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Mirtazapine for fibromyalgia in adults (Review)

Welsch P, Bernardy K, Derry S, Moore RA, Häuser W

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[Intervention Review]

Mirtazapine for fibromyalgia in adults

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ABSTRACT

Background

Fibromyalgia is a clinically defined chronic condition of unknown etiology characterised by chronic widespread pain, sleep disturbance, cognitive dysfunction, and fatigue. Many patients report high disability levels and poor quality of life. Drug therapy aims to reduce key symptoms, especially pain, and improve quality of life. The tetracyclic antidepressant, mirtazapine, may help by increasing serotonin and noradrenaline in the central nervous system (CNS).

Objectives

To assess the efficacy, tolerability and safety of the tetracyclic antidepressant, mirtazapine, compared with placebo or other active drug(s) in the treatment of fibromyalgia in adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, SCOPUS, the US National Institutes of Health, and the World Health Organization (WHO) International Clinical Trials Registry Platform for published and ongoing trials, and examined reference lists of reviewed articles, to 9 July 2018.

Selection criteria

Randomised controlled trials (RCTs) of any formulation of mirtazapine against placebo, or any other active treatment of fibromyalgia, in adults.

Data collection and analysis

Two review authors independently extracted study characteristics, outcomes of efficacy, tolerability and safety, examined issues of study quality, and assessed risk of bias, resolving discrepancies by discussion. Primary outcomes were participant-reported pain relief (at least 50% or 30% pain reduction), Patient Global Impression of Change (PGIC; much or very much improved), safety (serious adverse events), and tolerability (adverse event withdrawal). Other outcomes were health-related quality of life (HRQoL) improved by 20% or more, fatigue, sleep problems, mean pain intensity, negative mood and particular adverse events. We used a random-effects model to calculate risk difference (RD), standardised mean difference (SMD), and numbers needed to treat. We assessed the evidence using GRADE and created a 'Summary of findings' table.

Main results

Three studies with 606 participants compared mirtazapine with placebo (but not other drugs) over seven to 13 weeks. Two studies were at unclear or high risk of bias in six or seven of eight domains. We judged the evidence for all outcomes to be low- or very low-quality because of poor study quality, indirectness, imprecision, risk of publication bias, and sometimes low numbers of events.

There was no difference between mirtazapine and placebo for any primary outcome: participant-reported pain relief of 50% or greater (22% versus 16%; RD 0.05, 95% confidence interval (CI) -0.01 to 0.12; three studies with 591 participants; low-quality evidence); no data available for PGIC; only a single serious adverse event for evaluation of safety (RD -0.00, 95% CI -0.01 to 0.02; three studies with 606 participants; very low-quality evidence); and tolerability as frequency of dropouts due to adverse events (3% versus 2%; RD 0.00, 95% CI -0.02 to 0.03; three studies with 606 participants; low-quality evidence).

Mirtazapine showed a clinically-relevant benefit compared to placebo for some secondary outcomes: participant-reported pain relief of 30% or greater (47% versus 34%; RD 0.13, 95% CI 0.05 to 0.21; number needed to treat for an additional beneficial outcome (NNTB) 8, 95% CI 5 to 20; three studies with 591 participants; low-quality evidence); participant-reported mean pain intensity (SMD -0.29, 95% CI -0.46 to -0.13; three studies with 591 participants; low-quality evidence); and participant-reported sleep problems (SMD -0.23, 95% CI -0.39 to -0.06; three studies with 573 participants; low-quality evidence). There was no benefit for improvement of participant-reported improvement of HRQoL of 20% or greater (58% versus 50%; RD 0.08, 95% CI -0.01 to 0.16; three studies with 586 participants; low-quality evidence); participant-reported fatigue (SMD -0.02, 95% CI -0.19 to 0.16; two studies with 533 participants; low-quality evidence); participant-reported negative mood (SMD -0.67, 95% CI -1.44 to 0.10; three studies with 588 participants; low-quality evidence); or withdrawals due to lack of efficacy (1.5% versus 0.1%; RD 0.01, 95% CI -0.01 to 0.02; three studies with 605 participants; very low-quality evidence).

There was no difference between mirtazapine and placebo for participants reporting any adverse event (76% versus 59%; RD 0.12, 95 CI -0.01 to 0.26; three studies with 606 participants; low-quality evidence). There was a clinically-relevant harm with mirtazapine compared to placebo: in the number of participants with somnolence (42% versus 14%; RD 0.24, 95% CI 0.18 to 0.30; number needed to treat for an additional harmful outcome (NNTH) 5, 95% CI 3 to 6; three studies with 606 participants; low-quality evidence); weight gain (19% versus 1%; RD 0.17, 95% CI 0.11 to 0.23; NNTH 6, 95% CI 5 to 10; three studies with 606 participants; low-quality evidence); and elevated alanine aminotransferase (13% versus 2%; RD 0.13, 95% CI 0.04 to 0.22; NNTH 8, 95% CI 5 to 25; two studies with 566 participants; low-quality evidence).

Authors' conclusions

Studies demonstrated no benefit of mirtazapine over placebo for pain relief of 50% or greater, PGIC, improvement of HRQoL of 20% or greater, or reduction of fatigue or negative mood. Clinically-relevant benefits were shown for pain relief of 30% or greater, reduction of mean pain intensity, and sleep problems. Somnolence, weight gain, and elevated alanine aminotransferase were more frequent with mirtazapine than placebo. The quality of evidence was low or very low, with two of three studies of questionable quality and issues over indirectness and risk of publication bias. On balance, any potential benefits of mirtazapine in fibromyalgia were outweighed by its potential harms, though, a small minority of people with fibromyalgia might experience substantial symptom relief without clinically-relevant adverse events.

PLAIN LANGUAGE SUMMARY

Mirtazapine for treating fibromyalgia in adults

Bottom line

Mirtazapine at 15 mg to 45 mg daily is unlikely to substantially reduce pain in people with fibromyalgia. Mirtazapine can cause drowsiness, weight gain, and liver damage. A small number of people may experience some improvement (moderate pain relief, better sleep) without side effects from mirtazapine, but that cannot be predicted. The off-label use of mirtazapine can be considered, if established treatment options have failed.

Background

People with fibromyalgia often have chronic (longer than 3 months) widespread pain, and problems with sleeping, thinking, exhaustion, and poor quality of life. There is no cure for fibromyalgia. Treatments aim to improve symptoms (pain, sleep problems, fatigue) and quality of life.

Serotonin and noradrenaline are chemicals produced by the human body and are involved in pain, sleep, and mood. Low serotonin levels have been found in people with fibromyalgia. The antidepressant, mirtazapine, increases serotonin and noradrenaline levels in the brain.

Study characteristics

In July 2018 we searched for clinical trials where mirtazapine was used to treat fibromyalgia in adults. We found three studies with 606 participants. Studies were seven to 13 weeks long. They compared mirtazapine 15 mg to 45 mg daily against a fake medication (placebo).

Key results

There was no difference between mirtazapine and placebo for any primary outcome: mirtazapine and placebo reduced pain by 50% in two of 10 people (low-quality evidence). Only one single serious adverse event was available for evaluation of safety (very low-quality evidence). Three of 10 participants with mirtazapine and two of 10 participants with placebo dropped out of the trial due to side effects (low-quality evidence).

Mirtazapine reduced pain by 30% or more in five out of 10 people, compared with three out of 10 with placebo (low-quality evidence). It was also better for average pain intensity (low-quality evidence) and sleep problems (low-quality evidence). Mirtazapine was not better than placebo in reducing fatigue, depression, or improving health-related quality of life (low-quality evidence). Mirtazapine and placebo were no different in how many participants experienced a side effect (low-quality evidence). People dropped out at the same rate with mirtazapine and placebo or because they felt the drug did not work (low-quality evidence). For some side effects, mirtazapine was worse than placebo. This was true for drowsiness (4 out of 10 with mirtazapine, 1 out of 10 with placebo), weight gain (2 out of 10 with mirtazapine, 0 out of 10 with placebo), and high liver enzymes (1 out of 10 with mirtazapine, 0 out of 10 with placebo) (low-quality evidence).

Quality of the evidence

Two of the studies were of poor quality. We rated the quality of the evidence 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. We judged that the evidence was mostly of low-quality, which means that while the research provides some indication of the likely effect, the true effect may be substantially different. The main issues were poor study quality, decisions about the types of people included in the studies, risk of important information not being published, and sometimes low numbers of events.

SUMMARY OF FINDINGS

Summary of findings 1. Mirtazapine compared with placebo for adult participants with fibromyalgia

Mirtazapine compared with placebo for adult participants with fibromyalgia

Patient or population: adult participants with fibromyalgia

Settings: study centres

Intervention: mirtazapine 15 mg/d to 45 mg/d

Comparison: placebo

Outcomes (study duration of 7 to 13 weeks)	Probable outcome with mirtazapine (95% CI)	Probable outcome with placebo (95% CI)	Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
Participant-reported pain relief of 50% or greater (substantial improvement)	218 (200 to 236) per 1000	158 (145 to 171) per 1000	RD 0.05 (-0.01 to 0.12)	591 (3 studies)	Low[a]	NNTB not calculated due to lack of statistically significant difference between mirtazapine and placebo
Safety: serious adverse events	1 event in 334 participants	0 event ins 271 participants	RD 0.00 (-0.01 to 0.02)	606 (3 studies)	Very low[b]	Meaningful calculations not possible with a single event
Tolerability: withdrawals due to adverse events	33 (30 to 39) per 1000	22 (20 to 24) per 1000	RD 0.01 (-0.02 to 0.03)	606 (3 studies)	Low[a]	NNTB not calculated due to lack of statistically significant difference between mirtazapine and placebo
Participant-reported pain relief of 30% or greater (moderate improvement)	472 (434 to 510) per 1000	336 (309 to 363) per 1000	RD 0.13 (0.05 to 0.21)	591 (3 studies)	Low[a]	NNTB was 8 (95% CI 5 to 20). Only 149 extra participants in trials of zero treatment effect to move NNTB for pain relief of 30% or greater from 8 to limit for clinical utility of 10 (25% of total number available)
Participant-reported sleep problems (scale: 0 to 28; higher scores indicate more sleep problems)	Mean sleep problems score was 4.9 points lower (1.3 to 8.3 points lower)	Baseline mean score 11.4 (SD 5.9)[c]	SMD -0.23 (-0.39 to -0.06)	573 (3 studies)	Low[a]	NNTB 10 (95% CI 7 to 12)

Somnolence	423 (389 to 457) per 1000	136 (125 to 147) per 1000	RD 0.24 (0.18 to 0.30)	606 (3 studies)	Low[a]	NNTH 5 (95% CI 3 to 6)
Weight gain	189 (180 to 200) per 1000	19 per 1000 (not calculated)	RD 0.17 (0.11 to 0.23)	606 (3 studies)	Low[a]	NNTH 6 (95% 5 to 9)

CI: confidence interval; **NNTB:** number needed to treat for an additional benefit; **NNTH:** number needed to treat for an additional harm; **PGIC:** Patient Global Impression of Change; **RD:** risk difference;**SMD**: standardised mean difference

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.

[a]Downgraded twice for indirectness (participants with inflammatory rheumatic diseases and depressive disorders excluded in > 50% of studies) and risk of publication bias.
[b]Downgraded three times for imprecision due to low event rate, indirectness, and risk of publication bias.
[c]From Miki 2016; N = 422 participants; Japanese version of the Insomnia severity index.

BACKGROUND

This review is based on a template for reviews of drugs used to relieve fibromyalgia. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Appendix 1).

Description of the condition

Fibromyalgia has been defined as widespread pain that lasts for longer than three months, with pain on palpation at 11 or more of 18 specified tender points (Wolfe 1990). It is frequently associated with other symptoms, such as poor sleep, fatigue, and depression (Häuser 2015a; Wolfe 2014). Fibromyalgia symptoms can be assessed by self-report of the patient via the fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the American College of Rheumatology (ACR) preliminary diagnostic criteria for fibromyalgia (the Fibromyalgia Symptom Questionnaire) (Wolfe 2011a). For a clinical diagnosis, the ACR 1990 classification criteria (Wolfe 1990), the ACR 2010 preliminary diagnostic criteria (Wolfe 2010), and the 2016 criteria can be used (Wolfe 2016). Lacking a specific laboratory test, diagnosis is established by a history of the key symptoms and the exclusion of somatic diseases sufficiently explaining the key symptoms (Häuser 2015a).

Fibromyalgia is a heterogenous condition. The definite aetiology (cause) of this syndrome remains unknown. A model of interacting biological and psychosocial variables in the predisposition, triggering, and development of the chronicity of fibromyalgia symptoms has been suggested (Üceyler 2017). Genetics (Arnold 2012a; Lee 2012), depression (Chang 2014; Forseth 1999), physical and sexual abuse in childhood (Häuser 2011), obesity combined with physical inactivity (Mork 2010), sleep problems (Mork 2012), and smoking (Choi 2011), might predispose a person to the development of fibromyalgia. Inflammatory rheumatic diseases (Lee 2013; Wolfe 2011b), psychosocial stress (e.g. workplace and family conflicts) and physical stress (e.g. infections, surgery, accidents) might trigger the onset of chronic widespread pain and fatigue (Clauw 2014). Depression and post-traumatic stress disorder worsen fibromyalgia symptoms (Häuser 2013b; Lange 2010).

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

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

People with fibromyalgia often report high disability levels and poor quality of life, along with extensive use of medical care (Häuser 2015a). Many people with fibromyalgia are significantly disabled, and experience moderate or severe pain for many years (Bennett 2007). Chronic painful conditions comprised five of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and are responsible for considerable loss of quality of life and employment, and increased health costs (Moore 2014a).

Fibromyalgia pain is known to be 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, combining pharmacological interventions with physical or cognitive interventions, or both. Interventions aim to reduce the key symptoms of fibromyalgia (pain, sleep problems, fatigue) and the associated symptoms (e.g. depression, disability) and to improve daily functioning (Fitzcharles 2012; Macfarlane 2017; Petzke 2017). Conventional analgesics are usually not effective. Treatment is often by so-called pain modulators, such as antidepressants like duloxetine and amitriptyline (Häuser 2013a; Lunn 2014; Moore 2012a), or antiepileptics like gabapentin or pregabalin (Cooper 2017; Moore 2009; Wiffen 2013). The proportion of people who achieve worthwhile pain relief (typically at least a 50% reduction in pain intensity; Moore 2013a) is small, generally only 10% to 15% more than with placebo, with number needed to treat for an additional beneficial outcome (NNTB) usually between 6 and 14 (Wiffen 2013). Those who do experience good levels of pain relief with pregabalin also benefit from substantial improvements in other symptoms, such as fatigue, function, sleep, depression, anxiety, and ability to work, with significant improvement in quality of life (Moore 2010b; Moore 2014a). 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

Mirtazapine is an atypical antidepressant with noradrenergic and specific serotonergic activity. It is licensed for use in major depressive disorders, but not in fibromyalgia. It is also used off-label for a variety of other disorders, including anxiety-related disorders and insomnia. Mirtazapine is administered orally, preferably once a day at bedtime. The recommended dosages for the treatment of depression range between 15 mg/d and 45 mg/d.

Mirtazapine is regarded to be a well-tolerated and safe antidepressant. Studies have demonstrated a significantly lower percentage of participants reporting any adverse clinical experiences with mirtazapine (65%) when compared with placebo (76%) or amitriptyline (87%) (Montgomery 1995). Moreover, dropout rates due to adverse clinical experiences were significantly lower than in the amitriptyline treatment group. Data show there are few cardiotoxic properties when used in participants with heart failure (Montgomery 1995).

How the intervention might work

Mirtazapine blocks the alpha 2 adrenergic auto- and heteroreceptors (enhancing noradrenaline release), and selectively antagonises the 5-hydroxytryptamine receptor 2 (5-HT2) serotonin receptors in the central and peripheral nervous system. It also enhances serotonin neurotransmission at the 5-HT1 receptor 1 and blocks the histaminergic and muscarinic receptors. Mirtazapine is not a serotonin norepinephrine reuptake inhibitor but increases serotonin and noradrenaline by other mechanisms of action (Kent 2000). Based on these pharmacological mechanisms, mirtazapine is classified as a noradrenergic and specific serotonergic antidepressant. In structure, mirtazapine can also be classified as a tetracyclic antidepressant (Antilla 2000). Based on its pharmacologic profile, mirtazapine has the potential to be beneficial in the treatment of fibromyalgia, especially in people who suffer from sleep disturbances (Dolder 2012).

Why it is important to do this review

The serotonin-norepinephrine reuptake inhibitor antidepressants, duloxetine and milnacipran, have been approved by the Food and Drug Administration (FDA), but not by the European Medicines Agency (EMA) for fibromyalgia (Häuser 2013a). Both drugs increase the availability of serotonin 5-HT and norepinephrine at CNS synaptic clefts. They have the potential to reduce pain by correcting the functional deficit of 5-HT and norepinephrine neurotransmission in the descending inhibitory pain pathway. These antidepressants are effective in relieving one key symptom of fibromyalgia, namely pain, but do not reduce sleep problems to a clinically-relevant degree (Häuser 2013a). There is a need for additional pharmacological therapeutic options for the treatment of the key fibromyalgia symptoms of pain, sleep problems and fatigue.

A patient survey in 2012 demonstrated that mirtazapine was rarely used by patients with fibromyalgia (Häuser 2012). However, uncontrolled trials suggested that mirtazapine might be effective in relieving fibromyalgia symptoms (Samborski 2004). The use of mirtazapine to reduce sleep problems is discussed in fibromyalgia Internet chats (WebMD Fibromyalgia Community 2009). Mirtazapine increases the pain threshold in healthy adults (Arnold 2008). Moreover, a large (594 participants), open, postmarketing survey of the use of mirtazapine in people with chronic pain and concomitant depression, demonstrated that after six weeks almost 70% of participants reported light or no pain on a faces scale, compared with 90% having severe or worst pain at baseline (Freynhagen 2006). There is, therefore, a need to evaluate the efficacy, tolerability and safety of mirtazapine in fibromyalgia in order to assist people with fibromyalgia and doctors in shared decision making on additional pharmacological treatment options.

The standards used to assess evidence in chronic pain trials have changed substantially, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The most important change is the move from using average pain scores, or average change in pain scores, to the number of people who have a large decrease in pain (by at least 50%) and who continue in treatment, ideally in trials of eight to 12 weeks or longer. Pain intensity reduction of 50% or more has been shown to correlate with improvements in comorbid symptoms, function, and quality of life for people with chronic pain (Conaghan 2015; Moore 2013a; Peloso 2016), and specifically fibromyalgia (Moore 2010b; Straube 2011). These standards are set out in the reference guide for pain reviews (PaPaS 2012).

In this Cochrane Review we assessed evidence using methods that make both statistical and clinical sense, and used a developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). We required a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc.), and requirements for clinically-relevant benefit (number needed to treat for an additional beneficial outcome (NNTB) is less than 10); Moore 1998). This approach sets high standards and marks a departure from how reviews were conducted previously.

OBJECTIVES

To assess the efficacy, tolerability and safety of the tetracyclic antidepressant, mirtazapine, compared with placebo or other active drug(s) in the treatment of fibromyalgia in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with double-blind assessment of participant outcomes following four weeks of treatment or longer. We included trials with a parallel, cross-over, and enriched enrolment randomised withdrawal design. We did not include N-of-1 studies. We required full journal publication, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts with sufficient data for analysis. We did not include short abstracts (usually meeting reports). We excluded studies that were nonrandomised, studies of experimental pain, case reports, and clinical observations.

Types of participants

Studies included adult participants aged 18 years and above, diagnosed with fibromyalgia using the American College of Rheumatology (ACR) 1990 classification criteria (Wolfe 1990), the ACR 2010 preliminary diagnostic criteria (Wolfe 2010), or the modified ACR 2010 preliminary diagnostic criteria (research criteria) (Wolfe 2011a).

Types of interventions

We included studies that administered mirtazapine at any dose, by any route, for the relief of fibromyalgia symptoms, compared to placebo or any active comparator.

Types of outcome measures

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

These are defined as at least 30% pain relief over baseline (moderate), at least 50% pain relief over baseline (substantial), much or very much improved on Patient Global Impression of

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

Primary outcomes

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

Secondary outcomes

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

Search methods for identification of studies

Electronic searches

We searched the following databases from inception and without language restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL via Cochrane Register of Studies Online) on 9 July 2018.
- MEDLINE (via Ovid) from 1947 to 9 July 2018.
- Embase (via Ovid), from 1974 to 9 July 2018.
- Scopus (via Ovid) from 1974 to 9 July 2018.

The search strategies for CENTRAL, MEDLINE, Embase, SCOPUS, and other databases are shown in Appendix 2, Appendix 3, Appendix 4, Appendix 5, and Appendix 6, respectively.

Searching other resources

We reviewed the bibliographies of any RCTs and review articles identified. We searched the following clinical trial databases to identify additional published or unpublished data: US National Insitutes of Health (ClinicalTrials.gov), and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/). We contacted investigators and study sponsors for additional information.

Data collection and analysis

Selection of studies

We determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria, and obtained full copies of the remaining studies. Two review authors (WH, PW) made the decisions. Two review authors (WH, PW) then read these studies independently and reached agreement about inclusion by discussion. We did not anonymise the studies in any way before assessment. We created a PRISMA flow chart (Moher 2009).

Data extraction and management

Two review authors (WH, RAM) extracted data independently using a standard form and checked for agreement before entry into Review Manager 5 (Review Manager 2014). We extracted information about the study setting, demographic and clinical variables of the participants, number of participants treated, drug and dosing regimen, comedication, study design (placebo or active control; parallel, cross-over, or enriched enrolment randomised withdrawal), study duration and follow-up, 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

We used the Oxford Quality Score as the basis for inclusion (Jadad 1996), limiting inclusion to studies that were randomised and double-blind as a minimum.

Two review authors (WH, RAM) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), 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) or unclear risk of bias (when the method used to generate the sequence was not clearly stated). We excluded studies at a high risk of bias that use a nonrandom 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) or unclear risk of bias (when method 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 detection 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 stated that it was blinded and described the method used to achieve blinding, for example, identical tablets, matched in appearance and smell) or unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We excluded studies at a high risk of bias where participants and study personnel were not blinded.
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that outcome assessor was not involved in treatment); unclear risk of bias (study stated that the assessor was blinded but did not provide an adequate description of how it was achieved); high risk of bias (outcome assessors not blinded to treatment).
- 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' analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); or high risk of bias (used 'completer' analysis).
- Reporting bias due to selective outcome reporting (reporting bias). We checked if an a priori study protocol was available and if all outcomes of the study protocol were reported in the publications of the study. We assessed the methods used to deal with incomplete data as: low risk of reporting bias if the study protocol was available and all of the study's prespecified (primary and secondary) outcomes that were of interest in the review were reported in the prespecified way, or if the study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon); high risk of reporting bias if not all of the study's prespecified primary outcomes were reported; one or more primary outcomes was reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis; the study report did not include results for a key outcome that would be expected to have been reported for such a study. We assessed the methods as unclear risk of bias if insufficient information was available to permit judgement of 'low risk' or 'high risk'.
- Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (when there were 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).
- Group similarity at baseline (selection bias). We assessed similarity of the study groups at baseline for the most important prognostic clinical and demographic indicators. We assigned a low risk of bias if groups were similar at baseline for demographic factors, value of main outcome measure(s) and important prognostic factors. We assigned an unclear risk of bias if important prognostic clinical and demographic indicators were not reported, and a high risk of bias if groups were not similar at baseline for demographic factors, value of main outcome measure(s), and important prognostic factor.

Two review authors (WH, PW) made quality ratings separately for each of the eight methodology quality indicators as defined by the 'Risk of bias' tool. We defined a study to be of high quality if six to eight of the domains were at low risk of bias, to be of moderate quality if three to five of eight domains were at low risk of bias, and to be of low quality if zero to two of eight domains were at low risk of bias (Schaefert 2015).

Measures of treatment effect

We calculated number needed to treat for an additional beneficial outcome (NNTB) as the reciprocal of the absolute risk reduction (ARR; McQuay 1998). For unwanted effects, the NNTB becomes the number needed to treat for an additional harmful outcome (NNTH) and is calculated in the same manner.

We used the following terms to describe adverse outcomes in terms of harm or prevention of harm.

- When significantly fewer adverse outcomes occurred with treatment than with control (placebo or active), we used the term: 'number needed to treat to prevent one event (NNTp)'.
- When significantly more adverse outcomes occurred with treatment compared with control (placebo or active), we used the term: 'number needed to treat for an additional harmful outcome (NNTH)'.

In the event we judged there to be clinical heterogeneity between the studies, and so we used a random-effects analysis throughout.

For dichotomous data we calculated risk differences (RDs) (inverse variance method) with 95% confidence intervals (CIs) using a random-effects model (see below). We set the threshold for a clinically-relevant benefit for categorical variables as a NNTB of less than 10 (Moore 2008).

For continuous data we calculated standardised mean differences (SMDs) with 95% CIs using a random-effects model. We used Cohen's categories to evaluate the magnitude of the effect size, calculated by SMD, with Hedges' g of 0.2 = small, 0.5 = medium and 0.8 = large (Cohen 1988). We considered $g < 0.2$ to be a 'not substantial' effect size. We assumed a minimally important difference if Hedges' g was ≥ 0.2 (Fayers 2014). We calculated the NNTB for continuous variables (sleep problems, fatigue) using the Wells calculator software available at Cochrane Musculoskeletal

editorial office, which estimates from SMDs the proportion of participants who benefit from treatment. We used a minimal clinically important difference of 20% for the calculation of NNTB from SMDs for continuous outcomes.

Unit of analysis issues

We split the control treatment arm between active treatment arms in a single study if the active treatment arms were not combined for analysis.

Dealing with missing data

We used intention-to-treat (ITT) analysis where the ITT population consists of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one postbaseline assessment. We assigned missing participants zero improvement wherever possible. Where standard deviations (SDs) were not reported, we calculated them from P values, CIs or standard errors, where reported in articles (Higgins 2011). Where 30% and 50% pain relief rates and 20% Fibromyalgia Impact Questionnaire (FIQ) improvement rates were not reported and not provided on request, we calculated them from means and SDs by a validated imputation method (Furukawa 2005).

Assessment of heterogeneity

We dealt with clinical heterogeneity by combining studies that examined similar conditions. We assessed statistical heterogeneity visually (L'Abbé 1987), and with the use of the I^2 statistic. When the I^2 value was greater than 50%, we considered possible reasons for this.

Assessment of reporting biases

We aimed to use dichotomous outcomes of known utility and of value to people with fibromyalgia (Hoffman 2010; Moore 2010b; Moore 2010c; Moore 2010d; Moore 2013a).

We assessed 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 of 10 or higher; Moore 2008).

Data synthesis

We planned to use a fixed-effect model for meta-analysis. However, we judged there to be clinical heterogeneity between the studies, and so we used a random-effects analysis throughout.

We undertook quantitative synthesis and present data in forest plots where sufficient data were available. In the event of substantial clinical heterogeneity, we switched off the totals in the forest plots.

We undertook a meta-analysis only if participants, interventions, comparisons, and outcomes were judged to be sufficiently similar to ensure an answer that is clinically meaningful, and only where there were data from at least two studies and 200 participants for analysis.

We used Review Manager 5 for meta-analysis (Review Manager 2014), and Excel for NNTB and NNTH.

Quality of the evidence

We used the GRADE approach to assess the quality of evidence related to each of the key outcomes listed in Types of outcome measures (Chapter 12, Higgins 2011), and to interpret findings (Guyatt 2011; Langendam 2013). The GRADE approach defines the quality of the evidence as the extent of confidence in the estimates of treatment benefits and their safety as follows.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: 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: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (Chapter 12, Higgins 2011).

- 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 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.

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).

We considered the following potential reasons to downgrade the quality of evidence (Guyatt 2011; Häuser 2015b).

- Limitations of study design: where more than 50% of participants were from low-quality studies as defined by the 'Risk of bias' tool.
- Inconsistency of results: where point estimates varied widely across studies or CIs of studies showed minimal or no overlap (Guyatt 2011).
- Imprecision: where there was only one study or, where there was more than one study, the total number of participants was fewer than 400 or where there were so few data that the results were

highly susceptible to the random play of chance (McQuay 1998; Thorlund 2011).

- Indirectness: if exclusion of participants with inflammatory rheumatic disease or anxiety and depressive disorders, or both, in the included studies resulted in ≥ 50% of the total patient collective of the systematic review coming from studies in which participants with inflammatory rheumatic or anxiety and depressive disorders, or both, were excluded. This takes into account whether the question being addressed by the systematic review diverged from the available evidence, in terms of the population in routine clinical care.
- Imputation: if studies used last observation carried forward (LOCF) imputation in circumstances where there were substantial differences in adverse event withdrawals (Moore 2012b).
- Publication bias: where there was potential for publication bias, based on the amount of unpublished data required to make the result clinically irrelevant (Moore 2008), or where there was any concern over selective reporting influencing efficacy or harm estimates.

We paid particular attention to inconsistency, indirectness and imprecision. In addition, circumstances arose where the overall rating for a particular outcome needs to be adjusted as recommended by GRADE guidelines (Guyatt 2013a); for example, where 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 report the level of evidence as very low-quality (Guyatt 2013b).

Two review authors (KB, WH) independently made quality ratings separately for each of the 14 outcomes.

'Summary of findings' table

We created a 'Summary of findings' table to provide outcome-specific information concerning the overall quality of evidence from studies included in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes we considered (Summary of findings 1).

Summary of findings 1 includes outcomes of participant-reported pain relief of 50% or greater, PGIC (moderate and/or substantial), participant-reported fatigue and sleep problems, withdrawals due to adverse events, weight gain and serious adverse events.

Subgroup analysis and investigation of heterogeneity

We did not plan subgroup analyses since experience of previous reviews indicated that there would be too few data for any meaningful subgroup analysis.

Sensitivity analysis

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

RESULTS

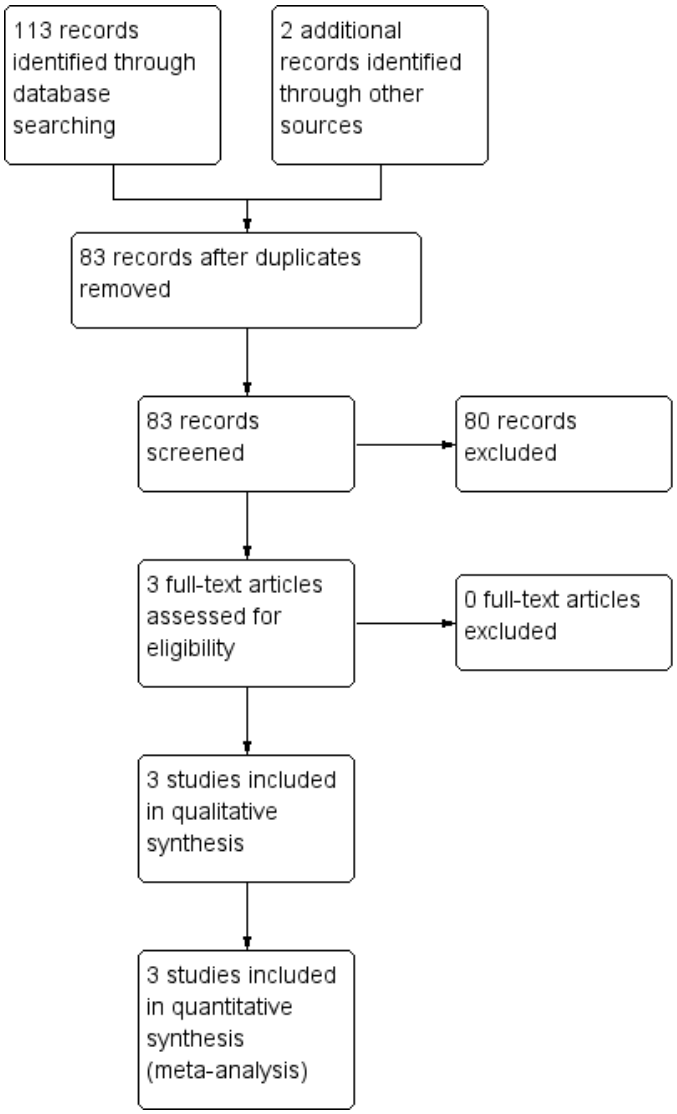
Description of studies

Results of the search

The searches of the four databases (see Electronic searches) retrieved 113 records. Our searches of the trials registers identified two further studies. Our screening of the reference lists of the included publications did not reveal additional randomised controlled trials (RCTs). We therefore had a total of 115 records. Once we removed duplicates, we had a total of 83 records. We excluded 80 records based on titles and abstracts. We obtained the full text of the remaining three records. We added no records to 'Characteristics of studies awaiting classification'. We identified no ongoing studies. For a further description of our screening process, see the study flow diagram (Figure 1).

We included three studies in the qualitative and quantitative analysis (Figure 1).

Figure 1. Study flow diagram.



Included studies

We included three studies involving 606 participants. See the Characteristics of included studies table for a full description of the studies.

Study characteristics

Two studies were conducted in multiple research centres in Japan (JapicCTI-101176; Miki 2016), and one study was conducted in a single centre in Thailand (Yeephu 2013). Two studies were labelled "phase 2b" studies (JapicCTI-101176; Yeephu 2013), and one a "phase 3" study (Miki 2016). All studies had a parallel design. Two studies had a one to two week single-blind run-in phase (JapicCTI-101176; Miki 2016). Double-blind study duration was seven weeks in one study (short-term study) (JapicCTI-101176), and 13 or 14 weeks in two studies (medium-term studies) (Miki 2016; Yeephu 2013). Two studies were started after 2010 (JapicCTI-101176; Miki 2016), one study was started in 2008 (Yeephu 2013).

The two Japanese studies were funded by the manufacturer of the respective drug (JapicCTI-101176; Miki 2016). One study did not report on conflicts of interest (JapicCTI-101176). One study reported that the authors received payments by the sponsor of the study for consultancies or were employees of the sponsor of the study (JapicCTI-101176; Miki 2016). The Thai study was funded by a public scholarship; authors stated that they had no potential financial conflict of interest (Yeephu 2013).

Participant characteristics

One study included participants over 18 years old (Yeephu 2013); two included participants between 20 and 64 years (JapicCTI-101176; Miki 2016). Diagnosis of fibromyalgia was established by all studies by the American College of Rheumatology (ACR) 1990 classification criteria (Wolfe 1990). All studies required a pain score > 3/10 for inclusion.

All studies excluded participants with somatic diseases, including inflammatory rheumatic diseases. Two studies excluded participants with depression and current antidepressant treatment

(JapicCTI-101176; Yeephu 2013). One study excluded participants with major depression (Miki 2016). There were no reports of participants with anxiety disorders being excluded or not.

The median of the mean age was 44 years (range 43 to 45 years; one study included only women; Yeephu 2013). The percentage of female participants in the Japanese studies was 86% and 95%. All participants were Asian (Thai, Japanese).

Interventions

Mirtazapine dosage was fixed at 30 mg/d in Miki 2016. Dosing was 15 mg/d, 30 mg/d, or 45 mg/d according to tolerability in JapicCTI-101176, and 15 mg/d or 30 mg/d according to tolerability in Yeephu 2013. The rescue medication in JapicCTI-101176 and Miki 2016 was acetaminophen (paracetamol) up to 1.5 g/day, aspirin up to 300 mg/day, and any nonsteroidal agent (up to 3 days). Yeephu 2013 did not report on rescue medication.

None of the three studies compared mirtazapine with another active drug.

Excluded studies

There were no excluded studies.

Risk of bias in included studies

In general, the risks of bias of included studies differed between the studies (see Figure 2 and Figure 3 for 'Risk of bias' summary and graph). Detailed information regarding risk of bias assessments of every study are given in the Characteristics of included studies table. One study met the predefined criteria of moderate methodological quality (Miki 2016), and two studies had low methodological quality, due to unclear or high risk of bias in seven of eight domains (JapicCTI-101176), and in six of eight domains (Yeephu 2013).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

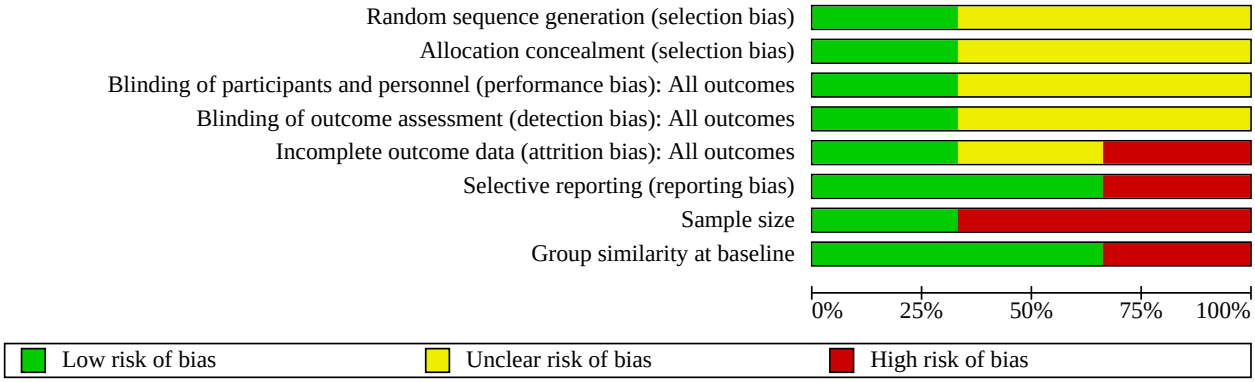
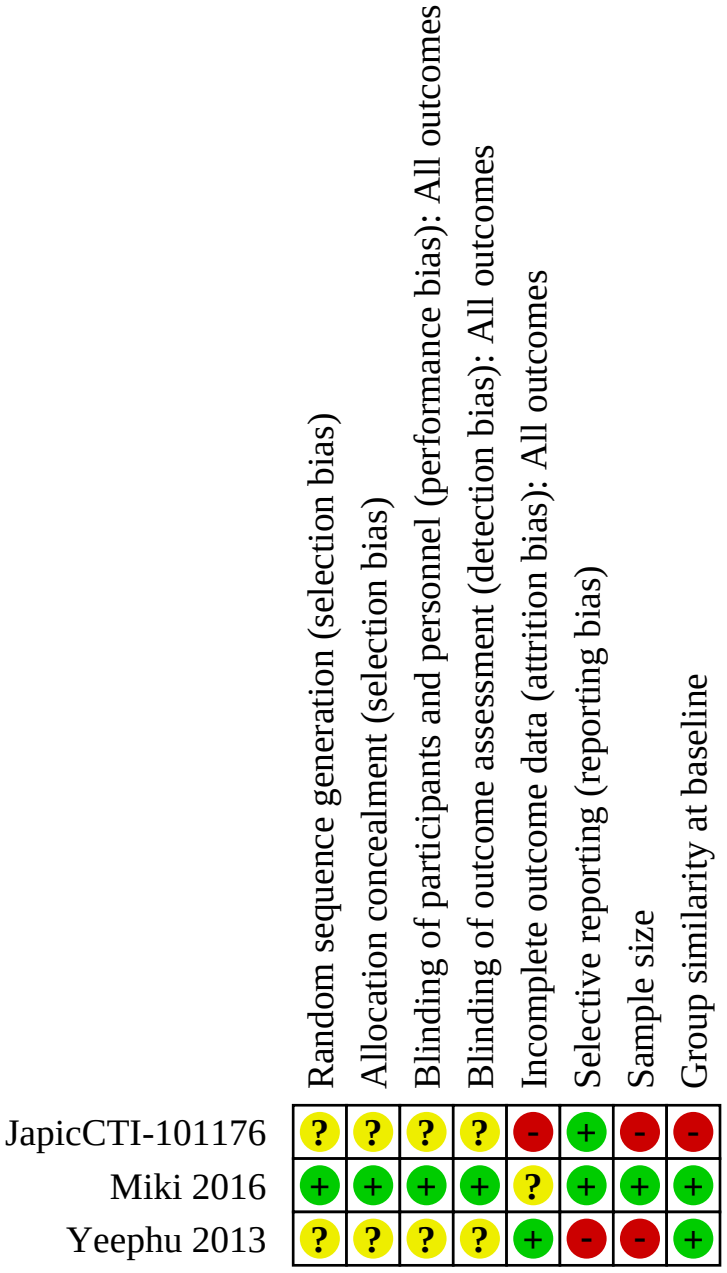


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation was adequately described and therefore judged at low risk of bias in a single study (Miki 2016), and not adequately described and therefore judged at unclear risk of bias in two studies (JapicCTI-101176; Yeephu 2013).

Allocation concealment was adequately described and judged at low risk of bias in a single study (Miki 2016), and not adequately described and therefore judged at unclear risk of bias in two studies (JapicCTI-101176; Yeephu 2013).

Blinding

Blinding of participants and personnel and of outcome assessors was adequately described and judged at low risk of bias in a single study (Miki 2016), and not adequately described and therefore of unclear risk of bias in two studies (JapicCTI-101176; Yeephu 2013).

Incomplete outcome data

One study used last observation carried forward (LOCF) to impute missing data and we judged it at unclear risk of bias (Miki 2016). One study used baseline observation carried forward data for mean pain intensity, which we judged at low risk of bias (Yeephu 2013). One study provided completer analysis on request (JapicCTI-101176), and we judged it at high risk of bias.

Selective reporting

Two studies reported the outcomes as outlined in the protocol, and we judged them to be at low risk of bias (JapicCTI-101176; Miki 2016). One study did not report the outcome 'fatigue' as outlined in the protocol and did not provide the data on request. We judged it to be high risk of bias (Yeephu 2013).

Sample size bias

We judged sample size to be at low risk of bias in Miki 2016 (≥ 200 participants per treatment arm), and high risk of bias in JapicCTI-101176 and Yeephu 2013 (< 50 participants per treatment arm).

Group similarity at baseline

We detected no significant differences in demographic and clinical variables at baseline between the study groups (low risk of bias) in two studies (Miki 2016; Yeephu 2013). We judged JapicCTI-101176 to be at high risk of bias because we found a clinically-relevant difference in baseline variables (duration of fibromyalgia diagnosis).

Effects of interventions

See: **Summary of findings 1** Mirtazapine compared with placebo for adult participants with fibromyalgia

We judged there to be clinical heterogeneity between the studies, and so we used a random-effects analysis throughout.

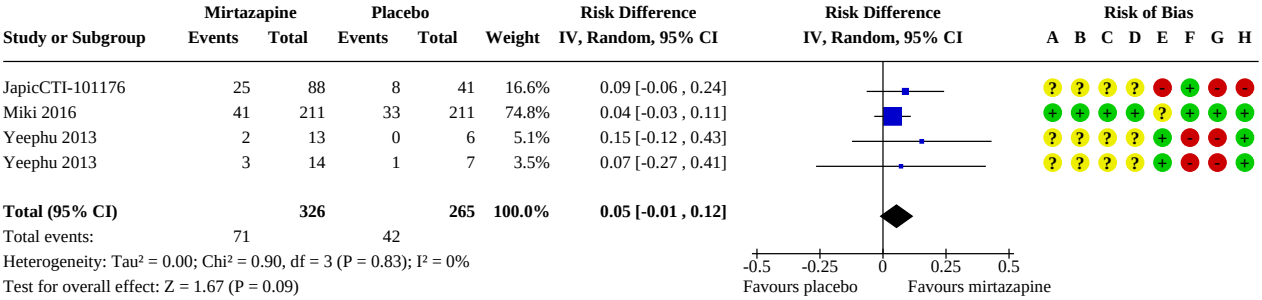
Primary outcomes

Participant-reported pain relief of 50% or greater

Pain was assessed by the average pain over the last 24 hours recorded in a pain diary on a numeric rating scale 0 to 10 in two studies (JapicCTI-101176; Miki 2016). The other study used a visual analogue scale ranging from 0 to 100 without reporting the time frame (Yeephu 2013). The outcome was calculated by an imputation method for Yeephu 2013 (Furukawa 2005).

We entered three studies with 591 participants into an analysis of the risk difference (RD) of participant-reported pain relief of 50% or greater; it was reported by 71/326 (22%) participants in the mirtazapine and 42/265 (16%) participants in the placebo group. The RD was 0.05 (95% confidence interval (CI) -0.01 to 0.12; Analysis 1.1; Figure 4). According to the predefined criteria, there was no clinically-relevant benefit from taking mirtazapine. The quality of evidence was low, downgraded due to indirectness and risk of publication bias .

Figure 4. Forest plot of comparison: 1 Mirtazapine versus placebo at the end of treatment, outcome: 1.1 Participant-reported pain relief of 50% or greater.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Sample size
(H) Group similarity at baseline

Patient Global Impression of Change (PGIC) 'very much improved'

PGIC was assessed only by one study, reporting the less stringent/easier outcome of 'any improvement' (Yeephu 2013). No study reported the number of participants who reported to be much or very much improved. The quality of evidence was very low.

Safety (serious adverse events)

Two studies used physical and laboratory tests (JapicCTI-101176; Miki 2016). One study relied on subjective reports of the participants (Yeephu 2013).

We entered three studies, with 606 participants, into an analysis of serious adverse events. Serious adverse events occurred in 1/334 (0.3%) participants in the mirtazapine group and in 0/271 (0%) in the placebo group. The RD was -0.00 (95% CI -0.01 to 0.02; Analysis 1.2). According to the predefined criteria, there was no clinically-relevant harm from taking mirtazapine. The quality of evidence was very low, downgraded due to indirectness and imprecision and risk of publication bias.

Tolerability (withdrawals due to adverse events)

Subjective adverse events were assessed by all studies by open questions to the participants. All reported the number of participants dropping out due to adverse events.

We entered three studies, with 606 participants, into an analysis of withdrawals due to adverse events. Adverse event withdrawal occurred in 11/334 participants (3.3%) in the mirtazapine group and 8/272 (2.2%) in placebo. The RD was 0.00 (95% CI - 0.02 to 0.03; Analysis 1.3). According to the predefined criteria, there was no clinically-relevant harm from taking mirtazapine. The quality of evidence was low, downgraded due to indirectness and risk of publication bias.

Secondary outcomes

Participant-reported pain relief of 30% or greater

Pain was assessed by a diary reporting mean pain over the previous 24 hours on a numeric rating scale 0 to 10 in two studies (JapicCTI-101176; Miki 2016). The other used a visual analogue scale ranging from 0 to 100 without reporting the time frame (Yeephu 2013). The outcome was calculated by an imputation method for Yeephu 2013 (Furukawa 2005).

We entered three studies, with 591 participants, into an analysis of the RD of participant-reported pain relief of 30%; it was reported by 154/326 participants (47%) in the mirtazapine group and 89/265 (34%) participants in the placebo group. The RD was 0.13 (95% CI 0.05 to 0.21; Analysis 1.4). The number needed to treat for an additional beneficial outcome (NNTB) was 8 (95% CI 5 to 20). According to the predefined categories, this was a clinically meaningful benefit. The quality of evidence was low, downgraded due to indirectness and risk of publication bias.

PGIC 'much improved'

PGIC was assessed only by one study, reporting the less stringent/easier outcome of 'any improvement' (Yeephu 2013). The quality of evidence was very low.

Participant-reported sleep problems

We found one study that used the Pittsburgh Sleep Quality Index (JapicCTI-101176), one used the Insomnia Severity Index (Miki 2016), and one used the Jenkins Sleep Scale (Yeephu 2013).

We entered three studies, with 573 participants, into an analysis of the effects of mirtazapine on reduction of sleep disturbances. The standardised mean difference (SMD) was -0.23 (95% CI -0.39 to -0.06). Based on Cohen's categories, the effect on fatigue of mirtazapine versus placebo was small (Analysis 1.5). According to the predefined categories, there was a clinically meaningful benefit from taking mirtazapine. The quality of evidence was low, downgraded due to indirectness and risk of publication bias.

Participant-reported fatigue

Fatigue was assessed by the single item of the Fibromyalgia Impact Questionnaire (FIQ; visual analogue scale 0 to 10) in two studies (JapicCTI-101176; Yeephu 2013), but one did not report this outcome (Yeephu 2013). The other used the subscale 'vitality' of the Short Form Health Survey 36 (VAS 0 to 100) (Miki 2016).

We entered two studies with 533 participants into an analysis of the effects of mirtazapine on fatigue. The SMD was -0.02 (95% CI -0.19 to 0.16; Analysis 1.6). According to the predefined criteria, there was no clinically-relevant benefit from taking mirtazapine. The quality of evidence was low, downgraded due to indirectness and risk of publication bias.

Participant-reported mean pain intensity

Pain intensity was assessed by a diary reporting mean pain over the previous 24 hours on a numeric rating scale 0 to 10 in two studies (JapicCTI-101176; Miki 2016). One study used a visual analogue scale ranging from 0 to 100 without reporting the time frame (Yeephu 2013).

We entered three studies, with 591 participants, into an analysis of the effects of mirtazapine on pain intensity reduction. The SMD was -0.29 (95% CI -0.46 to -0.13). According to Cohen's categories the effect on pain of mirtazapine compared to placebo was small (Analysis 1.7). According to the predefined categories there was a clinically meaningful benefit from taking mirtazapine. The quality of evidence was low, downgraded due to indirectness and risk of publication bias.

Participant-reported improvement of health-related quality of life (HRQoL) of 20% or greater

All studies used the total score of the Fibromyalgia Impact Questionnaire (FIQ). The responder rates were calculated for all studies by an imputation method (Furukawa 2005).

We entered three studies, with 586 participants, into an analysis of the effects of mirtazapine on HRQoL. Improvement of HRQoL of 20% or greater was reported by 188/324 participants (58%) in the mirtazapine group and 131/262 (50%) participants in the placebo group. The RD was 0.08 (95% CI -0.01 to 0.16; Analysis 1.8). According to the predefined criteria, there was no clinically-relevant benefit by mirtazapine. The quality of evidence was low, downgraded due to indirectness and risk of publication bias.

Participant-reported negative mood

Yeephu 2013 used the Hamilton Depression Rating Scale (HDRS). The other studies used the Beck Depression Inventory (BDI) II.

We entered three studies, with 588 participants, into an analysis of the effects of mirtazapine on the reduction of negative mood. The SMD was -0.67 (95% CI -1.44 to 0.10; Analysis 1.9). According to the predefined criteria, there was no clinically-relevant benefit from taking mirtazapine. The quality of evidence was low, downgraded due to indirectness and risk of publication bias.

Withdrawals due to lack of efficacy

This adverse event was reported by all studies.

We entered three studies, with 605 participants into an analysis of withdrawals due to lack of efficacy; 5/333 participants (1.5%) dropped out due to lack of efficacy in the mirtazapine group and 0/271 (0%) in the placebo group. The RD was 0.01 (95% CI -0.01 to 0.02; Analysis 1.10). According to the predefined criteria, there was no clinically-relevant harm from taking mirtazapine. The quality of evidence was very low, downgraded due to indirectness and imprecision and risk of publication bias.

Participants reporting any adverse event

This adverse event was reported by all studies.

We entered three studies, with 606 participants, into an analysis of at least one adverse event; 255/334 participants (76%) reported at least one adverse event in the mirtazapine group and 159/272 (59%) in the placebo group. The RD was 0.12 (95% CI -0.01 to 0.26; Analysis 1.11). According to the predefined criteria, there was no clinically-relevant harm from taking mirtazapine. The quality of evidence was low, downgraded due to indirectness and risk of publication bias.

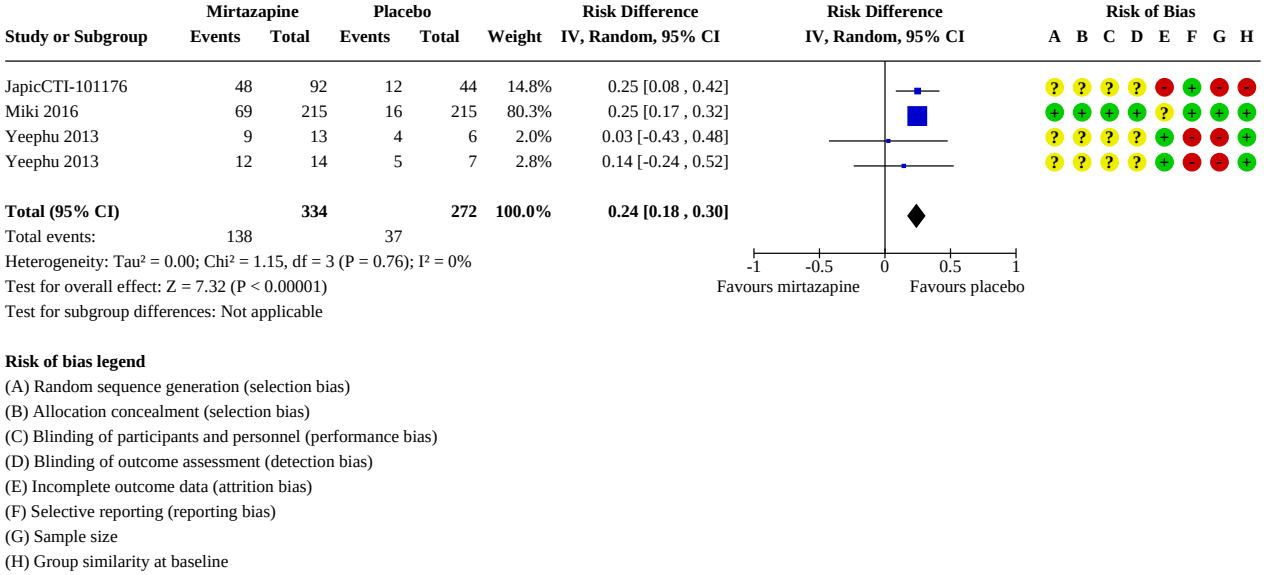
Specific adverse events

Somnolence

This adverse event was reported by all studies.

We entered three studies, with 606 participants, into an analysis of somnolence as an adverse event; 138/334 participants (42%) reported somnolence in the mirtazapine group and 37/272 (14%) in the placebo group. The RD was 0.24 (95% CI 0.18 to 0.30; Analysis 1.12; Figure 5). The number needed to treat for an additional harmful outcome (NNTH) from taking mirtazapine was 5 (95% CI 3 to 6) . According to the predefined categories, there was a clinically meaningful harm from taking mirtazapine. The quality of evidence was low, downgraded due to indirectness and risk of publication bias.

Figure 5. Forest plot of comparison: 1 Mirtazapine versus placebo at the end of treatment, outcome: 1.12 Specific adverse event (somnolence).



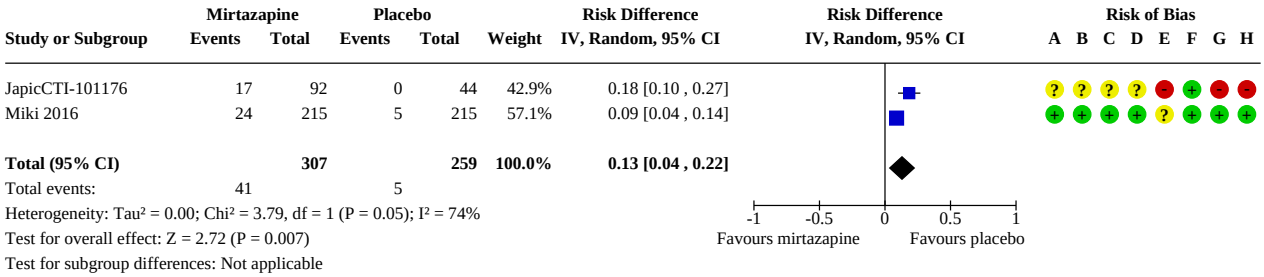
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Sample size
(H) Group similarity at baseline

Weight gain

This adverse event was reported by all studies.

We entered three studies, with 606 participants, into an analysis of weight gain as an adverse event; 63/334 (19 %) of participants in the mirtazapine group had weight gain recorded as an adverse event and 3/272 (1.1%) in the placebo group. The RD was 0.17 (95% CI 0.11 to 0.23; Analysis 1.13; Figure 6). The NNTH by taking mirtazapine was 6 (95% CI 5 to 10). According to the predefined categories, there was a clinically meaningful harm from taking mirtazapine. The quality of evidence was low, downgraded due to indirectness and risk of publication bias.

Figure 6. Forest plot of comparison: 1 Mirtazapine versus placebo at the end of treatment, outcome: 1.14 Specific adverse event (elevated alanine aminotransferase).



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Sample size
(H) Group similarity at baseline

One study reported an average weight gain of 4.5 kg within 13 weeks with mirtazapine 30 mg/d group, 2 kg with mirtazapine 15 mg/d group, and 1 kg with placebo (Yeephu 2013).

Elevated alanine aminotransferase

The outcome was reported by two studies (JapicCTI-101176; Miki 2016).

We entered two studies, with 566 participants, into an analysis of elevated alanine aminotransferase as an adverse event; 41/307 participants (13%) in the mirtazapine group and 5/259 (1.9%) in the placebo group had an elevated alanine aminotransferase recorded. The RD was 0.13 (95% CI 0.04 to 0.22; Analysis 1.14). The NNTH by taking mirtazapine was 8 (95% CI 5 to 25). According to the predefined categories, there was a clinically meaningful harm from taking mirtazapine. The quality of evidence was low, downgraded due to indirectness and risk of publication bias.

Investigation of heterogeneity

There was high statistical heterogeneity in the outcome of fatigue, any adverse event, and elevated alanine aminotransferase. We did not find any obvious clinical reasons for this heterogeneity.

Publication bias

We tested the largest efficacy estimate of pain relief of 30% or greater for the potential for publication bias (Moore 2008). We calculated that 149 extra participants would have had to have been included in entirely negative trials (zero treatment effect) to move the NNTB for pain relief of 30% or greater from 8 to our limit for clinical utility of 10. That is only 25% of the number of participants involved in the calculation, and we judged the potential for publication bias to be high.

Because there was a significant risk of publication bias for an important secondary efficacy outcome, and because publication bias could affect all outcomes, we downgraded our estimation of evidence quality by at least one category for all outcomes.

DISCUSSION

Summary of main results

The tetracyclic antidepressant, mirtazapine, did not show a statistically significant benefit compared to placebo in participant-reported pain relief of 50% or greater, in participant-reported improvement of health-related quality of life (HRQoL) of 20% or greater, or in reduction of fatigue and negative mood. Mirtazapine showed a clinically-relevant benefit compared to placebo in participant-reported pain relief of 30% or greater and in the reduction of mean pain intensity and of sleep problems. There were no statistically significant differences between mirtazapine and placebo in the frequency of withdrawals due to adverse events or due to lack of efficacy and of serious adverse events. There was a clinically-relevant harm from taking mirtazapine compared to placebo in the number of participants with somnolence, weight gain, and elevated alanine aminotransferase.

There is low-quality evidence that some people with fibromyalgia will experience moderate pain relief and reduced sleep problems from taking mirtazapine. However, the potential benefits might be outweighed by the potential harms (somnolence, weight gain).

Overall completeness and applicability of evidence

We cannot rule out the possibility that negative study results have not been published or have been missed by our search strategy. An additional 25% of participants in zero effect studies would eliminate any clinical relevance for the largest efficacy effect, that of at least 30% pain relief.

The applicability (external validity) of evidence is limited for the following reasons.

- The studies were performed in research centres and not in routine clinical care. The efficacy of drug therapies in fibromyalgia seems to be higher in the context of randomised controlled trials (RCTs) than in routine clinical care (Wolfe 2013b).

- The substantial placebo response rate seen across all of the mirtazapine trials impedes the appraisal of the efficacy of mirtazapine in fibromyalgia. However, the high placebo response rates seen with mirtazapine have been observed in all fibromyalgia drug trials (Häuser 2011; Häuser 2012).
- The exclusion criteria were strict. Some concomitant medications commonly used to treat fibromyalgia symptoms were not permitted in the included studies. This excluded a large number of participants who were unwilling, or unable, to come off medications, such as other antidepressants and anticonvulsants. For this reason, participant selection in the RCTs was biased towards recruiting participants with less severe symptoms than are seen in the community (Fuller-Thomson 2012). Participants with other medical disorders, such as inflammatory rheumatic diseases, which are frequently associated with fibromyalgia, were also excluded. The study results cannot be applied to people with so-called secondary fibromyalgia (associated with inflammatory rheumatic diseases; Clauw 1995). The largest study excluded all potential participants with major depression (Miki 2016), though this is frequently associated with fibromyalgia (Fuller-Thomson 2012).
- The majority of included participants were Japanese women between 20 and 64 years. Compared to studies with Food and Drug Administration (FDA) approved medications for fibromyalgia (duloxetine, milnacipran, pregabalin; Derry 2017; Häuser 2013a), in which North American and European participants prevailed, the low number of participants dropping out of the studies due to adverse events in the mirtazapine studies is astonishing. We do not know if the study results are valid for other races, adolescents, men and participants > 64 years.
- The long-term efficacy and safety of mirtazapine in fibromyalgia cannot be assessed by the studies included in the review. We did not find long-term, open-label extension studies with mirtazapine in our searches.
- The place of mirtazapine compared to other drugs and nonpharmacological therapies in the treatment of fibromyalgia symptoms still needs to be determined.

Quality of the evidence

The quality of evidence ranks from low to very low across the different outcomes. The likelihood that the effect could be substantially different is high. The main limiting factors, which were the reason for downgrading confidence in all outcomes, were indirectness and the potential for publication bias, though high risk of bias in two of the three studies and small numbers of events for some outcomes also contributed. In addition, two of the included studies were sponsored by pharmaceutical companies (JapicCTI-101176; Miki 2016). We assessed the quality of evidence in this review on the data presented in peer reviewed journals, published clinical trial date (JapicCTI-101176), and some additional details provided on request by the pharmaceutical companies or principal investigators. However, not all requested data were provided, so we had to calculate some standard deviations (SDs) and outcomes.

Potential biases in the review process

We searched for unpublished studies with mirtazapine, but cannot be certain that we identified all other studies that might have been performed but not published.

We may have overestimated the risk of bias of some studies that were carried out to the highest standards, but did not report some details of methodology (e.g. randomisation and blinding procedures).

Some included studies used statistical methods (last observation carried forward (LOCF)) that may bias results towards exaggerating the efficacy of drugs (Moore 2012b). We could not assess the potential effects, nor allow for any possible bias in the use of these methods. We considered the study not to be at high risk as the adverse event withdrawal rates for mirtazapine and placebo were low (around 3%) and not very different (Moore 2012b).

The influence of permitted cointerventions (e.g. rescue medication) on positive effects and adverse events was unclear because type and dosage of cointerventions were neither clearly reported nor controlled for. The type and dose of permitted cointerventions (e.g. rescue medication) was not clearly reported, so we were unable to assess their influence on outcomes of either efficacy or harm.

This review included 606 participants. To capture rare and potentially severe adverse events would require a much larger data set, e.g. to capture an adverse event with a frequency of 1:100,000, 300,000 patient-observations would be necessary (Andersohn 2008). Rare complications of mirtazapine include hyponatraemia (Viramontes 2016), leucopenia (Civalier 2009), and gastrointestinal bleeding (Na 2017).

Agreements and disagreements with other studies or reviews

We are not aware of another systematic review on mirtazapine in fibromyalgia. We cannot confirm the conclusion of an uncontrolled trial that mirtazapine is an effective and promising treatment in fibromyalgia (Samborski 2004). The high incidence of weight gain and elevated liver enzymes with mirtazapine in fibromyalgia is in line with studies of mirtazapine in other chronic pain syndromes (Riediger 2017), and in depression (Watanabe 2011). Nausea, vomiting and sexual dysfunction have been less frequently found in mirtazapine than in selective serotonin reuptake inhibitor (SSRI) and serotonin and norephinephrin reuptake inhibitor (SNRI) trials in depression and point to a unique adverse event profile of mirtazapine (Watanabe 2011).

AUTHORS' CONCLUSIONS

Implications for practice

For people with fibromyalgia

Only a minority of people may benefit from treatment with mirtazapine in terms of meaningful relief of pain and sleep problems, without clinically-relevant side effects. The majority of people will not experience substantial relief of fibromyalgia symptoms, or will experience clinically-relevant side effects (weight gain, somnolence, liver damage), or both.

For physicians

Mirtazapine is not approved for fibromyalgia in any country. Mirtazapine is approved for depressive disorders in many countries.

Because of the side effect profile of mirtazapine, an off-label therapeutic trial might be considered in people who do not tolerate duloxetine or milnacipran due to gastrointestinal adverse events (nausea, vomiting). If mirtazapine is being considered for the treatment of fibromyalgia, a frank discussion between the physician and patient about the potential benefits and harms of the treatment options is important. The warnings (suicide risk, concomitant use of monoaminoxidase inhibitors, agranulocytosis) and precautions (hepatotoxicity, weight gain, increase of cholesterol/triglycerides) should be discussed (FDA 2017). It is important to define realistic goals of treatment (e.g. pain relief of 30% or more or improvement of daily functioning, or both; Petzke 2017).

The optimal treatment dosage of mirtazapine remains to be determined. A dose response has not yet been demonstrated. Higher doses were associated with more weight gain in one study (Yeephu 2013). Therefore a starting dose of 15 mg/d at bedtime seems reasonable. It is mandatory to continue treatment for responders only, that is to say in those who reach the predefined treatment goals with a reasonable tolerability of mirtazapine (Petzke 2017).

Therapy of fibromyalgia with drugs only is discouraged since current best practices in fibromyalgia guidelines recommend using the combination of pharmacological therapy with aerobic exercise and psychological therapies (Macfarlane 2017; Petzke 2017). This is especially true for symptoms where mirtazapine is ineffective, but other therapies are effective, e.g. aerobic exercise for fatigue (Bidonde 2017), and cognitive-behavioral therapies for depression (Bernardy 2018).

Since few participants achieve a worthwhile response with mirtazapine, it is important to establish stopping rules, so that when someone does not respond within a specified time, they can be switched to an alternative treatment. This will reduce the number of participants exposed to adverse events in the absence of benefit.

For policy-makers

Since no single treatment is effective in a majority of individuals with fibromyalgia, the relatively small number who benefit may be considered worthwhile, particularly if a) established treatment options have failed, b) appropriate switching or stopping rules are in place, and c) prescribing is under the control of physicians experienced in treating people with fibromyalgia.

For funders

Treatment with mirtazapine for fibromyalgia may be considered worthwhile, particularly if a) established treatment options have failed, and b) switching and stopping rules are in place in case the predefined treatment goals are not reached or the drug is not well-tolerated, or both. Treatment should be supervised by a physician experienced in the use of mirtazapine.

Implications for research

General

Analysis of all studies investigating mirtazapine in fibromyalgia at the level of individual patient data could provide important information, e.g. whether or not a clinically important pain response delivers large functional and quality of life benefits. Moreover, a reanalysis of the data using baseline observation carried forward, and responder analysis where discontinuation is classified as nonresponse, would allow a determination of the true efficacy of mirtazapine in fibromyalgia. All journals should follow the rules of the *BMJ* that reports that randomised trials will only be considered for publication if the authors commit to making the relevant anonymous patient level data available on reasonable request (Godlee 2012).

Studies in any continent with the inclusion of people with inflammatory rheumatic diseases, osteoarthritis and mental disorders (depressive and anxiety disorders, post-traumatic stress disorder) are necessary to provide external validity of the study findings.

A standardised psychiatric interview at study entry could stratify participants according to comorbid anxiety and depressive disorders.

Generalisability of results requires study populations that are equally recruited from every continent.

It is mandatory that details of adverse event assessments (spontaneous reports, open question structured questions, symptom questionnaires) are reported by the studies because the type and frequency of adverse events is influenced by modes of assessment (Häuser 2012). Adverse events are to be reported using the International Conference on Harmonization guidelines, and coded within organ classes using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0; ICH 2015). It is desirable that regulatory agencies standardise the assessment strategies of adverse events in RCTs.

It is important to control for potential effects of cointerventions on outcomes.

Measurement (endpoints)

We recommend the use of responder criteria for the key symptoms and functional domains of fibromyalgia, namely pain, sleep problems, fatigue, depression, health-related quality of life (HRQoL) and physical function (disability). The following responder criteria (from baseline to end of treatment) for clinical trials have been suggested: ≥ 30% pain reduction; ≥ 10% improvement in SF (Short Form Health Survey)-36 physical function or ≥ 10% improvement in Fibromyalgia Impact Questionnaire (FIQ) physical function; ≥ 20% improvement in two of the following domains: fatigue (FIQ tiredness), sleep (FIQ rested), depression (FIQ depression), anxiety (FIQ anxiety), or cognition (Multiple Ability Self-Report Questionnaire (MASQ)) (Arnold 2012b). For HRQoL, a ≥ 20% reduction of the FIQ total score has been suggested to be clinically-relevant (Luciano 2014).

Comparison between active treatments

It is important to compare mirtazapine not only with placebo, but also with drugs of known efficacy, such as amitriptyline or

pregabalin. In addition, more studies with defined subgroups (e.g. major depression; no adequate response to a specific drug treatment) are necessary.

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CHARACTERISTICS OF STUDIES

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

JapicCTI-101176

Study characteristics	
Methods	**Study setting:** multicentre study (10 research centres) in Japan **Study period:** June 2010 to June 2011 **Study design:** parallel **Duration therapy:** one week washout, one week single-blind run-in, 7 weeks mirtazapine 15 mg/d or 30 mg/d or 45 mg/d flexible at bedtime (3-week dose-adjustment period and 4-week fixed-dose period)
Participants	**Participants:** Mirtazapine: N = 92; 86.4% women, 100% Japanese, mean age 42.5 (SD 10.3) years; pain baseline (0 - 10) 6.1 (SD 1.2): months after diagnosis 67.5 (SD 66.8) Placebo: N = 44; 95% women, 100% Japanese, mean age 44.7 (SD 9.7) years; pain baseline (0 - 10) 6.1 (SD 1.3): months after diagnosis 86.9 (SD 81.3) **Inclusion criteria:** ACR classification criteria for fibromyalgia. The VAS score for pain is ≥ 40 mm at the initiation of observation period and at the initiation of treatment period. The average NRS score for pain is ≥ 4 during the observation period. Participants who received sufficient explanation on the objectives, method and meaning of this study and can give voluntary consent in writing. Age 20 - 64 years **Exclusion criteria:** Placebo responder during the observation period. Participant with pain from other diseases or pathologies than fibromyalgia. Participant with inflammatory musculoskeletal disease, rheumatic disease except fibromyalgia. Participants with treated but uncontrolled hepatic disease, renal disease, cardiovascular disease, respiratory disease, gastrointestinal disease, endocrine disease, or cerebrovascular disease, or other clinically significant concomitant physical disease. Participants with or with the history of schizophrenia, other psychotic disorders, or manic depression. Participants with

JapicCTI-101176 *(Continued)*

	diagnosed depression who are treated with medication. Participants with or with the history of convulsive disorders such as epilepsy. Participants who took a MAO inhibitor within one week (7 days) before the initiation of observation period. Participants who are pregnant or breastfeeding, or who wish to be pregnant during the study. Participants who have participated in any other clinical study within 3 months (90 days) before the initiation of observation period
Interventions	**Active drug:** mirtazapine 15 or 30 or 45 mg at bedtime for 7 weeks **Placebo:** 7 weeks **Rescue medication and permitted co-therapies:** as-needed use of acetaminophen (up to 1.5 g/d), aspirin (up to 300 mg/d), nonbenzodiazepines (zopiclone or zolpidem), any nonsteroidal anti-inflammatory drug (up to 7 days), and dextromethorphan was permitted. Any nonstudy drug that might affect pain scoring (e.g. antidepressants, antiepileptics, pregabalin, narcotics, and narcotic analogues) was prohibited from the beginning of the run-in period (Visit 1) to the end of the treatment period (Visit 7). Participants were allowed to receive a drug to treat any stably controlled concomitant condition without modification of its dosage throughout the treatment period if the drug had been instituted before the start of the run-in period
Outcomes	**Primary outcomes** **Participant-reported pain relief of 50% or greater:** last 24 hours diary mean pain (NRS 0 - 10). Data provided on request **PGIC very much improved:** not assessed **Serious AEs:** data provided on request **Withdrawal due to AEs:** reported **Secondary outcomes** **Participant-reported pain relief of 30% or greater:** last 24 hours diary mean pain (NRS 0 - 10). Data provided on request **PGIC much improved:** not assessed **Participant-reported sleep problems**: Pittsburgh Sleep Quality Index (NRS 0 - 21). Data provided on request **Participant-reported fatigue:** FIQ single VAS (0 - 10) scale. Data provided on request **Participant-reported mean pain intensity:** Last 24 hours diary mean pain (NRS 0 - 10): Data provided on request **Participant-reported improvement of health-related quality of life of 20% or greater:** Japanese version of the FIQ (VAS 0 - 100). Mean and SDs provided on request. Responder rates calculated by imputation method using the number of participants at baseline (BOCF) **Participant-reported negative mood:** Beck Depression Inventory II (0 - 63). Data provided on request **Withdrawal due to lack of efficacy:** data provided on request **Any AEs:** during the double-blind treatment period, subjects in both groups were asked about their symptoms in an open-ended fashion. Symptoms collected in this way and abnormal physical and laboratory findings observed were reported as AEs. Data provided on request **Specific AEs:** during the double-blind treatment period, subjects in both groups were asked about their symptoms in an open-ended fashion. Symptoms collected in this way and abnormal physical and laboratory findings observed were reported as AEs. Data provided on request
Notes	**Funding sources:** Funded by Meiji Seika Pharma Co, Ltd. **Declaration of interest of primary investigators:** not reported

JapicCTI-101176 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided on request
Allocation concealment (selection bias)	Unclear risk	No details provided on request
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided on request
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided on request
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis of data provided on request
Selective reporting (reporting bias)	Low risk	Outcomes provided as requested
Sample size	High risk	< 50 participants in placebo arm
Group similarity at baseline	High risk	Longer duration of fibromyalgia diagnosis in placebo group

Miki 2016

Study characteristics

Methods	**Study setting:** multicentre study (57 research centres) in Japan **Study period:** November 2012 to February 2014 **Study design:** parallel **Duration therapy:** no information on duration of washout phase. Two weeks single-blind placebo run-in, one week mirtazapine 15 mg/d, 12 weeks mirtazapine 30 mg/d fixed dose
Participants	**Participants:** Mirtazapine: N = 211; 82.5% women, 100% Japanese, mean age 45.0 (SD 10.0) years; pain baseline (0 - 10) 5.9 (SD 1.1): years after diagnosis 4.4 (SD 4.0) Placebo: N = 211; 82 % women, 100% Japanese, mean age 45.3 (SD 10.3) years; pain baseline (0 - 10) 6.0 (SD 1.1): years after diagnosis 4.4 (SD 4.4) **Inclusion criteria:** ACR 1990 criteria; age 20 to 64 years; pain score of ≥ 40 on a 100 VAS during screening period **Exclusion criteria:** VAS pain score reduced by ≥ 30% at week -1 or 0 compared with week -2 or a NRS pain score reduced by ≥ 2 at week 0 compared with week -1. Participants with refractory FM, which was defined as participants who were simultaneously taking 3 drugs (pregabalin + an antidepressant + an-

Miki 2016 *(Continued)*

	other antiepileptic drug) or a narcotic analgesic. Any coexisting inflammatory disease (e.g. rheumatoid arthritis) as indicated by an erythrocyte sedimentation rate > 40 mm/hour, C-reactive protein ≥ 1.0 mg/dL, antinuclear antibody titre ≥ 320-fold, or rheumatoid factor level >100 IU/mL. Presence of pain from any nonorganic disease other than FM. Established diagnosis of chronic fatigue syndrome, sleep apnoea syndrome, or restless leg syndrome. Any concomitant or previous clinically important disease (e.g. uncontrolled autoimmune, hepatic or renal disease) or psychoneurological disorder (e.g. schizophrenia, manic depressive psychosis, and epilepsy). Participants who met the criteria for major depression episodes according to diagnosis module A of the Mini-International Neuropsychiatric Interview or participants with a total score of ≥ 6 points for the risk of suicide in module C12. National Glycohemoglobin standardisation Programme haemoglobin A1c ≥ 6.9%. Use of any monoamine oxidase inhibitor within 14 days before randomisation. Previous use of mirtazapine for pain control
Interventions	**Active drug:** one week mirtazapine 15 mg/d, 12 weeks mirtazapine 30 mg/d fixed **Placebo:** 13 weeks **Rescue medication and allowed co-therapies:** subjects were prohibited from using any nonstudy drug (e.g. antidepressants, antiepileptics, pregabalin, narcotics, and narcotic analogs) or nonpharmacological treatment (e.g. surgery, electroconvulsive therapy, electrostimulation therapy, acupuncture and moxibustion, and nerve block) that might affect pain scoring. Participants using analgesics discontinued these drugs in the washout period, and concomitant analgesics were prohibited during the treatment period. As-needed use of acetaminophen (up to 1.5 g/d), aspirin (up to 300 mg/d), any nonsteroidal anti-inflammatory drug (up to 3 days), and dextromethorphan was permitted. Subjects were allowed to receive a drug to treat any stably controlled concomitant condition without modification of its dosage throughout the treatment period if the drug had been instituted before the start of the run-in period. Subjects were also allowed to receive any nonpharmacological anti-FM treatment, such as physical (e.g. exercise and hyperthermia) and psychological therapy (e.g. biofeedback treatment and cognitive behavioral therapy), without modification of its protocol, provided that the treatment had been instituted ≥ 30 days before the start of the run-in period
Outcomes	**Primary outcomes** **Participant-reported pain relief of 50% or greater:** last 24 hours diary mean pain (NRS 0 - 10). Number of responders reported **PGIC very much improved:** not assessed **Serious AEs:** during the double-blind treatment period, subjects in both groups were asked about their symptoms in an open-ended fashion. Symptoms collected in this way and abnormal physical and laboratory findings observed were reported as AEs. **Withdrawal due to AEs:** reported **Secondary outcomes** **Participant-reported pain relief of 30% or greater:** last 24 hours diary mean pain (NRS 0 - 10). Number of responders reported **PGIC much improved:** not assessed **Participant-reported sleep problems**: Japanese Insomnia Severity Index (NRS 0 - 28); SD provided on request **Participant-reported fatigue:** SF-36 subscale vitality (0 - 100) **Participant-reported mean pain intensity:** last 24 hours diary mean pain (NRS 0 - 10): SD provided on request **Participant-reported improvement of health-related quality of life of 20% or greater:** Japanese version of the FIQVAS 0-100). Mean and SDs provided on request. Responder rates calculated by imputation method (Furukawa 2005) **Participant-reported negative mood:** Beck Depression Inventory II (0 - 63), provided on request

Miki 2016 *(Continued)*

	Withdrawal due to lack of efficacy: reported
	Any AEs: during the double-blind treatment period, subjects in both groups were asked about their symptoms in an open-ended fashion. Symptoms collected in this way and abnormal physical and laboratory findings observed were reported as AEs.
	Specific AEs: during the double-blind treatment period, subjects in both groups were asked about their symptoms in an open-ended fashion. Symptoms collected in this way and abnormal physical and laboratory findings observed were reported as AEs. Data provided on request
Notes	**Funding sources:** Funded by Meiji Seika Pharma Co, Ltd.
	Declaration of interest of primary investigators: K. Miki, M. Murakami, H. Oka, K. Osada received honorarium from Meiji Seika Pharma Co, Ltd. K. Onozawa and S. Yoshida are employees of Meiji Seika Pharma Co, Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated allocation sequence, which was delivered by a telephone randomisation service (randomisation manager) not involved in subject recruitment or treatment to ensure allocation concealment
Allocation concealment (selection bias)	Low risk	The randomisation manager securely kept the randomisation list and confirmed that the blinding was maintained until the official decoding of the randomisation list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The manager also checked and confirmed the similarity between the active and placebo tablets regarding appearance, shape, size, packaging, and labelling
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant-reported outcomes; participants were adequately blinded to intervention. Blinding of outcome assessors of safety not adequately described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Last observation carried forward (LOCF) method
Selective reporting (reporting bias)	Low risk	All outcomes reported as outlined in JapicCTI-101176
Sample size	Low risk	> 200 participants per study arm
Group similarity at baseline	Low risk	No significant differences in demographic and clinical baseline characteristics of the study groups

Yeephu 2013

Study characteristics

Methods	**Study setting:** single centre study at the Department of Rehabilitation Medicine and Pain Clinic, Department of Anesthesiology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand
	Study period: December 2008 to December 2011

Yeephu 2013 *(Continued)*

	Study design: parallel **Duration therapy:** the investigational drug was introduced to subjects at a lower starting dose of 7.5 mg (half tablet) and titrated up to the randomised dose over 1 or 2 weeks and then continued with stable dosage for 13 weeks
Participants	**Participants:** Mirtazapine 15 mg: N = 13; 100% women, 100% Thai, mean age 42.7 (SD 12.6) years; pain baseline (0 - 100) 60.2 (SD 14.1): years after diagnosis 1.1 (SD 1.3) Mirtazapine 30 mg: N = 14; 100% women, 100% Thai, mean age 43.9 (SD 9.4) years; pain baseline (0 - 100) 63.7 (SD 12.8): years after diagnosis 0.8 (SD 1.1) Placebo: N = 13; 100% women, 100% Thai, mean age 47.4 (SD 10.5) years; pain baseline (0-10) 60.2 (SD 14.1): years after diagnosis 1.1 (SD 1.3) **Inclusion criteria:** ACR 1990 criteria; age 18 years or older; pain score of ≥ 40 on a 100 VAS during screening period; descended from Thai parents **Exclusion criteria:** Any severe or unstable physical or psychiatric disorder; inflammation, injury, or trauma in the previous month; substance abuse within the past year; serious suicide risk; comorbid inflammatory rheumatic diseases such as systemic lupus erythematosus or rheumatoid arthritis; were pregnant or breastfeeding; had allergic history to any constituent of investigational products; or had severe allergic reactions to multiple medications. Additional exclusion were use of medications or herbal agents with CNS activity; regular use of analgesics, with the exception of acetaminophen up to 2 g/day, and chronic use of sedatives/hypnotics. Individuals who were unable to discontinue medications that might affect the study results (i.e. all antidepressants; mood stabilisers; antipsychotics; sleep aids, such as hypnotics; tranquillizers; sedating antihistamines and benzodiazepines; all analgesics, including anticonvulsants; muscle relaxants; stimulant medications, such as dextroamphetamine and methylphenidate; any other medications used for the treatment of FM) or were unable to adhere to the follow-up schedule of the study were excluded, as were participants who would not agree with avoidance or stable maintenance of unconventional or alternative therapies, such as Thai traditional massage. Participants with FM with concurrent depressive disorder identified at screening were not excluded. During the index visit, all participants were interviewed by the counselling psychologist about thoughts of harming themselves and/or suicidal ideation. If those risks were detected, the individual was withdrawn from the study
Interventions	**Active drug:** Mirtazapine 7.5 mg/d and titrated up to the randomised dose of 15 mg/d or 30 mg/d over 1 or 2 weeks and then continued with stable dosage for 13 weeks **Placebo:** 14 to 15 weeks **Rescue medication and allowed co-therapies:** not reported
Outcomes	**Primary outcomes** **Participant-reported pain relief of 50% or greater:** pain, time frame not reported (VAS 0 - 100); number of responders not reported. Calculated by imputation method (Furukawa 2005) **PGIC very much improved:** assessed; only rates of 'any improvement' reported **Serious AEs:** "Patients were encouraged to contact the investigators at any time for consultation regarding any symptoms of concern to them." No reports of physical examination or laboratory test **Withdrawal due to AEs:** reported **Secondary outcomes** **Participant-reported pain relief of 30% or greater:** pain, time frame not reported (VAS 0 - 100); number of responders reported **PGIC much improved:** assessed; only rates of 'any improvement' reported

Yeephu 2013 *(Continued)*

	Participant-reported sleep problems: Jenkins Sleep Scale (NRS 0 - 20). No SDs reported and not provided on request. SD calculated according to *Cochrane Handbook* based on P value (0.1) **Participant-reported fatigue:** FIQ, subscale fatigue (VAS 0 - 10); not reported and not provided on request **Participant-reported mean pain intensity:** pain, time frame not reported (VAS 0 - 100). SD extracted from figure **Participant-reported improvement of health-related quality of life of 20% or greater:** FIQ (VAS 0 - 100). SD not reported. SD calculated according to *Cochrane Handbook* based on P value (0.1). Calculated by imputation method (Furukawa 2005) **Participant-reported negative mood:** Hamilton Depression Rating Scale (0 - 53). SD not reported. SD calculated according to *Cochrane Handbook* based on P value (0.1) (Higgins 2011) **Withdrawal due to lack of efficacy:** reported **Any AEs:** methods of assessment and data not reported and not provided on request **Specific AEs:** methods of assessment not reported and not provided on request. Weight gain and somnolence reported. No reports on technical findings
Notes	**Funding sources:** this study was supported by a scholarship from the Commission on Higher Education Staff Development Project for the Joint PhD Programme in Biopharmaceutical Sciences, Thailand. Mirtazapine used in this study was purchased from a retail pharmacy distributor at market prices **Declaration of interest of primary investigators:** authors reported none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Participant-reported outcomes; blinding of participants to intervention not adequately described. Blinding of outcome assessors of safety not adequately described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Baseline observation forward method
Selective reporting (reporting bias)	High risk	Outcome fatigue not reported as outlined in NCT00919295
Sample size	High risk	< 50 participants per treatment arm
Group similarity at baseline	Low risk	No significant differences in demographic and clinical baseline characteristics of the study groups

ACR: American College of Rheumatology; AE: adverse event; FIQ: Fibromyalgia Impact Questionnaire; FM: fibromyalgia; MAO: monoamine oxidase; N = number of participants; NRS: numeric rating scale; SD: standard deviation; VAS: visual analogue scale.

DATA AND ANALYSES

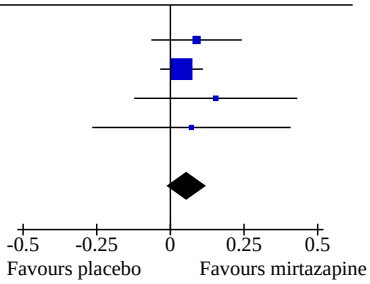
Comparison 1. Mirtazapine versus placebo at the end of treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Participant-reported pain relief of 50% or greater	3	591	Risk Difference (IV, Random, 95% CI)	0.05 [-0.01, 0.12]
1.2 Safety (serious adverse events)	3	606	Risk Difference (IV, Random, 95% CI)	0.00 [-0.01, 0.02]
1.3 Tolerability (dropouts due to adverse events)	3	606	Risk Difference (IV, Random, 95% CI)	0.00 [-0.02, 0.03]
1.4 Participant-reported pain relief of 30% or greater	3	591	Risk Difference (IV, Random, 95% CI)	0.13 [0.05, 0.21]
1.5 Participant-reported sleep problems	3	573	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.39, -0.06]
1.6 Participant-reported fatigue	2	533	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.19, 0.16]
1.7 Participant-reported mean pain intensity	3	591	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.46, -0.13]
1.8 Participant-reported improvement of HRQoL by 20% or more	3	586	Risk Difference (IV, Random, 95% CI)	0.08 [-0.01, 0.16]
1.9 Participant-reported negative mood	3	588	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.44, 0.10]
1.10 Withdrawals due to lack of efficacy	3	605	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.02]
1.11 Participants with any adverse event	3	606	Risk Difference (IV, Random, 95% CI)	0.12 [-0.01, 0.26]
1.12 Specific adverse event (somnolence)	3	606	Risk Difference (IV, Random, 95% CI)	0.24 [0.18, 0.30]
1.13 Specific adverse event (weight gain)	3	606	Risk Difference (IV, Random, 95% CI)	0.17 [0.11, 0.23]
1.14 Specific adverse event (elevated alanine aminotransferase)	2	566	Risk Difference (IV, Random, 95% CI)	0.13 [0.04, 0.22]

Analysis 1.1. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 1: Participant-reported pain relief of 50% or greater

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
JapicCTI-101176	25	88	8	41	16.6%	0.09 [-0.06 , 0.24]
Miki 2016	41	211	33	211	74.8%	0.04 [-0.03 , 0.11]
Yeephu 2013	2	13	0	6	5.1%	0.15 [-0.12 , 0.43]
Yeephu 2013	3	14	1	7	3.5%	0.07 [-0.27 , 0.41]
Total (95% CI)		**326**		**265**	**100.0%**	**0.05 [-0.01 , 0.12]**
Total events:	71		42			

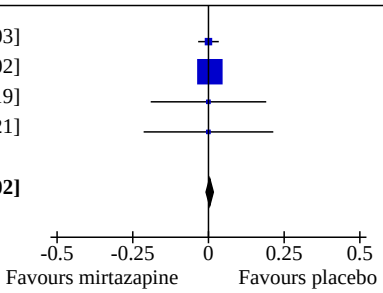
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 3 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 2: Safety (serious adverse events)

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
JapicCTI-101176	0	92	0	44	12.3%	0.00 [-0.03 , 0.03]
Miki 2016	1	215	0	215	87.0%	0.00 [-0.01 , 0.02]
Yeephu 2013	0	14	0	7	0.4%	0.00 [-0.19 , 0.19]
Yeephu 2013	0	13	0	6	0.3%	0.00 [-0.21 , 0.21]
Total (95% CI)		**334**		**272**	**100.0%**	**0.00 [-0.01 , 0.02]**
Total events:	1		0			

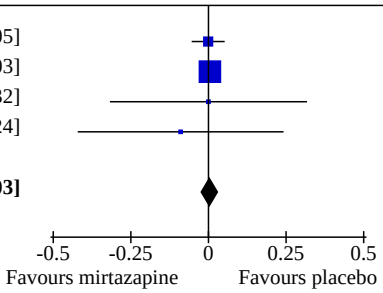
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 3: Tolerability (dropouts due to adverse events)

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
JapicCTI-101176	2	92	1	44	23.7%	-0.00 [-0.05 , 0.05]
Miki 2016	6	215	5	215	75.1%	0.00 [-0.03 , 0.03]
Yeephu 2013	2	14	1	7	0.7%	0.00 [-0.32 , 0.32]
Yeephu 2013	1	13	1	6	0.6%	-0.09 [-0.42 , 0.24]
Total (95% CI)		**334**		**272**	**100.0%**	**0.00 [-0.02 , 0.03]**
Total events:	11		8			

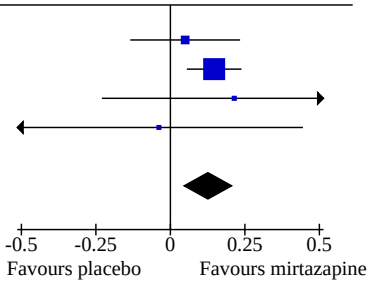
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 3 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.84)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 4: Participant-reported pain relief of 30% or greater

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
JapicCTI-101176	43	88	18	41	18.6%	0.05 [-0.13 , 0.23]
Miki 2016	96	211	65	211	75.4%	0.15 [0.06 , 0.24]
Yeephu 2013	9	14	3	7	3.2%	0.21 [-0.23 , 0.66]
Yeephu 2013	6	13	3	6	2.7%	-0.04 [-0.52 , 0.44]
Total (95% CI)		**326**		**265**	**100.0%**	**0.13 [0.05 , 0.21]**
Total events:	154		89			

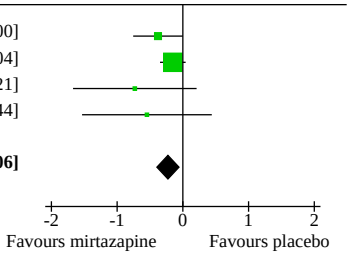
Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 3 (P = 0.69); I² = 0%
Test for overall effect: Z = 3.10 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 5: Participant-reported sleep problems

Study or Subgroup	Mirtazapine Mean	Mirtazapine SD	Mirtazapine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
JapicCTI-101176	6.34	2.92	87	7.63	4.25	40	19.8%	-0.38 [-0.76 , -0.00]
Miki 2016	8.08	5.38	204	8.92	5.61	202	74.2%	-0.15 [-0.35 , 0.04]
Yeephu 2013	1.73	7.58	14	7.5	7.58	7	3.2%	-0.73 [-1.67 , 0.21]
Yeephu 2013	2.58	8.6	13	7.5	8.6	6	2.9%	-0.55 [-1.53 , 0.44]
Total (95% CI)			**318**			**255**	**100.0%**	**-0.23 [-0.39 , -0.06]**

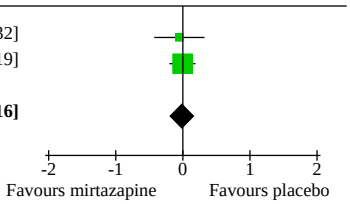
Heterogeneity: Tau² = 0.00; Chi² = 2.68, df = 3 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.65 (P = 0.008)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 6: Participant-reported fatigue

Study or Subgroup	Mirtazapine Mean	Mirtazapine SD	Mirtazapine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
JapicCTI-101176	5.49	2.26	87	5.61	2.35	40	21.3%	-0.05 [-0.43 , 0.32]
Miki 2016	-9.02	1.13	204	-8.61	113	202	78.7%	-0.01 [-0.20 , 0.19]
Total (95% CI)			**291**			**242**	**100.0%**	**-0.02 [-0.19 , 0.16]**

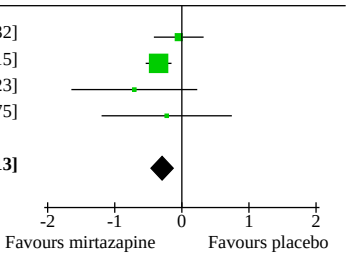
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.86)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 7: Participant-reported mean pain intensity

Study or Subgroup	Mirtazapine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
JapicCTI-101176	4.41	2.18	88	4.51	2.08	41	19.9%	-0.05 [-0.42 , 0.32]
Miki 2016	4.18	1.84	211	4.84	1.96	211	74.1%	-0.35 [-0.54 , -0.15]
Yeephu 2013	38.29	10	14	45.67	10	7	3.1%	-0.71 [-1.65 , 0.23]
Yeephu 2013	42.79	13	13	45.67	10	6	2.9%	-0.23 [-1.20 , 0.75]
Total (95% CI)			**326**			**265**	**100.0%**	**-0.29 [-0.46 , -0.13]**

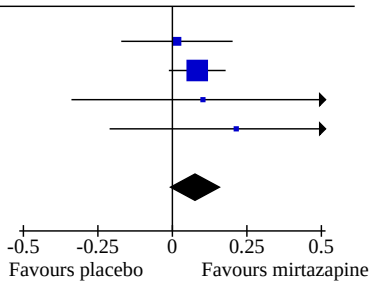
Heterogeneity: Tau² = 0.00; Chi² = 2.77, df = 3 (P = 0.43); I² = 0%
Test for overall effect: Z = 3.49 (P = 0.0005)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 8: Participant-reported improvement of HRQoL by 20% or more

Study or Subgroup	Mirtazapine Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI
JapicCTI-101176	47	87	21	40	19.2%	0.02 [-0.17 , 0.20]
Miki 2016	120	210	102	209	73.7%	0.08 [-0.01 , 0.18]
Yeephu 2013	10	13	4	6	3.4%	0.10 [-0.34 , 0.54]
Yeephu 2013	11	14	4	7	3.7%	0.21 [-0.21 , 0.64]
Total (95% CI)		**324**		**262**	**100.0%**	**0.08 [-0.01 , 0.16]**
Total events:	188		131			

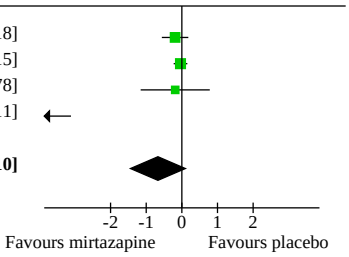
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 3 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.82 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 9: Participant-reported negative mood

Study or Subgroup	Mirtazapine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
JapicCTI-101176	9.61	8.61	88	11.37	10.39	41	32.3%	-0.19 [-0.56 , 0.18]
Miki 2016	8.6	8.04	210	8.91	8.31	209	34.2%	-0.04 [-0.23 , 0.15]
Yeephu 2013	2.92	7.7	13	4.42	7.7	6	22.5%	-0.19 [-1.16 , 0.78]
Yeephu 2013	1.75	0.51	14	4.42	0.51	7	11.0%	-5.03 [-6.94 , -3.11]
Total (95% CI)			**325**			**263**	**100.0%**	**-0.67 [-1.44 , 0.10]**

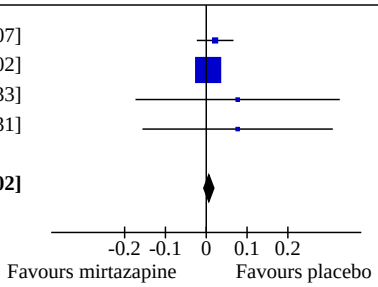
Heterogeneity: Tau² = 0.44; Chi² = 26.06, df = 3 (P < 0.00001); I² = 88%
Test for overall effect: Z = 1.71 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 10: Withdrawals due to lack of efficacy

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
JapicCTI-101176	2	92	0	44	7.5%	0.02 [-0.02 , 0.07]
Miki 2016	1	215	0	215	92.0%	0.00 [-0.01 , 0.02]
Yeephu 2013	1	13	0	6	0.2%	0.08 [-0.17 , 0.33]
Yeephu 2013	1	13	0	7	0.3%	0.08 [-0.16 , 0.31]
Total (95% CI)		**333**		**272**	**100.0%**	**0.01 [-0.01 , 0.02]**
Total events:	5		0			

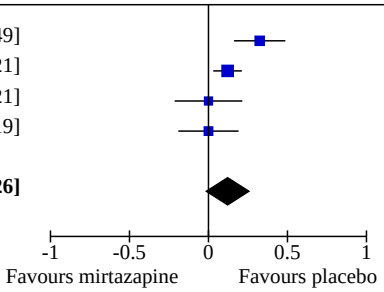
Heterogeneity: Tau² = 0.00; Chi² = 2.13, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 11: Participants with any adverse event

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
JapicCTI-101176	80	92	24	44	25.0%	0.32 [0.16 , 0.49]
Miki 2016	148	215	122	215	33.4%	0.12 [0.03 , 0.21]
Yeephu 2013	13	13	6	6	19.7%	0.00 [-0.21 , 0.21]
Yeephu 2013	14	14	7	7	21.9%	0.00 [-0.19 , 0.19]
Total (95% CI)		**334**		**272**	**100.0%**	**0.12 [-0.01 , 0.26]**
Total events:	255		159			

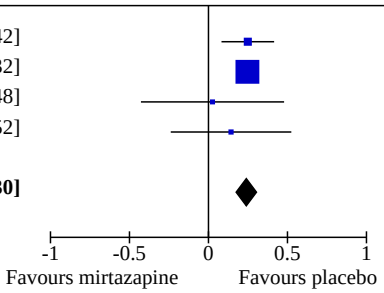
Heterogeneity: Tau² = 0.01; Chi² = 8.72, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 12: Specific adverse event (somnolence)

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
JapicCTI-101176	48	92	12	44	14.8%	0.25 [0.08 , 0.42]
Miki 2016	69	215	16	215	80.3%	0.25 [0.17 , 0.32]
Yeephu 2013	9	13	4	6	2.0%	0.03 [-0.43 , 0.48]
Yeephu 2013	12	14	5	7	2.8%	0.14 [-0.24 , 0.52]
Total (95% CI)		**334**		**272**	**100.0%**	**0.24 [0.18 , 0.30]**
Total events:	138		37			

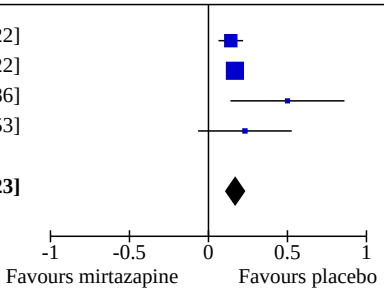
Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 3 (P = 0.76); I² = 0%
Test for overall effect: Z = 7.32 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 13: Specific adverse event (weight gain)

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
JapicCTI-101176	13	92	0	44	36.9%	0.14 [0.06 , 0.22]
Miki 2016	38	215	2	215	56.7%	0.17 [0.11 , 0.22]
Yeephu 2013	9	14	1	7	2.6%	0.50 [0.14 , 0.86]
Yeephu 2013	3	13	0	6	3.8%	0.23 [-0.07 , 0.53]
Total (95% CI)		**334**		**272**	**100.0%**	**0.17 [0.11 , 0.23]**
Total events:	63		3			

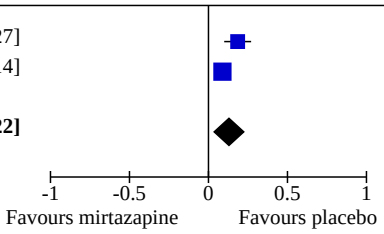
Heterogeneity: Tau² = 0.00; Chi² = 3.86, df = 3 (P = 0.28); I² = 22%
Test for overall effect: Z = 5.61 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 14: Specific adverse event (elevated alanine aminotransferase)

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
JapicCTI-101176	17	92	0	44	42.9%	0.18 [0.10 , 0.27]
Miki 2016	24	215	5	215	57.1%	0.09 [0.04 , 0.14]
Total (95% CI)		**307**		**259**	**100.0%**	**0.13 [0.04 , 0.22]**
Total events:	41		5			

Heterogeneity: Tau² = 0.00; Chi² = 3.79, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 2.72 (P = 0.007)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Methodological considerations for chronic pain

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

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011b; Moore 2011c), back pain (Moore 2010d), and arthritis (Moore 2010c), as well as in fibromyalgia (Straube 2010); in all cases average results usually describe the experience of almost no one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.
2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials of less than 12 weeks duration, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010c); the effect is particularly strong for less effective analgesics.
3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis to 30% in fibromyalgia (Moore 2009; Moore 2010c; Moore 2013b; Moore 2014b; Straube 2008). A Cochrane

Review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009).

4. Individual patient analyses of pregabalin studies in fibromyalgia indicate that patients who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010b; Moore 2014a).
5. Imputation methods, such as last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012b).

Appendix 2. Search strategy for CENTRAL

1 mirtazapine.tw. (1764)

2 Fibromyalgia/ (7710)

3 (fibromyalgia or fibrositis or FMS).tw. (13609)

4 2 or 3 (14696)

5 1 and 4 (10)

6 randomized controlled trial.pt. (466962)

7 controlled clinical trial.pt. (94240)

8 randomized.ab. (400181)

9 placebo.ab. (187995)

10 drug therapy.fs. (2009551)

11 randomly.ab. (278329)

12 trial.ab. (419543)

13 groups.ab. (1712839)

14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (4095339)

15 exp animals/ not humans.sh. (4421683)

16 14 not 15 (3535698)

17 5 and 16 (4)

Appendix 3. Search strategy for MEDLINE via Pubmed

1 mirtazapine.tw. (1764)

2 Fibromyalgia/ (7710)

3 (fibromyalgia or fibrositis or FMS).tw. (13609)

4 2 or 3 (14696)

5 1 and 4 (10)

6 randomized controlled trial.pt. (466962)

7 controlled clinical trial.pt. (94240)

8 randomized.ab. (400181)

9 placebo.ab. (187995)

10 drug therapy.fs. (2009551)

11 randomly.ab. (278329)

12 trial.ab. (419543)

13 groups.ab. (1712839)

14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (4095339)

15 exp animals/ not humans.sh. (4421683)

16 14 not 15 (3535698)

17 5 and 16 (10)

Appendix 4. Search strategy for Embase

1 Fibromyalgia/ (16842)

2 (fibromyalgia or fibrositis or FMS).tw. (19614)

3 mirtazapine/ (10827)

4 mirtazapine.tw. (2690)

5 1 or 2 (23900)

6 3 or 4 (10955)

7 5 and 6 (118)

8 random$.tw. (1211901)

9 factorial$.tw. (30702)

10 crossover$.tw. (62786)

11 cross over$.tw. (27665)

12 cross-over$.tw. (27665)

13 placebo$.tw. (257796)

14 (doubl$ adj blind$).tw. (180256)

15 (singl$ adj blind$).tw. (19675)

16 assign$.tw. (317389)

17 allocat$.tw. (117921)

18 volunteer$.tw. (222420)

19 Crossover Procedure/ (52320)

20 double-blind procedure.tw. (237)

21 Randomized Controlled Trial/ (459684)

22 Single Blind Procedure/ (28083)

23 or/8-22 (1876528)

24 (animal/ or nonhuman/) not human/ (5356208)

25 23 not 24 (1665611)

26 7 and 25 (21)

Appendix 5. SCOPUS

(TITLE-ABS-KEY (mirtazapine) AND TITLE-ABS-KEY ((fibromyalgia OR fibrositis OR fms)) AND TITLE-ABS-KEY (random* OR trial* OR crossover* OR control*): 71

Appendix 6. Other databases

US National Insitutes of Health (ClinicalTrials.gov)

Mirtazapine and fibromyalgia: 1

World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/)

Mirtazapine and fibromyalgia: 3

WHAT'S NEW

Date	Event	Description
27 July 2020	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 6, 2017
Review first published: Issue 8, 2018

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

CONTRIBUTIONS OF AUTHORS

WH, SD and RAM drafted the protocol. All authors had input into the protocol development and agreed the final version.
WH and PW developed and ran the searches. The PaPaS Information Specialist provided support.
WH, KB and PW selected which studies to include.
WH, KB and PW extracted data from studies.
WH entered data into Review Manager 5 (Review Manager 2014), and carried out the analysis. PW checked data entry.

All authors interpreted analysis.

DECLARATIONS OF INTEREST

PW: none known. PW is a specialist pain physician and manages patients with fibromyalgia.

KB: none known. KB is a clinical psychologist and manages patients with fibromyalgia. She is a member of the German guideline group on fibromyalgia.

SD: 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 (2015), Menarini (215), and Novartis (2015) on understanding pharmacokinetics, trial design, and network meta-analysis. He has received honoraria from Omega Pharma/Perrigo Pharma (2016, 2017), Futura Pharma (2015, 2016), RB (2015, 2017), and the Advertising Standards Authority (2016) for providing advice on trial and data analysis methods. He has received honoraria for lectures from RB (2015) and Novartis (2016).

WH is a specialist in general internal medicine, psychosomatic medicine and pain medicine, who treats patients with fibromyalgia. He is a member of the medical board of the German Fibromyalgia Association. He is the head of the steering committee of the German guideline group on fibromyalgia and a member of the steering committee of the European League Against Rheumatism (EULAR) updated recommendations on the management of fibromyalgia. He received speaking fees for one educational lecture from Grünenthal (2015) on pain management.

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

- Oxford Pain Relief Trust, UK

  General institutional support

External sources

- National Institute for Health Research (NIHR), UK

  NIHR Cochrane Programme Grant: 13/89/29 - Addressing the unmet need of chronic pain: providing the evidence for treatments of pain

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We contacted authors and sponsors of studies for missing data.

NOTES

At July 2020 we are not aware of any potentially relevant studies likely to change the conclusions. This is not an active area of research and so this review has now been stabilised following discussion with the authors and editors. If appropriate we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitates major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents, Tricyclic [adverse effects] [*therapeutic use]; Fibromyalgia [*drug therapy]; Mianserin [adverse effects] [*analogs & derivatives] [therapeutic use]; Mirtazapine; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans