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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

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Scientific summary

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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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