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Antipsychotics for fibromyalgia in adults (Review)

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[Intervention Review]

Antipsychotics for fibromyalgia in adults

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ABSTRACT

Background

This review is one of a series on drugs used to treat fibromyalgia. Fibromyalgia is a clinically well-defined chronic condition of unknown aetiology characterised by chronic widespread pain that often co-exists with sleep problems and fatigue. It affects approximately 2% of the general population. Up to 70% of patients with fibromyalgia meet the criteria for a depressive or anxiety disorder. People often report high disability levels and poor health-related quality of life. Drug therapy focuses on reducing key symptoms and disability, and improving health-related quality of life. Antipsychotics might reduce fibromyalgia and associated mental health symptoms.

Objectives

To assess the efficacy, tolerability and safety of antipsychotics in fibromyalgia in adults.

Search methods

We searched CENTRAL (2016, Issue 4), MEDLINE and EMBASE to 20 May 2016, together with reference lists of retrieved papers and reviews and two clinical trial registries. We also contacted trial authors.

Selection criteria

We selected controlled trials of at least four weeks duration of any formulation of antipsychotics used for the treatment of fibromyalgia in adults.

Data collection and analysis

We extracted the data from all included studies and two review authors independently assessed study risks of bias. We resolved discrepancies by discussion. We performed analysis using three tiers of evidence. We derived first tier evidence from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to substantial pain intensity reduction, intention-to-treat analysis without imputation for drop-outs, at least 200 participants in the comparison, eight to 12 weeks duration, parallel design), second tier evidence from data that failed to meet one or more of these criteria and that we considered at some risk of bias but with adequate numbers in the comparison, and third tier evidence from data involving small numbers of participants that we considered very likely to be biased or used outcomes of limited clinical utility, or both. We rated the quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Main results

We included a total of four studies with 296 participants.

Three studies with 206 participants compared quetiapine, an atypical (second-generation) antipsychotic, with placebo. One study used a cross-over design and two studies a parallel-group design. Study duration was eight or 12 weeks. Quetiapine was used in all studies with a bedtime dosage between 50 and 300 mg/day. All studies had one or more sources of potential major bias and we judged them to be at moderate risk of bias overall. The primary outcomes in this review were participant-reported pain relief of 50% or greater, Patient Global Impression of Change (PGIC) much or very much improved, withdrawal due to adverse events (tolerability) and serious adverse events (safety).

Second tier evidence indicated that quetiapine was not statistically superior to placebo in the number of participants with a 50% or more pain reduction (very low quality evidence). No study reported data on PGIC. A greater proportion of participants on quetiapine reported a 30% or more pain reduction (risk difference (RD) 0.12, 95% confidence interval (CI) 0.00 to 0.23; number needed to treat for an additional benefit (NNTB) 8, 95% CI 5 to 100) (very low quality evidence). A greater proportion of participants on quetiapine reported a clinically relevant improvement of health-related quality of life compared to placebo (RD 0.18, 95% CI 0.05 to 0.31; NNTB 5, 95% CI 3 to 20) (very low quality evidence). Quetiapine was statistically superior to placebo in reducing sleep problems (standardised mean difference (SMD) -0.67, 95% CI -1.10 to -0.23), depression (SMD -0.39, 95% CI -0.74 to -0.04) and anxiety (SMD -0.40, 95% CI -0.69 to -0.11) (very low quality evidence). Quetiapine was statistically superior to placebo in reducing the risk of withdrawing from the study due to a lack of efficacy (RD -0.14, 95% CI -0.23 to -0.05) (very low quality evidence). There was no statistically significant difference between quetiapine and placebo in the proportion of participants withdrawing due to adverse events (tolerability) (very low quality evidence), in the frequency of serious adverse events (safety) (very low quality evidence) and in the proportion of participants reporting dizziness and somnolence as an adverse event (very low quality evidence). In more participants in the quetiapine group a substantial weight gain was noted (RD 0.08, 95% CI 0.02 to 0.15; number needed to treat for an additional harm (NNTH) 12, 95% CI 6 to 50) (very low quality evidence). We downgraded the quality of evidence by three levels to a very low quality rating because of limitations of study design, indirectness (patients with major medical diseases and mental disorders were excluded) and imprecision (fewer than 400 patients were analysed).

One parallel design study with 90 participants compared quetiapine (50 to 300 mg/day flexible at bedtime) to amitriptyline (10 to 75 mg/day flexible at bedtime). The study had three major risks of bias and we judged it to be at moderate risk of bias overall. We downgraded the quality of evidence by two levels to a low quality rating because of indirectness (patients with major medical diseases and mental disorders were excluded) and imprecision (fewer than 400 patients were analysed). Third tier evidence indicated no statistically significant differences between the two drugs. Both drugs did not statistically significantly differ in the reduction of average scores for pain, fatigue, sleep problems, depression, anxiety and for limitations of health-related quality of life and in the proportion of participants reporting dizziness, somnolence and weight gain as a side effect (low quality evidence). Compared to amitriptyline, more participants left the study due to adverse events (low quality evidence). No serious adverse events were reported (low quality evidence).

We found no relevant study with other antipsychotics than quetiapine in fibromyalgia.

Authors' conclusions

Very low quality evidence suggests that quetiapine may be considered for a time-limited trial (4 to 12 weeks) to reduce pain, sleep problems, depression and anxiety in fibromyalgia patients with major depression. Potential side effects such as weight gain should be balanced against the potential benefits in shared decision making with the patient.

PLAIN LANGUAGE SUMMARY

Antipsychotics for fibromyalgia symptoms in adults

Bottom line

Quetiapine may be considered for 4 to 12 weeks to reduce pain, sleep problems, depression and anxiety in fibromyalgia patients with major depression. Potential side effects such as weight gain should be balanced against the potential benefits.

Background

People with fibromyalgia often have chronic (longer than three months) widespread pain, as well as sleep problems, problems with thinking and exhaustion. They often report severe limitations of daily functioning and poor quality of life. Therapies focus on reducing key symptoms and disability, and improving health-related quality of life. In addition, many patients with fibromyalgia suffer from depression. Medicines used to treat depression can reduce the main symptoms in some people with fibromyalgia. Quetiapine is a drug for the treatment of psychosis (an abnormal condition of the mind described as involving a loss of contact with reality), which is also licensed for the treatment of major depression in some countries.

Study characteristics

In May 2016, we searched for clinical trials in which antipsychotics were used to treat symptoms of fibromyalgia in adults. We found a total of four studies with 298 participants. We found three studies with 208 participants, which were eight and 12 weeks long and compared quetiapine, an antipsychotic, against a fake medication (placebo). One hundred and sixty-six participants were diagnosed with major depression. We also found one study comprising 90 patients that compared quetiapine to an antidepressant named amitriptyline, which is frequently used in the treatment of fibromyalgia. Five people in this study were diagnosed with major depression.

Key results and quality of the evidence

Quetiapine was not better than a fake medication in achieving a pain reduction of 50% or more (very low quality evidence). Quetiapine was better than the fake medication in achieving a pain reduction of 30% or more, reducing sleep problems, and improving depressed mood and anxiety (very low quality evidence). Quetiapine was better than the fake medication in improving health-related quality of life. Fewer participants dropped out of the trial due to lack of efficacy with quetiapine than with fake medication (very low quality evidence). There was no difference in tolerability and safety between quetiapine and a fake medication (very low quality evidence). For some people, quetiapine led to substantial weight gain and somnolence (sleepiness).

Quetiapine and amitriptyline (an antidepressant which is frequently used to improve sleep and reduce pain in people with fibromyalgia) did not differ in the reduction of average scores for pain, fatigue, sleep problems, depression, anxiety and for limitations of health-related quality of life. Both drugs did not differ in the proportion of patients reporting dizziness, somnolence and weight gain as a side effect (low quality evidence). Compared with amitriptyline, more people experienced side effects and left the study due to side effects with quetiapine (low quality evidence). No serious side effects with either drug were reported (low quality evidence).

We found no relevant study with other antipsychotics than quetiapine in fibromyalgia.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Antipsychotics compared with placebo for fibromyalgia

Patient or population: adults with fibromyalgia

Settings: research centres

Intervention: quetiapine 50 to 300 mg daily

Outcomes	Probable outcome with intervention	Probable outcome with placebo	SMD, risk difference and NNTB/NNTH (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
At least 50 % pain relief	85 per 1000	27 per 1000	NNTB not calculated because of lack of statistical significance RD 0.04 (-0.02 to 0.10)	155 (2 studies)	⊕⊕⊕⊕ very low 1,2,3	—
Patient Global Impression of Change much or very much improved	No data					
Sleep problems (Scale 0 to 21; higher scores indicate more sleep problems) ⁴	—	—	The mean sleep problems in the intervention groups was 0.67 standard deviations lower (1.1 to 0.23 lower) NNTB 4 (2 to 12) SMD -0.67 (-1.1 to -0.23)	87 (2 studies)	⊕⊕⊕⊕ very low 1,2,3	—
Depression (Scale 0 to 50) ⁵	—	—	The mean depression in the intervention groups was 0.39 standard deviations lower (0.74 to 0.04 lower) NNTB 6 (3 to 53) SMD -0.39 (-0.74 to -0.04)	207 (3 studies)	⊕⊕⊕⊕ very low 1,2,3	—

Withdrawals due to adverse events	293 per 1000	178 per 1000	NNTH not calculated because of lack of statistical significance RD 0.10 (-0.06 to 0.27)	155 (2 studies)	⊕○○○ very low 1,2,3	—
Serious adverse events	12 per 1000	10 per 1000	NNTH not calculated because of lack of statistical significance RR -0.00 (-0.03 to 0.03)	206 (3 studies)	⊕○○○ very low 1,2,3	—
Substantial weight gain	85 per 1000	0 per 1000	NNTH 12 (95% CI 0.02 to 0.15) RD 0.08 (0.02 to 0.15)	155 (2 studies)	⊕○○○ very low 1,2,3	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the risk ratio of the intervention (and its 95% CI).
CI: confidence interval; **NNTB:** number needed to treat for an additional benefit; **NNTH:** number needed to treat for an additional harm; **RD:** risk difference; **SD:** standard deviation; **SMD:** standardised mean difference

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Limitations of study design (> 50% participants in low quality studies).

²Imprecision: fewer than 400 participants.

³Indirectness: patients with major medical diseases and mental disorders, except major depression, were excluded.

⁴Potvin 2012: baseline score for sleep problems in control group: 12.8 (SD 4.3). Higher scores indicate more sleep problems.

⁵McIntyre 2014: baseline score for depression 24.6 (SD 11.5). Higher scores indicate more depression.

BACKGROUND

This review is based on a template for reviews of drugs used to relieve fibromyalgia symptoms. 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) and fibromyalgia (Mease 2009).

Description of the condition

Fibromyalgia is defined by the American College of Rheumatology (ACR) 1990 classification criteria as widespread pain that lasts for longer than three months, with tenderness on palpation at 11 or more of 18 specified tender points (Wolfe 1990). Chronic widespread pain is frequently associated with other symptoms such as poor sleep, fatigue and depression (Wolfe 2014). Patients often report high disability levels and poor quality of life along with extensive use of medical care (Häuser 2015a). 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 ACR Preliminary Diagnostic Criteria for Fibromyalgia (so-called Fibromyalgia Symptom Questionnaire) (Wolfe 2011). For a clinical diagnosis, the ACR 1990 classification criteria (Wolfe 1990) and the ACR 2010 preliminary diagnostic criteria (Wolfe 2010) can be used. 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 (Wolfe 2010). The indexing of fibromyalgia within the international classification of diseases is under debate. While some rheumatologists have thought of it as a specific pain disorder and central sensitivity syndrome (Clauw 2014; Yunus 2008), recent research points at small fibre pathology in a subgroup of fibromyalgia patients that may be of pathophysiological importance (Oaklander 2013; Üçeyler 2013a). In psychiatry and psychosomatic medicine, fibromyalgia symptoms are categorised as a functional somatic syndrome, a bodily distress syndrome, a somatic symptom disorder or a somatoform disorder (Häuser 2014).

Fibromyalgia is a heterogenous condition. The definite aetiology (causes) 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 (Sommer 2012). Depression (Forseth 1999), genetics (Arnold 2013; Lee 2012), obesity combined with physical inactivity (Mork 2010), physical and sexual abuse in childhood (Häuser 2011), sleep problems (Mork 2012), and smoking predict future development of fibromyalgia (Choi 2010). Psychosocial stress (e.g. working place and family conflicts) and physical stress (e.g. infections, surgery, accidents) might trigger the onset of chronic widespread pain and fatigue (Clauw 2014; Sommer 2012). Depression and post-traumatic stress disorder worsen fibromyalgia symptoms (Häuser 2013a; Lange 2010).

Several factors are associated with the pathophysiology (functional changes associated with or resulting from disease) of fibromyalgia, but the relationship is unclear. The functional changes include alteration of sensory processing in the brain, reduced reactivity of the hypothalamus-pituitary-adrenal axis to stress, increased pro-inflammatory and reduced anti-inflammatory cytokine profiles (produced by cells involved in inflammation), disturbances in neurotransmitters such as dopamine and serotonin, and small fibre pathology (Oaklander 2013; Sommer 2012; Üçeyler 2013a).

Prolonged exposure to stress, as outlined above, may contribute to these functional changes in predisposed individuals (Bradley 2009).

Fibromyalgia is common. Numerous studies have investigated prevalence in different settings and countries. A 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%) (Queiroz 2013). The change in diagnostic criteria does not appear to have significantly affected estimates of prevalence (Wolfe 2013). Estimates of prevalence in specific populations vary greatly, but have been reported to be as high as 9% in female textile workers in Turkey and 10% in metalworkers in Brazil (59% in those with repetitive strain injury; Queiroz 2013).

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 recommended by recent evidence-based guidelines, with pharmacological treatment being combined with physical or cognitive training, 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 (Eich 2012; Fitzcharles 2013). Conventional analgesics are usually not effective. Treatment is often offered with antidepressants like serotonin and noradrenaline reuptake inhibitors (Häuser 2013b; Lunn 2014), tricyclic agents such as amitriptyline (Moore 2015), or anticonvulsants like gabapentin or pregabalin (Moore 2011a; Üçeyler 2013b; Wiffen 2013). The proportion of people who achieve worthwhile pain relief (typically at least a 50% reduction in pain intensity) is small (Moore 2013a), and generally only 10% to 25% more than with placebo, with numbers needed to treat to benefit (NNTB) between 9.8 and 14 (Kalso 2013; Wiffen 2013). Those who do experience good levels of pain relief by pregabalin, however, also benefit from substantial reductions in other symptoms, such as fatigue, function, sleep, depression, anxiety and ability to work, with significant improvement in quality of life (Moore 2010c; Straube 2011). Fibromyalgia is not particularly different from other chronic pain for the small proportion of trial participants who have a good response to analgesic treatment (Moore 2013b).

Description of the intervention

There is a need for additional pharmacological therapeutic options for the treatment of fibromyalgia symptoms. Antipsychotics (also known as neuroleptics) are a class of psychiatric medication primarily used to manage psychosis symptoms such as hallucinations or disordered thought, in particular in schizophrenia and bipolar disorder. Antipsychotics are increasingly used in the management of non-psychotic mental disorders such as anxiety disorders (Ammar 2015), depressive disorders (Edwards 2013), post-traumatic stress disorder (Wang 2013), and somatoform disorders (Kleinstäuber 2014). These non-psychotic mental disorders are frequently associated with fibromyalgia (Galek 2013). For these reasons, antipsychotics have been used to treat fibromyalgia symptoms (Rico-Villademoros 2014). The role of antipsychotics as adjuvant analgesics for chronic pain is a subject of longstanding controversy in terms of their efficacy and safety (Seidel 2013).

How the intervention might work

In addition to blocking dopamine (D2) receptors, which accounts for their efficacy in treating psychoses, second-generation antipsychotics (so-called atypical antipsychotics) can act upon different adrenergic, acetylcholine, catecholamines, histamine and serotonin receptors in the brain. First- and second-generation antipsychotics have shown analgesic properties both in an experimental setting and in humans, although most of the available evidence for the treatment of human pain concerns older antipsychotics and involves clinical trials performed several decades ago (Calandre 2012). In addition, several second-generation antipsychotics, risperidone, olanzapine and quetiapine, have shown efficacy in the treatment of some anxiety disorders (Ammar 2015). Some second-generation antipsychotics, mainly quetiapine, aripiprazole and amisulpiride, have demonstrated antidepressant activity, with quetiapine approved for the treatment of bipolar depression and refractory major depression, and aripiprazole approved as an adjunctive treatment for major depressive disorder (Edwards 2013). Finally, several old and new antipsychotics, including promethazine, levomepromazine, olanzapine, quetiapine and ziprasidone, have been shown to improve sleep parameters in healthy participants. Each of these properties suggests that antipsychotics could represent a new potential alternative for the treatment of some key fibromyalgia symptoms, such as pain and sleep problems, and of some minor symptoms, such as anxiety and depression (Calandre 2012). As second-generation antipsychotics may have both fewer extrapyramidal side effects and additional benefits (Seidel 2013), such a new drug treatment may be useful for fibromyalgia treatment.

Why it is important to do this review

The serotonin and norepinephrine reuptake inhibitors duloxetine and milnacipran and the anticonvulsant pregabalin have been approved by the US Food and Drug Administration (FDA), but not by the European Medical Agencies (EMA), for the management of fibromyalgia (Häuser 2013b; Üçeyler 2013b). Antipsychotics have been approved as adjunctive treatment for major depression in most countries worldwide. The use of antipsychotics in fibromyalgia has been reported in case series and uncontrolled trials (Rico-Villademoros 2014). Therefore, there is a need to evaluate the efficacy, tolerability and safety of antipsychotics in fibromyalgia in order to assist fibromyalgia patients 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 patients who have a marked decrease in pain (by at least 50%) and who continue in treatment, ideally in trials of 8 to 12 weeks or longer. Pain intensity reduction of 50% or more has been shown to correlate with improvements in comorbid symptoms, function and quality of life. These standards are set by the Cochrane Pain, Palliative and Supportive Care Review Group (Cochrane PaPaS Group 2011).

This Cochrane review assesses the evidence in ways that make both statistical and clinical sense, and uses developing criteria for what constitutes reliable evidence in chronic pain. This sets high standards and marks a change from how reviews were done previously (Moore 2010a).

OBJECTIVES

To assess the efficacy, tolerability and safety of antipsychotics in fibromyalgia in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they were randomised or quasi-randomised controlled trials (RCTs) following four weeks of treatment or longer. We enrolled studies with a parallel, cross-over and enriched enrollment randomised withdrawal design. Trials should have at least 10 participants per treatment arm. 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 non-randomised, 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 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 2011).

Types of interventions

Antipsychotics at any dose, by any route, administered for the relief of fibromyalgia symptoms and 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 of studies 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. Patients 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).

We included a 'Summary of findings' table as per the guidelines given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The 'Summary of findings' table includes the primary outcomes as outlined below.

Primary outcomes

- Participant-reported pain relief of 50% or greater
- PGIC much or very much improved
- Withdrawal due to adverse events (tolerability)
- Serious adverse events (safety)

Secondary outcomes

- Participant-reported pain relief of 30% or greater
- Sleep problems (continuous variable)
- Depression (continuous variable)
- Anxiety (continuous variable)
- Fatigue (continuous variable)
- Participant-reported improvement of health-related quality of life in the Fibromyalgia Impact Questionnaire (FIQ) (Bennett 2009) of 14% or greater
- Withdrawals due to lack of efficacy
- Participants experiencing any adverse event
- Other specific adverse events such as somnolence, dizziness and weight gain

Search methods for identification of studies

Electronic searches

We searched the following databases without language restrictions:

- Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 4);
- MEDLINE via Ovid (1946 to 20 May, 2016);
- EMBASE via Ovid (1974 to 20 May, 2016).

See [Appendix 2](#) for the MEDLINE search strategy, [Appendix 3](#) for the CENTRAL search strategy and [Appendix 4](#) for the EMBASE search strategy.

Searching other resources

We screened the bibliographies of identified randomised trials and relevant review articles for additional information. We also contacted the authors of RCTs with antipsychotics in fibromyalgia and known experts in the field for potential unpublished trials and data.

For ongoing studies, we searched clinical trial databases including ClinicalTrials.gov (<https://clinicaltrials.gov/>) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (<http://apps.who.int/trialsearch/>). We contacted investigators or study sponsors for missing data.

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 did not satisfy the inclusion criteria, and obtained full copies of the remaining studies; two review authors (WH, BW) made the decisions. Both of them read these studies independently and reached agreement by discussion. We did not anonymise the studies in any way before assessment. We created a Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) flow chart to illustrate our study selection process.

Data extraction and management

Two review authors (WH, NÜ) independently extracted data using a pre-standardised data extraction form and checked for agreement before entering data into Cochrane's statistical software, [Review Manager 2014](#). We included information about the study setting, demographic and clinical variables of the patients, number of participants treated, drug and dosing regimen, co-medication, study design (placebo or active control), 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

Two authors (WH, NÜ) independently assessed risk of bias in included studies using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), with any disagreements resolved by discussion.

We assessed the following risks of bias for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (i.e. any truly random process, for example random number table; computer random number generator); unclear risk of bias (when the method used to generate the sequence is not clearly stated); high risk of bias (e.g. allocation is generated in terms of odd or even numbers in the date of birth, date of hospital admission or hospital record number, as well as in the case of allocation by judgement of the physician, the patient's wishes, results of a laboratory test or availability of the intervention).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (for example, telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (when the method is not clearly stated); high risk of bias (systematic selection bias if participants and investigators could possibly foresee allocations, for example due to the use of an openly available treatment plan (e.g. a list with randomly generated numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed, non-opaque or not sequentially numbered).
- Blinding of participants and personnel/treatment providers (systematic performance bias). We assessed the methods used to blind participants and personnel/treatment providers from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, for example, identical tablets; matched in appearance and smell); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved); high risk (blinding of participants was not ensured, e.g. tablets different in form or taste).
- 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 states that outcome assessor was not involved in treatment); unclear risk of bias (study states that the assessor was blinded but does not provide an adequate description of how it was achieved); high risk: data analysis was conducted by the investigators.

- 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 (fewer than 10% of participants did not complete the study and/or used 'baseline observation carried forward' analysis); unclear risk of bias (used 'last observation carried forward' (LOCF) analysis); 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 in the study protocol were reported in the publications of the study. There is low risk of reporting bias if the study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way, or if the study protocol is not available but it is clear that the published reports contain all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon). There is a high risk of reporting bias if not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (for example subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
- Group similarity at baseline (selection bias). We assessed similarity of the study groups at baseline for the most important prognostic clinical and demographic indicators. There is low risk of bias if groups are similar at baseline for demographic factors, value of main outcome measure(s) and important prognostic factors. There is an unclear risk of bias if baseline for demographic factors, value of main outcome measure(s), and important prognostic factors are not or incompletely reported. There is high risk of bias if groups are not similar at baseline for demographic factors, value of main outcome measure(s) and important prognostic factors.
- Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

We defined studies with 0 to 2 unclear or high risks of bias to be high quality studies, with 3 to 5 unclear or high risks of bias to be moderate quality studies, and with 6 to 8 unclear or high risks of bias to be low quality studies (Häuser 2015b).

Measures of treatment effect

We calculated numbers needed to treat for an additional benefit (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 harm (NNTH) and is calculated in the same manner. For dichotomous data we calculated risk differences (RRD) (method inverse variance) with 95% confidence intervals (CIs) using a random-effects model because we found clinical heterogeneity (different numbers of patients with major depressive disorder in both placebo-controlled studies) (Assessment of heterogeneity). We set the threshold for a clinically relevant benefit or a clinically relevant harm for categorical variables as a NNTB or NNTH of less than 10 (Moore 2008). For continuous data we calculated standardised mean differences (SMDs) with 95% confidence intervals (CIs) using a random-effects model because we found clinical heterogeneity (different numbers of patients with major depressive disorder in both placebo-controlled studies). 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 labelled $g < 0.2$ to be a 'not substantial' effect size. We assumed a minimally important difference if Hedges' g was ≥ 0.2 (Fayers 2014). We calculated the numbers needed to treat for an additional outcome of benefit (NNTB) for continuous variables (sleep problems, depression) using the Wells calculator software available at the Cochrane Musculoskeletal Group editorial office, which estimates the proportion of patients who will benefit from treatment from SMDs. The estimation of responders is nearly independent from the minimally important difference (MID) (Norman 2001). We used a minimal clinically important difference of 15% for the calculation of NNTB from SMDs for all 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. We included one study with a cross-over design because separated data from the two periods were reported.

Dealing with missing data

Where means or standard deviations (SDs) were missing, we attempted to obtain these data through contacting trial authors. Where SDs were not available from trial authors, we calculated them from t -values, CIs or standard errors, where reported in articles (Higgins 2011). Where 30% and 50% pain reduction rates and 14% 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 from combining studies by analysing the inclusion and exclusion criteria of the studies included. We assessed statistical heterogeneity visually (L'Abbé 1987), and with the use of the I^2 statistic. When I^2 was greater than 50%, we considered the possible reasons.

Assessment of reporting biases

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 an NNTB of 10 or higher) (Moore 2008).

Data synthesis

We used a random-effects model for meta-analysis because there was significant clinical heterogeneity due to different numbers of patients with major depression in both placebo-controlled studies.

We analysed data in the following three tiers according to outcome and freedom from known sources of bias.

- The first tier used data meeting current best standards, where studies report the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of LOCF or other imputation method for drop-outs, report an intention-to-treat (ITT) analysis, last eight or more weeks, have a parallel-group design, and have at least 200 participants (preferably at least 400) in the comparison (Moore 1998; Moore 2010a; Moore 2012). We reported these top-tier results first.
- The second tier used data from at least 200 participants but where one or more of the above conditions was not met (for example, reporting at least 30% pain intensity reduction, using LOCF or a completer analysis, or lasting four to eight weeks).
- The third tier of evidence related to data from fewer than 200 participants, or where there were expected to be significant problems because, for example, of very short duration studies of less than four weeks, where there was major heterogeneity between studies, or where there were shortcomings in allocation concealment, attrition or incomplete outcome data. For this third tier of evidence, no data synthesis is reasonable, and may be misleading, but an indication of beneficial effects might be possible.

We employed the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (Guyatt 2011 a) to interpret findings (Langendam 2013), and the GRADE profiler (GRADEpro GDT 2015) allowed us to import data from Review Manager 5.3 (Review Manager 2014) to create 'Summary of findings' tables. These tables 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. The GRADE approach defines the quality of the evidence as the extent of confidence in the estimates of treatment benefits and their safety. We made quality ratings separately for each of the 12 outcomes. We downgraded the quality of evidence from 'high quality' by one level for each of the following factors encountered (Guyatt 2011 b; Häuser 2015b):

- Limitations of study design: more than 50% of participants were from low quality studies as defined by the 'Risk of bias' tool.

- Inconsistency of results: the I^2 value was above 50%.
- Indirectness: we assessed whether the question being addressed by the systematic review diverged from the available evidence, in terms of the population in routine clinical care, if exclusion of patients with clinically relevant somatic disease and/or major mental disorders in the included studies resulted in $\geq 50\%$ of the total patient collective of the systematic review coming from studies in which patients with relevant somatic disease and/or major mental disorders were excluded.
- Imprecision: there was only one trial or where there was more than one trial, the total number was fewer than 400 patients.
- Publication bias: all studies were initiated and funded by the manufacturer of the drug.

We categorised the quality of evidence as follows (Guyatt 2011 a):

- 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 the 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; any estimate of effect is very uncertain.

Subgroup analysis and investigation of heterogeneity

We planned to pursue subgroup analyses (studies with and without stratifying for comorbid mental disorders; different antipsychotics) if there were at least two studies available.

Sensitivity analysis

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

RESULTS

Description of studies

Results of the search

The initial searches identified nine potentially relevant studies in CENTRAL, 38 in MEDLINE and 62 in EMBASE. In addition, we identified one additional study in ClinicalTrials.gov and one study by handsearch. After reading the full reports and after receiving the data from the unpublished study, we included four studies in the review (Calandre 2014; McIntyre 2014; NCT01458964, Potvin 2012), of which we entered three studies into quantitative analysis (McIntyre 2014; NCT01458964; Potvin 2012) (see Figure 1).

Figure 1. Study flow diagram.

Included studies

We included four studies with 296 participants using quetiapine into qualitative analysis (Calandre 2014; McIntyre 2014; NCT01458964; Potvin 2012), and three studies with 206 participants into quantitative analysis (McIntyre 2014; NCT01458964, Potvin 2012).

Study recruitment was reported by three studies and was from multiple sources including general practitioners, rheumatologists, pain units, advertisements in local newspapers, radio or television and local self help organisations (Calandre 2014; McIntyre 2014; NCT01458964). Three studies were conducted in tertiary (university) centres (Calandre 2014; NCT01458964; Potvin 2012), and one study was conducted in a regional hospital (McIntyre 2014). The study investigators were affiliated with a department of neuroscience (Calandre 2014), or with a department of psychiatry (NCT01458964; Potvin 2012). One study did not report the affiliation with a department of the authors (McIntyre 2014). All studies were conducted in a single centre. Two studies were conducted in Canada (McIntyre 2014; Potvin 2012), and one study each in Spain (Calandre 2014) and the USA (NCT01458964).

Studies enrolled adult participants with a mean age ranging between 48 and 50 years. Two studies included only women (NCT01458964; Potvin 2012); the remaining studies included more than 95% women. In all included studies diagnosis of fibromyalgia was established by the ACR 1990 classification criteria (Wolfe 1990) (see Table 1). One study required a diagnosis of comorbid major depression for inclusion (McIntyre 2014). All studies excluded

patients with major medical diseases and patients with major mental disorders, except major depression (see Table 1).

Three studies used a parallel-group design (Calandre 2014; McIntyre 2014; Potvin 2012). One used a cross-over study design (NCT01458964). This study provided data from the first phase separately. There was a one-week washout between phases in the cross-over study (NCT01458964).

Study duration was eight weeks in one study (McIntyre 2014) and 12 weeks in the remaining studies.

The dosage of quetiapine was flexible between 50 and 300 mg/day in two studies (McIntyre 2014; Potvin 2012), flexible between 50 and 300 mg/day in one study (Calandre 2014) and fixed at 200 mg/day in one study (NCT01458964). In one study with an active comparator, the dosage of amitriptyline was 10 to 75 mg/day, flexible (Calandre 2014).

Excluded studies

We excluded one study. The reasons for exclusion are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

Each study had a high risk of bias in at least one domain (see Figure 2 and Figure 3). The overall methodological study quality according to the predefined criteria was low in two studies (McIntyre 2014; Potvin 2012), and moderate in two studies (Calandre 2014; NCT01458964).

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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Small sample size bias
Calandre 2014	+	+	-	?	-	+	-
McIntyre 2014	?	?	+	?	?	+	-
NCT01458964	+	+	?	-	?	+	-
Potvin 2012	?	?	?	?	?	-	?

Allocation

All studies were randomised. Random sequence generation and allocation concealment were of low risk in [Calandre 2014](#) and [NCT01458964](#), and unclear in the remaining studies.

Blinding

Two studies adequately described the method used to achieve double-blinding with a low risk of bias ([McIntyre 2014](#); [NCT01458964](#)). One study had a high risk of bias because of its open-label design ([Calandre 2014](#)). The remaining study had an unclear risk of bias.

Incomplete outcome data

Three studies used a last observation forward analysis (unclear risk of bias) ([McIntyre 2014](#); [NCT01458964](#); [Potvin 2012](#)). One study that

had a high risk of bias used a modified intention-to-treat-analysis (at least one measurement after baseline) ([Calandre 2014](#)).

Selective reporting

A study protocol was available for each study (low risk of bias).

Other potential sources of bias

The demographic characteristics of the study groups were similar in all studies. Three studies had a high risk of bias due to small sample sizes (fewer than 50 patients per treatment arm) ([Calandre 2014](#); [McIntyre 2014](#); [NCT01458964](#)), and one study had an unclear risk of bias (50 to 100 patients per treatment arm) ([Potvin 2012](#)).

Effects of interventions

See: [Summary of findings for the main comparison](#)

Quetiapine versus placebo

There was second tier evidence available for this comparison. We downgraded the quality of evidence by three levels to a very low rating because of limitations of study design, indirectness (patients with major medical diseases and mental disorders were excluded) and imprecision (fewer than 400 patients analysed).

Primary outcomes

Participant-reported pain relief of 50% or greater

We entered two studies with 155 participants into the analysis. There was very low quality evidence that there was no statistically significant difference between quetiapine and placebo. Seven of 82 (8.5%) participants with quetiapine and 2/73 (2.7%) participants with placebo reported pain relief of 50% or greater (risk difference (RD) 0.04, 95% confidence interval (CI) -0.02 to 0.10; P value = 0.21; $I^2 = 0\%$) (see [Analysis 1.1](#)).

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

This analysis was not possible because these data were not available.

Withdrawal due to adverse events (tolerability)

We entered two studies with 155 participants into the analysis. There was very low quality evidence that there was no statistically significant difference between quetiapine and placebo. Twenty-four of 82 (29.3%) participants with quetiapine and 13/73 (17.8%) participants with placebo dropped out due to adverse events (RD 0.10, 95% CI -0.06 to 0.27; P value = 0.21; $I^2 = 24\%$) (see [Analysis 1.2](#)).

Serious adverse events (safety)

We entered three studies with 206 participants into the analysis. There was very low quality evidence that there was no statistically significant difference between quetiapine and placebo. One of 86 (1.2%) participants in the quetiapine group (reason: neurocardiogenic syncope as recurrence of pre-existing condition) and 1/99 (1.0%) participants in the placebo group (reason: pulmonary embolism) reported a serious adverse event (RD -0.00, 95% CI -0.03 to 0.03; P value = 0.96; $I^2 = 0\%$) (see [Analysis 1.3](#)).

Secondary outcomes

Participant-reported pain relief of 30% or greater

We entered two studies with 155 participants into the analysis. There was very low quality evidence that there was a statistically significant difference between quetiapine and placebo. Twenty of 82 (24.4%) participants with quetiapine and 8/73 (11.0%) participants with placebo reported pain relief of 30% or greater (RD 0.12, 95% CI 0.00 to 0.23; P value = 0.04; $I^2 = 0\%$). The number needed to treat for an additional benefit (NNTB) was 8 (95% CI 5 to 100). According to the predefined categories there was a clinically relevant benefit with quetiapine (see [Analysis 1.4](#)).

Sleep problems

We entered two studies with 87 participants into the analysis. There was very low quality evidence that quetiapine was superior to placebo in reducing sleep problems (standardised mean difference (SMD) -0.67, 95% CI -1.10 to -0.23; P value = 0.003; $I^2 = 0\%$). According to Cohen's categories, there was a medium effect size indicating a minimal clinically important improvement (see [Analysis 1.5](#)).

Depression

We entered three studies with 207 participants into an analysis of depression. There was very low quality evidence that quetiapine was superior to placebo in reducing depressed mood (SMD -0.39, 95% CI -0.74 to -0.04; P value = 0.03; $I^2 = 31\%$). According to Cohen's categories, there was a small effect size indicating a minimal clinically important improvement (see [Analysis 1.6](#)).

Anxiety

We entered three studies with 206 participants into an analysis of anxiety. There was very low quality evidence that quetiapine was statistically significantly superior to placebo in reducing anxiety (SMD -0.40, 95% CI -0.69 to -0.11; P value = 0.009; $I^2 = 6\%$). According to Cohen's categories, there was a small effect size indicating a minimal clinically important improvement (see [Analysis 1.7](#)).

Fatigue

We did not conduct the predefined quantitative analysis because the data were not included in the three publications and not provided on request. Participants on quetiapine had a significant improvement (P value = 0.001) on the fatigue subscale of the Fibromyalgia Impact Questionnaire (FIQ), with a mean score reduction of 2.07 ± 2.46 when comparing baseline (8.62 ± 1.38) to week 12 (6.55 ± 2.56) before cross-over. Placebo had no effect (P value = 0.12), with a mean score reduction of 0.82 ± 1.83 when comparing baseline (8.86 ± 1.23) to week 12 (8.04 ± 1.75) ([NCT01458964](#)).

Participant-reported improvement of health-related quality of life in the FIQ of 14% or greater

We entered three studies with 206 participants into the analysis. There was very low quality evidence that quetiapine was superior to placebo. Fifty-three of 107 (49.5%) participants in the quetiapine group and 32/99 (32.3%) participants in the placebo group reported a reduction of 14% or more of the FIQ total score (RD 0.18, 95% CI 0.05 to 0.31; P value = 0.008; $I^2 = 0\%$). The NNTB was 5 (95% CI 3 to 20). According to the predefined categories there was a clinically relevant benefit from quetiapine (see [Analysis 1.8](#)).

Withdrawals due to lack of efficacy

We entered two studies with 155 participants into the analysis. There was very low quality evidence that quetiapine was statistically significantly superior over placebo in reducing drop-out due to lack of efficacy. Two of 82 (2.4%) in the quetiapine group and 13/73 (17.8%) in the placebo group dropped out due to lack of efficacy (RD -0.14, 95% CI -0.23 to -0.05; P value = 0.003; $I^2 = 0\%$). The NNTB was 7 (95% CI 4 to 20). According to the predefined categories there was a clinically relevant benefit from quetiapine (see [Analysis 1.9](#)).

Participants experiencing any adverse event

This analysis was not possible because these data were not available.

Other specific adverse events

Somnolence

We entered three studies with 206 participants into an analysis of somnolence as adverse event. There was very low quality evidence that there was no statistically significant difference between quetiapine and placebo. Fifty-nine of 107 (55.1%) participants in

the quetiapine group and 28/93 (30.1%) participants in the placebo group reported somnolence as an adverse event (RD 0.22, 95% CI -0.06 to 0.50; P value = 0.12; I^2 = 86%) (see [Analysis 1.10](#)).

Dizziness

We entered three studies with 206 participants into the analysis. There was very low quality evidence that there was no statistically significant difference between quetiapine and placebo. Twenty-seven of 107 (25.2%) participants in the quetiapine group and 22/99 (22.2%) participants in the placebo group reported dizziness as an adverse event (RD 0.05, 95% CI -0.05 to 0.14; P value = 0.33; I^2 = 0%) (see [Analysis 1.11](#)).

Substantial weight gain (> 5 kg)

We entered two studies with 155 participants into the analysis. There was very low quality evidence that there was a statistically significant difference between quetiapine and placebo. In 7/82 (8.5%) participants with quetiapine and 0/73 (0%) participants with placebo a substantial weight gain was noted (RD 0.08, 95% CI 0.02 to 0.15; P value = 0.01; I^2 = 0%). The number needed to treat for an additional harm (NNTH) was 12 (95% CI 6 to 50). According to the predefined categories there was no clinically relevant harm from quetiapine (see [Analysis 1.12](#)).

Antipsychotics versus amitriptyline

There was only third tier evidence available for this comparison. For this third tier evidence, no data synthesis was reasonable and may have been misleading. We therefore did not conduct the planned meta-analysis and the study results are presented in a narrative fashion. The overall methodological study quality according to the predefined criteria was moderate. We downgraded the quality of evidence by two levels to low because of indirectness (participants with major medical diseases and mental disorders, except major depression, were excluded) and of imprecision (only one study available). The study used a non-inferiority design with the mean change from baseline to endpoint in the FIQ total score as the primary outcome. The non-inferiority threshold was established at eight points. The authors failed to demonstrate the non-inferiority of quetiapine compared to amitriptyline ([Calandre 2014](#)).

Primary outcomes

Participant-reported pain relief of 50% or greater

There were missing data, therefore this analysis was not possible. There was no statistically significant difference between the two drugs in mean pain reduction (P value = 0.84).

PGIC much or very much improved

This analysis was not possible because these data were not available.

Withdrawal due to adverse events (tolerability)

There was low quality evidence that more participants dropped out due to adverse events on quetiapine (14/45 (31.1%)) than on amitriptyline (3/45 (6.7%)) (P value = 0.003).

Serious adverse events (safety)

No serious adverse events were reported in both groups.

Secondary outcomes

Participant-reported pain relief of 30% or greater

There were missing data, therefore this analysis was not possible.

Sleep problems

There was low quality evidence that there was no statistically significant difference between the two drugs. The mean change from baseline in the quetiapine group was -3.9 ± 4.3 and in the amitriptyline group was -3.8 ± 4.1 (P value = 0.62).

Depression

There was low quality evidence that there was no statistically significant difference between the two drugs. The mean change from baseline in the quetiapine group was -2.1 ± 7.9 and in the amitriptyline group was -4.2 ± 7.6 (P value = 0.25).

Anxiety

There was low quality evidence that there was no statistically significant difference between the two drugs. The mean change from baseline in the quetiapine group was -5.5 ± 11.2 and in the amitriptyline group was -5.9 ± 10.1 (P value = 0.63).

Fatigue

There was low quality evidence that there was no statistically significant difference between the two drugs. The mean change from baseline in the quetiapine group was -1.1 ± 2.3 and in the amitriptyline group was -1.3 ± 2.3 (P value = 0.77).

Participant-reported improvement of health-related quality of life in the FIQ of 14% or greater

There was low quality evidence that there was no statistically significant difference between the two drugs. Sixteen of 33 (48.5%) participants on quetiapine and 25/43 (58.1%) participants on amitriptyline reported a reduction on the FIQ of 14% or greater (P value = 0.40).

Withdrawals due to lack of efficacy

There were missing data, therefore the analysis was not possible.

Participants experiencing any adverse event

There was low quality evidence that there was no statistically significant difference between the two drugs. Forty-five of 45 (100%) participants in the quetiapine group and 42/45 (93.3%) participants in the amitriptyline group reported at least one adverse event (P value = 0.08).

Other specific adverse events

Somnolence

There was low quality evidence that there was no statistically significant difference between the two drugs. Fifteen of 45 (33.3%) participants in the quetiapine group and 13/45 (28.9%) participants in the amitriptyline group reported somnolence (P value = 0.21).

Dizziness

There was low quality evidence that there was no statistically significant difference between the two drugs. Seventeen of 45 (37.8%) participants in the quetiapine group and 12/45 (26.7%) participants in the amitriptyline group reported dizziness (P value = 0.26).

Weight gain

There was low quality evidence that there was no statistically significant difference between the two drugs. Weight gain was observed in 7/45 (15.6%) participants in the quetiapine group and in 5/45 (11.1%) participants in the amitriptyline group (P value = 0.54).

Assessment of publication bias

One hundred and sixty-five participants would have to have been included in entirely negative (zero treatment effect) trials to breach the pre-set level of utility (a NNTB of 10 or more).

Subgroup analysis and investigation of heterogeneity

The planned subgroup analyses (e.g. studies with and without stratification for comorbid mental disorders) were not possible due to an insufficient number of studies. Most notably, we could not perform subgroup analysis of participants with and without major depression because two studies included participants with and without major depression. Data for an individual patient data analysis were not provided.

The heterogeneity of all quantitative analyses was below 50% except for somnolence with an I^2 of 86%.

Sensitivity analysis

We did not perform sensitivity analysis because we did not identify individual peculiarities of the studies under investigation during the review process that were suitable for sensitivity analyses.

DISCUSSION

Summary of main results

We included a total of four studies with 298 participants. Three randomised controlled studies compared the second-generation antipsychotic quetiapine to placebo in 208 participants with fibromyalgia, with and without current major depression. Second tier and very low quality evidence indicated that quetiapine was not superior to placebo in inducing substantial (50% or more) pain reduction in some participants. Second tier and very low quality evidence indicated that quetiapine was superior to placebo in inducing moderate (30% or more) pain reduction, in inducing a minimal clinically important difference in health-related quality of life and in reducing average scores for sleep problems, depressed mood and anxiety to a clinically relevant degree in some participants. Participants taking quetiapine did not drop out due to adverse events nor report more serious adverse events than did participants taking placebo. Somnolence and substantial weight gain were clinically relevant side effects of quetiapine.

The review also found one randomised controlled study with a non-inferiority design, which compared the antipsychotic quetiapine with the tricyclic antidepressant amitriptyline in 90 participants with fibromyalgia, with and without current major depression. Third tier and low quality evidence indicated that there was no difference between the two drugs in the outcomes of efficacy (reduction of mean scores for pain, health-related quality of life, sleep problems, fatigue, depression, anxiety) and safety. More participants dropped out due to adverse events in the quetiapine group than in the amitriptyline group.

We did not find randomised controlled trials with other antipsychotics than quetiapine.

Overall completeness and applicability of evidence

The overall completeness and applicability of the evidence were poor. The usefulness of the available evidence is limited because reporting quality was poor by current standards (Moore 2010a). The authors of two studies did not provide additional information on request (McIntyre 2014; Potvin 2012). The applicability of the evidence to routine clinical care is limited because patients with mental disorders other than major depression and with major medical diseases were excluded by all studies.

Quality of the evidence

We found the evidence for most outcomes to be of very low quality, primarily due to risks of bias such as limitations of study design and imprecise results because of small study sample sizes.

Potential biases in the review process

The absence of publication bias (unpublished trials showing no benefit of antipsychotics over placebo) can never be proved. We carried out a broad search for studies and feel it is unlikely that significant amounts of relevant data remain unknown to us.

Agreements and disagreements with other studies or reviews

Our results are in line with those of a narrative review on the role of antipsychotics in fibromyalgia, which concluded that very low quality evidence has demonstrated the superiority of quetiapine over placebo in treating comorbid major depression and sleep disturbance, and that quetiapine failed to demonstrate non-inferiority to amitriptyline in terms of improving overall symptomatology (Rico-Villademoros 2014).

Our conclusions are also in line with those of a Cochrane review on antipsychotics in acute and chronic pain, which found that antipsychotics might be considered as an add-on therapy in the treatment of some painful conditions, for example fibromyalgia (Seidel 2013). Nevertheless, side effects have to be considered before using antipsychotics (Seidel 2013). The use of atypical antipsychotics can be associated with substantial weight gain and resulting metabolic syndrome (Ventriglio 2015). Chronic pain syndromes such as fibromyalgia and obesity are significant comorbidities, which adversely impact each other (Okifuji 2015). The use of atypical antipsychotics in obese patients with fibromyalgia should therefore be carefully considered.

Quetiapine reduced anxiety and depression in all studies included into analysis (McIntyre 2014; Potvin 2012; NCT01458964). A systematic review with network meta-analysis found that all standard-dose atypical antipsychotics for the adjunctive treatment of therapy-resistant depression are efficacious in reducing depressive symptoms. However, atypical antipsychotics should be prescribed with caution due to abundant evidence of side effects (Zhou 2015).

AUTHORS' CONCLUSIONS

Implications for practice

For people with fibromyalgia

There is no convincing, unbiased, high quality evidence to suggest that the atypical antipsychotic quetiapine is superior to the antidepressant amitriptyline, a standard drug used for the treatment of fibromyalgia (Abilin 2013). A small number of patients may obtain a minimal clinical or greater benefit from quetiapine in terms of a moderate pain reduction, a reduction of sleep problems, depression and anxiety, and improvement in health-related quality of life. Adverse events (somnolence, weight gain) may limit its clinical usefulness. We found no relevant study of other antipsychotics than quetiapine in fibromyalgia.

For physicians

Antipsychotics are not licensed for fibromyalgia in any country. Quetiapine is licensed for the treatment of major depression in some countries. There is no other current guideline recommendation for the use of any antipsychotic in the management of fibromyalgia (Abilin 2013). Quetiapine may be considered for a time-limited trial (4 to 12 weeks) to reduce sleep problems and depression in fibromyalgia patients with major depression if antidepressants such as duloxetine have failed. Duloxetine is approved for the treatment of fibromyalgia in all continents except Europe and for the treatment of major depression in most countries worldwide (Häuser 2013b). Since relatively few participants achieve a worthwhile response with quetiapine, 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 appropriate stopping rules are in place.

For funders

Quetiapine and other atypical antipsychotics with a low risk of weight gain may be worth considering as a potential treatment

in fibromyalgia patients with major depression, as there are few proven effective drug treatments.

Implications for research

General

The trials in this review used the last observation carried forward (LOCF) imputation method for study withdrawals, therefore post-hoc individual participant-level analyses using baseline observation carried forward (BOCF) would be appropriate to strengthen the findings.

Further international studies, which include people with major medical diseases and mental disorders such as anxiety disorders, are necessary to provide external validity of the study findings.

Measurement (endpoints)

Responder criteria for a clinically relevant improvement of sleep problems and fatigue should be defined.

Comparison between active treatments

Any comparisons in future trials should be made with placebo and other drugs with known efficacy, such as amitriptyline or pregabalin. In addition, studies comparing single therapies (e.g. atypical antipsychotics) versus combination therapies (e.g. atypical antipsychotics and aerobic exercise) are necessary.

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REFERENCES

References to studies included in this review

Calandre 2014 {published data only}

Calandre EP, Rico-Villademoros F, Galán J, Molina-Barea R, Vilchez JS, et al. Quetiapine extended-release (Seroquel-XR) versus amitriptyline monotherapy for treating patients with fibromyalgia: a 16-week, randomized, flexible-dose, open-label trial. *Psychopharmacology* 2014;**231**:2525-31.

McIntyre 2014 {published data only}

McIntyre A, Paisley D, Kouassi E, Gendron A. Quetiapine fumarate extended-release for the treatment of major depression with comorbid fibromyalgia syndrome: a double-blind, randomized, placebo-controlled study. *Arthritis and Rheumatism* 2014;**66**:455-61.

NCT01458964 {published and unpublished data}

NCT01458964. Quetiapine compared with placebo in the management of fibromyalgia. <https://clinicaltrials.gov/ct2/show/NCT01458964?term=quetiapine+and+fibromyalgia&rank=3> 8 July 2014; data provided on request.

Potvin 2012 {published data only}

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

References to studies excluded from this review

Moldofsky 1980 {published data only}

Moldofsky H, Lue FA. The relationship of alpha and delta EEG frequencies to pain and mood in 'fibrositis' patients treated with chlorpromazine and L-tryptophan. *Electroencephalography Clinical Neurophysiology* 1980;**50**:71-80.

Additional references

Ablin 2013

Ablin J, Fitzcharles MA, Buskila D, Shir Y, Sommer C, et al. Treatment of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines with special emphasis on complementary and alternative therapies. *Evidence Based Complementary Alternative Medicine* 2013;**2013**:485272.

Ammar 2015

Ammar G, Naja WJ, Pelissolo A. Treatment-resistant anxiety disorders: a literature review of drug therapy strategies. *Encephale* 2015;**41**(3):260-5.

Arnold 2013

Arnold LM, Fan J, Russell IJ, Yunus MB, Khan MA, Kushner I, et al. The fibromyalgia family study: a genome-wide linkage scan study. *Arthritis and Rheumatism* 2013;**65**:1122-8.

Bennett 2009

Bennett RM, Bushmakina AG, Cappelleri JC, Zlateva G, Sadosky AB. Minimal clinically important difference in the fibromyalgia impact questionnaire. *Journal of Rheumatology* 2009;**36**:1304-11.

Bradley 2009

Bradley LA. Pathophysiology of fibromyalgia. *American Journal of Medicine* 2009;**122**:S22-30.

Calandre 2012

Calandre EP, Rico-Villademoros F. The role of antipsychotics in the management of fibromyalgia. *CNS Drugs* 2012;**26**:135-53.

Choi 2010

Choi CJ, Knutsen R, Oda K, Fraser GE, Knutsen SF. The association between incident self-reported fibromyalgia and nonpsychiatric factors: 25-years follow-up of the Adventist Health Study. *Journal of Pain* 2010;**11**:994-1003.

Clauw 2014

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

Cochrane PaPaS Group 2011

Cochrane Pain, Palliative & Supportive Care Review Group. PaPaS Author and Referee Guidance. Authoring or assessing a Cochrane Protocol, Review, or Review Update for the PaPaS Review Group. Document version 1. September 2011. <http://papas.cochrane.org/papas-documents> (accessed 22 August 2015).

Cohen 1988

Cohen J. Statistical Power Analysis for the Behavioral Sciences. Lawrence Erlbaum Associates, 1998.

Dworkin 2008

Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Journal of Pain* 2008;**9**(2):105-21. [DOI: [10.1016/j.jpain.2007.09.005](https://doi.org/10.1016/j.jpain.2007.09.005)]

Edwards 2013

Edwards SJ, Hamilton V, Nherera L, Trevor N. Lithium or an atypical antipsychotic drug in the management of treatment-resistant depression: a systematic review and economic evaluation. *Health Technology Assessment* 2013;**17**:1-190.

Eich 2012

Eich W, Häuser W, Arnold B, Bernardy K, Brückle W, Eidmann U, et al. Fibromyalgia syndrome. General principles and coordination of clinical care and patient education. *Schmerz* 2012;**26**:268-75.

Fayers 2014

Fayers PM, Hays RD. Don't middle your MID: regression to the mean shrinks estimates of minimally important differences. *Quality Life Research* 2014;**23**:1-4.

Fitzcharles 2013

Fitzcharles MA, Ste-Marie PA, Goldenberg DL, Pereira JX, Abbey S, Choinière M, et al. 2012 Canadian guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary. *Pain Research Management* 2013;**18**:119-26.

Forseth 1999

Forseth KO, Husby G, Gran JT, Førre O. Prognostic factors for the development of fibromyalgia in women with self-reported musculoskeletal pain. A prospective study. *Journal of Rheumatology* 1999;**26**:2458-67.

Furukawa 2005

Furukawa TA, Cipriani A, Barbui C, Brambilla P, Watanabe N. Imputing response rates from means and standard deviations in meta-analyses. *International Clinical Psychopharmacology* 2005;**20**:49-52.

Galek 2013

Galek A, Erbslöh-Möller B, Köllner V, Kühn-Becker H, Langhorst J. Mental disorders in patients with fibromyalgia syndrome: screening in centres of different medical specialties. *Schmerz* 2013;**27**:296-304.

GRADEpro GDT 2015 [Computer program]

Brozek J, Oxman A, Schünemann H. GRADEpro Guideline Development Tool. McMaster University (developed by Evidence Prime, Inc.), 2015.

Guyatt 2011 a

Guyatt G, Oxman AD, Akl EA. GRADE guidelines: 1. Introduction- GRADE evidence profiles and summary of findings tables. *Journal Clinical Epidemiology* 2011;**64**:383-94.

Guyatt 2011 b

Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *Journal of Clinical Epidemiology* 2011;**64**:1277-82.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Häuser 2011

Häuser W, Kosseva M, Üceyler N, Klose P, Sommer C. Emotional, physical, and sexual abuse in fibromyalgia syndrome: a systematic review with meta-analysis. *Arthritis Care & Research* 2011;**63**:808-20.

Häuser 2013a

Häuser W, Galek A, Erbslöh-Möller B, Köllner V, Kühn-Becker H, Langhorst J, et al. Posttraumatic stress disorder in fibromyalgia syndrome: prevalence, temporal relationship between posttraumatic stress and fibromyalgia symptoms, and impact on clinical outcome. *Pain* 2013;**154**:1216-23.

Häuser 2013b

Häuser W, Urrútia G, Tort S, Üceyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: [10.1002/14651858.CD010292](https://doi.org/10.1002/14651858.CD010292)]

Häuser 2014

Häuser W, Henningsen P. Fibromyalgia syndrome - a somaform disorder?. *European Journal of Pain* 2014;**18**:1052-9.

Häuser 2015a

Häuser W, Ablin J, Fitzcharles MA, Littlejohn J, Luciano JV, et al. Fibromyalgia. *Nature Reviews Disease Primers* 2015;**1**:15022. [DOI: [10.1038/nrdp.2015.22](https://doi.org/10.1038/nrdp.2015.22)]

Häuser 2015b

Häuser W, Klose P, Welsch P, Petzke F, Nothacker M, et al. Methodology of the development of the updated LONTS guidelines for long-term administration of opioids in noncancer pain. *Schmerz* 2015;**29**:8-34.

Kalso 2013

Kalso E, Aldington DJ, Moore RA. Drugs for neuropathic pain. *BMJ* 2013;**347**:f7339. [DOI: [10.1136/bmj.f7339](https://doi.org/10.1136/bmj.f7339)]

Kleinstäuber 2014

Kleinstäuber M, Witthöft M, Steffanowski A, van Marwijk H, Hiller W, Lambert MJ. Pharmacological interventions for somatoform disorders in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: [10.1002/14651858.CD010628.pub2](https://doi.org/10.1002/14651858.CD010628.pub2)]

L'Abbé 1987

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

Lange 2010

Lange M, Petermann F. Influence of depression on fibromyalgia: a systematic review. *Schmerz* 2010;**24**:326-33.

Langendam 2013

Langendam MW, Akl EA, Dahm P, Glasziou P, Guyatt G, et al. Assessing and presenting summaries of evidence in Cochrane Reviews. *Systematic Reviews* 2013;**2**:81.

Lee 2012

Lee YH, Choi SJ, Ji JD, Song GG. Candidate gene studies of fibromyalgia: a systematic review and meta-analysis. *Rheumatology International* 2012;**32**:417-26.

Lunn 2014

Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database of Systematic Reviews* 2014, Issue 1. [DOI: [10.1002/14651858.CD007115](https://doi.org/10.1002/14651858.CD007115)]

McQuay 1998

McQuay H, Moore R. An Evidence-based Resource for Pain Relief. Oxford: Oxford University Press, 1998. [ISBN: 978-0192630483]

Mease 2009

Mease P, Arnold LM, Choy EH, Clauw DJ, Crofford LJ, Glass J, et al. Fibromyalgia Syndrome Module at OMERACT 9. *Journal of Rheumatology* 2009;**36**:2318–29.

Moore 1998

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

Moore 2008

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

Moore 2009

Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: [10.1002/14651858.CD007076.pub2](https://doi.org/10.1002/14651858.CD007076.pub2)]

Moore 2010a

Moore RA, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al. "Evidence" in chronic pain - establishing best practice in the reporting of systematic reviews. *Pain* 2010;**150**(3):386–9. [DOI: [doi:10.1016/j.pain.2010.05.011](https://doi.org/10.1016/j.pain.2010.05.011)]

Moore 2010b

Moore RA, Moore OA, Derry S, Peloso PM, Gammaitoni AR, Wang H. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. *Annals of the Rheumatic Diseases* 2010;**69**(2):374–9. [DOI: [doi:10.1136/ard.2009.107805](https://doi.org/10.1136/ard.2009.107805)]

Moore 2010c

Moore RA, Straube S, Paine J, Phillips CJ, Derry S, McQuay HJ. Fibromyalgia: moderate and substantial pain intensity reduction predicts improvement in other outcomes and substantial quality of life gain. *Pain* 2010;**149**(2):360–4. [DOI: [10.1016/j.pain.2010.02.039](https://doi.org/10.1016/j.pain.2010.02.039)]

Moore 2010d

Moore RA, Smugar SS, Wang H, Peloso PM, Gammaitoni A. Numbers-needed-to-treat analyses - do timing, dropouts, and outcome matter? Pooled analysis of two randomized, placebo-controlled chronic low back pain trials. *Pain* 2010;**151**(3):592–7. [DOI: [doi:10.1016/j.pain.2010.07.013](https://doi.org/10.1016/j.pain.2010.07.013)]

Moore 2011a

Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: [10.1002/14651858.CD007938.pub2](https://doi.org/10.1002/14651858.CD007938.pub2)]

Moore 2011b

Moore RA, Straube S, Paine J, Derry S, McQuay HJ. Minimum efficacy criteria for comparisons between treatments using

individual patient meta-analysis of acute pain trials: examples of etoricoxib, paracetamol, ibuprofen, and ibuprofen/paracetamol combinations after third molar extraction. *Pain* 2011;**152**(5):982–9. [DOI: [doi:10.1016/j.pain.2010.11.030](https://doi.org/10.1016/j.pain.2010.11.030)]

Moore 2011c

Moore RA, Mhuirheartaigh RJ, Derry S, McQuay HJ. Mean analgesic consumption is inappropriate for testing analgesic efficacy in post-operative pain: analysis and alternative suggestion. *European Journal of Anaesthesiology* 2011;**28**(6):427–32. [DOI: [10.1097/EJA.0b013e328343c569](https://doi.org/10.1097/EJA.0b013e328343c569)]

Moore 2012

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

Moore 2013a

Moore RA, Straube S, Aldington D. Pain measures and cut-offs - 'no worse than mild pain' as a simple, universal outcome. *Anaesthesia* 2013;**68**(4):400–12. [DOI: [10.1111/anae.12148](https://doi.org/10.1111/anae.12148)]

Moore 2013b

Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. *BMJ* 2013;**346**:f2690. [DOI: [10.1136/bmj.f2690](https://doi.org/10.1136/bmj.f2690)]

Moore 2014

Moore RA, Cai N, Skljarevski V, Tölle TR. Duloxetine use in chronic painful conditions - individual patient data responder analysis. *European Journal of Pain* 2014;**18**(1):67–75. [DOI: [10.1002/j.1532-2149.2013.00341.x](https://doi.org/10.1002/j.1532-2149.2013.00341.x)]

Moore 2015

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

Mork 2010

Mork PJ, Vasseljen O, Nilsen TI. Association between physical exercise, body mass index, and risk of fibromyalgia: longitudinal data from the Norwegian Nord-Trøndelag Health Study. *Arthritis Care & Research* 2010;**62**:611–7.

Mork 2012

Mork PJ, Nilsen TI. Sleep problems and risk of fibromyalgia: longitudinal data on an adult female population in Norway. *Arthritis and Rheumatism* 2012;**64**:281–4.

Norman 2001

Norman GR, Sridhar FG, Guyatt GH, Walter SD. Relation of distribution- and anchor-based approaches in interpretation of changes in health-related quality of life. *Medical Care* 2001;**39**:1039–47.

O'Brien 2010

O'Brien EM, Staud RM, Hassinger AD, McCulloch RC, Craggs JG, Atchison JW, et al. Patient-centered perspective on treatment

outcomes in chronic pain. *Pain Medicine* 2010;**11**(1):6-15. [DOI: [10.1111/j.1526-4637.2009.00685.x](https://doi.org/10.1111/j.1526-4637.2009.00685.x)]

Oaklander 2013

Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain* 2013;**154**:2310-6.

Okifuji 2015

Okifuji A, Hare BD. The association between chronic pain and obesity. *Journal Pain Research* 2015;**14**:399-408.

Queiroz 2013

Queiroz LP. Worldwide epidemiology of fibromyalgia. *Current Pain and Headache Reports* 2013;**17**(8):356. [DOI: [10.1007/s11916-013-0356-5](https://doi.org/10.1007/s11916-013-0356-5)]

Review Manager 2014 [Computer program]

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

Rico-Villademoros 2014

Rico-Villademoros F, Calandre EP, Slim M. Current status of atypical antipsychotics for the treatment of fibromyalgia. *Drugs Today* 2014;**50**:435-44.

Seidel 2013

Seidel S, Aigner M, Ossege M, Pernicka E, Wildner B, Sycha T. Antipsychotics for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: [10.1002/14651858.CD004844.pub3](https://doi.org/10.1002/14651858.CD004844.pub3)]

Sommer 2012

Sommer C, Häuser W, Burgmer M, Engelhardt R, Gerhold K, Petzke F, et al. Etiology and pathophysiology of fibromyalgia syndrome. *Schmerz* 2012;**26**:259-67.

Straube 2008

Straube S, Derry S, McQuay HJ, Moore RA. Enriched enrollment: definition and effects of enrichment and dose in trials of pregabalin and gabapentin in neuropathic pain. A systematic review. *British Journal of Clinical Pharmacology* 2008;**66**(2):266-75. [DOI: [10.1111/j.1365-2125.2008.03200.x](https://doi.org/10.1111/j.1365-2125.2008.03200.x)]

Straube 2010

Straube S, Derry S, Moore RA, Paine J, McQuay HJ. Pregabalin in fibromyalgia - responder analysis from individual patient data. *BMC Musculoskeletal Disorders* 2010;**11**:150. [doi: [10.1186/1471-2474-11-150](https://doi.org/10.1186/1471-2474-11-150)]

Straube 2011

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

Sultan 2008

Sultan A, Gaskell H, Derry S, Moore RA. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic

review of randomised trials. *BMC Neurology* 2008;**8**:29. [DOI: [10.1186/1471-2377](https://doi.org/10.1186/1471-2377)]

Ventriglio 2015

Ventriglio A, Gentile A, Stella E, Bellomo A. Metabolic issues in patients affected by schizophrenia: clinical characteristics and medical management. *Frontiers in Neuroscience* 2015;**9**:297.

Wang 2013

Wang HR, Woo YS, Bahk WM. Atypical antipsychotics in the treatment of posttraumatic stress disorder. *Clinical Neuropharmacology* 2013;**36**:216-22.

Wiffen 2013

Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice ASC, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* 2013, Issue 11. [DOI: [10.1002/14651858.CD010567.pub2](https://doi.org/10.1002/14651858.CD010567.pub2)]

Wolfe 1990

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis and Rheumatism* 1990;**33**:160-72.

Wolfe 2010

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care & Research* 2010;**62**:600-10.

Wolfe 2011

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *Journal of Rheumatology* 2011;**38**:1113-22.

Wolfe 2013

Wolfe F, Brähler E, Hinz A, Häuser W. Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population. *Arthritis Care & Research* 2013;**64**(5):777-85. [DOI: [10.1002/acr.21931](https://doi.org/10.1002/acr.21931)]

Wolfe 2014

Wolfe F, Walitt BT, Häuser W. What is fibromyalgia, how is it diagnosed and what does it really mean?. *Arthritis Care & Research* 2014;**66**:969-71. [DOI: [10.1002/acr.22207](https://doi.org/10.1002/acr.22207)]

Yunus 2008

Yunus MB. Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. *Seminars in Arthritis and Rheumatism* 2008;**37**:339-52.

Zhou 2015

Zhou X, Keitner GI, Qin B, Ravindran AV, Bauer M, Del Giovane C, et al. Atypical antipsychotic augmentation for treatment-resistant depression: a systematic review and network meta-analysis. *International Journal of Psychopharmacology* 2015;**18**(11):pyv060.

Üçeyler 2013a

Üçeyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Schmid A, et al. Small fibre pathology in patients with fibromyalgia syndrome. *Brain* 2013;**136**:e247.

Üçeyler 2013b

Üçeyler N, Sommer C, Walitt B, Häuser W. Anticonvulsants for fibromyalgia. *Cochrane Database of Systematic Reviews* 2013, Issue 10. [DOI: [10.1002/14651858.CD010782](https://doi.org/10.1002/14651858.CD010782)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Calandre 2014

Methods	<p>Study setting: single-centre study (Institute of Neuroscience); recruitment from general practitioners, rheumatologists, pain units and/or fibromyalgia patient associations; Spain</p> <p>Study design: parallel</p> <p>Duration of therapy: 12 weeks</p> <p>Follow-up: none</p>
Participants	<p>Demographic and clinical criteria:</p> <p><i>Quetiapine:</i> N = 45, 100% women, race not reported, mean age 49.7 ± 7.9 years; 7% current major depression</p> <p><i>Amitriptyline:</i> N=45; 95.6% women; race not reported; 50.6 ± 8.2 years; 4 % current major depression</p>
Interventions	<p>Quetiapine: flexible between 50 and 300 mg/day at bedtime</p> <p>Amitriptyline: flexible between 10 and 75 mg/day at bedtime</p> <p>Rescue or allowed medication: the patients were allowed to take medications prescribed for concomitant diseases that did not exclude them from eligibility. As a rescue medication for pain, up to 3 g daily of paracetamol was permitted throughout the study. Up to 3 mg daily of bromazepam was allowed for treating anxiety and/or insomnia only during the first 4 weeks after randomisation.</p>
Outcomes	<p>50% pain relief or greater: Brief Pain Inventory Severity (0 to 10)</p> <p>At least 14% improvement in health-related quality of life (FIQ): assessed</p> <p>Drop-out due to adverse events: assessed</p> <p>Serious adverse events: assessed</p> <p>Sleep problems: Pittsburgh sleep quality scale</p> <p>Fatigue: FIQ subscale fatigue (0 to 10)</p> <p>Pain relief of 30% or greater: Brief Pain Inventory Severity (0 to 10)*</p> <p>Depression: Beck Depression Inventory</p> <p>Anxiety: State Anxiety Inventory</p> <p>Withdrawals due to lack of efficacy: reported</p> <p>Participants experiencing any adverse event: reported</p> <p>Specific adverse events: dizziness, somnolence and weight gain reported</p>

Calandre 2014 (Continued)

Notes

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Conflicts of interest: authors declared conflicts of interest

Assessment of adverse events: the safety measurements included ECG, vital signs, complete blood count, blood chemistry, urinalysis and adverse event recording. ECG, vital signs and blood and urine analyses were performed on the screening visit and at the end of the trial. The adverse events were recorded at every visit following randomisation and included those spontaneously reported by the patient and those reported in response to a non-leading question from the investigator.

*Calculated by imputation method

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer program available online"
Allocation concealment (selection bias)	Low risk	By clinical research organisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Investigators were not blinded (open-label)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Modified intention-to-treat analysis (every randomised patient who had at least one post-baseline visit)
Selective reporting (reporting bias)	Low risk	No differences between outcomes as outlined in protocol (NCT00766350) and reported outcomes in publication
Small sample size bias	High risk	Fewer than 50 patients per treatment arm

McIntyre 2014

Methods

Study setting: single-centre study in a regional hospital; type of department not reported; recruitment by a specialist care setting via family physician referrals, the Emergency or Inpatient Unit at a Regional Hospital, and via advertisements in local newspapers, radio or television; Canada

Study design: parallel

Duration of therapy: 8 weeks

Follow-up: none

Participants

Demographic and clinical criteria

Quetiapine: N = 38; 98% women; race not reported, mean age 52 ± 9 years; 100% current major depressive disorder

McIntyre 2014 (Continued)

Placebo: N = 34; 95% women; race not reported; mean age 50 ± 10 years; 100% current major depressive disorder

Interventions

Active drug: quetiapine XR was administered orally once daily in the evening, starting at a dosage of 50 mg/day for the first 2 days then titrated up to 150 mg/day. After 2 weeks, the dosage could be doubled to 300 mg/day at the discretion of the investigator, using patient tolerance and response as guidelines. Patients who were not able to tolerate a dosage of 150 mg/day were withdrawn from the study.

Placebo

Rescue or allowed medication: psychotropic drugs (i.e. antipsychotics, antidepressants, anxiolytics, lithium, mood-stabilising anticonvulsants and sedative-hypnotics other than those permitted) were prohibited during the course of the study, as were other nonprescription agents used for the treatment of depression (e.g. St. John's wort). Patients receiving an antidepressant for their current episode underwent a washout period of 7 days prior to the baseline visit. Other somatic treatments for depression such as transcranial magnetic stimulation or electroconvulsive therapy were not permitted within 6 months of enrollment in the study. Permitted concomitant medications were restricted to a stable dose of zopiclone (3.5 to 15 mg), temazepam (15 to 60 mg) or gabapentin (300 to 700 mg) or a stable dose of analgesic/opioids for at least 4 weeks prior to entering the study

Outcomes

50% pain relief or greater: FIQ Subscale Pain (0 to 10)

At least 14% improvement in health-related quality of life (FIQ): assessed *

Drop-out due to adverse events: reported

Serious adverse events: reported

Sleep problems: FIQ subscale sleep (0 to 10)

Fatigue: FIQ subscale fatigue (0 to 10) **

Pain relief of 30% or greater: assessed *

Depression: Hamilton Depression Rating Scale

Anxiety: Hamilton Anxiety Rating Scale

Withdrawals due to lack of efficacy: reported

Participants experiencing any adverse event: not reported **

Specific adverse events: somnolence, dizziness, weight gain

Notes

Funding: the trial was funded by AstraZeneca Pharmaceuticals

Conflicts of interest: authors declared conflicts of interest

Assessment of adverse events: adverse events and compliance were assessed at every visit following the initial visit (no further details provided). Vital signs, weight, waist circumference, height and concomitant medications were assessed at baseline/screening and at every visit thereafter. Electrocardiography, a pregnancy test and a physical examination were conducted at the baseline/screening visit and at study completion. Laboratory parameters (i.e. haematologic studies including a complete blood cell count, lipid profiles, hepatic enzyme activity, urine chemistry and urine drug screen) were assessed at the time of screening and at the end of the study. Liver function tests, haematologic analyses and fasting blood glucose determinations were repeated at week 4.

* Calculated by imputation method

** Not provided on request

Risk of bias

McIntyre 2014 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported and not provided on request
Allocation concealment (selection bias)	Unclear risk	No details reported and not provided on request
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Tablets identical in appearance"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported and not provided on request
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF
Selective reporting (reporting bias)	Low risk	No differences between outcomes reported in NCT00675896 and in publication
Small sample size bias	High risk	Fewer than 50 patients per treatment arm

NCT01458964

Methods	<p>Study setting: single-centre study in university psychiatry centre; referral: radio and television advertisements, flyers. Some participants learnt of the study through clinicaltrials.gov; referrals from the Quillen College of Medicine physicians; USA</p> <p>Study design: cross-over</p> <p>Duration of therapy: 12 weeks each with a 1 week washout period</p> <p>Follow-up: none</p>
Participants	<p>Demographic and clinical criteria</p> <p><i>Both groups:</i> N = 37; 100% women*; all Caucasian *, mean age 47.7 ± 7.8 years; 39% probable current major depressive disorder (BDI score > 28)</p>
Interventions	<p>Active drug: quetiapine at a dosage of 100 mg for 1 week increasing to a target dosage of 200 mg for 11 weeks</p> <p>Placebo: sugar pill</p> <p>Rescue or allowed medication: not used</p>
Outcomes	<p>50% pain relief or greater: FIQ Subscale Pain (0 to 10) *</p> <p>At least 14% improvement in health-related quality of life (FIQ): assessed *</p> <p>Drop-out due to adverse events: reported *</p> <p>Serious adverse events: reported *</p> <p>Sleep problems: Pittsburgh Sleep Quality Index *</p>

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Fatigue: FIQ subscale fatigue (0 to 10) *

Pain relief of 30% or greater: assessed *

Depression: Beck Depression Inventory *

Anxiety: State-Trait Anxiety Inventory *

Withdrawals due to lack of efficacy: reported *

Participants experiencing any adverse event: not reported

Specific adverse events: somnolence, dizziness, weight gain

Notes

Funding: the trial was funded by AstraZeneca Pharmaceuticals

Conflicts of interest: authors declared conflicts of interest

Assessment of adverse events: at each visit, we took vital signs and inquired about any adverse events. At visits 1, 6 and 12 (baseline, week 12 and week 25/completion) we assessed weight, waist-circumference, fasting blood glucose, HDL, triglycerides and blood pressure. These labs were also ordered at the time of withdrawal if a patient did not complete the study. Adverse events were recorded and deferred to the Principal Investigator's discretion concerning necessary treatment, interventions, referral to another physician or withdrawal from the study. Patients who experienced serious adverse events were admitted to the hospital for further assessment and treatment, and these events were reported to the sponsor (AstraZeneca) (data provided on request)

* Data from the first period (before cross-over) provided on request

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation and allocation of treatment was done by an MD, who was not involved in any ratings or contact with patients (provided on request)
Allocation concealment (selection bias)	Low risk	The randomisation and allocation of treatment was done by an MD, who was not involved in any ratings or contact with patients (provided on request)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Similar appearance of quetiapine and placebo (data provided on request)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Investigator involved in data analysis
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF analysis
Selective reporting (reporting bias)	Low risk	No differences between outcomes reported in NCT01458964 and in data provided
Small sample size bias	High risk	Fewer than 50 patients per treatment arm

Potvin 2012

Methods	<p>Study setting: single-centre university study, further details of setting and recruitment not provided; affiliation of the authors was department of psychiatry; Canada</p> <p>Study design: parallel</p> <p>Duration of therapy: 12 weeks</p> <p>Follow-up: none</p>
Participants	<p>Demographic and clinical criteria:</p> <p><i>Quetiapine:</i> N = 61, 100% women, 100% Caucasian, mean age 50 ± 11.7 years, 20.0% current major depressive disorder</p> <p><i>Placebo:</i> N = 59; 100% women; 100% Caucasian; mean age 49.1 ± 8.7 years; 15.4% current major depressive disorder</p>
Interventions	<p>Active drug: initial dose of 50 mg/day the first 3 days and then at 100 mg/day up to day 7. From day 8 thereafter, a flexible dose between 50 and 300 mg/day was used, based on therapeutic response and tolerability</p> <p>Placebo</p> <p>Rescue or allowed medication: at baseline, fibromyalgia patients in the quetiapine group received the following adjuvant drugs: anticonvulsants (n = 13), antidepressants (n = 19), nonsteroidal anti-inflammatory drugs (n = 13), opioids (n = 17) and anxiolytics (n = 8). Patients in the placebo group received anticonvulsants (n = 9), antidepressants (n = 15), non-steroidal anti-inflammatory drugs (n = 19), opioids (n = 12) and anxiolytics (n = 10)</p>
Outcomes	<p>50% pain relief or greater: FIQ Subscale Pain (0 to 10)</p> <p>At least 14% improvement in health-related quality of life (FIQ): assessed *</p> <p>Drop-out due to adverse events: not reported and not provided on request</p> <p>Serious adverse events: reported</p> <p>Pain relief of 30% or greater: FIQ Subscale Pain (0 to 10)</p> <p>Sleep problems: Pittsburgh Sleep Quality Index (0 to 21)</p> <p>Depression: Hamilton Depression Rating Scale **</p> <p>Anxiety: Hamilton Anxiety Rating Scale **</p> <p>Fatigue: FIQ Subscale Fatigue (0 to 10) **</p> <p>Withdrawals due to lack of efficacy: not reported **</p> <p>Participants experiencing any adverse event: not reported **</p> <p>Specific adverse events: somnolence and dizziness reported; weight gain not reported **</p>
Notes	<p>Funding: the investigator-initiated trial was funded by AstraZeneca Pharmaceuticals</p> <p>Conflicts of interest: authors declared conflicts of interest</p> <p>Assessment of adverse events: at screening/baseline and at the final visit, electrocardiograms, physical examinations and laboratory tests were assessed. Laboratory analyses included haematology (full blood count), lipid profile (cholesterol and triglycerides) and hepatic enzymes. At each study visit, vital signs were recorded, medication compliance was assessed via pill count and adverse events were recorded. (No further details provided).</p> <p>*Calculated by imputation method</p>

Potvin 2012 (Continued)

**Not provided on request

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported except that randomisation was stratified for major depressive disorder
Allocation concealment (selection bias)	Unclear risk	No details reported and not provided on request
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported and not provided on request
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported and not provided on request
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Last observation carried forward (LOCF) analysis
Selective reporting (reporting bias)	High risk	No differences between study protocol NCT00983320 and published results; number of patients dropping out due to adverse events not reported and not provided on request
Small sample size bias	Unclear risk	50 to 100 patients per treatment arm

BDI: Beck Depression Inventory

ECG: electrocardiography

FIQ: Fibromyalgia Impact Questionnaire

HDL: high-density lipoprotein (cholesterol)

LOCF: last observation carried forward

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Moldofsky 1980	Comparison of chlorpromazine with L-tryptophane. No recognised diagnostic criteria used ("fibrositis"). Fewer than 10 patients in each treatment arm.

DATA AND ANALYSES

Comparison 1. Antipsychotics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ≥ 50% pain relief	2	155	Risk Difference (IV, Random, 95% CI)	0.04 [-0.02, 0.10]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Drop-out due to adverse events	2	155	Risk Difference (IV, Random, 95% CI)	0.10 [-0.06, 0.27]
3 Serious adverse events	3	206	Risk Difference (IV, Random, 95% CI)	-0.00 [-0.03, 0.03]
4 $\geq$ 30% pain reduction	2	155	Risk Difference (IV, Random, 95% CI)	0.12 [0.00, 0.23]
5 Sleep problems	2	87	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.10, -0.23]
6 Depression	3	206	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.74, -0.04]
7 Anxiety	3	206	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.69, -0.11]
8 $\geq$ 14% improvement of health-related quality of life	3	206	Risk Difference (M-H, Random, 95% CI)	0.18 [0.05, 0.31]
9 Drop-out due to lack of efficacy	2	155	Risk Difference (M-H, Random, 95% CI)	-0.14 [-0.23, -0.05]
10 Somnolence	3	206	Risk Difference (M-H, Random, 95% CI)	0.22 [-0.06, 0.50]
11 Dizziness	3	206	Risk Difference (IV, Random, 95% CI)	0.05 [-0.05, 0.14]
12 Substantial weight gain	2	155	Risk Difference (IV, Random, 95% CI)	0.08 [0.02, 0.15]

Analysis 1.1. Comparison 1 Antipsychotics versus placebo, Outcome 1 $\geq$ 50% pain relief.

Analysis 1.2. Comparison 1 Antipsychotics versus placebo, Outcome 2 Drop-out due to adverse events.

Analysis 1.3. Comparison 1 Antipsychotics versus placebo, Outcome 3 Serious adverse events.

Analysis 1.4. Comparison 1 Antipsychotics versus placebo, Outcome 4 $\geq 30\%$ pain reduction.

Analysis 1.5. Comparison 1 Antipsychotics versus placebo, Outcome 5 Sleep problems.

Analysis 1.6. Comparison 1 Antipsychotics versus placebo, Outcome 6 Depression.

Analysis 1.7. Comparison 1 Antipsychotics versus placebo, Outcome 7 Anxiety.

Analysis 1.8. Comparison 1 Antipsychotics versus placebo, Outcome 8 >= 14% improvement of health-related quality of life.

Analysis 1.9. Comparison 1 Antipsychotics versus placebo, Outcome 9 Drop-out due to lack of efficacy.

Analysis 1.10. Comparison 1 Antipsychotics versus placebo, Outcome 10 Somnolence.

Analysis 1.11. Comparison 1 Antipsychotics versus placebo, Outcome 11 Dizziness.

Analysis 1.12. Comparison 1 Antipsychotics versus placebo, Outcome 12 Substantial weight gain.

ADDITIONAL TABLES

Table 1. Inclusion and exclusion criteria of the studies included in the review

Study	Inclusion criteria	Exclusion criteria
Calandre 2014	<ul style="list-style-type: none"> Aged 18 to 70 years Fulfilled the 1990 American College of Rheumatology classification criteria Scoring a minimum of 40 on the Fibromyalgia Impact Questionnaire (FIQ) total score and a minimum of 4 on the average pain severity item in the Brief Pain Inventory (BPI) 	<ul style="list-style-type: none"> Pregnancy, lactation and women of childbearing age not using a valid contraception method Any DSM-IV-R Axis I psychiatric disorder other than major depression Major severe depression as evidenced by a Beck Depression Inventory (BDI) score of ≥ 30 Substance and/or alcohol dependence Current clinically relevant cardiovascular, cerebrovascular, renal, hepatic or respiratory disease or any other serious physical illness Uncontrolled diabetes mellitus Unwillingness to discontinue drugs prescribed for fibromyalgia Received quetiapine or amitriptyline within 1 year of randomisation Patients who at randomisation had a change in the FIQ total score of $\geq 20\%$ in relation to the value determined at the screening visit.
McIntyre 2014	<ul style="list-style-type: none"> Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Diagnostic criteria for MDD as confirmed by the Mini-International Neuropsychiatric Interview score of 22 on the 17-item Hamilton Depression Rating (HAM-D) scale and a score of 4 on the Clinical Global Impression-Severity (CGI-S) scale (i.e. moderately ill) at screening and baseline (study day 0) Diagnosis of fibromyalgia was confirmed by the investigator according to the American College of Rheumatology 1990 criteria 	<ul style="list-style-type: none"> DSM-IV Axis I disorder other than MDD and a chronic pain disorder within 6 months History of an inadequate response to treatment (duration of 6 weeks) with 2 antidepressants during the current depressive episode; diagnosis of a DSM-IV Axis II disorder with a major impact on the patient's current psychiatric status Use of quetiapine 25 mg/day for insomnia within 7 days of enrollment Female patients of childbearing potential without adequate contraception Pregnant or breastfeeding patients Acute, unstable or significant and untreated medical illness
NCT01458964	<ul style="list-style-type: none"> Age 18 to 60, inclusive 	<ul style="list-style-type: none"> Pregnant or breastfeeding

Table 1. Inclusion and exclusion criteria of the studies included in the review (Continued)

	<ul style="list-style-type: none"> Females of childbearing potential using a reliable method of contraception AND negative urine pregnancy test Widespread pain present for at least 3 months Widespread encompassing both sides of the body, as well as above and below the waist Pain in at least 11 of 18 tender points as determined by a physician 	<ul style="list-style-type: none"> Use of any of the following in the 14 days prior to enrollment: ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, troleandomycin, indinavir, nelfinavir, ritonavir, fluvoxamine, saquinavir phenytoin, carbamazepine, barbiturates, rifampin, St. John's Wort and glucocorticoids Administration of a depot antipsychotic injection within one dosing interval (for the depot) before enrollment Substance or alcohol dependence at enrollment (except in full or recovery, and except nicotine or caffeine dependence) Abuse of any of the following within 4 weeks of enrollment: opiates, amphetamine, barbiturate, cocaine, cannabis or hallucinogen Medical conditions that would affect study treatment Unstable or inadequately treated medical illness (e.g. diabetes, angina pectoris, hypertension) as judged by investigator Involvement in the planning and conduct of the study Previous enrollment or randomisation of treatment in the present study Participation in another drug trial within 4 weeks prior to enrollment in this study or longer Admitted to hospital for diabetes mellitus (DM) related illness in past 12 weeks Not under physician's care for DM Physician responsible for DM care has indicated that DM is uncontrolled Physician responsible for DM care has not approved participation in the study Have not been on the same dose of DM medicine and/or diet for the 4 weeks prior to starting the study For thiazolidinediones (glitazones) this period should not be less than 8 weeks Taking insulin and the daily dose on one occasion in the past 4 weeks has been more than 10% above or below the mean dose in the preceding 4 weeks A low white blood cell count
Potvin 2012	<ul style="list-style-type: none"> Female patients, older than 18 years Meeting the American College of Rheumatology criteria for the diagnosis of fibromyalgia Unsatisfactory response to their previous pharmacological treatment, defined as a score of 4 or greater on the pain severity item of the French version of the Fibromyalgia Impact Questionnaire (FIQ) 	<ul style="list-style-type: none"> Receiving an antipsychotic Pregnancy or females of childbearing potential without adequate contraception Risk of suicide Any Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I psychiatric disorder other than MDD Any clinically meaningful unstable, renal, hepatic, cardiovascular, respiratory, cerebrovascular disease or other serious, progressive physical illness and diabetes mellitus

DM: Diabetes mellitus

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

FIQ: Fibromyalgia Impact Questionnaire

MDD: Major depressive disorder

APPENDICES

Appendix 1. Methodological considerations for chronic pain

There have been several recent changes in how efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria of 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 longer, 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 inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment.

We summarise some of the recent insights that must be considered in this new review below.

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), arthritis (Moore 2010b), 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 shorter than 12 weeks, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010b); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
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 2010b; Moore 2013b; Moore 2014; Straube 2008; Sultan 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). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.
4. Individual patient analyses 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 2010c; Moore 2014).
5. Imputation methods like 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 2012).

Appendix 2. Search strategy for MEDLINE (OVID)

- 1 exp Antipsychotic Agents/ (105756)
- 2 (antipsychotic* or neuroleptic*).tw. (41565)
- 3 ("droperidol" or "prochlorperazine" or "sultopride").tw. (2748)
- 4 (amisulpride or chlormethiazole or clomethiazole or distraneurin or chlorpromazine or aminazine or chloramine).tw. (14150)
- 5 ("chloramines" or "chlordelazine" or contamin or "fenactil" or "largactil" or "propaphenin" or "thorazine" or "flupenthixol decanoate" or emirgil or "flupenthixol" or "fluaxol" or "flupentixol").tw. (2066)
- 6 (("alpha" and "flupenthixol") or alpha flupenthixol or ("cis" and "flupenthixol") or cis flupenthixol or "fluphenazine" or fluphenazine depot or fluphenazine decanoate or "flufenazin" or ("fluphenazine" and "hydrochloride") or fluphenazine hydrochloride or "lyogen" or prolixin or "haloperidol").tw. (18239)
- 7 (haldol or methotrimeprazine or levomepromazine or levomepromazine or levopromazine or tiserin or tizercine or tizertsin or loxapine or (loxapine and succinate) or loxapine succinate or oxilapine or clozapine or (loxapine and monohydrochloride)).tw. (998)
- 8 (("loxapine" and ("maleic acid" or "maleate")) or "loxitane" or "amoxapine" or "asendin" or "desmethyloxapine" or "olanzapine" or "perphenazine" or chloropiperazine or "perfenazine" or "trilafon" or "pimozide" or "prothipendyl").tw. (9345)
- 9 ("quetiapine" or "fumarates" or "fumarate" or "risperidone" or risperdal or "sulpiride" or "dogmatil" or "eglonyl" or "thioridazine" or "melleril" or "mellaril" or "meleril" or "sonapax" or ("thioridazine" and "hydrochloride") or "thioridazine hydrochloride").tw. (19715)
- 10 (("tiapride" and "hydrochloride") or "tiapride hydrochloride" or "tiapride" or "tiapridal" or "trifluoperazine" or ("trifluoperazine" and "hydrochloride") or "trifluoperazine hydrochloride" or "trifluoperazine" or "triftazin" or "stelazine" or "clopenthixol" or "cisordinol" or "zuclopenthixol" or "clozapine" or ("metylperon" or "melperone") and hydrochloride) or "ziprasidone" or "zotepine").tw. (14423)
- 11 or/1-10 (135332)

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- 12 Fibromyalgia/ (6671)
- 13 (fibromyalgia or fibrositis or FMS).tw. (10502)
- 14 12 or 13 (11516)
- 15 11 and 14 (51)
- 16 randomized controlled trial.pt. (405645)
- 17 controlled clinical trial.pt. (91263)
- 18 randomized.ab. (298465)
- 19 placebo.ab. (155708)
- 20 drug therapy.fs. (1816249)
- 21 randomly.ab. (211512)
- 22 trial.ab. (309818)
- 23 groups.ab. (1337054)
- 24 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (3421297)
- 25 exp animals/ not humans.sh. (4084521)
- 26 24 not 25 (2915889)
- 27 15 and 26 (38)

Appendix 3. Search strategy for CENTRAL (*The Cochrane Library*)

#1 MeSH descriptor: [Antipsychotic Agents] explode all trees

#2 (antipsychotic* or neuroleptic*):ti,ab,kw (Word variations have been searched)

#3 ("droperidol" or "prochlorperazine" or "sultopride"):ti,ab,kw (Word variations have been searched)

#4 (amisulpride or chlormethiazole or clomethiazole or distraneurin or chlorpromazine or aminazine or chloramine):ti,ab,kw (Word variations have been searched)

#5 ("chloramines" or "chlordelazine" or contamin or "fenactil" or "largactil" or "propaphenin" or "thorazine" or "flupenthixol decanoate" or emirgil or "flupenthixol" or "fluaxol" or "flupentixol"):ti,ab,kw (Word variations have been searched)

#6 (("alpha" and "flupenthixol") or alpha flupenthixol or ("cis" and "flupenthixol") or cis flupenthixol or "fluphenazine" or fluphenazine depot or fluphenazine decanoate or "flufenazin" or ("fluphenazine" and "hydrochloride") or fluphenazine hydrochloride or "lyogen" or prolixin or "haloperidol"):ti,ab,kw (Word variations have been searched)

#7 (haldol or methotrimeprazine or levomepromazine or levomepromazine or levopromazine or tiserцин or tizercine or tizertsin or loxapine or (loxapine and succinate) or loxapine succinate or oxilapine or clozapine or (loxapine and monohydrochloride)):ti,ab,kw (Word variations have been searched)

#8 (("loxapine" and ("maleic acid" or "maleate")) or "loxitane" or "amoxapine" or "asendin" or "desmethyloxapine" or "olanzapine" or "perphenazine" or chloropiperazine or "perfenazine" or "trilafon" or "pimozide" or "prothipendyl"):ti,ab,kw (Word variations have been searched)

#9 ("quetiapine" or "fumarates" or "fumarate" or "risperidone" or risperdal or "sulpiride" or "dogmatil" or "eglonyl" or "thioridazine" or "melleril" or "mellaril" or "meleril" or "sonapax" or ("thioridazine" and "hydrochloride") or "thioridazine hydrochloride"):ti,ab,kw (Word variations have been searched)

#10 ("tiapride" and "hydrochloride") or "tiapride hydrochloride" or "tiapride" or "tiapridal" or "trifluoperazine" or ("trifluoperazine" and "hydrochloride") or "trifluoperazine hydrochloride" or "trifluoroperazine" or "triftazin" or "stelazine" or "clopenthixol" or "cisordinol" or "zuclopenthixol" or "clozapine" or ("metylperon" or "melperone") and hydrochloride) or "ziprasidone" or "zotepine"):ti,ab,kw (Word variations have been searched)

#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

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#12 MeSH descriptor: [Fibromyalgia] this term only

#13 (fibromyalgia or fibrositis or FMS):ti,ab,kw (Word variations have been searched)

#14 #12 or #13

#15 #11 and #14

Appendix 4. Search strategy for EMBASE (OVID)

1 exp Antipsychotic Agents/ (234817)

2 (antipsychotic* or neuroleptic*).tw. (63606)

3 ("droperidol" or "prochlorperazine" or "sultopride").tw. (3699)

4 (amisulpride or chlormethiazole or clomethiazole or distraneurin or chlorpromazine or aminazine or chloramine).tw. (18009)

5 ("chloramines" or "chlordelazine" or contamin or "fenactil" or "largactil" or "propaphenin" or "thorazine" or "flupenthixol decanoate" or emirgil or "flupenthixol" or "fluanxol" or "flupenthixol").tw. (5463)

6 (("alpha" and "flupenthixol") or alpha flupenthixol or ("cis" and "flupenthixol") or cis flupenthixol or "fluphenazine" or fluphenazine depot or fluphenazine decanoate or "flufenazin" or ("fluphenazine" and "hydrochloride") or fluphenazine hydrochloride or "lyogen" or prolixin or "haloperidol").tw. (23033)

7 (haldol or methotrimeprazine or levomepromazine or levomepromazine or levopromazine or tiserin or tizerine or tizertsin or loxapine or (loxapine and succinate) or loxapine succinate or oxilapine or clozapine or (loxapine and monohydrochloride)).tw. (4671)

8 (("loxapine" and ("maleic acid" or "maleate")) or "loxitane" or "amoxapine" or "asendin" or "desmethyloxapine" or "olanzapine" or "perphenazine" or chloropiperazine or "perfenazine" or "trilafon" or "pimozide" or "prothipendyl").tw. (14726)

9 ("quetiapine" or "fumarates" or "fumarate" or "risperidone" or risperdal or "sulpiride" or "dogmatil" or "eglonyl" or "thioridazine" or "melleril" or "mellaril" or "meleril" or "sonapax" or ("thioridazine" and "hydrochloride") or "thioridazine hydrochloride").tw. (32263)

10 (("tiapride" and "hydrochloride") or "tiapride hydrochloride" or "tiapride" or "tiapridal" or "trifluoperazine" or ("trifluoperazine" and "hydrochloride") or "trifluoperazine hydrochloride" or "trifluoroperazine" or "triftazin" or "stelazine" or "clopenthixol" or "cisordinol" or "zuclopenthixol" or "clozapine" or ("metylperon" or "melperone") and hydrochloride) or "ziprasidone" or "zotepine").tw. (19876)

11 or/1-10 (261184)

12 Fibromyalgia/ (14467)

13 (fibromyalgia or fibrositis or FMS).tw. (16544)

14 12 or 13 (20347)

15 11 and 14 (382)

16 random\$.tw. (1005343)

17 factorial\$.tw. (26023)

18 crossover\$.tw. (54078)

19 cross over\$.tw. (24245)

20 cross-over\$.tw. (24245)

21 placebo\$.tw. (223139)

22 (doubl\$ adj blind\$).tw. (159394)

23 (singl\$ adj blind\$).tw. (16361)

24 assign\$.tw. (268835)

25 allocat\$.tw. (96179)

26 volunteer\$.tw. (196673)

27 Crossover Procedure/ (43745)

28 double-blind procedure.tw. (228)

29 Randomized Controlled Trial/ (380355)

30 Single Blind Procedure/ (20623)

31 or/16-30 (1588153)

32 (animal/ or nonhuman/) not human/ (4852272)

33 31 not 32 (1406811)

34 15 and 33 (62)

FEEDBACK

Feedback received, 31 August 2016

Summary

Name: **Ciro Manzo**

Email Address: cirmanzo@libero.it

Affiliation: Rheumatologic outpatient clinic Hospital "Mariano Lauro" , Sant'Agnello (Naples, Italy) - Dementia's Center, distretto sanitario 51 ASL NA 3 sud (Naples, Italy)

Role: chief - geriatric consultant

Comment

Patients with major depression are depressed and not affected by fibromyalgia. This is particularly right in elderly patients with major depression in which the somatic complaints are more present than in other periods of life.

There are strong differences among the different diagnostic criteria pointed out by ACR (Wolfe et al, 2010 - Bennett et al, 2013) : the review by Wallitt et al. says nothing about this important selection bias.

When quetiapine is taken at bedtime (as in the studies considered), its effects are on sleep disorders and their consequences . But some clinical features in fibromyalgia are not a consequence (or not only) of sleep disorders and assumption of quetiapine not only at bedtime can realize a meaningful improve on other aspects of quality of life.

Further clarification requested; received 2 September 2016

The most important selection bias used by Walitt et al. are : 1) they considered studies in which the patient with fibromyalgia had a depression, too. Instead, the majority of fibromyalgic patients are not affected by major depression ; 2) in all the studies they considered, quetiapine was taken at bedtime.. So they limited their evaluations only for patients in which disturbances of sleep are the main causal (or concausal) factor on the various items evaluated.

I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment.

Reply

Response prepared by author Winfried Häuser

Ad 1: Selection bias: It is not true, that we "considered studies in which the patient with fibromyalgia had a depression" to be included into the review. Please have a look at our inclusion criteria: "Types of participants: Studies included adult participants aged 18 years and above, diagnosed with fibromyalgia using the 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 2011)."

Please have a look at the inclusion criteria of the studies too: "One study required a diagnosis of comorbid major depression for inclusion (McIntyre 2014)." Please have a look in [Characteristics of included studies](#): the percentage of patients with major depression ranged from 7% to 40% in the remaining studies.

Ad 2: Quetiapine at bedtime: Sleep disturbances / unrefreshed sleep is a main symptom of FMS according to the ACR 2010 and 2011 criteria. Nearly all FM-patients report sleep problems. In addition, due to the side effect (somnolence) of some psychoactive drugs, they are given at bedtime for FM patients, e.g. amitriptyline too. I do not see a major limitation (limited applicability) of the studies reviewed because of the intake of quetiapine only at bedtime.

Contributors

Feedback Editor Kate Seers, Managing Editor Anna Erskine, and Co-ordinating Editor Christopher Eccleston.

WHAT'S NEW

Date	Event	Description
15 September 2016	Feedback has been incorporated	See Feedback .

HISTORY

Protocol first published: Issue 7, 2015

Review first published: Issue 6, 2016

Date	Event	Description
12 September 2016	Amended	Missing '%' added to NCT01458964 Characteristics for included studies table.
13 June 2016	Amended	Minor changes to wording in Declarations of interest .
13 June 2016	Review declared as stable	See Published notes .

CONTRIBUTIONS OF AUTHORS

WH and BW drafted the protocol. PK and WH developed and ran the search. The PaPaS Trials Search Co-ordinator provided support. BW and WH selected which studies to include. NÜ and WH extracted data from studies. WH entered data into RevMan and carried out the analysis. Data entry was checked by NÜ. All authors interpreted the analysis. WH drafted the final review and will be responsible for future updates. All authors approved the final version of the manuscript.

DECLARATIONS OF INTEREST

BW none known; BW is a specialist pain physician and manages patients with fibromyalgia.

PK: none known.

NÜ is a neurologist and pain physician who treats patients with fibromyalgia. She is member of the German guideline group on fibromyalgia. She received travel grants, research support and speaker honoraria from Genzyme (2014, 2015, 2016). She received a travel grant from Shire (2014, 2015). She received speaker honoraria from Baxalta (2014, 2015).

TP none known; TP is a specialist pain physician and manages patients with fibromyalgia.

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 on fibromyalgia and a member of the steering committee of the European League Against Rheumatism (EULAR) update recommendations on the management of fibromyalgia. He received speaking fees for one educational lecture each from MSD Sharpe & Dohme (2014) and Grünenthal (2015) on pain management.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Rut und Klaus-Bahlsen-Stiftung, Germany.

P Klose was supported by the Rut und Klaus-Bahlsen-Stiftung

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the eligibility criteria for types of studies from two weeks duration to four weeks. Trials should have at least 10 participants per treatment arm and this has been added to [Types of studies](#).

We added blinding of participants and personnel/treatment providers (systematic performance bias), selective outcome reporting (reporting bias) and group similarity at baseline (selection bias) to the 'Risk of bias' assessment.

We switched the analysis method for dichotomous outcomes from risk ratio to risk difference. We set the threshold for a clinically relevant benefit or harm to a NNTB and NNTH of less than 10 ([Moore 2008](#)).

We added 'in adults' to the title, for consistency with other PaPaS reviews on fibromyalgia in adults.

NOTES

A new search within two years is not likely to identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Amitriptyline [therapeutic use]; Analgesics, Non-Narcotic [therapeutic use]; Antipsychotic Agents [*therapeutic use]; Fibromyalgia [*drug therapy]; Quetiapine Fumarate [*therapeutic use]; Randomized Controlled Trials as Topic; Sleep Wake Disorders [drug therapy]

MeSH check words

Adult; Humans