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Pharmacological therapies for fibromyalgia (fibromyalgia syndrome) in adults - an overview of Cochrane Reviews (Protocol)

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[Overview of Reviews Protocol]

Pharmacological therapies for fibromyalgia (fibromyalgia syndrome) in adults - an overview of Cochrane Reviews

R Andrew Moore[1], Emma Fisher[2], Winfried Häuser[3], Rae Frances Bell[4], Serge Perrot[5], Julia Bidonde[6], Souzi Makri[7], Sebastian Straube[8]

[1]Plymouth, UK. [2]Cochrane Pain, Palliative and Supportive Care Group, Pain Research Unit, Churchill Hospital, Oxford, UK. [3]Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München, München, Germany. [4]Emerita, Regional Centre of Excellence in Palliative Care, Haukeland University Hospital, Bergen, Norway. [5]Service de Médecine Interne et Thérapeutique, Hôtel Dieu, Université Paris Descartes, INSERM U 987, Paris, France. [6]School of Rehabilitation Science, College of Medicine, University of Saskatchewan, Saskatoon, Canada. [7]Cyprus League Against Rheumatism, Nicosia , Cyprus. [8]Department of Medicine, Division of Preventive Medicine, University of Alberta, Edmonton, Canada

Contact address: R Andrew Moore, andrew.moore@omkltd.org.

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (overview). The objectives are as follows:

To provide an overview of the therapeutic efficacy of pharmacological therapies for fibromyalgia (fibromyalgia syndrome) in adults, and to report on adverse events associated with their use. The major comparison of interest will be with placebo.

BACKGROUND

This protocol is based on a template for Cochrane Reviews of medicines used to relieve pain associated with fibromyalgia syndrome (FMS). The aim is for Cochrane Reviews to use the same or similar methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Appendix 1), and in FMS in particular (Arnold 2012).

Description of the condition

FMS has been defined traditionally as widespread pain that lasts for longer than three months, with pain on palpation at 11 or more of 18 specified tender points (Wolfe 1990). For the International Classification of Diseases ICD-11 of the World Health Organisation WHO, FMS was relocated from its legacy ICD-10 chapter location to a new category block in the Symptoms, signs chapter, as an inclusion term under Chronic Primary Pain (CWP). It is currently coded as an inclusion term under CWP (Code MG30.01). The WHO uses the term fibromyalgia syndrome and not the term fibromyalgia (FM). FMS is defined as a form of CWP (pain in at least 4 of 5 body regions or in at least 3 or 4 body quadrants) associated with sleep disorders, cognitive dysfunction, and somatic symptoms. The symptoms have been present at a similar level for at least three months and are not better accounted for by another diagnosis (Nicholas 2019; World Health Organization 2020).

For a clinical diagnosis, the ACR 1990 classification criteria (Wolfe 1990), the ACR 2010 preliminary diagnostic criteria (Wolfe 2010), the 2011 diagnostic criteria (Wolfe 2011), the 2016 diagnostic criteria (Wolfe 2016), the ACTTION-APS Pain Taxonomy (AAPT) diagnostic criteria (Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION)) public-private partnership with the U.S. Food and Drug Administration (FDA), and the American Pain Society (APS) are used (Arnold 2019). Diagnosis is established by a history of the key symptoms and the exclusion of somatic diseases sufficiently explaining the key symptoms (Häuser 2015). FMS symptoms can be assessed by patient's self-report, via the fibromyalgia criteria and severity scales for clinical and epidemiological studies, a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia, the so-called Fibromyalgia Symptom Questionnaire (Wolfe 2011). The severity of the AAPT criteria of sleep problems or fatigue, or both, are assessed by the physician (Arnold 2019). Clinical guidelines have suggested a clinical work-up with detailed history taking of a FMS-like symptom cluster, complete physical examination and some laboratory tests to screen for somatic diseases which can fully explain FMS-like symptoms and/or might contribute to CWP and fatigue (Fitzcharles 2013, Häuser 2015, Arnold 2019).

A definite aetiology (cause) of this syndrome remains unknown. A model of interacting biological and psychosocial variables in the predisposition, triggering, and development of the chronicity of fibromyalgia symptoms has been suggested (Üceyler 2017). A systematic review of prospective cohort studies in the general population on risk factors of CWP and FMS identified various childhood difficulties (e.g. physical and sexual abuse), female sex (except with pre-existing medical disorders), older/middle age, smoking, high body mass index, alcohol abstinence, and pre-existing medical disorders in adulthood. The strongest associations were with sleep disorders, headaches and other pains, depression, and illness behaviour (Creed 2020). Genome-wide association studies investigated genes potentially involved in FMS pathogenesis highlighting that genetic factors are possibly responsible for up to 50% of the disease susceptibility. Potential candidate genes found associated to FMS are SLC64A4, TRPV2, MYT1L, and NRXN3 (D'Agnelli 2019). Triggering of fibromyalgia symptoms in predisposed persons by inflammatory rheumatic diseases and psychosocial stress (e.g. workplace and family conflicts) is largely ensured whereas the evidence on physical stress (e.g. infections, surgery, accidents) as triggering factors is inconclusive (Häuser 2015).

Several factors are associated with the pathophysiology (functional changes associated with or resulting from disease) of fibromyalgia, but the precise relationship to symptoms of the disorder is unclear (Üceyler 2017). The best established pathophysiological features are those of central sensitisation; that is, augmented pain and sensory processing in the central nervous system (CNS), with increased functional connectivity to pro-nociceptive brain regions and decreased connectivity to antinociceptive regions, and accompanying changes in CNS neurotransmitters as well as the size and shape of brain regions (Cagnie 2017; Clauw 2014). Other findings include sympathetic nervous system dysfunction (Martínez-Martínez 2014), increased pro-inflammatory and reduced anti-inflammatory cytokine profiles (produced by cells involved in inflammation) (Üceyler 2011), and small fibre pathology (Üceyler 2017).

Fibromyalgia is common. A review indicated a global mean prevalence of 2.7% (range 0.4% to 9.3%), and a mean in the Americas of 3.1%, in Europe of 2.5%, and in Asia of 1.7% (Queiroz 2013). Fibromyalgia is more common in women, with a female to male ratio of 3:1 (4.2%:1.4%). Estimates of prevalence in specific populations vary greatly, but have been reported to be as high as 9% in female textile workers in Turkey and 10% in metalworkers in Brazil (59% in those with repetitive strain injury; Queiroz 2013). The change in diagnostic criteria does not appear to have significantly affected estimates of prevalence (Wolfe 2013, Häuser 2021).

The clinical picture (symptoms, disability) of people meeting FMS criteria is heterogenous. FMS can be associated with mental disorders (mainly anxiety and depressive disorders) and other chronic secondary pain syndromes such as inflammatory rheumatic diseases and osteoarthritis (Fitzcharles 2018). Overlap of FMS and various chronic primary pain syndromes is prevalent, too. The U.S. Congress and National Institutes of Health has recommended to use the term Chronic Overlapping Pain Conditions (COPCs) for pain conditions which involve many organ systems: vulvodynia, temporomandibular disorders, myalgic encephalomyelitis/chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, chronic tension-type headache, chronic migraine headache and chronic low back pain (Maixner 2016). Prevalence rates for FMS in these various conditions range from 20% to 65% (Fitzcharles 2018). Mild, moderate and severe forms of FMS can be differentiated (Häuser 2018). Symptom severity and the extent of disability of people with FMS is associated with somatic and psychological comorbidities (Häuser 2015), and occupational characteristics such as physically demanding jobs and work tasks (Palstam 2017). Most people with FMS report high disability levels and poor quality of life, along with extensive use of medical care (Häuser 2015). There is often significant disability, with moderate or severe pain experienced for many years (Bennett 2007).

Fibromyalgia symptoms are known to be difficult to treat effectively, with only a minority of individuals experiencing a clinically-relevant benefit from any one intervention. A range of non-pharmacological and pharmacological interventions is or may be used, depending on the particular clinical situation and licensed indications of medicines.

A stepwise and graduated approach depending on the key symptoms and the extent of disability is recommended by recent clinical guidelines (Macfarlane 2017; Petzke 2017). Guidelines recommend starting with education, defining realistic goals of therapy (improvement of daily functioning), and non-pharmacological therapies such as exercise and psychological therapies though evidence of major effectiveness of these is limited (Geneen 2017; Williams 2020). A multidisciplinary approach, combining pharmacological interventions with physical or cognitive interventions, is advocated for severe forms of FMS (Macfarlane 2017; Petzke 2017). Reasons for preferring non-pharmacological therapies as first line therapies include non-pharmacological therapies having more ubiquitous clinically relevant effects on FMS symptom domains - pain, sleep disturbance, fatigue, affective symptoms (depression/anxiety), functional deficit and cognitive impairment - and less side effects than medications (Perrot 2014). Positive, yet declining effects of non-pharmacological therapies such as cognitive-behavioral therapies (Bernardy 2018), and multicomponent treatments (Arnold 2012), could be demonstrated in follow-ups after the end of treatment.

Conventional analgesics are usually not effective. Treatment is often by so-called pain modulators, such as antidepressants like duloxetine and amitriptyline (Häuser 2013; Lunn 2014; Moore 2012a), or antiepileptics like gabapentin or pregabalin (Cooper 2017; Moore 2009; Üceyler 2013, Wiffen 2013). The proportion of people who achieve worthwhile pain relief even with effective interventions (typically at least a 50% reduction in pain intensity; Moore 2013a), is small, generally only 10% to 15% more than with placebo, with number needed to treat for an additional beneficial outcome (NNTB) usually between 6 and 14 (Wiffen 2013). Those who do experience good levels of pain relief with pregabalin also benefit from substantial improvements in other symptoms, such as fatigue, function, sleep, depression, anxiety, and ability to work, with significant improvement in quality of life (Moore 2010b; Moore 2014a; Straube 2011). Fibromyalgia is similar to other chronic pain conditions in that only a small proportion of trial participants have a good response to treatment (Moore 2013b).

Description of the interventions

The exact number and types of pharmacological therapies that might be used for the treatment of fibromyalgia is not known. Medicines from a number of different classes have been used to treat fibromyalgia in clinical practice, and trials and Cochrane Reviews of efficacy are likely to be found covering the following drug classes:

1. antidepressants (e.g. amitriptyline or other tricyclic antidepressants, duloxetine, milnacipran, mirtazapine);
2. antiepileptics (e.g. gabapentin, pregabalin, topiramate);
3. antipsychotics (e.g. quetiapine);
4. cannabinoids (e.g. nabilone);
5. nonsteroidal anti-inflammatory medicines (NSAIDs, e.g. diclofenac, ibuprofen, naproxen);
6. opioids (e.g. morphine, oxycodone, tramadol).

It is also possible, or even likely, that other pharmacological therapies outside these classes have been tested, and reviews may be available. For the purposes of this overview, we define pharmacological as relating to the use and effects of medicines, and define medicines or medicine as a defined or undefined chemical that is ingested or otherwise introduced into the body.

How the intervention might work

Because of the large range of medicines that might possibly be found for this overview, and because different medicines within a particular class can have different modes of action, no meaningful discussion of how interventions might work is possible here, especially give the unknown aetiology of FMS. As this overview will concentrate on Cochrane Reviews, and each will have its own section on how that particular intervention works, readers are directed to those sections of the individual reviews.

Why it is important to do this overview

The standards used to assess evidence in chronic pain trials have changed substantially, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The most important change is the move from using average pain scores, or average change in pain scores, to the number of people who have a large decrease in pain (by at least 50%) and who continue in treatment, ideally in trials of 8 to 12 weeks or longer. Pain intensity reduction of 50% or more has been shown to correlate with improvements in comorbid symptoms, function, and quality of life for people with chronic pain (Conaghan 2015; Moore 2013a; Peloso 2016), and specifically fibromyalgia (Moore 2010b; Straube 2011).

There is now increasing recognition that results based on a small number of small underpowered studies may well give an incorrect or highly imprecise answer to a clinical question. Many studies in chronic pain have historically been relatively small, and analysis of smaller trials in Cochrane Reviews has been criticised (AlBalawi 2013; Roberts 2015). An analysis on the impact of study size in Cochrane Reviews has highlighted this issue, and pointed out that if two adequately powered studies are available, then omitting all underpowered studies makes little or no difference to the result (Turner 2013). The standard Cochrane 'Risk of bias' assessment does not include size, unless added by authors. Some items, like inconsistency or heterogeneity may be a consequence of small size (IntHout 2015; Turner 2013), but in any event, simulation studies demonstrate that the chances of heterogeneity tests accurately detecting true homogeneity or heterogeneity with a small number of small studies is almost random (Gavaghan 2000). Alternative approaches not available in Review Manager 5 software (Review Manager 2020), may offer a way forward in some circumstances (Kulinskaya 2015). There are potentially large effects of random chance when the numbers of events are small (Flather 1997; Moore 1998; Pogue 1997; Pogue 1998). A simulation exercise suggests that, in most circumstances, a minimum data requirement is 250 to 500 events, such as a participant achieving adequate pain relief (Thorlund 2011).

A 1996 survey indicated that 90% of meta-analyses of analgesic interventions had methodological flaws that could limit their validity, and that meta-analyses of low quality produced significantly more positive conclusions (Jadad 1996a). Even in good quality Cochrane Reviews, the use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) to summarise the certainty of evidence indicates that fewer than 20% of reviews actually have any high quality evidence (Fleming 2016). Judging systematic review quality is difficult. AMSTAR (A MeaSurement Tool to Assess systematic Reviews) is most often used, and a newer version now exists in AMSTAR-2 (Shea 2017). This is a generic tool examining what is regarded as best practice in systematic review methodology, and its use in back pain indicated that 86% of systematic reviews provided low or critically low confidence in their results in cannabis-based medicine reviews for pain (Moore 2020), 90% in exercise therapy for low back pain (Almeida 2020), 99% in bariatrics (Storman 2020), and 100% in spine surgery (Dettori 2020). Cochrane Reviews rated mainly moderate or high confidence (Almeida 2020; Moore 2020).

Beyond the generic, there are also specific criteria important to pain studies, including adequate initial pain for a sensitive assay (Moore 2010a), the importance of patient centred outcomes (Moore 2013a), underestimation of pain by professionals when compared with patients (Seers 2018), and the importance of imputation method in some circumstances (Moore 2012b). These methods have been used for judging the quality of systematic reviews of cannabis-based medicines (Moore 2020).

This overview will examine how Cochrane Reviews of fibromyalgia meet these criteria as well as summarising the current available knowledge. It aims to set high standards and mark a departure from how overview reviews were conducted previously, and inform on how reporting of Cochrane Reviews on fibromyalgia may be improved.

OBJECTIVES

To provide an overview of the therapeutic efficacy of pharmacological therapies for fibromyalgia (fibromyalgia syndrome) in adults, and to report on adverse events associated with their use. The major comparison of interest will be with placebo.

METHODS

Criteria for considering reviews for inclusion

We will include all Cochrane Reviews of pharmacological therapies for the treatment of fibromyalgia in adults. These are likely to involve only randomised, controlled double-blind trials (RCTs), but we will also include those examining non-randomised studies.

Search methods for identification of reviews

We will search the most recent issue of the Cochrane Database of Systematic Reviews (via the Cochrane Library). The search strategy is presented in Appendix 2.

Data collection and analysis

Two review authors will independently select reviews for inclusion, carry out assessments of methodological quality, extract data, analyse data if required, assess how the review authors have used the GRADE criteria and make their own GRADE assessments based on the information provided. Because some of the overview authors are also authors of Cochrane Reviews likely to be included in the overview, care will be taken that any final decisions on any assessments are made by non-conflicted authors of that review. Final assessments will require the agreement of all authors.

Selection of reviews

Included reviews will assess RCTs or non-randomised studies evaluating the effects of any pharmacological intervention given for relief of fibromyalgia pain, compared with placebo or a different active treatment, and provide:

1. details of inclusion and exclusion criteria;
2. details of databases searched and relevant search strategies;
3. patient-reported pain relief; and
4. summary results for at least one desired outcome.

Data extraction and management

We will extract data in the included reviews using a standard piloted data extraction form, using original study reports only if specific data are missing.

We will collect information on:

1. number of included studies and participants;
2. drug, dose, and route of administration;
3. baseline demographic measures, pain, and other measures;
4. any additional methodological information that may be of importance.

We will extract information from randomised studies on risk difference (RD), or risk ratio (RR), and number needed to treat for an additional beneficial outcome (NNTB), number needed to treat to prevent an event (NNTp), and number needed to treat for an additional harmful outcome (NNTH), or calculate these from available data.

We anticipate that reviews may use a variety of outcome measures, with the majority using standard subjective scales (numerical rating scale or visual analogue scale) for pain intensity or pain relief, or both. We are particularly interested in the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008).

These are defined as at least 30% pain relief over baseline (moderate), at least 50% pain relief over baseline (substantial), much or very much improved on Patient Global Impression of Change (PGIC), (moderate), and very much improved on PGIC (substantial). These dichotomous outcomes should be used where pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50%, and with pain not worse than mild (Moore 2013a; O'Brien 2010).

As FMS is a long lasting condition, we will seek outcomes as close as possible to three months (13 weeks) after treatment, the most commonly used duration of clinical trials. We will not use outcomes earlier than one month (four weeks).

Primary outcomes

1. Participant-reported pain relief of 50% or greater (substantial improvement)
2. PGIC very much improved (substantial improvement)
3. Safety: participants experiencing any serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the person, or may require an intervention to prevent one of the above characteristics or consequences
4. Tolerability: withdrawals due to adverse events

Secondary outcomes

1. Participant-reported pain relief of 30% or greater (moderate improvement)
2. PGIC much or very much improved (moderate improvement)
3. Participant-reported sleep problems (continuous outcome: we will prefer composite measures over single item scales)
4. Participant-reported fatigue (continuous outcome: we will prefer composite measures over single item scales)
5. Participant-reported mean pain intensity (continuous outcome: we will prefer change from baseline scores over intensity at the end of the study)
6. Participant-reported health-related quality of life (we will prefer disease-specific instruments such as the Fibromyalgia Impact Questionnaire (FIQ) over generic instruments. If FIQ scores are reported we will calculate the number of participants with a clinically-relevant improvement of 20% or greater
7. Participant-reported negative mood (continuous outcome: we will prefer composite measures such as the Beck Depression Inventory (BDI) or the Hospital Anxiety and Depression (HAD) scale over single item scales)
8. Withdrawals due to lack of efficacy
9. Participants with any adverse event
10. Participants with specific adverse events: somnolence; substantial weight gain; elevated liver enzymes are examples

Assessment of methodological quality of included reviews

Assessment of review quality will be made by a minimum of two authors, with discussion with other authors where necessary to make a consensus determination.

We will assess each included review to determine if it satisfies the criteria specified in the AMSTAR 2 tool for rigorous methodological certainty (Shea 2017). We will also conduct additional validity checks of potential critical importance in the evaluation of analgesic efficacy (Moore 2020). These will include the following.

- Were included studies both randomised and double blind (Jadad 1996b)?
- Did the review use defined diagnostic criteria for fibromyalgia?
- Did the reviews include only studies in which patients made their own assessment of pain? (Professional and patient assessment often disagrees, with professionals significantly underestimating pain (Seers 2018).)
- Did the reviews use studies with defined minimum pain intensity of moderate or severe pain? (Mild pain can reduce the sensitivity of trials to demonstrate an analgesic effect (Moore 2010a).)
- Did the reviews examine study size as a confounding factor in any analysis of efficacy? (Systematic reviews have been criticised for being over-confident of results with inadequate data (AlBalawi 2013; Roberts 2015; Turner 2013); there is increasing evidence of the importance of small trial size, both because of random chance [16,52,76], and as an important source of bias (Dechartres 2013; Dechartres 2014; IntHout 2015; Nüesch 2010).)
- Did the review examine susceptibility to publication bias?
- Did the reviews examine or comment upon imputation methods for missing data as potential source of bias?

We will also investigate two additional criteria not covered by these criteria; these are:

- did the reviews analyse the inclusion and exclusion criteria of the studies and discuss the utility of the study results to the people with fibromyalgia in routine clinical care?
- did the reviews analyse if the studies analysed the impact of the use of rescue medication on study findings?

For each review, we will assess the susceptibility to publication bias by calculating the number of participants in studies with zero effect (RR = 1) that would be needed to give an NNTB too high to be clinically relevant (Moore 2008). In this case, we will use as a cut-off for clinical relevance, NNTB values of 10 and 20 for the outcome of participant reported pain relief of 30% or greater, or 50% or greater. We use this method because statistical tests for presence of publication bias have been shown to be unhelpful (Thornton 2000).

Data synthesis

We will use information on the selected efficacy outcomes to draw up comparisons of analgesic efficacy, using indirect comparisons of different medicines from almost identical clinical trial conditions, with placebo as a common comparator (Glenny 2005; Song 2003). It is known that direct comparison studies are almost completely absent, and probably too small to be of value, but we will note where they impart useful observations.

If the selected efficacy outcomes are not provided in an individual review, wherever possible we will calculate them from the data provided. We plan no further data synthesis. In this unlikely event, outcome data for at least 200 participants will have to be available for any outcome (Moore 1998). Where appropriate we will use or calculate risk ratio (RR) or risk difference (RD) with 95% confidence intervals (CIs) using a fixed-effect model (Morris 1995). We will use or calculate NNTB and NNTH with 95% CIs using the pooled number of events, using the method devised by Cook and Sackett (Cook 1995). We will assume a statistically significant difference from control when the 95% CI of the RR does not include the number one or for the RD the number zero.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE system to assess the certainty of the evidence related to the key outcomes listed in 'Types of outcome measures', as appropriate (Appendix 3). Two review authors will independently rate the certainty of each outcome independently of

any GRADE evaluation in the original reports. We will pay particular attention to how the review authors have used GRADE criteria.

We will pay particular attention to inconsistency, where point estimates vary widely across studies, or CIs of studies showing minimal or no overlap (Guyatt 2011). Small studies have been shown to overestimate treatment effects, probably because the conduct of small studies is more likely to be less rigorous, allowing critical criteria to be compromised (Dechartres 2013; Nüesch 2010), and large studies often have smaller treatment effects (Dechartres 2014).

In addition, there may be circumstances where the overall rating for a particular outcome needs to be adjusted as recommended by GRADE guidelines (Guyatt 2013a; Schünemann 2021). For example, if there are so few data that the results are highly susceptible to the random play of chance, or if studies use last observation carried forward (LOCF) imputation in circumstances where there are substantial differences in adverse event withdrawals, one would have no confidence in the result, and would need to downgrade the certainty of the evidence by three levels, to very low certainty. In circumstances where there are no data reported for an outcome, we will report the level of evidence as very low certainty (Guyatt 2013b).

We will use the following descriptors for levels of evidence (EPOC 2015); substantially different in this context implies a large enough difference that it might affect a decision.

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

We will use the amount and certainty of evidence to report results in a hierarchical way, as has been done previously (Moore 2015; Wiffen 2017). We will split the available information into five groups, essentially according to the GRADE descriptors.

1. Medicines and doses for which Cochrane Reviews found no information (very low-certainty evidence).
2. Medicines and doses for which Cochrane Reviews found inadequate information: fewer than 200 participants in comparisons, in at least two studies (very low-certainty evidence in the review).
3. Medicines and doses for which Cochrane Reviews found evidence of effect, but where results were potentially subject to publication bias. We will consider the number of additional participants needed in studies with zero effect (relative benefit of one) required to change the NNTB for at least 50% maximum pain relief to an unacceptably high level (in this case the arbitrary NNTB of 10) (Moore 2008). Where this number is less than 400 (equivalent to four studies with 100 participants per comparison, or 50 participants per group), we will consider the results to be susceptible to publication bias and therefore unreliable (low-certainty evidence).
4. Medicines and doses for which Cochrane Reviews found no evidence of effect or evidence of no effect: more than 200 participants in comparisons, but where there was no statistically significant difference from placebo (moderate- or high-certainty evidence).
5. Medicines and doses for which Cochrane Reviews found evidence of clinically relevant effect, where results were reliable and not subject to potential publication bias (high-certainty evidence).

'Summary of findings' tables

We will consider creating 'Summary of findings' tables for seven outcomes, if the data allow, and it is considered appropriate (Pollock 2021). The proposed template is in Appendix 4.

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Patrick Welsch, Petra Klose, Sheena Derry, and Philip J Wiffen were authors of the original protocol.

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APPENDICES

Appendix 1. Methodological considerations for chronic pain

There have been several recent changes in how the efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria for what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with 'any improvement'. Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be of longer duration, up to 12 weeks, and longer trials provide a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, and we are now applying stricter criteria for the inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment. To summarise some of the recent insights that must be considered in this new review:

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011a; Moore 2011b), back pain (Moore 2010d), and arthritis (Moore 2010c), as well as in fibromyalgia (Straube 2010); in all cases average results usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.
2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials of less than 12 weeks' duration, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010c); the effect is particularly strong for less effective analgesics,
3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis to 30% in fibromyalgia (Moore 2009; Moore 2010c; Moore 2013b; Moore 2014b; Straube 2008). A Cochrane Review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009).
4. Individual patient analyses of pregabalin studies in fibromyalgia indicate that patients who get good pain relief (moderate or better), have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010b; Moore 2014a).
5. Imputation methods such as last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012b).

Appendix 2. Search strategy

#1 MeSH descriptor: [Fibromyalgia] explode all trees and with qualifier(s): [Drug therapy - DT]

#2 "fibromyalgia":ti (Word variations have been searched)

#3 #1 or #2

Appendix 3. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (Schünemann 2021).

1. **High**: randomised trials; or double-upgraded observational studies
2. **Moderate**: downgraded randomised trials; or upgraded observational studies
3. **Low**: double-downgraded randomised trials; or observational studies
4. **Very low**: triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports

Factors that may decrease the quality level of a body of evidence are:

1. limitations in the design and implementation of available studies suggesting high likelihood of bias;
2. indirectness of evidence (indirect population, intervention, control, outcomes);
3. unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
4. imprecision of results (wide confidence intervals);
5. high probability of publication bias.

Factors that may increase the quality level of a body of evidence are:

1. large magnitude of effect;
2. all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect;
3. dose-response gradient.

Appendix 4. Template Summary of Findings table

Outcomes(follow up; weeks)	Probable outcome with active	Probable outcome with placebo	RR, RD, NNT, NNH, NNTp(95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
Pain relief of 50% or more						
PGIC very much improved						
Serious adverse events						
Withdrawals due to adverse events						
Pain relief of 30% or more						
PGIC much or very much improved						
Withdrawal due to lack of efficacy						

WHAT'S NEW

Date	Event	Description
13 August 2021	New citation required but no major changes	Addition of AMSTAR-2 and pain critical items to evaluations of reviews to be included in this overview. New author team to align with parallel overview review on non-pharmacological interventions. Minor changes in text to bring the protocol in line with current standards and to update with more recent relevant publications. Title updated to include 'fibromyalgia syndrome'.

HISTORY

Protocol first published: Issue 10, 2018

CONTRIBUTIONS OF AUTHORS

RAM, WH, and EF drafted the amended protocol. All authors had input into the protocol development and agreed the final version. RAM is the guarantor.

DECLARATIONS OF INTEREST

RAM: none known; RAM is an author of several Cochrane Reviews of pharmacological interventions for FMS, and in 2021 RAM received an honorarium from Biogen for advice relating to possible future design of randomised trials in diabetic neuropathy.

EF: none known.

WH: none known. WH is a specialist in general internal medicine, psychosomatic medicine and pain medicine, who treats people with FMS. He is a member of the medical board of the German Fibromyalgia Association and of the European Network of Fibromyalgia Associations. He is affiliated with the German Pain Society and is the head of the steering committee of the guideline on FMS of the Association

of the Scientific Medical Societies in Germany. He is member of the steering committee of the European League Against Rheumatism (EULAR) update recommendations on the management of fibromyalgia. He receives royalties from Hypnos Publishers for a CD with medical hypnosis for FMS. He has published systematic reviews and opinions on fibromyalgia pharmacological and non-pharmacological treatment.

RFB: none known.

SP: none known; SP is a specialist in rheumatology and pain medicine, who treats people with FMS. He is a member of the steering committee of the European League Against Rheumatism (EULAR) update recommendations on the management of fibromyalgia. SP has published opinions on fibromyalgia treatment, and is affiliated to the Société Française d'Etude et de Traitement de la Douleur (French Society on Pain; SFTED) that has published recommendations on the treatment of fibromyalgia.

JB: none known.

SM: none known.

SS: none known; SS is a specialist occupational medicine physician and some of the patients he assesses have chronic painful conditions including fibromyalgia.

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