuropathy, bleeding disorders, language difficulties, and past treatment with acupuncture	Sham treatment **Time and frequency of treatment session:** Unclear **Duration of treatment (weeks):** 3 **Follow-up:** None	Electroacupuncture **Time and frequency of treatment session:** Unclear **Duration of treatment (weeks):** 3 **Follow-up:** None	**Number randomised** C: 34, **E:** 36 **Symptom severity** C: Mean severity of disease – scale 1–5 (1 = best): 3.0 (0.1) E: Mean severity of disease – scale 1–5 (1 = best): 2.8 (0.1) **Comorbidity** NR
Di Pierro 2017[117] Ref ID 202 **Country:** Italy **Number of study centres:** NR **Funding:** NR	**Intervention category:** PBO/Sham vs. antioxidant (CoQ10) **Intervention:** Control vs. coenzyme Q10 (CoQ10) **Inclusion criteria:** FM diagnosis based on ACR diagnostic criteria **Exclusion criteria:** Acute infectious disease within the previous 4 weeks; past or present neurological, psychiatric, metabolic, autoimmune, allergy-related, dermal, or chronic inflammatory disease; undesirable habits	Control (CoQ10-free supplement provided in sachets) **Time and frequency of treatment session:** BID **Duration of treatment (weeks):** 12 **Follow-up:** 6 months [= 3 months first phase and crossed over for a further 3 months]	Coenzyme Q10 (CoQ10) **Time and frequency of treatment session:** 2 × 200 mg/day **Duration of treatment (weeks):** 12 **Follow-up:** 6 months [= 3 months first phase and crossed over for a further 3 months]	**Number randomised** **C:** 10 (crossover trial first phase only) E: 12 (crossover trial first phase only) **Symptom severity** C: Widespread pain index: 11.2 (4.0); Pain VAS: 7.4 (2.1), **E:** Widespread pain index: 9.6 (4.7); Pain VAS: 6.4 (2.5) **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
	(smoking, excess alcohol consumption); medical conditions other than fibromyalgia which required glucocorticoid treatment, analgesics, or antidepressant drugs; past or current substance abuse or dependence; and pregnancy or current breastfeeding			
Ericsson 2016[98] Ref ID 326 **Country:** Sweden **Number of study centres:** NR. The paper is a substudy of a multicentre RCT which describes both resistance training and control exercises taking place at a physiotherapist and local gym at four different sites, but also states that data collection was completed in three sites (Gothenburg, Stockholm and Linköping) **Funding:** Supported by the Swedish Rheumatism Association, the Swedish Research Council, the Health and Medical Care Executive Board of Västra Götaland Region, ALF-LUA at Sahlgrenska University Hospital, Stockholm and Östergötland County Councils (ALF), and AFA Insurance and Gothenburg Center for Person Centered Care (GPCC).	**Intervention category:** Relaxation vs. strengthening LD **Intervention:** Relaxation (active control) vs. resistance exercise **Inclusion criteria:** Women aged 20–65 years, meeting the ACR 1990 classification criteria for FM **Exclusion criteria:** **Comorbidity** High blood pressure (> 160/90 mmHg), osteoarthritis in hip or knee, other severe somatic or psychiatric disorders, causes of pain other than FM, high consumption of alcohol, participation in a rehabilitation programme within the past year, regular resistance exercise or relaxation exercise twice a week or more, inability to understand or speak Swedish, and not being able to refrain from analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) or hypnotic drugs for 48 hours prior to examinations.	Relaxation (active control) **Time and frequency of treatment session:** Twice weekly. The duration is unclear. The only details reported are that relaxation therapy lasted for approximately 25 minutes, followed by stretching exercises **Duration of treatment (weeks):** 15 **Follow-up:** None	Resistance exercise **Time and frequency of treatment session:** 1 hour twice weekly **Duration of treatment (weeks):** 15 **Follow-up:** None	**Number randomised** **C:** 63, **E:** 67 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Fonseca 2021[86] Ref ID 271 **Country:** Brazil **Number of study centres:** NR	**Intervention category:** Education vs. Mx Exercise AQ **Intervention:** Health education vs. aquatic physiotherapy **Inclusion criteria:** FM diagnosis, aged between 25 and 60 years, BMI below 30 kg/cm^2, fluent in Portuguese, and gave signed written informed consent.	Health education **Time and frequency of treatment session:** 60 minutes once weekly with a 1-week pause between the sixth and seventh weeks. Participants were also encouraged to spend 45 minutes of their day doing the taught activities.	Aquatic physiotherapy **Time and frequency of treatment session:** 60 minutes once weekly with a 1-week pause between the sixth and seventh weeks. **Duration of treatment (weeks):** 11 **Follow-up:** None	**Number randomised** **C:** 19, **E:** 27 **Symptom severity** NR **Comorbidity** NR
Funding: Supported by the Centro Universitáriode Formiga -MG; Fundação de Amparode Pesquisa do Estado de Minas Gerais. The authors declare no conflict of interest.	**Exclusion criteria:** Illiterate; no FM diagnosis; past or present chronic inflammatory disease (i.e. spondyloarthritis and ankylosing spondylitis); or autoimmune diseases (i.e. systemic lupus erythematosus or rheumatoid arthritis); past or present psychiatric diseases (i.e. major depression, schizophrenia, and bipolar disorder); acute infectious disease at the time of data collection; using anti-allergic, antibiotics or anti-inflammatory drugs in the last 3 months; pregnant or breastfeeding; lack of pharmacological stability for at least 3 months before randomisation. After the start of the intervention, women were excluded if they had < 80% attendance , felt bad during the proposed activities, became pregnant, or changed medications during the study period.	**Duration of treatment (weeks):** 11 **Follow-up:** None		
Gilron 2016[127] Ref ID 157 **Country:** Canada **Number of study centres:** 1 **Funding:** Supported by CIHR (Canadian Institutes of Health) Grant #CIHR-MOP-106489 and a CIHR-Pfizer Rx&D Collaborative Research Investigator Program (CIHR Grant #MSH-55041).	**Intervention category:** PBO/Sham vs. gabapentinoids vs. SRI vs. gabapentinoids + SRI **Intervention:** Placebo vs. pregabalin vs. duloxetine vs. pregabalin + duloxetine **Inclusion criteria:** FM according to the ACR 1990 diagnostic criteria, aged 18 to 70 years, had sufficient cognitive function and language skills for the study, experienced daily pain (≥ 4/10) for at least 3 months, with AST and ALT ≤ 20% and serum creatinine ≤ 50% greater than the upper normal limit.	Matching placebo **Time and frequency of treatment session:** As matched experimental group **Duration of treatment (weeks):** 6 **Follow-up:** None	E1: Pregabalin E2: Duloxetine E3: Pregabalin + duloxetine **Time and frequency of treatment session:** E1: Pregabalin. Target daily dosage ceiling of 450 mg of pregabalin (maximum 3 capsules BID) E2: Duloxetine. Target daily dosage ceiling of 120 mg of	**Number randomised** 41 (crossover trial) **Symptom severity** Baseline pain intensity (0–10 NRS), mean (SD) 5.7 (1.3); whole population **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
			duloxetine (maximum 4 capsules daily in the evening) E3: Pregabalin + duloxetine, as in pregabalin alone and duloxetine alone groups	
	Exclusion criteria: The presence of a painful condition other than FM, including inflammatory rheumatic disease, major organ system disease, hypersensitivity to any of the study medications, and a severe mood disorder as diagnosed by a psychiatrist and/or active suicidal ideation, history of significant abuse of illicit drugs, prescription drugs, or alcohol and/or taking more than 200 mg oral morphine equivalents/day, uncontrolled hypertension, diabetes, HIV, narrow-angle glaucoma, or malignancies or enrolment in other investigational studies. Participants requiring continued treatment with medications that adversely interact with the study medications or with hereditary problems of fructose intolerance, glucose galactose malabsorption, or sucrose isomaltase insufficiency were excluded. Pregnancy and lactation were exclusion criteria, and women of childbearing potential were required to use a highly effective form of contraception.		**Duration of treatment (weeks):** 6 **Follow-up:** None	
Goldway 2019[74] Ref ID 227 **Country:** Israel **Number of study centres:** 1 **Funding:** Funded by the Israeli Ministry of Science, Technology and Space (Grant No. 3-11170), by the Kamin Program of the Israel	**Intervention category:** PBO/ modulation **Intervention:** Sham NF vs. neurofeedback (Amyg-EFP-NF) **Inclusion criteria:** FM diagnosis according to the ACR 2010 criteria **Exclusion criteria:** Other chronic pain syndromes, major neuropsychiatric illness and recently changed/initiated pharmacotherapy.	Sham neurofeedback **Time and frequency of treatment session:** 10 biweekly sessions **Duration of treatment (weeks):** 5 **Follow-up:** Up to 3 years	Neurofeedback (AMYG-EFP-NF) **Time and frequency of treatment session:** 10 biweekly sessions **Duration of treatment (weeks):** 5 **Follow-up:** Up to 3 years	**Number randomised** C: 12, E: 31 **Symptom severity** C: Pain (VAS, McGill, FIQ pain), mean (SD) 2.88.73 [SIC] (1.1) E: Pain (VAS, McGill, FIQ pain), mean (SD) 2.73 (0.9) **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Innovation Authority and by the Israeli Pain Association Research Grant and the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 602186				
Gómez-Hernández 2020[79] Ref ID 603 **Country:** Spain **Number of study centres:** 1 **Funding:** No funding	**Intervention category:** Aerobic LD vs. aerobic LD + Flex/skill LD **Intervention:** Control vs. flexibility **Inclusion criteria:** Women with a FM diagnosed according to the ACR criteria. **Exclusion criteria:** Any health condition for which physical exercise was contraindicated, a history of regular physical exercise (three times a week) in the previous three months, severe cardiopulmonary problems, a serious psychiatric disorder, inflammatory rheumatoid disease, or unstable hypertension.	CONTROL (stationary cycling) **Time and frequency of treatment session:** Cycling: 12 minutes, 3 sessions per week, for 12 weeks **Duration of treatment (weeks):** 12 **Follow-up:** None	1. Flexibility (stretching). 2. Stationary cycling, as in the control group. **Time and frequency of treatment session:** Stretching: 45 minutes, 1 session per week, for 12 weeks; cycling: 12 minutes, 3 sessions per week, for 12 weeks; **Duration of treatment (weeks):** 12 **Follow-up:** None	**Number randomised** C: 32, E: 32 **Symptom severity** NR **Comorbidity** NR
González-Viejo 2005[132] Ref ID 279 **Country:** Spain **Number of study centres:** NR **Funding:** NR	**Intervention category:** Ultrasound T + Manual T vs. SSRI **Intervention:** Ultrasonography plus physical therapy vs. sertraline, 50 mg/24 h **Inclusion criteria:** Inclusion criteria unclear. Included patients were aged between 42 and 52 years old, with an average of 47.5 years and with a diagnosis of fibromyalgia according to ACR criteria. **Exclusion criteria:** High blood pressure, pregnancy, lactation and use of antidepressants for at least 4 weeks.	[French-language publication] Ultrasonography + physical therapy **Time and frequency of treatment session:** Physical therapy: unclear duration; Ultrasound: 5 minutes on each trigger point, 5 days a week for 3 weeks **Duration of treatment (weeks):** 3 **Follow-up:** 6 months	[French-language publication] Sertaline **Time and frequency of treatment session:** 50 mg/day, as a single dose, for 6 months. **Duration of treatment (weeks):** 24 **Follow-up:** 6 months	**Number randomised** C: 34, E: 36 **Symptom severity** NR **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Guinot 2021[72] Ref ID 2313 **Country:** France **Number of study centres:** 1 **Funding:** Supported by the APICIL Foundation	**Intervention category:** PBO/ Sham + multicomponent vs. neuromodulation + multicomponent (Aerobic LD + Flex/skill AQ + relaxation + education) **Intervention:** Sham rTMS + multicomponent therapy vs. rTMS + multicomponent therapy (aerobic training, land-based + pool-based therapy [balance and posture work] + relaxation + education) **Inclusion criteria:** FM diagnosis according to ACR criteria; VAS pain score of ≥ 40 mm; naive for rTMS; aged > 18 years; no antidepressants, pain killers, corticosteroids, or non-steroidal anti-inflammatory drugs 3 months before screening. **Exclusion criteria:** FM associated with chronic inflammatory or autoimmune disease; neuromuscular disease; a severe psychiatric condition (posttraumatic stress syndrome or depression); unable to exercise on a cycle ergometer, having cardiac or pulmonary disease, having undergone physical reconditioning within 2 years prior to enrolment; BMI of > 35 kg/m^2; contraindication to rTMS, including a history of seizures; restless legs syndrome or sleep apnoea syndrome; pregnant or breastfeeding women; patients living > 45 minutes driving time from the hospital.	Sham rTMS + multicomponent therapy 1. Muti-component programme as in the active rTMS group. 2. Sham rTMS. **Time and frequency of treatment session:** Unclear but assumed to be the same as the experimental group **Duration of treatment (weeks):** 12 **Follow-up:** None	rTMS (a non-invasive brain stimulation technique) + multicomponent therapy (aerobic training on land + pool-based therapy + relaxation + education). **Time and frequency of treatment session:** A 2-week induction phase (5 sessions per week), followed by a 12-week, gradually decreasing maintenance phase, 2 sessions for week 3 (the first week of exercise training), and then 1 session per week for weeks 4, 6, 9, and 13; one session is for 20 minutes; aerobic training + pool-based therapy + relaxation: 3 sessions per week, for 12 weeks; one session is 135 minutes; educational therapy: 1-hour monthly session **Duration of treatment (weeks):** 12 **Follow-up:** None	**Number randomised** C: 19, E: 20 **Symptom severity** C: Mean (SD) Pain VAS (100 mm): 57.3 (16.1) E: Mean (SD) Pain VAS (100 mm): 60.9 (14.9) **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Haak 2008[110] Ref ID 1609 **Country:** Sweden **Number of study centres:** NR **Funding:** NR	**Intervention category:** UC vs. Mind–body Ex LD **Intervention:** Waiting list control vs. qigong **Inclusion criteria:** Female, aged ≥ 18 years and have had a FM diagnosis for at least 6 months. **Exclusion criteria:** Severe depression, psychosis, other severe diseases, suicidal risk or drug or alcohol dependency.	Waiting list control. No further details. **Time and frequency of treatment session:** Not described. **Duration of treatment (weeks):** 7 **Follow-up:** 4-months follow-up data not usable)	Qigong **Time and frequency of treatment session:** The total amount of time for the whole programme was 11.5 hours. All subjects were also encouraged during the programme to practise qigong, with the support of a free instruction tape, twice a day at home (2620 minutes). **Duration of treatment (weeks):** 7 **Follow-up:** 4-months (follow-up data not usable)	**Number randomised** C: 28, E: 29 **Symptom severity** NR **Comorbidity** NR
Haugmark 2021[112] Ref ID 2302 **Country:** Norway **Number of study centres:** NR – Presume multicentre because the VTP was organised in local communities **Funding:** Supported by the Norwegian South-Eastern Regional Health Authority (grant number 2016015).	**Intervention category:** UC vs. PT/BT gen **Intervention:** TAU vs. multicomponent programme **Inclusion criteria** Aged 20–50 years with FM diagnosed according to the ACR 2010 criteria and widespread pain that had lasted for at least 3 months. **Exclusion criteria:** Inflammatory rheumatic disease, severe psychiatric disorder, another disease that did not allow physical activity, unable to understand or write Norwegian, and not employed for more than 2 years.	1. TAU: no study intervention other than diagnostic clarification and the patient education session but were free to attend any treatment and activity at their own initiative. **Time and frequency of treatment session:** One 3-hour patient education programme and oral information about the study. **Duration of treatment (weeks):** 12 **Follow-up:** 12 months from baseline	Multicomponent programme: a 10-session Norwegian mindfulness-based and acceptance-based programme, the Vitality Training Programme (VTP), followed by 12 weeks of physical activity (PA) counselling. **Time and frequency of treatment session:** VTP: 10 weekly 4-hour sessions plus a booster session after approximately 6 months; PA NR; and one 3-hour patient education programme and oral information about the study. **Duration of treatment (weeks):** 12 **Follow-up:** 12 months from baseline	**Number randomised** C: 85, E: 85 **Symptom severity** NR **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Ide 2008[69] Ref ID 493 **Country:** Brazil **Number of study centres:** NR **Funding:** NR	**Intervention category:** PBO/Sham vs. Mind–body Ex AQ **Intervention:** Control vs. aquatic respiratory exercise-based programme (ARG) **Inclusion criteria:** Women with FMS according to 1990 ACR criteria with time availability, means of transportation, and acceptance of the training routine (no more than 25% of absences). **Exclusion criteria:** Musculoskeletal, respiratory, neurological, cardiovascular, skin diseases or hydrophobia that precluded participation in an aquatic exercise programme and any other regular exercise activity. Patients who were institutionalised were also excluded.	Control (supervised recreational activities) **Time and frequency of treatment session:** 1 hour, once a week, for 4 weeks **Duration of treatment (weeks):** 4 **Follow-up:** None	Aquatic respiratory exercise-based programme (ARG) **Time and frequency of treatment session:** ARG: 1 hour, four times a week, for 4 weeks; recreational activities: 1 hour, once a week, for 4 weeks **Duration of treatment (weeks):** 4 **Follow-up:** None	**Number randomised** C: 20, E: 20 **Symptom severity** The population studied consisted of severely affected patients presenting mean pain values > 7 on the 10-cm VAS (ARG = 7.50 ± 2.09; CTL = 8.47 ± 1.59) and FIQ pain scale (ARG = 7.39 ± 1.93; CTL = 7.76 ± 2.05). **Comorbidity** C: shortness of breath 70.6%; dyspnoea VAS (0–10), mean (SD): 3.65 (3.08) E: shortness of breath 72.2%; dyspnoea VAS (0–10), mean (SD): 4.28 (3.12)
Jiao 2019[54] Ref ID 215 **Country:** China **Number of study centres:** 1 **Funding:** Supported by a grant from the Capital Project of Characteristic Clinical Application (Z/41107002514094). ClinicalTrials.gov identifier: NCT0338 1131	**Intervention category:** UC vs. Mind–body Ex LD **Intervention:** Wait list (stable usual therapy) vs. Ba-Duan-Jin **Inclusion criteria:** Patients who met the ACR criteria for fibromyalgia and were aged 18 to 70 years	Wait list (stable usual therapy) **Time and frequency of treatment session:** 1 hour of fibromyalgia education prior to study commencement. **Duration of treatment (weeks):** 12 **Follow-up:** None	Ba-Duan-Jin **Time and frequency of treatment session:** 1 hour of fibromyalgia education prior to study commencement followed by (1) supervised session: 60 minutes, twice weekly, for 12 weeks; (2) practice at home: 16 minutes daily	**Number randomised** C: 31, E: 31 **Symptom severity** C: Mean (SD) Pain VAS (0–100, high scores indicate greater pain): 55.2 (21.1) E: Mean (SD) Pain VAS (0–100, high scores indicate greater pain): 55.6 (20.5)
	Exclusion criteria: Patients were excluded if they had practised Ba-Duan-Jin, Tai Chi, yoga, or other forms of qigong exercise in the 12 months prior to study recruitment; had dementia, cancer, or other serious medical conditions that might confound the study's results. Other exclusions included: any poorly controlled comorbid medical conditions, such as thyroid disease, inflammatory arthritis, systemic lupus erythematosus, rheumatoid arthritis, myositis, vasculitis or Sjogren syndrome; pregnancy or planned pregnancy within the study period; or patients residing more than 70 miles from the research site.		**Duration of treatment (weeks):** 12 **Follow-up:** None	**Comorbidity** C: cardiovascular diseases: 26%; osteoarthritis/osteoporosis: 13%; tumour: 13%; ovarian cyst/adenomyosis: 13%; respiratory diseases: 0; depression: 3%; migraine: 0; irritable bowel syndrome: 3%; temporomandibular arthritis: 0 E: cardiovascular diseases: 16%; osteoarthritis/osteoporosis: 10%; tumour: 7%; ovarian cyst/adenomyosis: 3%; respiratory diseases: 10%; depression: 7%; migraine: 7%; irritable bowel syndrome: 3%; temporomandibular arthritis: 3%

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Jones 2012[83] Ref ID 210 **Country:** USA **Number of study centres:** NR **Funding:** Primary Funding Source: National Institutes of Health/NIAMS 5R21 AR053506 NIH/ NCCAM1K23AT006392-01.	**Intervention category:** Education vs. Mind–body Ex LD **Intervention:** Education vs. Tai Chi **Inclusion criteria:** ≥ 40 years, meeting the classification of FM per the ACR 1990 criteria and approval by a healthcare provider for participation. **Exclusion criteria:** Practised Tai Chi within the past 6 months, had exercised > 30 minutes three times weekly for past 3 months, unable to independently ambulate without assistive devices, had BPI pain severity or interference scores < 5, planned elective surgery during study period, actively involved in health-related litigation, or unwilling to keep all treatments/medications steady throughout the study period.	Education **Time and frequency of treatment session:** 90 minutes, twice weekly for 12 weeks **Duration of treatment (weeks):** 12 **Follow-up:** None	Tai Chi **Time and frequency of treatment session:** 90 minutes, twice weekly for 12 weeks **Duration of treatment (weeks):** 12 **Follow-up:** None	**Number randomised** C: 50, E: 51 **Symptom severity** C: BPI severity 5.7; BPI interference 6.1; FIQ pain 7.1; Self-efficacy pain 51.4 E: BPI severity 5.4; BPI interference 6.3; FIQ pain 6.9; Self-efficacy pain 52.3 **Comorbidity** NR
Kong 2021[100] Ref ID 716 **Country:** Korea **Number of study centres:** Unclear **Funding:** None	**Intervention category:** UC vs. PT/BT gen **Intervention:** Control vs. CBT **Inclusion criteria:** NR **Exclusion criteria:** NR	[Korean-language publication] Control (appears to be wait list) **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 8 **Follow-up:** 12 weeks from randomisation	[Korean-language publication] CBT **Time and frequency of treatment session:** 90–120 minutes, once a week, for 8 weeks **Duration of treatment (weeks):** 8 **Follow-up:** 4 weeks after the intervention (12 weeks from randomisation)	**Number randomised** C: 30, E: 30 **Symptom severity** NR **Comorbidity** C: Yes: 53.3%; No: 46.7% E: Yes: 60.0%; No: 40.0%
Kurt 2016[82] Ref ID 687 **Country:** Turkey **Number of study centres:** NR **Funding:** None	**Intervention category:** Balneotherapy vs. balneotherapy + mix exercise AQ vs. mix exercise AQ **Intervention:** Balneotherapy vs. balneotherapy + exercise vs. exercise **Inclusion criteria:** Female patients with FM according to the 2010 ACR diagnostic criteria and who had no modification of pharmacological treatment over the last three months.	Balneotherapy **Time and frequency of treatment session:** 20 minutes, 5 days a week, for 3 weeks. **Duration of treatment (weeks):** 3 **Follow-up:** 3 months (after the end of intervention)	E1: Balneotherapy + exercise **Time and frequency of treatment session:** Balneotherapy: 20 minutes, 5 days a week, for 3 weeks; Exercise: 25 minutes, extended to 35 minutes one week later in a gradual intensification pattern, 5 days a week, for 3 weeks	**Number randomised** C: 40, E1: 40, E2: 40 **Symptom severity** NR **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
	Exclusion criteria: Abnormal haemogram, sedimentation rate, biochemistry, urinalysis, and thyroid function tests, cardiac, respiratory, gastrointestinal, renal, or haematological disorders and neurological, or psychiatric disorders too severe to allow participation in balneotherapy or exercise programme, pregnancy, cancer, having advanced osteoarthritis, joint malformation, spinal disorders, or trauma within the last 3 months, inflammatory rheumatic disorders, history of smoking, having had modifications related to fibromyalgia medications within the last 3 months or alcohol intake or involvement in a physical therapy programme within the last year.		**Duration of treatment (weeks):** 3 **Follow-up:** 3 months (after the end of intervention) E2: Exercise **Time and frequency of treatment session:** 20 minutes, 5 days a week, for 3 weeks. **Duration of treatment (weeks):** 3 **Follow-up:** 3 months (after the end of intervention)	
Lami 2018[63] Ref ID 458 **Country:** Spain **Number of study centres:** 1 **Funding:** Supported by the Spanish Ministry of Science and Innovation (ref. PSI2009-13765PSIC) and Spanish Ministry of Economy and Competitiveness (ref.PSI2014-58379-P).	**Intervention category:** UC vs. PT/BT gen vs. PT/BT sleep **Intervention:** Usual medical care (UMC) vs. CBT-P (CBT for pain) vs. CBT-IP (CBT for insomnia and pain) **Inclusion criteria:** Women aged between 25 and 65 meeting the ACR 1990 diagnostic criteria for FM for > 6 months and stable dose/intake of analgesics, antidepressants, or other drugs (sleep and pain) at least 1 month before the study, not being treated with another psychological therapy; and meeting the diagnostic criteria for insomnia (DSM-IV-TR; American Psychiatric Association, APA, 2000).	Usual medical care (UMC) No detail provided **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 10 (treatment 9 weeks and assessment at 10 weeks) **Follow-up:** 3 months (after the end of intervention)	E1: CBT for pain (CBT-P) **Time and frequency of treatment session:** 90 minutes, once a week, for 9 weeks **Duration of treatment (weeks):** 10 (treatment 9 weeks and assessment at 10 weeks) **Follow-up:** 3 months (after the end of intervention) E2: CBT for insomnia and pain (CBT-IP) **Time and frequency of treatment session:** 90 minutes, once a week, for 9 weeks	**Number randomised** C: 42, E1: 42, E2: 42 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
	Exclusion criteria: Major concomitant medical conditions (e.g. inflammatory rheumatic disease, endocrine disturbances, neurological disorder, cancer, recent surgery) or pregnancy; mental disorders with severe symptoms (e.g. major depression with suicide ideation, schizophrenia, personality disorder) or other organic sleep disorder (i.e. apnoea); having a severe dependence of hypnotic drugs; and having irregularities in circadian rhythms at the time of the study (e.g. rotating work shifts).		**Duration of treatment (weeks):** 10 (treatment 9 weeks and assessment at 10 weeks) **Follow-up:** 3 months (after the end of intervention)	
Lauche 2016[57] Ref ID 217 **Country:** Germany **Number of study centres:** 1 **Funding:** NR	**Intervention category:** UC vs. PBO/Sham vs. non-MSM practice **Intervention:** UC vs. sham cupping vs. cupping therapy **Inclusion criteria:** Aged between 18 and 75 years with fibromyalgia diagnosed by a specialist and confirmed by the ACR 2010 diagnostic criteria with moderate pain of 45 mm or higher on a VAS, with 100 mm described as 'worst pain imaginable'.	C1: UC (wait list) **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 18 days **Follow-up:** 3 months (assumed to be from randomisation) C2: Sham cupping therapy	Cupping therapy **Time and frequency of treatment session:** 2 sessions per week (one session lasted about 30 minutes), a total of 5 sessions within 18 days **Duration of treatment (weeks):** 18 days **Follow-up:** 3 months (assumed to be from randomisation)	**Number randomised** C1: 46, C2: 48, E: 47 **Symptom severity** NR **Comorbidity** NR
NB Pneumed GmbH provided cupping equipment and prepared the sham cupping devices. The provider had no other role in the study.	**Exclusion criteria:** Pain due to inflammatory rheumatic disorder, any major psychiatric disorder, severe depression or substance abuse, any severe comorbidity such as cancer or neurological disorders, recently initiated or modified drug treatment, prior injections or acupuncture within the past 3 months or during the trial, treatment with opioids or steroidal pain medication. Medications with non-steroidal anti-inflammatory drugs or antidepressants were admitted if the dosage was kept constant during the trial. Pregnant or lactating women or patients taking part in other clinical trials were excluded.	**Time and frequency of treatment session:** 2 sessions per week (one session lasted about 30 minutes), a total of 5 sessions within 18 days **Duration of treatment (weeks):** 18 days **Follow-up:** 3 months (assumed to be from randomisation)		

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Liu 2012[70] Ref ID 110 **Country:** USA **Number of study centres:** NR **Funding:** NR	**Intervention category:** PBO/Sham vs. Mind–body Ex LD **Intervention:** sham vs. qigong **Inclusion criteria:** Women diagnosed with FM, based on the ACR 1990 criteria, aged between 18 and 70 years, either not participating in or willing to discontinue FM treatment with trans-cutaneous electrical nerve stimulation, biofeedback, tender-point injections, acupuncture, yoga, Tai Chi, and anaesthetic or narcotic patches. Patients on a stable dosage of medication for pain, sleep, or mild depression were not excluded from the study, providing that they met all criteria described. Participants were instructed to maintain their regular exercise activities, but not to participate in any new exercise programme during the intervention period. **Exclusion criteria:** Severe psychiatric illness; major depressive episode; significant suicide risk; abuse of alcohol, benzodiazepines, or other drugs; a history of behaviour that would prohibit compliance for the duration of the study; active cardiovascular, pulmonary, hepatic, renal, gastrointestinal, or autoimmune disease; current systemic infection; active cancer; unstable endocrine disease; severe sleep apnoea; prostate enlargement or other genitourinary disorder (male patients); pregnancy or breastfeeding (female patients) or had any condition that would make it difficult to keep calm during qigong exercises.	Specially developed sham qigong exercise **Time and frequency of treatment session:** 1. Training: 2 sessions (no details) 2. Group session after training: 45–60 minutes, once a week, for 6 weeks; 3. Home practice: 15–20 minutes, twice a week, for 6 weeks **Duration of treatment (weeks):** 6 **Follow-up:** None	Qigong **Time and frequency of treatment session:** 1. Training: 2 sessions (no details); 2. Group session after training: 45–60 minutes, once a week, for 6 weeks; 3. Home practice: 15–20 minutes, twice a week, for 6 weeks. **Duration of treatment (weeks):** 6 **Follow-up:** None	**Number randomised** C: 6, E: 8 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
López-Rodríguez 2013[92] Ref ID 248 **Country:** Spain [Spanish language publication] **Number of study centres:** NR **Funding:** Council of Economy, Innovation and Science of the Junta de Andalucia, Spain and the European Union through the European programme Regional Development Fund.	**Intervention category:** Flex/skill LD vs. aerobic AQ **Intervention:** Stretching vs. aquatic biodance **Inclusion criteria:** Aged between 18 and 68 years with a diagnosis of fibromyalgia according to ACR criteria, absence of any physical or psychological condition that prohibits participation in the exercise programmes, unchanged pharmacological treatment and no participation in any other type of physical therapy during the course of the study. **Exclusion criteria:** NR	Stretching **Time and frequency of treatment session:** 1 hour twice a week **Duration of treatment (weeks):** 12 **Follow-up:** None	Aquatic biodance **Time and frequency of treatment session:** 1 hour, carried out twice a week **Duration of treatment (weeks):** 12 **Follow-up:** None	**Number randomised** C: 38, E: 38 **Symptom severity** C: Symmetry of pain (needs translation check) Yes 13/30 (43.3%); No 17/30 (56.7%) E: Symmetry of pain (needs translation check) Yes 10/29 (34.5%); No 19/29 (65.5%) **Comorbidity** NR
Lynch 2012[55] Ref ID 327 **Country:** Canada **Number of study centres:** 1 **Funding:** Funded by a Pfizer Neuropathic Pain Research Award.	**Intervention category:** UC vs. Mind–body Ex LD **Intervention:** control (wait list/UC) vs. qigong **Inclusion criteria:** Eligible participants met the ACR 1990 criteria for fibromyalgia and reported widespread pain bilaterally with pain above and below the waist and axial skeletal pain for 3 months or longer, as well as at least 11/18 tender points. Medications must have been stable for at least 14 days prior to participation, and the average 7-day pain score had to be ≥ 4.0 on an 11-point NRS. **Exclusion criteria:** Participants were excluded if they had already practised qigong or if they had a significant medical disorder that would compromise participant safety.	Control (wait list/UC) **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 8 **Follow-up:** 6 months (presumed from randomisation)	Qigong **Time and frequency of treatment session:** Training: 3 consecutive half-days; Group session: 60 minutes once a week for 8 weeks; self-practice at home 45–60 minutes per day for 8 weeks; **Duration of treatment (weeks):** 8 **Follow-up:** 6 months (presumed from randomisation)	**Number randomised** C: 47, E: 53 **Symptom severity** NR **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Maddali Bongi 2012[115] Ref ID 154 **Country:** Italy **Number of study centres:** 1 **Funding:** NR	**Intervention category:** Mind–body Ex LD vs. Mind–body Ex LD **Intervention:** Qigong (QG) vs. Rességuier method (RM) **Inclusion criteria:** Diagnosis of FM according to the ACR criteria. **Exclusion criteria:** NR	Qigong (QG) **Time and frequency of treatment session:** 45-minute sessions: 2 sessions per week for the first 3 weeks and 1 session per week in weeks 4–7 with a total of 10 sessions. **Duration of treatment (weeks):** 7 **Follow-up:** 12 weeks from the end of the second intervention	Rességuier method (RM) **Time and frequency of treatment session:** 60-minute sessions: 2 sessions per week for the first 3 weeks and 1 session per week in weeks 4–7 with a total of 10 sessions. **Duration of treatment (weeks):** 7 **Follow-up:** 12 weeks from the end of the second intervention	**Number randomised** 38 (crossover trial) **Symptom severity** C: (*n* = 15) Pain (NRS 0 = best, 10 = worst), mean (SD): 7.82 (0.89) E: (*n* = 15) Pain (NRS 0 = best, 10 = worst), mean (SD): 7.58 (0.89) **Comorbidity** C: (*n* = 15, first phase) irritable bowel syndrome: 60%; irritable bladder syndrome: 20%; cephalalgia: 60%; restless leg syndrome: 66.7%; orthostatic hypotension: 20% E: (*n* = 15, first phase) irritable bowel syndrome: 86.7%; irritable bladder syndrome: 20%; cephalalgia: 53.3%; restless leg syndrome: 46.7%; orthostatic hypotension: 40%
Maddali Bongi 2016[84] Ref ID 153 **Country:** Italy **Number of study centres:** 1 **Funding:** NR. but note that the authors declared that they did not receive any financial support or any other benefit that could have created a potential conflict of interest	**Intervention category:** Education vs. Mind–body Ex LD **Intervention:** Control (FMS educational lesson) vs. Tai Ji Quan (TJQ) **Inclusion criteria:** NR **Exclusion criteria:** NR	Education (FM educational sessions) **Time and frequency of treatment session:** Two lessons per week. The lesson duration was NR **Duration of treatment (weeks):** 16 **Follow-up:** None	Tai Ji Quan (TJQ) **Time and frequency of treatment session:** Twice a week for 16 weeks, with sessions lasting 60 min each **Duration of treatment (weeks):** 16 **Follow-up:** None	**Number randomised** C: 25, E: 25 **Symptom severity** C: Widespread pain index (scores range 0 to 19 sites): 11.91 (4.151) E: Widespread pain index (range 0 to 19 sites): 11.73 (4.10) **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Maindet 2021[51] Ref ID 704 **Country:** France **Number of study centres:** 5 **Funding:** supported by the Association Francaise pour la Recherche Thermale (AFRETH), a non-profit organisation.	**Intervention category:** UC vs. balneotherapy **Intervention:** UC vs. spa therapy **Inclusion criteria:** Patients were eligible if they gave informed consent, had fibromyalgia for over a year, based on the ACR 2010 criteria, had received stable medical treatment over the previous 3 months, had a FIQ score ≥ 39 (moderate to severe fibromyalgia), were aged > 18 years, were available for the 3-week residential spa therapy within 6 weeks of inclusion (immediate group) or after the 6-month follow-up visit (delayed group), and were available for a 12-month follow-up visit.	UC Participants followed their usual treatment up to the 6-month follow-up visit. They received the 3-week spa therapy thereafter. **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 24 **Follow-up:** 6 months (after the 6-month assessment, i.e. 12 months)	Spa therapy **Time and frequency of treatment session:** 3-week treatment (2 hours in the morning for 18 days) received within 6 weeks of inclusion, including optional weekly walking training, conference attendance and access to on-site gym facilities (unspecified duration) **Duration of treatment (weeks):** 24 (3-week treatment within 6 weeks; assessment at 24 weeks) **Follow-up:** 6 months (after the 6-month assessment, i.e. 12 months)	**Number randomised** C: 108, E: 110 **Symptom severity** C: Widespread pain index score, mean (SD): 13.8 (2.8); Symptom severity scale score, mean (SD): 9.8 (1.6); Pain VAS (patient diary, 0–100), mean (SD): 59.6 (14.0). (*n* = 96) E: Widespread pain index score, mean (SD): 14.3 (3.0); Symptom severity scale score, mean (SD): 10.0 (1.5); Pain VAS (patient diary, 0–100), mean (SD): 61.4 (17.1). (*n* = 93)
	Exclusion criteria: Contra-indication or intolerance to any aspect of the spa treatments (progressive cancer, behavioural disorders, immune deficiency, patient with psychosis on medication or not), rheumatology spa treatment in the current calendar-year, changes in pain-related treatments in the previous 3 months, other known severe chronic diseases, such as severe asthma, severe cardiac, respiratory, hepatic or renal insufficiency, progressive inflammatory rheumatic disease and inflammatory colitis.			**Comorbidity** C: psychological trauma/prolonged stress: 71 (65.7); depression: 58 (53.7); irritable bowel syndrome: 54 (50.0); migraine: 37 (34.3); neuropathic pain: 15 (13.9); other neurological disease: 22 (20.4); menopause: 42 (38.9); rheumatic disease: 29 (26.9); sleep apnoea: 15 (13.9); Raynaud's disease: 7 (6.5); cancer: 2 (1.9) E: psychological trauma/prolonged stress: 64 (59.3); depression: 64 (59.3); irritable bowel syndrome: 63 (58.3); migraine: 24 (22.2); neuropathic pain: 20 (18.5); other neurological disease: 21 (19.4); menopause: 49 (45.4); rheumatic disease: 33 (30.6); sleep apnoea: 18 (16.7); Raynaud's disease: 16 (14.8); cancer: 6 (5.6)

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Mameli 2014[140] Ref ID 292 **Country:** Italy **Number of study centres:** 1 **Funding:** NR but note the authors expressed gratitude to Defiante/Sigma-Tau Industrie Farmaceutiche Riunite S.p.A. for supplying oxytocin and placebo nasal spray. The authors declared that they had no financial or non-financial conflict of interest.	**Intervention category:** PBO/Sham vs. endogenous hormones **Intervention:** Placebo vs. oxytocin **Inclusion criteria:** Women with fibromyalgia according to the ACR criteria, aged 18–70 years, resident in a location that allowed the patient to comply with the scheduled visits, understood the aims of the study, and agreed to participate and sign the informed consent form. **Exclusion criteria:** Diagnosis of other disorders that, in the physician's opinion, may constitute a danger for the patient's participation in the study, pregnancy, breastfeeding, or non-use of contraceptive methods, and start of pharmacological treatment dating back < 2 months.	Placebo nasal spray **Time and frequency of treatment session:** Use of spray as in the active nasal spray group. **Duration of treatment (weeks):** 3 **Follow-up:** None	Oxytocin nasal spray **Time and frequency of treatment session:** 1 puff, equal to 0.1 ml oxytocin, 4 IU). Doses were equal to 5 puffs, twice a day (40 IU daily), during the first week, and 10 puffs, BID (80 IU daily), from the second week. **Duration of treatment (weeks):** 3 **Follow-up:** None	**Number randomised** 14 (crossover trial) **Symptom severity** NR **Comorbidity** Affected by mental disorders, (%). mood disorders: 64.3%; anxiety disorders: 57.1%; sleep disorders: 7.1%; eating disorders: 7.1%; psychotic disorders: 7.1%; more than one: 50.0%
Martínez 2014[87] Ref ID 118 **Country:** Spain **Number of study centres:** 1 **Funding:** Supported by the Spanish Ministry of Science and Innovation (research project SEJ2006-07513). Author CDP was supported by a FPU grant from the Spanish Ministry of Education (AP 2007-02965). Research by author GBC was funded by Spanish Ministry of Science and Innovation grant (INNPACTO IPT300000-2010-10) and by Spanish Ministry of Education grant (EDU2010-21215).	**Intervention category:** Education vs. PT/BT sleep **Intervention:** Sleep hygiene educational programme vs. CBT-I **Inclusion criteria:** Women aged between 25 and 60 years meeting the diagnostic criteria for FM (ACR 1990 criteria) and the diagnostic criteria for insomnia (American Psychiatric Association [APA] 2000) who had FM for more than 6 months and had stable intake of analgesics, antidepressants or other drugs at least 1 month before the study. **Exclusion criteria:** Pregnancy; medical history of significant head injury or neurological disorder; major concomitant medical conditions; major depressive disorder with suicide ideation or other major Axis I diagnoses (APA, 2000); symptoms of sleep-disruptive comorbidities with insomnia; an apnoea–hypopnoea index or periodic limb movement-related arousal index of 15 or more per hour of sleep; severe hypnotic dependence; and being treated with another psychological or physical therapy at the time of the study.	Sleep hygiene (SH) educational programme **Time and frequency of treatment session:** 90 minutes, once a week for 6 weeks **Duration of treatment (weeks):** 6 **Follow-up:** 3 months and 6 months after the intervention	CBT for insomnia (CBT-I) **Time and frequency of treatment session:** 90 minutes, once a week for 6 weeks **Duration of treatment (weeks):** 6 **Follow-up:** 3 and 6 months after the intervention	**Number randomised** C: 32, E: 32 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Martínez-Rodríguez 2020[94] Ref ID 213 **Country:** Spain **Number of study centres:** NR **Funding:** None	**Intervention category:** Nutrition vs. nutrition **Intervention:** Control (Mediterranean diet) vs. Tryptophan (Try) and magnesium (Mg)-enriched Mediterranean diet **Inclusion criteria:** Women aged 40–60 years with a FM diagnosis based on the ACR 2016 criteria and absence of oral medication intake. Participants were requested not to make any changes to their lifestyle and follow the suggested dietary pattern during the intervention programme. **Exclusion criteria:** Use of analgesics, vitamin-containing supplements, other drugs for the treatment of fibromyalgia symptoms and participation in other clinical trials.	Mediterranean diet (control group) **Time and frequency of treatment session:** Each participant was met weekly and contacted by phone twice per week by a dietitian to check compliance. **Duration of treatment (weeks):** 16 **Follow-up:** None	Try and Mg-enriched Mediterranean diet (experimental group) The experimental group received a Mediterranean diet enriched with a higher dose of Try (tryptophan) and Mg (magnesium) (60 mg of Try and 60 mg of Mg) derived from eating walnuts at both breakfast and dinner (3–5 units). **Time and frequency of treatment session:** Each participant was met weekly and contacted by phone twice per week by a dietitian to check compliance. **Duration of treatment (weeks):** 16 **Follow-up:** None	**Number randomised** C: 11, E: 11 **Symptom severity** NR **Comorbidity** NR
Mataran-Penarrocha 2011[78] Ref ID 659 **Country:** Spain **Number of study centres:** 1 **Funding:** NR	**Intervention category:** PBO/Sham vs. non-MSM practice **Intervention:** Placebo vs. craniosacral therapy **Inclusion criteria:** FM diagnosis by a rheumatology specialist, aged 16–65 years and agreement to attend afternoon therapy sessions. **Exclusion criteria:** Presence of physical disease, psychological disease, infection, fever, hypotension or skin disorders or respiratory alterations that would limit the application of the treatments.	Sham treatment (placebo) **Time and frequency of treatment session:** Two weekly 30-minute sessions **Duration of treatment (weeks):** 25 **Follow-up:** assessments were repeated at 30 minutes, 6 months and 1 year after the last session of the 25-week treatment programme. Assessments at 25, 51, and 77 weeks from randomisation.	Craniosacral therapy **Time and frequency of treatment session:** Two weekly sessions of 1 h **Duration of treatment (weeks):** 25 **Follow-up:** Assessments were repeated at 30 minutes, 6 months and 1 year after the last session of the 25-week treatment programme. Assessments at 25, 51, and 77 weeks from randomisation.	**Number randomised** C: 52, E: 52 **Symptom severity** NR **Comorbidity** C: arthritis: 8.8%; chorea: 3.9%; Type I diabetes: 5.8%; Type II diabetes: 8%; ulcerous colitis: 3.5% E: arthritis: 6.2%; chorea: 2.1%; Type I diabetes: 3.2%; Type II diabetes: 7%; ulcerous colitis: 6.5%

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Mease 2008[126] Ref ID 2539 **Country:** USA **Number of study centres:** 79 **Funding:** Supported by Pfizer Inc., Ann Arbor, Michigan, USA. The authors received financial support as follows: Dr. Mease received research grant support from Pfizer Inc., Cypress Bioscience, Forest Laboratories, Inc., Eli Lilly and Company, Allergan, Wyeth Pharmaceuticals, Jazz Pharmaceuticals, and Fralex Therapeutics. Dr. Russell received research grant support from Pfizer Inc., Eli Lilly and Company, Allergan, Boehringer Ingelheim, Cypress Biosciences, Inc.,	**Intervention category:** PBO/Sham vs. gabapentinoids vs. gabapentinoids vs. gabapentinoids **Intervention:** Placebo vs. pregabalin 300 mg/day vs. pregabalin 450 mg/day vs. pregabalin 600 mg/day **Inclusion criteria:** Men and women aged ≥ 18 years who met the ACR classification criteria for FM, had an average pain score ≥ 4 on an 11-point numeric rating scale and reported a score ≥ 40 mm on the 100-mm VAS of the Short-Form McGill Pain Questionnaire (SF-MPQ) at screening and randomisation visits. Women of childbearing potential were required to use an adequate method of contraception.	Placebo **Time and frequency of treatment session:** Treatment was administered in 2 divided does daily. **Duration of treatment (weeks):** 13 **Follow-up:** None	E1: Pregabalin 300 mg/day E2: Pregabalin 450 mg/day E3: Pregabalin 600 mg/day **Time and frequency of treatment session:** All pregabalin treatment groups began with a dosage of 150 mg/day, and the dosage was escalated to the fixed, randomised dosage within the first week of treatment. Dosage escalation was followed by 12 weeks of treatment at the fixed, randomised dosage. Treatment was administered in 2 divided doses daily. **Duration of treatment (weeks):** 13 **Follow-up:** None	**Number randomised** C: 190, E1: 185, E2: 183, E3: 190 **Symptom severity** C: BL pain score, mean (SD): 7.2 (1.2) E1: BL pain score, mean (SD): 7.1 (1.4) E2: BL pain score, mean (SD): 7.1 (1.4) E3: BL pain score, mean (SD): 7.0 (1.3) **Comorbidity** NR
Jazz Pharmaceuticals, Grunenthal GMB, and Pierre Fabré. Dr. Arnold received research grant support from Eli Lilly and Company, Pfizer, Inc., Cypress Biosciences Inc., Wyeth Pharmaceuticals, Sanofi-Aventis, Boehringer Ingelheim, Allergan, and Forest Laboratories Inc. Dr. Florian, Mr. Young, and Ms Martin are employees of Pfizer and own stock in Pfizer. Dr. Sharma was an employee of Pfizer when the study was conducted and owns stock in Pfizer.	**Exclusion criteria:** Previous participation in a trial of pregabalin, evidence of inflammatory or rheumatological disease, other severe pain disorders, clinically significant or unstable medical or psychological conditions, a calculated creatinine clearance ≤ 60 ml/min, severe depression, or receiving or applying for disability benefits.			

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Merchant 2001[113] Ref ID 470 **Country:** USA **Number of study centres:** NR **Funding:** Supported in part by a contract and grant from Sun Chlorella Corporation of Kyoto, Japan	**Intervention category:** PBO/Sham vs. nutrition **Intervention:** Placebo (tablet and liquid) vs. dietary supplementation with chlorella extract (tablet and liquid) **Inclusion criteria:** Males and females aged between 18 and 70 years, meeting the ACR criteria for FM diagnosis and scoring ≥ four on at least one of two self-administered 10 cm VASs for pain and overall well-being. Participants had to be lactose tolerant [lactose was the major component of the placebo tablets]. **Exclusion criteria:** NR	Placebo (tablet and liquid) **Time and frequency of treatment session:** Daily for 3 months **Duration of treatment (weeks):** 12 (3 months treatment, 1 month wash-out period, then 3 months after cross over; study duration 7 months) **Follow-up:** None	Chlorella extract (tablet and liquid) **Time and frequency of treatment session:** Daily for 3 months **Duration of treatment (weeks):** 12 (3 months treatment, 1 month wash-out period, then 3 months after cross over; study duration 7 months) **Follow-up:** None	**Number randomised** 43 (crossover trial) **Symptom severity** NR **Comorbidity** NR
Miró 2011[88] Ref ID 2540 **Country:** Spain **Number of study centres:** 1 **Funding:** Supported by the Spanish Ministry of Science and Innovation (research projects SEJ2006-07513, PSI2008-03595PSIC and PSI2009-1365PSIC).	**Intervention category:** Education vs. PT/BT sleep **Intervention:** Sleep hygiene vs. CBT-I **Inclusion criteria:** Unclear but probably women who met the ACR 1990 diagnostic criteria for FM and the APA 2000 criteria for insomnia **Exclusion criteria:** Pregnancy; medical history of significant head injury or neurological disorder; major concomitant medical conditions; major depressive disorder with suicide ideation or other major Axis I diagnoses; symptoms of sleep-disruptive comorbidities with insomnia; apnoea–hypopnoea index or periodic limb movement-related arousal index of 15 or more per hour of sleep; severe hypnotic dependence, and being treated with another psychological or physical therapy at the time of the study.	Sleep hygiene (SH) **Time and frequency of treatment session:** 90 minutes, once a week for 6 weeks **Duration of treatment (weeks):** 6 **Follow-up:** None	CBT for insomnia (CBT-I) **Time and frequency of treatment session:** 90 minutes, once a week for 6 weeks **Duration of treatment (weeks):** 6 **Follow-up:** None	**Number randomised** C: 22, E: 22 **Symptom severity** NR **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Mirzaei 2018[77] Ref ID 1967 **Country:** Iran **Number of study centres:** NR **Funding:** NR	**Intervention category:** PBO/Sham + SSRI vs. nutrition + SSRI **Intervention:** Trazodone + placebo vs. trazodone + vitamin D **Inclusion criteria:** Females aged 20–70 years who met the ACR criteria of FM and had serum levels of 25 (OH) D under 30 ng/ml **Exclusion criteria:** Metabolic disease; diabetes mellitus (DM); rheumatic disorders; psychological disorders, such as major depression; liver diseases; chronic kidney disease (CKD); cancer; cardiovascular diseases; malabsorption; pregnancy; and intolerance of trazodone. Patients taking steroids or vitamin D supplements and hospitalised patients were also excluded.	Trazodone + placebo. **Time and frequency of treatment session:** Patients received the same dose of trazodone as the other (trazodone + vitamin D) group at bedtime along with a placebo. **Duration of treatment (weeks):** 8 **Follow-up:** None	Trazodone + vitamin D **Time and frequency of treatment session:** 50,000 IU oral vitamin D weekly along with 25 mg dose of trazodone at bedtime daily. **Duration of treatment (weeks):** 8 **Follow-up:** None	**Number randomised** C: 37, E: 37 **Symptom severity** C: Mean (SD) Widespread pain index: 13.5 (3.4) E: Mean (SD) Widespread pain index: 12.2 (2.4) **Comorbidity** NR
Mist 2012[85] Ref ID 641 **Country:** USA **Number of study centres:** NR **Funding:** National Institutes of Health/NIAMS 5R21 AR053506 NIH/ NCCAM1K23AT006392-01.	**Intervention category:** Education vs. Mind–body Ex LD **Intervention:** Education vs. Tai Chi **Inclusion criteria:** adults aged ≥ 40 years meeting ACR 1990 criteria for FM, and had participation approved by a healthcare provider. **Exclusion criteria:** Individuals were excluded if they had practised Tai Chi within the past 6 months, had exercised > 30 min three times weekly for past 3 months, could not independently ambulate without assistive devices, had BPI pain severity or interference scores < 5, had planned elective surgery during study period, were actively involved in health-related litigation, or were unwilling to keep all treatments/medications steady throughout the study period.	Education **Time and frequency of treatment session:** 90 minutes twice weekly **Duration of treatment (weeks):** 12 **Follow-up:** None	Tai Chi **Time and frequency of treatment session:** 90 minutes twice weekly **Duration of treatment (weeks):** 12 **Follow-up:** None	**Number randomised** C: 50, E: 51 **Symptom severity** C: BPI severity: 5.7; BPI interference: 6.1 E: BPI severity: 5.4; BPI interference: 6.3 **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Moldofsky 2010[133] Ref ID 147 **Country:** USA **Number of study centres:** 21 **Funding:** Supported by Jazz Pharmaceuticals, Inc. Palo Alto, California, USA.	**Intervention category:** PBO/Sham vs. CNS depressant vs. CNS depressant **Intervention:** Placebo vs. SXB 4.5 g vs. SXB 6 g **Inclusion criteria** A score of > 4 on a 0–10 point pain VAS, based on patient diary records for the week prior to randomisation, agreement to discontinue opiates, antidepressants, cyclobenzaprine and tramadol during the study and continue with any preexisting non-pharmacological regimens; restrict rescue analgesic therapies to the use of acetaminophen ≤ 4000 mg/day, ibuprofen ≤ 1200 mg/day, naproxen ≤ 660 mg/day, or ketoprofen ≤ 75 mg/day; forego ingestion of alcohol; and for women who were not surgically sterile or postmenopausal ≥ 2 years, use a medically accepted contraceptive method **Exclusion criteria:** Inflammatory rheumatic disease; a painful disorder other than FM; hyper- or hypothyroidism; a medical or psychological condition that might compromise participation in the study; an apnoea–hypopnoea index > 15 per hour on a screening PSG (exempted if using satisfactory continuous positive airway pressure therapy that controlled the apnoea/hypopnoea); a seizure disorder; history of head trauma resulting in loss of consciousness; migraine headaches; intracranial surgery; current or recent history (within 1 year) of any substance abuse disorder (including alcohol); succinic semialdehyde dehydrogenase deficiency; taking SXB or any investigational therapy in the 30 days prior to the screening visit; any past use of anticonvulsants for epilepsy; unwillingness to stop using anticonvulsants for pain, any antidepressant (exempted if discontinued for at least 5 half-lives), sleep aids (such as hypnotics, tranquilisers, and antihistamines;	Placebo **Time and frequency of treatment session:** Given nightly at bedtime and 2.5–4 hours later in 2 evenly divided doses **Duration of treatment (weeks):** 8 **Follow-up:** None	E1: SXB 4.5 g/night. E2: SXB 6 g/night. **Time and frequency of treatment session:** Given nightly at bedtime and 2.5–4 hours later in 2 evenly divided doses **Duration of treatment (weeks):** 8 **Follow-up:** None	**Number randomised** C: 66, E1: 62, E2: 67 **Symptom severity** Mean PVAS, mm (SD) randomised (whole pop): 66.0 (16.5); completers (whole pop): 66.4 (16.1) **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
	non-sedating antihistamines were exempt), or benzodiazepines; serum creatinine > 2.0 mg/dl; abnormal liver function tests; a positive pregnancy test; an electrocardiogram that disclosed a clinically significant arrhythmia or an atrioventricular conduction delay greater than first-degree block; pending worker's compensation litigation or other monetary settlements; or an occupation that required night-shift work.			
Molina-Torres 2016[90] Ref ID 341 **Country:** Spain **Number of study centres:** 1 **Funding:** NR	**Intervention category:** Electro T vs. occlusal SS **Intervention:** Laser therapy vs. occlusal stabilisation splint **Inclusion criteria:** FM diagnosis and presence of TMDs, a pretreatment VAS score of > 30 mm, muscular pain confirmed by palpation, availability for the study's schedule, and willingness to attend the evening sessions of therapy. **Exclusion criteria:** History of recent trauma, use of therapeutic co-interventions during treatment, indicated for surgical treatment of the temporomandibular joint, physical or mental illness that precluded attendance at therapy sessions, pain attributable to a confirmed neck pain condition, acute infection, and collagen vascular disease.	Laser therapy **Time and frequency of treatment session:** 1 session per week **Duration of treatment (weeks):** 12 **Follow-up:** None	Occlusal stabilisation splint **Time and frequency of treatment session:** 8 hours per night **Duration of treatment (weeks):** 12 **Follow-up:** None	**Number randomised** C: 29, E: 29 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Moustafa 2015[73] Ref ID 346 **Country:** Egypt **Number of study centres:** 1 **Funding:** NR	**Intervention category:** PBO/Sham + multimodal (PT/BT gen + Flex/skill LD) vs. manual T + multimodal (PT/BT gen + Flex/skill LD) **Intervention:** Control (multimodal programme consisting of education, CBT and stretching exercise; plus manual contact similar to manipulative therapy) vs. upper cervical manipulative therapy + multimodal programme **Inclusion criteria:** Patients who met the ACR 1990 criteria for FM, had experienced symptoms for at least 48 months with no recent remission of symptoms, reported a pain intensity score > 4, were aged between 40 and 65 years, reported a score ≥ 59 on the FIQ, and were able to read and comprehend English, had a limited C1-C2 ROM based on the flexion-rotation test (FRT).	Manual contact plus multimodal programme 1. Manual contact 2. Multicomponent programme (consisting of education, CBT and stretching exercise) **Time and frequency of treatment session:** Education: 2 hours, once a week, for 12 weeks; CBT: 2 hours, once a week, for 12 weeks; Exercise: 1 hour, 2 times a week, for 12 weeks. **Duration of treatment (weeks):** 12 **Follow-up:** 1 year (after the end of intervention)	Upper cervical manipulative therapy + multimodal programme 1. Multimodal programme (education, CBT and stretching exercise). As in the control group. 2. Upper cervical manipulative therapy (low-velocity cervical joint mobilisation techniques and high-velocity manipulation techniques for the treatment of cervical joint disorders) **Time and frequency of treatment session:** Education: 2 hours, once a week, for 12 weeks. CBT: 2 hours, once a week, for 12 weeks. Exercise: 1 hour, 2 times a week, for 12 weeks; manipulative therapy: upper cervical manipulative therapy 3 times a week for 4 weeks, followed by maintenance spinal manipulation 1 session per week for the following 8 weeks. **Duration of treatment (weeks):** 12 **Follow-up:** 1 year (after the end of intervention)	**Number randomised** C: 60, E: 60 **Symptom severity** NR **Comorbidity** NR
	Exclusion criteria: Rheumatoid disease; unstable hypertension; severe cardiopulmonary problems; chronic viral infection; a history of any significant medical conditions, including hepatitis, herpes, lupus, multiple sclerosis, rheumatoid arthritis, polio, epilepsy, rheumatic fever, cancer, history of neck or back surgeries; and any psychiatric disorder affecting participant compliance.			

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Munguía-Izquierdo 2008[56] Ref ID 199 **Country:** Spain **Number of study centres:** 1 **Funding:** Supported by the European Social Funds and Regional Government of Aragon (Spain: grant no. B187/2004).	**Intervention category:** UC vs. mixed exercise AQ **Intervention:** Control vs. aquatic exercise **Inclusion criteria:** Women aged 18–60 years with a diagnosis of FM confirmed according to the ACR criteria. **Exclusion criteria:** History of morbid obesity, known cardiopulmonary diseases, endocrine or allergic disturbances uncontrolled, severe trauma, frequent migraines, inflammatory rheumatic diseases, severe psychiatric illness, other diseases that prevent physical loading, pregnancy attending another type of physical or psychological therapy, a history of regular physical activity more strenuous than slow-paced walking a maximum of 2 times a week over 4 months before study entry.	Control The control group was instructed not to change their habits regarding physical activities during the period. **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 16 **Follow-up:** None	Aquatic exercise **Time and frequency of treatment session:** 10 minutes of warming up, 10 to 20 minutes of strength exercises, 20–30 minutes of aerobic exercises, and 10 minutes of cooling down, 3 times a week for 16 weeks **Duration of treatment (weeks):** 16 **Follow-up:** None	**Number randomised** C: 25, E: 35 **Symptom severity** C: Tender-point count (0–18): 16.1 (2.9) E: Tender-point count (0–18): 15.2 (3.6) **Comorbidity** NR
Nadal-Nicolás 2020[68] Ref ID 2308 **Country:** Spain **Number of study centres:** NR **Funding:** No external funding.	**Intervention category:** PBO/Sham vs. Manual T **Intervention:** Placebo (sham ultrasound) vs. Manual T **Inclusion criteria:** Women diagnosed with FM according to ACR 2016 criteria. In addition, the axial region of the neck and upper back must have been affected. **Exclusion criteria:** Other physical therapy or physical exercise treatment; not having a sufficient cognitive level to participate in the study or unable to attend the sessions.	Sham ultrasound (placebo) **Time and frequency of treatment session:** 15 minutes, twice a week, for 4 weeks **Duration of treatment (weeks):** 4 **Follow-up:** None	Manual T **Time and frequency of treatment session:** 15 minutes, twice a week, for 4 weeks **Duration of treatment (weeks):** 4 **Follow-up:** None	**Number randomised** C: 15, E: 15 **Symptom severity** C: Mean (SD) Pain VAS (0 = no pain, 10 = worst pain): 5.1 (2.2) E: Mean (SD) Pain VAS (0 = no pain, 10 = worst pain): 5.4 (2.6) **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Nelson 2010[106] Ref ID 331 **Country:** USA **Number of study centres:** NR **Funding:** Supported by NIH/NCCAM Grant 1R21 AT000930-01A2 and the Oregon Health and Science University General Clinical Research Center through PHS Grant 5 M01 RR000334.	**Intervention category:** PBO/Sham vs. neuromodulation **Intervention:** Sham vs. low-energy neurofeedback system (LENS) **Inclusion criteria:** Diagnosis of primary FM according to ACR 1990 criteria; duration of FM symptoms ≥ 1 year; aged ≥ 18 years; self-reported cognitive difficulties; no other major chronic pain condition; no neurological disorder; no history of traumatic brain injury; no chronic infection; no other unstable medical condition; no history of spinal, including neck, surgery; not psychotic, imminently suicidal, or homicidal; no current substance abuse; not currently taking sustained-release opiates on a daily basis; willing to maintain stable FM treatments throughout the study; no history of electroconvulsive therapy (ECT); able to read and understand English; and not currently engaged in or planning litigation regarding their physical condition or applying for disability. **Exclusion criteria:** NR	Sham LENS **Time and frequency of treatment session:** 22 treatment sessions **Duration of treatment (weeks):** Unclear (22 sessions) **Follow-up:** 12 and 24 weeks (3 and 6 months after the intervention)	Low-energy neurofeedback system (LENS) **Time and frequency of treatment session:** 22 treatment sessions **Duration of treatment (weeks):** Unclear (22 sessions) **Follow-up:** 12 and 24 weeks (3 and 6 months after the intervention)	**Number randomised** C: 21, E: 21 **Symptom severity** NR **Comorbidity** NR
Ohta 2012[123] Ref ID 222 **Country:** Japan **Number of study centres:** 44 **Funding:** Pfizer Japan, Inc. Medical writing support was provided by Joshua Fink PhD, of UBC Scientific Solutions, and funded by Pfizer, Inc.	**Intervention category:** PBO/Sham vs. Gabapentinoids **Intervention:** Placebo vs. pregabalin 300 or 450 mg **Inclusion criteria:** Aged ≥ 18 years and met the ACR 1990 criteria for FM, with a score of ≥ 40 mm on the 100 mm pain VAS at Visit 2, and had assessed and documented their pain score on at least four of the past 7 days prior to Visit 2 while recording an average pain score of ≥ 4 on the 11-point numeric rating scale	Placebo **Time and frequency of treatment session:** BID (morning and evening) **Duration of treatment (weeks):** 15 **Follow-up:** 1 week after treatment/16 weeks from randomisation	Pregabalin 300 or 450 mg **Time and frequency of treatment session:** BID (morning and evening). Treatment was started at 150 mg/day, escalated to 300 mg/day 1e week later, and to 450 mg/day after another week. The dose was adjusted (increased or decreased) until Visit 5 of the study, after which the maintenance dose was either 300 mg/day or 450 mg/day	**Number randomised** **C:** 250, E: 251 **Symptom severity** NR **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
	Exclusion criteria: Patients were excluded if they had a decrease of ≥ 30% on their pain VAS during the placebo run-in period (at Visit 2 compared with Visit 1), and if they were being treated for depression, were at risk of suicide or self-harm in the opinion of the study investigator, had an active malignancy or a history of malignancy, had a creatinine clearance rate ≤ 60 ml/minute, or experienced pain which might potentially affect assessment or self-evaluation of FM.		**Duration of treatment (weeks):** 15 **Follow-up:** 1 week after treatment/16 weeks from randomisation	
Onieva-Zafra 2019[64] Ref ID 689 **Country:** Spain **Number of study centres:** NR **Funding:** NR	**Intervention category:** UC vs. relaxation **Intervention:** Control vs. guided imagery **Inclusion criteria:** NR **Exclusion criteria:** NR	Control Group discussions. **Time and frequency of treatment session:** Three 1.5-hour sessions **Duration of treatment (weeks):** Unclear but possibly 8 weeks **Follow-up:** Both groups were assessed using the same measures at baseline, post-intervention (week 4), and upon completion of the study (week 8).	Guided imagery (GI) **Time and frequency of treatment session:** Three 1.5-hour group sessions + The intervention group was asked to perform 1 GI exercise per day at least 4 or 5 times per week over a period of 8 weeks. **Duration of treatment (weeks):** Unclear but presume 8 weeks **Follow-up:** Both groups were assessed using the same measures at baseline, postintervention (week 4), and upon completion of the study (week 8).	**Number randomised** C: 27, E: 29 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Pauer 2011[139] Ref ID 148 **Country:** Europe (Denmark, 2 centres, France 5, Germany 5, Italy 6, Portugal 4, Spain 4, Sweden 4, Switzerland 3, The Netherlands 5, and UK 5) or in Asia, Australia, and the Americas (Australia 4, Canada 12, India 4, Korea 3, Mexico 4, and Venezuela 3). **Number of study centres:** 73 **Funding:** Supported by Pfizer Inc.	**Intervention category:** PBO/Sham vs. gabapentinoids vs. gabapentinoids vs. gabapentinoids **Intervention:** Placebo vs. pregabalin 300 mg/day vs. pregabalin 450 mg/day vs. pregabalin 600 mg/day **Inclusion criteria:** Males and females aged ≥ 18 years meeting the ACR 1990 criteria for FM, had at least moderate pain (average pain score ≥ 4 on an 11-point NRS) during baseline assessment, and had a score ≥ 40 mm on the 100-mm pain VAS of the Short-Form McGill Pain Questionnaire at screening and randomisation. **Exclusion criteria:** Patients who demonstrated a high placebo response (≥ 30% decrease on the VAS following the 1-week run-in period compared with screening.	Placebo **Time and frequency of treatment session:** BID for 14 weeks **Duration of treatment (weeks):** 14 **Follow-up:** None	E1: Pregabalin 300 mg/day, E2: Pregabalin 450 mg/day, E3: Pregabalin 600 mg/day, **Time and frequency of treatment session:** All pregabalin groups received 2 divided doses daily **Duration of treatment (weeks):** 14 **Follow-up:** None	**Number randomised** **C:** 184, E1: 184, E2: 182, E3: 186 **Symptom severity** C: Mean (SD) pain score (range 0–10): 6.68 (1.48); Mean (SD) number of painful tender points: 17.0 (1.6) E1: Mean (SD) pain score (range 0–10): 6.76 (1.29); Mean (SD) number of painful tender points: 17.0 (1.7) E2: Mean (SD) pain score (range 0–10): 6.57 (1.31); Mean (SD) number of painful tender points: 17.2 (1.7) E3: Mean (SD) pain score (range 0–10): 6.59 (1.37); Mean (SD) number of painful tender points: 17.2 (1.5) **Comorbidity** NR
Picard 2013[104] Ref ID 275 **Country:** France **Number of study centres:** 1 **Funding:** Fondation de France, UB 032115.	**Intervention category:** UC vs. relaxation **Intervention:** Wait list vs. self-hypnosis **Inclusion criteria:** Women diagnosed with FM according to the ACR 1990 criteria for at least 6 months **Exclusion criteria:** Chronic inflammatory arthritis and/or peripheral or central neuropathic pain, treated with opioids, and/or severe psychiatric illness, according to the Diagnostic and Statistical Manual of Mental Disorder, fourth edition, or a history of substance abuse.	Wait list No further detail **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 12 (treatment duration unclear; assessment at 3 months) **Follow-up:** Assumed 3 months (6 months from randomisation)	Self-hypnosis **Time and frequency of treatment session:** Five 1-hour sessions. The time interval between each session was 8, 15, 21, and 28 days, respectively (adds up to 72 days) **Duration of treatment (weeks):** 12 (treatment duration unclear; assessment at 3 months) **Follow-up:** Assumed 3 months (6 months from randomisation)	**Number randomised** C: 31, E: 31 **Symptom severity** C: NRS (no pain (0) to the most intense pain imaginable (10)): 6.80 (1.5) E: NRS (no pain (0) to the most intense pain imaginable (10)): 7.16 (0.5) **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Potvin 2012[116] Ref ID 230 **Country:** Canada **Number of study centres:** NR **Funding:** NR	**Intervention category:** PBO/Sham vs. AP **Intervention:** Placebo + current medication vs. quetiapine extended-release (XR) as add-on to current medication **Inclusion criteria:** Unclear. Females aged > 18 years meeting the ACR criteria for FM and had a score of ≥ 4 on the pain severity item of the French version of the FIQ.	Placebo + current medication **Time and frequency of treatment session:** QD **Duration of treatment (weeks):** 12 **Follow-up:** None	Quetiapine extended-release (XR) as add-on to current medication for FM **Time and frequency of treatment session:** Quetiapine up to 300 mg daily as a single dose per day. The initial dose was 50 mg/day the first 3 days and then 100 mg/day up to day 7. From day 8 thereafter, a flexible dose between 50 and 300 mg/day was used	**Number randomised** C: 26, E: 25 **Symptom severity** NR **Comorbidity** NR
	Exclusion criteria: Already receiving an AP; pregnancy; females of childbearing potential without adequate contraception; risk of suicide; any Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Axis I psychiatric disorder other than MDD; any clinically meaningful unstable, renal, hepatic, cardiovascular, respiratory, cerebrovascular disease, or other serious, progressive physical illness; and diabetes mellitus.		**Duration of treatment (weeks):** 12 **Follow-up:** None	
Prados 2020[97] Ref ID 2269 **Country:** Spain **Number of study centres:** NR – presume 1 **Funding:** Supported by the Spanish Ministry of Science and Innovation through project PSI2009-13765.	**Intervention category:** PT/BT gen vs. PT/BT sleep **Intervention:** CBT-P (CBT for pain) vs. CBT-C (CBT for pain and insomnia combined) **Inclusion criteria:** Women with FM aged between 24 and 62 years diagnosed with FM according to the ACR 1990 criteria having significant self-reported insomnia according to well-established diagnostic criteria and following a stable medication regime over the past month.	CBT for pain (CBT-P) **Time and frequency of treatment session:** 90 minutes, once a week, for 9 weeks **Duration of treatment (weeks):** 9 **Follow-up:** None	CBT for pain and insomnia combined (CBT-C) **Time and frequency of treatment session:** 90 minutes, once a week, for 9 weeks **Duration of treatment (weeks):** 9 **Follow-up:** None	**Number randomised** C: 19, E: 20 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
	Exclusion criteria: Pregnancy, major medical conditions (e.g. inflammatory rheumatic diseases, uncontrolled endocrine disorders, cancer) including a clinical history of significant head injury or neurological disorder; severe psychopathology such as major depression with suicide ideation, schizophrenia, personality disorder; suffering from other sleep disorders that better explained insomnia; severe dependence on hypnotic drugs, and being enrolled in another physical or psychological treatment during the study period.			
Racine 2019[102] Ref ID 296 **Country:** UK **Number of study centres:** 1 **Funding:** Financial support included a bequest from the estate of Mrs. Beryl Ivey to Dr. Warren R. Nielson and an Earl Russell Trainee Grant from Western University, London, Ontario to Dr. Melanie Racine.	**Intervention category:** UC vs. PT/BT gen vs. UC vs. PT/BT gen **Intervention:** Delayed operant learning (OL) vs. immediate operant learning (OL) vs. delayed energy conservation (EL) vs. Immediate energy conservation (EL) **Inclusion criteria:** Patients with FM who were able to provide informed consent, aged ≥ 18 years, able to understand and speak English, met the ACR 1990 or 2010 criteria for FM, had never received a formal activity pacing treatment, and did not present with a psychological disorder or cognitive impairment that might prevent benefiting from an activity pacing treatment (e.g. psychosis, severe depression). **Exclusion criteria:** NR	Delayed operant learning **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 10 **Follow-up:** 12 weeks (3 months after the intervention)	E1: Immediate operant learning (OL) E2: Delayed energy conservation (EL) E3: Immediate energy conservation (EL) **Time and frequency of treatment session:** Immediate OL/EL: 2 hours, once a week, for 10 weeks; delayed OL/EL: none **Duration of treatment (weeks):** 10 **Follow-up:** 12 weeks (3 months after the intervention)	**Number randomised** C: 36, E1: 54, E2: 35, E3: 53 **Symptom severity** NR **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Reuter 2017[118] Ref ID 310 **Country:** Germany **Number of study centres:** 1 **Funding:** Financed from internal hospital funds. No external funding or sponsors.	**Intervention category:** PBO/Sham vs. CNS depressant **Intervention:** Placebo vs. oral gamma-hydroxybutyrate (GHB) **Inclusion criteria:** Met the ACR 1990 criteria for FM, were female with command of the German language, and provided written informed consent. **Exclusion criteria:** Pregnancy and individual comorbid mental psychiatric diagnoses (e.g. schizophrenia, major depressive disorder), use of sedative medication (sedatives, hypnotics), use of opioids, pending retirement, age under 18 and over 80 years, arterial hypertension and specific physical illnesses (e.g. epilepsy, severe renal dysfunction, tumour diseases).	Placebo A placebo consisting of isotonic saline **Time and frequency of treatment session:** 25 mg/kg 1 hour before going to bed with a repeat dose if the patient had been awake for more than 1 hour **Duration of treatment (weeks):** 15 **Follow-up:** None	Oral gamma-hydroxybutyrate (GHB) **Time and frequency of treatment session:** 25 mg/kg body weight 1 hour before going to bed with a repeat dose if the patient had been awake for more than 1 hour **Duration of treatment (weeks):** 15 **Follow-up:** None	**Number randomised** C: 12, E: 13 **Symptom severity** C: Pain severity (MPI), mean (SD): 3.4 (0.9) E: Pain severity (MPI), mean (SD): 3.9 (1.2) **Comorbidity** C: depressive disorders: 42%; anxiety disorders: 42% E: depressive disorders: 46%; anxiety disorders: 38%
Russell 2011[135] Ref ID 228 **Country:** USA **Number of study centres:** 74 clinical sites **Funding:** Sponsored by Jazz Pharmaceuticals, Inc. I.J.R. received research grants from Allergan, Grüenthal, Jazz Pharmaceuticals, Pfizer, and UCB and participated in the speakers' bureaus for Pfizer and Eli Lilly, and as a consultant to Jazz Pharmaceuticals, Ortho-McNeil-Janssen,	**Intervention category:** PBO/Sham vs. CNS depressant vs. CNS depressant **Intervention:** Placebo vs. SXB 4.5 g vs. SXB 6 g **Inclusion criteria:** Men and women ≥ 18 years old who met the ACR 1990 criteria for FM and had a BMI of < 40 kg/m^2, and a score of ≥ 50 on a 100-mm Pain VAS. Patients were required to be naive to SXB, and to discontinue opiates, benzodiazepines, muscle relaxants,	Placebo **Time and frequency of treatment session:** A bedtime dose and a second equal dose 2.5–4 hours later. **Duration of treatment (weeks):** 14 **Follow-up:** None	E1: SXB 4.5 g, oral solution E2: SXB 6 g, oral solution **Time and frequency of treatment session:** A bedtime dose and a second equal dose 2.5–4 hours later. The SXB 6 g group received the 4.5 g dose for the first fortnight **Duration of treatment (weeks):** 14 **Follow-up:** None	**Number randomised** **C:** 183, E1: 182, E2: 183 **Symptom severity** C: Pain VAS (0–100) mean (SD): 71.6 (12.9) E1: Pain VAS (0–100) mean (SD): 71.9 (12.7) E2: Pain VAS (0–100) mean (SD): 72.3 (13.4) **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Pfizer, and UCB. He holds no company stock or positions. A.J.H. received research grants from the National Fibromyalgia Association and the National Fibromyalgia Research Association and has participated as an investigator for Jazz Pharmaceuticals and as a speaker for Eli Lilly and Forest Laboratories. He holds no company stock or positions. T.J.S. has received research funding from Jazz Pharmaceuticals, Cephalon, GlaxoSmithKline, Takeda Pharmaceuticals, Sanofi-Aventis, Somaxon, Merck, and Pfizer; and has participated in speakers' bureaus for Cephalon, Jazz Pharmaceuticals, Sepracor, GlaxoSmithKline, Sanofi-Aventis, Takeda Pharmaceuticals, and Boehringer Ingelheim. S.A., Y.G.W., and D.G. are employees of Jazz Pharmaceuticals and hold company stock.	anticonvulsants, antidepressants, dopamine agonists, tramadol, and any other medications that might influence the outcome; discontinue ingestion of alcohol for the entire duration of the study; maintain any pre-existing nutritional or exercise regimen and any behavioural, massage, physical, or cognitive therapies; and use only acetaminophen (≤ 4 g/day) as rescue pain medication. Aspirin was permitted at ≤ 325 mg/day, solely for cardiac protection. Women who were either surgically sterile or ≥ 2 years post-menopausal were required to have a negative pregnancy test. Women of childbearing potential had to have a negative pregnancy test, could not be nursing or lactating, and were required to use a medically accepted birth control throughout the study. Patients with a BMI of ≥ 35 and < 40 kg/m^2 were required to undergo polysomnography at screening to rule out sleep apnoea. Patients diagnosed with sleep apnoea had to be on stable continuous positive airway pressure for 30 days before baseline, and to remain on it for the duration of the study. **Exclusion criteria:** Inflammatory rheumatic disease; any painful disorder other than FM, including chronic persistent migraine; any medical or psychiatric condition that might confound study results (including major depressive disorder and generalised anxiety disorder); current or previous substance-use disorder, including alcohol abuse; any history of clinically significant seizure disorder or head trauma; or past intracranial surgery, major depressive disorder, generalised			

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
	anxiety disorder, occupation requiring variable shifts or routine night shifts, any pending litigation, monetary settlements, or disability evaluation for chronic pain and/or FM, serum creatinine > 2.0 mg/dl, thyroid-stimulating hormone < 0.3 or > 6 µU/ml, abnormal liver function tests, serum bilirubin more than 1.5 times the upper limit of normal, or electro-cardiographic demonstration of clinically significant arrhythmia or conduction delay.			
Samartin-Veiga 2021[75] Ref ID 1787 **Country:** Spain **Number of study centres:** 5 **Funding:** The Spanish Government (Ministerio de Econom´ıa y Competitividad; ref PSI2016-75313-R). A.J. González-Villar was supported by a grant from the Portuguese Foundation for Science and Technology within the scope of the Individual Call for Stimulus to Scientific Employment 2017. N. Samartin-Veiga was supported by a grant from the Spanish Government (Ministerio de Econom´ıa y Competitividad; grant number BES-2017-082684).	**Intervention category:** PBO/Sham vs. neuromodulation vs. neuromodulation vs. neuromodulation **Intervention:** Sham tDCS vs. M1-tDCS (classic) vs. DLPFC-tDCS (classic) vs. OIC-tDCS (novel) **Inclusion criteria:** A diagnosis of FM, meeting the ACR 2010 criteria for FM and aged between 25 and 65 years. **Exclusion criteria:** Immune system pathology or comorbidities that could explain the main symptomatology of FM; risk factors for the tDCS procedure (such as epilepsy or family history of epilepsy), history of substance abuse, presence of psychiatric diseases (other than depression and anxiety), presence of brain damage, dementia, or Parkinson disease, taking drugs that block sodium or calcium channels and unchanged medication patterns in the 2 previous months.	Sham tDCS **Time and frequency of treatment session:** 15 sessions of 20 minutes each, scheduled 5 consecutive days/week **Duration of treatment (weeks):** Unclear but assumed that treatment 3 weeks and assessment at 4 weeks **Follow-up:** 6 and 12 months	E1. tDCS (transcranial direct-current stimulation) targeted on the primary motor cortex (M1) E2: tDCS targeted on the left DLPFC E3: tDCS targeted on the OIC **Time and frequency of treatment session:** 15 sessions of 20 minutes each, scheduled 5 consecutive days/week **Duration of treatment (weeks):** Unclear but assumed that treatment 3 weeks and assessment at around 4 weeks. **Follow-up:** 6 and 12 months	**Number randomised** C: 30, E1: 34, E2: 33, E3: 33 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
San Mauro Martin 2019[58] Ref ID 651 **Country:** Spain **Number of study centres:** NR **Funding:** Supported by AVEDIAN (manufacturer of the turmeric supplement).	**Intervention category:** UC vs. nutrition **Intervention:** No supplement vs. turmeric-based food supplement **Inclusion criteria:** Women aged 30–60 years, with fibromyalgia diagnosis, were following the IGUBAC Diet®, and completed the informed consent. Criteria for diagnosis of fibromyalgia included generalised pain in at least 4 of 5 regions (left upper, right upper, left lower, right lower axial) and symptoms present at a similar level for at least 3 months, regardless of other clinically important illnesses. **Exclusion criteria:** Severe psychiatric disorder, renal disease, cardiovascular disease, were pregnant or breastfeeding, allergic to turmeric or were under corticoids medication.	No supplement None of the participants in this group ingested the food supplement. Unclear if all followed the IGUBAC diet. **Time and frequency of treatment session:** 1 month following IGUBAC Diet **Duration of treatment (weeks):** 4 **Follow-up:** None	Turmeric-based food supplement The study group was supplemented during 1 month with a turmeric-based supplement of 500 mg, Avecurm by Avedian and followed the IGUBAC diet® (Inflammatory Gut-Brain Axis Control diet). **Time and frequency of treatment session:** 1 month with a turmeric-based supplement of 500 mg **Duration of treatment (weeks):** 4 **Follow-up:** None	**Number randomised** C: 7, E: 6 **Symptom severity** C: Grade III (high disability) pain: 100% E: Intermediate-high pain: (67%); Grade II pain: 33.3% **Comorbidity** Whole population (NR by intervention group): cardiovascular disease (*n* = 5), thyroid disease (*n* = 3), arthritis (*n* = 2), depression (*n* = 2) and scleroderma (*n* = 1)
Sarmento 2020[71] Ref ID 409 **Country:** USA **Number of study centres:** 1 **Funding:** None	**Intervention category:** PBO/Sham vs. Mind–body Ex LD **Intervention:** Sham vs. qigong **Inclusion criteria:** Females aged between 18 and 70 years, non-obese (BMI ≤ 30) with the diagnosis of FM given by a physician according to the ACR 2010 or the ACR 1990 criteria. **Exclusion criteria:** Regular use of opioids (any opioid prescription for at least 60 days within 6 months); major depressive disorders; autoimmune, endocrine disorders or chronic inflammatory illness; abuse of alcohol, benzodiazepines, or other drugs; severe psychiatric illness; active cardiovascular, pulmonary illness; current systemic infection; active cancer; severe sleep apnoea (as classified by the Apnoea–Hypopnoea Index); pregnancy or breastfeeding. Participants on a stable dosage of medication for sleep, pain, or mild depression were not excluded.	SHAM Qigong **Time and frequency of treatment session:** Weekly training session (unclear duration) for 2 weeks, followed by a 45-minute weekly session for 8 weeks **Duration of treatment (weeks):** 10 **Follow-up:** None	QIGONG **Time and frequency of treatment session:** Weekly training session (unclear duration) for 2 weeks, followed by a 45-minute weekly session for 8 weeks **Duration of treatment (weeks):** 10 **Follow-up:** None	**Number randomised** C: 14, E: 14 **Symptom severity** C: FM intensity (severity classification according to the FIQR): moderate, 57.6 (16.7) E: FM intensity (severity classification according to the FIQR): moderate, 52.1 (18.5) **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Schmidt 2011[62] Ref ID 349 **Country:** Germany **Number of study centres:** NR **Funding:** Supported by the Samueli Institute, Alexandria, VA, and by the Manfred Köhnlechner Stiftung, Munich, Germany.	**Intervention category:** UC vs. PBO/Sham vs. PT/BT gen **Intervention:** Wait list vs. active control (inc. muscle relaxation and stretching) vs. mindfulness-based stress reduction (MBSR) **Inclusion criteria:** Women aged 18–70 years with fibromyalgia defined by the ACR criteria; command of the German language and motivation to participate. **Exclusion criteria:** Life-threatening diseases, evidence of suppressed immune functioning, or participation in other clinical trials.	C1: Wait list control Patients randomised to this group received no active treatment but were offered their choice of either intervention at conclusion of the short-term follow-up period. **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 8 **Follow-up:** 8 weeks post-treatment C2: Active control Participation in an 8-week group of size and weekly format similar to that of the MBSR programme with stretching exercise replacing the mindfulness practice and training **Time and frequency of treatment session:** 2.5-hour session every week, **Duration of treatment (weeks):** 8 **Follow-up:** 8 weeks post-treatment	Mindfulness-based stress reduction (MBSR) **Time and frequency of treatment session:** 2.5-hour session every week, and an additional 7-hour all-day session on a weekend day **Duration of treatment (weeks):** 8 **Follow-up:** 8 weeks post-treatment	**Number randomised** C: 59, E1: 59, E2: 59 **Symptom severity** NR **Comorbidity** Reported for the whole trial sample: 58% had a clinically relevant depression score (i.e. score > 23 in the German version of the CES-D scale) and an elevated degree of trait anxiety (mean STAI, 50.0, SD = 10.3), higher than that of 89% of women aged 30–59 years and 80% of women aged 60 years or more in the German norm population and cored worse than 96% of the German norm population of the same sex and age for physical symptoms.

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Senna 2012[65] Ref ID 345 **Country:** Egypt **Number of study centres:** 1 **Funding:** NR	**Intervention category:** UC vs. weight loss **Intervention:** No weight loss vs. dietary weight loss **Inclusion criteria:** Men and women with obesity, aged 18–70 years, who met the ACR 1990 criteria of FM **Exclusion criteria:** Medical disorder that would affect body weight, inflammatory arthritis, autoimmune disease, unstable medical or psychiatric illness, night-shift jobs, psychosis, or a medication regimen that had not been stable for at least 2 months prior to baseline, pregnancy or women who were attempting to conceive.	No weight loss (control) **Time and frequency of treatment session:** NR **Duration of treatment (weeks):** 24 **Follow-up:** None	Dietary weight loss **Time and frequency of treatment session:** NR **Duration of treatment (weeks):** 24 **Follow-up:** None	**Number randomised** C: 43, E: 43 **Symptom severity** NR **Comorbidity** NR
Simister 2018[61] Ref ID 265 **Country:** Canada **Number of study centres:** NR **Funding:** Supported by a financial grant from the Health Sciences Centre Foundation, Winnipeg, Manitoba, Canada.	**Intervention category:** UC vs. PT/BT gen **Intervention:** TAU vs. online ACT + TAU **Inclusion criteria:** Aged ≥ 18 years with a formal diagnosis of FM, and self-reported pain intensity rating of at least 4/10 on a rating scale (0 representing no pain). **Exclusion criteria:** Presence of comorbidities such as rheumatological conditions, other conditions affecting the immune system (e.g. chronic fatigue syndrome, multiple sclerosis, lupus), brain injury, cognitive impairment that would limit a participant's ability to complete informed consent, active psychosis, substance abuse, untreated severe major depression or bipolar disorder, active suicidality, or current active injury claim.	TAU **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 8 **Follow-up:** 12 weeks (5 months after the start of the study)	Online ACT and TAU 1. TAU as in the TAU group. 2. Online ACT. **Time and frequency of treatment session:** Participants had 2 months to complete the online treatment programme. Participants completed the modules at their own pace but were encouraged to spend approximately 1 week to complete each module. **Duration of treatment (weeks):** 8 **Follow-up:** 12 weeks (5 months after the start of the study)	**Number randomised** C: 34, E: 33 **Symptom severity** NR **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Slim 2017[95] Ref ID 1811 **Country:** Spain **Number of study centres:** 1 **Funding:** NR	**Intervention category:** Nutrition vs. nutrition **Intervention:** Gluten-free diet vs. hypocaloric diet **Inclusion criteria:** Aged ≥ 18 years with a minimum of 5/14 gluten-sensitivity symptoms and negative transglutaminase antibodies according to serological testing **Exclusion criteria:** Presence of any disease that could prevent the patients from following any of the anticipated dietary interventions, a current or previous history of substance abuse, and pregnancy or lactation.	Gluten-free diet **Time and frequency of treatment session:** One dietary orientation session **Duration of treatment (weeks):** 24 **Follow-up:** None	Hypocaloric diet (HCD) **Time and frequency of treatment session:** Small meals divided into 5 portions per day: breakfast, a mid-day snack, lunch, an afternoon snack, and dinner to ensure that daily energy intake did not exceed a maximum of 1500 kcal/day **Duration of treatment (weeks):** 24 **Follow-up:** None	**Number randomised** C: 35, E: 40 **Symptom severity** C: Widespread pain index: 17.4 (2.2); BPI severity:6.67 (1.70); BPI interference: 7.13 (1.72) E: Widespread pain index: 16.8 (2.5); BPI severity: 6.93 (1.42); BPI interference: 7.25 (1.56) **Comorbidity** NR
Spaeth 2012[134] Ref ID 122 **Country:** France, Germany, Italy, The Netherlands, Poland, Spain, UK and USA **Number of study centres:** 108 study centres in eight countries (France, Germany, Italy, The Netherlands, Poland, Spain, UK and USA). **Funding:** Sponsored and funded by Jazz Pharmaceuticals, Inc.	**Intervention category:** PBO/Sham vs. CNS depressant vs. CNS depressant **Intervention:** Placebo vs. SXB 4.5 g vs. SXB 6 g **Inclusion criteria:** Women or men aged ≥ 18 years meeting the ACR criteria for FM with a BMI < 40 kg/m^2 and an average score of 50 or greater on a 100-mm pain VAS. Participants had to discontinue medications, herbal remedies and/or devices that might influence	Placebo **Time and frequency of treatment session:** Taken nightly in two equal doses, one at bedtime and the second 2.5–4 hour later **Duration of treatment (weeks):** 14 **Follow-up:** None	E1: SXB 4.5 g/night. Oral solution. E2: SXB 6 g/night. Oral solution. **Time and frequency of treatment session:** SXB 4.5 g/night: Taken nightly in two equal doses, one at bedtime and the second 2.5–4 hour later; SXB 6 g/night: SXB 4.5 g/night during the first 2 weeks and then SXB 6 g/night for the remaining 12 weeks **Duration of treatment (weeks):** 14 **Follow-up:** None	**Number randomised** C: 188, E1: 195, E2: 190 **Symptom severity** C: Pain VAS (0–100) mean (SD): 72.6 (12.9) E1: Pain VAS (0–100) mean (SD): 70.5 (13.0) E2: Pain VAS (0–100) mean (SD): 72.2 (14.0) **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
	outcome; non-pharmacological treatments for fibromyalgia had to remain unchanged, and only paracetamol (acetaminophen) was allowed as rescue medication. Subjects with a BMI of ≥ 35 kg/m^2 < 40 kg/m^2 had to have polysomnography at screening to rule out obstructive sleep apnoea (OSA). Participants with OSA had to be on stable continuous positive airway pressure (CPAP) for 30 days prior to baseline and continue CPAP for the study duration. **Exclusion criteria:** Any painful disorder other than fibromyalgia and/or any medical or psychiatric condition that might compromise study participation (including current major depressive disorder and generalised anxiety disorder), a current or previous substance-use disorder, including alcohol abuse; previously taken γ-hydroxybutyrate or SXB; or previous participation in clinical trials with SXB.			
Toprak Celenay 2020[109] Ref ID 333 **Country:** Turkey **Number of study centres:** 1 **Funding:** The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.	**Intervention category:** Flex/skill LD vs. Flex/skill LD + Manual T **Intervention:** Spinal stabilisation exercise (SSE) vs. spinal stabilisation exercise (SSE) + kinesio taping (KT) **Inclusion criteria:** Women aged 18–65 years diagnosed with FM according to the ACR 1990 criteria, and had moderate or severe pain according to VAS score **Exclusion criteria:** Neurological, infectious and endocrine diseases, malignancy, pregnancy, medication changes during the study, allergic to taping, unable to complete the questionnaires, any condition interfering with the exercises (advanced cardiac, respiratory, or musculoskeletal problems), or had received any intervention including an exercise programme or physical therapy in the previous 6 months.	Spinal stabilisation exercise (SSE) **Time and frequency of treatment session:** SSE: 60 minutes, twice a week, for 6 weeks **Duration of treatment (weeks):** 6 **Follow-up:** None	Spinal stabilisation exercise (SSE) + kinesio taping (KT). **Time and frequency of treatment session:** SSE: 60 minutes, twice a week, for 6 weeks; KT: twice a week, for 6 weeks **Duration of treatment (weeks):** 6 **Follow-up:** None	**Number randomised** C: 21, E: 21 **Symptom severity** NR **Comorbidity** NR

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Udina-Corte 2020[108] Ref ID 2309 **Country:** Spain **Number of study centres:** 1 **Funding:** The research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.	**Intervention category:** PBO/Sham vs. Electro T **Intervention:** Sham vs. neuro-adaptive electrostimulation (NAE) **Inclusion criteria:** Female, aged between 18 and 65 years, previous diagnosis of FM by a rheumatologist following the ACR 2010 criteria. **Exclusion criteria:** Inflammatory rheumatic condition; planned elective surgery during the study period; ongoing unresolved disability claims; and symptoms of bipolar disorder, major depressive disorder, panic disorder, and/or psychosis.	Sham NAE (placebo) **Time and frequency of treatment session:** 30 minutes, twice a week, for 4 weeks (8 sessions) **Duration of treatment (weeks):** 4 **Follow-up:** 3 months	Neuro-adaptive electrostimulation (NAE) **Time and frequency of treatment session:** 30 minutes, twice a week, for 4 weeks (8 sessions) **Duration of treatment (weeks):** 4 **Follow-up:** 3 months	**Number randomised** C: 19, E: 23 **Symptom severity** C: Pain intensity VAS = 0; no pain, and VAS = 10; maximum pain]: 6.3 (1.0) E: Pain intensity VAS = 0; no pain, and VAS = 10; maximum pain]: 6.4 (1.7) **Comorbidity** NR
Van Gordon 2017[96] Ref ID 198 **Country:** UK **Number of study centres:** 'multiple sites' **Funding:** No financial support	**Intervention category:** PT/BT gen vs. PT/BT gen **Intervention:** CBT vs. meditation awareness training (MAT) (= mindfulness-based intervention) **Inclusion criteria:** FM diagnosis, aged between 18 and 65 years, able to read and write using the English language, not currently undergoing formal psychotherapy, no changes in psychopharmacology type or dosage 1 month prior to intervention (although stable prescription medication was permitted), not currently practising mindfulness or meditation. **Exclusion criteria:** Participants who did not attend 7/8 weekly sessions were classed as having dropped out and were excluded from future assessment phases.	CBT for groups (CBTG) **Time and frequency of treatment session:** Eight weekly sessions lasting 2 hours **Duration of treatment (weeks):** 8 **Follow-up:** Post-treatment (presume 8 weeks) Follow-up 6 months (26 weeks)	Meditation awareness training (MAT) **Time and frequency of treatment session:** Eight weekly workshops (each lasting 2 hr) **Duration of treatment (weeks):** 8 **Follow-up:** Post-treatment (presume 8 weeks) Follow-up 6 months (26 weeks)	**Number randomised** C: 74, E: 74 **Symptom severity** NR **Comorbidity** NR

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Vitton 2004[136] Ref ID 328 **Country:** USA **Number of study centres:** 14 **Funding:** NR	**Intervention category:** PBO/Sham vs. SRI vs. SRI **Intervention:** Placebo vs. milnacipran 25 mg QD (single daily dose) vs. milnacipran 12.5 mg BID (two divided doses) **Inclusion criteria:** Aged between 18 and 70 years meeting the ACR 1990 criteria for FM. **Exclusion criteria:** Severe psychiatric illness; significant risk of suicide according to the investigator's judgement; alcohol or other drug abuse; a history of significant cardiovascular, respiratory, endocrine, genitourinary, liver or kidney disease; autoimmune disease; systemic infection; cancer or current chemotherapy; significant sleep apnoea; life expectancy of < 1 year; active peptic ulcer or inflammatory bowel disease.	Placebo **Time and frequency of treatment session:** As milnacipran 12.5 mg two doses **Duration of treatment (weeks):** 12 **Follow-up:** End of 8-week constant dose phase (12 weeks from randomisation)	E1: Milnacipran 25 mg QD (single daily dose) E2: Milnacipran 12.5 mg BID (two divided doses). **Time and frequency of treatment session:** 25 mg of milnacipran in one (25 mg q.d.) or two (12.5 mg b.i.d.) daily doses **Duration of treatment (weeks):** 12 **Follow-up:** End of 8-week constant-dose phase (12 weeks from randomisation)	**Number randomised** C: 28, E1: 46, E2: 51 **Symptom severity** NR **Comorbidity** NR
Wang 2010[89] Ref ID 245 **Country:** USA **Number of study centres:** 1 **Funding:** Supported by a grant (R21AT003621) from the National Center for Complementary and Alternative Medicine of the National Institutes of Health, the American College of Rheumatology Research and Education Foundation Health Professional Investigator Award, and the Boston Claude D. Pepper Older Americans Independence Center Research Career Development Award.	**Intervention category:** Education + Flex/skill LD vs. Mind–body Ex LD **Intervention:** Control (wellness education and stretching) vs. Tai Chi **Inclusion criteria:** Aged ≥ 21 years and meeting the ACR 1990 diagnostic criteria for FM. **Exclusion criteria:** Participation in Tai Chi training within the past 6 months; serious medical conditions that might limit participation; other diagnosed medical conditions known to contribute to FM symptoms, such as thyroid disease, inflammatory arthritis, systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, myositis, vasculitis, or Sjögren syndrome; pregnancy or planning to become pregnant during the study period; and persons who were unable to pass the Mini–Mental State Examination [i.e. those with a score ≤ 24 (out of 30) points].	Wellness education and stretching **Time and frequency of treatment session:** 60-minute supervised sessions held twice a week; 20 minutes daily at home **Duration of treatment (weeks):** 12 **Follow-up:** 12 weeks (24 weeks from randomisation)	Tai Chi **Time and frequency of treatment session:** 60-minute supervised sessions held twice a week; 20 minutes daily at home **Duration of treatment (weeks):** 12 **Follow-up:** 12 weeks (24 weeks from randomisation)	**Number randomised** C: 33, E: 33 **Symptom severity** NR **Comorbidity** C: heart disease: 0; hypertension: 18%; diabetes: 3% E: heart disease: 0; hypertension: 36%; diabetes: 18%

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Wang 2018[81] Ref ID 276 **Country:** USA **Number of study centres:** 1 **Funding:** Supported by the National Center for Complementary and Integrative Health of the National Institutes of Health (NIH, R01AT006367 and K24AT007323), the National Center for Research Resources, NIH (UL1 RR025752) and the National Center for Advancing Translational Sciences, NIH (UL1TR000073 and UL1TR001064). RAF and KRF are supported in part by supported by the US Department of Agriculture, under agreement No 58-1950-4-003 and the Boston Claude D Pepper Older Americans Independence Center (1P30AG031679).	**Intervention category:** Aerobic LD vs. Mind–body Ex LD vs. Mind–body Ex LD vs. Mind–body Ex LD vs. Mind–body Ex LD **Intervention:** Aerobic exercise (twice weekly for 24 weeks) vs. Tai Chi 1 × 12 weeks (once weekly for 12 weeks) vs. Tai Chi 2 × 12 weeks (twice weekly for 12 weeks) vs. Tai Chi 1 × 24 weeks (once weekly for 24 weeks) vs. Tai Chi 2 × 24 weeks (twice weekly for 24 weeks) **Inclusion criteria:** Aged ≥ 21 and meeting the ACR 1990 and 2010 diagnostic criteria for FM and a widespread pain index of ≥ 7, symptom severity of ≥ 5 and absence of a disorder that would otherwise explain pain. Participants had to be willing to complete the 12-week or 24-week intervention, including exercise sessions once or twice weekly.	Aerobic exercise (twice weekly for 24 weeks) **Time and frequency of treatment session:** 60 minutes supervised session held twice a week plus 30 minutes daily at home **Duration of treatment (weeks):** 24 **Follow-up:** 26 weeks (52 weeks from randomisation)	E1: Tai Chi (once weekly for 12 weeks) **Time and frequency of treatment session:** 60 minutes supervised session once a week; 30 minutes daily at home **Duration of treatment (weeks):** 12 **Follow-up:** 40 weeks (52 weeks from randomisation) E2: Tai Chi (twice weekly for 12 weeks). **Time and frequency of treatment session:** 60 minutes supervised session twice a week; 30 minutes daily at home **Duration of treatment (weeks):** 12 **Follow-up:** 40 weeks (52 weeks from randomisation) E3: Tai Chi (once weekly for 24 weeks)	**Number randomised** C: 75, E1: 39, E2: 37, E3: 39, E4: 36 **Symptom severity** C: Mean (SD) symptom severity scale score (range 0–12, higher scores reflect more severe symptoms): 8.7 (2.0) E1: Mean (SD) symptom severity scale score (range 0–12, higher scores reflect more severe symptoms): 8.1 (1.9) E2: Mean (SD) symptom severity scale score (range 0–12, higher scores reflect more severe symptoms): 8.7 (2.1) E3: Mean (SD) Symptom severity scale score (range 0–12, higher scores reflect more severe symptoms): 8.6 (2.2)
	Exclusion criteria: Participation in Tai Chi or other similar types of complementary and alternative medicine within the past 6 months; serious medical conditions that might limit participation; other diagnosed medical conditions, such as inflammatory arthritis or connective tissue diseases; women who were pregnant or were planning a pregnancy during the study period; unable to speak English; and unable to pass the mini-mental state examination (score < 24 out of 30).		**Time and frequency of treatment session:** 60 minutes supervised session once a week; 30 minutes daily at home **Duration of treatment (weeks):** 24 **Follow-up:** 26 weeks (52 weeks from randomisation) E4: Tai Chi (twice weekly for 24 weeks) **Time and frequency of treatment session:** 60 minutes supervised session	E4: Mean (SD) symptom severity scale score (range 0–12, higher scores reflect more severe symptoms): 9.0 (1.7) **Comorbidity** C: heart disease 5.3%; hyper tension 17.3%; diabetes 1.3% E1: heart disease 18.0%; hyper tension 20.5%; diabetes 12.8% E2: heart disease 10.8%; hyper tension 46.0%; diabetes 13.5% E3: heart disease 2.6%; hyper tension 36.8%; diabetes 5.3% E4: heart disease 13.9%; hyper tension 44.4%; diabetes 13.9%

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
			twice a week; 30 minutes daily at home **Duration of treatment (weeks):** 24 **Follow-up:** 26 weeks (52 weeks from randomisation)	
Williams 2010[101] Ref ID 273 **Country:** USA **Number of study centres:** 1 **Funding:** Supported in part by Grant numbers R01-AR050044 (NIAMS/NIH), and DAMD 17-00-2-0018 (Department of Defense).	**Intervention category:** UC vs. PT/BT gen **Intervention:** Standard care vs. web-enhanced behavioural self-management programme (WEB-SM) ['CBT' in Cocrane SR] + standard care **Inclusion criteria:** Aged ≥ 18 years meeting the ACR criteria for FM, under the standard medical care of a physician for at least 3 months prior to enrolment, and possess basic computer literacy and computer access.	Standard care (STD). **Time and frequency of treatment session:** None **Duration of treatment (weeks):** 24 **Follow-up:** None	Web-enhanced behavioural self-management programme (WEB-SM) + standard care (STD). **Time and frequency of treatment session:** 13 modules over 6 months **Duration of treatment (weeks):** 24 **Follow-up:** None	**Number randomised** C: 59, E: 59 **Symptom severity** NR **Comorbidity**
	Exclusion criteria: Severe physical impairment that precluded receiving/using the website or using the self-management skills contained on the website, comorbid medical illnesses capable of causing a worsening of physical functional status independent of FM (e.g. cardiopulmonary disorders, uncontrolled endocrine or allergic disorders, malignancy within 2 years, psychiatric disorder involving a history of psychosis, current suicide risk or attempt within 2 years of the study, or substance abuse within 2 years, Prior CBT for pain management, and a pending disability compensation or the receipt of disability compensation for < 2 years.			C: Axis I psychiatric diagnoses. Recurrent major depression: 5.1%; panic disorder: 22.0%; Generalised anxiety disorder: 8.5%; post-traumatic stress disorder: 0; Axis II – any personality disorder: 8.5% E: Axis I psychiatric diagnoses. Recurrent major depression: 11.9%); panic disorder: 18.6%; generalised anxiety disorder: 11.9%; post-traumatic stress disorder: 1.7%; Axis II – any personality disorder: 32.2%

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Wong 2018[111] Ref ID 220 **Country:** South Korea **Number of study centres:** 1 **Funding:** NR	**Intervention category:** UC vs. Mind–body Ex LD **Intervention:** Control vs. Tai Chi **Inclusion criteria:** Women with FM according to ACR 1990 criteria **Exclusion criteria:** Pulmonary, cardiovascular, renal, adrenal, pituitary, severe psychiatric, thyroid diseases, the use of hormone replacement therapy during the 6 months prior the study, any medication changes in the previous year, receiving psychological or physical therapy, had a history of steady exercise or received exercise training in the last year.	Control Participants in the control group did not participate in any supervised or unsupervised exercise protocol and were asked to maintain their regular lifestyle habits **Time and frequency of treatment session:** **Duration of treatment (weeks):** 12 **Follow-up:** None	Tai Chi **Time and frequency of treatment session:** 55-minute sessions 3 times a week **Duration of treatment (weeks):** 12 **Follow-up:** None	**Number randomised** C: 19, E: 18 **Symptom severity** NR **Comorbidity** NR
Wu 2021[76] Ref ID 2311 **Country:** Taiwan **Number of study centres:** 1 **Funding:** Supported by a grant from the Ministry of Science and Technology, Taiwan (MOST-105-2314-B-038-052-MY3).	**Intervention category:** PBO/Sham vs. neuromodulation **Intervention:** Telephone support (control) vs. neurofeedback **Inclusion criteria:** Aged ≥ 18 years and diagnosed with FM according to the ACR 2010 criteria. **Exclusion criteria:** Shift work (work that takes place outside traditional daytime hours, including evening, night, and rotating shifts); medical history of head injury or neurological disorder; present psychopathological disorder; malignant neoplasm; or pregnancy, a Polysymptomatic Distress Scale score < 13.	Telephone support (attention control) **Time and frequency of treatment session:** Weekly telephone support (10 minutes) **Duration of treatment (weeks):** 8 **Follow-up:** None	Neurofeedback **Time and frequency of treatment session:** 30 minutes per session, a total of 20 sessions over 8 weeks **Duration of treatment (weeks):** 8 **Follow-up:** None	**Number randomised** C: 20 E: 60 **Symptom severity** NR **Comorbidity** C: coronary heart disease: 20.0%; insomnia: 0; depression: 20.0%; anxiety: 10.0%; panic: 0; dry eyes: 0; migraine: 5.0%; rheumatic disease: 5.0%; E: coronary heart disease: 7.5%; insomnia: 3.8%; depression: 26.3%; anxiety: 8.8%; panic: 2.5%; dry eyes: 93.8%; migraine: 1.3%; rheumatic disease: 5.0%

continued

TABLE 18 Characteristics of studies eligible for the NMA (*continued*)

Study ID, country, funding	Intervention category and eligibility criteria	Control (C) intervention details	Experimental (E) intervention details	Participants' clinical characteristics at baseline
Zhang 2021[207] Ref ID 2316 **Country:** China **Number of study centres:** 22 **Funding:** Sponsored by Pfizer. The sponsor was involved in aspects of study design, data collection, and analysis.	**Intervention category:** PBO/Sham vs. gabapentinoids **Intervention:** Placebo vs. pregabalin **Inclusion criteria:** Men or women (nonpregnant, nonlactating), ≥ 18 years of age, who met ACR 1990 criteria for FM and had a score of ≥ 40 mm at screening and randomisation on a 100-mm pain VAS (0 indicates 'no pain'). **Exclusion criteria:** A high placebo response (≥ 30% decrease on 100-mm VAS at randomisation relative to screening), pain due to other conditions that might confound assessment; prior participation in a pregabalin clinical trial; history of failed pregabalin treatment; current pregabalin use; diagnosis of severe depression; active malignancy; or an immunocompromised status. Participants with creatinine clearance ≤ 60 ml/min were also excluded.	Placebo **Time and frequency of treatment session:** NR **Duration of treatment (weeks):** 14 **Follow-up:** None	Pregabalin (300–450 mg/day, flexible dose) **Time and frequency of treatment session:** Study medication was administered orally BID, starting at 150 mg/day (75 mg BID) in Week 1 and increasing to 300 mg/day for Week 2. At the end of Week 2, the dose was either maintained at 300 mg/day (150 mg BID) or increased to 450 mg/day (225 mg BID) at entry into the 12-week fixed-dose treatment period, depending on tolerability and response. **Duration of treatment (weeks):** 14 **Follow-up:** None	**Number randomised** C: 164 (randomised and treated) (total of 343 randomised, data reported for 334 only), E: 170 (randomised and treated) **Symptom severity** C: Pain score based on an 11-point NRS from 0 ('no pain') to 10 ('worst possible pain'), mean (SD): 6.2 (1.4) E: Pain score based on an 11-point NRS from 0 ('no pain') to 10 ('worst possible pain'), mean (SD): 6.2 (1.4) **Comorbidity** NR

AP, antipsychotics; AQ, aquatic or pool-based; BDI, Beck Depression Inventory; BID, twice daily Flex/skill, Flexibility/neuro-motor skills exercise; FM, fibromyalgia; FMS, fibromyalgia syndrome; LD, land-based; Mx Exercise, mix (aerobic and anaerobic) exercise; PT/BT gen, generic psychological or behavioural therapy; QD, once daily; Ref ID, reference ID; TCA, tricyclics or tricyclic antidepressant; Tx, treatment; w, weeks.

Appendix 3 Characteristics of studies not eligible for the network meta-analysis

TABLE 19 Characteristics of studies not eligible for the NMA

Study ID (author, year, reference ID)	Intervention categories (control vs. experimental)	Intervention name (control vs. experimental)	Time (weeks) End of treatment (Tx), or first assessment (Ax), if later	Number randomised	Age (years), mean (SD)	Gender (%) male/female
Sanudo 2015[179] Ref ID 593	UC	UC	24	16	55 (6.9)	0/100
	Aerobic LD	Aerobic exercise	24	16	58 (8)	0/100
Buskila 2001[174] Ref ID 369	UC	Control	10 days	24	54.3 (8.0)	0/100
	Balneotherapy	Balneotherapy	10 days	24	54.6 (8.4)	0/100
Dönmez 2005[167] Ref ID 289	UC	Control	2	14	43.1 (6.9)	0/100
	Balneotherapy	Spa therapy	2	16	43.3 (7.5)	0/100
Saral 2016[173] Ref ID 361	UC	Control	24	22	43.7 (1.1)	0/100
	Short-term interdisciplinary (PT/BT gen + Exercise LD + Education)	Short-term interdisciplinary treatment group (CBT, exercise and education)	24 (Tx 2 days; Ax at 24w)	22	43.2 (9.2)	0/100
	Long-term interdisciplinary (PT/BT gen + Exercise LD + Education)	Long-term interdisciplinary treatment (CBT, exercise and education)	24 (Tx 10w; Ax at 24w)	22	38.3 (9.8)	0/100
Maddali Bongi 2010[177] Ref ID 487	UC	Wait list	8	22	46.4 (10.5)	5/95
	Mind–body Ex LD	The Rességuier method	8	22	44.4 (13.1)	9/91
Salaffi 2015[208] Ref ID 249	UC	UC	12	76 Whole pop	49.6 (12.3)	8/92
	Multicomponent (Mx Exercise LD + Education)	Multicomponent exercise (aerobic, muscle strength training and education)	12		48.3 (11.3)	6/94
Lichtbroun 2001[180] Ref ID 691	UC	Wait-line	3	60 whole pop	50 (23–82) median (range), whole pop	3/97 whole pop
	PBO/Sham	Sham CES (cranial Electro T stimulation)	3			
	Neuromodulation	Active CES	3			

TABLE 19 Characteristics of studies not eligible for the NMA (*continued*)

Study ID (author, year, reference ID)	Intervention categories (control vs. experimental)	Intervention name (control vs. experimental)	Time (weeks) End of treatment (Tx), or first assessment (Ax), if later	Number randomised	Age (years), mean (SD)	Gender (%) male/female
Taylor 2013[190] Ref ID 225	UC	UC	8	18	48.6 (9.8)	7/93
	PBO/Sham	Sham CES (cranial electrical stimulation)	8	20	51.5 (10.9)	7/93
	Neuromodulation	Active CES	8	19	51.9 (10.6)	6/94
Bourgault 2015[194] Ref ID 295	UC	Wait list control	11	29	46.7 (11.4)	7/93
	PT/BT gen	Passage programme (multicomponent self-management of FMS)	11	29	50.0 (9.2)	7/93
Cash 2015[192] Ref ID 278	UC	Wait list control	8	40	NR	0/100
	PT/BT gen	Mindfulness-based stress reduction	8	51	NR	0/100
Hedman-Lagerlöf 2018[195] Ref ID 299	UC	Wait list	10	70	49.3 (10.0)	1/99
	PT/BT gen	Internet-delivered exposure treatment	10	70	51.8 (10.7)	3/97
Rickardsson 2021[201] Ref ID 1763	UC	Wait list	8	56	50.6 (11.1)	21/79
	PT/BT gen	iACT (internet-delivered acceptance and commitment therapy)	8	57	48.4 (12.1)	28/72
McCrae 2018[157] Ref ID 117	UC	Wait list control	8	13	60.3 (7.2)	0/100
	PT/BT gen	CBT for pain (CBT-P)	8	17	50.8 (14.4)	13/88
	PT/BT sleep	CBT for insomnia (CBT-I)	8	22	59.5 (9.9)	0/100
McCrae 2019[23] Ref ID 30	UC	UC wait list control	8	37	52.3 (11.2)	0/100
	PT/BT gen	CBT for pain (CBT-P)	8	37	51.5 (10.6)	8/92
	PT/BT sleep	CBT for insomnia (CBT-I)	8	39	54.1 (11.0)	0/100

continued

TABLE 19 Characteristics of studies not eligible for the NMA (*continued*)

Study ID (author, year, reference ID)	Intervention categories (control vs. experimental)	Intervention name (control vs. experimental)	Time (weeks) End of treatment (Tx), or first assessment (Ax), if later	Number randomised	Age (years), mean (SD)	Gender (%) male/ female
Wigers 1996[169] Ref ID 321	UC	TAU	14	20	46 (9)	5/95
	PT/BT gen	Stress-management treatment	14	20	44 (12)	10/90
	Aerobic LD	Aerobic exercise	14	20	43 (9)	10/90
Edinger 2005[187] Ref ID 26	UC	UC	6	11	48.3 (9.1)	0/100
	Education	Sleep hygiene	6	18	46.5 (9.0)	6/94
	PT/BT gen	CBT	6	18	50.1 (6.9)	6/94
Soares 2002[200] Ref ID 642	UC	Waiting-list control	10	17	43(12)	0/100
	Education	Educational intervention	10	18	47 (8)	0/100
	PT/BT gen	Behavioural intervention	10	18	45 97)	0/100
da Silva 2018[193] Ref ID 284	UC	Control (pharmacological treatment only)	10?	20	40 (2) whole pop	0/100
	PHOTOTHERAPY	Photobiomodulation therapy (PHO)	10	20		0/100
	Mx Exercise LD	Exercise training (EXT)	10	20		0/100
	Phototherapy + Mx Exercise LD	Photobiomodulation therapy (PHO) + exercise training (EXT)	10	20		0/100
Geler Kulcu 2009[150] Ref ID 434	UC	Control	Unclear (15 sessions, 15w?)	20	36.4 (12.6)	0/100
	Strength LD	Strength training	Unclear (15 sessions, 15w?)	40	37.3 (10.9)	8/93
Häkkinen 2001[170] Ref ID 334	UC	Control	21	10	37 (5)	0/100
	Strength LD	Strength training	21	11	39 (6)	0/100

TABLE 19 Characteristics of studies not eligible for the NMA (*continued*)

Study ID (author, year, reference ID)	Intervention categories (control vs. experimental)	Intervention name (control vs. experimental)	Time (weeks) End of treatment (Tx), or first assessment (Ax), if later	Number randomised	Age (years), mean (SD)	Gender (%) male/female
Ammer 1999[153] Ref ID 1367	PBO/Sham	Whirl pool with plain water	Unclear	13	55.7 (11.6)	*n* = M1, F10
	Balneotherapy	Whirl pool with addition of valerian	Unclear	13	53.2 (10.9)	*n* = M?, F12
	Balneotherapy	Whirl pool with addition of pine oil	Unclear	13	54.8 (10.4)	*n* = M?, F7
Gillis 2006[172] Ref ID 355	PBO/Sham	Neutral time management (control)	4.5 wk (Tx 4 days, Ax at 1m after that)	83 whole pop	50.3 (23–72) median (range), whole pop	3/97 whole pop
	BT/PT generic	At-home written emotional disclosure	4.5 wk (Tx 4 days, Ax at 1m after that)			
Almeida 2003[188] Ref ID 200	PBO/Sham	Sham	4	40 whole pop	57 (5)	0/100
	Electro T	Combined therapy (pulsed ultrasound and interferential current) (CTPI)	4		56 (6)	0/100
Fernández García 2011[209] Ref ID 323	PBO/Sham	Placebo	8	31 whole pop	52.4 (5.9)	0/100
	Electro T	Laser	8		51.6 (6.2)	0/100
Gür 2002[162] Ref ID 197	PBO/Sham	Placebo laser treatment	2	20	NR	0/100
	Electro T	Active laser treatment	2	20	NR	0/100
Hargrove 2012[163] Ref ID 234	PBO/Sham	Sham	11	46	54.0 (10.1)	11/89
	Electro T	Non-invasive cortical electrostimulation	11	45	51.3 (11.1)	5/95
Lauretti 2013[191] Ref ID 267	PBO/Sham	Placebo group	1	13	35 (8)	10/90
	Electro T	Single TENS group	1	13	32 (8)	8/92
	Electro T	Electro T	1	13	30 (12)	0/100

continued

TABLE 19 Characteristics of studies not eligible for the NMA (*continued*)

Study ID (author, year, reference ID)	Intervention categories (control vs. experimental)	Intervention name (control vs. experimental)	Time (weeks) End of treatment (Tx), or first assessment (Ax), if later	Number randomised	Age (years), mean (SD)	Gender (%) male/female
Norregaard 1997[181] Ref ID 1165	PBO/Sham	Hot packs (control)	12	8	55 (10)	NR
	Flex/skill LD	Steady exercise	12	15	51 (14)	NR
	Aerobic LD	Aerobic exercise	12	15	44 (8)	NR
Kravitz 2006[211] Ref ID 488	PBO/Sham	Sham Flexyx Neurotherapy System (FNS)	11	31	48.1 (8.9)	6/94
	Neuromodulation	The FNS	11	33	45.9 (9.5)	9/91
Maestú 2013[165] Ref ID 277	PBO/Sham	Sham	8	33	40.7 (6.7) whole pop	0/100
	Neuromodulation	Very low-intensity transcranial magnetic stimulation	8	34		0/100
Mhalla 2011[160] Ref ID 160	PBO/Sham	Sham stimulation	25 (14 treatments over 21 weeks and 1 follow-up visit at week 25)	20	49.6 (10.0)	0/100
	Neuromodulation	rTMS		20	51.8 (11.6)	0/100
Pujol 2019[175] Ref ID 371	PBO/Sham	Placebo	3	39	53.7 (8.1) whole pop	0/100
	Neuromodulation	Vibrotactile stimulation	3	38	–	0/100
Roizenblatt 2007[159] Ref ID 232	PBO/Sham	Sham tDCS	5 days	10	50.8 (10.2)	0/100
	Neuromodulation	tDCS of M1	5 days	11	54.8 (9.3)	0/100
	Neuromodulation	tDCS of left DLPFC	5 days	11	54.2 (7.4)	0/100
Darnall 2020[183] Ref ID 1916	PBO/Sham	Audio-only version of virtual reality (VR) programme	3	50	*n* = 39 with data. 25–34 years: 8%; 35–44 years: 21%; 45–54 years: 31%; 55–64 years: 18%; 65–74 years: 23%	67/33
	Non-MSM practice	Virtual reality (VR)	3	47	*n* = 35 with data. 25–34 years: 9%; 35–44 years: 14%; 45–54 years: 31%; 55–64 years: 31%; 65–74 years: 14%	74/26

TABLE 19 Characteristics of studies not eligible for the NMA (*continued*)

Study ID (author, year, reference ID)	Intervention categories (control vs. experimental)	Intervention name (control vs. experimental)	Time (weeks) End of treatment (Tx), or first assessment (Ax), if later	Number randomised	Age (years), mean (SD)	Gender (%) male/female
Biasi 1999[154] Ref ID 530	PBO/Sham	Placebo	Unclear	40 (whole pop)	48.8 whole pop	5/95 whole pop
	Non-MSM practice	Pure copper wire sheet as bedsheet	Unclear (Italian paper)			
Martin 2006[210] Ref ID 337	PBO/Sham	Simulated acupuncture	6–7 (6 treatments during a 2–3-week period; Ax at 4 weeks after treatment)	25	51.7 (14.1)	4/96
	Non-MSM practice	Acupuncture		25	47.9 (11.2)	0/100
Alves 2013[196] Ref ID 314	PBO/Sham	Placebo	16	16	49.0 (10.1)	0/100
	Nutrition	Creatine monohydrate	16	16	48.7 (8.4)	0/100
Calandre 2021[202] Ref ID 1887	PBO/Sham	Placebo	12	56	55.5 (8.6)	2/98
	Nutrition	Multi-strain probiotic vsl#3®	12	54	56.0 (7.5)	4/96
Rossini 2007[171] Ref ID 339	PBO/Sham	Placebo (capsule and injection)	10	52	46.3 (10.4)	3/97 whole pop
	Nutrition	Acetyl L-carnitine (LAC), capsule and injection	10	50	47.3 (11.7)	
Colbert 1999[178] Ref ID 534	PBO/Sham	Sham	16	15	48.2 (11.1)	0/100
	Non-MSM practice	Magnetic mattress pad	16	15	51.2 (13.5)	0/100
Braz 2013[176] Ref ID 381	PBO/Sham	Placebo	12	17	41.6 (10)	0/100
	Tricyclics	Amitriptyline	12	16	44.3 (8)	0/100
	Nutrition	Panax ginseng	12	19	43.6 (9.6)	0/100

continued

TABLE 19 Characteristics of studies not eligible for the NMA (*continued*)

Study ID (author, year, reference ID)	Intervention categories (control vs. experimental)	Intervention name (control vs. experimental)	Time (weeks) End of treatment (Tx), or first assessment (Ax), if later	Number randomised	Age (years), mean (SD)	Gender (%) male/female
Gür 2002[156] Ref ID 357	PBO/Sham	Placebo laser	Unclear if 8 or 2 weeks	25	28.5 (6.3)	24/76
	Tricyclics	Amitriptyline	Unclear if 8 or 2 weeks	25	30.1 (8.7)	16/84
	Electro T	Electro T	Unclear if 8 or 2 weeks	25	30.4 (6.9)	20/80
Jones 2008[161] Ref ID 254	PBO/Sham drug + PBO/Sham exercise	Placebo drug plus diet recall but no exercise (diet and exercise control group; diet recall = attention control)	26	54	49.8 (7.9)	0/100
	PBO/Sham drug + Mx Exercise LD	Placebo plus exercise (drug control group)	26	47	49.6 (7.7)	5/95
	Acetylcholine esterase inhibitor + PBO/Sham exercise	Pyridostigmine plus diet recall but no exercise (exercise control group)	26	53	49.3 (7.9)	7/93
	Acetylcholine esterase inhibitor + Mx Exercise LD	Pyridostigmine plus exercise	26	53	49.1 (8.9)	0/100
Altan 2004[212] Ref ID 2507	Balneotherapy	Balneotherapy (with no exercise)	12	25	43.9 (6.3)	0/100
	Balneotherapy + Mx Exercise AQ	Pool-based exercise	12	25	43.1 (6.4)	0/100
Montesó-Curto 2015[205] Ref ID 250	Botox cervical infiltration	Cervical infiltration with botulinum toxin (control)	7	23	58.9 (10.9) whole pop	3/97 whole pop
	PT/BT generic	Group problem-solving therapy	7	25		
	Botox cervical infiltration + BT/PT generic	Cervical infiltration with botulinum toxin + group problem-solving therapy	7	24		

TABLE 19 Characteristics of studies not eligible for the NMA (*continued*)

Study ID (author, year, reference ID)	Intervention categories (control vs. experimental)	Intervention name (control vs. experimental)	Time (weeks) End of treatment (Tx), or first assessment (Ax), if later	Number randomised	Age (years), mean (SD)	Gender (%) male/female
Sanchez 2012[219] Ref ID 1409	Education	Sleep hygiene	6	13	48.8 (4.4)	0/100
	PT/BT sleep	CBT-I	6	13	44.8 (5.3)	0/100
Moretti 2012[189] Ref ID 204	Electro T	Combined therapy (ultrasound and interferential therapy) once weekly	12	25	53.2 (4.8)	0/100
	Electro T	Combined therapy (ultrasound and interferential therapy) twice weekly	12	25	52.6 (4.9)	0/100
Genc 2015[182] Ref ID 1379	Flex/skill LD	At-home exercise (flexibility and stretching)	6	27	36.9	0/100
	Aerobic LD + Flex/skill LD	Aerobic + at-home exercise (flexibility and stretching)	6	27	35.1	0/100
Vitorino 2006[217] Ref ID 208	Manual T	Conventional physiotherapy [including (1) surface heating by infrared lamp; (2) stretching; (3) aerobic exercise; and (4) relaxation (massage)]	3	25	46.6 (8.4)	0/100
	Mx Exercise AQ + Manual T AQ	Hydrotherapy [including (1) warm-up, (2) stretching, (3) aerobic exercises, and (4) relaxation (massage)]	3	25	48.9 (9.2)	0/100
Ceballos-Laita 2021[184] Ref ID 2291	Mx Exercise LD	Therapeutic exercise (TE)	10	16	53.0 (10.7)	0/100
	Education + Mx Exercise LD	Pain neurophysiology education + Therapeutic exercise	10	16	52.1 (10.3)	0/100
Correia Moretti 2016[199] Ref ID 595	Mx Exercise LD	Control (aerobic exercise + stretching)	12	10	44.8 (13.4)	0/100
	Manual T + Mx Exercise LD	Pompage (Manual T) + aerobic exercise + stretching	12	13	44.9 (6.6)	0/100

continued

TABLE 19 Characteristics of studies not eligible for the NMA (*continued*)

Study ID (author, year, reference ID)	Intervention categories (control vs. experimental)	Intervention name (control vs. experimental)	Time (weeks) End of treatment (Tx), or first assessment (Ax), if later	Number randomised	Age (years), mean (SD)	Gender (%) male/female
Toprak Celenay 2017[164] Ref ID 240	Mx Exercise LD	Exercise	6	24	42.5 (8.3)	0/100
	Mx Exercise LD + Manual T	Exercise + connective tissue massage	6	25	39.9 (9.5)	0/100
Takiguchi 2008[197] Ref ID 397	Non-MSM practice	Trad Chinese acupuncture	8	5	45.6 (7.1)	0/100
	Non-MSM practice	Acupuncture at 8 tender points	8	7	44.3 (7.2)	0/100
Collazo Chao 2013[152] Ref ID 598	Non-MSM practice	Acupuncture	24	30	58 (28–70) mean (range), whole pop	8/92 whole pop
	Non-MSM practice	Cranio-puncture (scalp acupuncture)	24	30	–	–
Pagliai 2020[143] Ref ID 2296	Nutrition	Control – wheat products (pasta, bread, crackers, biscuits)	8	20 (crossover trial)	48.9 (12.3) –	5/95 –
	Nutrition	Replacement diet with khorasan wheat products	8			
Field 2002[218] Ref ID 602	Relaxation/Meditation	Relaxation therapy	5	Total 20 (24 reported in the abstract)	50.9 (mean) –	NR
	Manual T	Massage therapy	5			NR
Bircan 2008[166] Ref ID 280	Strength LD	Strengthening exercise	8	13	46.0 (8.5)	0/100
	Aerobic LD	Aerobic exercise	8	13	48.3 (5.3)	0/100
Azad 2000[168] Ref ID 297	Tricyclics	Amitriptyline (10–25 mg at start and increase up to 100 mg/day)	6	41	30.2 (11.7)	17/83
	Nutrition	Vegetarian diet	6	37	31.7 (12.4)	27/73
Aldaoseri 2019[198] Ref ID 441	Tricyclics	Amitriptyline (10 mg/day in escalating dose)	12	160 whole pop)	34.3 (9.5)	7/93
	Nutrition	Vitamin D (cholecalciferol 50,000 IU/week)	12		–	–
	Tricyclics + Nutrition	Vitamin D + amitriptyline	12		–	–

TABLE 19 Characteristics of studies not eligible for the NMA (*continued*)

Study ID (author, year, reference ID)	Intervention categories (control vs. experimental)	Intervention name (control vs. experimental)	Time (weeks) End of treatment (Tx), or first assessment (Ax), if later	Number randomised	Age (years), mean (SD)	Gender (%) male/female
Edwards 2000[144] Ref ID 631	PBO/Sham	Placebo	12	12 crossover trial	45.6 (5.9)	0/100
	Antioxidant	Anthocyandins 40 mg/day	12			
Scharf 2003[145] Ref ID 206	PBO/Sham	Placebo	4	24 crossover trial	48.9 (20–69) mean (range)	0/100
	CNS depressants	SXB 6.0 g/day	4			
Arnold 2015[146] Ref ID 367	PBO/Sham	Placebo	6	197 crossover trial	50.1 (10.0)	7/93
	Gabapentinoids	Pregabalin [starting dose 150 mg/day (75 mg BID), escalating to 300 mg/day (150 mg BID) or 450 mg/day (225 mg BID)]	6			
Arnold 2016[155] Ref ID 283	PBO/Sham	Placebo	15 (adolescent only)	53	14.7 (1.2)	17/83
	Gabapentinoids	Pregabalin	15 (adolescent only)	54	14.6 (1.2)	11/89
Roth 2012[147] Ref ID 233	PBO/Sham	Placebo	4	119 crossover trial	48.4 (22–77) mean (range)	13/87
	Gabapentinoids	Pregabalin (starting 150 mg/day, uptitrated to 300–450 mg/day)	4			
Zhang 2021[207] Ref ID 2316	PBO/Sham	Placebo	14	164 (*n* randomised and treated)	43.5 (10.6)	12/88
	Gabapentinoids	Pregabalin	14	170 (*n* randomised and treated; total of 343 randomised)	44.5 (11.5)	16/84
Younger 2013[186] Ref ID 373	PBO/Sham	Placebo	12	15	42.3 (13.0)	0/100
	Opioid antagonist	Oral naltrexone 4.5 mg/day	12	16	42.7 (12.9)	0/100
Roehrs 2020[148] Ref ID 27	PBO/Sham	Placebo	9 days	10 (cross-over trial)	50.0 (9.1)	0/100
	Orexin antagonists	Suvorexant, 20 mg	9 days			

continued

TABLE 19 Characteristics of studies not eligible for the NMA (*continued*)

Study ID (author, year, reference ID)	Intervention categories (control vs. experimental)	Intervention name (control vs. experimental)	Time (weeks) End of treatment (Tx), or first assessment (Ax), if later	Number randomised	Age (years), mean (SD)	Gender (%) male/ female
Sadreddini 2008[185] Ref ID 320	PBO/Sham	Placebo	16	50	58.8 (5.1)	0/100
	SERMs	Raloxifen	16	50	52.1 (4.0)	0/100
Distler 2010[216] Ref ID 1565	PBO/Sham	Placebo	12	34	49.0 (7.0)	12/88
	Serotonin receptor antagonist and dopamine receptor agonist	Terguride titrated to a maximum 3 mg/day	12	65	48.5 (6.1)	11/89
Arnold 2010[158] Ref ID 318	PBO/Sham	Placebo	12	267	49.6 (10.8)	6/94
	SRI	Duloxetine (initiated at 30 mg/day and escalated to 60 mg/day)	12	263	50.7 (11.3)	7/93
Arnold 2005[215] Ref ID 1491	PBO/Sham	Placebo	12	120	49.6 (10.9) whole pop	0/100
	SRI	Duloxetine 60 mg QD	12	118		0/100
	SRI	Duloxetine 60 mg BID	12	116		0/100
Anderberg 2000[214] Ref ID 1474	PBO/Sham	Placebo	16	19	48.6 (7.5) whole pop	0/100
	SSRI	Citalopram doses varied between 20 and 40 mg daily	16	21		0/100
Abdel Fattah 2020[203] Ref ID 2317	Gabapentinoids	Pregabalin monotherapy	12	29	35.8 (6.3)	0/100
	Gabapentinoids + SRI	Pregabalin and milnacipran	12	29	35.0 (7.4)	0/100
Ware 2010[149] Ref ID 11	Tricyclics	Amitriptyline (10–20 mg before bedtime)	2	32 crossover trial	49.5 (11.2)	16/84
	Cannabinoid	Nabilone (0.5–1.0 mg before bedtime)	2			

TABLE 19 Characteristics of studies not eligible for the NMA (*continued*)

Study ID (author, year, reference ID)	Intervention categories (control vs. experimental)	Intervention name (control vs. experimental)	Time (weeks) End of treatment (Tx), or first assessment (Ax), if later	Number randomised	Age (years), mean (SD)	Gender (%) male/female
Acet 2017[213] Ref ID 1972	Tricyclics	Amitriptyline (initiated at daily 10 mg, increased to 25 mg)	12	25	39.2 (9.0)	0/100
	Gabapentinoids	Pregabalin (initiated at daily 150 mg and slowly increased to 450 mg oral dose)	12	36	36.5 (6.7)	0/100
Capaci 2002[204] Ref ID 481	Tricyclics	Amitriptyline (first two weeks 10 mg/day, later 20 mg/day)	8	20	42.1 (11.0)	10/90
	SSRI	Paroxetine (first weeks 20 mg/day, later 40 mg/day)	8	20	45.7 (4.5)	10/90
Ramzy 2017[206] Ref ID 360	Tricyclics + Gabapentinoids	Amitriptyline (25 mg/day) with pregabalin (75 mg/day) (control)	24	24	56.9 (6.8)	0/100
	SRI + Gabapentinoids	Venlafaxine (75 mg/day) with pregabalin (75 mg/day)	24	25	44.0 (6.3)	0/100
	SSRI + Gabapentinoids	Paroxetine (25 mg/day) with pregabalin (75 mg/day)	24	26	46.2 (7.6)	0/100
Çelebi 2016[151] Ref ID 495	SRI	Neurotic duloxetine 60 mg/day	12	Total 120 (*N* in each group unclear)	41.3 (10.6)	0/100
	SRI	Extrovert duloxetine 60 mg/day	12		34.5 (10.4)	0/100
	Gabapentinoids	Neurotic pregabalin 300 mg/day	12		45.1 (8.0)	0/100
	Gabapentinoids	Extrovert pregabalin 300 mg/day	12		42.9 (9.1)	0/100

AP, antipsychotics; AQ, aquatic or pool-based; Ax, assessment; BID, twice daily; Flex/skill, Flexibility/neuro-motor skills exercise; FMS, fibromyalgia syndrome; LD, land-based; Mx Exercise, mix (aerobic and anaerobic) exercise; PT/BT gen, generic psychological or behavioural therapy; QD, once daily; Ref ID, reference ID; TCA, tricyclics or tricyclic antidepressant; Tx, treatment; w, weeks.

Appendix 4 Risk-of-bias summary: review authors' judgements about each risk-of-bias item for each included study eligible for the network meta-analysis

Intention-to-treat

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
704	Maindet 2021	Balneotherapy	UC	PSQI	NA	+	!	−	−	+	−
2297	Ceca 2020	Flex/skill LD	UC	PSQI	NA	!	−	−	−	+	−
237	Castro-Sánchez 2014	Manual T	UC	PSQI	NA	+	+	+	+	+	+
215	Jiao 2019	Mind-body Ex LD	UC	PSQI	NA	+	!	−	−	+	−
327	Lynch 2012	Mind-body Ex LD	UC	PSQI	NA	+	−	−	−	+	−
199	Munguía-Izquierdo 2008	Mx Exercise AQ	UC	PSQI	NA	+	!	−	−	+	−
217	Lauche 2016	Non-MSM practice	UC & PBO/Sham (2 arms)	PSQI	NA	+	!	+	−	+	−
651	San Mauro Martin 2019	Nutrition	UC	PSQI	NA	+	−	−	−	+	−
268	Barmaki 2019	Nutrition	UC & PBO/Sham (2 arms)	PSQI	NA	!	!	+	−	+	−
1397	Amutio 2018	PT/BT gen	UC	PSQI	NA	+	!	+	−	+	−
265	Simister 2018	PT/BT gen	UC	PSQI	NA	+	!	+	−	+	−
349	Schmidt 2011	PT/BT gen	UC & PBO/Sham (2 arms)	PSQI	NA	+	!	+	−	+	−
458	Lami 2018	PT/BT gen & sleep (2 arms)	UC	PSQI	NA	!	−	−	−	+	−
689	Onieva-Zafra 2019	Relaxation/Meditation	UC	PSQI	NA	!	−	+	−	+	−
345	Senna 2012	Weight loss	UC	PSQI	NA	!	!	+	−	+	−
358	Arcos-Carmona 2011	Aerobic LD + Relaxation/Meditation	PBO/Sham	PSQI	NA	!	−	+	−	+	−
711	Castro-Sanchez 2011	Manual T	PBO/Sham	PSQI	NA	+	−	−	−	+	−
2308	Nadal-Nicolás 2020	Manual T	PBO/Sham	PSQI	NA	!	−	+	−	+	−
493	Ide 2008	Mind-body Ex AQ	PBO/Sham	PSQI	NA	−	−	−	−	+	−
110	Liu 2012	Mind-body Ex LD	PBO/Sham	PSQI	NA	!	−	+	−	+	−
409	Sarmento 2020	Mind-body Ex LD	PBO/Sham	PSQI	NA	−	−	+	+	+	−
2313	Guinot 2021	Neuromodulation + Multicompoment T (Aerobic LD + Flex/skill AQ + Relaxation + Education)	PBO/Sham + Multicompoment T	PSQI	NA	!	+	+	+	+	!
346	Moustafa 2015	Manual T + Multimodal (PT/BT gen + Flex/skill LD)	PBO/Sham + Multimodal	PSQI	NA	+	!	+	−	+	−
227	Goldway 2019	Neuromodulation	PBO/Sham	PSQI	NA	!	−	−	+	+	−
1787	Samartin-Veiga 2021	Neuromodulation	PBO/Sham	PSQI	NA	!	+	+	+	+	!
2311	Wu 2021	Neuromodulation	PBO/Sham	PSQI	NA	+	!	−	−	+	−
1967	Mirzaei 2018	Nutrition + SSRI	PBO/Sham + SSRI	PSQI	NA	!	+	+	+	+	!
659	Mataran-Penarrocha 2011	Non-MSM practice	PBO/Sham	PSQI	NA	!	−	−	+	+	−
603	Gómez-Hernández 2020	Aerobic LD + Flex/skill LD	Aerobic LD	PSQI	NA	!	!	+	−	+	−
209	de Medeiros 2020	Mind-body Ex LD	Aerobic AQ	PSQI	NA	+	!	+	−	+	−
276	Wang 2018	Mind-body Ex LD (4 groups)	Aerobic LD	PSQI	NA	+	!	−	−	+	−
687	Kurt 2016	BalneoT + Mx Exercise AQ & Mx Ex AQ (2 groups)	Balneotherapy	PSQI	NA	!	−	+	−	+	−
210	Jones 2012	Mind-body Ex LD	Education	PSQI	NA	!	!	+	−	+	−
153	Maddali Bongi 2016	Mind-body Ex LD	Education	PSQI	NA	!	!	+	−	+	−
641	Mist 2012	Mind-body Ex LD	Education	PSQI	NA	+	!	+	−	+	−
271	Fonseca 2021	Mx Exercise AQ	Education	PSQI	NA	!	!	+	−	+	−
118	Martínez 2014	PT/BT sleep	Education	PSQI	NA	+	−	−	−	+	−
2540	Miró 2011	PT/BT sleep	Education	PSQI	NA	+	−	−	−	!	−
245	Wang 2010	Mind-body Ex LD	Education + Flex/skill LD	PSQI	NA	+	!	+	−	+	−
341	Molina-Torres 2016	Occlusal SS	Electro T	PSQI	NA	+	!	+	−	+	−
243	Calandre 2009	Mind-body Ex AQ	Flex/skill AQ	PSQI	NA	+	!	−	−	+	−
248	López-Rodríguez 2013	Aerobic AQ	Flex/skill LD	PSQI	NA	!	−	−	−	+	−
238	Castro Sánchez 2019	Non-MSM practice	Manual T	PSQI	NA	+	!	+	−	+	−
213	Martínez-Rodríguez 2020	Nutrition (enriched Medit)	Nutrition (Medit)	PSQI	NA	!	!	−	−	+	−
1811	Slim 2017	Nutrition (hypocaloric)	Nutrition (GF)	PSQI	NA	+	−	−	−	+	−
198	Van Gordon 2017	PT/BT gen	PT/BT gen	PSQI	NA	+	!	−	−	+	−
2269	Prados 2020	PT/BT sleep	PT/BT gen	PSQI	NA	!	−	+	−	+	−
326	Ericsson 2016	Strengthening LD	Relaxation/Meditation	PSQI	NA	+	!	−	−	+	−
376	Castel 2013	Multidisciplinary (PT/BT gen + Mx Exercise LD + Mx Exercise AQ)	UC	MOS-SS	NA	!	!	+	−	+	−
716	Kong 2021	PT/BT gen	UC	MOS-SS	NA	!	!	−	−	!	−
273	Williams 2010	PT/BT gen	UC	MOS-SS	NA	+	!	−	−	+	−
281	Castel 2012	PT/BT gen & PT/BT gen + Relaxation/Meditation (2 arms)	UC	MOS-SS	NA	!	!	+	−	+	−
275	Picard 2013	Relaxation/Meditation	UC	MOS-SS	NA	!	!	−	−	+	−
583	Amirova 2017	Relaxation/Meditation	UC & PBO/Sham (2 arms)	MOS-SS	NA	+	!	−	−	+	−
331	Nelson 2010	Neuromodulation	PBO/Sham	MOS-SS	NA	!	−	−	+	+	−
296	Racine 2019	PT/BT gen (2 arms)	UC (2 arms)	MOS-SS	NA	+	−	−	−	+	−
2309	Udina-Corte 2020	Electro T	PBO/Sham	JSS	NA	!	−	−	+	+	−
2323	Curtis 2021	Hyperbaric oxygen therapy	UC	JSS	NA	+	!	+	−	+	−
333	Toprak Celenay 2020	Flex/skill LD + Manual T	Flex/skill LD	JSS	NA	!	−	−	−	+	−
1609	Haak 2008	Mind-body Ex LD	UC	VNS (SQNRS proxy)	NA	!	!	+	−	+	−
220	Wong 2018	Mind-body Ex LD	UC	VAS (SQNRS proxy)	NA	!	−	−	−	+	−
2302	Haugmark 2021	PT/BT gen	UC	NRS (SQNRS proxy)	NA	+	!	−	−	+	−
470	Merchant 2001	Nutrition	PBO/Sham	VAS (SQNRS proxy)	NA	!	−	−	+	+	−
218	Deluze 1992	Non-MSM practice	PBO/Sham	Scale (SQNRS proxy)	NA	+	−	−	+	+	−
154	Maddali Bongi 2012	Mind-body Ex LD	Mind–body Ex LD	NRS (SQNRS proxy)	NA	+	−	−	−	+	−
230	Potvin 2012	AP	PBO/Sham	PSQI	NA	!	+	−	+	+	−
202	Di Pierro 2017	Antioxidant (CoQ10)	PBO/Sham	PSQI	NA	+	!	+	−	+	−
310	Reuter 2017	CNS depressant	PBO/Sham	PSQI	NA	!	−	−	+	+	−
253	Calandre 2014	AP	Tricyclics	PSQI	NA	+	!	−	−	+	−
370	de Zanette 2014	Endogenous hormone + PBO/Sham & Endogenous hormone + Tricyclics (2 arms)	Tricyclics + PBO/Sham	PSQI	NA	!	+	+	+	+	!

+ Low risk
! Some concerns
− High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

FIGURE 10 Risk-of-bias summary: review authors' judgements about each risk-of-bias item for each included study eligible for the NMA.

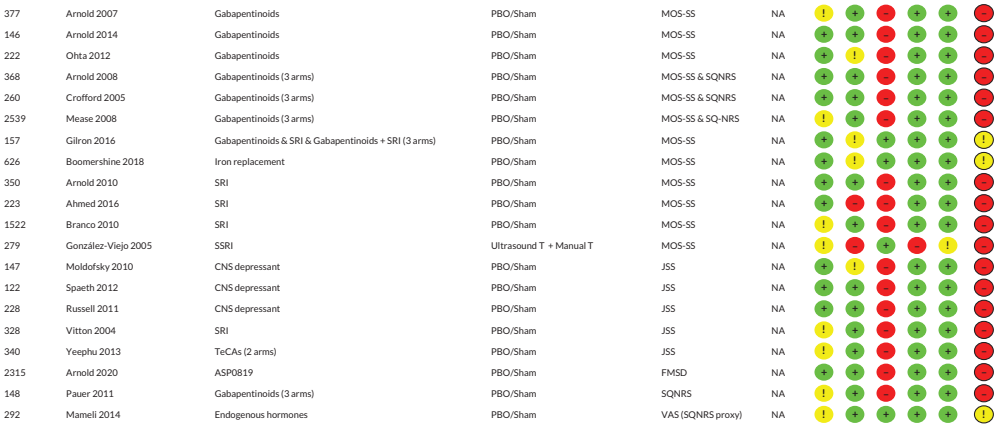

FIGURE 10 Continued

Appendix 5 Interventions and the number of participants

TABLE 20 Interventions and the number of participants

Treatment	Sleep	FIQ	SF-36 mental health summary score	SF-36 physical summary score
	n	*n*	*n*	*n*
Placebo/Sham	2087	2263	1167	1355
Education + Flexibility exercise LD	33	33	33	33
Mind–body Ex LD	465	420	281	281
Aerobic exercise LD	107	107	75	75
Education	182	182	22	22
Flexibility exercise AQ	N/A	39	N/A	
UC	924	559	153	153
Aerobic exercise AQ	59	59	N/A	
Nutrition	42	73	36	36
Balneotherapy	127	37		
PT/BT generic	352	145		
Manual T	59	45		
Relaxation	116	67		
Electro T	49	20	20	20
Flexibility exercise LD	79	57		
PT/BT sleep	94	77		
Mind–body Ex AQ	18	60		
Mixed exercise AQ	97	89		
Weight loss	41	41		
Neuromodulation	158	76		
Non-MSM practice	75	47	47	47
Dental splint	29	N/A		
Hyperbaric oxygen therapy	9	9		
Aerobic exercise LD + Flexibility exercise LD	32	32		
PT/BT generic + Relaxation	N/A	29		
Multidisciplinary	81	81		
Flexibility exercise LD + Manual T	17	17		
Balneotherapy + Mixed exercise AQ	36	36		

TABLE 20 Interventions and the number of participants (*continued*)

Treatment	Sleep	FIQ	SF-36 mental health summary score	SF-36 physical summary score
	n	*n*	*n*	*n*
Tricyclics	43	43		
AP	53	53		
Endogenous hormones	14	N/A		
Antioxidant	12	12	12	12
SRI	668	573	556	556
Iron replacement	N/A	38		
Gabapentinoid	1474	737	245	245
Analgesic	90	90		
CNS depressants	469	881	489	874
Strengthening exercise LD	56	N/A		

AQ, aquatic; FIQ, Fibromyalgia Impact Questionnaire; LD, land-based.

Appendix 6 Node splitting

TABLE 21 Node splitting for sleep outcome

	Direct		Indirect		Difference	
Treatment	**MD**	**95% CI**	**MD**	**95% CI**	**MD**	**95% CI**
Placebo/sham						
Mind–body Ex LD	−1.00	(−2.63 to 0.63)	0.33	(−1.46 to 2.12)	−1.33	(−3.12 to 0.46)
UC	0.21	(−0.83 to 1.25)	−0.78	(−2.21 to 0.65)	0.99	(−0.44 to 2.41)
Nutrition	0.26	(−1.86 to 2.38)	−0.59	(−2.63 to 1.44)	0.85	(−1.18 to 2.89)
PT/BT generic	−0.01	(−2.11 to 2.10)	−0.57	(−2.60 to 1.47)	0.56	(−1.47 to 2.59)
Manual T	−0.31	(−2.54 to 1.92)	−0.72	(−2.81 to 1.37)	0.41	(−1.68 to 2.50)
Relaxation	−0.37	(−2.47 to 1.73)	−1.42	(−3.45 to 0.61)	1.05	(−0.98 to 3.08)
Electro T	−0.98	(−3.13 to 1.17)	0.31	(−1.74 to 2.36)	−1.30	(−3.35 to 0.76)
Non-MSM practice	−1.26	(−2.78 to 0.25)	−0.37	(−2.10 to 1.35)	−0.89	(−2.61 to 0.83)
AP	−1.29	(−3.43 to 0.85)	−0.01	(−2.06 to 2.04)	−1.28	(−3.33 to 0.77)
Education + Flexibility exercise LD						
Mind–body Ex LD	−0.81	(−2.91 to 1.28)	−0.38	(−2.41 to 1.65)	−0.43	(−2.46 to 1.59)
Mind–body Ex LD						
Aerobic Ex LD	0.05	(−2.01 to 2.10)	2.06	(0.05 to 4.06)	−2.01	(−4.02 to −0.01)
Education	0.54	(−0.69 to 1.76)	−0.35	(−1.90 to 1.20)	0.89	(−0.66 to 2.43)
UC[a]	−0.86	(−1.88 to 0.17)	1.40	(−0.01 to 2.82)	−2.26	(−3.68 to −0.84)
Aerobic exercise AQ[a]	−0.97	(−2.92 to 0.99)	−5.66	(−7.61 to −3.70)	4.69	(2.73 to 6.65)
Aerobic exercise LD						
Aerobic exercise LD + flexibility exercise LD	−4.56	(−6.81 to −2.31)	0.29	(−1.81 to 2.39)	−4.85	(−6.95 to −2.75)
Education						
PT/BT sleep	−0.77	(−2.30 to 0.75)	−1.34	(−3.07 to 0.39)	0.56	(−1.16 to 2.29)
Mixed exercise AQ	0.12	(−2.03 to 2.28)	−0.63	(−2.68 to 1.43)	0.75	(−1.30 to 2.80)
UC						
Nutrition	−0.13	(−1.71 to 1.44)	1.02	(−0.73 to 2.78)	−1.16	(−2.91 to 0.60)
Balneotherapy	0.04	(−2.03 to 2.11)	−1.29	(−3.30 to 0.72)	1.33	(−0.69 to 3.34)
PT/BT generic	−0.37	(−1.12 to 0.38)	0.68	(−0.53 to 1.89)	−1.05	(−2.26 to 0.16)
Manual T	−0.54	(−2.66 to 1.58)	−0.13	(−2.17 to 1.91)	−0.41	(−2.45 to 1.63)
Relaxation	−0.66	(−2.77 to 1.44)	0.39	(−1.65 to 2.42)	−1.05	(−3.08 to 0.98)
Flexibility exercise LD[a]	−0.79	(−2.74 to 1.16)	3.90	(1.94 to 5.85)	−4.69	(−6.65 to −2.74)

TABLE 21 Node splitting for sleep outcome (*continued*)

	Direct		Indirect		Difference	
Treatment	**MD**	**95% CI**	**MD**	**95% CI**	**MD**	**95% CI**
PT/BT sleep	−0.56	(−2.70 to 1.57)	−0.82	(−2.86 to 1.23)	0.25	(−1.79 to 2.30)
Mixed exercise AQ	−0.92	(−3.02 to 1.19)	0.70	(−1.33 to 2.73)	−1.62	(−3.65 to 0.41)
Weight loss	−0.98	(−3.07 to 1.10)	0.28	(−1.74 to 2.30)	−1.26	(−3.29 to 0.76)
Non-MSM practice	−0.28	(−2.35 to 1.79)	−1.80	(−3.82 to 0.21)	1.53	(−0.49 to 3.54)
Hyperbaric oxygen therapy	−4.34	(−7.16 to −1.51)	0.55	(−1.81 to 2.90)	−4.88	(−7.24 to −2.53)
Multidisciplinary	1.97	(−0.10 to 4.04)	0.20	(−1.81 to 2.22)	1.76	(−0.25 to 3.78)
Aerobic exercise AQ						
Flexibility exercise LD[a]	4.71	(2.66 to 6.75)	0.01	(−1.99 to 2.02)	4.69	(2.69 to 6.70)
Balneotherapy						
Mixed exercise AQ	0.97	(−1.13 to 3.08)	−0.36	(−2.39 to 1.68)	1.33	(−0.70 to 3.36)
Balneotherapy + mixed exercise AQ	0.97	(−1.13 to 3.08)	−1.68	(−3.71 to 0.35)	2.66	(0.62 to 4.69)
PT/BT generic						
PT/BT sleep	−0.74	(−2.28 to 0.79)	0.03	(−1.70 to 1.77)	−0.78	(−2.51 to 0.95)
Relaxation						
Strengthening exercise, LD	−0.34	(−2.41 to 1.73)	1.21	(−0.81 to 3.22)	−1.54	(−3.56 to 0.47)
Electro T						
Dental splint	−0.63	(−2.73 to 1.48)	1.97	(−0.06 to 4.00)	−2.59	(−4.62 to −0.56)
Flexibility exercise LD						
Flexibility exercise LD + Manual T	0.29	(−1.85 to 2.43)	−1.01	(−3.06 to 1.04)	1.30	(−0.75 to 3.35)
Mixed exercise AQ						
Balneotherapy + mixed exercise AQ	0.00	(−2.10 to 2.10)	2.66	(0.63 to 4.69)	−2.66	(−4.69 to −0.63)
Tricyclics						
AP	−0.02	(−2.11 to 2.06)	−2.58	(−4.60 to −0.55)	2.55	(0.53 to 4.58)

AQ, aquatic; CI, confidence interval; LD, land-based; MD, mean difference.
a Statistical evidence of inconsistency.

TABLE 22 Node splitting for FIQ

Treatment	Direct		Indirect		Difference	
	MD	95% CI	MD	95% CI	MD	95% CI
Placebo/sham						
Mind–body Ex LD	−19.37	(−31.28 to −7.46)	−14.88	(−19.72 to −10.05)	−4.48	(−9.31 to 0.35)
UC	−0.41	(−5.62 to 4.80)	4.79	(1.60 to 7.99)	−5.21	(−8.40 to −2.01)
Nutrition	−6.06	(−15.00 to 2.88)	1.12	(−3.07 to 5.30)	−7.18	(−11.37 to −2.99)
PT/BT generic[a]	−0.18	(−8.18 to 7.82)	−11.89	(−15.85 to −7.93)	11.71	(7.75 to 15.67)
Relaxation	0.07	(−10.97 to 11.11)	7.92	(3.26 to 12.57)	−7.85	(−12.50 to −3.19)
Mixed exercise AQ	2.05	(−7.14 to 11.24)	−1.82	(−6.07 to 2.42)	3.87	(−0.37 to 8.12)
Non-MSM practice	−5.10	(−16.36 to 6.16)	−11.71	(−16.41 to −7.01)	6.61	(1.91 to 11.31)
AP	−6.80	(−20.02 to 6.42)	2.32	(−2.77 to 7.41)	−9.12	(−14.21 to −4.03)
Education + Flexibility exercise LD						
Mind–body Ex LD	−18.40	(−30.93 to −5.87)	−32.86	(−37.81 to −27.90)	14.46	(9.50 to 19.41)
Mind–body Ex LD						
Aerobic exercise LD	6.88	(−4.02 to 17.78)	21.82	(17.20 to 26.45)	−14.94	(−19.57 to −10.32)
Education	9.18	(0.66 to 17.69)	16.70	(12.61 to 20.79)	−7.52	(−11.61 to −3.44)
UC	17.70	(9.48 to 25.92)	16.01	(12.00 to 20.03)	1.69	(−2.32 to 5.71)
Aerobic exercise AQ	7.00	(−6.57 to 20.57)	11.87	(6.71 to 17.03)	−4.87	(−10.03 to 0.29)
Aerobic exercise LD						
Aerobic exercise LD + Flexibility exercise LD	−10.62	(−19.96 to −1.28)	19.09	(14.81 to 23.37)	−29.71	(−33.99 to −25.43)
Education						
PT/BT sleep[a]	−14.17	(−23.21 to −5.12)	7.81	(3.60 to 12.03)	−21.98	(−26.19 to −17.77)
Mixed exercise AQ	13.60	(1.06 to 26.14)	−1.71	(−6.66 to 3.25)	15.31	(10.35 to 20.26)
Flexibility exercise LD						
Mixed exercise AQ	−3.71	(−15.11 to 7.69)	3.95	(−0.78 to 8.68)	−7.66	(−12.39 to −2.93)
UC						
Nutrition	−4.67	(−17.40 to 8.05)	−6.89	(−11.89 to −1.90)	2.22	(−2.78 to 7.21)
PT/BT generic	−6.77	(−12.07 to −1.48)	−11.56	(−14.79 to −8.34)	4.79	(1.57 to 8.01)
Manual T	−10.06	(−20.80 to 0.67)	−1.00	(−5.59 to 3.58)	−9.06	(−13.65 to −4.47)
Relaxation	2.69	(−8.21 to 13.59)	−5.16	(−9.78 to −0.53)	7.85	(3.22 to 12.47)
PT/BT sleep[a]	0.37	(−10.43 to 11.17)	−24.66	(−29.26 to −20.06)	25.03	(20.43 to 29.63)
Mixed exercise AQ	−3.90	(−14.02 to 6.22)	11.41	(6.95 to 15.86)	−15.31	(−19.76 to −10.85)
Weight loss	−4.60	(−14.34 to 5.14)	−1.18	(−5.55 to 3.19)	−3.42	(−7.79 to 0.95)
Non-MSM practice	−8.30	(−19.80 to 3.20)	−1.69	(−6.44 to 3.06)	−6.61	(−11.36 to −1.86)

TABLE 22 Node splitting for FIQ (*continued*)

	Direct		Indirect		Difference	
Treatment	**MD**	**95% CI**	**MD**	**95% CI**	**MD**	**95% CI**
Hyperbaric oxygen therapy	−27.20	(−38.18 to −16.22)	0.48	(−4.16 to 5.12)	−27.68	(−32.32 to −23.04)
PT/BT generic + Relaxation	−15.60	(−24.45 to −6.75)	−0.90	(−5.07 to 3.27)	−14.70	(−18.87 to −10.53)
Multidisciplinary	−18.20	(−29.02 to −7.38)	−0.32	(−4.92 to 4.29)	−17.88	(−22.49 to −13.28)
Aerobic exercise AQ						
Flexibility exercise LD	13.81	(1.88 to 25.74)	14.69	(9.86 to 19.53)	−0.88	(−5.72 to 3.95)
Balneotherapy						
Aerobic exercise AQ	7.10	(−3.39 to 17.59)	0.58	(−3.95 to 5.12)	6.52	(1.98 to 11.05)
PT/BT generic						
PT/BT sleep	−2.25	(−14.26 to 9.76)	−9.43	(−14.28 to −4.58)	7.18	(2.33 to 12.03)
PT/BT generic + Relaxation	−3.20	(−12.04 to 5.64)	−17.90	(−22.06 to −13.74)	14.70	(10.54 to 18.86)
Flexibility exercise LD						
Flexibility exercise LD + Manual T	−5.53	(−24.94 to 13.88)	−9.07	(−15.24 to −2.90)	3.54	(−2.63 to 9.71)
Mixed exercise AQ						
Balneotherapy + mixed exercise AQ	−7.30	(−17.82 to 3.22)	−0.57	(−5.11 to 3.98)	−6.73	(−11.28 to −2.19)
Tricyclics						
AP	4.10	(−7.61 to 15.81)	−14.09	(−18.88 to −9.30)	18.19	(13.40 to 22.98)

AQ, aquatic; CI, confidence interval; LD, land-based; MD, mean difference.
a Statistical evidence of inconsistency.

Appendix 7 Characteristics of the patient-reported outcome measures development studies (non-fibromyalgia patients)

TABLE 23 Characteristics of the PROMs development studies (non-fibromyalgia patients)

PROM, country, author ID	Sample size	Participants, characteristics	Methods of the study
JSS USA Jenkins 1988[38]	ATC Health Change Study Total *n* = 250 Recovery study Total *n* = 467 Total *n* = 717	**ATC study** Age (years), mean (range): 37.1 (25–49) Gender, %: male, 100% Race/ethnicity: NR Marital status, %: married 89%; separated, divorced, or widowed 7%; unattached 4% Sociodemographic status, %: living in 'a good or one of the best' neighbourhoods 79%, living in an 'average' neighbourhood 20%, living in 'one of the poorer' neighbourhoods 17% **Recovery study** Age (years), mean (range): 54.9 (25–69) Gender, *n* (%): male, 80%; female, 20% Race/ethnicity: 'most were white' Marital status: NR Sociodemographic status: NR	The original tool was developed for use in the general population with a sample of US air traffic controllers (ATC study), and cardiac surgery patients (Recovery study). Both instruments were self-completed/reported by the participants. The ATC instrument was administered once. The Recovery study instrument was administered on three occasions: a few days prior to surgery, 6 months after surgery and 12 months after surgery. Internal consistency of the items in the two instruments was measured, and the test–retest reliability of the instrument in the Recovery study was measured.
MOS-SS USA Hays 1992[37]	Total *n* = 3053	Age (years), mean (range): 54 (18–98) Gender, %: male, 39%; female, 61% Race/ethnicity, %: white, 79%, non-white, 21% Marital status: NR Sociodemographic status: education (years) mean: 13	The MOS-SS was developed and initially tested in the US general population and a large sample of individuals with chronic illnesses.
PSQI USA Buysse 1989[36]	Healthy controls (good sleepers) *n* = 52; People with major depressive disorder (poor sleepers) *n* = 34; (outpatients *n* = 24 and inpatients *n* = 10 at the Western Psychiatric Institute) People with sleep/wake complaints who were outpatients at the Sleep Evaluation Centre, Western Psychiatric Institute & Clinic (poor sleepers) *n* = 62 [Disorder of Initiating and Maintaining Sleep (DIMS, *n* = 45) or Disorders of Excessive Somnolence (DOES, *n* = 17)] Total *n* = 148	Age Healthy controls: mean 59.9 years (range: 24–83); Depressives: mean 50.9 years (range: 21–80); DIMS: mean 44.8 years (range: 20–80); DOES: mean 42.2 years (range: 19–57) Gender Healthy controls: male, 40 (76%); female, 12 (24%) Depressives: male, 25 (66%); female, 9 (34%) DIMS: male, l6 (36%); female, 29 (64%) DOES: male, 8 (47%); female, 9 (53%) Total: male, 89 (60%); female, 59 (40%) Race/ethnicity: NR Marital status: NR Sociodemographic status: NR	Items in the original version of the tool were derived from clinical intuition and experience with sleep disorder patients, a review of previously published sleep quality questionnaires, and clinical experience with the instrument during 18 months of field testing. Test–retest reliability was assessed with paired *t*-tests and Pearson product-moment correlations for PSQI global score, component scores and individual items, at Time 1 vs. Time 2.

ATC, air traffic controller; DIMS, disorder of initiating and maintaining sleep; DOES, disorders of excessive somnolence.

Appendix 8 Quantitative evidence synthesis: research protocol deviations

Literature searches (ongoing trials)

As per the research protocol, we searched relevant electronic databases to identify ongoing clinical trials. The search yielded a total of 316 clinical trial citations, out of which 254 were obtained from CENTRAL, while separate searches on ClinicalTrials.gov and WHO ICTRP resulted in 44 and 18 trial citations, respectively. However, due to the large number of identified trials and the timescale of the project, we found it impractical to assess all of them for eligibility.

Types of outcome measures

In the research protocol, we stated that 'The choice of primary and secondary outcomes will be discussed and agreed upon by our Advisory Group'. Based on the advice we received from the members of our Advisory Group, we decided to assess 'sleep quality', 'sleep efficiency' and 'sleep duration' as relevant sleep outcomes. In the absence of an accepted quality-of-life tool specific to fibromyalgia, we decided to use SF-36 and the FIQ as a proxy for quality-of-life measures.

Risk-of-bias assessment

We decided not to use the ORBIT methodological approach for assessing the presence of selective outcome reporting bias, as we considered that this was not necessary. Following the guidance for the Cochrane RoB2 tool, we did not identify any issue of selective reporting bias related to the primary outcome of sleep quality, because we specified that only results using specific measurement scales were eligible for inclusion in the NMA (i.e. PROMs validated for fibromyalgia patients).

Analysis

In the research protocol we indicated that we would use the GRADE methods on rating the certainty of evidence from NMA. After considering the current available methods, we decided to use the CINeMA approach, which is a web application based on the GRADE framework and has been adopted by other authors.

Methods not implemented

Due to the scarcity of relevant information available from the included studies, it proved unfeasible to perform meta-regression or sensitivity analyses to assess potential sources of heterogeneity.

EME
HSDR
HTA
PGfAR
PHR

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