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Thorpe J, Shum B, Moore RA, Wiffen PJ, Gilron I.
Combination pharmacotherapy for the treatment of fibromyalgia in adults.
Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD010585.
DOI: [10.1002/14651858.CD010585.pub2](https://doi.org/10.1002/14651858.CD010585.pub2).

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	4
OBJECTIVES	4
METHODS	4
RESULTS	7
Figure 1.	8
Figure 2.	12
Figure 3.	13
DISCUSSION	24
AUTHORS' CONCLUSIONS	25
ACKNOWLEDGEMENTS	26
REFERENCES	28
CHARACTERISTICS OF STUDIES	34
ADDITIONAL TABLES	58
APPENDICES	59
WHAT'S NEW	61
HISTORY	62
CONTRIBUTIONS OF AUTHORS	62
DECLARATIONS OF INTEREST	62
SOURCES OF SUPPORT	62
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	62
INDEX TERMS	63

[Intervention Review]

Combination pharmacotherapy for the treatment of fibromyalgia in adults

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group

Publication status and date: Edited (no change to conclusions), published in Issue 2, 2020.

Citation: Thorpe J, Shum B, Moore RA, Wiffen PJ, Gilron I. Combination pharmacotherapy for the treatment of fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD010585. DOI: [10.1002/14651858.CD010585.pub2](https://doi.org/10.1002/14651858.CD010585.pub2).

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ABSTRACT

Background

Fibromyalgia is a chronic widespread pain condition affecting millions of people worldwide. Current pharmacotherapies are often ineffective and poorly tolerated. Combining different agents could provide superior pain relief and possibly also fewer side effects.

Objectives

To assess the efficacy, safety, and tolerability of combination pharmacotherapy compared to monotherapy or placebo, or both, for the treatment of fibromyalgia pain in adults.

Search methods

We searched CENTRAL, MEDLINE, and Embase to September 2017. We also searched reference lists of other reviews and trials registries.

Selection criteria

Double-blind, randomised controlled trials comparing combinations of two or more drugs to placebo or other comparators, or both, for the treatment of fibromyalgia pain.

Data collection and analysis

From all studies, we extracted data on: participant-reported pain relief of 30% or 50% or greater; patient global impression of clinical change (PGIC) much or very much improved or very much improved; any other pain-related outcome of improvement; withdrawals (lack of efficacy, adverse events), participants experiencing any adverse event, serious adverse events, and specific adverse events (e.g. somnolence and dizziness). The primary comparison was between combination and one or all single-agent comparators. We also assessed the evidence using GRADE and created a 'Summary of findings' table.

Main results

We identified 16 studies with 1474 participants. Three studies combined a non-steroidal anti-inflammatory drug (NSAID) with a benzodiazepine (306 participants); two combined amitriptyline with fluoxetine (89 participants); two combined amitriptyline with a different agent (92 participants); two combined melatonin with an antidepressant (164 participants); one combined carisoprodol, paracetamol (acetaminophen), and caffeine (58 participants); one combined tramadol and paracetamol (acetaminophen) (315 participants); one combined malic acid and magnesium (24 participants); one combined a monoamine oxidase inhibitor with 5-hydroxytryptophan (200 participants); and one combined pregabalin with duloxetine (41 participants). Six studies compared the combination of multiple agents with each component alone and with inactive placebo; three studies compared combination

pharmacotherapy with each individual component but did not include an inactive placebo group; two studies compared the combination of two agents with only one of the agents alone; and three studies compared the combination of two or more agents only with inactive placebo.

Heterogeneity among studies in terms of class of agents evaluated, specific combinations used, outcomes reported, and doses given prevented any meta-analysis. None of the combinations of drugs found provided sufficient data for analysis compared with placebo or other comparators for our preferred outcomes. We therefore provide a narrative description of results. There was no or inadequate evidence in any comparison for primary and secondary outcomes. Two studies only reported any primary outcomes of interest (patient-reported pain relief of 30%, or 50%, or greater). For each 'Risk of bias' item, only half or fewer of studies had unequivocal low risk of bias. Small size and selective reporting were common as high risk of bias.

Our GRADE assessment was therefore very low for primary outcomes of pain relief of 30% or 50% or greater, PGIC much or very much improved or very much improved, any pain-related outcome, participants experiencing any adverse event, any serious adverse event, or withdrawing because of an adverse event.

Three studies found some evidence that combination pharmacotherapy reduced pain compared to monotherapy; these trials tested three different combinations: melatonin and amitriptyline, fluoxetine and amitriptyline, and pregabalin and duloxetine. Adverse events experienced by participants were not serious, and where they were reported (in 12 out of 16 studies), all participants experienced them, regardless of treatment. Common adverse events were nausea, dizziness, somnolence, and headache.

Authors' conclusions

There are few, large, high-quality trials comparing combination pharmacotherapy with monotherapy for fibromyalgia, consequently limiting evidence to support or refute the use of combination pharmacotherapy for fibromyalgia.

PLAIN LANGUAGE SUMMARY

Combinations of drugs versus single drugs to treat fibromyalgia pain in adults

Bottom line

There is no good evidence to prove or disprove that combining drugs is better than using single drugs for fibromyalgia.

Background

People with fibromyalgia experience constant, widespread pain, sleep problems, and fatigue. Common drugs such as paracetamol (acetaminophen) and ibuprofen are not usually effective. Medicines used to treat epilepsy or depression can sometimes be effective for fibromyalgia and other forms of long-lasting pain where there may be nerve damage. Many individuals with fibromyalgia take many different drugs to deal with pain. We did this review to find the evidence about using combinations of drugs compared to single drugs.

Study characteristics

In September 2017 we searched for clinical trials where combinations of medicines were used for fibromyalgia pain in adults. We found 16 studies evaluating combinations of drugs versus one drug for fibromyalgia pain.

Key results

These studies looked at combinations of all sorts of different drugs, but did not provide enough data to draw any conclusions. Many of the studies did not directly compare a combination of drugs with each single drug. They sometimes compared a combination of medicines with only one of the medicines in the combination, or with only placebo. This limited our ability to make any conclusions.

Most studies did not report any of the outcomes important to people with fibromyalgia. Some studies showed that a combination of drugs is better at reducing pain than one drug alone, but other studies showed that one drug alone is better than a combination of drugs. Other studies did not find any difference between combinations of drugs and single drugs.

Side effects were not severe, and generally were not different between combination therapy and monotherapy.

Quality of the evidence

We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results. Overall, the quality of evidence for important outcomes was very low. None of the combinations of drugs provided enough information for our preferred outcomes. We think that new studies will be very likely to change any conclusions drawn from these studies.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Any combination of two or more drugs compared with placebo or other comparators, or both, for fibromyalgia

Any combination of two or more drugs compared with placebo or other comparators, or both, for fibromyalgia

Patient or population: adults with fibromyalgia

Settings: community

Intervention: any combination of two or more drugs (note: our searches found nine combinations of drugs)

Comparison: placebo and/or other comparators

Outcome	Result	GRADE
Patient-reported pain relief of 30% or greater	No or insufficient data for analysis for any combination of drugs	Very low quality, as no data for analysis
Patient-reported pain relief of 50% or greater	No or insufficient data for analysis for any combination of drugs	Very low quality, as no data for analysis
Patient-reported global impression of clinical change much or very much improved (moderate improvement)	No or insufficient data for analysis for any combination of drugs	Very low quality, as no data for analysis
Any pain-related outcome indicating some improvement	No or insufficient data for analysis for any combination of drugs	Very low quality, as no data for analysis
Participants experiencing any adverse event	No or insufficient data for analysis for any combination of drugs	Very low quality, as no data for analysis
Participants experiencing any serious adverse event	No or insufficient data for analysis for any combination of drugs	Very low quality, as no data for analysis
Withdrawals due to adverse events	No or insufficient data for analysis for any combination of drugs	Very low quality, as no data for analysis

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

BACKGROUND

Description of the condition

Fibromyalgia is a complex, multisystem disorder characterised by a constellation of symptoms including chronic widespread pain lasting longer than three months, sleep disturbance, fatigue, irritable bowel syndrome, depressed mood and cognitive dysfunction. The severe and varied symptoms of fibromyalgia are reflected in functional disability and impaired quality of life (Arnold 2012; Wolfe 2009). While some rheumatologists have thought of fibromyalgia as a specific pain disorder, other investigators have characterised it as a bodily distress syndrome or a physical symptom disorder, or somatoform disorder (Wolfe 2014). It is a heterogeneous condition in which there is abnormal processing of the sensation of pain. The causes are not well understood, but it has features in common with neuropathic pain, including changes in the central nervous system. Moreover, people with neuropathic pain and people with fibromyalgia experience similar sensory phenomena (Koroshetz 2011).

Fibromyalgia is highly prevalent, affecting 3% to 5% of the general population, with a female predominance (Gran 2003; Wolfe 1995). A recent estimate of global mean prevalence of fibromyalgia is 2.7%, with a mean in North America of 3.1%, in Europe of 2.5%, and in Asia of 1.7% (Queiroz 2013). However, estimates can vary depending on specific populations. For example, fibromyalgia prevalence is 9% in female textile workers in Turkey and 10% in metalworkers in Brazil (Queiroz 2013), and as high as 22.2% in people diagnosed with migraine and 39% in people with low back pain (Hüppe 2004). In addition to being personally devastating to the afflicted individual and his or her family, fibromyalgia also exerts a major adverse socioeconomic impact on society (e.g. see Silverman 2009; White 1999).

Fibromyalgia pain is difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical or cognitive interventions, or both. In those treated with pharmacotherapy, the proportion of people who achieve worthwhile pain relief (at least a 50% reduction in pain intensity; Moore 2013a) is generally only 10% to 25% more than with placebo, with numbers needed to treat for an additional beneficial outcome usually between 4 and 10 (Wiffen 2013). Those who do experience good levels of pain relief, however, also benefit from substantial reductions in other symptoms, such as fatigue, function, impaired sleep, depression, anxiety, and impaired ability to work, with significant improvement in quality of life (Moore 2010a; Moore 2014; Straube 2011). Fibromyalgia is not particularly different from other chronic pain in that only a small proportion of trial participants have a good response to treatment (Moore 2013b).

Description of the intervention

Over the past 30 years, hundreds of randomised controlled trials have evaluated a wide variety of pharmacological interventions (e.g. NSAIDs, antidepressants, opioids and anticonvulsants) and non-pharmacological interventions (e.g. exercise, acupuncture and cognitive behavioural therapy) for the treatment of various aspects of fibromyalgia (Clauw 2014; Goldenberg 2004). In addition to exercise and cognitive behavioural therapy, pharmacotherapy remains an important and proven strategy for the management of

fibromyalgia and its associated morbidities. However, adherence to most American College of Rheumatology-recommended drugs is low, suggesting that many people with fibromyalgia are not satisfied with current pharmacotherapy options (Liu 2016). Indeed, current drugs reduce pain by only 25% to 40% on average and meaningful relief occurs in only 40% to 60%, in part due to incomplete drug efficacy and dose-limiting adverse effects (Hauser 2009a; Hauser 2009b; Sultan 2008). Several systematic reviews, using the outcome of at least 50% pain relief in longer-term trials (8 to 14 weeks), indicate that drug-specific response rates are low and numbers needed to treat for an additional beneficial outcome (NNTBs) are high; this is the case with pregabalin (Derry 2016), gabapentin (Cooper 2017), milnacipran (Cording 2015), duloxetine (Lunn 2009; Sultan 2008) and amitriptyline (Moore 2015b). For many drugs, the evidence is limited and does not show any obvious benefit, for example with lacosamide (Hearn 2012). The importance of the outcome of at least 50% pain relief is that good pain reduction also results in improved sleep, fatigue, depression, symptoms, quality of life and work (Moore 2010a; Straube 2011). It is also what people with fibromyalgia want from treatment (O'Brien 2010).

These limitations in clinical practice have led some to hypothesise that a combination of different analgesic drugs acting through different mechanisms may provide superior outcomes compared to monotherapy (Mease 2008). Combining analgesics has proven to produce additive effects in acute pain (Moore 2012a) and possibly also in neuropathic pain (Chaparro 2012).

How the intervention might work

When given as monotherapy, most drugs for fibromyalgia often have intrinsic limitations in their analgesic efficacy, dose-limiting side effects, or both. Combining two or more drugs with different pharmacological mechanisms has the potential to provide additive or possibly even synergistic effects in pain reduction, producing superior outcomes compared to monotherapy, provided that there is less additivity in terms of drug side effects in the combination.

Why it is important to do this review

The appealing rationale for combination pharmacotherapy has led to the practice of polypharmacy in clinical practice. Data indicate that at least 34% of people with fibromyalgia are being prescribed two or more analgesic medications at the same time (Berger 2007). However, given the potential for both pain reduction and drug side effects to be compounded in a drug combination, rigorous combination-specific evidence must exist in order to provide a rationale for the practice of combination pharmacotherapy. The question of whether using two or more drugs together really is better than using any one alone also needs to be answered.

OBJECTIVES

To assess the efficacy, safety, and tolerability of combination pharmacotherapy compared to monotherapy or placebo, or both, for the treatment of fibromyalgia pain in adults.

METHODS

Criteria for considering studies for this review

Types of studies

Double-blind, randomised controlled studies comparing combinations of two or more drugs to placebo or at least one

other comparator, or both, for the treatment of fibromyalgia pain. Studies must include pain assessment as a primary or secondary outcome. We required full journal publications or summary clinical trial reports, and excluded brief abstracts. We also excluded non-randomised studies, case reports and other clinical observations.

Types of participants

Adult participants (18 years and older) with a diagnosis of fibromyalgia.

Types of interventions

Combinations of two or more different drugs administered by any route.

Types of outcome measures

Studies needed to report pain assessment as either the primary or secondary outcome.

We anticipated that a variety of outcome measures would have been used in the studies. We expected that the majority of studies would use standard subjective scales for pain intensity or pain relief, or both, and we paid particular attention to 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).

Primary outcomes

- Patient-reported pain relief of 30% or greater
- Patient-reported pain relief of 50% or greater
- Patient-reported global impression of clinical change (PGIC) much or very much improved
- Patient-reported global impression of clinical change (PGIC) very much improved

Secondary outcomes

- Any pain-related outcome indicating some improvement
- Participants experiencing any adverse event
- Participants experiencing any serious adverse event
- Withdrawals due to adverse events
- Withdrawals due to lack of efficacy
- Specific adverse events, particularly somnolence and dizziness

Search methods for identification of studies

Electronic searches

We searched the following databases for studies:

- Cochrane Central Register of Controlled Trials (CENTRAL Issue 8 of 12, 2017, via *The Cochrane Library*)
- MEDLINE & MEDLINE in Process (via Ovid) 1946 to 5/9/17;
- Embase (via Ovid) 1974 to 2017 week 36.

The search strategies used can be found in [Appendix 1](#). There were no language or date restrictions applied to the searches.

Searching other resources

We searched ISCRTN Registry (<https://www.isrctn.com>), and clinicaltrials.gov (www.clinicaltrials.gov) in September 2017 and the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) in September 2017 to identify additional completed or ongoing studies. We also searched the reference lists of published reviews on the subject of fibromyalgia pharmacotherapy for eligible clinical trials.

Data collection and analysis

Selection of studies

We determined study eligibility by reading each study identified by the search. Two review authors read all citations independently and reached agreement by discussion. We did not anonymise the studies before assessment.

Data extraction and management

Two review authors (JT and IG) extracted data using a standard form and double-checked for agreement before entry into Review Manager 5 (RevMan 5) or completing any other analysis (RevMan 2014). We included information about the pain condition and number of participants treated, drugs and dosing regimens, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals and adverse events (participants experiencing any adverse event or serious adverse event).

Assessment of risk of bias in included studies

Two review authors (JT and IG) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and adapted from those used by Cochrane Pregnancy and Childbirth, with any disagreements resolved by discussion. We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (i.e. any truly random process, for example random number table; computer random number generator); unclear risk of bias (when the method used to generate the sequence is not clearly stated). We excluded studies at a high risk of bias that used a non-random process (for example, odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (for example, telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (when method is not clearly stated). We excluded studies that did not conceal allocation and were therefore at a high risk of bias (for example, open list).
- Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (e.g. study states that it was blinded and

describes the method used to achieve blinding, for example, identical tablets, matched in appearance and smell); or unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved). We excluded studies at a high risk of bias that were not double-blind.

- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind outcome assessors as to which intervention participants received. We assessed the methods as: low risk of bias (e.g. study states that data collectors were blinded to allocation, or outcome measures being assessed were objective and not subject to bias); or unclear risk of bias (it was unclear and not stated anywhere that the outcome assessors were blinded to treatment allocation). We excluded studies with a high risk of bias for outcome assessment.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (i.e. less than 10% of participants did not complete the study or used 'baseline observation carried forward' (BOCF) analysis, or both); unclear risk of bias (used 'last observation carried forward' (LOCF) analysis); or high risk of bias (used 'completer' analysis).
- Selective reporting (checking for possible reporting bias). We assessed studies for reporting bias by determining how closely the published reports matched with protocols on registered databases. We assessed this as: low risk of bias (study protocol was registered and all outcomes listed appeared in the published report); unclear risk of bias (study protocol was not registered so no assessment could be made); or high risk of bias (study protocol was registered and there were some discrepancies between outcomes in the protocol and the published report).
- Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (i.e. 200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); or high risk of bias (fewer than 50 participants per treatment arm). 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).
- Trial duration (checking for possible biases confounded by short trial lengths). We assessed studies as being at low risk of bias (at least seven weeks' duration); unclear risk of bias (three to six weeks' duration); or high risk of bias (less than three weeks' duration).
- Similarities of baseline characteristics. We assessed studies as being at low risk of bias (no statistically significant differences in baseline measures of sex ratio, average age, or pain scores between groups); unclear risk of bias (no statistical comparison reported in baseline measures of sex ratio, average age, and/or pain scores between groups); high risk of bias (there was a statistical difference between groups at baseline for sex ratio, average age, and/or pain scores).

Measures of treatment effect

The primary comparison of interest was between the combination of study drug(s) and any or all single-agent comparators. We also considered comparisons of each drug combination and any other

placebo or active treatment comparators, or both. We planned to combine studies if they evaluated the same drug class combination at roughly similar doses and durations of treatment. We planned to perform any analyses of study data for binary outcomes using RevMan 5.

We planned to calculate NNTB as the reciprocal of the absolute risk reduction (ARR) (McQuay 1998). For unwanted effects, this number becomes the number needed to treat for an additional harmful outcome (NNTH) and is calculated in the same manner. We planned to use dichotomous data to calculate risk ratio (RR) with 95% confidence intervals (CI) using a fixed-effect model unless we found significant statistical heterogeneity. We did not plan to use continuous data in any analyses.

Unit of analysis issues

In studies involving more than one active treatment group, we planned to divide the control treatment group among active treatment arms.

Dealing with missing data

We planned to use intention-to-treat (ITT) analysis where the ITT population consisted of participants who were randomised, took at least one dose of the assigned study medication and provided at least one post-baseline assessment. Missing participants were to be assigned zero improvement.

Assessment of heterogeneity

We planned to only combine studies evaluating similar conditions for analysis, so as to avoid clinical heterogeneity. We planned to use visual data assessment with L'Abbé plots (L'Abbé 1987) and calculation of the I^2 statistic (Higgins 2003) to explore statistical heterogeneity when the I^2 statistic was greater than 50%.

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility (Moore 2010a). The review did not depend on what authors of the original studies chose to report or not, though we anticipated difficulties with studies failing to report any dichotomous results. We extracted continuous data, which probably poorly reflect efficacy and utility, and therefore used them for illustrative purposes only. We planned to undertake assessment of publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean a NNTB or NNTH of 10 or higher) (Moore 2008).

Data synthesis

We planned to use a fixed-effect model for any conducted meta-analyses. However, if it were deemed appropriate to combine heterogeneous studies, we planned to use a random-effects model.

At least 200 participants would have to be available for any outcome before we pooled studies (Moore 1998). Where appropriate we used or calculated risk ratio (RR) or risk difference (RD) with 95% confidence intervals (CI) using a fixed-effect model (Morris 1995). We used or calculated NNTB and NNTH with 95% CIs using the pooled number of events, using the method devised by Cook and Sackett (Cook 1995). We assumed a statistically significant difference from control when the 95% CI of the RR did not include 1 or the RD, 0.

Quality of the evidence

We used the GRADE approach to assess the quality of evidence related to each of the key outcomes, and reported our judgement on the quality of the evidence in the 'Summary of findings' table (Schünemann 2011b; Appendix 2). We assessed potential for publication bias, based on the amount of unpublished data required to make the result clinically irrelevant (Moore 2008).

We decreased the grade rating by one (-1) or two (-2) (up to a maximum of -3 to 'very low') if we identified:

- serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1);
- high probability of reporting bias (-1).

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

'Summary of findings' table

We included a 'Summary of findings' table as set out in the Cochrane Pain, Palliative and Supportive Care (PaPaS)

author guide (PaPaS 2012), and recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a). We planned to include, where possible, outcomes equivalent to moderate or substantial benefit of at least 30% and at least 50% pain-intensity reduction, PGIC (at least moderate improvement) (Dworkin 2008), any pain-related outcome indicating some improvement, participants experiencing any adverse event, participants experiencing any serious adverse event, and withdrawals due to adverse events.

Subgroup analysis and investigation of heterogeneity

We grouped studies according to specific combinations of drug classes (e.g. opioids and anticonvulsants).

Sensitivity analysis

We did not plan any sensitivity analyses because the evidence base was known to be too small to allow reliable analysis.

RESULTS

Description of studies

Results of the search

After excluding duplicates, we identified 723 citations using the search criteria outlined in the protocol. Two authors (IG and JT) independently applied the inclusion/exclusion criteria to all 723 citations, resulting in 57 studies that we scrutinised in more detail. Of these 57 citations, 16 studies fulfilled the inclusion criteria for this review (Figure 1).

Figure 1. Flow diagram

Figure 1. (Continued)

We searched clinicaltrials.gov, controlled-trials.com, and the WHO International Clinical Trials Registry Platform for ongoing or recently completed combination fibromyalgia studies using a comparable search strategy. This search only resulted in three potentially relevant studies ([NCT00991848](#); [NCT01323374](#); [NCT01850420](#)). No results for any of these studies were available at the time of this review. Study details are provided in the [Characteristics of ongoing studies](#) table.

Included studies

Study selection

Sixteen studies met our criteria for inclusion in this systematic review.

- Three studies (306 participants randomised) involved a combination of an NSAID with a benzodiazepine ([Kravitz 1994](#); [Quijada-Carrera 1996](#); [Russell 1991](#)).
- Two studies (89 participants randomised) evaluated amitriptyline combined with fluoxetine ([Goldenberg 1996](#); [Zucker 2006](#)).
- Two studies (92 participants randomised) compared amitriptyline with a drug from a different class of medication (naproxen: [Goldenberg 1986](#); lidocaine: [Vlainich 2010](#)).
- Two studies (164 participants randomised) evaluated the effects of melatonin combined with an antidepressant ([de Zanette 2014](#); [Hussain 2011](#)).
- One study (58 participants randomised) evaluated the combination of carisoprodol, paracetamol (acetaminophen), and caffeine ([Vaeroy 1989](#)).
- One study (315 participants randomised) assessed the combination of tramadol with paracetamol (acetaminophen) ([Bennett 2003](#)).
- One study (24 participants randomised) combined malic acid with magnesium ([Russell 1995](#)).
- One study (200 participants randomised) combined a monoamine oxidase inhibitor (MAOI) with 5-hydroxytryptophan (5-HTP) ([Nicolodi 1996](#)).

- One study (41 participants randomised) combined pregabalin with duloxetine ([Gilron 2016](#)).

Most studies (nine) diagnosed fibromyalgia using the 1990 ([Wolfe 1990](#)) American College of Rheumatology (ACR) guidelines ([Bennett 2003](#); [Gilron 2016](#); [Goldenberg 1996](#); [Hussain 2011](#); [Nicolodi 1996](#); [Quijada-Carrera 1996](#); [Russell 1995](#); [Vlainich 2010](#); [Zucker 2006](#)). One study used the updated 2010 ([Wolfe 2010](#)) ACR classification guidelines ([de Zanette 2014](#)). Two studies used older criteria for diagnosing fibromyalgia from [Yunus 1981](#) ([Goldenberg 1986](#); [Kravitz 1994](#)). Participants in one study met the criteria outlined in both [Yunus 1981](#) and [Smythe 1979](#) ([Vaeroy 1989](#)). One study reported the proportion of their study population who met the 1990 ACR fibromyalgia diagnostic criteria (> 87%), and criteria outlined in [Yunus 1981](#) (> 97%), [Wolfe 1985](#) (> 97%), [Smythe 1977](#) (88%), and [Campbell 1983](#) (88%) ([Russell 1991](#)).

See [Characteristics of included studies](#) table for full characteristics of all included studies.

Study design

See [Table 1](#) for information on study methodology. There are 16 included studies, with a total of 1474 participants randomised.

Ten of the 16 included studies used a parallel study design ([Bennett 2003](#); [de Zanette 2014](#); [Goldenberg 1986](#); [Hussain 2011](#); [Kravitz 1994](#); [Nicolodi 1996](#); [Quijada-Carrera 1996](#); [Russell 1991](#); [Vaeroy 1989](#); [Vlainich 2010](#)). Three studies used a cross-over design ([Gilron 2016](#); [Goldenberg 1996](#); [Russell 1995](#)). The remaining study was designed as a series of individual N-of-1 trials (i.e. involving multicross-over combinations) ([Zucker 2006](#)). Two studies included an open-label component after a double-blind phase ([Russell 1991](#); [Russell 1995](#)).

One study assessed the combination of three different agents ([Vaeroy 1989](#)), while the remaining 13 studies assessed the combination of two drugs ([Bennett 2003](#); [de Zanette 2014](#); [Gilron 2016](#); [Goldenberg 1986](#); [Goldenberg 1996](#); [Hussain 2011](#); [Kravitz 1994](#); [Nicolodi 1996](#); [Quijada-Carrera 1996](#); [Russell 1991](#); [Russell 1995](#); [Vlainich 2010](#); [Zucker 2006](#)). Nine studies involved the

comparison of the combination with each drug alone (de Zanette 2014; Gilron 2016; Goldenberg 1986; Goldenberg 1996; Hussain 2011; Kravitz 1994; Nicolodi 1996; Quijada-Carrera 1996; Russell 1991). Six of these nine studies also included a placebo-only comparator group (Gilron 2016; Goldenberg 1986; Goldenberg 1996; Kravitz 1994; Quijada-Carrera 1996; Russell 1991), and one of these nine studies also had a treatment arm that received a different single drug that was not part of the combination arm (Nicolodi 1996). Three studies compared a combination of drugs to a placebo only (Bennett 2003; Russell 1995; Vaeroy 1989). Two studies compared the combination of two drugs to only one of the drugs alone (Vlainich 2010; Zucker 2006). All but one study used medications in tablet or capsule form, taken orally; Vlainich 2010 administered one agent orally and one agent intravenously.

Permitted concomitant analgesic medications

One study did not specify whether concomitant medications were permitted during the trial (Nicolodi 1996).

Three studies did not permit the use of concomitant analgesic medications (Hussain 2011; Quijada-Carrera 1996; Vlainich 2010). Hussain 2011 excluded participants if they were taking analgesics, anti-inflammatories, or antioxidants such as aspirin. While Vlainich 2010 did not provide details on concomitant medications, in a subsequent overlapping publication containing some of the same data, the authors describe the exclusion of participants if they had used any analgesics with a central nervous system action such as antidepressants, anticonvulsants, opioids, or neuroleptics within four weeks of study enrolment (Vlainich 2011). However, neither Vlainich 2010 nor Hussain 2011 explicitly stated that additional medications were not permitted during the trial. Quijada-Carrera 1996 required participants to discontinue psychotropic drugs, analgesics, and NSAIDs for at least three weeks before study enrolment, and excluded participants from efficacy analyses if they took any of these prohibited medications during the trial. Participants were permitted to take paracetamol (acetaminophen) during the wash-out period only.

Russell 1991 permitted paracetamol (acetaminophen) during a two-week washout period before the study start. Four studies permitted the use of paracetamol (acetaminophen) only (Goldenberg 1986; Goldenberg 1996; Russell 1995; Zucker 2006). Most participants in Goldenberg 1986 and Russell 1995 did not take paracetamol (acetaminophen) during the trial; the number of participants taking paracetamol (acetaminophen) is not reported in Goldenberg 1996 or Zucker 2006. One study permitted participants to take any medication needed, and compared the use of additional drugs (defined as at least one tablet daily for three consecutive days) between treatment groups (Vaeroy 1989). Ten of 23 participants in the placebo group and none of 20 participants in the combination group used tricyclic antidepressants, anxiolytics, or sedatives, while 13 of 23 participants in the placebo group and four of 20 participants in the combination group used analgesics for pain relief; the most frequently used medication was paracetamol (acetaminophen).

Bennett 2003 permitted the use of either a low-dose selective serotonin reuptake inhibitors (SSRI) or St. John's wort, and also allowed the use of one of the sedatives zolpidem or flurazepam; however, use was restricted to participants who had been on steady doses for at least one month prior to study enrolment. Thirty of 156 participants in the combination group and 26 of 157

participants in the placebo group took an SSRI for depression; the primary outcome result did not change when these participants were included or excluded in analyses. Two studies permitted the use of NSAIDs, paracetamol (acetaminophen), or opioids (de Zanette 2014; Gilron 2016). de Zanette 2014 permitted participants to remain on analgesic medications provided these drugs were not adjusted during the study. Additionally, all participants could use paracetamol (acetaminophen), ibuprofen, Dorflex® (35 mg orfenadrine citrate, 300 mg dipyron, 50 mg caffeine), codeine, or tramadol. Within three months of study enrolment, 50 of 63 participants had used paracetamol (acetaminophen)/dipyron, 26 of 63 had used an NSAID, and 1 of 63 had used an opioid regularly. During the study, 42 of 63 participants were taking an antidepressant, five of 63 were taking an anticonvulsant, and seven of 63 were taking a benzodiazepine. Treatment groups did not differ significantly in their use of analgesics. Gilron 2016 permitted participants to use NSAIDs, paracetamol (acetaminophen), and/or opioids at a stable dose throughout the trial. Ten of 24 participants took paracetamol (acetaminophen), 11 of 41 participants took NSAIDs, 1 of 41 took codeine, 2 of 41 took baclofen, 2 of 41 took methocarbamol, and 1 of 41 took glucosamine.

Study outcomes

Seven studies did not specify a primary outcome versus a secondary outcome (Goldenberg 1986; Hussain 2011; Kravitz 1994; Nicolodi 1996; Russell 1991; Vaeroy 1989; Vlainich 2010).

- All 16 studies reported pain scores, 12 of which used visual analogue scales (VAS) (Bennett 2003; de Zanette 2014; Goldenberg 1986; Goldenberg 1996; Hussain 2011; Kravitz 1994; Nicolodi 1996; Quijada-Carrera 1996; Russell 1991; Russell 1995; Vaeroy 1989; Zucker 2006), and two of which used numerical rating scales (Gilron 2016; Vlainich 2010) for pain. Most studies also reported other indices of pain or discomfort, including the number of tender points or tender points index (Bennett 2003; Gilron 2016; Goldenberg 1986; Goldenberg 1996; Kravitz 1994; Quijada-Carrera 1996; Russell 1991; Russell 1995; Vlainich 2010; Zucker 2006), duration or presence/absence of morning stiffness (Quijada-Carrera 1996; Russell 1991; Vlainich 2010), myalgic score (Bennett 2003), pressure pain threshold at various tender points (de Zanette 2014; Russell 1991; Russell 1995; Vaeroy 1989), pain relief (Bennett 2003; Gilron 2016; Kravitz 1994), pain reduction during the conditioned pain modulation task (de Zanette 2014), and VAS scores for general feeling of sickness (Vaeroy 1989). One study reported the cumulative time to discontinuation from study participation (Bennett 2003).
- Nine studies included an assessment of sleep quality (Bennett 2003; de Zanette 2014; Gilron 2016; Goldenberg 1986; Goldenberg 1996; Hussain 2011; Quijada-Carrera 1996; Vaeroy 1989; Zucker 2006), and one study measured fatigue and sleep disorders as present/absent at baseline versus after treatment (Vlainich 2010).
- One study assessed physical activity (Kravitz 1994).
- Nine studies included several other secondary outcomes including the Fibromyalgia Impact Questionnaire (FIQ) (Bennett 2003; de Zanette 2014; Gilron 2016; Goldenberg 1996; Hussain 2011; Zucker 2006), the Brief Pain Inventory (Gilron 2016), the Short Form McGill Pain Questionnaire (SF-MPQ) (Gilron 2016), the Beck Depression Inventory (Gilron 2016; Goldenberg 1996; Kravitz 1994), the Center for Epidemiologic Studies Depression Scale (Russell 1991; Russell 1995), the Hamilton Depression

Scale (Russell 1991), the Hamilton Anxiety Rating Scale (Kravitz 1994; Russell 1991), the Beck Anxiety Inventory (Gilron 2016), the Health Assessment Questionnaire (Russell 1991; Russell 1995), the Short-Form (36) Health Survey (SF-36) (Bennett 2003; Gilron 2016), the Hassles Scale (Russell 1995), and the Medical Outcomes Study Sleep Scale (Gilron 2016).

- Eight studies recorded the number of adverse events/side effects (Bennett 2003; Gilron 2016; Goldenberg 1996; Kravitz 1994; Nicolodi 1996; Russell 1991; Vaeroy 1989; Zucker 2006).
- One study assessed the presence/absence of subjective edema, paresthesia, and headache before and after treatment (Vlainich 2010)
- Three studies reported the number of participants taking various concomitant analgesics in addition to study drugs during the trial (de Zanette 2014; Gilron 2016; Vaeroy 1989).
- Six studies included a global assessment or improvement score, or both (Goldenberg 1986; Goldenberg 1996; Kravitz 1994; Quijada-Carrera 1996; Russell 1991; Zucker 2006).
- Finally, one study quantified blood levels of brain-derived neurotrophic factor (de Zanette 2014).

Excluded studies

We excluded 37 studies. A justification for each full-text study that we excluded can be seen in the [Characteristics of excluded studies](#) table. Briefly, we excluded all single-blind (Qin 2009), add-

on (Cuatrecasas 2007; Cuatrecasas 2011; Cuatrecasas 2012; Farmer 2010; Holman 2005; Leader 2009; Potvin 2012; Rico-Villademoros 2009; Vilchez 2009), non-randomised (Zborovsky 1994), and open-label studies (Bagis 2013; Calandre 2007; Calandre 2011; Cantini 1994; Cantini 1995; Cuatrecasas 2007; Farmer 2010; Fossaluzza 1992; Leader 2009; Lister 2002; Mease 2013; Ramzy 2017; Rico-Villademoros 2009; Settel 1967; Vilchez 2009), as well as all studies involving a non-drug therapy such as acupuncture, Chinese herbal medicine, botulinum toxin, and vitamins or other micronutrients (Ali 2009; Jacobs 1990; Lange 2011; Lister 2002; Porta 1999; Porta 2000; Zhao 2009), studies whose populations did not consist solely of those with fibromyalgia (Choi 2015; Le Gallez 1988; Porta 1999; Porta 2000; Szirmai 1974). The [Characteristics of excluded studies](#) table gives reasons for exclusions.

We identified two secondary publications of data in included studies (Bennett 2003; Vlainich 2011).

Risk of bias in included studies

Two review authors (JBT and IG) independently evaluated each study using the Cochrane 'Risk of bias' tool (Higgins 2011b). The risk ratings for each source of potential bias in included studies are shown in [Figure 2](#), and the percentage of studies falling into each risk rating category (low, unclear, and high) for each source of potential bias is shown in [Figure 3](#). Details and justification for each rating are included in the [Characteristics of included studies](#) table.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Size of study	Trial Duration	Similarities of Baseline Characteristics
Albertoni Giraldes 2016	+	?	?	?	?	+	?	?	?
Bennett 2003	?	+	+	+	+	?	?	+	+
de Zanette 2014	?	+	+	+	+	+	-	?	-
Gilron 2016	+	+	+	+	+	+	-	?	+
Goldenberg 1986	?	?	?	?	+	?	-	?	?
Goldenberg 1996	+	+	+	+	?	?	-	?	+
Hussain 2011	?	?	?	?	?	-	-	+	?
Kravitz 1994	?	?	?	?	?	-	-	?	?
Nicolodi 1996	?	?	?	?	?	-	?	+	?
Pridgen 2017	?	+	+	+	?	+	?	+	?

Figure 2. (Continued)

Pridgen 2017	?	+	+	+	?	+	?	+	?
Quijada-Carrera 1996	+	?	?	?	-	?	-	+	+
Russell 1991	?	?	+	+	+	?	-	?	?
Russell 1995	?	?	+	?	?	?	-	?	+
Vaeroy 1989	?	?	+	+	?	?	-	+	?
Vlainich 2010	+	?	?	?	+	-	-	?	+
Zucker 2006	+	+	?	?	+	?	-	?	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Allocation

Only five studies reported randomisation methods (Gilron 2016; Goldenberg 1996; Quijada-Carrera 1996; Vlainich 2010; Zucker 2006), and only five studies reported the method of allocation concealment (Bennett 2003; de Zanette 2014; Gilron 2016; Goldenberg 1996; Zucker 2006).

Blinding

Only seven studies gave appropriate detail on how participants and personnel were blinded (Bennett 2003; de Zanette 2014; Gilron

2016; Goldenberg 1996; Russell 1991; Russell 1995; Vaeroy 1989). We classified seven studies as having an unclear risk of bias for participant and personnel blinding (Goldenberg 1986; Hussain 2011; Kravitz 1994; Nicolodi 1996; Quijada-Carrera 1996; Vlainich 2010; Zucker 2006).

Eight studies did not describe in appropriate detail how outcome assessment was protected from bias by blinding (Goldenberg 1986; Hussain 2011; Kravitz 1994; Nicolodi 1996; Quijada-Carrera 1996; Russell 1995; Vlainich 2010; Zucker 2006). We rated six studies as

having low detection bias (Bennett 2003; de Zanette 2014; Gilron 2016; Goldenberg 1996; Russell 1991; Vaeroy 1989).

Incomplete outcome data

We judged six studies to have an unclear risk of bias for incomplete outcome data (Goldenberg 1996; Hussain 2011; Kravitz 1994; Nicolodi 1996; Russell 1995; Vaeroy 1989). Of these studies, two did not mention whether or not there was any attrition of study participants (Hussain 2011; Nicolodi 1996). The remaining studies did describe the number of withdrawals with varying levels of detail; however, questions remained due to lack of reporting of the final sample size (Goldenberg 1996; Russell 1995), sample sizes that appeared inconsistent with the number of reported study withdrawals (Goldenberg 1996; Kravitz 1994; Russell 1995), and lack of detail about which treatment participants were on when they withdrew from the trial (Russell 1995; Vaeroy 1989). Seven studies had a low risk for attrition bias (Bennett 2003; de Zanette 2014; Gilron 2016; Goldenberg 1986; Russell 1991; Vlainich 2010; Zucker 2006), while we rated one study as having a high risk for attrition bias due to uneven withdrawal rates between treatment groups (Quijada-Carrera 1996).

Selective reporting

Eleven studies did not have registered protocols (Bennett 2003; Goldenberg 1986; Goldenberg 1996; Hussain 2011; Kravitz 1994; Nicolodi 1996; Quijada-Carrera 1996; Russell 1991; Russell 1995; Vaeroy 1989; Zucker 2006). Eight of these studies had an unclear risk of bias for this reason (Bennett 2003; Goldenberg 1986; Goldenberg 1996; Russell 1991; Russell 1995; Vaeroy 1989; Zucker 2006) or because of a lack of information to allow for a determination (Quijada-Carrera 1996). Three studies had registered protocols (de Zanette 2014; Gilron 2016; Vlainich 2010). The protocols did not differ in significant ways from the published reports of two of these studies, and we therefore rated them as having a low risk of bias (de Zanette 2014; Gilron 2016). Four studies had a high risk of bias for selective reporting, due to one or more of the following: inappropriate statistical analyses, data interpretation not supported by the statistical analyses performed, lack of detail about outcome measures in the methods section, and outcome measures discussed in the methods section for which no data were shown (Hussain 2011; Kravitz 1994; Nicolodi 1996; Vlainich 2010).

Size of study

We assessed all included studies for risk of bias in terms of sample size. Most studies had very small sample sizes, with fewer than 50 participants per arm (de Zanette 2014; Gilron 2016; Goldenberg 1986; Goldenberg 1996; Hussain 2011; Kravitz 1994; Quijada-Carrera 1996; Russell 1991; Russell 1995; Vaeroy 1989; Vlainich 2010; Zucker 2006) and we therefore classified them as having a high risk of bias. Two studies had 50 to 199 participants per arm and we therefore classified them as unclear risk (Bennett 2003; Nicolodi 1996).

Trial duration

We assessed all included studies for risk of bias in terms of trial length (Moore 2010b). No trials were shorter than four weeks in duration. Nine studies had treatment period durations of three to six weeks, falling into the unclear risk category (de Zanette 2014; Gilron 2016; Goldenberg 1986; Goldenberg 1996; Kravitz 1994; Russell 1991; Russell 1995; Vlainich 2010; Zucker 2006). We

classified five studies as low risk in terms of trial duration, with treatment periods of at least seven weeks (Bennett 2003; Hussain 2011; Nicolodi 1996; Quijada-Carrera 1996; Vaeroy 1989).

Similarities of baseline

We also assessed all included studies for risk of bias with respect to similarities in age, sex ratio, and pain scores at baseline between groups. Seven studies had a low risk of bias for similarities of baseline characteristics, with age, sex ratio, and pain scores at baseline being statistically similar between groups (Bennett 2003; Gilron 2016; Goldenberg 1996; Quijada-Carrera 1996; Russell 1995; Vlainich 2010; Zucker 2006). Six studies had an unclear risk of bias for similarities of baseline characteristics because comparisons were not made between treatment groups for age, sex ratio, and/or pain scores (Goldenberg 1986; Hussain 2011; Kravitz 1994; Nicolodi 1996; Russell 1991; Vaeroy 1989). One study had a high risk of bias for similarities of baseline characteristics because one treatment group had significantly higher baseline pain scores than the other treatment groups (de Zanette 2014).

Effects of interventions

See: **Summary of findings for the main comparison** Any combination of two or more drugs compared with placebo or other comparators, or both, for fibromyalgia

None of the combinations of drugs found provided sufficient data for analysis compared with placebo or other comparators for our preferred outcomes. We therefore provide a narrative description of results.

Our GRADE assessment for all outcomes found very low-quality evidence. At a minimum, there were few or no results for analysis, and there were frequently other risk of bias issues in addition (Summary of findings for the main comparison).

NSAIDs combined with benzodiazepines

Three trials combined an NSAID with a benzodiazepine (Kravitz 1994; Quijada-Carrera 1996; Russell 1991).

Kravitz 1994 compared the combination of alprazolam and ibuprofen to each drug on its own and to a double placebo in a four-group, parallel-design, five-week study. The study randomised 64 participants and conducted analyses on the 61 participants who completed at least one week on treatment (the evaluable cohort), and on the 45 participants who completed all five weeks on the study drug.

Russell 1991 also evaluated the effects of alprazolam and ibuprofen, alone and in combination, along with a double-placebo treatment in a six-week, four-group, parallel-design study. The study randomised 78 participants; they included 76 in the safety analysis, and the 63 participants who completed the trial were included in the efficacy analysis.

Quijada-Carrera 1996 compared the effects of tenoxicam and bromazepam alone and in combination in a four-group, placebo-controlled, parallel-design, eight-week trial. The study randomised 164 participants and analyzed them on an ITT basis; 134 participants completed at least three weeks of treatment and were also analyzed separately.

Kravitz 1994

Patient-reported pain relief of 30% or greater

No results were reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported pain relief of 50% or greater

No results were reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much or very much improved

No results were reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

No results were reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes of interest that were reported on in this study were VAS pain scores, VAS pain relief scores, number of tender points, global improvement from baseline, withdrawals due to lack of efficacy, participants experiencing any adverse event, withdrawals due to adverse events and specific adverse events, particularly somnolence and dizziness. Serious adverse events were not reported.

When comparing VAS pain scores of the 45 study completers between groups for each week in the trial, there were no significant differences. In the evaluable cohort, VAS pain relief scores were significantly different in weeks four and five, with the alprazolam group having significantly higher relief scores compared to the double placebo at both weeks, and compared to the combination group at week four.

Only at week four was there a statistically significant difference in the number of tender points, with the ibuprofen- and alprazolam-alone groups having significantly fewer tender points than the combination and placebo groups.

No statistically significant differences were seen in either clinician-rated or self-rated global improvement scores at any week during the study. However, only those participants who completed all five weeks of the study had clinical global improvement scores indicating much or very much improved (score of 1 or 2).

While not statistically significant, clinicians rated more participants in the ibuprofen and alprazolam groups (70% and 58%, respectively) as being much or very much improved by the end of the trial, compared to the combination and double-placebo groups (40% and 30%, respectively).

Eleven participants withdrew from the study due to a lack of efficacy of treatment; their group allocations were not disclosed.

Adverse events were as expected, with sedation, drowsiness, fatigue, and weakness being more common in all participants receiving alprazolam. Participants in all groups experienced headache and gastrointestinal (GI) symptoms. Headache was more severe in the alprazolam group, and GI symptoms were more severe in all participants receiving ibuprofen.

Two participants withdrew from the study due to adverse events, and both had been randomised to the combination therapy group.

Russell 1991

Patient-reported pain relief of 30% or greater

No results were reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported pain relief of 50% or greater

No results were reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much improved

No results were reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

No results were reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Some secondary outcomes of interest were recorded in this study, including severity of tenderness, tender point index, VAS pain scores, physician's global perception of overall disease severity, and withdrawals due to adverse events.

Within-group comparisons indicated statistically significant improvement in dolorimeter scores, tender point index, pain scores, and physician-rated global assessment scores between baseline and week six of treatment; however, there was no statistically significant difference in the change from baseline between treatment groups.

Comparing the combination group to the double-placebo group suggested that the combination treatment significantly decreased pain and tender point index, but not dolorimeter score or physician-rated global assessment.

The number of participants reporting adverse events was not provided. However, only six participants withdrew from the study due to adverse events, four of whom were in the placebo group and experienced blurred vision, GI problems, headaches, emesis, and nasal congestion. Only one participant in the combination

group withdrew due to adverse events, reporting rash, adenopathy, headaches, swelling, and increased pain.

Quijada-Carrera 1996

Patient-reported pain relief of 30% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported pain relief of 50% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

This study reported outcomes related to pain including participant global assessment of fibromyalgia, VAS pain scores, duration of morning stiffness, and number of tender points; it also reported withdrawals due to adverse events.

In the analysis of participants who completed at least three weeks of treatment, there was no statistically significant effect of treatment on participant-rated global assessment. In the ITT analysis, significantly more participants in the combination group (29%) had clinically significant improvement scores compared to the tenoxicam-only group (10%).

The proportion of participants experiencing clinically significant improvement from baseline in pain (defined as a decrease of at least 25%), sleep quality (defined as more rested upon awakening), and duration of morning stiffness (defined as at least a 25% decrease) did not differ statistically between treatment groups.

The proportion of participants with a reduction of at least four tender points compared to baseline was significantly higher in the combination group compared to the bromazepam group, but no other groups.

No average scores were reported in this study; rather, the proportion of participants experiencing improvement from baseline in each outcome was reported.

Nine participants withdrew from the study due to adverse events; 52 participants overall reported experiencing adverse events (7, 18, 14, and 13 in the placebo, tenoxicam, bromazepam, and combination groups, respectively).

The most common side effects reported were gastralgia (tenoxicam, bromazepam, and combination groups), nausea (placebo and tenoxicam groups), headache (tenoxicam group), and drowsiness (bromazepam group).

The study authors concluded that combination therapy was not significantly better than placebo, likely due to low power in the study, and a higher than expected response to placebo treatment.

Amitriptyline combined with fluoxetine

Two studies evaluated the efficacy of amitriptyline and fluoxetine alone and in combination (Goldenberg 1996; Zucker 2006).

Goldenberg 1996, a cross-over design trial, gave amitriptyline, fluoxetine, combination therapy, and placebo to participants sequentially for six-week durations each. The study randomised 31 participants, and included 24 participants, who completed at least one treatment period, in the analyses.

Zucker 2006 also evaluated the combination of fluoxetine and amitriptyline in the treatment of fibromyalgia, but only compared this combination to amitriptyline monotherapy using an N-of-1 trial design in which participants received three sequential, six-week, cross-over trials involving a defined sequence of amitriptyline-combination pairs. The study enrolled 58 participants. Thirty-four participants completed all treatment periods and 46 participants completed at least two treatment periods; both subsets of participants were analyzed.

Goldenberg 1996

Patient-reported pain relief of 30% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported pain relief of 50% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes of interest related to pain were: FIQ scores, VAS pain scores, VAS global well-being scores, and tender point scores; withdrawals due to adverse events were also reported.

Compared to the placebo treatment outcomes, amitriptyline and fluoxetine monotherapy significantly improved self-reported VAS scores of pain, sleep, and global well-being, and also improved FIQ scores.

Combination therapy resulted in significantly larger improvements in these four outcomes compared to each monotherapy.

No statistically significant differences between treatment groups were seen in the VAS scores for physician-rated global well-being, fatigue, or feeling refreshed.

Similarly, there was no statistically significant influence of treatment on the Beck Depression Inventory score and on the tender point score, although the study authors noted that the combination therapy was associated with the greatest improvements in these measures.

Analyses on the change from baseline to week six of treatment produced similar trends, with the combination treatment resulting in the largest improvement and the placebo treatment the smallest (significance not specified).

A greater than 25% improvement to FIQ scores was seen in 12/19 participants on combination therapy, 7/22 receiving fluoxetine, 5/21 receiving amitriptyline, and 1/19 receiving placebo (significance not specified).

When all four outcomes (VAS for global well-being, pain, and physician-rated global well-being, and tender point score) were combined into a composite change score out of 100, an improvement by at least 25 points was seen in five participants taking combination therapy, five receiving fluoxetine, two receiving amitriptyline, and one receiving placebo (significance not specified).

Nine of 12 participants who withdrew from the study cited either adverse reactions to the medication (one fluoxetine, three combination, one placebo) or worsening fibromyalgia symptoms (three fluoxetine, one during a washout period) as the reason.

The study authors concluded that the combination of amitriptyline and fluoxetine was more effective than placebo and either monotherapy in improving FIQ scores, and in participant-rated VAS scores of global well-being, pain, and sleep.

Zucker 2006

Patient-reported pain relief of 30% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported pain relief of 50% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes of interest related to pain included FIQ scores, VAS scores of global well-being and pain, and tender point scores. Withdrawals due to adverse events were also reported.

Participants receiving combination therapy had significantly improved FIQ scores, VAS pain scores, and tender point exam scores compared to those receiving amitriptyline alone.

There were no statistically significant differences between treatments in other outcome measures (VAS scores of global well-being, sleep, fatigue, and feeling refreshed upon awakening).

Eight participants withdrew due to adverse events, the most frequently reported of which were sedation, headache, "dryness", and GI-related symptoms. Seven out of eight participants were taking combination therapy when they withdrew, and one was taking amitriptyline.

The study authors concluded that combination therapy, in comparison to amitriptyline monotherapy, improved FIQ scores.

Amitriptyline combined with a drug from another class of medication

Two studies combined amitriptyline with another agent ([Goldenberg 1986](#); [Vlainich 2010](#)).

[Goldenberg 1986](#) compared the combination of amitriptyline and naproxen to each monotherapy and to double placebo in a six-week, four-group, parallel-design trial. The study randomised 62 participants, and included the 58 participants who completed the study in the analysis. They evaluated participants at baseline, and at two, four, and six weeks after starting treatment.

[Vlainich 2010](#) compared amitriptyline monotherapy to combination therapy of amitriptyline and intravenous lidocaine in a four-week, two-group, parallel-design study. The study randomised and analyzed 30 participants.

Goldenberg 1986

Patient-reported pain relief of 30% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported pain relief of 50% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes of interest related to pain were recorded in this study, and included VAS scores of global assessment of fibromyalgia symptoms and pain, in addition to tender point scores. Adverse events were also reported.

The study authors ran a profile analysis, which evaluated the effectiveness of each drug rather than the monotherapies and combination therapy.

The results of this analysis indicated that participants receiving amitriptyline either alone or in combination with naproxen exhibited significantly larger improvements in VAS scores of global assessment, pain, sleep difficulty, fatigue, and morning tiredness, and tender point scores.

There was no statistically significant effect of naproxen on any of these outcomes.

Additionally, participants receiving amitriptyline alone or in combination experienced significant improvements in global assessment, pain, sleep difficulty, fatigue, morning tiredness, and tender point scores between baseline and week six; no statistically significant improvements were seen in participants receiving naproxen monotherapy or placebo.

No statistically significant differences in any of the outcome measures were noted between amitriptyline monotherapy and combination therapy.

Although eight participants experienced adverse events, none withdrew for this reason. Adverse events experienced were dry mouth (4 participants total in the combination group and the amitriptyline monotherapy group), dyspepsia (1 participant in the naproxen monotherapy group, 1 participant in the placebo group), and diarrhoea (1 participant in the naproxen monotherapy group, and 1 participant in the placebo group).

The study authors concluded that amitriptyline monotherapy and amitriptyline in combination with naproxen resulted in significant improvements in all outcome measures compared to placebo treatment. However, the trial did not have the power or sample size to detect any statistically significant differences between amitriptyline monotherapy and combination therapy. As a result of this, the study authors could not determine whether naproxen enhanced the efficacy of amitriptyline.

Vlainich 2010

Patient-reported pain relief of 30% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported pain relief of 50% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes of interest recorded in this study, related to pain, include VAS pain scores, and number of tender points. Adverse events were also reported.

VAS pain scores and the number of tender points decreased significantly from baseline to week four of treatment in both groups; however, there were no statistically significant differences in pain scores or the number of tender points between treatment groups.

The number of participants experiencing fatigue, subjective edema, and morning stiffness did not change statistically significantly from baseline to week four of treatment in either group or between groups.

The number of participants experiencing sleep disorders, paraesthesia, and headache all decreased significantly from baseline to week four within groups, but no significant differences were seen between groups in these measures.

Adverse events were not discussed in this report.

The study authors concluded that treatment with amitriptyline and lidocaine did not reduce pain significantly more than treatment with amitriptyline alone.

Melatonin combined with an antidepressant

We included two studies in this category ([de Zanette 2014](#); [Hussain 2011](#)).

[Hussain 2011](#) combined both low and high doses of melatonin with fluoxetine and compared them to fluoxetine monotherapy and high-dose melatonin monotherapy for eight weeks in a four-group,

parallel trial. The number of participants randomised was not specified; 101 participants completed the study and were analyzed.

[de Zanette 2014](#), a recent study, compared the combination of melatonin with amitriptyline to each drug as a monotherapy in a six-week, three-group, parallel-design trial. The study randomised 63 participants and analyzed them on an ITT basis; 57 participants completed the trial.

Hussain 2011

Patient-reported pain relief of 30% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported pain relief of 50% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

The only outcomes recorded in this study were health-related quality-of-life parameters and symptoms parameters on the FIQ.

Compared to baseline, FIQ scores were improved by 21.5% in the fluoxetine group, 18.9% in the melatonin monotherapy group, 28.8% in the low-dose melatonin + fluoxetine group, and 28.9% in the high-dose melatonin + fluoxetine group; all within-group comparisons of FIQ scores from baseline were statistically significant.

Within-group comparisons showed that pain scores were significantly reduced by all treatments compared to baseline scores, by: 14.3% in fluoxetine group, 27% in the melatonin group, 27.3% in the low-dose melatonin + fluoxetine group, and 30% in the high-dose melatonin + fluoxetine group.

Only in both combination groups were all FIQ parameters (pain, fatigue, rest/sleep, stiffness, anxiety, and depression) improved significantly compared to baseline.

The presence of adverse events was not mentioned in this study.

The study authors concluded that melatonin, alone or in combination, was effective in improving FIQ scores. No statistical comparisons were made between treatment groups in this study,

precluding the ability to assess whether combination therapy is superior to monotherapy.

de Zanette 2014

Patient-reported pain relief of 30% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported pain relief of 50% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary Outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes of interest related to pain included VAS pain scores, FIQ scores, pressure pain thresholds, number of tender points, and amount of analgesics used in the last week of treatment. Adverse events were also reported.

Participants receiving melatonin either alone or in combination had significantly lower VAS pain scores compared to participants receiving amitriptyline monotherapy.

Conditioned pain modulation response was tested to assess the function of participants' descending modulatory systems. Participants receiving melatonin alone or in combination with amitriptyline had significantly reduced pain scores in the conditioned pain modulation task compared to participants receiving amitriptyline monotherapy.

A comparison of the change from baseline in FIQ score and pain pressure threshold revealed significantly larger improvements in the combination therapy compared to both monotherapy groups.

While all treatments significantly reduced the dose of analgesics, decreased the number of tender points, and improved sleep quality compared to baseline, there were no statistically significant differences between treatments in these outcome measures.

Thirteen out of 21 participants in the amitriptyline group, 10/21 in the melatonin monotherapy group, and 9/21 in the combination group experienced adverse events.

Adverse events listed were minor (nausea, mild dizziness, weight gain, and dry mouth), or major (severe dizziness, vivid nightmares,

crippling drowsiness, severe headache, behavioural changes, and increased pain).

The incidence of minor adverse events was significantly lower in the combination group compared to the amitriptyline monotherapy group.

The study authors concluded that while all treatments resulted in pain reduction, participants receiving melatonin alone or in combination with amitriptyline experienced slightly larger improvements in pain scores than those receiving amitriptyline monotherapy, and participants receiving combination therapy experienced slight improvements in FIQ scores and pressure pain threshold scores compared to participants receiving either monotherapy.

Carisoprodol combined with paracetamol (acetaminophen) and caffeine

[Vaeroy 1989](#) was the only study that compared the combination of carisoprodol, paracetamol (acetaminophen), and caffeine to placebo, in a parallel-design, eight-week study. They randomised 58 participants, and 43 participants completed all eight weeks of the trial.

Vaeroy 1989

Patient-reported pain relief of 30% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported pain relief of 50% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes of interest related to pain, that were included in this study, are pressure pain threshold, tender point scores, VAS pain scores, and the use of additional analgesic medication. Adverse events and withdrawals due to lack of efficacy were also reported.

Significantly fewer participants in the combination therapy group reported taking additional medication during the trial (4/20), compared to participants in the placebo group (14/23)

who took additional medication including analgesics, tricyclic antidepressants, anxiolytics, and sedatives.

On VAS scores of pain, sleep quality, and general feeling of sickness, participants in the combination therapy group improved significantly compared to baseline scores, and participants receiving placebo had significantly improved pain and sleep quality scores.

Between-group analyses did not indicate any significant differences between combination therapy and placebo on VAS scores for pain, sleep, or general feeling of sickness.

Pressure pain thresholds decreased significantly from baseline in 7 of 10 tender point sites in participants receiving combination therapy, versus only 1/10 in participants in the placebo group (significance not specified, although a 2 x 2 Fisher's Exact test performed on the proportions shows statistical significance).

The only adverse event reported was drowsiness, which went away within three to four days of treatment; group allocation was not stated.

Three out of 15 withdrawals were a result of lack of efficacy. No information on the treatment group these participants were randomised to was given.

The study authors concluded that the combination of carisoprodol, paracetamol (acetaminophen), and caffeine improves pain scores, sleep quality, and general feeling of sickness, in addition to increasing pressure pain thresholds at 7 of 10 tender point sites. However, placebo treatment was also associated with statistically significant improvements in pain scores and sleep quality, although not general feeling of sickness. Moreover, there were no statistically significant differences in VAS pain, sleep quality, and general feeling of sickness scores between treatment groups after eight weeks. The study authors suggested that the improvements in pain and sleep quality seen in the placebo group were likely due to the large amount of extra medication taken by these participants.

Tramadol combined with paracetamol (acetaminophen)

[Bennett 2003](#) was the only study that tested the combination of tramadol with paracetamol (acetaminophen), comparing this combination to placebo treatment in a 13-week, parallel-design trial (). The study randomised 315 participants; 313 participants were analyzed on an ITT basis for treatment efficacy; 312 participants were included in safety analyses. In this study, 175 of 315 participants (56%) withdrew before the final assessment; how the outcomes at the final assessment were made is not clear, but the implication in the paper is that the method was the last observation carried forward, and this can be the source of significant over-estimation of treatment effects ([Moore 2012b](#)).

Bennett 2003

Patient-reported pain relief of 30% or greater

Significantly more participants in the combination therapy group (65/156) experienced moderate pain relief (at least a 30% reduction in pain scores) compared to the placebo group (37/157).

We judged the quality of evidence for 30% or greater pain relief to be very low. We downgraded the quality of evidence by three levels for indirectness of evidence because the study compared combination

pharmacotherapy to placebo only, because imputation where there are high withdrawal rates can lead to very significant over-estimation of treatment effect, and because of the limited number of events (Moore 1998; Thorlund 2011).

Patient-reported pain relief of 50% or greater

Substantial pain relief (at least a 50% reduction in pain scores) was seen in significantly more participants receiving combination therapy (54/156) compared to participants receiving placebo (29/157).

We judged the quality of evidence for 50% or greater pain relief to be very low. We downgraded the quality of evidence by three levels for indirectness of evidence because combination pharmacotherapy was compared to placebo only, because imputation where there are high withdrawal rates can lead to very significant over-estimation of treatment effect, and because of the limited number of events (Moore 1998; Thorlund 2011).

Patient-reported global impression of clinical change much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes of interest recorded in this study were time to discontinuation due to lack of efficacy, VAS pain scores, VAS pain relief scores, number of tender points and myalgic scores, FIQ scores, and adverse events.

The primary outcome of this study was the time to discontinuation from the study. Significantly more participants in the placebo group discontinued for any reason compared to participants in the combination group (62% versus 48%, respectively).

Similarly, significantly more participants taking placebo discontinued due to lack of efficacy (51%) than did participants taking combination therapy (29%).

VAS pain scores, pain relief scores, and the number of tender points were significantly lower in the combination therapy group compared to the placebo group, after adjusting for baseline values.

Adjusting for baseline values, FIQ score was significantly improved after treatment with combination therapy compared to placebo, as were the scores for the FIQ subscales physical impairment, feel good, do job, pain, rest, stiffness, and anxiety.

Similarly, the combination therapy group had significantly better scores on five measures on the SF-36 (physical functioning, role-physical, bodily pain, reported health transition, and physical component summary), after adjusting for baseline values.

Withdrawal from study participation due to adverse events was noted in 29 of 156 and 18 of 156 participants in the combination group and placebo group, respectively.

Significantly more participants in the combination group (118/156) compared to the placebo group (87/156) reported at least one adverse event.

The most commonly reported combination treatment-related side effects were nausea (14), dizziness, somnolence, and constipation (five each); the most common placebo treatment-related side effects were nausea (seven) and somnolence (five).

The study authors concluded that the combination of tramadol and paracetamol (acetaminophen) was moderately effective in reducing pain and pain-related symptoms of fibromyalgia.

Malic acid combined with magnesium

Russell 1995 was the only study that compared the combination of malic acid and magnesium to placebo in a two-period (four weeks per period), cross-over design trial (Russell 1995). The study randomised 24 participants; they analyzed the 20 participants who completed the study for efficacy; and monitored all 24 participants for adverse events.

Russell 1995

Patient-reported pain relief of 30% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported pain relief of 50% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes of interest included in this study related to pain were VAS pain scores, tender point index, and tender point average. Adverse events were also reported.

No statistically significant differences were seen between any outcomes measured during placebo treatment and combination treatment (VAS pain scores, tender point index, tender point average, Health Assessment Questionnaire scores, Center for

Epidemiologic Studies Depression scale scores, and anxiety assessed by the Hassle scale scores).

Thirteen out of 24 participants reported experiencing at least one adverse event, but no adverse events were considered to be associated with malic acid or magnesium.

Combination therapy with malic acid and magnesium did not significantly improve any outcome measures in the blinded trial. However, in a subsequent open-label trial in which 18 participants were given higher doses for a longer period of time, pain and tender point index scores were significantly reduced compared to baseline values.

The study authors concluded that although the blinded trial did not show superiority of combination therapy over placebo, results from the open-label study suggested that pain symptoms were improved when malic acid and magnesium were given at a higher dose for a longer treatment period.

Monoamine oxidase inhibitor (MAOI) combined with 5-hydroxytryptophan (5-HTP)

[Nicolodi 1996](#) was the only study that evaluated the efficacy of the MAOI paroxetine or phenelzine alone, 5-HTP alone, the combination of these two classes of agents, and amitriptyline alone in a 12-month, parallel-design trial. No information was given on the number of participants randomised; 200 participants were analyzed.

Nicolodi 1996

Patient-reported pain relief of 30% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported pain relief of 50% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

One secondary outcome related to pain reported was VAS pain scores. Adverse events were also reported.

All treatments resulted in significantly reduced pain scores compared to baseline scores when compared within groups.

The study authors stated that the improvement in pain scores was significantly greater in participants receiving combination therapy compared to monotherapy or treatment with amitriptyline; however, these analyses were not shown.

No participants experiencing side effects withdrew from the study; no side effects reported were considered to be severe.

The most commonly reported adverse events were stiffness (9.5%) and nausea (9.5%) during the placebo pretreatment period, stomach-ache (8%) and insomnia (6%) in the MAOI group, stomach-ache (8%) in both the 5-HTP group and the combination therapy group, and drowsiness (20%) and dizziness (6%) in the amitriptyline group.

The study authors concluded that combination therapy of an MAOI plus 5-HTP was more effective in reducing pain compared to each monotherapy and amitriptyline therapy.

Pregabalin combined with duloxetine

[Gilron 2016](#) was the only study that examined the efficacy of a combination of pregabalin and duloxetine in the treatment of fibromyalgia, compared to each drug alone, and to placebo alone in a four-period (6 weeks per period) cross-over design trial. The study randomised 41 participants and included them in adverse effects analyses; the 39 participants who completed at least two treatment periods were included in efficacy analyses.

Gilron 2016

Patient-reported pain relief of 30% or greater

Combination therapy produced a 28% reduction in pain scores from baseline, which was significantly larger than that produced by pregabalin monotherapy (1.4%) and placebo (7.1%).

Statistically significant differences in the proportion of participants experiencing at least moderate global pain relief were seen in comparisons between combination therapy (68%) versus each monotherapy (42% pregabalin and 39% duloxetine) and versus placebo (18%), and between duloxetine monotherapy versus placebo.

We judged the quality of evidence for 30% or greater pain relief to be very low. We downgraded the quality of evidence by three levels for indirectness of evidence because of the limited number of participants (39 providing data) and events in this multiple cross-over study ([Moore 1998](#); [Thorlund 2011](#)).

Patient-reported pain relief of 50% or greater

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Patient-reported global impression of clinical change very much improved

Results were not reported for this outcome. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes

We judged the quality of evidence for all secondary outcomes to be very low. We downgraded the quality of evidence by three levels due to lack of data.

Secondary outcomes of interest reported were VAS pain scores, worst pain intensity over the last 24 hours, nocturnal pain intensity, global pain relief scores, SF-MPQ scores, FIQ scores, Brief Pain Inventory (BPI) scores, number of tender points, and adverse events.

The primary outcome in the trial was pain intensity over the past 24 hours, averaged across the seven days during which participants received their maximal tolerated dose (MTD) of study drug(s). Pain was significantly reduced by both the combination treatment and the duloxetine monotherapy compared to placebo and to pregabalin monotherapy. Pain did not differ significantly between combination therapy and duloxetine monotherapy, or between pregabalin monotherapy and placebo. Worst pain on a scale from 0 to 10 in the past 24 hours, averaged across seven days at MTD, was significantly lower during combination therapy (4.5) compared to placebo (6.0) and pregabalin monotherapy (5.9), but did not differ statistically significantly from that reported during duloxetine monotherapy (4.8). Similarly, nocturnal pain was significantly lower during combination therapy (3.2) compared to placebo (4.4) and pregabalin monotherapy (4.2), but did not differ statistically significantly from that reported during duloxetine monotherapy (3.8).

There were no statistically significant differences in the number of tender points between the treatment groups.

Combination therapy was associated with significantly improved SF-MPQ, FIQ, and SF-36 scores compared to both monotherapy treatments and to placebo.

Medical Outcomes Study Sleep Scale scores were significantly improved with combination therapy compared to placebo and duloxetine monotherapy.

Adverse events were reported during each treatment. At MTD, the frequency of two adverse events differed significantly based on treatment. Drowsiness occurred significantly more frequently during combination therapy (26.5%) compared to duloxetine monotherapy (5.3%) and placebo treatment (5.3%), and insomnia was reported significantly more often by participants taking placebo (34.2%) compared to those taking combination therapy (11.8%) and those taking pregabalin monotherapy (7.9%).

Participants who withdrew from the study were given the option to withdraw from their current treatment and start the next randomised treatment. Withdrawals due to adverse events occurred during placebo treatment (one participant), pregabalin monotherapy (one participant), duloxetine monotherapy (three participants), and combination therapy (two participants). Of these participants, three chose to continue with the next treatment

period (two who withdrew from duloxetine monotherapy, and one who withdrew from combination therapy).

There were no statistically significant differences in the number of tender points between the treatment groups.

Combination therapy was associated with significantly improved SF-MPQ, FIQ, and SF-36 scores compared to both monotherapy treatments and to placebo.

Medical Outcomes Study Sleep Scale scores were significantly improved with combination therapy compared to placebo and duloxetine monotherapy.

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At MTD, the frequency of two adverse events differed significantly based on treatment. Drowsiness occurred significantly more frequently during combination therapy (26.5%) compared to duloxetine monotherapy (5.3%) and placebo treatment (5.3%), and insomnia was reported significantly more often by participants taking placebo (34.2%) compared to those taking combination therapy (11.8%) and those taking pregabalin monotherapy (7.9%).

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Withdrawals due to adverse events occurred during placebo treatment (one participant), pregabalin monotherapy (one participant), duloxetine monotherapy (three participants), and combination therapy (two participants). Of these participants, three chose to continue with the next treatment period (two who withdrew from duloxetine monotherapy, and one who withdrew from combination therapy).

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Withdrawals due to adverse events occurred during placebo treatment (one participant), pregabalin monotherapy (one

participant), duloxetine monotherapy (three participants), and combination therapy (two participants). Of these participants, three chose to continue with the next treatment period (two who withdrew from duloxetine monotherapy, and one who withdrew from combination therapy).

Meta-analyses

We did not conduct meta-analyses of the trials investigating combinations of NSAIDs and benzodiazepines (Kravitz 1994; Quijada-Carrera 1996; Russell 1991), amitriptyline and fluoxetine (Goldenberg 1996; Zucker 2006), or melatonin and antidepressants (de Zanette 2014; Hussain 2011). These studies did not report data on the primary outcomes of interest to this review (individual participant-level data on pain relief or global impression of change), and there were many sources of heterogeneity (for example, different drugs, dosages, and participant populations used) that precluded the validity of meta-analysis.

DISCUSSION

Summary of main results

Sixteen studies met our criteria to be included in this systematic review. Given how common combination pharmacotherapy is for the treatment of fibromyalgia (Berger 2007), it is surprising that there are few high-quality randomised controlled trials comparing the efficacy of combination pharmacotherapy with monotherapy at reducing pain in people with fibromyalgia. Only nine included studies compared combination pharmacotherapy with each monotherapy (de Zanette 2014; Gilron 2016; Goldenberg 1986; Goldenberg 1996; Hussain 2011; Kravitz 1994; Nicolodi 1996; Quijada-Carrera 1996; Russell 1991). The remaining five studies compared combination pharmacotherapy with only one monotherapy (Vlainich 2010; Zucker 2006) or with inactive placebo (Bennett 2003; Russell 1995; Vaeroy 1989).

Overall, there was very little evidence to support or refute the hypothesis that combination pharmacotherapy is superior to monotherapy for treating fibromyalgia pain. In particular, there was little to no data on the specific outcomes of this review (pain relief 30% or greater, pain relief 50% or greater, global impression of clinical change much or very much improved, any pain-related outcome indicating some improvement, any adverse event, any serious adverse event, withdrawals due to adverse event). The limited number of studies comparing combination therapy with all monotherapies (9/16 identified for this review), the small sample sizes employed (50 or more per treatment arm in most cases), and the relatively short duration of each trial (6 weeks or less in most cases) diminishes our ability to draw firm conclusions. There were some studies assessing similar drug combinations, but meta-analyses were precluded due to variable dosing, medications, and outcomes.

The heterogeneity between included trials makes it difficult to summarise the findings about adverse events reported by participants taking placebo, monotherapy, or combination pharmacotherapy. However, in the 12 studies that reported adverse events, none reported serious adverse events, and there was no clear preponderance of adverse events in combination pharmacotherapy groups versus monotherapy groups (Bennett 2003; de Zanette 2014; Gilron 2016; Goldenberg 1986; Goldenberg 1996; Kravitz 1994; Nicolodi 1996; Quijada-Carrera 1996; Russell

1991; Russell 1995; Vaeroy 1989; Zucker 2006). Therefore, based upon the current evidence, there is no evidence of harm with the use of combination pharmacotherapy compared to monotherapy in the treatment of fibromyalgia. However, the quality of the evidence is very low, and therefore new studies will likely change the conclusions that can be drawn. Moreover, since adverse events are specific to the drug(s) being taken, this conclusion cannot be generalised to all combination pharmacotherapies for fibromyalgia; safety and tolerability of each combination must be examined in comparison to its individual components.

Overall completeness and applicability of evidence

We cannot draw a firm conclusion that all combination therapies are superior or inferior to monotherapies for fibromyalgia.

We grouped the 16 included studies in this review into eight categories based on the class of drugs evaluated.

- NSAIDs + benzodiazepines (Kravitz 1994; Quijada-Carrera 1996; Russell 1991);
- Celecoxib + famciclovir (Pridgen 2017);
- Amitriptyline + fluoxetine (Goldenberg 1996; Zucker 2006);
- Amitriptyline + another agent (Albertoni Giraldes 2016; Goldenberg 1986; Vlainich 2010);
- Melatonin + amitriptyline (de Zanette 2014; Hussain 2011);
- Carisoprodol + paracetamol (acetaminophen) + caffeine (Vaeroy 1989);
- Tramadol + paracetamol (acetaminophen) (Bennett 2003);
- Malic acid + magnesium (Russell 1995);
- MAOI + 5-HT (Nicolodi 1996); and
- Pregabalin + duloxetine (Gilron 2016).

There was conflicting evidence in the NSAIDs + benzodiazepines subgroup. Russell 1991 found improvements in tender point index and participant-rated pain scores when comparing the combination of ibuprofen and alprazolam with placebo treatment, but not with each monotherapy. On the other hand, Quijada-Carrera 1996 found some improvements after combination tenoxicam-bromazepam therapy compared to bromazepam monotherapy (number of tender points) or tenoxicam monotherapy (marked improvement or asymptomatic rating given to the global status of disease), but no difference between combination therapy and placebo treatment. Finally, Kravitz 1994 concluded that alprazolam and ibuprofen monotherapies were slightly better than the combination of these drugs in reducing fibromyalgia symptoms.

Other subgroups (carisoprodol + paracetamol (acetaminophen) + caffeine, tramadol + paracetamol (acetaminophen), and amitriptyline + fluoxetine) provided evidence to support combination pharmacotherapy, but included studies that only compared combination therapy to inactive placebo (Bennett 2003; Vaeroy 1989) or one monotherapy alone (Zucker 2006). Still other subgroups (melatonin + antidepressant, and MAOIs + 5-HTP) included studies that provided inconclusive data due to lack of statistical comparisons between groups (Hussain 2011; Nicolodi 1996).

Finally, two subgroups included studies that provided no evidence for superiority of combination therapy over monotherapy (malic acid + magnesium, and amitriptyline + another drug), but only

compared combinations with inactive placebo (Russell 1995) or one monotherapy (Vlainich 2010). The remaining studies either provided support for (de Zanette 2014; Gilron 2016; Goldenberg 1996) or against (Goldenberg 1986) combination pharmacotherapy over monotherapy, and all studies compared distinct combinations. We cannot draw firm conclusions for any combination due to the limited number of studies examining each combination with each monotherapy, the small sample sizes, and the short trial durations. There was considerable variability between trials in terms of inclusion and exclusion criteria. But the most relevant of these was the criteria used for diagnosing fibromyalgia in potential study participants. Nine trials used the 1990 ACR criteria (Bennett 2003; Gilron 2016; Goldenberg 1996; Hussain 2011; Nicolodi 1996; Quijada-Carrera 1996; Russell 1995; Vlainich 2010; Zucker 2006). One trial used the updated 2010 ACR criteria, which are broader (de Zanette 2014). Three trials used criteria outlined in Yunus 1981 (Goldenberg 1986; Kravitz 1994; Vaeroy 1989). One trial did not use published guidelines, but reported that 76 out of 78 participants met the Yunus 1981 criteria (Russell 1991). It is possible that these differences in fibromyalgia diagnostic criteria between studies contributed to variability in study results.

Quality of the evidence

Although most studies had unclear or low risk of bias for issues related to randomisation and blinding, there were several issues with the quality of many of the included studies in this review. Two studies made conclusions that were not clearly supported by their statistical analyses (Hussain 2011; Nicolodi 1996). Most studies had an unclear or high risk of bias due to small sample sizes (fewer than 50 participants per arm) or short trial durations (7 weeks or less), or both. Most studies (11/16) used a parallel design (the remaining three used a cross-over design), leading to limited power especially given that most of these parallel-design studies also had small sample sizes and short durations. Several of the included studies are old and therefore did not use the 1990 (or 2010) ACR diagnostic criteria for fibromyalgia, indicating that some of the participants in these studies may not meet the diagnostic criteria for fibromyalgia today (Goldenberg 1986; Kravitz 1994; Russell 1991; Vaeroy 1989). Imputation methods may have been an issue with some studies. For example, for one large 13-week study, the withdrawal rate was 56% (Bennett 2003).

While not strictly a matter of quality, the lack of studies comparing each monotherapy separately and combined was surprising.

Although they met our criteria for inclusion, five out of 16 included studies only compared combination treatment to one monotherapy or to placebo alone. This tremendously limits our ability to conclude anything about the superiority or inferiority of combination therapy to monotherapy.

Our GRADE assessments were consequently very low for primary outcomes of pain relief of 30% or 50% or greater, PGIC very much or much or very much improved, any pain-related outcome, participants experiencing any adverse event, any serious adverse event, or withdrawing because of an adverse event. This was a result of a number of factors, including heterogeneity among studies in terms of class of agents evaluated, specific combinations used, outcomes reported, and doses given prevented any meta-analysis; none of the combinations of drugs found provided

sufficient data for analysis compared with placebo or other comparators for our preferred outcomes.

Potential biases in the review process

We do not believe there is a substantial risk for bias in our review process. We had fairly liberal inclusion criteria, avoiding exclusion of studies on the basis of the language they were published in alone. The only risk for bias in the review process is that related to publication bias: trials may be more likely to be published if they have a positive result. It is therefore possible that data showing no difference between combination therapies and monotherapies exist, but are not accessible because they are not published. Our search did include some studies with negative results, and the clinical question is of great importance for fibromyalgia, and we judge that unpublished studies are a large source of bias in our review.

Agreements and disagreements with other studies or reviews

There are many reviews on pharmacotherapy for the treatment of fibromyalgia, but few focus on the specific topic of whether or not combination pharmacotherapy is superior to monotherapy for treating fibromyalgia. Some broader reviews include a comment on combination therapy for fibromyalgia, stating that despite the paucity of evidence to support it, polypharmacy is necessary to alleviate discomfort in many participants because fibromyalgia is a multifaceted disease with diverse symptoms (Calandre 2015; Dale 2016; Gerardi 2016; Han 2011). Mease 2008 reviewed several promising monotherapies for the treatment of fibromyalgia, but also provided the rationale for combination therapy, citing two of our included studies (Bennett 2003; Goldenberg 1986), and proposed a trial design to test the question of whether medications can act synergistically or additively to reduce fibromyalgia symptoms safely. In a more recent review on combination versus monotherapy, Calandre 2012 cites 10 studies that examine the efficacy of combination pharmacotherapy; six of these studies are also included in our review (Bennett 2003; Goldenberg 1986; Goldenberg 1996; Hussain 2011; Russell 1991; Vaeroy 1989), while the other four are open-label trials that were also identified in our search and excluded. No meta-analyses were undertaken since this was simply a narrative review; however, their conclusions are similar to our own: there is some evidence to suggest that combination pharmacotherapy may be superior to monotherapy, but more research on specific drug combinations is needed due to the current lack of studies on the topic.

AUTHORS' CONCLUSIONS

Implications for practice

For people with fibromyalgia

There are currently no pharmacotherapy options for fibromyalgia that sufficiently treat all symptoms while avoiding the risk of adverse events that could make fibromyalgia symptoms worse. Further research is necessary before determining if combinations of medications with different mechanisms of action can reduce fibromyalgia symptoms and cause fewer side effects than monotherapy.

For clinicians

There are very few high-quality clinical trials evaluating the efficacy of specific drug combinations for treating fibromyalgia, which precludes us from useful in-depth meta-analyses. As a result of this lack of data, clinical decisions about whether to treat fibromyalgia with monotherapy or combination pharmacotherapy may be based only on one or two double-blind, randomised controlled trials and very small numbers of participants and events, depending on the drug combination in question. Individual studies point in different directions, to the superiority of combination therapy, to the superiority of monotherapy, or to no difference. In other words, whether or not combination pharmacotherapy is effective for treating fibromyalgia pain depends largely on the specific drugs under investigation, and generalisations are impossible.

Using the GRADE approach to assess each study, evidence varied for different drug combinations and was very low quality. Reasons for evidence being determined as very low quality varied across studies and drug combinations but generally included lack of directness (i.e. comparing a combination to only one or even none of its single-agent components), small sample sizes, short trial duration, and other statistical analysis issues. Taken together, available evidence does not allow us to draw firm conclusions about any of the combinations included in this review.

Care should be taken when prescribing multimodal pharmacotherapy to ensure that adverse events are closely monitored and the risk for toxicity does not outweigh the potential benefits of combination therapy. Given some of the previous combinations studied, it should be emphasised that combining drugs that cause serotonin reuptake inhibition (e.g. amitriptyline, desipramine, duloxetine) with other serotonin reuptake inhibitors (e.g. tramadol) may cause 'serotonin syndrome' – a potentially fatal condition marked by altered mental status, hyperactivity, and neuromuscular dysfunction. It should also be noted that benzodiazepines are not recommended by the American Pain Society, the European League Against Rheumatism, or the Association of the Scientific Medical Societies in Germany for the treatment of fibromyalgia (Hauser 2010).

For policy makers and funders of the intervention

Based on the results of this systematic review, there is currently insufficient evidence to support the routine use of any specific drug combination for the treatment of fibromyalgia pain. However, there is some evidence to support the use of combination therapy for fibromyalgia and real-world studies indicate that various drug combinations are widely used for this condition. These observations and knowledge gaps point to a compelling need for new and improved research to identify:

- favourable combinations that could improve patient care outcomes and
- unfavourable combinations that are either associated with unacceptable adverse effects or cost-ineffective for this condition.

Implications for research

General

Many of the studies meeting our inclusion criteria for this review had similar issues with small sample sizes, low power, short trial

duration, and incomplete comparisons (for example, comparing a combination with placebo only, or comparing a combination of two drugs with only one of the drugs given as a monotherapy). These shortcomings prevent us from drawing strong conclusions about whether medications with different mechanisms of action can act additively or synergistically when given in combination.

We suggest, as do many others (Calandre 2015; Dale 2016; Gerardi 2016; Han 2011), that more research is necessary. Given the compelling (but scant) evidence for combination pharmacotherapy found in several studies, future clinical trials evaluating combinations of the best-tolerated and most effective treatments should be conducted. More studies testing the same types of combinations will enable meta-analysis of multiple trials to determine which combinations (if any) are well-tolerated and effective. As it stands, these issues have not been adequately addressed in the literature.

Design

Special focus should be placed on designing studies that include treatment arms for the combination of two or more agents and for each individual agent in addition to a placebo arm (Mease 2008). Including a placebo group will ensure that methods to quantify outcome measures have assay sensitivity to detect a treatment effect. Including each agent as a monotherapy will allow us to conclude whether the combination of two agents is superior to each agent alone, which will help answer the question of whether multiple medications can act synergistically or additively. Future studies should be planned with later meta-analysis in mind.

It is unclear whether radically different trial designs, such as that using an enriched-enrolment, randomised withdrawal method would be appropriate for this clinical question, but it may be worth considering and has been used in fibromyalgia trials with some success (Moore 2015a). A different approach to consider might be a more pragmatic design that acknowledges that there are considerable differences between individuals in terms of drug response, and that these are not predictable (Moore 2010c). Such a design may be open to investigation of the effects of combinations in people with modest but inadequate response to one drug, mimicking an approach common in clinical practice.

Measurement (endpoints)

Trials should report outcomes of known importance to people with fibromyalgia, such as pain scores and adverse events, and should also use several imputation methods for the large numbers who withdraw from treatment.

Comparison between active treatments

Studies involving other treatments including non-pharmacological interventions may be valuable in this context. A multi-component approach reflects current practice.

ACKNOWLEDGEMENTS

This work was funded, in part, by research funding from the Canadian Institutes of Health Research.

Cochrane Review Group funding acknowledgement: this project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Pain, Palliative and Supportive Care (PaPaS). The views and opinions expressed therein

are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Albertoni Giraldes 2016 {published data only}

Albertoni Giraldes AL, Salomão R, Leal PD, Brunialti MK, Sakata RK. Effect of intravenous lidocaine combined with amitriptyline on pain intensity, clinical manifestations and the concentrations of IL-1, IL-6 and IL-8 in patients with fibromyalgia: a randomized double-blind study. *International Journal of Rheumatic Diseases* 2016;**19**(10):946-53.

Bennett 2003 {published data only}

* Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. *American Journal of Medicine* 2003;**114**(7):537-45.

Bennett RM, Schein J, Kosinski MR, Hewitt DJ, Jordan DM, Rosenthal NR. Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. *Arthritis and Rheumatology* 2005;**4**:519-27.

de Zanette 2014 {published data only}

de Zanette SA, Vercelino R, Laste G, Rozisky JR, Schwertner A, Machado CB, et al. Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: a phase II, randomized, double-dummy, controlled trial. *BMC Pharmacology and Toxicology* 2014;**15**:1-14.

Gilron 2016 {published data only}

Gilron I, Chaparro LE, Tu D, Holden RR, Milev R, Towheed T, et al. Combination of pregabalin with duloxetine for fibromyalgia. *Pain* 2016;**157**:1532-40.

Goldenberg 1986 {published data only}

Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. *Arthritis and Rheumatism* 1986;**29**(11):1371-7.

Goldenberg 1996 {published data only}

Goldenberg DL, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis and Rheumatism* 1996;**39**(11):1852-9.

Hussain 2011 {published data only}

Hussain SAR, Al-Khalifa II, Jasim NA, Gorial FI. Adjuvant use of melatonin for treatment of fibromyalgia. *Journal of Pineal Research* 2011;**50**(3):267-71.

Kravitz 1994 {published data only}

Kravitz HM, Katz RS, Helmke N, Jeffriess H, Bukovsky J, Fawcett J. Alprazolam and ibuprofen in the treatment of fibromyalgia – report of a double-blind placebo-controlled study. *Journal of Musculoskeletal Pain* 1994;**2**(1):3-27.

Nicolodi 1996 {published data only}

Nicolodi M, Sicuteri F. Fibromyalgia and migraine, two faces of the same mechanism. *Recent Advances in Tryptophan Research* 1996;**398**:373-9.

Pridgen 2017 {published data only}

Pridgen WL, Duffy C, Gendreau JF, Gendreau RM. A famciclovir + celecoxib combination treatment is safe and efficacious in the treatment of fibromyalgia. *Journal of Pain Research* 2017;**10**:451-60.

Quijada-Carrera 1996 {published data only}

Quijada-Carrera J, Valenzuela-Castaño A, Povedano-Gómez J, Fernández-Rodríguez A, Hernández-Mediano W, Gutierrez-Rubio A, et al. Comparison of tenoxicam and bromazepam in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. *Pain* 1996;**65**(2):221-5.

Russell 1991 {published data only}

Russell IJ, Fletcher EM, Michalek JE, McBroom PC, Hester GG. Treatment of primary fibrositis/fibromyalgia syndrome with ibuprofen and alprazolam. A double-blind, placebo-controlled study. *Arthritis and Rheumatism* 1991;**34**(5):552-60.

Russell 1995 {published data only}

Russell IJ, Michalek JE, Flechas JD, Abraham GE. Treatment of fibromyalgia syndrome with Super Malic®: a randomized, double blind, placebo controlled, crossover pilot study. *Journal of Rheumatology* 1995;**22**(5):953-8.

Vaeroy 1989 {published data only}

Vaerøy H, Abrahamsen A, Førre Ø, Kåss E. Treatment of fibromyalgia (fibrositis syndrome): a parallel double blind trial with carisoprodol, paracetamol and caffeine (Somadril comp®) versus placebo. *Clinical Rheumatology* 1989;**8**(2):245-50.

Vlainich 2010 {published data only}

Vlainich R, Issy AM, Gerola LR, Sakata RK. Effect of intravenous lidocaine on manifestations of fibromyalgia. *Pain Practice* 2010;**10**(4):301-5.

Vlainich R, Issy AM, Sakata RK. Effect of intravenous lidocaine associated with amitriptyline on pain relief and plasma serotonin, norepinephrine, and dopamine concentrations in fibromyalgia. *Clinical Journal of Pain* 2011;**27**(4):285-8.

Zucker 2006 {published data only}

Zucker DR, Ruthazer R, Schmid CH, Feuer JM, Fischer PA, Kieval RI, et al. Lessons learned combining N-of-1 trials to assess fibromyalgia therapies. *Journal of Rheumatology* 2006;**33**(10):2069-77.

References to studies excluded from this review

Ali 2009 {published data only}

Ali A, Njike VY, Northrup V, Sabina AB, Williams AL, Liberti LS, et al. Intravenous micronutrient therapy (Myers' Cocktail)

for fibromyalgia: a placebo-controlled pilot study. *Journal of Alternative and Complementary Medicine* 2009;**15**(3):247-57.

Bagis 2013 {published data only}

Bagis S, Karabiber M, As I, Tamer L, Erdogan C, Atalay A. Is magnesium citrate treatment effective on pain, clinical parameters and functional status in patients with fibromyalgia? *Rheumatology International* 2013;**33**(1):167-72.

Bennett 2005 {published data only}

Bennett RM, Schein J, Kosinski MR, Hewitt DJ, Jordan DM, Rosenthal NR. Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. *Arthritis and Rheumatology* 2005;**53**(4):519-27.

Calandre 2007 {published data only}

Calandre EP, Morillas-Arques P, Rodriguez-Lopez CM, Rico-Villademoros F, Hidalgo J. Pregabalin augmentation of quetiapine therapy in the treatment of fibromyalgia: an open-label, prospective trial. *Pharmacopsychiatry* 2007;**40**(2):68-71.

Calandre 2011 {published data only}

Calandre EP, Morillas-Arques P, Molina-Barea R, Rodriguez-Lopez CM, Rico-Villademoros F. Trazodone plus pregabalin combination in the treatment of fibromyalgia: a two-phase, 24-week, open-label uncontrolled study. *BMC Musculoskeletal Disorders* 2011;**12**(95):1-9.

Cantini 1994 {published data only}

Cantini F, Bellandi F, Niccoli L, Di Munno O. Fluoxetine associated with cyclobenzaprine to treat fibromyalgia [Fluoxetina associate a ciclobenzaprina nel trattamento della fibromyalgia]. *Minerva Medica* 1994;**85**(3):97-100.

Cantini 1995 {published data only}

Cantini F, Niccoli L, Bellandi F, Di Munno O. Effectiveness of fluoxetine associated with cyclobenzaprine in the treatment of fibromyalgia: twelve-months-follow up results. *Reumatismo* 1995;**85**:103-8.

Choi 2015 {published data only}

Choi JW, Lee CJ, Lee SM, Shin BS, Jun B, Sim WS. Effect of hyaluronidase addition to lidocaine for trigger point injection in myofascial pain syndrome. *Pain Practice* 2015 Oct 7 [Epub ahead of print]. [DOI: [10.1111/papr.12362](https://doi.org/10.1111/papr.12362)]

Cuatrecasas 2007 {published data only}

Cuatrecasas G, Riudavets C, Güell MA, Nadal A. Growth hormone as concomitant treatment in severe fibromyalgia associated with low IGF-1 serum levels. A pilot study. *BMC Musculoskeletal Disorders* 2007;**8**(119):1-9.

Cuatrecasas 2011 {published data only}

Cuatrecasas CA, Gonzalez MJ, Fernandez-Sola J, Garcia-Fructuoso F, Sesmiolo F, Lage M, et al. Effect of growth hormone as add-on treatment in severe fibromyalgia syndrome. Results from the IIIB, CT27560 placebo-controlled, multicenter trial. *Annals of the Rheumatic Diseases* 2011;**70**(Suppl 3):562.

Cuatrecasas 2012 {published data only}

Cuatrecasas G, Alegre C, Fernandez-Solà J, Gonzalez MJ, Garcia-Fructuoso F, Poca-Dias V, et al. Growth hormone treatment for sustained pain reduction and improvement in quality of life in severe fibromyalgia. *Pain* 2012;**153**(7):1382-9.

Farmer 2010 {published data only}

Farmer M, Dayani N, Trugman J, Wang Y, Gendreau R. Effect of adding milnacipran to pregabalin in the management of fibromyalgia: a randomized, open-label, controlled study. *Journal of Pain* 2010;**11**(4):S17.

Fossaluzza 1992 {published data only}

Fossaluzza V, De Vita S. Combined therapy with cyclobenzaprine and ibuprofen in primary fibromyalgia syndrome. *International Journal of Clinical Pharmacology Research* 1992;**12**(2):99-102.

Ghini 2016 {published data only}

Ghini M, Carpenito G, Mascia MT. Effects of a paracetamol and tramadol fixed-dose combination on pain, asthenia, cognitive disorders and sleep quality in fibromyalgia. *Clinical and Experimental Rheumatology* 2016;**34**(2 Suppl 96):S152.

Holman 2005 {published data only}

Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. *Arthritis and Rheumatism* 2005;**52**(8):2495-505.

Jacobs 1990 {published data only}

Jacobs JWG, Rasker JJ, Van Riel PLCM, Gribnau FWJ. Rheumajecta and Vasolastine treatment of primary fibromyalgia: results of a randomized, placebo-controlled, double-blind study [Behandeling met Rheumajecta en Vasolastine van primaire fibromyalgie; resultaten van een gerandomiseerd, placebo-gecontroleerd, dubbelblind onderzoek]. *Nederlands Tijdschrift voor Geneeskunde* 1990;**134**(14):693-7.

Johnson 1997 {published data only}

Johnson SP. Fluoxetine and amitriptyline in the treatment of fibromyalgia. *Journal of Family Practice* 1997;**44**(2):128.

Lange 2011 {published data only}

Lange M, Krohn-Grimberghe B, Petermann F. Medium-term effects of a multimodal therapy on patients with fibromyalgia. Results of a controlled efficacy study [Mittelfristige effekte einer multimodalen behandlung bei patienten mit fibromyalgiesyndromergebnisse einer kontrollierten wirksamkeitsstudie]. *Der Schmerz* 2011;**25**(1):55-61.

Leader 2009 {published data only}

Leader A, Amital D, Rubinow A, Amital H. An open-label study adding creatine monohydrate to ongoing medical regimens in patients with the fibromyalgia syndrome. *Annals of the New York Academy of Sciences* 2009;**1173**(1):829-36.

Le Gallez 1988 {published data only}

Le Gallez P, Reeve FB, Crawley MA, Bird HA. A double-blind comparison of ibuprofen, placebo and ibuprofen with

meptazinol in soft tissue rheumatism. *Current Medical Research and Opinion* 1988;**10**(10):663-7.

Lister 2002 {published data only}

Lister RE. An open, pilot study to evaluate the potential benefits of coenzyme Q10 combined with Ginkgo biloba extract in fibromyalgia syndrome. *Journal of International Medical Research* 2002;**30**(2):195-9.

Mease 2013 {published data only}

Mease PJ, Farmer MV, Palmer RH, Gendreau RM, Trugman JM, Wang Y. Milnacipran combined with pregabalin in fibromyalgia: a randomized, open-label study evaluating the safety and efficacy of adding milnacipran in patients with incomplete response to pregabalin. *Therapeutic Advances in Musculoskeletal Disease* 2013;**5**(3):113-26.

Nollen 1990 {published data only}

Nollen AJG. Treatment of primary fibromyalgia using Rheumajecta and Vasolastine: results of a randomized, placebo-controlled, double-blind study [Behandeling van primaire fibromyalgie met Rheumajecta en Vasolastine: resultaten van een gerandomiseerde, placebo-gecontroleerde, dubbelblinde studie]. *Nederlands Tijdschrift voor Geneeskunde* 1990;**134**(21):1062-3.

Porta 1999 {published data only}

Porta M. The use of botulinum toxin type A in the treatment of myofascial pain syndromes. *Riabilitazione* 1999;**32**(2):49-55.

Porta 2000 {published data only}

Porta M. A comparative trial of botulinum toxin type A and methylprednisolone for the treatment of myofascial pain syndrome and pain from chronic muscle spasm. *Pain* 2000;**85**(1-2):101-5.

Potvin 2012 {published data only}

Potvin S, Morin M, Cloutier C, Gendron A, Bissonnette A, Marchand S. Add-on treatment of quetiapine for fibromyalgia: a pilot, randomized, double-blind, placebo-controlled 12-week trial. *Journal of Clinical Psychopharmacology* 2012;**32**(5):684-7.

Pridgen 2014 {published data only}

Pridgen W, Duffy C, Gendreau J, Gendreau RM. A combination of celecoxib and famciclovir is efficacious in the treatment of fibromyalgia: results of a phase IIa randomized, double-blind, placebo-controlled study. *Arthritis and Rheumatology* 2014;**66**:S826-7.

Qin 2009 {published data only}

Qin L, Jiang F, et al. Effect of treating fibromyalgia syndrome with the combination of tramadol and amitriptyline. *Chinese Journal of Rural Medicine and Pharmacy* 2009;**8**:18-19.

Ramzy 2017 {published data only}

Ramzy EA. Comparative efficacy of newer antidepressants in combination with pregabalin for fibromyalgia syndrome: a controlled, randomized study. *Pain Practice* 2017;**17**(1):32-40.

Recla 2009 {published data only}

Recla JM, Sarantopoulos CD. Combined use of pregabalin and memantine in fibromyalgia syndrome treatment: a novel analgesic and neuroprotective strategy?. *Medical Hypotheses* 2009;**73**(2):177-83.

Rico-Villademoros 2009 {published data only}

Rico-Villademoros F, Hidalgo J, Morillas-Arques P, Vilchez JS, Delgado-Rodriguez A, Calandre EP. An open-label study of levopromazine (methotrimeprazine) as an add-on therapy in fibromyalgia management. *Clinical and Experimental Rheumatology* 2009;**27**(5):S16-20.

Settel 1967 {published data only}

Settel E. Efficacy of phenylbutazone-prednisone combination in the treatment of acute lumbosacral fibrositis: a survey of 96 cases. *Current Therapeutic Research, Clinical and Experimental* 1967;**9**(4):197-9.

Szirmai 1974 {published data only}

Szirmai E, Sachs V. Experimental investigation of the effect of a combination of quinine, lithium and salicylic acid by means of various methods [Experimentelle prüfung der wirkung einer chinin-lithium-salicylat-kombination mit verschiedenen methoden]. *Arzneimittelforschung* 1974;**24**(9):1322-5.

Vilchez 2009 {published data only}

Vilchez JS, Calandre EP, Rico-Villademoros F, Molina-Barea R, Rodriguez-Lopez CM, Garcia-Carrillo J. Ropinirole as a coadjuvant treatment in the management of refractory patients with fibromyalgia: a case series. *European Neuropsychopharmacology* 2009;**19**(Suppl 3):S270.

Vlainich 2011 {published data only}

Vlainich R, Issy AM, Sakata RK. Effect of intravenous lidocaine associated with amitriptyline on pain relief and plasma serotonin, norepinephrine, and dopamine concentrations in fibromyalgia. *Clinical Journal of Pain* 2011;**27**(4):285-8.

Zborovsky 1994 {published data only}

Zborovsky AB, Babyeva AR, Grekhov RA. The combination of the local therapy with dimethylsulfoxide and NSAIDs and acupuncture in the treatment of patients with fibromyalgia. *Zeitschrift für Rheumatologie* 1994;**53**(2):112.

Zhao 2009 {published data only}

Zhao RH, Zhu YB. Observation on therapeutic effect of herb-partitioned moxibustion on fibromyalgia syndrome. *Zhongguo Zhen Jiu* 2009;**29**(3):200-2.

References to ongoing studies

NCT00991848 {published data only}

Lidocaine on manifestations of fibromyalgia (LIMAFIBRO). Ongoing study January 2005.

NCT01323374 {published data only}

Study to assess the clinical benefit of droxidopa and droxidopa/carbidopa in subjects with fibromyalgia (FMS201). Ongoing study January 2009.

NCT01850420 {published data only}

A study of IMC-1 in patients with fibromyalgia. Ongoing study May 2013.

Additional references
Arnold 2012

Arnold LM, Clauw DJ, Dunegan LJ, Turk DC, FibroCollaborative. A framework for fibromyalgia management for primary care providers. *Mayo Clinic Proceedings* 2012;**87**(5):488-96.

Berger 2007

Berger A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and healthcare costs of patients with fibromyalgia syndrome. *International Journal of Clinical Practice* 2007;**61**(9):1498-508.

Calandre 2012

Calandre EP, Rico-Villademoros F, Rodriguez-Lopez CM. Monotherapy or combination therapy for fibromyalgia treatment?. *Current Rheumatology Reports* 2012;**14**:568-75.

Calandre 2015

Calandre EP, Rico-Villademoros F, Slim M. An update on pharmacotherapy for the treatment of fibromyalgia. *Expert Opinion on Pharmacotherapy* 2015;**16**(9):1347-68.

Campbell 1983

Campbell SM, Clark S, Tindall EA, Forehand ME, Bennett RM. Clinical characteristics of fibrositis. I. A "blinded," controlled study of symptoms and tender points. *Arthritis and Rheumatism* 1983;**26**(7):817-24.

Chaparro 2012

Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 7. [DOI: [10.1002/14651858.CD008943.pub2](https://doi.org/10.1002/14651858.CD008943.pub2)]

Clauw 2014

Clauw DJ. Fibromyalgia: a clinical review. *JAMA* 2014;**311**(15):1547-55.

Cook 1995

Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ (Clinical Research Ed)* 1995;**310**:452-4.

Cooper 2017

Cooper TE, Derry S, Wiffen PJ, Moore RA. Gabapentin for fibromyalgia pain in adults. *Cochrane Database of Systematic Reviews* 2017, Issue 1. [DOI: [10.1002/14651858.CD012188.pub2](https://doi.org/10.1002/14651858.CD012188.pub2)]

Cording 2015

Cording M, Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for pain in fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 10. [DOI: [10.1002/14651858.CD008244.pub3](https://doi.org/10.1002/14651858.CD008244.pub3)]

Dale 2016

Dale R, Stacey B. Multimodal treatment of chronic pain. *Medical Clinics of North America* 2016;**100**:55-64.

Dechartres 2013

Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ* 2013;**346**:f2304. [DOI: [10.1136/bmj.f2304](https://doi.org/10.1136/bmj.f2304)]

Derry 2016

Derry S, Cording M, Wiffen PJ, Law S, Phillips T, Moore RA. Pregabalin for pain in fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2016, Issue 9. [DOI: [10.1002/14651858.CD011790.pub2](https://doi.org/10.1002/14651858.CD011790.pub2)]

Dworkin 2008

Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Journal of Pain* 2008;**9**(2):105-21.

Gerardi 2016

Gerardi MC, Batticciotto A, Talotta R, Di Franco M, Atzeni F, Sarzi-Puttini P. Novel pharmaceutical options for treating fibromyalgia. *Expert Review of Clinical Pharmacology* 2016;**9**(4):559-65.

Goldenberg 2004

Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA* 2004;**292**(19):2388-95.

Gran 2003

Gran JT. The epidemiology of chronic generalized musculoskeletal pain. *Best Practice & Research. Clinical Rheumatology* 2003;**17**(4):547-61.

Guyatt 2013a

Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):151-7. [DOI: [10.1016/j.jclinepi.2012.01.006](https://doi.org/10.1016/j.jclinepi.2012.01.006)]

Guyatt 2013b

Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):158-72. [DOI: [10.1016/j.jclinepi.2012.01.012](https://doi.org/10.1016/j.jclinepi.2012.01.012)]

Han 2011

Han C, Lee S-J, Seo H-J, Wang S-M, Park M-H, Patkar AA, et al. Available therapies and current management of fibromyalgia: focusing on pharmacologic agents. *Drugs of Today* 2011;**47**(7):539-57.

Hauser 2009a

Hauser W, Bernardy K, Uceyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA* 2009;**301**(2):198-209.

Hauser 2009b

Hauser W, Bernardy K, Uçeyler N, Sommer C. Treatment of fibromyalgia syndrome with gabapentin and pregabalin--a meta-analysis of randomized controlled trials. *Pain* 2009;**145**(1-2):69-81.

Hauser 2010

Hauser W, Thieme K, Turk DC. Guidelines on the management of fibromyalgia syndrome - a systematic review. *European Journal of Pain* 2010;**14**(1):5-10.

Hearn 2012

Hearn L, Derry S, Moore RA. Lacosamide for neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 2. [DOI: [10.1002/14651858.CD009318.pub2](https://doi.org/10.1002/14651858.CD009318.pub2)]

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2011a

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b

Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. *BMJ* 2011;**343**(d5928):1-9.

Hüppe 2004

Hüppe A, Brockow T, Raspe H. Chronic widespread pain and tender points in low back pain: a population-based study. *Zeitschrift für Rheumatologie* 2004;**63**(1):76-83.

Jadad 1996

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**:1-12.

Koroschetz 2011

Koroschetz J, Rehm SE, Gockel U, Brosz M, Freynhagen R, Tolle TR, et al. Fibromyalgia and neuropathic pain - differences and similarities. A comparison of 3057 patients with diabetic neuropathy and fibromyalgia. *BMC Neurology* 2011;**11**(55):1-8.

L'Abbé 1987

L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Annals of Internal Medicine* 1987;**107**:224-33.

Liu 2016

Liu Y, Qian C, Yang M. Treatment patterns associated with ACR-recommended medications in the management of fibromyalgia in the United States. *Journal of Managed Care & Specialty Pharmacy* 2016;**22**(3):263-71.

Lunn 2009

Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy or chronic pain. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: [10.1002/14651858.CD007115](https://doi.org/10.1002/14651858.CD007115)]

McQuay 1998

McQuay H, Moore R. *An Evidence-based Resource for Pain Relief*. Oxford: Oxford University Press, 1998. [ISBN: 0-19-263048-2]

Mease 2008

Mease PJ, Seymour K. Fibromyalgia: should the treatment paradigm be monotherapy or combination pharmacotherapy?. *Current Pain and Headache Reports* 2008;**12**(6):399-405.

Moore 1998

Moore RA, Gavaghan D, Tramèr MR, Collins SL, McQuay HJ. Size is everything - large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;**78**(3):209-16. [DOI: [10.1016/S0304-3959\(98\)00140-7](https://doi.org/10.1016/S0304-3959(98)00140-7)]

Moore 2008

Moore RA, Barden J, Derry S, McQuay HJ. Managing potential publication bias. In: McQuay HJ, Kalso E, Moore RA editor(s). *Systematic Reviews in Pain Research: Methodology Refined*. Seattle: IASP Press, 2008:15-24. [ISBN: 978-0-931092-69-5]

Moore 2010a

Moore RA, Straube S, Paine J, Phillips CJ, Derry S, McQuay HJ. Fibromyalgia: moderate and substantial pain intensity reduction predicts improvement in other outcomes and substantial quality of life gain. *Pain* 2010;**149**(2):360-4.

Moore 2010b

Moore RA, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al. ACTINPAIN Writing Group of the IASP Special Interest Group on Systematic Reviews in Pain Relief, Cochrane Pain Palliative and Supportive Care Systematic Review Group Editors. "Evidence" in chronic pain - establishing best practice in reporting of systematic reviews. *Pain* 2010;**150**(3):369-89.

Moore 2010c

Moore RA, Derry S, McQuay HJ, Straube S, Aldington D, Wiffen P, et al. Clinical effectiveness: an approach to clinical trial design more relevant to clinical practice, acknowledging the importance of individual differences. *Pain* 2010;**149**(2):173-6. [DOI: [10.1016/j.pain.2009.08.007](https://doi.org/10.1016/j.pain.2009.08.007)]

Moore 2012a

Moore RA, Derry CJ, Derry S, Straube S, McQuay HJ. A conservative method of testing whether combination analgesics produce additive or synergistic effects using evidence from acute pain and migraine. *European Journal of Pain* 2012;**16**(4):585-91.

Moore 2012b

Moore RA, Straube S, Eccleston C, Derry S, Aldington D, Wiffen P, et al. Estimate at your peril: imputation methods for patient withdrawal can bias efficacy outcomes in chronic pain trials using responder analyses. *Pain* 2012;**153**(2):265-8. [DOI: [10.1016/j.pain.2011.10.004](https://doi.org/10.1016/j.pain.2011.10.004)]

Moore 2013a

Moore RA, Straube S, Aldington D. Pain measures and cut-offs - "no worse than mild pain" as a simple, universal outcome. *Anaesthesia* 2013;**68**(4):400-12.

Moore 2013b

Moore R, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. *BMJ* 2013;**346**:1-6.

Moore 2014

Moore RA, Derry S, Taylor RS, Straube S, Phillips CJ. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. *Pain Practice* 2014;**14**(1):79-94.

Moore 2015a

Moore RA, Wiffen PJ, Eccleston C, Derry S, Baron R, Bell RF, et al. Systematic review of enriched enrolment, randomised withdrawal trial designs in chronic pain: a new framework for design and reporting. *Pain* 2015;**156**(8):1382-95. [DOI: [10.1097/j.pain.000000000000088](https://doi.org/10.1097/j.pain.000000000000088)]

Moore 2015b

Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 7. [DOI: [10.1002/14651858.CD011824](https://doi.org/10.1002/14651858.CD011824)]

Morris 1995

Morris JA, Gardner MJ. Calculating confidence intervals for relative risk, odds ratios and standardised ratios and rates. In: Gardner MJ, Altman DG editor(s). *Statistics with Confidence - Confidence Intervals and Statistical Guidelines*. London: British Medical Journal, 1995:50-63.

Nüesch 2010

Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ* 2010;**341**:c3515. [DOI: [10.1136/bmj.c3515](https://doi.org/10.1136/bmj.c3515)]

O'Brien 2010

O'Brien EM, Staud RM, Hassinger AD, McCulloch RC, Craggs JG, Atchison JW, et al. Patient-centered perspective on treatment outcomes in chronic pain. *Pain Medicine* 2010;**11**(1):6-15.

PaPaS 2012

Cochrane Pain, Palliative and Supportive Care Group. PaPaS Author and Referee Guidance. papas.cochrane.org/papas-documents Accessed 29 August 2016.

Queiroz 2013

Queiroz LP. Worldwide epidemiology of fibromyalgia. *Current Pain and Headache Reports* 2013;**17**(8):1-6.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schünemann 2011a

Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Schünemann 2011b

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Silverman 2009

Silverman S, Dukes EM, Johnston SS, Brandenburg NA, Sadosky A, Huse DM. The economic burden of fibromyalgia: comparative analysis with rheumatoid arthritis. *Current Medical Research and Opinion* 2009;**25**(4):829-40.

Smythe 1977

Smythe HA, Moldofsky H. Two contributions to understanding the "fibrositis syndrome". *Bulletin on the Rheumatic Diseases* 1977;**28**(1):928-31.

Smythe 1979

Smythe HA. Fibrositis as a disorder of pain modulation. *Clinics in Rheumatic Diseases* 1979;**5**(3):823-32.

Straube 2011

Straube S, Moore RA, Paine J, Derry S, Phillips CJ, Hallier E, et al. Interference with work in fibromyalgia: effect of treatment with pregabalin and relation to pain response. *BioMed Central Musculoskeletal Disorders* 2011;**12**:125. [DOI: [10.1186/1471-2474-12-125](https://doi.org/10.1186/1471-2474-12-125)]

Sultan 2008

Sultan A, Gaskell H, Derry S, Moore RA. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. *BioMed Central Neurology* 2008;**8**:29.

Thorlund 2011

Thorlund K, Imberger G, Walsh M, Chu R, Glud C, Wetterslev J, et al. The number of patients and events required to limit the risk of overestimation of intervention effects in meta-analysis--a simulation study. *PLoS One* 2011;**6**(10):e25491. [DOI: [10.1371/journal.pone.0025491](https://doi.org/10.1371/journal.pone.0025491)]

White 1999

White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: direct health care costs of fibromyalgia syndrome in London, Canada. *Journal of Rheumatology* 1999;**26**(4):885-9.

Wiffen 2013

Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice ASC, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. *Cochrane*

Database of Systematic Reviews 2013, Issue 11. [DOI: [10.1002/14651858.CD010567.pub2](https://doi.org/10.1002/14651858.CD010567.pub2)]

Wolfe 1985

Wolfe F, Hawley DJ, Cathey MA, Caro XJ, Russell IJ. Fibrositis: symptom frequency and criteria for diagnosis. An evaluation of 291 rheumatic disease patients and 58 normal individuals. *Journal of Rheumatology* 1985;**12**(6):1159-63.

Wolfe 1990

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee.. *Arthritis Rheum.* 1990 Feb;**33**(2):160-72.

Wolfe 1995

Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis and Rheumatism* 1995;**38**(1):19-28.

Wolfe 2009

Wolfe F. Fibromyalgia wars. *Journal of Rheumatology* 2009;**36**(4):671-8.

Wolfe 2010

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity.. *Arthritis Care Res* 2010 May;**62**(5):600-10.

Wolfe 2014

Wolfe F, Walitt BT, Hauser W. What is fibromyalgia, how is it diagnosed and what does it really mean?. *Arthritis Care and Research* 2014;**66**(7):969-71.

Yunus 1981

Yunus M, Masi AT, Calabro JJ, Miller KA, Feigenbaum SL. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. *Seminars in Arthritis and Rheumatism* 1981;**11**(1):151-71.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Albertyn Giraldez 2016

Methods	Randomised, double-blind, parallel-group design study
Participants	42 people with FM of both genders, aged 18-60 years, were included in the study after approval by the Ethics Committee (number 1711/09) and signing the consent form. Participants' inclusion followed the 1990 ACR criteria
Interventions	Group 1: 240 mg lidocaine in 125 mL of saline solution, once a week for 4 weeks (T1, T2, T3 and T4) Group 2: 125 mL of saline, once a week for 4 weeks (T1, T2, T3 and T4) All participants received amitriptyline
Outcomes	The following were assessed: pain intensity before treatment (T0) and at 1, 2, 3, 4 and 8 weeks after treatment; clinical manifestations; FIQ before and at 4 and 8 weeks after; the levels of IL 1, 6 and 8 before and at 4 and 8 weeks after treatment
Notes	This study was registered in ClinicalTrials.gov ID: NCT01391598

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using Randomizer software (Urbaniak & Plous, Lancaster, PA, USA). The randomly selected groups were placed in numbered envelopes. The envelopes were then randomly selected on the day of administration of the solution to define in which group each patient was included. The solution was prepared by a nurse, and the researcher did not know which treatment the participants were receiving.

Albertoni Giraldes 2016 (Continued)

Allocation concealment (selection bias)	Unclear risk	Blinding method not described. "This work was a prospective, randomized, double-blind and placebo-controlled study."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding method not described. "This work was a prospective, randomized, double-blind and placebo-controlled study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding method not described. "This work was a prospective, randomized, double-blind and placebo-controlled study."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Four participants (2/group) lost to follow-up and no mention of ITT analysis or handling of missing data
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section are reported in the results section.
Size of study	Unclear risk	4 weeks' trial duration may be associated with a higher risk of bias compared to ≥ 12 weeks
Trial Duration	Unclear risk	19 participants per treatment arm may be associated with a higher risk of bias compared to ≥ 50
Similarities of Baseline Characteristics	Unclear risk	No significant differences between treatment groups

Bennett 2003

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-design, 13-week trial
Participants	<p>18-75 year olds diagnosed with FM using 1990 ACR criteria, with pain scores of ≥ 40 mm on a 100 mm VAS.</p> <p>443 were screened, 315 were randomised, 313 were eligible for ITT efficacy analysis, and 312 were eligible for safety analysis.</p> <p>Mean age: 49 (active treatment arm); 51 (placebo arm); proportion of women: 93% (active treatment arm) and 95% (placebo arm)</p> <p>Screening and washout phase occurred for up to 3 weeks before study start.</p> <p>Potential participants were excluded if tramadol therapy had failed previously, if they had used tramadol within the prior 30 days, and if they had any other pain that was more severe than FM pain.</p>
Interventions	<p>Tramadol/paracetamol (acetaminophen): 1 tablet/d containing 37.5 mg tramadol and 325 mg paracetamol (acetaminophen) titrated up over 10 days to 4 tablets/d; thereafter, 1-2 tablets 4 times/d up to a maximum of 8 tablets daily (300 mg tramadol + 2600 mg paracetamol (acetaminophen)); versus</p> <p>Placebo: matching placebo was given in a similar schedule. Both treatments lasted 13 weeks.</p>
Outcomes	Time to discontinuation due to lack of efficacy or any reason, pain on a 100 mm VAS, pain relief rating scale from -1 to 4, and adverse events, all recorded on days 1, 14, 28, 56, and 91; number of tender points (of 18), myalgic score (0-3), 10-item FIQ, SF-36, and 12-item sleep questionnaire, all recorded at the first (day 1) and last (day 91) visits. Adverse events were also recorded at each study visit; these

Bennett 2003 (Continued)

were either spontaneously reported by the participants or reported in response to general nondirected questioning.

Notes Of 315 randomised, 175 withdrew (77 from active treatment, 98 from placebo arm); efficacy analysis was on an ITT basis, for which there were 313 eligible participants (took at least 1 dose of medication and had at least 1 efficacy measurement taken); 312 participants were used in safety analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were assigned sequentially in 1:1 fashion at each site using a randomised list of medication codes", but how the randomised list was generated is unclear.
Allocation concealment (selection bias)	Low risk	"Tramadol/paracetamol (acetaminophen) or matching placebo tablets were prepared by the sponsor and dispensed in bottles containing 100 tablets."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Each bottle had a two-part tear-off label; study medication identification was concealed and could only be revealed in case of emergency. Treatment assignments were not revealed to study subjects, investigators, clinical staff, or study monitors until all subjects had completed therapy and the database had been finalized."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Treatment assignments were not revealed to study subjects, investigators, clinical staff, or study monitors until all subjects had completed therapy and the database had been finalized."
Incomplete outcome data (attrition bias) All outcomes	Low risk	77/158 combination arm participants discontinued prematurely (39 due to lack of efficacy), and 98/157 placebo arm participants discontinued prematurely (72 due to lack of efficacy). Other reasons for premature discontinuation were protocol violation, adverse events, choice, and loss to follow-up. Distribution was even between the groups (more discontinued from the placebo arm due to lack of efficacy, but this was the primary outcome of the study).
Selective reporting (reporting bias)	Unclear risk	The protocol for this trial was not registered.
Size of study	Unclear risk	50-199 participants per arm (156 in the combination arm, and 157 in the placebo arm)
Trial Duration	Low risk	≥ 7 weeks (13-week trial)
Similarities of Baseline Characteristics	Low risk	There were no significant differences between groups in terms of age, sex ratio, and pain scores at baseline

de Zanette 2014

Methods	Randomised, double-blind, parallel-design, 6-week trial
Participants	<p>18-65 year old women diagnosed with FM using the 2010 ACR criteria, who were refractory to their current treatments, and who had a pain score of ≥ 50 on a 100 mm VAS during the baseline week before randomisation.</p> <p>63 participants were randomised; 57 participants completed the study; all 63 participants were included in the statistical analyses on an ITT basis.</p>

de Zanette 2014 (Continued)

Mean age: 49.8 (amitriptyline), 47.4 (melatonin), 49.7 (amitriptyline + melatonin).

Participants were allowed to remain on medications, but the medication doses could not be adjusted once the study started.

Potential participants were excluded if they had inflammatory rheumatic disease, autoimmune disease, other painful disorder, history of substance abuse, pregnant or breastfeeding, or history of neurologic, oncologic, or ischemic heart disease, or kidney or hepatic insufficiency. Participants were not excluded if they had a history of major depressive disorder as long as it wasn't the main reason for their functional impairment or study enrolment.

Interventions	<p>Amitriptyline + melatonin: 25 mg amitriptyline + 10 mg melatonin at bedtime every day; versus</p> <p>Amitriptyline + placebo: 25 mg amitriptyline + placebo at bedtime every day; versus</p> <p>Melatonin + placebo: 10 mg melatonin + placebo at bedtime every day</p> <p>All treatments lasted 6 weeks</p>
Outcomes	<p>Pain scores on a 100 mm VAS recorded daily during the week before treatment and during the last week of treatment; pain reduction on a NPS from 0-10 during the conditioned pain modulation task; amount of analgesics used during the last week of treatment; number of tender points; FIQ scores; pressure pain thresholds assessed using an algometer; Pittsburgh Sleep Quality Index; and brain-derived neurotrophic factor serum levels.</p> <p>Outcomes were assessed at baseline and after 6 weeks of treatment.</p> <p>Adverse events were assessed through questioning about any changes that occurred during treatment.</p>
Notes	Small trial: 21 participants per arm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Before the recruitment phase, envelopes containing the protocol materials were prepared. Each envelope was sealed and numbered sequentially and contained an allocated treatment." However, it is not clear how the randomisation was obtained.
Allocation concealment (selection bias)	Low risk	"Each envelope was sealed and numbered sequentially and contained an allocated treatment. After the participant consented to participate in the trial, in the sequence, the nurse, who administered the medications, opened the envelope. During the entire protocol timeline, two investigators who were not involved in patient evaluations were responsible for blinding and randomization procedures. Other individuals who were involved in patient care were unaware of the treatment group to which the patients belonged."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants took the same number of capsules, regardless of whether they contained active or placebo medication. "The capsules were manufactured in such a way that the placebo and active treatment had the same size, color, smell and flavor."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>"Other individuals who were involved in patient care were unaware of the treatment group to which the patients belonged...Two independent medical examiners that were blind to the group assignments were trained to administer the pain scales and conduct the psychological tests."</p> <p>"We used the double-dummy method and shield placement to prevent the patient and team members from following the patients to control assessment bias."</p>

de Zanette 2014 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	21 participants per group were recruited; 2 participants per group withdrew before study completion due to major side effects. Withdrawals from the study were evenly distributed across groups.
Selective reporting (reporting bias)	Low risk	Protocol registered at www.clinicaltrials.gov was comparable to the published data reported.
Size of study	High risk	< 50 participants per arm
Trial Duration	Unclear risk	3-6 weeks (6-week trial)
Similarities of Baseline Characteristics	High risk	There was no statistically significant difference between groups in terms of sex ratio and age at baseline. But pain scores were significantly higher in the combination group than the other groups at baseline.

Gilron 2016

Methods	Randomised, double-blind, placebo-controlled, cross-over design, four 6-week period trial
Participants	<p>18-70 year olds diagnosed with FM using the 1990 ACR criteria, who had daily pain scores of $\geq 4/10$ for ≥ 3 months, with alanine transaminase (ALT) and aspartate transaminase (AST) $\leq 20\%$ and serum creatinine $\leq 50\%$ than the upper normal limit. Participants were required to discontinue prohibited drugs starting 7 days before study treatment. Participants could take NSAIDs, paracetamol (acetaminophen), and/or opioids (≤ 200 mg oral morphine equivalents) at a steady dose throughout the trial.</p> <p>41 participants were recruited; 33 participants completed all 4 treatment periods; 39 participants completed at least 2 treatment periods, and were included in efficacy analyses.</p> <p>All 41 participants who took at least 1 dose of any medication on trial were included in adverse event analyses. Median age: 56; 88% of participants were female.</p> <p>Potential participants were excluded if they had a painful condition as severe as (or worse than) but distinct from FM, major organ system disease, hypersensitivity to any study drugs, severe mood disorder, history of significant abuse of illicit drugs, prescription drugs, or alcohol, uncontrolled hypertension, diabetes, HIV, narrow-angle glaucoma, or malignancies, if they were taking drugs that interact adversely with study drugs, if they had problems of fructose intolerance, glucose galactose malabsorption, or sucrose isomaltase insufficiency, or if they were pregnant or breastfeeding.</p>
Interventions	<p>Pregabalin + duloxetine: 75 mg pregabalin twice a day + 30 mg duloxetine twice a day, both titrated up to the MTD during the first 24 days of treatment (to a maximum of 450 mg pregabalin and 120 mg duloxetine), remaining at the MTD from days 25-31, and tapering down from days 32-41, with day 42 a complete washout; versus</p> <p>Pregabalin + placebo: pregabalin in the same regimen described above + placebo capsules; versus</p> <p>Duloxetine + placebo: duloxetine in the same regimen described above + placebo capsules; versus</p> <p>Double placebo: placebo capsules only.</p> <p>Treatments lasted 6 weeks each</p>
Outcomes	The following outcomes were assessed during the 7 days at MTD: pain intensity over the past 24 h, worst pain intensity over the past 24 h, and nocturnal pain intensity, each rated on a NRS from 0-10 every day and averaged across the 7 days; global pain relief from -1 to 4; SSF-MPQ; FIQ; Brief Pain Inventory; Beck Depression Inventory-II; SF-36; Beck Anxiety Inventory; Medical Outcomes Study Sleep Scale; number of tender points; blinding questionnaires; and study drug MTDs.

Gilron 2016 (Continued)

Adverse events were also evaluated by open-ended questioning over the phone twice a week with a research nurse.

Notes

Small trial: 39 participants analyzed for treatment efficacy. The study was stopped prematurely due to an interim analysis that indicated superiority of the combination treatment over 1 monotherapy treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"As per a balanced Latin Square crossover, double-dummy design, participants were allocated, in a double-blind randomised fashion, to one of 24 possible sequences. A trial pharmacist prepared a concealed allocation schedule by computer-randomizing these sequences, in blocks of four, to a consecutive number series. Participants were assigned the next consecutive number and the corresponding sequence of study medications was dispensed."
Allocation concealment (selection bias)	Low risk	"A trial pharmacist prepared a concealed allocation schedule."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"For each set of capsules, active drug and placebo capsules were identical in appearance." "According to blinding questionnaire responses, correct guesses about treatment assignment among participants receiving placebo, pregabalin, duloxetine, and combination were made by 52%, 38%, 43%, and 31% of participants respectively."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Among participants receiving placebo, pregabalin, duloxetine, and combination, correct guesses made by the research nurse about treatment assignment were made for 45%, 29%, 43%, and 34%, respectively."
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of study dropouts and the reasons for withdrawal are outlined in the text and in Figure 1. Of 41 participants recruited, 39 were included in efficacy analyses (those who completed at least 2 treatment periods). 33 participants completed all 4 treatment periods.
Selective reporting (reporting bias)	Low risk	Protocol registered at www.controlled-trials.com was comparable to the published data reported
Size of study	High risk	< 50 participants per arm
Trial Duration	Unclear risk	3-6 weeks (6-week treatment periods)
Similarities of Baseline Characteristics	Low risk	Age, sex ratio, and pain scores were reported at baseline. Statistical comparisons were not made between groups, but since this is a cross-over trial, little difference is expected

Goldenberg 1986

Methods	Randomised, double-blind, placebo-controlled, parallel design, 6-week trial
Participants	Men and women who met the diagnostic criteria for FM modified from Yunus 1981, and who scored ≥ 4 on a 10 cm VAS evaluating either pain or FM symptoms; 62 participants were randomised, and 58 completed the study

Goldenberg 1986 (Continued)

Mean age: 43.8; 95% of the participants were female.

Analgesics, antidepressants, anti-inflammatory medications, sleeping medications, and other central nervous system-active medications were discontinued 72 h before the first study visit; 10% of participants, evenly distributed across treatment groups, took the only allowable medication (paracetamol [acetaminophen]) aside from study drugs.

Potential participants were excluded if they had a history of peptic ulcer disease or cardiac arrhythmias, or if they were taking medications that could not be stopped.

Interventions	<p>Amitriptyline + naproxen: 500 mg naproxen twice/d + 25 mg amitriptyline once/night; versus</p> <p>Naproxen + placebo: 500 mg naproxen twice/d + amitriptyline placebo; versus</p> <p>Amitriptyline + placebo: 25 mg amitriptyline once/night + naproxen placebo; versus</p> <p>Double placebo: 2 doses of placebo/d.</p> <p>All treatments lasted 6 weeks.</p>
Outcomes	<p>The following outcomes were assessed at pretreatment, and at weeks 2, 4, and 6: participant-administered 10 cm VAS scales assessing a) global FM symptoms, b) pain or stiffness, c) fatigue, d) difficulty with sleep, and e) feelings upon awakening; physician-administered 10 cm VAS for global evaluation; and tender point score.</p> <p>The authors did not specify how adverse events were assessed.</p>
Notes	<p>This is a small trial, with 58 study completers; sample sizes per treatment arm are not indicated. Statistical analysis did not assess the efficacy of each regimen, but instead assessed the efficacy of each drug.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...each patient was randomly assigned to 1 of 4 treatment groups using a method that assured balanced assignment (19)." Reference 19 has a list of potential options, but which one was chosen for this study is not stated.
Allocation concealment (selection bias)	Unclear risk	There is no information given to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	All participants took the same number of tablets, regardless of whether they contained active drug or placebo. "Patients, as well as the examining physician, were 'blinded' as to specific treatment." However, tablet appearance is not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Patients, as well as the examining physician, were 'blinded' as to specific treatment." No mention of how physicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 out of 62 participants failed to return for a second study visit, and were therefore classified as study dropouts and were not included in the analysis. The dropout rate was low, and was similar across all 4 treatment arms (1 per arm)
Selective reporting (reporting bias)	Unclear risk	The protocol for this trial was not registered.
Size of study	High risk	< 50 participants per arm

Goldenberg 1986 (Continued)

Trial Duration	Unclear risk	3-6 weeks (6 weeks)
Similarities of Baseline Characteristics	Unclear risk	Age, sex ratio, and pain scores were reported at baseline, but not by treatment group. The study authors stated that pain scores did not differ between groups at baseline, but the comparison for age or sex ratio between groups was not shown.

Goldenberg 1996

Methods	Randomised, double-blind, placebo-controlled, cross-over design, four 6-week period trial	
Participants	<p>18-60 year olds diagnosed with FM using the 1990 ACR criteria, who had a pain rating of ≥ 30 on a 100 mm VAS and who had a score of ≤ 18 on the Hamilton Rating Scale for Depression, and who had been experiencing FM symptoms for 2-20 years prior to enrollment.</p> <p>31 participants were randomised; 19 completed the study; 24 completed at least 1 treatment period and were included in the analysis.</p> <p>Mean age: 43.2; 90% of participants were female. All central nervous system active medications, NSAIDs, and analgesics (excluding paracetamol [acetaminophen]) were discontinued for at least 1 week before the study start.</p> <p>Potential participants were excluded if they had a history of systemic illness including cardiac, kidney, hematologic, or liver disease, or if they had major depression.</p>	
Interventions	<p>Amitriptyline + fluoxetine: 20 mg fluoxetine every morning + 25 mg amitriptyline at bedtime; versus</p> <p>Amitriptyline + placebo: fluoxetine placebo every morning + 25 mg amitriptyline at bedtime; versus</p> <p>Fluoxetine + placebo: 20 mg fluoxetine every morning + amitriptyline placebo at bedtime; versus</p> <p>Double placebo: 1 fluoxetine placebo every morning, and 1 amitriptyline placebo at bedtime.</p> <p>All treatments lasted 6 weeks, with 2-week washout periods between each treatment phase.</p>	
Outcomes	<p>All evaluations were done at the beginning and at the end of each of the 6-week treatments for a total of 8 evaluations. Outcomes included: tender point score (sum of scores for each of 9 tender points); physician-administered 100 mm VAS for global well-being; participant-administered 100 mm VAS for pain, sleep disturbance, fatigue, feeling refreshed upon awakening, and global well-being; FIQ scores; Beck Depression Inventory scores; and adverse reactions to medications. Additionally, change scores within each treatment period were calculated for each outcome, and a composite change score out of 100 was calculated using the average of the changes in VAS scores for global well-being and pain, tender point score, and physician global VAS to measure change within each treatment period.</p>	
Notes	<p>31 participants were enrolled; 19 completed the study; 12 withdrew. Of the 12 withdrawals, 5 completed at least 1 treatment period, leaving 24 participants for which there was evaluable information. However, sample sizes reported in Table 2, range from 18-22, and this is not explained anywhere in the report.</p>	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The order of treatment was generated from a table of random numbers"

Goldenberg 1996 (Continued)

Allocation concealment (selection bias)	Low risk	"Using randomization tables, the pharmacy assigned patients..." implying that investigators were not involved in the randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants took the same number of tablets, regardless of whether they contained active drug or placebo, and "All tablets were identical in appearance"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All evaluations were done by a physician who had no prior contact with the patients"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of the 12 participants who dropped out of the study, 4 were in the fluoxetine arm, 1 was in the amitriptyline arm, 5 were in the combination arm, 1 was in the double placebo arm, and 1 was in a washout period following the combination treatment phase. Reasons cited for dropping out and treatment arm were given for each participant. It is stated that "all data on patients who completed at least 1 treatment period were analyzed for outcome", which implies that 7 of the 12 participants who dropped out during the first treatment period were not analyzed, leaving 24 participants for analysis. However, the final sample size is not clear, and the sample sizes shown for each of 9 outcomes in a table range from 18-22, while the abstract implies that 19 participants were analyzed.
Selective reporting (reporting bias)	Unclear risk	The protocol for this trial was not registered.
Size of study	High risk	< 50 participants per arm
Trial Duration	Unclear risk	3-6 weeks (6 weeks)
Similarities of Baseline Characteristics	Low risk	Age, sex ratio, and pain scores were reported at baseline. Comparisons were not made between groups since this is a cross-over study. Comparisons were made between those who completed the trial and those who dropped out, and no significant differences were seen.

Hussain 2011

Methods	Randomised, double-blind, parallel-design, 8-week trial	
Participants	18-65 year olds diagnosed with FM using the 1990 ACR criteria. 101 participants were enrolled and completed the study; Mean age: 38.8; 94% of participants were female. Potential participants were excluded if they had any other marked pathologic disorder that may have interfered with the study outcomes, if they were pregnant or breastfeeding, or if they were taking analgesic or anti-inflammatory drugs or antioxidant therapy.	
Interventions	Fluoxetine + high-dose melatonin: 20 mg fluoxetine every morning + 5 mg melatonin every night; versus Fluoxetine + low-dose melatonin: 20 mg fluoxetine every morning + 3 mg melatonin every night; versus Fluoxetine + placebo: 20 mg fluoxetine every morning + melatonin placebo every night; versus Melatonin + placebo: 5 mg melatonin every night + fluoxetine placebo every morning.	

Combination pharmacotherapy for the treatment of fibromyalgia in adults (Review)

Hussain 2011 (Continued)

All treatments lasted 60 days.

Outcomes	<p>The following outcomes were assessed at baseline and after 60 days/8 weeks of treatment: health-related quality of life parameters from the FIQ (physical improvement, feel good, work missed, and doing work), and symptoms parameters from the FIQ (pain, fatigue, rest/sleep, stiffness, anxiety, and depression), and total FIQ score.</p> <p>Adverse events were not reported in this study.</p>
Notes	<p>This is a small trial, with 23-27 participants per treatment arm. No between-group comparisons were made; only within-group differences from baseline to day 60 (or week 8) of treatment were analyzed. However, statements about the superiority of one treatment over the other are made without justification. The first health-related quality of life parameter listed (physical improvement) is incorrect – the FIQ assesses physical <i>impairment</i>. In the abstract and results sections, the authors imply that treatments were given for 8 weeks, but in the methods section, they imply that treatments were given for 60 days.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomly allocated into four groups". There are no details about how randomisation was generated.
Allocation concealment (selection bias)	Unclear risk	There is no information given to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	All participants took the same number of capsules, regardless of whether they contained active drug or placebo. It is not clear whether or not all capsules were identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is no information given to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There is no information given to permit judgement.
Selective reporting (reporting bias)	High risk	Inappropriate statistics were done for the conclusions drawn, with only within-group comparisons made. Very little detail is given in the methods about outcomes. The protocol was not registered.
Size of study	High risk	< 50 participants per arm
Trial Duration	Low risk	≥ 7 weeks (8 weeks)
Similarities of Baseline Characteristics	Unclear risk	Age, sex ratio, and pain scores at baseline were reported, but no statistical comparisons were made between groups.

Kravitz 1994

Methods	Randomised, double-blind, placebo-controlled, parallel-design, 5-week trial
Participants	Those diagnosed with FM using Yunus 1981 criteria. Aged ≥ 18 years.

Kravitz 1994 (Continued)

Participants completed a 1-week, single-blind washout period during which they received 4 ibuprofen placebo pills/d and 1 alprazolam placebo pill/d before starting the double-blind phase of the study.

64 were randomised; 3 withdrew before the double-blind phase, leaving 61 evaluable participants (those who took double-blind medication for at least 1 week and had at least 1 assessment); 45 completed the entire study.

Mean age: 48.4; 92% of evaluable participants were female.

Potential participants were excluded if they were pregnant or breastfeeding, if they had a history of allergy/sensitivity to benzodiazepines, ibuprofen, or aspirin, history of peptic ulcer or gastrointestinal bleeding, alcohol or drug abuse, history of psychosis or schizophrenia, major depression or suicidal ideation, FM due to autoimmune disease, malignancy, endocrine/metabolic, hepatic, or renal disease. Participants were not excluded if they had previous psychiatric illness as long as they were not ill at the time of enrolment.

Interventions	<p>Ibuprofen + alprazolam: 600 mg ibuprofen 4 times/d + alprazolam titrated up based on side effects and treatment response from 0.5 mg at bedtime, up to a maximum of 6 mg/d; versus</p> <p>Ibuprofen + placebo: 600 mg ibuprofen 4 times/d + alprazolam placebo; versus</p> <p>Alprazolam + placebo: ibuprofen placebo 4 times/d + alprazolam titrated from 0.5 mg at bedtime up to a maximum of 6 mg/d; versus</p> <p>Double placebo: ibuprofen placebo 4 times/d + alprazolam placebo at bedtime.</p> <p>Treatments lasted 5 weeks.</p>
Outcomes	<p>The following outcomes were assessed at the end of the washout week, and at the end of each subsequent treatment week: Hamilton Depression Rating Scale scores; Hamilton Anxiety Rating Scale scores; Beck Depression Inventory scores; pain, pain relief, and physical activity scored using a 100 mm VAS; number of tender points; severity of tenderness and muscle spasms or tension (none, mild, moderate, severe); global index of improvement using the clinician's and participant's clinical global improvement rating scale; and the number and type of adverse events experienced by participants.</p>
Notes	<p>This is a small trial, with 14-17 participants per arm. Participants were rated as having 0, 1, 2, or 3+ tender points during the musculoskeletal exam of 16 sites. Participants could have > 3 tender points per site, but the maximum score per site was 3, leading to a maximum tender points score of 48. After the 4th week evaluation, alprazolam dose (or matching placebo for the appropriate arms) was tapered; participants were told that alprazolam dose would be decreased and ibuprofen dose would remain steady for the last week of the trial.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomised to treatment". No details were given on how the randomisation was obtained
Allocation concealment (selection bias)	Unclear risk	There is no information given to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	All participants took the same number of tablets, regardless of whether they contained active drug or placebo. It is not clear whether or not the tablets were identical to each other. Although there are no explicit statements of blinding, there are statements implying that investigators were blinded, for example, "However, when the blind was broken at the conclusion of the study, we were surprised to discover that the only active medication this subject received was ibuprofen"

Kravitz 1994 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is no information given to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"There was no significant between-group difference in drop-out pattern or ratio of completers to non-completers". Reasons for dropout: side effects (3), ineffective medications (11), termination to go on vacation (1), no reason recorded (2); the breakdown of dropouts between treatment groups is not given. The 18% dropout rate is cited as fairly high, but no explanation for it is provided. 17 study withdrawals were detailed, but the final sample size reported accounts for only 16 dropouts.
Selective reporting (reporting bias)	High risk	There are two outcome measures for which there are no results presented: severity of tenderness and muscle spasms or tension, and tender point score. The protocol was not registered.
Size of study	High risk	< 50 participants per arm
Trial Duration	Unclear risk	3-6 weeks (5 weeks)
Similarities of Baseline Characteristics	Unclear risk	Age and sex ratio at baseline were reported, but not by treatment group. The authors stated that there was no between-group difference for age and sex ratio. Baseline pain scores are not mentioned.

Nicolodi 1996

Methods	Randomised, parallel-design, 12-month trial
Participants	Those diagnosed with FM using the 1990 ACR criteria and who had migraine without aura. Participants underwent a washout period for 1 month, and a subsequent 1-month period during which they took placebo; after this, participants were randomised into 4 treatment arms. 200 participants were enrolled; no information is given regarding mean age of participants, or proportion of women Potential participants were excluded if they had systemic diseases, hypertension, liver diseases or dysfunction, stomach diseases, ocular diseases, or mood disturbances, or if they were pregnant or breast-feeding.
Interventions	MAOI + 5-HTP: 5-10 mg/d paraglyline or 10-15 mg/d phenelzine + 400 mg/d 5-HTP; versus MAOI: 5-10 mg/d paraglyline or 10-15 mg/d phenelzine; versus 5-HTP: 400 mg/d 5-HTP; versus Amitriptyline: 10-50 mg/d amitriptyline All treatments lasted 12 months.
Outcomes	Daily pain was scored on a VAS from 0-4, from which average pain levels were calculated during the 1-month of placebo, and during the 12 months of active treatment; participants were asked to indicate all adverse events that occurred during treatment.
Notes	All participants also suffered from migraines without aura, diagnosed using the criteria outlined in 1988 by the International Headache Society. No details are given on how average pain scores were calculated, and no details are given on the blinding of the trial. Although all participants were given placebo.

Nicolodi 1996 (Continued)

bo during an initial washout phase, blinding is not mentioned anywhere in the study. Sample size of 50 participants per arm is inferred – no direct statements about sample size are made in the paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	There is no information given to permit judgement.
Allocation concealment (selection bias)	Unclear risk	There is no information given to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There is no information given to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is no information given to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"No one of the patients who experienced side-effects withdrew of the study" is the only statement about dropouts. Total sample size of 200 is mentioned, but no breakdown is given (although 50/group can be inferred for 2 of the 4 groups). It is not possible to assess whether or not there were any dropouts.
Selective reporting (reporting bias)	High risk	Very little detail is provided in the methods about outcomes of interest. The statistical analyses used were inappropriate, and the authors make statements that are not supported statistically (analyses only compared each active treatment group to placebo, not to other treatment groups). There are statements in the results section about anxiety/mood changes as assessed by self-administered questionnaires, but this is not mentioned in the methods. The protocol was not registered.
Size of study	Unclear risk	50-199 participants per arm
Trial Duration	Low risk	≥ 7 weeks (52 weeks)
Similarities of Baseline Characteristics	Unclear risk	Sex ratio and age at baseline were not reported. Baseline pain scores were reported, but not compared between groups.

Pridgen 2017

Methods	Placebo-controlled, randomised, double-blind, parallel-group design
Participants	Female or male patients, 18–70 years of age, who met the 2010 ACR Preliminary Diagnostic Criteria for FM were eligible for inclusion
Interventions	Enrolled patients received either an acute treatment dosage of famciclovir + celecoxib or placebo for the first week. IMC-1 group participants subsequently received a chronic suppressive dosage of famciclovir + celecoxib for the remaining 15 weeks of the study, whereas placebo-enrolled participants remained on placebo treatment.

Pridgen 2017 (Continued)

Outcomes	The primary efficacy outcome was response to treatment as assessed by the change from baseline in FM pain. To assess change in FM pain, both the 24-h recall NRS score and the 7-d recall pain score from the FIQ-R were analyzed.	
Notes	Specific doses of study medications not specified in trial publication	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Specific randomisation methods not specified. "To ensure balanced assignment of patients across treatment groups at each site, a centralized by-site randomization scheme was utilized."
Allocation concealment (selection bias)	Low risk	Specific randomisation methods not specified. "To ensure balanced assignment of patients across treatment groups at each site, a centralized by-site randomization scheme was utilized."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	For blinding purposes, famciclovir and celecoxib were overencapsulated; the same filler was used for both active and placebo capsules, and active and placebo study drug supplies were identical in appearance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	For blinding purposes, famciclovir and celecoxib were overencapsulated; the same filler was used for both active and placebo capsules, and active and placebo study drug supplies were identical in appearance.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	39% dropout rate in placebo group; 17% dropout rate in combination group; all participants who received at least 1 dose of study medication were included in the ITT analyses. The imputation method utilized for this study was a hybrid baseline observation carried forward (BOCF)/last observation carried forward (LOCF) approach to account for missing data and the reason for the data being missing
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section are reported in the results section.
Size of study	Unclear risk	N = 45-57 per arm which is between 50-200
Trial Duration	Low risk	16-week treatment period
Similarities of Baseline Characteristics	Unclear risk	Baseline characteristics were comparable across treatment groups

Quijada-Carrera 1996

Methods	Randomised, double-blind, placebo-controlled, parallel-design, 8-week trial	
Participants	<p>Those diagnosed with FM using the 1990 ACR criteria who were 18-70 years of age, had widespread pain at study entry, had lab tests within the normal limit, and who did not have more than 2 locations with degenerative radiographic signs (X-rays of cervical and lumbar spine, hands, knees, and hips were taken).</p> <p>322 patients were invited to participate; 164 were randomised and were evaluated on an ITT basis; 134 completed at least 3 weeks of treatment and were analyzed as the "evaluable cohort"; 110 completed all 8 weeks.</p>	

Quijada-Carrera 1996 (Continued)

Mean age: 43; 93% of participants were female.

Psychotropic drugs, NSAIDs, and analgesics were halted at least 3 weeks before study initiation; participants were allowed to take paracetamol (acetaminophen) during this washout period.

Potential participants were excluded if they were pregnant or breastfeeding, had a history of hypersensitivity to NSAIDs or benzodiazepines, had peptic ulceration, inflammatory joint diseases, connective tissue diseases, hematologic, muscular, neurologic, renal, or infectious disorders, if they did not take trial medication for at least 3 weeks, or if they took forbidden medications during the study (NSAIDs, analgesics, or psychotropic drugs).

Interventions	<p>Tenoxicam + bromazepam: 20 mg tenoxicam every morning + 3 mg bromazepam at bedtime every day; versus</p> <p>Tenoxicam + placebo: 20 mg tenoxicam every morning + bromazepam placebo at bedtime every day; versus</p> <p>Bromazepam + placebo: tenoxicam placebo every morning + 3 mg bromazepam at bedtime every day; versus</p> <p>Double placebo: tenoxicam placebo every morning and bromazepam placebo at bedtime every day.</p> <p>All treatments lasted 8 weeks.</p>
Outcomes	<p>The following were assessed at baseline and after 8 weeks on treatment: patient global assessment of FM compared to baseline on a scale of 3 (worse, no change or minimally improved, markedly approved or asymptomatic); sleep quality; duration of morning stiffness in minutes; pain on a 10 cm VAS; number of tender points.</p> <p>The study authors did not specify how adverse events were assessed.</p>
Notes	<p>Analysis was done both on the subset of participants who completed at least 3 weeks of treatment, and on all participants randomised on an ITT basis. No raw numbers or means are presented in the results section; instead, the proportion/number of participants experiencing clinically significant improvement compared to baseline is given, defined in the methods section for each outcome variable.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...we calculated that 41 patients would be needed to be randomised to each treatment group. The assignment scheme was generated using a table of random numbers..."
Allocation concealment (selection bias)	Unclear risk	There is no information given to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	All participants took the same number of capsules regardless of whether they contained active drug or placebo, but no mention of whether the capsules were all identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is no information given to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	High risk	164 were randomised, and 54 withdrew before 8 weeks. Participants dropped out due to side effects, lack of efficacy, "other" reasons unrelated to study medication, and 30 were lost to follow-up. There is an uneven dropout rate between the groups, with the combination group experiencing lower numbers of

Quijada-Carrera 1996 (Continued)

		dropouts (6 total, vs. 15, 17, and 16 for placebo, tenoxicam, and bromazepam groups, respectively).
Selective reporting (reporting bias)	Unclear risk	Averages for each outcome are not reported. Instead, the number of participants reporting improvement in each outcome is reported. The protocol was not registered.
Size of study	High risk	< 50 participants per arm
Trial Duration	Low risk	≥ 7 weeks (8 weeks)
Similarities of Baseline Characteristics	Low risk	Age, sex ratio, and pain scores at baseline were reported, and did not differ between treatment groups.

Russell 1991

Methods	Randomised, double-blind, placebo-controlled, parallel-design, 6-week trial
Participants	<p>18-65 year olds who had continuous musculoskeletal pain for 3 months and tenderness in at least 5 of 16 standard tender points.</p> <p>78 were randomised; 76 were eligible for safety analysis; 63 were eligible for efficacy analysis.</p> <p>Mean age: 47.3; 88.5% of participants were female.</p> <p>Participants went through a 2-week washout period during which they were only permitted to take paracetamol (acetaminophen); at the end of this 2-week washout period, baseline measures were obtained.</p> <p>Potential participants were excluded if they had other rheumatic diseases, chronic infections, untreated endocrine disorders, unstable seizure diathesis, psychiatric disorders, or active peptic ulceration.</p>
Interventions	<p>Ibuprofen + alprazolam: 600 mg ibuprofen 4 times/d + 0.5 mg alprazolam at bedtime every day, increased in 0.5 mg increments starting at week 3 of treatment to a maximum of 3.0 mg/d or until experiencing an adverse effect; versus</p> <p>Ibuprofen + placebo: 600 mg ibuprofen 4 times/d + alprazolam placebo at bedtime; versus</p> <p>Alprazolam + placebo: ibuprofen placebo 4 times/d + 0.5 mg alprazolam at bedtime every day, increased in 0.5 mg increments starting at week 3 up to a maximum of 3.0 mg/d or until experiencing an adverse effect; versus</p> <p>Double placebo: ibuprofen placebo 4 times/d + alprazolam placebo at bedtime every day.</p> <p>All treatments lasted 6 weeks.</p>
Outcomes	Severity of tenderness at 16 soft tissue sites assessed with a dolorimeter; tender point index (sum of severities at all 16 sites); pain on a 10 cm VAS; duration of morning stiffness in minutes; physician's global perception of overall FM severity on a 10-cm VAS; Health Assessment Questionnaire disability index assessing functional status; Hamilton Depression Scale, Hamilton Anxiety Scale, and Center for Epidemiologic Studies Depression Scale to assess psychological status; presence of any adverse events experienced was assessed by using a 24-item checklist to question participants at each visit. These items were evaluated at baseline and after 6 weeks of treatment.
Notes	2/78 participants met the FM diagnostic criteria from Yunus 1981 and from Wolfe 1985; 69/78 participants met the FM diagnostic criteria from Smythe 1978 and from Campbell 1983; 68/78 participants met the FM diagnostic criteria of the 1990 ACR. The first 6 weeks of this study were double-blinded; following this, an open-label study in which all participants were treated with ibuprofen + alprazolam was conducted for an additional 24 weeks. Although statistical analyses were used to compare the change

Russell 1991 (Continued)

from baseline to week 6 of treatment between groups, it is unclear how often outcome measures were taken; Figure 1 implies that tender point index and dolorimeter score were assessed at weeks 2 and 4 of treatment as well. It is not explicitly stated in the methods section how often outcome measures were assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	There is no information given to permit judgement.
Allocation concealment (selection bias)	Unclear risk	There is no information given to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants took the same number of tablets regardless of whether they contained active drug or placebo. Medication is referred to as "coded". No mention of whether the tablets were all identical.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All patients and staff were blinded to the randomization".
Incomplete outcome data (attrition bias) All outcomes	Low risk	102 were entered into study, 24 were excluded because they didn't meet eligibility criteria. Of the 78 remaining who were randomised, 2 were immediately lost to follow-up, and 76 were included in the safety analysis; in the blinded portion of the study, of these 76 participants, 13 were withdrawn before week 6, therefore 63 were included in efficacy analysis. The balance of these withdrawals across treatment groups is not given, but the final sample sizes are fairly balanced, implying that the dropouts occurred evenly across groups.
Selective reporting (reporting bias)	Unclear risk	The protocol for this trial was not registered.
Size of study	High risk	< 50 participants per arm
Trial Duration	Unclear risk	3-6 weeks (6 weeks)
Similarities of Baseline Characteristics	Unclear risk	Age, sex ratio, and pain scores at baseline were reported, but not by treatment group, and they were not compared statistically between groups.

Russell 1995

Methods	Randomised, double-blind, placebo-controlled, cross-over design, two 4-week period trial
Participants	<p>Those diagnosed with FM using the 1990 ACR criteria.</p> <p>29 participants were screened; 24 were randomised; 20 completed the blinded trial.</p> <p>Participants discontinued all FM medications (analgesic and sedative-hypnotic drugs) 2 weeks before study start.</p> <p>Mean age: 49; 87.5% of participants were female</p> <p>There were no exclusion criteria listed.</p>

Russell 1995 (Continued)

Interventions	Malic acid: 3 tablets (200 mg malic acid (Super Malic) + 50 mg magnesium hydroxide per tablet) twice a day for 4 weeks; versus Placebo: 3 placebo tablets twice a day for 4 weeks	
Outcomes	Pain on a 10-cm VAS; tender point index (sum of tenderness severity at 18 tender points); tender point average (mean tenderness at 18 tender points measured by dolorimeter); Health Assessment Questionnaire score; Centre for Epidemiologic Studies-Depression Scale score; Hassle Scale score. Outcomes were assessed at baseline (Week 0), at the end of the first treatment period (Week 4), at the end of the first washout (Week 6), at the end of the second treatment period (Week 10), and at the end of the second washout (Week 12). Adverse events were self-reported by participants in daily diaries.	
Notes	Participants took study drug and placebo for 4 weeks each, with a 2-week washout in between. After the double-blind trial, participants went through another 2-week washout, and then were placed on the study medication for 6 months as part of an open-label trial. Final sample size for efficacy analysis is unclear; 24 participants were included in the adverse event assessment, but 4/24 participants withdrew from the trial at varying time points (3 between Week 0 and Week 4, and 1 between Week 6 and Week 10).	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Those who successfully discontinued prestudy medications were randomised to 1 of 2 treatment sequences..." - no other details given.
Allocation concealment (selection bias)	Unclear risk	There is no information given to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Manufacturer provided an identically coated placebo that matched Super Malic with regard to appearance and taste".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Aside from being called a double-blind trial, there is no mention that the assessors were blinded to participant treatment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	24 were randomised; 4 were withdrawn before end of trial (Week 10): 3 decided not to continue during the first treatment period (Week 0 to 4), and 1 dropped out after Week 6 but before Week 10. Therefore, 20 participants completed the blinded trial. "The dropouts did not significantly differ from the completing study patients with respect to any of the baseline variables (data not shown)". Study authors don't mention which treatment the dropouts were on when they left the study. Moreover, the final sample size is not stated, and the statistical analysis description does not detail which participants were included in the analyses. The abstract implies 24 participants, but this does not account for the study withdrawals described.
Selective reporting (reporting bias)	Unclear risk	The protocol for this trial was not registered.
Size of study	High risk	< 50 participants per arm
Trial Duration	Unclear risk	3-6 weeks (4 weeks)

Russell 1995 (Continued)

Similarities of Baseline Characteristics	Low risk	Age, sex ratio, and pain scores at baseline were reported, and compared between the 2 cross-over treatment sequence groups. They did not differ statistically at baseline.
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Vaeroy 1989

Methods	Randomised, double-blind, placebo-controlled, parallel-design, 8-week trial	
Participants	<p>Women diagnosed with FM using the criteria of Smythe 1979 and Yunus 1981.</p> <p>58 participants were randomised; 43 participants completed the study.</p> <p>Mean age: 47.4</p> <p>Participants had been suffering from FM for 4-47 years. Participants discontinued all analgesic and sedative medications for 72 h before study start.</p> <p>Potential participants were excluded if they used prohibited drugs within 72 h of study start, or if they had any coexisting disorders</p>	
Interventions	<p>Carisprodol: 2 tablets containing 200 mg carisoprodol (Somadril comp®) + 160 mg paracetamol (acetaminophen) + 32 mg caffeine 3 times/d; versus</p> <p>Placebo: 2 placebo tablets 3 times/d.</p> <p>Treatments lasted 8 weeks each.</p>	
Outcomes	Outcomes were assessed at baseline and after 8 weeks of treatment. Participants rated their pain, sleep, and general feelings of sickness each on 10 cm VAS every day; participants recorded any extra medications they took during the study and any adverse events experienced on a daily basis; pressure pain threshold at 10 tender points was assessed at baseline and after 8 weeks of treatment using a dynamometer.	
Notes	Small trial: 20 participants in the active treatment group and 23 participants in the placebo group	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomly selected and each patient received one bottle containing either active medication...or placebo." No other details are given.
Allocation concealment (selection bias)	Unclear risk	No information given, except that there were randomisation codes, and participants received a bottle of medication at the start (which contained either active or placebo drugs).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"There were no detectable difference between the placebo tablets and the tablets containing active compounds regarding color, form, size or taste."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo tablets were identical, so participants remained blinded. Other outcome measures taken by study personnel were objective measures (using a dynamometer), so the data are likely to be unaffected by assessor bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	58 participants were enrolled and randomised, 43 of whom completed the study (23 placebo, 20 active). "Of the 58 patients who initially agreed to participate, 15 dropped out. Two of 15 did not return the VAS and gave no reason

Combination pharmacotherapy for the treatment of fibromyalgia in adults (Review)

Vaeroy 1989 (Continued)

for their noncompliance. Three of 15 dropped out due to lack of therapeutic effect. One of 15 decided not to participate as therapy was not required due to less pain than normal. The remaining 9 of 15 were excluded due to incomplete scoring of the VAS during the 8-week period of the study. Five patients completed 7 weeks, two completed 5 weeks, one completed 4 weeks, and one completed 3 weeks". The balance across treatment groups for dropouts is not given.

Selective reporting (reporting bias)	Unclear risk	The protocol for this trial was not registered.
Size of study	High risk	< 50 participants per arm
Trial Duration	Low risk	≥ 7 weeks (8 weeks)
Similarities of Baseline Characteristics	Unclear risk	Age, sex ratio, and pain scores at baseline were reported, but no statistical comparisons between groups were made.

Vlainich 2010

Methods	Randomised, double-blind, parallel-design, 4-week trial	
Participants	<p>18-60 year old women diagnosed with FM using the 1990 ACR criteria.</p> <p>30 participants were randomised and completed the study.</p> <p>Mean age: 44.7 in the amitriptyline arm, 40.9 in the amitriptyline + lidocaine arm.</p> <p>Potential participants were excluded if they had alterations in thyroid, rheumatological, renal, or hepatic function, if they had trauma, if they had rheumatic, neuromuscular, or psychiatric disease, if they had infectious arthropathy, or drug hypersensitivity, or if they were pregnant.</p>	
Interventions	<p>Amitriptyline + lidocaine: 12.5 mg amitriptyline every night for the first week, increased to 25 mg every night for the remaining 3 weeks + 240 mg lidocaine in 125 mL saline infused i.v. over 1 h once a week for 4 weeks; versus:</p> <p>Amitriptyline + placebo: 12.5 mg amitriptyline every night for the first week, increased to 25 mg every night for the remaining 3 weeks + 125 mL saline infused i.v. over 1 h once a week for 4 weeks.</p>	
Outcomes	<p>All outcomes were assessed at baseline, and weeks 1, 2, 3, and 4, but data are only provided for baseline and week 4. At these time points, pain was reported on a verbal numerical scale from 0-10 and the number of tender points was assessed; additionally, the number of participants experiencing sleep disorders, fatigue, subjective edema, morning stiffness paraesthesia, and headache was recorded.</p> <p>Adverse events were not assessed in this study.</p>	
Notes	Small trial: 15 participants per arm. Participants had been suffering from pain for an average of 5.6 years (amitriptyline alone arm) and 6.8 years (amitriptyline + lidocaine arm)	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The patients were allocated to two groups with the same number of patients by drawing lots".

Vlainich 2010 (Continued)

Allocation concealment (selection bias)	Unclear risk	There is no information given to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants in the placebo group received saline through i.v. instead of lidocaine. However, it is unclear whether the solutions were identical and if not, if data collectors and participants were protected from seeing the i.v. bags.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is no information given to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	A diagram of their protocol flow indicates that all participants randomised to the study completed it (no study dropouts)
Selective reporting (reporting bias)	High risk	How some outcome measures were assessed is not fully described. One outcome measure in the methods section (number of participants experiencing depression) is not reported in the results section, and two outcome measures reported in the results section (number of participants experiencing headache and morning stiffness) are not described in the methods section. Data collected at time points between baseline and week 4 (weeks 1, 2, and 3) are not shown.
Size of study	High risk	< 50 participants per arm
Trial Duration	Unclear risk	3-6 weeks (4 weeks)
Similarities of Baseline Characteristics	Low risk	Age, sex ratio, and pain scores at baseline were reported, and no statistically significant differences were found between treatment groups.

Zucker 2006

Methods	Randomised, double-blind, N-of-1 cross-over design, six 6-week period trial
Participants	<p>18-60 year olds diagnosed with FM using the 1990 ACR criteria who scored ≤ 18 on the Beck Depression Inventory scale. Participants halted their current FM medications for at least 1 week before study start, and were only allowed to take paracetamol (acetaminophen) in addition to their study medications for pain. 58 participants were enrolled; analyses were done on data from participants who completed at least 2 periods (1 session on each therapy, $n = 46$) and on data from participants who completed all 6 periods (3 sessions on each therapy, $n = 34$).</p> <p>Mean age: 43 years; 96.5% of participants were female.</p> <p>Potential participants were excluded if they had contraindications to study drugs, if they had comorbid conditions that might confound FM diagnosis or assessments, if women of childbearing potential did not agree to use appropriate contraception, if they did not stop current FM medications for at least 1 week prior to trial start, or if they used analgesics during the study period (with paracetamol [acetaminophen] being the exception).</p>
Interventions	<p>Amitriptyline + fluoxetine: 20 mg fluoxetine every morning + 25 mg amitriptyline every night; versus</p> <p>Amitriptyline + placebo: placebo every morning + 25 mg amitriptyline every night.</p> <p>Treatments lasted 6 weeks each; participants were given each treatment 3 times for a total of six 6-week treatment periods.</p>

Zucker 2006 (Continued)

Outcomes The following outcomes were assessed at baseline, at the end of each 6-week treatment period, and at a 3-month follow-up visit: FIQ score; participant-assessed 100 mm VAS scores on global well-being, pain, sleep, fatigue, and feeling refreshed upon awakening; physician-assessed 100 mm VAS scores on global well-being and stress; tender point examination score consisting of the sum of scores for each of 18 FM tender points. Participants were also asked at each study visit to report any other medications taken and any adverse events experienced.

Notes Small trial: 58 participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A central pharmacy prepared the blinded, random-ordered treatment kits and block-randomised the first treatment sets, so for every 20 kits prepared, 10 started treatment with AMT [amitriptyline] and 10 started with AMT+FL [amitriptyline + fluoxetine]"
Allocation concealment (selection bias)	Low risk	"A central pharmacy prepared the blinded, random-ordered treatment kits"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	All participants took the same number of pills, regardless of which treatment they were on; however, there is no information on whether all pills were identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is no information given to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of withdrawals and reasons for withdrawal are clearly outlined in Table 2.
Selective reporting (reporting bias)	Unclear risk	The protocol for this trial was not registered.
Size of study	High risk	< 50 participants
Trial Duration	Unclear risk	3-6 weeks (6 weeks)
Similarities of Baseline Characteristics	Low risk	Age, sex ratio, and pain scores at baseline were reported, but not compared between treatment groups since this is a cross-over study. Baseline characteristics were compared between recruitment sites (center vs. community), and no difference was found.

ACR: American College of Rheumatology; **FIQ:** Fibromyalgia Impact Questionnaire; **FM:** fibromyalgia; **ITT:** Intention to treat; **i.v.:** intravenous; **MAOI:** Monoamine Oxidase Inhibitor; **MTD:** Maximal Tolerated Dose; **N:** number (sample size); **NPS:** numerical pain scale; **NPS:** Numerical Pain Scale; **NRS:** numerical rating scale; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **SF-MPQ:** Short-Form McGill Pain Questionnaire; **SF-36:** Short Form 36 Health Survey; **VAS:** Visual Analogue Scale; **5-HTP:** 5-Hydroxytryptophan

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ali 2009	Micronutrients and vitamins are considered to be non-pharmacological therapy

Study	Reason for exclusion
Bagis 2013	Open-label study
Bennett 2005	Study population used in a previous study included in this systematic review.
Calandre 2007	Open-label study
Calandre 2011	Open-label study
Cantini 1994	Open-label study
Cantini 1995	Open-label study
Choi 2015	Not exclusive to fibromyalgia
Cuatrecasas 2007	Open-label add-on study
Cuatrecasas 2011	Conference abstract and add-on study
Cuatrecasas 2012	Add-on study
Farmer 2010	Conference abstract, open-label add-on study
Fossaluzza 1992	Open-label study
Ghini 2016	Open-label study
Holman 2005	Add-on study
Jacobs 1990	Non-pharmacological therapy (Vasolastine and Rheumajecta)
Johnson 1997	Review of a study included in this systematic review
Lange 2011	Non-pharmacological therapy
Le Gallez 1988	Patient population does not have fibromyalgia (soft tissue rheumatism)
Leader 2009	Open-label add-on study
Lister 2002	Open-label study using non-pharmacological therapy (coenzyme Q10 and <i>Gingko biloba</i> extract)
Mease 2013	Open-label study
Nollen 1990	Letter to the editor
Porta 1999	Patient population does not have fibromyalgia (myofascial pain syndrome), and botulinum toxin is considered to be non-pharmacological therapy
Porta 2000	Patient population does not have fibromyalgia (myofascial pain syndrome and chronic muscle spasm), and botulinum toxin is considered to be non-pharmacological therapy
Potvin 2012	Add-on study
Pridgen 2014	Conference abstract
Qin 2009	Single-blinded study

Study	Reason for exclusion
Ramzy 2017	Open-label study
Recla 2009	Study proposal and hypothesis
Rico-Villademoros 2009	Open-label add-on study
Settel 1967	Open-label case series
Szirmai 1974	Patient population does not have fibromyalgia (arterial circulatory disorders, muscle rheumatism, muscle trauma, arthritis and osteoarthritis, and neuralgia)
Vilchez 2009	Conference abstract, and open-label add-on case series
Vlainich 2011	Duplicated data from Vlainich 2010
Zborovsky 1994	Conference abstract, non-randomised study
Zhao 2009	Non-pharmacological therapy (herb partitioned moxibustion)

Characteristics of ongoing studies *[ordered by study ID]*

NCT00991848

Trial name or title	Lidocaine on manifestations of fibromyalgia (LIMAFIBRO)
Methods	Phase 1, double-blind, randomised, parallel-design, 4-week trial
Participants	Adults with fibromyalgia having pain in the 4 quadrants of the body for at least 3 months
Interventions	<p>Amytriptyline + lidocaine: daily treatment with 25 mg amitriptyline for 4 weeks + once-weekly i.v. administration of 240 mg lidocaine versus</p> <p>Amytriptyline + placebo: daily treatment with 25 mg amitriptyline for 4 weeks + once-weekly i.v. administration of saline placebo</p>
Outcomes	Pain intensity and clinical manifestations of fibromyalgia
Starting date	January 2005
Contact information	Study Chair: Rioko K. Sakata, Federal University of São Paulo. Responsible Party: Roberto Vlainich, Federal University of São Paulo
Notes	Similar to Vlainich 2010

NCT01323374

Trial name or title	Study to assess the clinical benefit of droxidopa and droxidopa/carbidopa in subjects with fibromyalgia (FMS201)
Methods	Phase 2, double-blind, randomised, placebo-controlled, parallel-design, 8-week trial

NCT01323374 (Continued)

Participants	Adults with fibromyalgia (diagnosed based on 1990 ACR criteria) who had pain VAS scores of 20 mm-90 mm on the SF-MPQ at screening and baseline visits
Interventions	Droxidopa: 200 mg, 400 mg, or 600 mg daily versus Carbidopa: 25 mg or 50 mg daily versus Droxidopa + carbidopa: their combination (all possible dosage pairings) versus Placebo
Outcomes	Pain, depression, fatigue, sleep disorder, quality of life, dose response relationship, optimal dose for treatment of fibromyalgia, adverse events, blood pressure, heart rate, ECG, and laboratory findings
Starting date	January 2009
Contact information	Principal Investigator: Ernest Choy, Department of Rheumatology, Kings College London. Sponsor: Chelsea Therapeutics, UK
Notes	

NCT01850420

Trial name or title	A study of IMC-1 in patients with fibromyalgia
Methods	Phase 2, double-blind, randomised, placebo-controlled, parallel-design, 16-week trial
Participants	Adults with fibromyalgia
Interventions	IMC-1: proprietary combination of famciclovir and celecoxib versus P placebo
Outcomes	Change in pain from baseline to week 16 of treatment, patient global impression of change from baseline to week 16 of treatment, FIQ scores
Starting date	May 2013
Contact information	Sponsor/responsible party: Innovative Med Concepts, LLC
Notes	Identified in database search as a conference abstract (Pridgen 2014)

ACR: American College of Rheumatologists; **ECG:** Electrocardiogram; **FIQ:** Fibromyalgia Impact Questionnaire; **i.v.:** intravenous; **SF-MPQ:** Short-Form McGill Pain Questionnaire;

ADDITIONAL TABLES

Table 1. Methodology of included trials

First author, year	Trial comparisons
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Table 1. Methodology of included trials *(Continued)*

	Place- bo-con- trolled	Combi- nation vs. only 1 compo- nent	Combina- tion vs. both components	Combina- tion vs. other
Albertoni Giraldes 2016	+	+		
Bennett 2003	+			
de Zanette 2014			+	
Gilron 2016	+		+	
Goldenberg 1986	+		+	
Goldenberg 1996	+		+	
Hussain 2011			+	
Kravitz 1994	+		+	
Nicolodi 1996			+	^a
Pridgen 2017	+			+
Quijada-Carrera 1996	+		+	
Russell 1991	+		+	
Russell 1995	+			
Vaeroy 1989	+			
Vlainich 2010		+		
Zucker 2006		+		

^a[Nicolodi 1996](#) compared a monoamine oxidase inhibitor, 5-hydroxytryptophan, their combination, and amitriptyline.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Library)

#1 MeSH descriptor: [Fibromyalgia] this term only

#2 MeSH descriptor: [Myofascial Pain Syndromes] explode all trees

#3 (fibromyalgia* or fibrositi* or myofascial pain):ti,ab,kw (Word variations have been searched)

#4 #1 or #2 or #3

#5 MeSH descriptor: [Drug Therapy, Combination] explode all trees

#6 (combin* or cotreat* or co-treat* or coadministr* or co-administr* or synerg* or isobol* or "add on*" or polytherapy):ti,ab,kw (Word variations have been searched)

#7 #5 or #6

#8 #4 and #7

MEDLINE (OVID)

1 Fibromyalgia/

2 exp Myofascial Pain Syndromes/

3 (fibromyalgia\$ or fibrositi\$ or myofascial pain).tw.

4 or/1-3

5 exp Drug Therapy, Combination/

6 (combin\$ or cotreat\$ or co-treat\$ or coadministr\$ or co-administr\$ or synerg\$ or isobol\$ or "add on\$" or polytherapy).tw.

7 or/5-6

8 4 and 7

9 randomized controlled trial.pt.

10 controlled clinical trial.pt.

11 randomized.ab.

12 placebo.ab.

13 drug therapy.fs.

14 randomly.ab.

15 trial.ab.

16 or/9-15

17 exp animals/ not humans.sh.

18 16 not 17

19 8 and 18

Embase (OVID)

1 Fibromyalgia/

2 Myofascial pain syndromes/

3 (fibromyalgia\$ or fibrositi\$ or myofascial pain).tw.

4 or/1-3

5 exp Drug Therapy, Combination/

6 (combin\$ or cotreat\$ or co-treat\$ or coadministr\$ or co-administr\$ or synerg\$ or isobol\$ or "add on\$" or polytherapy).tw.

7 or/5-6

8 4 and 7

9 random\$.tw.

10 factorial\$.tw.

- 11 crossover\$.tw.
- 12 cross over\$.tw.
- 13 cross-over\$.tw.
- 14 placebo\$.tw.
- 15 (doubl\$ adj blind\$).tw.
- 16 (singl\$ adj blind\$).tw.
- 17 assign\$.tw.
- 18 allocat\$.tw.
- 19 volunteer\$.tw.
- 20 Crossover Procedure/
- 21 double-blind procedure.tw.
- 22 Randomized Controlled Trial/
- 23 Single Blind Procedure/
- 24 or/9-23
- 25 (animal/ or nonhuman/) not human/
- 26 24 not 25
- 27 8 and 26

Appendix 2. 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 2011b](#)).

- **High:** randomised trials; or double-upgraded observational studies.
- **Moderate:** downgraded randomised trials; or upgraded observational studies.
- **Low:** double-downgraded randomised trials; or observational studies.
- **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:

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

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

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

WHAT'S NEW

Date	Event	Description
18 February 2020	Amended	Clarification added to Declarations of interest .

HISTORY

Protocol first published: Issue 6, 2013

Review first published: Issue 2, 2018

Date	Event	Description
3 July 2013	Amended	Minor amendment to the search strategy.

CONTRIBUTIONS OF AUTHORS

The title was registered by IG. The protocol was written by IG, BS, RAM and PW. JBT and IG assessed inclusion of papers and extracted data. JBT took on lead authorship for the full review and wrote up the review. IG, JBT, RAM and PW contributed to the final draft and approved the published version. IG will be responsible for the update.

DECLARATIONS OF INTEREST

JT: none known.

BS: none known.

RAM has received grant support from Grünenthal relating to individual, patient-level analyses of trial data regarding tapentadol in osteoarthritis and back pain (2015). He has received honoraria for attending boards with RB on understanding pharmacokinetics of drug uptake (2015). He has received honoraria from Omega Pharma (2016) and Futura Pharma (2016) for providing advice on trial and data analysis methods.

PW: none known.

IG is an anaesthesiologist and conducts clinical trials in acute and chronic pain conditions. He has received lecture/consultancy fees from Biogen (2016) and Adynxx (2015). IG, who is the lead and corresponding author on one of the included studies in this review, did not participate in data extraction or assessments pertaining to that study.

This review was identified in a 2019 audit as not meeting the current definition of the Cochrane Commercial Sponsorship policy. At the time of its publication it was compliant with the interpretation of the existing policy. As with all reviews, new and updated, at update this review will be revised according to 2020 policy update.

SOURCES OF SUPPORT

Internal sources

- Queen's University Department of Anesthesiology & Perioperative Medicine, Canada.

Research time support

External sources

- Canadian Institutes of Health Research - Industry-Partnered (Pfizer) Investigator Award to IG, Canada.

Salary support

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added a description of how we evaluated the quality of the evidence using GRADE, and we added a description of the criteria we used for rating the risk of bias as low, unclear, or high. We did not apply Oxford Quality Scores ([Jadad 1996](#)) to the studies assessed for inclusion due to redundancies with the 'Risk of bias' assessments used ([Higgins 2011a](#); [Higgins 2011b](#)).

We also refined our data analysis section to describe in detail methods we planned to use in the event of there being adequate data, and provided a justification and references for making judgements of very low quality evidence in the event of there being little or no data available.

INDEX TERMS

Medical Subject Headings (MeSH)

5-Hydroxytryptophan [therapeutic use]; Acetaminophen [therapeutic use]; Amitriptyline [therapeutic use]; Anti-Inflammatory Agents, Non-Steroidal [therapeutic use]; Antidepressive Agents [therapeutic use]; Benzodiazepines [therapeutic use]; Carisoprodol [therapeutic use]; Drug Therapy, Combination [methods]; Duloxetine Hydrochloride [therapeutic use]; Fibromyalgia [*drug therapy]; Fluoxetine [therapeutic use]; Magnesium [therapeutic use]; Malates [therapeutic use]; Melatonin [therapeutic use]; Monoamine Oxidase Inhibitors [therapeutic use]; Muscle Relaxants, Central [therapeutic use]; Pregabalin [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans