NIHR132999

What is the evidence for interventions used to manage sleep disturbances in people with fibromyalgia?
A comprehensive evidence synthesis to inform clinical practice and future research.

Research Protocol

Background

Fibromyalgia is a long-term condition characterised by chronic widespread 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.[1,2]

Sleep disturbance is reported as one of the most common symptoms by 95% of those living with fibromyalgia.[3] Nevertheless, fibromyalgia-related sleep problems are poorly managed in the NHS, with people continuing to seek help for many years after their initial fibromyalgia diagnosis.[2] In addition to negative impacts on the individual, fibromyalgia-related sleep disturbances present a significant health-economic problem, with an estimated 150,000 GP consultations per year in the UK.[2] 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), which all have an increased risk of drug dependency and undesirable side-effects (e.g. related to opioid use).[4-6]

The recent James Lind Alliance Priority Setting Partnerships process has identified research into interventions for managing sleep problems in people with fibromyalgia as one of their top priorities. 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.[7] Sleep problems have also been implicated in the development of depression among those with persistent pain.[8] 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 four-fold, with a follow-up period of up to 12 years.[9, 10] Conversely, and perhaps more importantly, having restorative sleep has been found to prospectively predict successful resolution of chronic widespread pain.[11]

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, perception of poor sleep quality. A meta-analysis of polysomnographic studies corroborate 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.[12] 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.[13] Specific sleep disorders are highly prevalent among people with fibromyalgia; over 50% of people with fibromyalgia meet criteria for chronic insomnia, over 40% have been estimated to have co-morbid restless leg syndrome and over a quarter exceed the clinical threshold for a diagnosis of obstructive sleep apnoea.[14-16]

The 2015 European guidelines for the management of fibromyalgia considered sleep as one of the key outcomes of interest.[17] Although general recommendations were made for managing sleep disturbances, these were graded as “weak” due to the paucity of published evidence at that time. Additionally, sleep management was not the primary focus of the guidelines. Furthermore, the guidelines working group could not perform a network meta-analysis for the management of sleep problems, which allows ranking of interventions according to their efficacy, and conducted an umbrella review instead. Now with an increased amount of data generated from high-quality randomised controlled trials (RCTs) of pharmacological (e.g. milnacipran, pregabalin, duloxetine, and suvorexant)[18-21] and non-pharmacological treatments (e.g. emotional awareness and expression therapy and cognitive-behavioural therapy for insomnia and pain management)[22, 23] there is the opportunity to conduct meta-analyses of direct and indirect evidence to evaluate the comparative effectiveness of different interventions for sleep management in fibromyalgia. This could be enhanced by incorporating findings from a synthesis of qualitative evidence regarding the acceptability of different interventions from a patient perspective. 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.

Notably, although evidence reviews have recently informed the National Institute of Health and Care Excellence (NICE) draft guidelines for the management of chronic pain, these cluster together a wide range of conditions (including generalised osteoarthritis, mechanical back pain, fibromyalgia) and are restricted to adult populations.[24] More importantly, they do not have a specific focus on sleep management.

The outcome of this research will provide a timely empirical evaluation of treatment strategies that are effective in addressing sleep problems in fibromyalgia and can be adopted in clinical practice in the NHS. We will also identify promising interventions that should be evaluated in future clinical trials, as well as interventions that are likely to be ineffective and therefore should not be offered to patients.

Aims and objectives

The overall aim of this project is to provide information to help patients' self-management, aid clinical decision-making, and guide future research by assessing the existing quantitative and qualitative evidence on the interventions used for the management of fibromyalgia-related sleep problems. The specific objectives of this assessment are the following:

i. To undertake a comprehensive evidence synthesis to assess the clinical effectiveness and safety of pharmacological and non-pharmacological treatments for the management of fibromyalgia-related sleep problems [quantitative evidence synthesis];
ii. To update and enhance a recently published qualitative evidence synthesis (Climent-Sanz (2020)) [25] to ascertain the experiences and expectations of people who receive treatments for fibromyalgia-related sleep problems [enhanced qualitative evidence synthesis];
iii. 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].

Research plan and outline of the methodology

Design

The proposed work, which aims to assess current interventions for the management of fibromyalgia-related sleep problems, consists of three main components:

- Quantitative evidence synthesis including pairwise and network meta-analyses
- Qualitative evidence synthesis
- PROMs analysis

Health technologies being assessed

Any pharmacological or non-pharmacological intervention for the management of sleep disturbances in fibromyalgia. This may include discrete interventions (e.g. cognitive behavioural therapy, physical therapy, sleep medications) and multi-component interventions, which comprise a combination of different interventions (e.g. physical exercise, cognitive behavioural therapy added to a graded motor imagery programme or a therapeutic neuroscience education programme) that may be delivered concurrently or sequentially.

Literature searches

Quantitative synthesis

Highly sensitive search strategies will be designed by an information specialist using appropriate subject headings and free text terms. The following electronic databases will be searched: MEDLINE, Embase, Science Citation Index, CINAHL, AMED, Cochrane Database of Systematic Reviews (CDSR), CENTRAL, APA PsycInfo, Database of Abstracts of review of Effects (DARE), and the NIHR Journals Library. A combination of database index terms and text words will be used to identify all sleep-related outcomes, even when they are not the primary research aim.

Ongoing studies will be identified through searching current Controlled Trials, Clinical Trials, and WHO International Clinical Trials Registry. The reference lists of all studies selected for full-text appraisal will be screened for additional studies. Experts in the field will be contacted for further reports and recent conference proceedings of key professional organisations will also be scrutinised.

For all searches, there will be no restrictions on the date or language of publication. All references will be exported to Endnote for recording and deduplication. A preliminary MEDLINE search is detailed in Appendix 1.

Qualitative synthesis

The search strategy of a recently published qualitative evidence synthesis, which explores the experiences and expectations of people who are treated for fibromyalgia-related sleep problems, will be updated to identify any potentially eligible new studies.[25]

PROMs' analysis

The PROMs search will be informed by a published review of PROMs on sleep quality in fibromyalgia.[26] We will refine and update our scoping search (March 2020) to identify any additional, relevant PROMs for the content analysis.

Methods of the quantitative evidence synthesis

We will follow recommendations from the Cochrane Handbook for Systematic Reviews of Interventions.[27]

Inclusion and exclusion criteria

The key eligibility criteria for the quantitative evidence review are summarised using a PICO framework in Table 1.

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)	Randomised controlled trial design

Study design

We will include parallel-group randomised controlled trials (RCTs) and cluster RCTs assessing the effectiveness of any intervention for the management of fibromyalgia-related sleep problems in both adults and children. Uncontrolled and non-randomised trials, case studies, letters, and editorial or opinion articles will be excluded. Systematic reviews will not be eligible for inclusion, but we will cross-check their list of included studies for relevance.

Participants

People of any age living with fibromyalgia. About the age limit by which to define the adult and children populations, we will accept the definitions used by the authors of the identified studies.

Interventions

Any intervention for the management of sleep problems in people with fibromyalgia including both pharmacological and non-pharmacological interventions.

Pharmacological treatments may include hormones (e.g., melatonin), antipsychotic (e.g., quetiapine), anticonvulsant (e.g., gabapentin, pregabalin), and antidepressant (e.g., amitriptyline) medications. We will consider eligible pharmacological treatments regardless of their dose or routes of administration. Non-pharmacological interventions may include physical therapies (e.g., land-based exercise, aquatic exercise, Tai Chi, yoga), cognitive behavioural therapy, dietary and lifestyle modifications, as well as complementary and alternative therapies (e.g., acupuncture).

Eligible interventions may include discrete interventions (e.g., cognitive behavioural therapy, physical therapy, administration of a sleep medication) as well as multi-component interventions, which comprise a combination of different interventions that may be delivered concurrently. Sequentially delivered interventions (i.e., interventions that include a pre-defined order of intervention delivery such as acute pharmacological intervention followed by longer-term non-pharmacological intervention) will also be eligible for inclusion.

Comparators

Valid comparators are usual care, placebo, no treatment (including waitlist) or another active intervention. We will exclude comparisons of two or more regimens of the same treatment (e.g., varying doses of a drug) if they do not include a placebo group.

Outcomes

We will include studies reporting data on specified outcome measures, irrespective of whether they are reported as primary or secondary endpoints. Studies that do not report any of the key outcomes will not be deemed suitable for inclusion.

The choice of primary and secondary outcomes will be discussed and agreed upon by our Advisory Group, which, in addition to the research project team, will comprise experts in the field of fibromyalgia, chronic pain and patient representatives. These discussions will be informed by the existing evidence on core outcome sets for fibromyalgia.

Any sleep-related outcomes reported in identified studies, irrespective of whether they are assessed as primary or secondary outcomes, will be deemed suitable for inclusion. These may include:

- Sleep quality
- Sleep efficiency (%; calculated as total sleep time/total time in bed x 100%)
- Duration of sleep/total sleep time
- Sleep onset latency (time to fall to sleep)
- Number and duration of awakenings
- Sleep stage measures
- Daytime sleepiness
- Fatigue
- Activities of daily living
- Quality of life (disease-specific measures)
- Adverse events

We anticipate that studies will use a variety of measures to define some of the above outcomes. Some of them may be self-reported (based on questionnaires and/or sleep diary) and some may be objectively measured (using polysomnography and/or actigraphy). Some clinical trials may report both subjective and objective measures. In discussion with the members of our Advisory Group, we will create a hierarchy of reported outcomes to select the outcomes on which to focus our analyses, taking into consideration what matters to both patients and health professionals. We anticipate that for people with fibromyalgia and health professionals who treat them assessment of 'sleep quality' (patient's experience of sleep and perceioved sleep quality) will be of particular importance.

Setting

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

Study selection and data extraction

Two review authors (CR, MI) will screen all the citations identified by the search strategies and retrieve full-text copies of potentially relevant studies, which will be assessed for eligibility. To ensure consistency, the two review authors (CR, MI) will independently screen 10% of all citations identified by the search strategies at the beginning of the study selection process.

Data extraction forms will be developed and piloted by the same two review authors and by our PPI co-applicant. Information on setting, characteristics of participants, characteristics of interventions and outcome measures will be recorded. Single data extraction will be undertaken by two review authors. To ensure accuracy, each review author will check the data extracted by the other review author for 10% of all included studies. Data from studies with multiple publications will be extracted and reported as a single study (the publication reporting the highest number of relevant outcomes will be considered the primary publication). A full list of excluded studies, alongside main reasons for exclusion, will be generated.

Risk of bias assessment

The risk of bias of each included study will be assessed by two review authors using the revised Cochrane risk of bias tool. [28] The review authors have considerable experience in conducting evidence syntheses and will independently double assess the first 10% of included studies to ensure consistency. The remaining studies will be divided between the two review authors for single assessment. While double assessment is generally recommended, the proposed approach has been adopted to improve the efficiency of the systematic review process and ensure the timely delivery of the project findings. The ORBIT methodological approach will be considered for assessing the presence of selective outcome reporting bias.[29]

Any disagreements or doubts during study selection, data extraction and risk of bias assessment will be resolved by discussion between the two review authors or consultation with a third review author.

Statistical analysis

The quantitative evidence synthesis will include pairwise and network meta-analyses spanning a range of complexity appropriate to the data and information available from RCTs. We will provide a description of the included studies based on important clinical and methodological characteristics. In the first instance, a random effects pair-wise meta-analysis model will be used to compare direct evidence from trials that evaluate similar interventions (comparability and similarity of various interventions will be agreed upon by the members of the project Advisory Group). Effect sizes will be reported as odds ratios with 95% confidence intervals for dichotomous outcomes, and as mean difference or standardised mean difference with 95% confidence intervals for continuous outcomes. Heterogeneity between studies results will be assessed on clinical criteria, by visual

inspection of forest plots, and by means of I^2 statistics. Analyses will be performed using Stata (version 16 or latest version).

We will then use network meta-analyses to combine results of direct and indirect comparisons in one analysis, using a Bayesian framework according to guidance from the NICE Decision Support Unit (DSU) and the PRISMA for network meta-analyses. We will use a binomial likelihood for binary outcomes and normal likelihood for continuous outcomes. Convergence will be assessed using trace and autocorrelation plots, and the Brooks-Gelman-Rubin statistic. We will estimate the ranking probabilities of the different interventions using the surface under the cumulative ranking curves (SUCRA), which gives probabilities of each intervention being ranked the best. We will use the node splitting method, which separates evidence on a particular comparison into direct and indirect evidence, to calculate the inconsistency of the models. When study arms use a mixture of interventions, we will consider using component network meta-analysis or similar models.[30, 31] The key assumptions of network meta-analysis models will be assessed using currently recommended methods. Potential sources of heterogeneity and/or inconsistency will be investigated using meta-regression or sensitivity analyses to assess any impact on derived treatment effect estimates. We will produce network diagrams for each outcome. The network meta-analyses will be run using WinBUGS software (version 1.4.3 or latest version) and Stata (version 16 or latest version).

The GRADE approach will be used to rate the certainty in estimates from network meta-analysis.[32]

Where data permit, secondary analyses of the following sub-groups will be considered:

- women versus men;
- children/adolescents versus adults;
- older adults versus young/middle age adults (according to the definitions provided by the studies' authors);
- people with autoimmune rheumatic disease versus people with no autoimmune rheumatic disease.

When outcome data cannot be combined in a meta-analysis, we will consider displaying important characteristics of each study (e.g. study quality) along with grouping each study based on its reported effect estimate using Harvest plots.[33]

Methods of the qualitative evidence synthesis

Design

A recently published qualitative evidence synthesis has provided an assessment of how people diagnosed with fibromyalgia experience and manage poor sleep quality.[25] We will update their searches, which were performed on 3 January 2020, and grade the certainty of all findings. Any new studies identified by our updated searches will be incorporated into the existing findings following the current recommendations for updating qualitative evidence syntheses.[34]

Inclusion and exclusion criteria

We will follow the eligibility criteria outlined by the published qualitative evidence synthesis.[25] We will focus on qualitative or mixed methods research exploring the experience and/or management of sleep problems in people diagnosed with fibromyalgia.[25]

The key eligibility criteria are summarised using the SPICE framework in Table 2.

Table 2. Summary of eligibility criteria for qualitative systematic review based on the SPICE framework

Setting	Perspective	Phenomenon of interest	Comparison	Evaluation
(Where?)	**(For whom?)**	**(What?)**	**(Compared with what?)**	**(With what result?)**
Any relevant setting	People with fibromyalgia	Sleep problems	None	Experience and management of sleep problems

Study selection and data extraction

Two review authors (CR, MI) will independently screen all citations identified by the updated searches and retrieve full-text copies of all potentially relevant studies, which will be assessed for eligibility. Information on the main characteristics of each identified study (e.g. aims and methods, populations involved) will be extracted into a data extraction form designed for this assessment. Data from the newly identified study by the updated searches will be extracted from the results sections of the included reports by one review author and checked by a second review author.

Risk of bias assessment

The CASP checklist will be used to assess the risk of bias of each included qualitative study.[35] To ensure consistency, two review authors will independently double-assess the risk of bias of the first 10% of the identified studies. Single assessment will be performed by the same review authors for the remaining studies. Any disagreements will be resolved by discussion between the review authors or consultation with a third review author.

Qualitative data analysis

Any new studies identified by our updated searches will be incorporated into the existing findings. The analytical approach adopted by the authors of the published qualitative evidence synthesis is presented in Appendix 2.

We will conduct a thematic analysis. We will scrutinise the identified new studies to identify main recurrent 'descriptive' themes and then develop higher-level 'analytical' themes to capture the phenomena described across the identified literature. Finally, to summarise the existing qualitative evidence 'landscape' and looking for areas of reciprocity but also divergence, we will aim to map the relationships between analytical themes. This process will involve constant comparison of the emerging theoretical constructs within the data from the analysed publications. The analysis will be conducted by two review authors (CR, MI) with assistance from a third author (KG) with experience of qualitative evidence synthesis; the initial reading and coding will be undertaken independently, and any disagreements resolved by consensus or arbitration by our patient partner. If studies are identified that report the perspectives of multiple stakeholders (i.e., patients, their partners, and their clinicians) individual analyses will be conducted by considering each group in isolation to generate both descriptive and analytical themes. The data would then be considered in juxtaposition to allow comparisons and contrasts to be developed. However, the perspectives of patients would always be considered of core importance and would be brought to the fore in the synthesis.

Certainty in the identified evidence

The recently published qualitative evidence synthesis has not included an assessment of the certainty of the identified evidence.[25] To enhance the quality of its findings and integrate them with the results of our quantitative synthesis, we will apply the Grading of Recommendations Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative research tool (GRADE-CERQual, https://www.cerqual.org)[36] to their reported findings and any new relevant identified study. The GRADE-CERQual

approach is based on four components which include: 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 working together will make an overall GRADE-CERQual assessment of confidence based on each thematic finding of the review. Judgments on the initial assumption will be that all findings are 'high confidence' and a reasonable representation of the phenomenon of interest, and then downgraded accordingly if there are concerns regarding any of the GRADE-CERQual components.

Methods of patient reported outcome measures (PROMs) analysis

Design

We will conduct a comprehensive analysis of existing fibromyalgia-specific patient-reported outcome measures (PROMs) of sleep quality. Although a recent published systematic review examined the psychometric properties of PROMs of sleep quality in fibromyalgia, the items contained within different measures have not previously been compared to each other.[26] It is also unclear if important sleep domains are captured in disease-specific quality of life outcome measures. For example, of two PROMs that measure disease-specific quality of life, one might have items that consider concepts such as pain, sleep quality, fatigue, and return to normal activities whilst the other might have items that consider pain and physical aspects 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 when evaluating intervention effectiveness. Using content analysis, we will examine the item variability of disease-specific PROMs for patients with fibromyalgia who are affected by sleep problems, compare the identified items to the findings of the enhanced qualitative evidence synthesis, assess the frequency of use of these measures in the trials identified by our search strategies, and compare findings to the relevant outcomes of interest.

The search strategy of the published review (available in the paper's appendix) was developed based on the COSMIN "search filters for finding studies on measurement properties" provided as an additional tool in the COSMIN website (https://www.cosmin.nl/tools/pubmed-search-filters/)[26] and was performed on March the 6th, 2020. We will update their search strategy to identify relevant recently published reports.

Inclusion criteria

We will focus on studies reporting sleep measures validated in people with fibromyalgia. All measures identified in the recent systematic review of PROMs of sleep quality in fibromyalgia[26] will be included in our PROMs analysis, irrespective of their validity as our purpose is to critique item coverage not psychometric properties (which are addressed by the existing review). Studies of sleep measures validated in people with other clinical conditions other than fibromyalgia will be excluded.

The published systematic review was carried out following the "COnsensus-based Standards for the selection of health Measurement Instruments" (COSMIN) [37] and the "Preferred Reporting Items for Systematic reviews and Meta-Analyses" (PRISMA) [38] guidelines. The review protocol was registered with PROSPERO (record IDCRD42018114218). The main objectives of this published review were to identify and describe the available PROMs of sleep quality in adults diagnosed with fibromyalgia and their psychometric properties. A summary of eligibility criteria for the published review of PROMs of sleep quality in fibromyalgia is shown in Table 3.

Table 3 Summary of eligibility criteria for published COSMIN systematic review of PROMs of sleep quality [28]

Type of studies	Type of participants
• Validation or cross-cultural adaptation studies. • The development studies for each of the included PROMs (to analyse the content validity for those PROMs originally developed in the context of fibromyalgia).	• Validation or cross-cultural adaptation studies involving adult participants (as defined by the studies' authors) diagnosed with fibromyalgia.

Study selection

Lierature searches results will be screened by the two review authors (CR, MI) to identify relevant studies reporting patient-reported outcome measures (instruments).

Analysis

The analysis will be informed by previous research that has analysed PROMs into individual outcome domains.[39] Specifically, data will be extracted on:

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

The individual verbatim items from each PROM will be analysed by using an inductive content analysis approach. All PROM items will be examined and systematically categorised into conceptual health domains according to the aspect which they aim to capture. Health domains will be generated inductively from the identified individual items, but will likely focus on aspects of physical health, mental health, and social functioning, informed by the WHO International Classification of Functioning, Disability and Health. Domain mapping will be conducted independently by the same two review authors with assistance from a senior member of the research team (KG), who has experience in PROMs coding. Any disagreements will be resolved through discussion or referred to another member of the team (DW or MB) as appropriate. The analysis of the disease-specific PROMs will investigate the reporting of input from patients in the item inception and development phases of these measures.

These findings will then be considered in consultation with patient partners alongside the findings from the enhanced qualitative evidence synthesis. This will allow us to identify whether any patient-relevant outcomes identified in the synthesis are missing from existing disease-specific PROMs and whether this is prevalent amongst those that lacked meaningful involvement and participation from patients during development.

Overall integration of findings

Individual outputs from each component of the proposed work (quantitative evidence synthesis, enhanced qualitative evidence synthesis, PROMs analysis) will be synthesised together to draw an overall summative conclusion of the existing evidence. For example, the thematic areas of relevance will be compared with the findings of the network meta-analysis to map outcomes identified in the qualitative evidence synthesis back onto the meta-analysis to determine whether all patient-relevant outcomes are being reported in existing trials in this clinical area. In addition, the findings from the qualitative synthesis will be used to provide explanatory data to support (or not support) intervention effectiveness, where appropriate.

Several methods exist for synthesising quantitative and qualitative research evidence in a systematic review but as yet there is no consensus on the optimal method to use.[40] The datasets, which will be both integrative and interpretive, will be combined and juxtaposed (i.e. discussed side-by-side) to produce a detailed explanatory narrative summary. This will contribute to a more nuanced understanding of differences in outcomes across sub-groups through a focus on patient-centred outcomes and experiences relevant to people who

receive treatments for fibromyalgia-related sleep problems. Specifically, integration of findings will be developed using a framework covering the following key steps: development of a 'theory' of how the intervention works, why and for whom; development of a preliminary synthesis; exploration of relationships within and between studies (or in this case, data types); assessment of the robustness of the synthesis product.[37] Ultimately, this integration will allow the intervention effects (both clinical and patient experience) to be viewed collectively which can better inform a holistic approach to the treatment of people with fibromyalgia-related sleep problems.

Dissemination activities

To maximise benefit from this project, our results will be disseminated to key stakeholders including patient partners and organisations, researchers, healthcare providers and policymakers. A detailed plan aiming at translation of findings into clinical practice and policy will be agreed by the Advisory Group for this project, which, in addition to the project team, comprises both clinical and patient experts. We are planning to develop an effective programme of dissemination of research findings in consultation with key stakeholders within the UK (NHS health professionals, patients, policymakers and the public). This will involve the development of optimum communication strategies to reach different target audiences including patient organisations and social media groups. The planned academic outputs of this research will comprise a detailed report of our evidence synthesis, which will be published in the NHIR Journals Library, as well as peer-reviewed publications in mainstream medical journals, including open access publications. When possible, members of the project team will present the findings of this research at relevant national and international meetings. We will also engage with NICE and relevant organisations involved in the preparation of national and international guidelines (e.g. International Association for the Study of Pain, European League Against Rheumatism, British Society of Rheumatology, American College of Rheumatology, British Psychological Society), prepare press releases and disseminate information through dedicated websites and Twitter accounts. In addition, our established links with influential organisations in this clinical area such as Versus Arthritis and Fibromyalgia Action UK will enable us to work with these groups and disseminate information through their websites.

Project Management

The project will be led by the University of Aberdeen. The project will be managed through a multidisciplinary Steering Group which includes researchers from the Health Services

Research Unit and the Epidemiology Group at the University of Aberdeen, clinician experts from the University of Warwick and the University of Nottingham in the UK, a colleague from the University of Michigan in the USA and a patient partner based in the UK. The Steering Group will be responsible for the strategic leadership of the project, monitoring of progress and ensuring that the project is delivered according to plan. The day-to-day running of the project will be conducted by the Project Management Group (PMG). The Principal Investigator (MB) and three members of the PMG (LA, KG, GJM) are based at the Institute of Applied Health Science (IAHS), University of Aberdeen, which is where the reviewers and information specialist employed on the grant will be based. MB will be responsible for overseeing the management and coordination of the project and for supervising the research staff employed on the grant with support from one-experienced co-applicant (DW), who is currently based at the University of Michigan in the USA. LA has extensive experience conducting network meta-analysis and will be responsible for conducting statistical analyses. KG will be responsible for overseeing the qualitative evidence synthesis and content analysis of patient-reported outcome measures. An Advisory Group, comprising of external clinical experts, methodologists, and patient partners, will be established to provide advice and guidance throughout the project. In particular, the Advisory Group, who will meet three times during the course of the project, will provide advice on important outcomes; assist in the interpretation of the findings of both the quantitative and qualitative evidence syntheses and provide patients' perspectives on pharmacological and non-pharmacological interventions for the management of fibromyalgia-related sleep problems and help to develop appropriate dissemination strategies. The key milestones are presented below.

NIHR 132999 – Project milestones on a month-by-month basis

	2021 Oct	Nov	Dec	2022 Jan	Feb	Mar	Apr	May	June	July	Aug	Sept
Consolidation of Advisory Group												
Development of research protocol												
Registration of research protocol in PROSPERO												
Design of data extraction forms												
Development of search strategies												
Literature searching and screening of search results												
1st Advisory Group meeting												
Assessment of full-text papers for inclusion												
Data extraction and risk of bias assessment												
2nd Advisory Group meeting												
Data analysis												
3rd Advisory Group meeting												
Writing up												
Final revision and format of final report												
Preparation of papers for journal publication												

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APPENDICES

Appendix 1. Medline search strategy for identification of clinical effectiveness evidence

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to October 22, 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 adj3 (disorder$ or problem$ or pattern$ or disturb$ or quality or hygiene or habit? or initiation or dysfunction$ or fragmentat$ or broken or inadequate or insufficient or depriv$)).tw,kf.
8	(wakefulness or waking or awake$ or sleeplessness or insomni$).tw,kf.
9	or/6-8
10	randomized controlled trial.pt.
11	controlled clinical trial.pt.
12	randomized.ab.
13	placebo.ab.
14	drug therapy.fs.
15	randomly.ab.
16	trial.ab.
17	groups.ab.
18	or/10-17
19	exp animals/ not humans/
20	18 not 19
21	5 and 9 and 20

Appendix 2. Analytical approach adopted by the published qualitative meta-synthesis on poor sleep quality experience and self-management strategies in fibromyalgia [excerpt from Climent-Sanz et al. 2020 paper] [(25)]

Section 2.9. Analyzing and Synthesizing Qualitative Findings

The synthesizing process was implemented considering two approaches proposed by Sandelowski and Barroso:[33] the qualitative metasummary, defined as "a quantitatively oriented aggregation of qualitative findings", and the qualitative metasynthesis, that is "an interpretive integration of qualitative findings that are themselves interpretive syntheses of data".[33]

For the qualitative metasummary, we reported the characteristics of the included studies, the frequency of appearance of each of the target findings, the interstudy frequency effect sizes (i.e., representation of sub-themes in individual studies), and the intrastudy intensity effect sizes (i.e., individual studies' contributions to sub-themes).

To metasynthesize the findings, the quotations of adult people diagnosed withFMwere established as the target finding and were imported, structured, and analyzed using the qualitative analysis software Nvivo12 Plus (QRS International, Melbourne, Australia).

In this metasynthesis, we took **the Symptom Management Theory (SMT)[37]** as a **biopsychosocial conceptual framework**. The SMT is a deductive, middle-range theory developed by Larson et al.[38] providing a new model for nurses to assess the patients' symptom experience in a comprehensive and multidimensional manner. Moreover, the SMT is also aimed at providing a framework for the development of symptom management strategies and to evaluate their outcomes in the biological, psychological, and social spheres of the patient.[37,56]

As previously stated, FM is a complex chronic health condition for which curative treatments are currently nonexistent. Therefore, the main approach is focused on developing symptom management strategies that help to alleviate the severity of symptoms such as pain, poor sleep quality, fatigue, and mood disturbances. Because of the latter, a symptom-focused conceptual framework could help us to understand how people diagnosed with FM experience the symptoms that characterize this health condition.

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