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Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia (Review)

Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W

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[Intervention Review]

Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia

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ABSTRACT

Background

Fibromyalgia is a clinically defined chronic condition of unknown etiology characterized by chronic widespread pain that often co-exists with sleep disturbances, cognitive dysfunction and fatigue. People with fibromyalgia often report high disability levels and poor quality of life. Drug therapy, for example, with serotonin and noradrenaline reuptake inhibitors (SNRIs), focuses on reducing key symptoms and improving quality of life. This review updates and extends the 2013 version of this systematic review.

Objectives

To assess the efficacy, tolerability and safety of serotonin and noradrenaline reuptake inhibitors (SNRIs) compared with placebo or other active drug(s) in the treatment of fibromyalgia in adults.

Search methods

For this update we searched CENTRAL, MEDLINE, Embase, the US National Institutes of Health and the World Health Organization (WHO) International Clinical Trials Registry Platform for published and ongoing trials and examined the reference lists of reviewed articles, to 8 August 2017.

Selection criteria

We selected randomized, controlled trials of any formulation of SNRIs against placebo or any other active treatment of fibromyalgia in adults.

Data collection and analysis

Three review authors independently extracted data, examined study quality, and assessed risk of bias. For efficacy, we calculated the number needed to treat for an additional beneficial outcome (NNTB) for pain relief of 50% or greater and of 30% or greater, patient's global impression to be much or very much improved, dropout rates due to lack of efficacy, and the standardized mean differences (SMD) for fatigue, sleep problems, health-related quality of life, mean pain intensity, depression, anxiety, disability, sexual function, cognitive disturbances and tenderness. For tolerability we calculated number needed to treat for an additional harmful outcome (NNTH) for withdrawals due to adverse events and for nausea, insomnia and somnolence as specific adverse events. For safety we calculated NNTH for serious adverse events. We undertook meta-analysis using a random-effects model. We assessed the evidence using GRADE and created a 'Summary of findings' table.

Main results

We added eight new studies with 1979 participants for a total of 18 included studies with 7903 participants. Seven studies investigated duloxetine and nine studies investigated milnacipran against placebo. One study compared desvenlafaxine with placebo and pregabalin. One study compared duloxetine with L-carnitine. The majority of studies were at unclear or high risk of bias in three to five domains.

The quality of evidence of all comparisons of desvenlafaxine, duloxetine and milnacipran versus placebo in studies with a parallel design was low due to concerns about publication bias and indirectness, and very low for serious adverse events due to concerns about publication bias, imprecision and indirectness. The quality of evidence of all comparisons of duloxetine and desvenlafaxine with other active drugs was very low due to concerns about publication bias, imprecision and indirectness.

Duloxetine and milnacipran had no clinically relevant benefit over placebo for pain relief of 50% or greater: 1274 of 4104 (31%) on duloxetine and milnacipran reported pain relief of 50% or greater compared to 591 of 2814 (21%) participants on placebo (risk difference (RD) 0.09, 95% confidence interval (CI) 0.07 to 0.11; NNTB 11, 95% CI 9 to 14). Duloxetine and milnacipran had a clinically relevant benefit over placebo in patient's global impression to be much or very much improved: 888 of 1710 (52%) on duloxetine and milnacipran (RD 0.19, 95% CI 0.12 to 0.26; NNTB 5, 95% CI 4 to 8) reported to be much or very much improved compared to 354 of 1208 (29%) of participants on placebo. Duloxetine and milnacipran had a clinically relevant benefit compared to placebo for pain relief of 30% or greater. RD was 0.10; 95% CI 0.08 to 0.12; NNTB 10, 95% CI 8 to 12. Duloxetine and milnacipran had no clinically relevant benefit for fatigue (SMD -0.13, 95% CI -0.18 to -0.08; NNTB 18, 95% CI 12 to 29), compared to placebo. There were no differences between either duloxetine or milnacipran and placebo in reducing sleep problems (SMD -0.07; 95 % CI -0.15 to 0.01). Duloxetine and milnacipran had no clinically relevant benefit compared to placebo in improving health-related quality of life (SMD -0.20, 95% CI -0.25 to -0.15; NNTB 11, 95% CI 8 to 14).

There were 794 of 4166 (19%) participants on SNRIs who dropped out due to adverse events compared to 292 of 2863 (10%) of participants on placebo (RD 0.07, 95% CI 0.04 to 0.10; NNTH 14, 95% CI 10 to 25). There was no difference in serious adverse events between either duloxetine, milnacipran or desvenlafaxine and placebo (RD -0.00, 95% CI -0.01 to 0.00).

There was no difference between desvenlafaxine and placebo in efficacy, tolerability and safety in one small trial.

There was no difference between duloxetine and desvenlafaxine in efficacy, tolerability and safety in two trials with active comparators (L-carnitine, pregabalin).

Authors' conclusions

The update did not change the major findings of the previous review. Based on low- to very low-quality evidence, the SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in the frequency of pain relief of 50% or greater, but for patient's global impression to be much or very much improved and in the frequency of pain relief of 30% or greater there was a clinically relevant benefit. The SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in improving health-related quality of life and in reducing fatigue. Duloxetine and milnacipran did not significantly differ from placebo in reducing sleep problems. The dropout rates due to adverse events were higher for duloxetine and milnacipran than for placebo. On average, the potential benefits of duloxetine and milnacipran in fibromyalgia were outweighed by their potential harms. However, a minority of people with fibromyalgia might experience substantial symptom relief without clinically relevant adverse events with duloxetine or milnacipran.

We did not find placebo-controlled studies with other SNRIs than desvenlafaxine, duloxetine and milnacipran.

PLAIN LANGUAGE SUMMARY

Serotonin and noradrenaline reuptake inhibitors for fibromyalgia

Bottom line

Duloxetine and milnacipran may reduce pain in people with fibromyalgia. However, some of these people may also experience side effects, such as nausea (feeling sick) and drowsiness. A minority of people with fibromyalgia experience symptom relief without side effects from duloxetine and milnacipran.

Background

People with fibromyalgia often have chronic (longer than three months) widespread pain, as well as problems with sleep, thinking and exhaustion. They often report poor health-related quality of life. There is no cure for fibromyalgia at present, so the treatments aim to relieve the symptoms and to improve health-related quality of life.

Serotonin and noradrenaline are chemicals which are produced by the human body, involved in the regulation of pain, sleep and mood. Low concentrations of serotonin have been reported in people with fibromyalgia. Serotonin and noradrenaline reuptake inhibitors (SNRIs) are a class of antidepressants that increase the concentration of serotonin and noradrenaline in the brain.

Study characteristics

In August 2017, we updated our searches for clinical trials in which SNRIs were used to treat symptoms of fibromyalgia in adults. We found eight new studies since the previous version of the review. In total, we found 18 studies with 7903 participants. The studies were four to 27 weeks long and compared the SNRIs desvenlafaxine, duloxetine and milnacipran against a fake medication (placebo). We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results.

Key results and quality of the evidence

Duloxetine and milnacipran were better than placebo in reducing pain by 50% or more and in improving global well-being (low-quality evidence). Duloxetine and milnacipran were better than placebo in improving health-related quality of life and in reducing fatigue (low-quality evidence). Duloxetine and milnacipran were not better than placebo in reducing sleep problems (low-quality evidence). More people dropped out of the trial due to side effects with duloxetine and milnacipran than with placebo (low-quality evidence). More people reported nausea and drowsiness with duloxetine and milnacipran than with placebo (low-quality evidence). Duloxetine, milnacipran and placebo did not differ in the frequency of serious side effects experienced (very low-quality evidence).

Summary of findings 1. Serotonin noradrenaline reuptake inhibitors compared with placebo for fibromyalgia - studies with parallel design

Serotonin noradrenaline reuptake inhibitors compared with placebo for fibromyalgia - studies with parallel design

Patient or population: people with fibromyalgia

Settings: study centers in North, Central and South America, Asia and Europe

Intervention: serotonin noradrenaline reuptake inhibitors (duloxetine, milnacipran)

Comparison: placebo

Outcomes	Probable outcome with intervention (95% CI)	Probable outcome with placebo	Relative effect SMD or risk difference (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Self-reported pain relief of 50% or greater	**309 per 1000 (282 to 344)**	**210 per 1000**	RD 0.09 (0.07 to 0.11)	6918 (15 studies)	⊕⊕⊖⊖ **low** [1,2]	NNTB 11 (95% CI 9 to 14)
Patient Global Impression to be much or very much improved (PGIC)	**519 per 1000 (459 to 573)**	**293 per 1000**	RD 0.19 (0.12 to 0.26)	2918 (6 studies)	⊕⊕⊖⊖ **low** [1,2]	NNTB 5 (95% CI 4 to 8)
Self-reported fatigue (20-100 scale) Higher scores indicate higher fatigue problem levels	Mean fatigue score was 2.6 points lower (1.0 to 5.0 points lower) based on a 20-100 scale	Baseline mean score 69.4 (SD 12.3)[3]	SMD -0.13 (-0.18 to -0.08)	6168 (12 studies)	⊕⊕⊖⊖ **low** [1,2]	NNTB 18 (95% CI 12 to 29)
Self-reported sleep problems (0-100 scale) Higher scores indicate higher sleep problem levels	Mean sleep problems score was 1.2 points lower (0.2 higher to 5.5 points lower) based on a 0-100 scale	Baseline mean score 68.0 (23.8)[4]	SMD -0.07 (-0.15 to 0.01)	4547 (8 studies)	⊕⊕⊖⊖ **low** [1,2]	NNTB not calculated due to lack of statistically significant difference
Self-reported health-related quality of life (0-100 scale) Higher scores indicate higher burden of disease (lower quality of life)	Mean health-related quality of life problems score was 3.9 points lower (2.3 to 5.3 points lower) based on a 0-100 scale	Baseline mean score 57.9 (SD 14.1)[5]	SMD -0.20 (-0.25 to -0.15)	6861 (14 studies)	⊕⊕⊖⊖ **low** [1,2]	NNTB 11 (95% CI 8 to 14)

Tolerability (withdrawal due to adverse events)	**191 per 1000 (172 to 210)**	**102 per 1000**	RD 0.07 (0.04 to 0.10)	7029 (15 studies)	⊕⊕⊖⊖ **low** [1,2]	NNTH 14 (95% CI 10 to 25)
Safety (serious adverse events)	**18 per 1000 (16 to 20)**	**21 per 1000**	RD -0.00 (-0.01 to 0.00)	6732 (13 studies)	⊕⊖⊖⊖ **Very low** [1,2,6]	NNTH not calculated due to lack of statistically significant difference

*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 **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **FIQ**: Fibromyalgia Impact Questionnaire; **MFI**: Multidimensional Fatigue Inventory; **MOS-Sleep problem index**: Medical Outcome Study - sleep problem index; **NNTB**: number needed to treat for an additional beneficial outcome; **NNTH**: number needed to treat for an additional harm; **NRS**: numerical rating scale; **RD**: risk difference; **SMD**: standardized mean difference; **VAS**: visual analog scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded once: indirectness: participants with major medical diseases and mental disorders except major depression excluded in > 50% of studies
[2]Downgraded once: publication bias
[3] Clauw 2008: N = 401 participants; MFI NRS 20-100 scale
[4] Mease 2009b: N = 223 participants; MOS Sleep problem index NRS 0-100 scale
[5] Arnold 2010b; N = 509 participants; FIQ VAS 0-80 scale
[6]Downgraded once: imprecision due to low event rate

BACKGROUND

Description of the condition

Fibromyalgia is defined by the American College of Rheumatology (ACR) 1990 classification criteria as widespread pain lasting 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 2013a). People with moderate and severe forms of fibromyalgia often report high disability levels and poor quality of life along with extensive use of medical care (Häuser 2015a; Häuser 2017). Fibromyalgia symptoms can be assessed by patient self-report using 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 2011a). For a clinical diagnosis, the ACR 1990 classification criteria (Wolfe 1990), the ACR 2010 preliminary diagnostic criteria (Wolfe 2010) and the 2016 criteria (Wolfe 2016) 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). For epidemiology studies, the modified ACR 2010 preliminary diagnostic criteria (survey criteria) can be used (Wolfe 2011a).

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 people with fibromyalgia that may be of pathophysiological importance (Üceyler 2017 a). In psychiatry and psychosomatic medicine, fibromyalgia symptoms are categorized as a functional somatic syndrome, a bodily distress syndrome, a physical symptom disorder, or a somatoform disorder (Häuser 2009; Häuser 2014).

Fibromyalgia is a heterogeneous condition. The definite etiology (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 (Üceyler 2017 a)). Inflammatory rheumatoid arthritis (Wolfe 2011a), depression (Chang 2015), genetics (Arnold 2013; Lee 2012), obesity combined with physical inactivity (Mork 2010), physical and sexual abuse in childhood (Häuser 2010a), sleep problems (Mork 2012), and smoking (Choi 2010) predict future development of fibromyalgia. 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; Üceyler 2017 a). Depression and post-traumatic stress disorder worsen fibromyalgia symptoms (Häuser 2013 a; 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 (so-called central sensitization), 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 nerve fibre pathology (Üceyler 2017 a). 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 its 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%. It is more common in women, with a female to male ratio of 3:1 (4.2%:1.4%) (Queiroz 2013). Estimates of prevalence in specific populations vary greatly, but have been reported as being as high as 9% in female textile workers in Turkey and 10% in metalworkers in Brazil (Queiroz 2013).The change in diagnostic criteria does not appear to have significantly affected estimates of prevalence (Wolfe 2013a).

Since specific treatment aimed at altering the pathogenesis is not possible, drug therapy that focuses on symptom reduction is ubiquitously employed.

Description of the intervention

Serotonin and noradrenaline (norepinephrine) reuptake inhibitors (SNRIs) act on noradrenergic and serotonergic neurons in the nervous system. Serotonin and noradrenaline are implicated in the mediation of endogenous pain inhibitory mechanisms.

How the intervention might work

Dysfunction of serotonin and noradrenaline transmission, which mediates endogenous analgesic mechanisms via the descending inhibitory pain pathways in the central nervous system, may play a key role in the pathophysiology of fibromyalgia. Researchers found that levels of metabolites of biogenic amines key to descending inhibition were lower than normal in at least three fibromyalgia body fluid compartments (Legangneux 2001; Russell 1992). Imbalance or deficiency in serotonin and noradrenaline is also associated with other key symptoms of fibromyalgia such as fatigue and cognitive deficits (Bradley 2009). Treatment with SNRI increases transmission of these neurotransmitters and may improve disease states associated with serotonin and noradrenaline deficiencies such as pain, fatigue and cognitive deficits.

Why it is important to do this review

There is a transatlantic difference in the approval of SNRIs as a treatment for fibromyalgia by drug agencies (Briley 2010). The SNRIs duloxetine and milnacipran have been approved by the US Food and Drug Administration (FDA), but not by the European Medical Agencies (EMA), for the management of fibromyalgia. The FDA stated that the sponsors of the two drugs had provided adequate evidence of their benefits and harms to support their indication for the management of fibromyalgia (Department of health & Human Services 2008; Department of health & Human Services 2009). The EMA, however, denied clinically relevant effects for both drugs, on the basis of a lack of robust evidence of efficacy, and because the adverse effects profile was considered to outweigh the benefits (EMA 2008; EMA 2010). We conducted a systematic review on SNRIs in fibromyalgia which included randomized controlled trials that had not been evaluated by the FDA and EMA in 2013 (Häuser 2013 b). Meanwhile, new randomized controlled trials with duloxetine (Leombruni 2015; Murakami 2015), and milnacipran (Bateman 2013; Matthey 2013; Staud 2015), were published that had not been evaluated by the FDA and EMA and by

the previous version of this review (Häuser 2013 b). With new data available, and in the light of the divergent appraisals of duloxetine and milnacipran by the FDA and EMA, we saw the need to evaluate the efficacy and safety of SNRIs according to recently established methodological standards of pain medicine (Moore 2010a), in order to assist people with fibromyalgia and doctors in shared decision making on pharmacological treatment options.

OBJECTIVES

To assess the efficacy, tolerability and safety of serotonin and noradrenaline reuptake inhibitors (SNRIs) compared with placebo or other active drug(s) in the treatment of fibromyalgia in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they were double blind, randomized and controlled trials (RCTs) following four weeks of treatment (titration and maintenance) or longer. We included studies with a parallel, cross-over and enriched enrolment randomized withdrawal (EERW) design. We included studies with a cross-over design where (a) separate data from the two periods were reported, or (b) data were presented that excluded a statistically significant carry-over effect, or (c) statistical adjustments were carried out in case of a significant carry-over effect. Trials had to have at least 20 participants per treatment arm and had to report at least one of the outcomes of efficacy as defined below and of tolerability and safety as defined below. 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-randomized, without control groups, studies of experimental pain, case reports, and clinical observations.

Types of participants

Adults (over 18 years) having a clinical diagnosis of fibromyalgia by any published, recognized and standardized criteria (Smythe 1981; Wolfe 1990; Wolfe 2010; Wolfe 2011b, Yunus 1981; Yunus 1982; Yunus 1984).

Types of interventions

We included trials comparing SNRIs with placebo or another active drug with proven efficacy to reduce fibromyalgia symptoms.

We allowed co-interventions, such as physical therapy or other drugs different from those being assessed in the trial.

We considered the following SNRIs in this review: desvenlafaxine, duloxetine, milnacipran, venlafaxine

Types of outcome measures

We followed some suggestions of the OMERACT Fibromyalgia Working Group (Mease 2009a), the Initiative of Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin 2009), and of best practice in the reporting of systematic reviews in chronic pain (Moore 2010a; Moore 2010b), for selecting outcome measures.

Primary outcomes

- Self-reported pain relief of 50% or greater. Number of participants who reported a pain relief of 50% or greater in parallel and cross-over design studies. For EERW design, loss of therapeutic response of self-reported pain relief was defined as less than 30% reduction in visual analog scale (VAS) pain from pre-drug exposure or worsening of fibromyalgia requiring alternative treatment.
- Patient perceived global improvement (Patient Global Impression of Change (PGIC), or Clinical Global Impression (CGI) of severity): number of participants who reported to be much or very much improved for parallel and cross-over design studies; number of participants who reported a loss of therapeutic response to be much or very much improved in studies with EERW design.
- Tolerability (withdrawals due to adverse events)
- Safety (serious adverse events)

Secondary outcomes

- Self-reported fatigue. We used the following preference: validated combined scale (e.g. Multidimensional Fatigue Inventory (MFI), Fatigue Severity Scale (FSS), Multidimensional Assessment of Fatigue (MAF) or other validated scales) over single item scales (e.g. Fibromyalgia Impact Questionnaire (FIQ) fatigue VAS, or other single item scales). We selected reduction of self-reported fatigue as the outcome for studies with a parallel and cross-over design, and loss of therapeutic response of self-reported fatigue in studies with an EERW design.
- Self-reported sleep problems. We used the following preference: validated combined scale (e.g. Medical Outcomes Study (MOS) sleep scale, or other validated scales), over single item assessment (e.g. FIQ sleep VAS, or other single item scales). We selected reduction of self-reported sleep problems as the outcome for studies with a parallel and cross-over design, and loss of therapeutic response of self-reported sleep problems in studies with an EERW design.
- Self-reported health-related quality of life (HRQoL) measured by the total score of the Fibromyalgia Impact Questionnaire (FIQ). We selected improvement of self-reported HRQoL as the outcome for studies with a parallel and cross-over design, and loss of therapeutic response of self-reported HRQoL in studies with an EERW design.
- Self-reported pain relief of 30% or greater. There was no comparable outcome in studies with an EERW design.
- Self-reported mean pain intensity. We used the following preferences: (a) we preferred electronic diaries over paper; (b) 24-hour recall pain, weekly recall pain with visual analog scale (VAS); (c) paper VAS, paper numeric 11-point ordinal scale (Numeric Rating Scale NRS), combined pain measures, pain drawings. We selected reduction of self-reported mean pain intensity as the outcome for studies with a parallel and cross-over design. There was no comparable outcome in studies with an EERW design.
- Self-reported depression. We used the following preference: validated combined scale (Beck Depression Inventory (BDI), or other validated scales), over single-item assessment (e.g. FIQ subscale for depression, or other single item scales). We selected reduction of self-reported depression as the outcome for studies with a parallel and cross-over design, and loss of therapeutic

response of self-reported depression in studies with an EERW design.

- Self-reported anxiety. We used the following preference: validated combined scale (Beck Anxiety Inventory (BAI), State Trait Anxiety Inventory (STAI), or other validated scales), over single item scale (FIQ anxiety VAS, or other single item scales). We selected reduction of self-reported anxiety as the outcome for studies with a parallel and cross-over design and loss of therapeutic response of self-reported anxiety in studies with an EERW design.
- Self-reported disability (impairment of physical function). We used the following preference: validated combined scale (Brief Pain Inventory (BPI) interference from pain, Short-Form Health Survey (SF-36) physical summary score, or other validated scales), over single item scale (FIQ physical impairment VAS, or other single item scales). We selected reduction of self-reported disability as an outcome for studies with a parallel and cross-over design, and loss of therapeutic response of self-reported disability in studies with an EERW design.
- Self-reported sexual function. We used the following preference: validated combined scale (Arizona Sexual Experience Scale, or other validated scale), over single item scale. We selected reduction of self-reported sexual problems as the outcome for studies with a parallel and cross-over design, and loss of therapeutic response of self-reported sexual problems in studies with an EERW design.
- Self-reported cognitive disturbances: validated combined scale (Multiple Ability Self-report Questionnaire (MASQ), or any other validated scale), over single item scale. We selected reduction of self-reported cognitive disturbances as the outcome for studies with a parallel and cross-over design, and loss of therapeutic response of self-reported cognitive disturbances in studies with an EERW design.
- Tenderness: measurement of tender point pain threshold
- Number of participants dropping out due to lack of efficacy
- Specific adverse events frequently associated with the use of SNRIs (nausea, somnolence, insomnia)

Search methods for identification of studies

Electronic searches

We ran three searches for the update, with the first in November 2015, the second in August 2016 and the third in August 2017. For this update we searched:

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 7) in the Cochrane Library;
- MEDLINE accessed through PubMed (Sept 2012 to August 2017);
- Embase accessed through SCOPUS (Sept 2012 to August 2017).

See Appendix 1 for details of all search strategies used. There were no language or date restrictions.

Searching other resources

We also searched the websites of the US National Institute of Health (www.clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) to August 2017 for ongoing trials. We searched bibliographies from reviewed articles and we retrieved relevant articles. Our search included all languages. We contacted content experts for unpublished and further possible studies.

Data collection and analysis

Selection of studies

Two review authors (WH, BW) independently scrutinized all the titles and abstracts revealed by the searches and determined which fulfilled the selection criteria. A third review author (NÜ) verified that the selection had been properly realized.

Data extraction and management

Three review authors (NÜ, PW, WH) extracted data independently onto a specially designed data extraction form. We would have resolved any disagreements by discussion with the third review author (BW), but this was not necessary. One author (WH) entered data into Review Manager 5 (RevMan 5) (RevMan 2014) and two authors (NÜ,PW) checked them. We resolved discrepancies by discussion.

Assessment of risk of bias in included studies

Two review authors (NÜ,WH) independently assessed the risk of bias of each included trial. We resolved disagreements by consensus and, if needed, referral to a third review author (BW).

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 (any truly random process, for example random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (for example, odd or even date of birth; hospital or clinic record number).
- **Allocation concealment** (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (for example, telephone or central randomization; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated).
- **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 assessors were blinded to the intervention or exposure status of participants; unclear risk of bias (study states that it was blinded but does not provide

an adequate description of how it was achieved); high risk: outcome assessors knew the intervention or exposure status of participants.

- **Incomplete outcome data** (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (fewer than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' (LOCF) analysis); or high risk of bias (used 'completer' analysis).
- **Reporting bias due to selective outcome reporting** (reporting bias). We checked if an a priori study protocol was available and if all outcomes of the study protocol were reported in the publications of the study. 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 include 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 high risk of bias if groups are not similar at baseline for demographic factors, value of main outcome measure(s) and important prognostic factor.
- **Size of study** (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm).

We defined studies with no to two unclear or high risks of bias to be high-quality studies, with three to five unclear or high risks of bias to be moderate-quality studies and with six to eight unclear or high risks of bias to be low-quality studies (Häuser 2015b).

Measures of treatment effect

Our effect measures of choice were risk differences (RD) for dichotomous data and standardized mean difference (SMD) for continuous data (using the inverse variance method). We used a random-effects model because we assumed that clinical heterogeneity would be present. We expressed uncertainty using 95% confidence intervals (CIs).

We calculated number needed to treat for an additional beneficial outcome (NNTB) as the reciprocal of the absolute risk reduction (ARR). For unwanted effects, the NNTB becomes the number needed to treat for an additional harmful outcome (NNTH) and is calculated in the same manner. For drop outs due to lack of efficacy, NNTp becomes the number of participants needed to prevent an additional unwanted outcome and is calculated in the same manner. For dichotomous data we calculated risk differences (RDs). The threshold for 'clinically relevant benefit' or 'clinically relevant harm' was set for categorical variables by an absolute risk reduction or increase of 10% or greater, corresponding to a NNTB or NNTH of 10 or less (Moore 2008).

We used Cohen's categories to evaluate the magnitude of the effect size, calculated by SMD, with values for Hedges' g as follows: 0.2 to 0.5 equating to a small effect size, 0.5 to 0.8 equating to a medium effect size, and more than 0.8 equating to a large effect size (Cohen 1988). We considered values of g less than 0.2 to equate to a 'not substantial' effect size (Häuser 2015b). The threshold 'clinically relevant benefit' was set for continuous variables by an effect size more than 0.2 (Fayers 2014).

We calculated the NNTBs for continuous variables (fatigue, sleep problems, HRQoL) using the Wells calculator software available at the Cochrane Musculoskeletal Group editorial office, which estimates, from the SMDs, the proportion of participants who will benefit from treatment if there was a statistically significant (P value ≤ 0.05) difference between SNRIs and control group (Norman 2001). We used a minimally important difference (MID) of 0.5 for calculation.

We calculated measures of treatment effect if at least two studies with at least 200 participants were available.

Unit of analysis issues

In trials comparing multiple SNRI-dosage arms with one placebo group, for continuous outcomes we adjusted the number of participants in the placebo group according to the number of participants in the different SNRI-dosage arms. For dichotomous variables we pooled the different SNRI dosage arms and compared the pooled results with the placebo arm.

Dealing with missing data

We used intention-to-treat (ITT) analysis data. The ITT population consisted of participants who were randomized, took the assigned study medication, and provided at least one post-baseline assessment. Wherever possible, we assigned zero improvement to missing participants. However, most studies in chronic pain report results, including responder results, using last observation carried forward. This has been questioned as being potentially biased, as withdrawal is an important outcome that makes last observation carried forward unreliable. Last observation carried forward can lead to overestimation of efficacy, particularly in situations where adverse event withdrawal rates differ between active and control groups. At this time it is unclear what strategy can actually be used to deal with missing data inside studies (Moore 2012). We examined and reported imputation strategies clearly.

Where means or SDs were missing, we attempted to obtain these data through contacting trial authors for the first version, but not for the update of the review. 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 rates of pain relief of 30% and 50% or greater 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 used the I^2 statistic for heterogeneity (Higgins 2003). I^2 statistic values less than 25% indicate low heterogeneity; values of 25% to 50% indicate moderate heterogeneity, and values of 50% or over indicate substantial heterogeneity (Deeks 2011).

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 undertook each meta-analysis using a random-effects model in RevMan 5 (RevMan 2014).

Quality of evidence

Two review authors (NÜ, WH) independently rated the quality of the outcomes. We used the GRADE system to rank the quality of the evidence using the GRADEprofiler Guideline Development Tool software (GRADEpro GDT), and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

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

- High: randomized trials; or double-upgraded observational studies
- Moderate: downgraded randomized trials; or upgraded observational studies
- Low: double-downgraded randomized trials; or observational studies
- Very low: triple-downgraded randomized trials; or downgraded observational studies; or case series/case reports

Factors that may decrease the quality level of a body of evidence are as follows.

- limitations in the design and implementation of available studies suggesting high likelihood of bias. We assumed that there were limitations in study design if more than 50% of participants were from low-quality studies, as defined by the 'Risk of bias' tool;
- indirectness of evidence (indirect population, intervention, control, outcomes). 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 participants with clinically relevant somatic disease (e.g. inflammatory rheumatic diseases) and/or depressive and anxiety disorders in the included studies resulted in 50% or more of the total participant collective of the systematic review coming from studies in which participants with clinically relevant somatic disease (e.g. inflammatory rheumatic diseases) and/or depressive and anxiety disorders had been excluded;
- unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
- imprecision of results (wide confidence intervals);
- high probability of publication bias. We assumed a publication bias if all studies were initiated and funded by the manufacturer of the drug.

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

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

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

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

'Summary of findings' table

We included a 'Summary of findings' table to present the main findings in a transparent and simple tabular format. In particular, we included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes.

We included the following outcomes in the 'Summary of findings' table.

- Self-reported pain relief 50% or greater
- Patient global impression to be much or very much improved
- Self-reported fatigue
- Self-reported sleep problems
- Self-reported health-related quality of life
- Withdrawal rates due to adverse events (tolerability)
- Serious adverse events (safety)

Subgroup analysis and investigation of heterogeneity

We performed a subgroup analysis of duloxetine, and milnacipran studies to test for potential differences in benefits and harms of these two drugs. We performed a subgroup analysis of studies with and without European participants to test for potential transatlantic differences between the efficacy and adverse events of SNRIs. A more detailed analysis of European versus non-European participants was not possible because the studies with mixed continent samples did not report how many participants were recruited from each continent. We decided to restrict the comparisons on pain relief of 50% or greater and dropout due to adverse events in order not to inflate the number of comparisons. To test the hypotheses of a subgroup effect, we used a test of interaction with a predetermined, two-tailed α value of 0.05 for subgroup analysis of studies with and without European participants (Altman 2003). We did not conduct the intended subgroup analyses with gender and pain because individual participant data were not available.

Sensitivity analysis

We planned to conduct sensitivity analyses (different statistical models applied, diagnostic criteria used in the trial, presence/absence of any mental or psychiatric disorder, and presence/absence of any concomitant systemic disease).

RESULTS

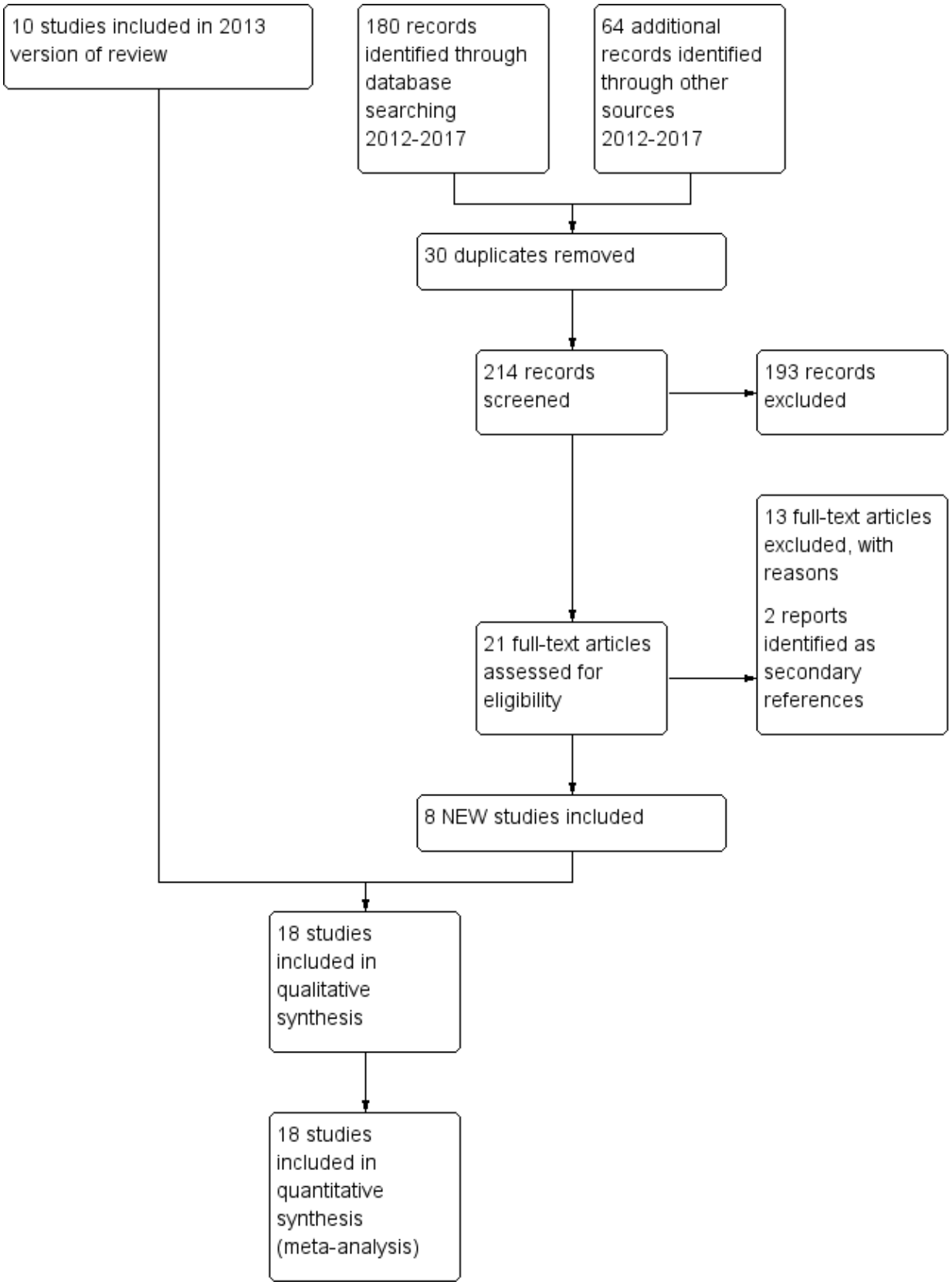
Description of studies

Results of the search

In the previous review, one excluded study (Gendreau 2005) was incorrectly categorized, and should have been a secondary reference to Vitton 2004. The total number of studies excluded in the 2013 review was nine. The total number of included studies in the 2013 review was 10 (11 reports).

The updated searches (last performed 8 August 2017) produced 214 records after duplicates were removed. We excluded 22 studies in total: we excluded nine in the 2013 review (Branco 2011; Chappell 2009b; Dwight 1998; Goldenberg 2010; Hsiao 2007; Mease 2010; Saxe 2012; Sayar 2003; NCT00369343) (total corrected in this review), and 13 additional studies for the update (Ahmed 2016; Ang 2013; Natelson 2015; NCT00725101; NCT00793520; NCT01108731; NCT01173055; NCT01234675; NCT01294059; NCT01331109; NCT01621191; Trugman 2014; Ziljstra 2002). One study with desvenlafaxine excluded in the 2013 review, available in clinicaltrials.gov and which did not report data suited for meta-analysis (NCT00369343), was published in a peer-reviewed journal in 2017. The published data were again not suited for meta-analysis (Allen 2017, secondary reference to (NCT00369343). One study with venlafaxine which was not found in the search for the 2013 review (Ziljstra 2002), was published in a peer-reviewed journal in 2015 (vanDerWeide 2015, secondary reference to Ziljstra 2002).The published data of both reports were not suited for meta-analysis. See the Characteristics of excluded studies table for further details about reasons for exclusion and Figure 1 for the study flow diagram.

Figure 1. Study flow diagram



Mohs 2012 is a secondary reference for Arnold 2010a, which was an included study in the 2013 review; Mease 2014 is a secondary reference for Clauw 2013, an included study added at this update.

We included eight new studies (nine reports) (Arnold 2012a; Bateman 2013; Clauw 2013; Leombruni 2015; Matthey 2013; Murakami 2015; NCT00697787; Staud 2015).

In sum, we included 18 studies in the qualitative and quantitative analysis. See the Characteristics of included studies table for a full description of the studies.

Included studies

We included eight studies with duloxetine (Arnold 2004; Arnold 2005; Arnold 2010a; Arnold 2012a; Chappell 2009a; Leombruni 2015; Murakami 2015; Russell 2008), nine studies with milnacipran (Arnold 2010b; Bateman 2013; Branco 2010; Clauw 2008; Clauw 2013; Matthey 2013; Staud 2015; Mease 2009b; Vitton 2004) and one study with desvenlafaxine (NCT00697787) in the analysis of placebo controlled trials. The eight studies with duloxetine included 11 study arms with different dosages of duloxetine. The studies with milnacipran contained 11 study arms with different dosages of milnacipran. Two studies were entered in the analysis of active drug controlled trials (Leombruni 2015; NCT00697787), one with duloxetine (Leombruni 2015) and one with desvenlafaxine (NCT00697787). One of these studies had three study arms (desvenlafaxine fixed dosage, pregabalin fixed dosage, placebo) (NCT00697787). The studies included a total of 7903 participants.

Study characteristics

All studies were conducted in multiple research centers except three single-center studies (Leombruni 2015; Matthey 2013; Staud 2015). Eight studies were conducted in the USA (Arnold 2004; Arnold 2005; Clauw 2008; Mease 2009b; Clauw 2013; NCT00697787; Staud 2015, Vitton 2004), two studies each in the USA and Puerto Rico (Arnold 2010a; Russell 2008) and in more than one continent (Arnold 2012a; Bateman 2013), one study each in the USA and Western Europe (Chappell 2009a), in the USA and Canada (Arnold 2010b) and in Japan (Murakami 2015), and three studies in Europe (Branco 2010; Leombruni 2015; Matthey 2013). All studies had a parallel design except one with an EERW design (Clauw 2013). Study duration ranged between 6 and 12 weeks in 11 studies (short-term studies) (Arnold 2004; Arnold 2005; Arnold 2010a; Arnold 2012a; Bateman 2013; Clauw 2013; Leombruni 2015; Matthey 2013; NCT00697787; Staud 2015; Vitton 2004) and between 13 and 26 weeks in four studies (medium-term studies) (Arnold 2010b; Branco 2010; Clauw 2008; Russell 2008). Two studies had a long-term duration (> 26 weeks) with 27 weeks each (Chappell 2009a; Mease 2009b). Two studies were started after 2010 (Leombruni 2015; Murakami 2015), the remaining studies were conducted between 2002 and 2010.

All studies were funded by the manufacturer of the respective drug except one study that did not report details of funding (Leombruni 2015). There was no investigator-initiated study or public funding. All authors but five (Arnold 2005; Arnold 2010a; Arnold 2010b; Leombruni 2015; NCT00697787) declared potential conflicts of interest. Two authors (Matthey 2013; Staud 2015) stated that they had no potential financial conflict of interest. The remaining authors who declared conflicts of interest, reported to have received payments by the sponsor of the study for consultancies and/or owned stocks or were employees of the sponsor of the study.

Participant characteristics

All studies included participants over 18 years old. Diagnosis of fibromyalgia was established by all studies by the ACR 1990 classification criteria (Wolfe 1990). All studies required a pain score of more than 3 for inclusion except for Chappell 2009a; NCT00697787; Staud 2015 and Vitton 2004, which did not require a minimum pain score for inclusion. Mease 2009b required a pain score of more than 4 for inclusion. Bateman 2013 required that participants reported no adequate reduction of fibromyalgia symptoms by previous treatment with duloxetine 60 mg a day. All studies excluded participants with somatic diseases, including inflammatory rheumatic diseases. All duloxetine studies included participants with mental disorders, except for major depression (all studies) and general anxiety disorder (all but one study Arnold 2010a). All milnacipran studies excluded participants with severe mental disorders including major depression except Vitton 2004. Middle-aged, white women prevailed in all studies: the median of the mean age was 49 years (range 47 to 55 years). The median of the percentage of women was 95% (range 82% to 100%). The median of the percentage of white people was 91% (range 0% to 97%). Three studies conducted in Europe (Branco 2010; Leombruni 2015; Matthey 2013) and two studies conducted in USA (NCT00697787; Staud 2015) did not report the ethnicity of the participants. The percentage of participants with major depressive disorder in the duloxetine studies ranged from 4% to 41%. A total of 4230 (mean 235; SD 55; minimum 23, maximum 795) participants were included in the active drug groups and 2997 (mean 167; SD 36; minimum 21, maximum 509) in the comparison groups.

Interventions

Duloxetine dosage was fixed, with 30 mg a day in Arnold 2012a and Russell 2008, 60 mg a day in Arnold 2005; Murakami 2015 and Russell 2008, and 120 mg a day in Arnold 2004; Arnold 2005 and Russell 2008. Duloxetine dosage was flexible with 30 mg or 60 mg a day in Leombruni 2015 and 60 mg or 120 mg a day in Arnold 2010a and Chappell 2009a. Milnacipran dosage was fixed, with 100 mg a day in Bateman 2013; Branco 2010; Clauw 2008; Mease 2009b and Staud 2015, and with 200 mg a day in Clauw 2008; Matthey 2013; Mease 2009b and Vitton 2004, and flexible (100 mg or 200 mg a day) in Arnold 2010b and Clauw 2013. In addition, one study compared duloxetine 60 mg a day, fixed, with L-carnitine 300 mg a day (Leombruni 2015), and one study compared desvenlafaxine 200 mg a day, fixed, with pregabalin 450 mg a day, fixed (NCT00697787). The other studies had a single SNRI arm. The rescue medication in duloxetine trials was acetaminophen (paracetamol) up to 2 g a day and aspirin up to 325 mg a day, and in milnacipran trials was hydrocodone up to 60 mg a day. The desvenlafaxine study did not report on rescue medication (NCT00697787).

Primary outcomes

Self-reported pain relief of 50% or greater

All studies used different measures for pain. We selected the predefined primary outcome variables of the studies for analysis. The duloxetine studies (Arnold 2004; Arnold 2005; Arnold 2010a; Arnold 2012a; Chappell 2009a; Murakami 2015; Russell 2008) assessed pain using the Brief Pain Inventory (BPI) 24 average pain score except Leombruni 2015, which used a VAS 0-10. The

milnacipran trials used the patient electronic diary 24-hour recall pain score (Arnold 2010b; Bateman 2013; Branco 2010; Clauw 2008; Clauw 2013; Matthey 2013; Staud 2015; Mease 2009b; Vitton 2004) and the desvenlafaxine study used pain score numeric rating scale (NRS) from 0 (no pain) to 10 (worst pain imaginable) (NRS 0-10) across the last 24 hours and seven days (NCT00697787).

Patient global impression much or very much improved

Patient global impression of change was assessed by all studies except three studies (NCT00697787; Staud 2015; Vitton 2004). However, five studies reported only average scores, which could not be used for the predefined analysis (Arnold 2012a; Branco 2010; Leombruni 2015; Matthey 2013; Murakami 2015). The desvenlafaxine study did not assess this outcome (NCT00697787).

Tolerability (withdrawals due to adverse events)

All studies reported the number of participants dropping out due to adverse events.

Safety (serious adverse events)

Four studies reported no details at all of the assessment (Bateman 2013; Leombruni 2015; NCT00697787; Staud 2015). The remaining studies used physical examination, electrocardiograms, and laboratory analysis for the assessment of adverse events. Four studies did not report details about how they had assessed subjective adverse symptoms (Arnold 2004; Arnold 2005; Arnold 2010a; Arnold 2010b). Three studies reported the recording of spontaneously-reported adverse events (Chappell 2009a; Russell 2008; Vitton 2004), another two studies reported spontaneously-reported and investigator-observed adverse events (Clauw 2008; Mease 2009b), and one study reported both spontaneously-reported and investigator-observed (use of non-leading questions) adverse events (Branco 2010). Two studies used the Columbia Suicide Severity Scale to assess suicidality (Arnold 2012a; Murakami 2015).

Secondary outcomes

Self-reported fatigue

Fatigue was assessed either by the single item of the FIQ (Arnold 2004; Arnold 2005; Arnold 2012a; Bateman 2013; Murakami 2015; Vitton 2004), or by a VAS 0-10 (Staud 2015) or by the Multidimensional Fatigue Inventory (MFI) (Arnold 2010a, Arnold 2010b; Branco 2010; Chappell 2009a; Clauw 2008; Clauw 2013; Matthey 2013; Mease 2009b). One study assessed fatigue by a visual analog scale (VAS) from 0 to 100 (Staud 2015). Two studies did not report the outcome (Bateman 2013; Leombruni 2015). One study did not assess this outcome (NCT00697787.

Self-reported sleep problems

The duloxetine studies, Arnold 2004; Arnold 2005; Arnold 2010a; Chappell 2009a; Murakami 2015 and Russell 2008 assessed sleep disturbances using the BPI sleep interference scale. However, three studies did not report the sleep outcomes (Arnold 2004; Arnold 2010a; Chappell 2009a). The duloxetine studies of Arnold 2012a and Leombruni 2015 did not assess sleep problems

Sleep was assessed by the Medical Outcomes Study (MOS) in four milnacipran studies (Branco 2010; Clauw 2008;Matthey 2013; Mease 2009b). The Vitton 2004 study used the Jenkins Sleep Scale. One milnacipran study did not report on the assessment of sleep outcomes (Arnold 2010b). The remaining milnacipran studies did not assess sleep problems (Arnold 2012a; Bateman 2013; Clauw 2013; Staud 2015).

The study with desvenlafaxine did not assess this outcome (NCT00697787).

Self-reported health-related quality of life

Two studies did not assess health-related quality of life (NCT00697787; Staud 2015). The remaining studies except Arnold 2010a used the FIQ-total score of which one study used the revised FIQ (Clauw 2013). Arnold 2010a used the Short Form Health Survey SF-36. One study did not report the FIQ total score (Leombruni 2015).

Self-reported pain relief of 30% or greater

All studies used different measures for pain. We selected the predefined primary outcome variables of the studies for analysis. The duloxetine studies (Arnold 2004; Arnold 2005; Arnold 2010a; Arnold 2012a; Chappell 2009a; Murakami 2015; Russell 2008) assessed pain using the Brief Pain Inventory (BPI) 24 average pain score except Leombruni 2015, which used a VAS 0 to 10 scale. The milnacipran trials assessed pain using the patient electronic diary 24-hour recall pain score (Arnold 2010b; Bateman 2013; Branco 2010; Clauw 2008; Clauw 2013; Matthey 2013; Staud 2015; Mease 2009b; Vitton 2004). The desvenlafaxine study used a pain score numeric rating scale (NRS) from 0 (no pain) to 10 (worst pain imaginable) (NRS 0-10) across the last 24 hours and seven days (NCT00697787).

Self-reported mean pain intensity

All studies used different measures for pain. We selected the predefined primary outcome variables of the studies for analysis. The duloxetine studies (Arnold 2004; Arnold 2005; Arnold 2010a; Arnold 2012a; Chappell 2009a; Murakami 2015; Russell 2008) assessed pain using the Brief Pain Inventory (BPI) 24 average pain score except Leombruni 2015, which used a VAS 0 to 10 scale. The milnacipran trials assessed pain using the patient electronic diary 24-hour recall pain score (Arnold 2010b; Bateman 2013; Branco 2010; Clauw 2008; Clauw 2013; Matthey 2013; Staud 2015; Mease 2009b; Vitton 2004). The desvenlafaxine study used a pain score numeric rating scale (NRS) from 0 (no pain) to 10 (worst pain imaginable) (NRS 0-10) across the last 24 hours and seven days (NCT00697787).

Self-reported depression

Arnold 2005 used the Hamilton Depression Rating Scale (HDRS), Leombruni 2015 the Hospital and Anxiety Depression Subscale Depression, Clauw 2013 and Vitton 2004 used the FIQ single item depression scale and Staud 2015 a VAS 0 to 100 scale. The remaining studies used the Beck Depression Inventory (BDI). The desvenlafaxine study did not assess this outcome (NCT00697787).

Self-reported anxiety

Four studies used the Beck Anxiety Inventory (BAI) to assess anxiety (Arnold 2004; Arnold 2010a; Arnold 2010b; Arnold 2012a), two studies used the Stait-Trait Anxiety Inventory (STAI) (Branco 2010; Matthey 2013), three studies used the FIQ single item scale (Clauw 2013; Murakami 2015; Vitton 2004), and Staud 2015 used a VAS 0 to 100. The remaining studies, including the desvenlafaxine study (NCT00697787), did not assess this outcome.

Self-reported disability

We used the BPI average interference scale as a measure of disability in six studies with duloxetine (Arnold 2004; Arnold 2005; Arnold 2010a; Arnold 2010b; Arnold 2012a; Branco 2010; Chappell 2009a; Russell 2008). The remaining seven studies used three different measures for disability/physical function, namely subscale data of: Multidimensional Health Assessment Questionnaire (MDHAQ) (Clauw 2008), the Short Form Health Survey physical component summary score (Clauw 2013; Leombruni 2015; Murakami 2015; Mease 2009b); and the FIQ single item subscale Bateman 2013; Vitton 2004). One study did not report the FIQ single item subscale score (Matthey 2013). Two studies did not assess this outcome (NCT00697787; Staud 2015).

Self-reported sexual function

Only three studies reported on the assessment of sexual function by the Arizona Sexual Experience Scale. However, one study did not report the data (Clauw 2008), and the other did not report the SDs (Mease 2009b). Only one study reported outcomes suitable for meta-analysis (Bateman 2013).

Self-reported cognitive disturbances

Three duloxetine studies assessed cognitive disturbances ('fibro fog') using the mental fatigue subscale of the MFI (Arnold 2010a; Chappell 2009a; Russell 2008), five milnacipran studies, using the Multiple Ability Self-report Questionnaire (MASQ) (Arnold 2010b; Bateman 2013; Branco 2010; Clauw 2008; Mease 2009b).

Tender point pain threshold

Only four duloxetine studies measured tender point pain threshold (Arnold 2004; Arnold 2005; Chappell 2009a; Russell 2008).

Dropout due to lack of efficacy

All the included studies reported this outcome except Clauw 2013 and Staud 2015.

Specific adverse events

Nausea

All the included studies reported this adverse event except Arnold 2004; Leombruni 2015; Matthey 2013; Staud 2015; and Vitton 2004.

Somnolence

All the duloxetine studies except Arnold 2004 reported this adverse event, as well as the desvenlafaxine study (NCT00697787). None of the studies with milnacipran reported on this outcome.

Insomnia

All the included studies reported this adverse event except Arnold 2004; Clauw 2013; Leombruni 2015; Murakami 2015; Matthey 2013; Staud 2015; and Vitton 2004.

Excluded studies

We excluded 22 studies in total. Five studies had fewer than 20 participants per treatment arm (Ahmed 2016; Natelson 2015; NCT00793520; NCT01108731; NCT01234675); 11 studies had no control group (Branco 2011; Chappell 2009b; Dwight 1998;Goldenberg 2010; Hsiao 2007; Mease 2010; NCT00725101; NCT01294059; NCT01331109; NCT01621191; Sayar 2003); two studies did not include outcomes of efficacy, which were preconditions to be included into our review (NCT01173055; Trugman 2014); one study combined milnacipran with education or psychological therapies (Ang 2013); one study duration was shorter than four weeks (Saxe 2012); one study was only published as an abstract (Ziljstra 2002); and for one study the study results were incompletely reported and not suited for quantitative analysis (NCT00369343).

Studies awaiting classification

We found one study with duloxetine 60 mg a day whose results were not reported (NCT01268631). The recruitment status of another study was unknown (NCT01268631).

Risk of bias in included studies

In general, the risks of bias of included studies differed between the studies (see Figure 2 and Figure 3 for 'Risk of bias' summary and graph). Detailed information regarding 'Risk of bias' assessments of every study are given in the Characteristics of included studies table. Seven studies met the predefined criteria of high quality for methodology (Arnold 2010a; Arnold 2010b; Branco 2010; Clauw 2008; Mease 2009b; Murakami 2015; Vitton 2004), seven studies of moderate quality for methodology (Arnold 2004; Arnold 2005; Arnold 2012a; Chappell 2009a; Matthey 2013; Russell 2008; Staud 2015) and four studies of low quality for methodology (Bateman 2013; Clauw 2013; Leombruni 2015; NCT00697787). The assessment is based on the reports in the publications. We did not request missing details of methods in the update of the review as we did in the first review because we did not get responses to some of our requests in the first version of the review.

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

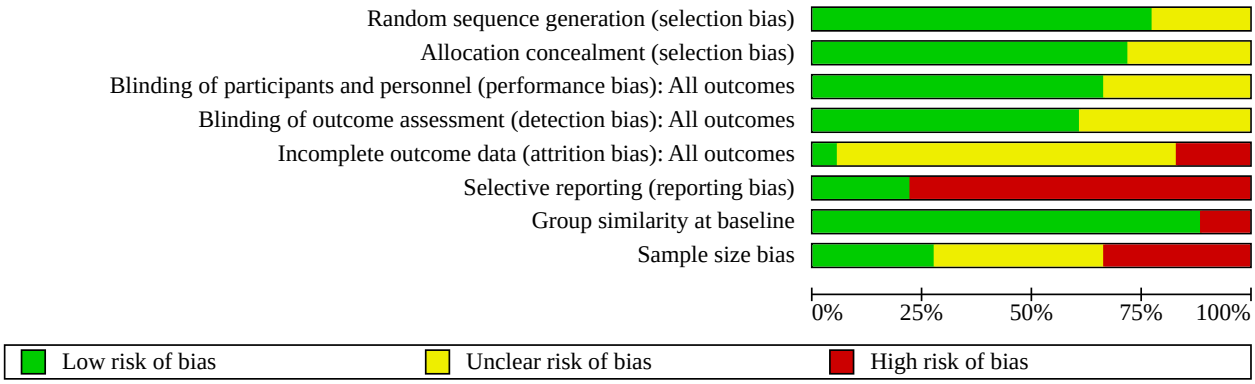
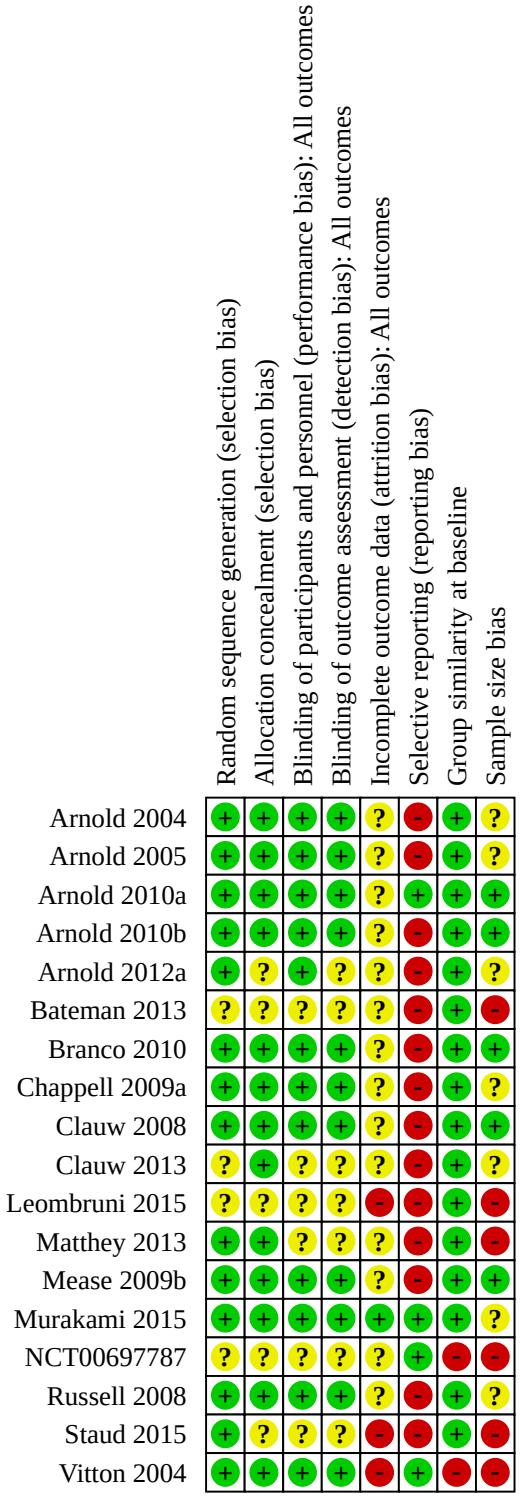


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Random sequence generation was adequately described and therefore all studies were at low risk of bias except Bateman 2013; Clauw 2013; Leombruni 2015; NCT00697787, Staud 2015 which did not adequately describe it (unclear risk of bias).

Allocation concealment was adequately described and therefore all studies were at low risk of bias except Arnold 2012a; Bateman 2013; Leombruni 2015 and NCT00697787, which did not adequately describe it (unclear risk of bias).

Blinding

Blinding of participants and personnel was adequately described in all studies except Bateman 2013; Clauw 2013; Leombruni 2015; Matthey 2013; NCT00697787 and Staud 2015, which did not adequately describe it (unclear risk of bias).

Blinding (detection bias)

Blinding of outcome assessors was adequately described in all studies except Arnold 2012a; Bateman 2013; Clauw 2013; Leombruni 2015; Matthey 2013; NCT00697787 and Staud 2015, which did not adequately describe it (unclear risk of bias).

Incomplete outcome data

Most outcomes of the study of Vitton 2004 were based on analysis of observed cases that were provided on request (high risk of bias). Leombruni 2015 and Staud 2015 also performed completer analysis (high risk of bias). Only Murakami 2015 provided analysis by the baseline observation carried forward method. The remaining studies imputed missing data by baseline or last observation carried forward and therefore we judged them to be at unclear risk of bias.

Selective reporting

Only Arnold 2010a; Murakami 2015; NCT00697787 and Vitton 2004 reported or provided on request all data of interest for this review if outlined in the protocol, and we judged them to be at low risk of bias. We judged the remaining studies to be at high risk of bias.

Other potential sources of bias

Group similarity at baseline

No significant differences in demographic and clinical variables between the study groups (low risk of bias) could be detected in the studies included except in NCT00697787 and Vitton 2004 (high risk of bias).

Sample size bias

The sample size was of a low risk of bias only in Arnold 2010a; Arnold 2010b; Branco 2010; Clauw 2008 and Mease 2009b. Six studies had a high risk of bias (Bateman 2013; Leombruni 2015; Matthey 2013; NCT00697787; Staud 2015; Vitton 2004) and seven studies an unclear risk of bias (Arnold 2004; Arnold 2005; Arnold 2012a; Chappell 2009a; Clauw 2013; Murakami 2015; Russell 2008).

Effects of interventions

See: **Summary of findings 1** Serotonin noradrenaline reuptake inhibitors compared with placebo for fibromyalgia - studies with parallel design

All SNRIs (desvenlafaxine, duloxetine, milnacipran) versus placebo, studies with parallel and cross-over design

Primary outcomes

Self-reported pain relief of 50% or greater

We entered 15 studies with 6918 participants into an analysis of the RD of participant-reported pain relief of 50% or greater. For this outcome, 1274 of 4104 (31.0%) participants with duloxetine and milnacipran and 591 out of 2814 (21.0%) participants in the placebo group reported pain relief of 50% or greater. The RD was 0.09 (95% CI 0.07 to 0.11) (see Analysis 1.1). NNTB was 11 (95% CI 9 to 14) (P value < 0.0001). According to the predefined categories there was no clinically meaningful benefit with duloxetine and milnacipran. The quality of evidence was low, downgraded due to indirectness and publication bias (see Summary of findings 1).

Patient global impression to be much or very much improved

We entered six studies with 2918 participants into an analysis of patient global impression much or very much improved. There were 888 participants out of 1710 (51.9%) with duloxetine and milnacipran and 354 of 1208 (29.3%) participants in the placebo group reported to be much or very much improved. The RD was 0.19 (95% CI 0.12 to 0.26) (see Analysis 1.2). NNTB was 5 (95% CI 4 to 8) (P value < 0.0001). According to the predefined categories there was a clinically meaningful benefit with duloxetine and milnacipran. The quality of evidence was low, downgraded due to indirectness and publication bias.

Tolerability (withdrawals due to adverse events)

We entered 15 studies, with 7029 participants, into an analysis of withdrawals due to adverse events. Out of 4166 participants with desvenlafaxine, duloxetine and milnacipran, 794 (19.1%) dropped out due to adverse events and 292 participants out of 2863 (10.2%) dropped out in the placebo group. The RD was 0.07 (95% CI 0.04 to 0.10). The NNTH with desvenlafaxine, duloxetine and milnacipran was 14 (95% CI 10 to 25) (P value < 0.0001) (see Analysis 1.3). According to the predefined categories there was no clinically meaningful harm with desvenlafaxine, duloxetine and milnacipran. The quality of evidence was low, downgraded due to indirectness and publication bias.

Safety (serious adverse events)

We entered 13 studies, with 6732 participants, into an analysis of serious adverse events. In 73 out of 4022 (1.8%) participants with desvenlafaxine, duloxetine and milnacipran and in 58 out of 2710 (2.1%) in the placebo group an adverse event was noted. The RD was -0.00 (95% CI -0.01 to 0.00) (P value 0.90) (Analysis 1.4). The quality of evidence was very low, downgraded due to indirectness, imprecision and publication bias.

Secondary outcomes

Self-reported fatigue

We entered 12 studies with 6168 participants into an analysis of the effects of desvenlafaxine, duloxetine and milnacipran on fatigue reduction. The SMD was -0.13 (95% CI -0.18 to -0.08) (P value < 0.001). Based on Cohen's categories, the effect on fatigue of SNRIs versus placebo was not substantial (Analysis 1.5). The quality of evidence was low, downgraded due to indirectness and publication bias.

Self-reported sleep problems

We entered eight studies, with 4547 participants, into an analysis of the effects of duloxetine and milnacipran on reduction of sleep disturbances. The overall effect on sleep disturbances was not significant (P value = 0.11) (see Analysis 1.6). The quality of evidence was low, downgraded due to indirectness and publication bias.

Self-reported health-related quality of life

We entered 14 studies, with 6861 participants, into an analysis of the effects of duloxetine and milnacipran on health-related quality of life. SMD was -0.20 (95% CI -0.25 to -0.15) (P value < 0.0001). Based on Cohen's categories the effect on disease-related quality of life of SNRIs versus placebo was not substantial (Analysis 1.7). The quality of evidence was low, downgraded due to indirectness and publication bias.

Self-reported pain relief of 30% or greater

We entered 15 studies, with 6924 participants, into an analysis of the RD of participant-reported pain relief of 30% or greater. There were 1653 out of 4105 participants (40.3%) with duloxetine and milnacipran and 888 out of 2819 (31.5%) participants in the placebo group who reported pain relief of 30% and more. The RD was 0.10 (95% CI 0.08 to 0.12). NNTB was 10 (95% CI 8 to 12) (P value < 0.0001) (Analysis 1.8). According to the predefined categories there was a clinically meaningful benefit with duloxetine and milnacipran. The quality of evidence was low, downgraded due to indirectness and publication bias.

Self-reported pain intensity

We entered 16 studies, with 7014 participants, into an analysis of the effects of desvenlafaxine, duloxetine and milnacipran on pain intensity reduction.The SMD was -0.22 (95% CI -0.27 to -0.17) (P value < 0.0001). According to Cohen's categories the effect on pain of desvenlafaxine, duloxetine and milnacipran compared to placebo was small (Analysis 1.9). According to the predefined categories there was a clinically meaningful benefit with duloxetine and milnacipran. The quality of evidence was low, downgraded due to indirectness and publication bias.

Self-reported depression

We entered 14 studies, with 6478 participants into an analysis of the effects of duloxetine and milnacipran on depression reduction. One study reported only the outcomes of one of three dosage groups (Russell 2008). SMD was -0.16 (95% CI -0.21 to -0.11) (P value < 0.0001) (Analysis 1.10). Based on Cohen's categories, the effect on depression of duloxetine and milnacipran versus placebo was not substantial. The quality of evidence was low, downgraded due to indirectness and publication bias.

Self-reported anxiety

We entered 9 studies, with 3533 participants, into an analysis of the effects of duloxetine and milnacipranon anxiety reduction. The overall effect on anxiety was not significant (P value = 0.21) (Analysis 1.11). The quality of evidence was low, downgraded due to indirectness and publication bias.

Self-reported disability

We entered 13 studies, with 6789 participants into an analysis of the effects of duloxetine and milnacipran on disability reduction. SMD was -0.21 (95% CI -0.26 to -0.16) (P value < 0.0001). Based on Cohen's categories the effect on disability of duloxetine and milnacipran versus placebo was small (Analysis 1.12). According to the predefined categories there was a clinically meaningful benefit with duloxetine and milnacipran. The quality of evidence was low, downgraded due to indirectness and publication bias.

Self-reported sexual function

One study with 100 participants assessed the effects of milnacipran on sexual function. There was no difference between milnacipran and placebo on sexual function (P value = 0.59). The quality of evidence was very low, downgraded due to indirectness, imprecision and publication bias.

Self-reported cognitive disturbances

We entered eight studies, with 5444 participants, into an analysis of the effects of duloxetine and milnacipran on cognitive disturbances. The overall effect on 'fibro fog' was significant (P value < 0.0001). SMD was -0.16 (95% CI -0.21 to -0.10). Based on Cohen's categories, the effect on cognitive disturbances of duloxetine and milnacipran versus placebo was not substantial (Analysis 1.13). The quality of evidence was low, downgraded due to indirectness and publication bias.

Tenderness

We entered five studies, with 1444 participants, which performed tender point pain threshold measurement. Duloxetine and milnacipran were superior to placebo in raising the tender point pain threshold (P value = 0.0007), suggesting less tenderness. SMD was -0.21 (95% CI -0.33 to -0.09). Based on Cohen's categories the effect on tenderness of duloxetine and milnacipran versus placebo was small (Analysis 1.14). According to the predefined categories there was a clinically meaningful benefit with duloxetine and milnacipran. The quality of evidence was low, downgraded due to indirectness and publication bias.

Dropout due to lack of efficacy

We entered 14 studies, with 6924 participants into an analysis of withdrawals due to lack of efficacy. Out of 4082 participants with desvenlafaxine, duloxetine and milnacipran, 264 (6.5%) dropped out due to lack of efficacy and 258 out of 2842 (9.1%) dropped out in the placebo group. The RD was -0.03 (95% CI -0.04 to -0.02). The number of participants needed to prevent an additional unwanted outcome (NNTp) with desvenlafaxine, duloxetine and milnaciprans was 33 (95% CI 25 to 50) (P value < 0.0001) (see Analysis 1.15). According to the predefined categories there was no clinically meaningful benefit by desvenlafaxine, duloxetine and milnacipran. The quality of evidence was low, downgraded due to indirectness and publication bias.

Specific adverse events

Nausea

We entered 12 studies, with 6606 participants, into an analysis of nausea as an adverse event. Out of 3918 participants with desvenlafaxine, duloxetine and milnacipran, 1253 (32.0 %) reported nausea and 382 out of 2688 participants reported nausea (14.2%) in the placebo group. The RD was 0.16 (95% CI 0.14 to 0.19). The NNTH with desvenlafaxine, duloxetine and milnacipran was 6 (95% CI 5 to 7) (P value < 0.0001) (see Analysis 1.16). According to the predefined categories there was a clinically meaningful harm with desvenlafaxine, duloxetine and milnacipran. The quality of

evidence was low, downgraded due to indirectness and publication bias.

Somnolence

We entered seven studies, with 2514 participants, into an analysis of somnolence as an adverse event. Out of 1426 participants with duloxetine and milnacipran, 155 (10.9%) reported somnolence and 51 participants out of 1088 (4.7%) reported somnolence in the placebo group. The RD was 0.05 (95% CI 0.02 to 0.08). The NNTH with SNRIs was 20 (95% CI 12 to 50) (P value = 0.0004) (see Analysis 1.17). According to the predefined categories there was no clinically meaningful harm with duloxetine and milnacipran. The quality of evidence was low, downgraded due to indirectness and publication bias.

Insomnia

We entered nine studies, with 5387 participants, into an analysis of insomnia as an adverse event. Out of 3119 participants with desvenlafaxine, duloxetine and milnacipran, 298 (9.6 %) reported insomnia and 132 participants out of 2268 (5.8%) reported insomnia in the placebo group. The RD was 0.03 (95% CI 0.01 to 0.04) (P value < 0.0001). The NNTH with desvenlafaxine, duloxetine and milnacipran was 33 (95% CI 25 to 100) (see Analysis 1.18). According to the predefined categories there was no clinically meaningful harm with desvenlafaxine, duloxetine and milnacipran. The quality of evidence was low, downgraded due to indirectness and publication bias.

All SNRIs versus placebo, studies with enriched enrolment randomized withdrawal design

We downgraded the quality of evidence by one level each to very low because of limitations of study design, indirectness and imprecision for all outcomes. We present a qualitative analysis of the data because there was only one study with 151 participants examining milnacipran available (Clauw 2013).

Primary outcomes

Loss of therapeutic response for self-reported pain relief

There were 35 of 100 (35%) participants in the milnacipran group and 32 of 51 (62.7%) participants in the placebo group who reported a loss of therapeutic response (P value 0.0008).

Loss of therapeutic response for patient's global impression to be much or very much improved

There were 22 of 100 participants (22%) in the milnacipran and 25 of 51 (49.0%) participants in the placebo group reported to be much or very much worse (P value 0.0009).

Tolerability (withdrawals due to adverse events)

Two of 100 (2%) participants in the milnacipran and 0 of 51 (0%) participants in the placebo group dropped out due to adverse events (P value 0.33).

Safety (serious adverse events)

One of 100 (1%) participants in the milnacipran and 0 of 51 (0%) participants in the placebo group experienced a serious adverse event (P value 0.58).

Secondary outcomes

Self-reported fatigue: Loss of therapeutic response

There were 36 of 100 participants (36%) in the milnacipran and 20 of 51 participants (39.2%) in the placebo group who reported a loss of therapeutic response of reduction of fatigue (P value 0.70).

Self-reported sleep problems: Loss of therapeutic response

This outcome was not assessed by the study.

Self-reported health-related quality of life: Loss of therapeutic response

This outcome was not reported by the study.

Self-reported depression: Loss of therapeutic response

This outcome was not reported by the study.

Self-reported anxiety: Loss of therapeutic response

This outcome was not reported by the study.

Self-reported disability: Loss of therapeutic response

There were 47 of 100 (47%) participants in the milnacipran and 26 of 51 (51%) participants in the placebo group who reported a loss of therapeutic response of reduction of self-reported disability (P value 0.82).

Self-reported sexual function: Loss of therapeutic response

This outcome was not assessed by the study.

Self-reported cognitive disturbances: Loss of therapeutic response

This outcome was not assessed by the study.

Tenderness: Loss of therapeutic response

This outcome was not assessed by the study.

Dropout due to lack of efficacy

This outcome was not reported sufficiently for meta-analysis.

Specific adverse events

Nausea

Four of 100 (4%) participants with milnacipran and 1 of 50 (2%) participants with placebo reported nausea as an adverse event (P value 0.52).

Somnolence

This outcome was not reported by the study.

Insomnia

This outcome was not reported by the study.

All SNRIs versus other active drugs

We present a qualitative analysis of the data because we analysed only two studies with fewer than 200 participants for this comparison. We downgraded the quality of evidence by one level each because of limitations of study design, indirectness and imprecision to very low for each outcome.

Primary outcomes

Self-reported pain relief of 50% or greater

This outcome was not reported by the studies analysed.

Patient global impression to be much or very much improved

This outcome was not reported by the studies analysed.

Tolerability (withdrawals due to adverse events)

Eight of 28 participants (28.6%) with duloxetine and 0 of 56 (0%) participants with L-carnitine withdrew due to side effects (P value 0.008). None of 42 (0%) participants with desvenlafaxine and six of 43 (14.0%) participants with pregabalin dropped out due to side effects (P value 0.02).

Safety (serious adverse events)

No serious adverse event was reported in the study with duloxetine versus L-carnitine. A serious adverse event was noted in one of the 42 (2.4%) participants with desvenlafaxine and in 1 of 43 (2.3%) participants with pregabalin (P value 0.99).

Secondary outcomes

Self-reported fatigue

This outcome was not reported by the studies analysed.

Self-reported sleep problems

This outcome was not reported by the studies analysed.

Self-reported health-related quality of life

This outcome was not reported by the studies analysed.

Self-reported pain relief of 30% or greater

This outcome was not reported by the studies analysed.

Self-reported pain intensity

There was no statistically significant difference between duloxetine and L-carnitine (P value 0.87).

Self-reported depression

There was no statistically significant difference between duloxetine and L-carnitine (P value 0.33).

Self-reported anxiety

There was no statistically significant difference between duloxetine and L-carnitine (P value 0.76).

Self-reported disability

There was no statistically significant difference between duloxetine and L-carnitine (P value 0.42).

Self-reported sexual function

This outcome was not reported by the studies analysed.

Self-reported cognitive disturbances

This outcome was not reported by the studies analysed.

Tenderness

This outcome was not reported by the studies analysed.

Dropout due to lack of efficacy

Three of 42 (7.1%) participants with desvenlafaxine and none of 43 participants with pregabalin dropped out due to lack of efficacy (P value 0.09). No participant with duloxetine and L-carnitine dropped out due to lack of efficacy.

Specific adverse events

Nausea

Six of 42 (14.3%) participants with desvenlafaxine and three of 43 (7.0%) participants with pregabalin reported nausea as an adverse event (P value 0.15).

Somnolence

Two of 42 (4.8%) participants with desvenlafaxine and six of 43 (13.6%) participants with pregabalin reported somnolence as an adverse event (P value 0.33).

Insomnia

One of 42 (2.4%) participants with desvenlafaxine and none of 43 (0%) participants with pregabalin reported insomnia as an adverse event (P value 0.31).

Heterogeneity

I^2 statistic of all comparisons was less than 25% except for the outcome 'withdrawal due to adverse events' in the comparison SNRIs versus placebo (60%) and the outcome 'withdrawal due to adverse events' in the comparison SNRIs versus other active drugs (95%).

Publication bias

Studies with 1459 participants with a null effect on patient global impression to be much or very much improved would have been required to make the result clinically irrelevant (NNTB of 10 or higher).

Subgroup analysis

Duloxetine and milnacipran

There was no difference between duloxetine and milnacipran in the rates of pain relief of 50% or greater (P value 0.53) (see Analysis 1.1), in the reduction of fatigue (P value 0.73) (see Analysis 1.5) and in improvement of health-related quality of life (P value 0.56) (see Analysis 1.7). Duloxetine was superior to milnacipran in the number of participants who reported to be much or very much improved (P value < 0.0001) (see Analysis 1.2) and in reducing sleep problems (P value 0.0006) (see Analysis 1.6). The dropout rate due to adverse events in milnacipran studies was higher than in duloxetine studies (P value 0.0007) (see Analysis 1.3). There was no difference between duloxetine and milnacipran in the frequency of serious adverse events (P value 0.90) (see Analysis 1.4).

There was no difference between duloxetine and milnacipran in the rates of pain relief of 30% and greater (P value 0.65) (see Analysis 1.8) and dropout rates due to lack of efficacy (P value 0.22) (see Analysis 1.15). There was no difference in reduction of mean pain intensity between duloxetine and milnacipran (P value 0.10) (see Analysis 1.9). Duloxetine was superior to milnacipran in reducing depression (P value 0.007) (see Analysis 1.10), disability (P value 0.01) (see Analysis 1.12) and cognitive disturbances (P value 0.02) (see Analysis 1.13). There was no difference between duloxetine

and milnacipran in reducing anxiety (P value 0.74) (see Analysis 1.11) and tenderness (P value 0.12) (see Analysis 1.14). There was no difference between duloxetine and milnacipran in the frequency of nausea (P value 0.12) (see Analysis 1.16) and insomnia (P value 0.39) (see Analysis 1.18).

Studies with and without European participants

The RD of pain relief of 50% and more and of withdrawals due to adverse events did not differ between studies without European participants than with European participants (see Additional Table 1).

Sensitivity analysis

We did not conduct the intended sensitivity analyses (different statistical models applied, diagnostic criteria used in the trial, according to the presence or absence of any mental or psychiatric disorder, presence or absence of any concomitant systemic disease), because the studies did not differ in these characteristics.

DISCUSSION

Summary of main results

The SNRIs duloxetine and milnacipran did not show a clinically relevant benefit compared to placebo in participant-reported pain relief of 50% or greater. The SNRIs duloxetine and milnacipran showed a clinically relevant benefit compared to placebo in participant-reported pain relief of 30% or greater and in increased patient-perceived global improvement. The SNRIs duloxetine and milnacipran had a clinically relevant benefit compared to placebo in reducing mean pain intensity, disability and tenderness. The effect of duloxetine and milnacipran compared to placebo in reducing fatigue, depression, limitations of health-related quality of life and cognitive disturbances was not clinically relevant. There were no differences between duloxetine or milnacipran and placebo in reducing sleep problems and anxiety. The dropout rate due to adverse events with duloxetine or milnacipran did not show a clinically relevant difference to placebo. There were no differences in the frequency of serious adverse events between duloxetine or milnacipran and placebo. Desvenlafaxine was not superior to placebo in mean pain intensity reduction.

Overall completeness and applicability of evidence

We are confident that we did not miss studies of SNRIs duloxetine and milnacipran, because all trials with these drugs had been registered with the application of an approval for fibromyalgia management by regulatory agencies. We cannot rule out the possibility that negative study results with other SNRIs have not been published or have been missed by our search strategy. We identified one study investigating desvenlafaxine that had been terminated prior to completion. The data available did not suggest any therapeutic effect (NCT00369343).

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

- The studies were performed in research centers and not in routine clinical care. It is known that the efficacy of drug therapies is higher in the context of RCTs than in routine clinical care (Routman 2010).
- The substantial placebo and nocebo response rates seen across all of the SNRI trials impede the appraisal of the efficacy and tolerability of SNRIs in fibromyalgia. However, the high degree of placebo and nocebo rates that have been seen with SNRIs have also been observed in all fibromyalgia drug trials (Häuser 2011; Häuser 2012).
- The exclusion criteria were strict. Participants were not allowed to take some defined concomitant medications for their fibromyalgia symptoms. This excluded a large number of participants who were unwilling, or unable, to come off medications, such as other antidepressants and anticonvulsants. For this reason, participant selection in the RCTs was biased towards recruiting participants with less severe symptoms than are seen in the community (Fuller-Thomson 2012). Participants with other medical disorders, such as inflammatory rheumatic diseases, which are frequently associated with fibromyalgia, were also excluded. The study results cannot be applied to people with so-called secondary fibromyalgia (associated with inflammatory rheumatic diseases) (Clauw 1995). All except one of the studies with milnacipran excluded all potential participants with major mental disorders, while the studies with duloxetine excluded all participants with major mental disorders except for those with major depression and general anxiety disorder. The study results cannot be applied to people with fibromyalgia and concomitant psychiatric disease, except for the duloxetine studies that suggest efficacy in fibromyalgia with major depression and general anxiety disorder.
- The majority of the participants were middle-aged women. The authors of the duloxetine studies provided a pooled subgroup analysis that demonstrated the efficacy of duloxetine in male participants (Russell 2008). A similar analysis was not available for milnacipran. Neither of the pharmaceutical companies (Eli-Lilly and Pierre Fabre/Forest Laboratories) presented a subgroup analysis of participants over 65 years of age.
- Only adult participants were included. Whether the study results can be applied to children or adolescents remains to be clarified. One study with milnacipran in adolescents with fibromyalgia was terminated early due to low enrolment (Arnold 2015).
- Even if the review included studies with a duration of therapy of up to 27 weeks, the long-term efficacy and safety of SNRIs in fibromyalgia cannot be assessed by the studies included. Long-term, open-label extension studies with duloxetine and milnacipran demonstrated a sustained symptom relief and tolerability in up to 20% of the participants who were enrolled in the RCT prior to the open-label period (Arnold 2013; Branco 2011; Mease 2010; Mease 2013, Murakami 2017).
- Even if the review included two RCTs that compared SNRIs with other active drugs, the definite importance of SNRIs compared to other drugs and non-pharmacological therapies still needs to be determined. The trial comparing desvenlafaxine with pregabalin was terminated early after Wyeth, the manufacturer of desvenlafaxine, was acquired by Pfizer, the manufacturer of pregabalin. There was no difference between the two drugs in pain reduction (NCT00697787). A network meta-analysis did not find relevant differences between drugs (tricyclic antidepressants, SNRIs, SSRIs and pregabalin) and aerobic exercise and cognitive behavioral therapies in mean pain reduction and total dropout rates (Nüesch 2013).

Quality of the evidence

The quality of evidence ranks from low to very low across the different outcomes. The likelihood that the effect could be substantially different is high or very high. The main limiting factors, which were the reasons for a decrease in quality in all outcomes, were indirectness and publication bias. All of the reviewed studies had been sponsored by pharmaceutical companies. The quality of evidence of this review is based on the data presented in peer reviewed journals and some additional details that were provided on request by the pharmaceutical companies or principal investigators. However, not all data requested were provided. A selective non-reporting of some negative study results on pain, sleep and anxiety, as well as non-reporting of serious adverse events is possible.

Potential biases in the review process

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

We might have overestimated the risk of bias of some studies that were added to this update and that did not report some details of methodology (e.g. randomization and blinding procedures). In contrast to the first version of this review we did not ask the study authors or the sponsors of the studies for the missing details.

Nearly all studies selected statistical methods (last observation carried forward) that bias results towards exaggerating the efficacy of drugs (Moore 2012).

The subgroup comparisons of duloxetine versus milnacipran for the outcomes patient global impression to be much or very much improved and of sleep problems were limited due to the small number of studies presenting results suitable for meta-analysis (patient impression of change) or assessing the outcome (sleep problems).

The influence of allowed co-interventions (e.g. rescue medication) on positive effects and adverse events was unclear because type and dosage of co-interventions were not clearly reported or controlled for.

This systematic review update included 7903 participants. To capture rare and potentially severe adverse events a larger data set would have been necessary. For example, to capture an adverse event with a frequency of 1:100,000, 300,000 patients would need to be observed (Andersohn 2008). Rare complications of SNRIs include suicide (Taylor 2013), severe liver injury (Voican 2014), hypertension (de Toledo 2007) and sexual dysfunction (Higgins 2010).

We were not able to perform individual participant data analyses because these data were not published or provided by the sponsors of the studies. Therefore we could not test if moderate or substantial pain reduction was associated with improvement of fatigue, function, sleep, depression, anxiety, ability to work, and general health status, as has been demonstrated for pregabalin in fibromyalgia (Moore 2010c). The NNTB for substantial pain relief with duloxetine and milnacipran in our analysis was lower than for relief of sleep problems and fatigue. In addition, sleep problems are a common side effect of SNRIs (Rahmadi 2011) and insomnia as an adverse event was more frequently reported by participants with SNRIs than with placebo in this review. Therefore it might be possible that a substantial improvement of fibromyalgia pain by duloxetine and milnacipran is not associated with a substantial improvement in other key symptom domains of fibromyalgia in some people.

Agreements and disagreements with other studies or reviews

We cannot share the conclusion of some reviews that the efficacy of duloxetine and milnacipran in the management of fibromyalgia has been proven (Arnold 2010c; Kyle 2010; Ormseth 2010; Ursini 2010). Neither drug has a benefit on all key symptoms of fibromyalgia. Our results are in line with Cochrane Pain and Palliative and Supportive Care reviews that analyse drugs for fibromyalgia separately. Cording 2015 included six studies with 4238 participants in total in a review of milnacipran in fibromyalgia. The review authors concluded that milnacipran 100 mg or 200 mg per day was effective only for a minority of people in the treatment of pain due to fibromyalgia, providing moderate levels of pain relief (at least 30%) to about 40% of participants, compared with about 30% with placebo. The use of last observation carried forward imputation may overestimate the efficacy of milnacipran. Using stricter criteria for 'responder' and a more conservative method of analysis gave lower response rates (about 26% with milnacipran versus 17% with placebo). Withdrawals for any reason were more common with milnacipran than placebo, and more common with 200 mg (NNTH 9) than 100 mg (NNTH 23), compared with placebo. This was largely driven by adverse event withdrawals, where the NNTH compared with placebo was 14 for 100 mg and 7 for 200 mg (Cording 2015). Lunn and co-authors included six studies involving 2249 participants with fibromyalgia. Duloxetine at 60 mg daily was effective for fibromyalgia over 12 weeks (RR for ≥ 50% reduction in pain 1.57, 95% CI 1.20 to 2.06; NNTB 8, 95% CI 4 to 21) and over 28 weeks (RR 1.58, 95% CI 1.10 to 2.27). Adverse events were common in both treatment and placebo arms but more common in the treatment arm, with a dose-dependent effect. Most adverse events were minor (Lunn 2014). Our results do confirm the conclusions of the aforementioned reviews, that tolerability and safety of both drugs is limited, because a substantial number of participants dropped out of trials due to adverse events. The most frequent adverse events in both drugs were nausea, dry mouth, headache, constipation and hyperhidrosis (increased perspiration) (Cording 2015). The lack of difference in serious adverse events between SNRI and placebo demonstrated that most adverse effects were considered minor.

We cannot share the conclusion of a systematic review that venlafaxine (which is metabolized to desvenlafaxine) is "at least modestly effective in treating fibromyalgia" (VanderWeide 2015). VanderWeide 2015 included one RCT with venlafaxine. There was no difference between venlafaxine and placebo in ITT analysis in pain reduction at the end of treatment (six weeks) (Ziljstra 2002). We found no differences between desvenlafaxine and placebo in pain reduction in one trial (NCT00697787).

The results of our subgroup comparisons of duloxetine and milnacipran are in line with the ones of network meta-analyses that did not find significant differences between the two drugs in pain reduction and tolerability (Lee 2016; Nüesch 2013). However, these network meta-analyses did not test for some other outcomes relevant for people with fibromyalgia. We found that duloxetine was superior to milnacipran in reducing sleep problems,

depression, disability, cognitive disturbances and improving global well-being.

Routine clinical care data call into question the long-term effectiveness or tolerability, or both, of duloxetine and milnacipran in the majority of people with fibromyalgia. A longitudinal study in people with fibromyalgia of the National Data Bank of Rheumatic Diseases found that pain scores were reduced significantly, but not clinically relevantly by 0.17 (95 % CI 0.03 to 0.30) units on an 11-point scale following the start of therapy with duloxetine or milnacipran or pregabalin. There was no significant improvement in fatigue or functional status with these drugs (Wolfe 2013b). In a retrospective analysis using a US claims database to identify adults with a first diagnosis of fibromyalgia between 2009 and 2011, the discontinuation rates were 52% for duloxetine and 72% for milnacipran after 12 months (Liu 2016). The one-year discontinuation rate of SSRI/SNRI antidepressants including duloxetine and milnacipran was 74% in patients of a large Israeli Health Maintenance Organisation (Ben-Ami 2017).

Considering the current differences in regulatory approval regarding the use of duloxetine and milnacipran in fibromyalgia in the USA and Japan versus Europe, it seems relevant to comment on whether our data support either of these positions. There was one European study each with duloxetine (Chappell 2009a) and milnacipran (Branco 2010). According to EMA analysis, duloxetine and milnacipran did not meet the primary endpoint of the study, namely the superiority over placebo in the reduction of mean pain intensity (EMA 2008; EMA 2010). Our analyses demonstrated a superiority of duloxetine and milnacipran respectively in pain relief of 50% or more. It is our view that the trial data show that the benefits of duloxetine and milnacipran (NNTB 11 for an incremental 50% pain reduction) are nearly counterbalanced by the risk of side effects (NNTH 14 for an incremental dropout rate due to adverse events). The data do not provide clear support for either of the regulatory positions over the other. Thus, our review cannot provide support for any of these regulatory positions.

AUTHORS' CONCLUSIONS

Implications for practice

For people with fibromyalgia

Only a minority of people may profit from treatment with the serotonin and noradrenaline reuptake inhibitors (SNRIs) duloxetine and milnacipran in terms of meaningful relief of fibromyalgia symptoms and a good tolerability of the drug. The majority of people will not experience substantial relief of fibromyalgia symptoms or will terminate the treatment because of adverse events, or both. There is no evidence for the efficacy of other SNRIs such as desvenlafaxine and venlafaxine.

For physicians

If duloxetine or milnacipran are being considered for the treatment of fibromyalgia, a frank discussion between the physician and patient about the potential benefits and harms of both drugs is important. The contraindications (concomitant use of monoamine oxidase inhibitors, uncontrolled narrow-angle glaucoma, substantial alcohol use or evidence of chronic liver damage) and warnings (suicidality, hepatotoxicity, serotonin syndrome, abnormal bleeding, discontinuation syndrome, elevated blood pressure, urinary hesitation and retention) are to be discussed (Häuser 2010b). Defining realistic goals of therapy (e.g. pain relief of 30% or more and/or improvement of daily functioning) by people with fibromyalgia and their physicians before starting drug treatment has been recommended (Häuser 2015b).

The recommended dosages are duloxetine 60 mg a day, and milnacipran 100 mg a day. A dose response has not been demonstrated. Higher doses are associated with more adverse events (Cording 2015; Häuser 2010b). Treatment has only been continued in responders, that is to say in people who reached the predefined treatment goals with a reasonable tolerability of duloxetine or milnacipran (Petzke 2017).

A class effect of SNRIs on fibromyalgia symptoms cannot be assumed. One study found no difference between four dosages of desvenlafaxine and placebo in mean pain intensity reduction (NCT00697787). One study found no differences between venlafaxine and placebo in all outcomes of efficacy (Ziljstra 2002).

Treating fibromyalgia with drugs only, such as SNRIs alone, is discouraged since current best practices in fibromyalgia guidelines recommend using the combination of pharmacological therapy with aerobic exercise and psychological therapies (Ablin 2013; MacFarlane 2017; Petzke 2017).This is especially true for symptoms where duloxetine and milnacipran are ineffective, but other therapies are effective, for example, aerobic exercise for fatigue (Häuser 2010c), and cognitive-behavioral therapies for depression (Bernardy 2017).

Since relatively few participants achieve a worthwhile response with SNRIs, 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. One study included in this review demonstrated that some people with fibromyalgia who do not respond to duloxetine might respond to milnacipran (Bateman 2013).

For policy-makers

Since no single treatment is effective in a majority of individuals with fibromyalgia, this relatively small number who benefit may be considered worthwhile, particularly if appropriate switching or stopping rules are in place.

For funders

Treatment with duloxetine and milnacipran for fibromyalgia may be considered worthwhile, particularly if switching and stopping rules are in place in case the predefined treatment goals are not reached or the drugs are not well tolerated, or both. It is important that the treatment is supervised by a physician experienced in the treatment with duloxetine and milnacipran.

Implications for research

General

Analysis of all studies investigating duloxetine and milnacipran in fibromyalgia at the level of individual participant data could provide important information, for example, whether or not a clinically important pain response delivers large functional and quality-of-life benefits. Moreover, a re-analysis of the data using baseline observation carried forward, and responder analysis where discontinuation is classified as non-response, would allow a

determination of the true efficacy of duloxetine and milnacipran in fibromyalgia. All journals should follow the BMJ rule that reports of randomized trials will only be considered for publication if the authors commit to making the relevant anonymous participant-level data available on reasonable request (BMJ).

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

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

There is bias towards studies conducted in USA. To provide generalizability of study results, study populations equally recruited from every continent are necessary.

It is necessary that the details of the assessment of adverse events (spontaneous reports, open questions, symptom questionnaires) are reported by the studies because the type and frequency of adverse events is influenced by the modes of assessment (Häuser 2012). It is mandatory that adverse events should be reported using the International Conference on Harmonization guidelines, and coded within organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) (International Council for Harmonisation 2016). It is desirable that regulatory agencies standardize the assessment strategies of adverse events in RCTs.

It is important to control for potential effects of co-interventions on outcomes.

Measurement (endpoints)

It is important to use responder criteria for a clinically relevant improvement of sleep problems, fatigue, depression and physical function (disability) (Arnold 2012b). Homogeneous outcomes for studies with an EERW design need to be defined.

Comparison between active treatments

It is important not only to compare with placebo but also with drugs with known efficacy, such as amitriptyline or pregabalin. In addition, more studies with defined subgroups (e.g. major depression, no adequate response to a specific drug treatment) are necessary.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Arnold 2004

Study characteristics	
Methods	**Study setting:** multicenter study with 18 outpatient research centers in USA **Study period:** July 2001-March 2002 **Study design:** parallel **Trial duration**: 3-30 days' screening, 1 week single-blind placebo run in, 12 weeks' therapy
Participants	**DLX:** N = 104; 88.5% female; 88.5% white; mean age 49.9 (SD 12.3) years; pain baseline (0-10) 6.1 (SD 1.8); 35.6% current major depression **Placebo:** N = 103; 89.3% female; 85.4% white; mean age 48.3 (SD 11.3) years; pain baseline (0-10) 6.1 (SD 1.7); 40.8% current major depression **Inclusion criteria:** ACR 1990 criteria; score ≥ 4 on the pain intensity item of the FIQ; age ≥ 18 years; with and without MDD **Exclusion criteria:** pain from traumatic injury or structural or regional rheumatic disease; rheumatoid arthritis, inflammatory arthritis, or autoimmune disease; unstable medical or psychiatric illness; current dysthymia, which is more resistant to treatment than major depression, or primary psychiatric disorder other than MDD; substance abuse in the last year; history of psychosis; pregnancy or breast feeding; unacceptable contraception in those of childbearing potential; involvement in disability reviews that might compromise treatment response; use of an investigational drug within 30 days; prior participation in a study of DLX; severe allergic reactions to multiple medications; intolerance to 3 psychoactive drugs or 1 SSRI; and failure to respond to 2 adequate regimens of 2 different classes of antidepressants for depression or FM. Concomitant medication exclusions included use of medications or herbal agents with CNS activity (antidepressants required a 7-day washout prior to visit 2 except for monoamine oxidase inhibitors, which required a 14-day washout, and fluoxetine, which required a 30-day washout); regular use of analgesics with the exception of acetaminophen up to 2 g/d and aspirin up to 325 mg/d; chronic use of sedatives, antiemetics, or antispasmodics; episodic use of anticoagulants; 3 months' stable therapy with antihypertensives, hormones, anti-arrhythmics, antidiarrhoeals, antihistamines, cough/cold preparations (excluding dextromethorphan), or laxatives; and initiation of or change in unconventional or alternative therapies
Interventions	**DLX** 120 mg. Titration from 20 mg/d to 60 mg twice/day during first 2 weeks of the therapy phase, as follows: 20 mg every day for 5 days, 20 mg twice/day for at least 3 days, 40 mg twice/day for at least 2 days, and 60 mg twice a day for the remainder of the study **Placebo** (N = 103) **Rescue and/or allowed medication**: acetaminophen (paracetamol) up to 2 g/d and aspirin up to 325 mg/d
Outcomes	**Pain:** BPI average pain severity (NRS 0-10); pain relief of ≥ 30% and ≥ 50% reported **PGIC much or very much improved:** not reported; average scores of PGIC (1-7) reported **Fatigue:** FIQ single item (VAS 0-10) **Sleep problems:** BPI (NRS 0-10): not reported **HRQoL:** FIQ total score (0-80) **AEs:** physical examination, ECGs, and laboratory analysis. Further details of assessment of AEs not reported. Frequency of nausea, somnolence and insomnia insufficiently reported (not suited for meta-analysis)

Arnold 2004 *(Continued)*

	Depression: BDI -II total score (NRS 0-63) **Anxiety:** BAI total score (NRS 0-63) **Disability:** BPI interference from pain (NRS 0-10) **Cognitive disturbances:** not assessed **Sexual function:** not assessed **Tenderness:** mean tender point threshold (kg/cm^2)
Notes	**Conflicts of interest:** Drs Crofford and Arnold have received consulting fees or honoraria in the last 2 years from Eli Lilly and Company (Dr.Crawford USD 10,000, Dr. Arnold USD 10,000). In addition to the authors employed by Eli Lilly and Company listed above, Dr. Goldstein's wife is employed by Eli Lilly and Company. **Funding:** Eli Lilly

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence using an interactive response system
Allocation concealment (selection bias)	Low risk	Central independent unit (details reported on request)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind (number and appearance of placebo capsules similar, details reported on request)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant-reported outcomes; participants were adequately blinded to intervention. Blinding of outcome assessors of safety adequately described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation using LOCF for efficacy data. ITT analysis
Selective reporting (reporting bias)	High risk	Outcomes: sleep problems, 30% pain reduction and SAEs not reported
Group similarity at baseline	Low risk	No significant group differences in demographic and clinical data at baseline
Sample size bias	Unclear risk	50-199 participants per treatment arm

Arnold 2005

Study characteristics

Methods	**Study setting:** multicenter study with 21 outpatient research centers in USA **Study design**: parallel

Arnold 2005 *(Continued)*

	Study period: November 2002-October 2003 **Duration therapy:** screening duration not reported: 12 weeks' therapy
Participants	**Total sample:** 100% female; 89.5% white; mean age 49.6 (SD 10.9) years; 26% current major depression "No significant differences among treatment groups were observed in any of the patient demographics or clinical characteristics including origin, age, gender, height, weight, primary diagnoses of major depressive disorder, or secondary diagnosis of anxiety" DLX 60 mg/d: N = 118; pain baseline (0-10) 6.4 (SD 1.4) DLX 120 mg/d: N = 116; pain baseline (0-10) 6.4 (SD 1.4) Placebo: N = 120; pain baseline (0-10) 6.5 (SD 1.5) **Inclusion criteria:** ACR 1990 criteria; score ≥ 4 on the pain intensity item of the FIQ; age ≥ 18 years; with and without MDD **Exclusion criteria:** pain from traumatic injury or structural or regional rheumatic disease; rheumatoid arthritis, inflammatory arthritis, or autoimmune disease; unstable medical or psychiatric illness; current primary psychiatric diagnosis other than MDD, a primary anxiety disorder within the past year (specific phobias allowed); substance abuse within the past year; serious suicide risk; pregnancy or breast-feeding; women who, in the opinion of the investigator, were treatment refractory or may have had an involvement in disability reviews that might compromise treatment response; severe allergic reactions to multiple medications; or prior participation in a study of DLX. Concomitant medication exclusions included use of medications or herbal agents with CNS activity; regular use of analgesics with the exception of acetaminophen up to 2 g/d and aspirin for cardiac prophylaxis up to 325 mg/d; chronic use of sedatives, antiemetics, or antispasmodics; and initiation of or change in unconventional or alternative therapies
Interventions	**DLX** 1-week, double-blind, study-drug tapering phase at which time dosage of study drug was reduced to DLX 30 mg/d for DLX 60 mg/d-treated participants and DLX 60 mg/d for DLX120 mg/d-treated participants; forced titration from 60 mg/d to 120 mg/d within 3 days **Placebo** **Rescue and or allowed medication**: acetaminophen up to 2 g/d and aspirin up to 325 mg/d
Outcomes	**Pain:** (BPI average pain severity (NRS 0-10) **PGIC much or very much improved:** not reported; average scores of PGIC (1-7) reported **Fatigue:** FIQ (VAS 0-10): not reported **Sleep problems:** BPI sleep interference (NRS 0-10) **HRQoL:** FIQ total score (0-80) **AEs:** physical examination, ECGs, and laboratory analysis. Details of assessment of AEs not reported. Frequency of nausea and somnolence reported; frequency insomnia not reported **Depression:** HDRS (NRS 0-52) **Anxiety:** FIQ (VAS 0-10): not reported **Disability:** BPI interference from pain (NRS 0-10) **Sexual function:** not assessed **Cognitive disturbances:** not assessed **Tenderness:** mean tender point threshold (kg/cm^2)

Arnold 2005 *(Continued)*

	Dropout due to lack of efficacy: reported
Notes	**Conflicts of interest:** not reported **Funding:** Eli Lilly

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence using an interactive response system (details reported on request)
Allocation concealment (selection bias)	Low risk	Central independent unit (details reported on request)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind (number and appearance of placebo capsules similar, details reported on request)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant-reported outcomes; participants were adequately blinded to intervention. Blinding of outcome assessors of safety adequately described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation using LOCF for efficacy data. ITT analysis
Selective reporting (reporting bias)	High risk	Outcomes of anxiety and fatigue not reported
Group similarity at baseline	Low risk	No significant group differences in demographic and clinical data at baseline
Sample size bias	Unclear risk	50-199 participants per treatment arm

Arnold 2010a

Study characteristics

Methods	**Study setting:** multicenter study with 48 outpatient research centers in USA and Puerto Rico **Study period:** June 2008-July 2009 **Study design:** parallel **Trial duration**: 5-30-day screening phase, the acute phase was 12 weeks' duration, double-blind, and placebo-controlled. After Week 12, participants in the placebo group were transitioned to active treatment and all participants continued for an additional 12 weeks of double-blind treatment. An optional 2-week drug-tapering phase was offered at the end of the 12-week continuation phase or for participants who discontinued early after receiving at least 2 weeks of study medication.
Participants	**DLX**: N = 263; 92.8% women; 77.6% white; mean age 50.7 (SD 11.3); pain baseline (0-10) 6.5 (SD 1.5); 16.7% current major depression; 7.2% current GAD Placebo: N = 267; 93.6% women; 77.2% white; mean age 49.6 (SD 10.8); pain baseline (0-10) 6.5 (SD 1.6); 19.9% current major depression; 9.0% current GAD

Arnold 2010a *(Continued)*

	I**nclusion criteria:** ACR 1990 criteria; score ≥ 4 on the pain intensity item of the FIQ; age ≥ 18 years; with and without MDD/GAD **Exclusion criteria**: current or diagnosed within the past year with any primary psychiatric disorder other than MDD or GAD defined by DSM-IV; clinically judged to be at serious risk of suicide; had any unstable medical illness likely to require intervention or hospitalization; pain symptoms unrelated to FM that could interfere with interpretation of outcome measures; regional pain syndromes; multiple surgeries or failed back syndrome; a confirmed current or previous diagnosis of rheumatoid arthritis, inflammatory arthritis, or other autoimmune disease; severe liver disease; pregnant or breast-feeding; or history of substance abuse within the past year. Participants were also excluded if they had been treated with an adequate trial of DLX and did not respond or could not tolerate DLX; were judged by the opinion of the investigator to be treatment-refractory in FM; or whose treatment response might be compromised by disability compensation issues.
Interventions	**DLX** was initiated at 30 mg and escalated to 60 mg after 1 week. At week 4 and week 8 visits, DLX dose was automatically escalated via IVRS by 30 mg daily for those participants who had < 50% reduction from baseline in their BPI 24-h pain score and the investigator had endorsed a dose increase. If the participant could not tolerate the dose increase, it was reduced to the pre-escalation dose via IVRS **Placebo** **Rescue and/or allowed medication**: acetaminophen up to 2 g/d and aspirin up to 325 mg/d
Outcomes	**Pain**: BPI 24-h average pain severity (NRS 0-10) **PGIC much or very much improved:** not reported; average scores of PGIC (1-7) reported **Fatigue:** MFI general fatigue (NRS 4-20) **Sleep problems:** bothered by sleep difficulties (NRS 0-10): data extracted from figure **HRQoL**: SF-36 physical component summary score (100-0) **AEs:** physical examination, ECGs, and laboratory analysis. Details of assessment of adverse symptoms not reported. Frequency of nausea, dizziness and insomnia reported **Depression:** BDI total score (NRS 0-63) **Anxiety:** BAI total score (NRS 0-63) **Disability:** BPI pain interference pain (NRS 0-10) **Sexual function:** not assessed **Cognitive disturbances:** MFI mental fatigue (NRS 4-20) **Tenderness:** not assessed **Dropout due to lack of efficacy:** reported
Notes	**Conflicts of interest**: not declared **Funding:** the study authors thank the Clinical Operations and Data Management teams of Lilly USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence using an interactive response system
Allocation concealment (selection bias)	Low risk	Central independent unit (details reported on request)

Arnold 2010a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind (number and appearance of placebo capsules similar-details reported on request)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant-reported outcomes; patients were adequately blinded to intervention. Blinding of outcome assessors of safety adequately described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation using LOCF for efficacy data. ITT analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported
Group similarity at baseline	Low risk	No significant group differences in demographic and clinical data at baseline
Sample size bias	Low risk	> 200 participants per treatment arm

Arnold 2010b

Study characteristics	
Methods	**Study setting:** multicenter study with 68 outpatient research centers in USA and Canada **Study period:** April 2006-June 2008 **Study design:** parallel **Trial duration:** screening and washout (1-4 weeks),baseline assessment (2 weeks), randomization/flexible dose escalation (4-6 weeks), stable dose (12 weeks), and randomized discontinuation (2 weeks)
Participants	**MLN:** N = 516; 96.6% female; 91.9% white; mean age 49.1 (SD 10.8) years; pain baseline (0-100) 63.1 (SD 12.5) **Placebo:** N = 509; 93.7% female; 90.0% white; mean age 48.7 (SD 10.6) years; pain baseline (0-10) 64.4 (SD 12.7) I**nclusion criteria:** 1990 ACR criteria, 18-70 years, raw score of ≥ 4 on the FIQ **Exclusion criteria:** previous exposure to MLN; treatment with an investigational drug within 30 days of screening; BDI score > 25 at screening or randomization; current major depressive episode as determined by MINI; significant risk of suicide according to investigator's judgment or results of the MINI or BDI; lifetime history of psychosis, hypomania, or mania; substance abuse; other severe psychiatric illness as determined by investigator judgment; history of behavior that would, in the investigator's judgment, prohibit compliance for the duration of the study; active or pending disability claim, workman's compensation claim, or litigation; pregnancy or breastfeeding; unacceptable contraception; active or unstable medical illness; prostate enlargement or other genitourinary disorder
Interventions	**MLN** flexible up to 100 mg/d (516 participants): MLN 12.5 mg on days 1-3; MLN 25 mg (12.5 mg twice daily) for 4 days; MLN 50 mg (25 mg twice daily) for 7 days; MLN 75 mg (37.5 mg twice daily) for 7 days; and MLN 100 mg (50 mg twice daily) for 7 days. If side effects developed, the dose of MLN could be temporarily reduced. **Placebo**

Arnold 2010b *(Continued)*

	Rescue and allowed medication: tramadol or hydrocodone between randomization and week 4 (end of dose escalation). Permitted analgesic medications were acetaminophen, aspirin, and NSAIDs
Outcomes	**Pain:** PED 24-h recall pain score (VAS 0-100) **PGIC much or very much improved:** reported **Fatigue:** MFI total (NRS 20-100) **Sleep problems:** BPI sleep interference: not reported **HRQoL:** FIQ total score **AEs:** physical examination, ECGs, and laboratory analysis. Details of assessment of adverse symptoms not reported. Frequency of nausea, dizziness and insomnia reported **Depression:** BDI total score (NRS 0-63) **Anxiety:** BAI total score (NRS 0-63) **Disability:** BPI pain interference pain (NRS 0-10) **Sexual function**: not assessed **Cognitive disturbances:** MASQ cognitive function (NRS 38-190) **Tenderness**: not assessed **Dropout due to lack of efficacy:** reported
Notes	**Conflicts of interest**: not declared **Funding:** the study was financially supported by Forest Laboratories, Inc. Forest Laboratories, Inc. and Cypress Bioscience, Inc. were responsible for the design and conduct of the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence using an interactive response system
Allocation concealment (selection bias)	Low risk	Central independent unit
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind (number and appearance of placebo capsules similar, details reported on request)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant-reported outcomes; participants were adequately blinded to intervention. Blinding of outcome assessors of safety adequately described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation using LOCF for efficacy data. ITT analysis
Selective reporting (reporting bias)	High risk	Outcomes of sleep and anxiety not reported

Arnold 2010b *(Continued)*

Group similarity at baseline	Low risk	No significant differences in clinical and demographic variables at baseline
Sample size bias	Low risk	> 200 participants per treatment arm

Arnold 2012a

Study characteristics	
Methods	**Study setting:** multicenter study with 29 outpatient research centers in USA, Mexico, Israel and Argentina **Study period:** September 2009-November 2010 **Study design:** parallel **Trial duration**: 5-30 days' screening and wash out; 12 weeks' therapy
Participants	**DLX** (N = 155): 94% women, 94% white, mean age 50.9 (SD 11.9) years, pain baseline (0-10) 6.5 (SD 1.5); 20.6% with major depressive disorder **Placebo** (N = 153): 96% women, 89% white, mean age 50.7 (SD 12.5) years; pain baseline (0-10) 6.4 (SD 1.7); 24.2% with major depressive disorder **Inclusion criteria:** ACR 1990 criteria; score ≥ 4 on the pain severity item of the BPI; age ≥ 18 years; with and without MDD **Exclusion criteria:** prior treatment with DLX; prior participation in a DLX study; a history of substance abuse within the past year; a primary psychiatric disorder other than MDD or GAD within the last year; a history of psychosis or bipolar disorder; clinically judged to be at risk of suicide; pregnant or breast-feeding; pain symptoms unrelated to FM that could interfere with interpretation of outcome measures; regional pain syndromes; failed back syndrome; chronic localized pain related to any past surgery, and a confirmed current or previous diagnosis of rheumatoid arthritis; inflammatory arthritis, or infectious arthritis; or an autoimmune disease. Participants who, in the opinion of the investigator, were judged to be treatment-refractory or whose response might be compromised by disability compensation, or had an unstable medical condition were also excluded. Concomitant medication exclusions included use of medications or herbal agents with primarily cCNS activity; regular use of analgesics other than acetaminophen up to 2 g/d and aspirin up to 325 mg for cardiac prophylaxis; topical lidocaine or capsaicin, antidepressants, anticonvulsants, barbiturates, muscle relaxants; chronic use of anti-emetics, hypnotics and sedatives; < 3 months stable therapy of antihypertensives, anti-arrhythmics, diuretics, and hormones; steroids other than episodic treatment of symptoms unrelated to FM; and benzodiazepine use for FM pain
Interventions	**DLX** 30 mg **Placebo** **Rescue and/or allowed medication**: some analgesics, such as non-steroidal antiinflammatory drugs and narcotics, were allowed episodically but only for acute injury or surgery
Outcomes	**Pain:** BPI) average pain severity (NRS 0-10) **PGIC much or very much improved**: not reported; average PGI assessed and reported **Fatigue:** FIQ single item (VAS 0-10): not reported **Sleep problems**: not assessed **Health-related Quality of life:** FIQ total score (0-80)

Arnold 2012a *(Continued)*

	AEs: vital signs, laboratory analyses, and the C-SSRS. Frequency of nausea, somnolence and insomnia reported **Depression:** BDI -II total score (NRS 0-63) **Anxiety:** BAI total score (NRS 0-63) **Disability:** BPI interference from pain (NRS 0-10) **Sexual function**: not assessed **Cognitive disturbances:** MFI mental fatigue (NRS 4-20) **Tenderness**: not assessed **Dropout due to lack of efficacy:** reported
Notes	**Conflicts of interest:** BAP and SZ are full time employees and stockholders at Eli Lilly and Company. LMA has received grants from and/or is a consultant for Eli Lilly and Company, Pfizer Inc, Cypress Bioscience Inc, Forest Laboratories, Boehringer Ingelheim, Novartis, Takedo,Grunenthal and Daiichi Sankyo. **Funding:** Eli Lilly

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer- generated random sequence by IVRS
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Capsules were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Participant-reported outcomes; participants were adequately blinded to intervention. Blinding of outcome assessors of safety adequately described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Modified BOCF for ITT-analysis (participants who discontinued because of an AE, the baseline value was used as the endpoint, and for all other participants, the last non-missing, post-baseline observation before rescue therapy (if any) was used as the endpoint)
Selective reporting (reporting bias)	High risk	Study protocol available at clinicaltrials.gov; NCT00965081. All predefined outcomes except fatigue reported
Group similarity at baseline	Low risk	No significant differences in demographic and clinical variables at baseline
Sample size bias	Unclear risk	100-199 participants per treatment arm

Bateman 2013

Study characteristics	
Methods	**Study setting:** multicenter study with 29 outpatient research centers in USA, Mexico, Israel and Argentina **Study period:** March-December 2010 **Study design:** parallel **Trial duration**: 2-week, open-label run-in, 10 weeks' therapy
Participants	**MLN** (N = 79): 92% women, 94% white, mean age 48.6 (SD 10.2) years; pain baseline (0-100) 65.4 (13.2) **Placebo** (N = 21): 91% women, 95% white, mean age 48.5 (SD 11.3) years; pain baseline (0-100) 65.2 (12.2) **Inclusion criteria:** female and male outpatients, aged 18–70 years, with a diagnosis of FM who had been receiving the recommended dosage of DLX 60 mg/d (ie, the maximum dosage recommended by the US Food and Drug Administration)17 at stable doses for at least 4 weeks prior to screening. DLX prescriptions had to be for the management of FM and not for the treatment of depression or another pain syndrome. Participants with a `1-week` VAS pain recall score ≥ 40 mm to ≤ 90 mm at screening were entered into the open-label, `run-in` period of this study and continued receiving DLX 60 mg/d for an additional 2 weeks in order to confirm that they were not having an adequate response to DLX under study conditions. After this 2-week run-in period, participants who continued to have a VAS pain score ≥ 40 mm and who still expressed dissatisfaction with treatment were eligible for randomization. A deliberately general question was used to evaluate treatment satisfaction (ie, “Are you satisfied with DLX treatment?”) in order to allow for any potential dissatisfaction (e.g. unsatisfactory improvement in pain or non-pain symptoms, poor tolerability, simple desire to try a new medication), as might occur in clinical practice.) **Exclusion criteria:** history or current diagnosis of serious psychiatric disorder; substantial alcohol use or abuse; behavior that would, in the investigator’s judgment, prohibit participation in the study; serious suicide risk; BDI 22-25; pregnancy or breastfeeding; unacceptable contraception in those of childbearing potential; untreated hypertension; cardiovascular disease, including myocardial infarction or stroke within the past 6 months; sitting mean systolic BP .160 mmHg or diastolic BP.100 mmHg; active or unstable medical illness; evidence of active liver disease; prostate enlargement or other genitourinary disorders; renal impairment (creatinine clearance, 30 mL/min); uncontrolled narrow-angle glaucoma; body mass index ≥ 45 kg/m2. Excluded concomitant medications included drugs with CNS activity, such as antidepressants, anorectics, antiepileptic agents, opiates, and related analgesics (e.g. oxycodone, codeine, tramadol, narcotic patches), dopamine agonists, stimulants, and sodium oxybate
Interventions	**MLN** 100 mg **Placebo** **Rescue and/or allowed medication**: acetaminophen, aspirin, and NSAIDs. Participants requiring short-term pain rescue medication were allowed opioid analgesics, but opioids were not permitted within days of scheduled study visits. Triptans were permitted for acute migraine treatment. Nonbenzodiazepine hypnotics were also allowed for participants requiring treatment of insomnia.
Outcomes	**Pain:** 1-week recall pain intensity (VAS 0-100) **PGIC much or very much improved**: reported **Fatigue:** FIQ single item (0-10): not reported **Sleep problems**: not assessed **HRQoL:** FIQ total score (0-100) **AEs**: no details reported. Frequency of nausea, dizziness and insomnia reported **Depression:** BDI -II total score; SD not reported

Bateman 2013 *(Continued)*

	Anxiety: FIQ single item (0-10) not reported **Disability:** FIQ single item (VAS 0-10) **Sexual function:** Arizona Sexual Experience Scale (5-30) **Cognitive disturbances:** MASQ (38-190) **Tenderness**: not assessed **Dropout due to lack of efficacy:** reported
Notes	**Conflicts of interest:** LB has received research support and speaker fees from Forest Laboratories, Inc. and Forest Research Institute, Inc. RHP, JMT, and YL are full-time employees of Forest Research Institute, Inc., a wholly owned subsidiary of Forest Laboratories, Inc., and hold stock in the parent company. **Funding:** Forest Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis by LOCF
Selective reporting (reporting bias)	High risk	All predefined outcomes of study protocol NCT01077375 reported except fatigue and anxiety
Group similarity at baseline	Low risk	No significant differences in clinical and demographic variables
Sample size bias	High risk	< 50 participants in placebo arm, 79 in active treatment arm

Branco 2010

Study characteristics

Methods	**Study setting:** multicenter study with 89 outpatient research centers in 13 European countries **Study period:** February 2006-September 2007

Branco 2010 *(Continued)*

	Study design: parallel **Trial duration:** 1- to 4-week washout period from disallowed medications, eligible participants entered a 2-week period in which they were trained in the use of the PED; 16 weeks' therapy; 2-week follow-up phase without treatment
Participants	**MLN:** N = 430; 95.1% female; ethnicity not reported; mean age 48.3 (SD 9.3) years; pain baseline (0-100) 65.5 (SD 12.9) **Placebo:** N = 446; 93.5% female; ethnicity not reported; mean age 49.2 (SD 10.3) years; pain baseline (0-100) 65.0 (SD 12.7) **Inclusion criteria:** 1990 ACR criteria; raw score ≥ 3 on physical function component of FIQ; baseline VAS pain intensity rating between 40-90 (0-100 scale) **Exclusion criteria:** severe psychiatric illness including GAD or current major depressive episode (assessed by MINI, BDI-27 score > 25), alcohol/substance abuse; significant cardiovascular, respiratory, rheumatoid, rheumatic, hepatic, renal, or other medical condition; systemic infection; epilepsy; active cancer; severe sleep apneas; unstable endocrine disease; active peptic ulcer or inflammatory bowel disease; prostatic enlargement or other genitourinary disorders (in male participants); pregnancy or breastfeeding; and history or behavior that would prohibit compliance for the duration of the study
Interventions	**MLN:** 25 mg once daily (evening dose, days 1 and 2); 25 mg twice daily (days 3–7); 50 mg (days 8–14); 50 mg (morning dose) and 100 mg (evening dose, days 15–21); and 100 mg (days 22–28). Participants then entered the 12-week stable-dose treatment period, followed by a 9-day down-titration phase and a 2-week follow-up phase without treatment. **Placebo** **Rescue or allowed medication**: not reported
Outcomes	**Pain:** PED 24-h recall pain score (VAS 0-100); 50% response rates not reported and not provided on request; calculated by imputation method **PGIC much or very much improved**: reported **Fatigue:** MFI total (NRS 20-100) **Sleep problems:** MOS-Sleep Index II (NRS 0-100) **HRQoL:** FIQ total score (VAS 0-100) **AEs:** physical examination, ECGs, and laboratory analysis. AEs were assessed throughout the study based on spontaneous reporting by participants, investigators' use of non-leading questions, and clinical evaluation. Frequency of nausea, dizziness and insomnia reported **Depression:** BDI total score (NRS 0-63) **Anxiety:** State-Trait Anxiety Inventory (NRS 20-80) **Disability:** BPI pain interference pain (NRS 0-10) **Sexual function**: not assessed **Cognitive disturbances:** MASQ cognitive function (NRS 38-190) **Tenderness:** not assessed **Dropout due to lack of efficacy:** reported
Notes	**Conflicts of interest:** Dr. Branco has received grant support as an investigator and consultant for Pierre Fabre Médicament. Drs. Zachrisson and Perrot have served as speakers and consultants for Pierre Fabre Médicament. Dr. Mainguy is an employee and shareholder of Pierre Fabre Médicament.

Branco 2010 *(Continued)*

Funding: Supported by Pierre Fabre Médicament, Boulogne, France

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence using an interactive response system (details provided on request)
Allocation concealment (selection bias)	Low risk	Central independent unit (details provided on request)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind (number and appearance of placebo capsules similar-details reported on request)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant-reported outcomes; participants were adequately blinded to intervention. Outcome assessors of safety were adequately blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation using LOCF for efficacy data. ITT analysis
Selective reporting (reporting bias)	High risk	50% pain reduction not reported and not provided on request; The FDA report on MLN stated that a female participant committed suicide and that this death was possibly related to MLN
Group similarity at baseline	Low risk	No significant differences in demographic and clinical variables at baseline
Sample size bias	Low risk	> 200 participants per treatment arm

Chappell 2009a

Study characteristics

Methods	**Study setting:** multicenter study with 36 outpatient research centers in Western Europe (Germany, Spain, Sweden, UK) and USA **Study period:** September 2005-December 2006 **Study design**: parallel **Trial duration:** 1 week's screening, 27 weeks' therapy
Participants	**DLX:** N = 162; 92.0% female; 92.6% white; mean age 50.8 (SD 10.1) years; pain baseline (0-10) 6.6 (SD 1.5); 22.2% current major depression **Placebo:** N = 168; 94.6% female; 89.3% white; mean age 50.2 (SD 11.3) years; pain baseline (0-10) 6.4 (SD 1.5); 22.6% current major depression **Inclusion criteria:** ACR 1990 criteria; age ≥ 18 years; with and without MDD **Exclusion criteria:** current or previous treatment with DLX; any current primary Axis I diagnosis other than MDD; pain symptoms related to traumatic injury, structural rheumatic disease, or regional rheumatic disease (such as osteoarthritis, bursitis, tendonitis); regional pain syndrome; multiple surg-

Chappell 2009a *(Continued)*

	eries or failed back syndrome; confirmed current or previous diagnosis of rheumatoid arthritis, inflammatory arthritis, infectious arthritis, or an autoimmune disease; and serious medical illness
Interventions	**DLX** 60 mg/d or 120 mg/d: participants randomly assigned to the DLX 60 mg treatment group underwent a titration in which they received DLX 30 mg for 1 week before receiving DLX 60 mg for 12 weeks. At visit 8 (week 13) participants who did not have 50% reduction in the BPI-Modified Short Form average pain score were blindly escalated to 120 mg. Those that could not tolerate this dose were allowed to return to the 60 mg dose. Participants were allowed to increase their dose to 120 mg at any time between visits 8 and 10 (weeks 13 and 23), based upon whether they had 50% reduction in their BPI average pain score. If at any time between visits 9 and 11 (weeks 18 and 27) participants had tolerability issues with the higher dose (120 mg), they were allowed to go back to the lower dose (60 mg). **Placebo** **Rescue or allowed medication**: not reported
Outcomes	**Pain:** BPI 24-h average pain severity (NRS 0-10) **PGIC much or very much improved**: not reported; mean scores of PGIC (NRS 1-7) reported **Fatigue**: MFI general fatigue (NRS 4-20) **Sleep problems:** BPI sleep interference (NRS 0-10): not reported **HRQoL:** FIQ total score (VAS 0-80) **AEs:** physical examination, ECGs, and laboratory analysis. AEs were assessed throughout the study based on spontaneous reporting by participants. Frequency of nausea, somnolence and insomnia reported **Depression**: BDI-II total score (NRS 0-63) **Anxiety:** FIQ anxiety (VAS 0-10): not reported **Disability:** BPI pain interference (NRS 0-10) **Sexual function**: not assessed **Cognitive disturbances:** MFI mental fatigue (NRS 4-20) **Tenderness:** mean tender point threshold (kg/cm^2) **Dropout due to lack of efficacy:** reported
Notes	**Conflicts of interest:** Drs. Chappell, Detke, and D'Souza are employees and stockholders of Eli Lilly and Company. Dr Wiltse is a former employee of Eli Lilly and Company. Dr Spaeth is a consultant to Allergan, Eli Lilly, Jazz, and Pierre Fabre Medicament, and is on the speaker bureaus of Eli Lilly and Pierre Fabre Medicament. Dr Bradley is a consultant for Eli Lilly, Pfizer, and Forest; has received grant/research support from the National Institutes of Health, the Agency for Healthcare Research and Quality, Eli Lilly, Pfizer, and the American Fibromyalgia Syndrome Association; has received honoraria from Eli Lilly, Pfizer, Forest, and the Society for Women's Health Research; is a member of the speaker/advisory board for Pfizer; and has received royalties from UpToDate Rheumatology **Funding:** Eli Lilly

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence stratified by major depression status within each study center

Chappell 2009a *(Continued)*

Allocation concealment (selection bias)	Low risk	Central independent unit (details reported on request)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind (number and appearance of placebo capsules similar, details reported on request)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant-reported outcomes; participants were adequately blinded to intervention. Blinding of outcome assessors of safety adequately described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation using LOCF for efficacy data. ITT analysis
Selective reporting (reporting bias)	High risk	Outcomes of sleep and anxiety not reported
Group similarity at baseline	Low risk	No significant differences in clinical and demographic variables at baseline
Sample size bias	Unclear risk	50-199 participants per treatment arm

Clauw 2008

Study characteristics	
Methods	**Study setting:** multicenter study with 86 outpatient research centers in USA **Study period:** November 2004-December 2006 **Study design:** parallel **Trial duration:** After a 1- to 4-week period for washout of prohibited medications, participants were trained in the use of the electronic study diary and entered a 2-week baseline period, during which baseline efficacy and safety values were recorded; 15 weeks' therapy
Participants	**MLN 100 mg/d:** N = 399; 97.0% female; 94.0% white; mean age 49.5 (SD 13.5) years; pain baseline (0-100) 64.6 (SD 13.5) **MLN 200 mg/d:** N = 396; 97.0% female; 92.9% white; mean age 50.4 (SD 10.6) years; pain baseline (0-100) 64.5 (SD 13.8) **Placebo:** N = 401; 94.8% female; 93.5% white; mean age 50.7 (SD 10.4) years; pain baseline (0-100) 65.7 (SD 13.3) **Inclusion criteria:** 1990 ACR criteria; raw score ≥ 4 on the physical function component of the FIQ; baseline VAS pain intensity rating between ≥ 40 (0-100 scale) **Exclusion criteria:** severe psychiatric illness including GAD or current major depressive episode (assessed by MINI), BDI-27 score > 25; alcohol/substance abuse; significant cardiovascular, respiratory, rheumatoid, rheumatic, hepatic, renal, or other medical condition; systemic infection; epilepsy; active cancer; severe sleep apneas; unstable endocrine disease; active peptic ulcer or inflammatory bowel disease; prostatic enlargement or other genitourinary disorders (in male participants); pregnancy or breastfeeding; and history or behavior that would prohibit compliance for the duration of the study
Interventions	**MLN** 100 mg/d or 200 mg/d: dose escalation within 3 weeks

Clauw 2008 *(Continued)*

	Placebo **Rescue medication**: hydrocodone up to 60 mg/d
Outcomes	**Pain:** PED 24-h recall pain score (VAS 0-100); 50% response rates not reported and not provided on request; calculated by imputation method **PGIC much or very much improved**: reported (NRS 1-7)* **Fatigue:** MFI total (NRS 20-100) **HRQoL:** FIQ total score (VAS 0-100) **AEs:** physical examination, ECGs, and laboratory analysis. AEs were assessed throughout the study based on spontaneous reporting by participants and investigators' observation. Frequency of nausea, dizziness and insomnia reported **Sleep problems:** MOS-Sleep Index II (NRS 0-100) **Depression:** BDI total score (NRS 0-63) **Anxiety:** FIQ anxiety (VAS 0-10): not reported **Disability:** MDHAQ disability subscale score **Sexual function**: Arizona Sexual Function Scale (5-50) **Cognitive disturbances:** MASQ cognitive function (NRS 38-190) **Tenderness**: not assessed **Dropout due to lack of efficacy:** reported
Notes	*Completer analysis **Conflicts of interest:** Dr. Clauw has received grant supports by Bioscience, Inc., and serves as a consultant to Cypress Bioscience, Forest Laboratories, and Pierre Fabre Medicament,all of which are involved in the development of MLN for FM. He also acts as a consultant to Eli Lilly and Company, Pfizer Inc., Procter & Gamble, and Wyeth Pharmaceuticals. He has owned stock in Cypress Bioscience. Dr. Mease has received research grant support from Allergan, Inc.; Cypress Bioscience; Forest Laboratories; Fralex Therapeutics Inc.; Jazz Pharmaceuticals; Eli Lilly; Pfizer; and Wyeth. Drs. Palmer and Wang are employees of Forest Research Institute and own stock in Forest November 2008 Laboratories. Dr. Gendreau is an employee of Cypress Bioscience and owns stock in that company. **Funding:** Forest Research Institute and Cypress Bioscience

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence using an interactive response system (details provided on request)
Allocation concealment (selection bias)	Low risk	Central independent unit (details provided on request)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind (number and appearance of placebo capsules similar, details reported on request)
Blinding of outcome assessment (detection bias)	Low risk	Participant-reported outcomes; patients were adequately blinded to intervention. Outcome assessors of safety were adequately blinded to the intervention

Clauw 2008 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation using baseline and LOCF for efficacy data. ITT analysis
Selective reporting (reporting bias)	High risk	Anxiety scores not reported and not provided on request
Group similarity at baseline	Low risk	No significant group differences in clinical and demographic variables
Sample size bias	Low risk	> 200 participants per treatment arm

Clauw 2013

Study characteristics	
Methods	**Study setting:** 58 study centers, USA **Study period:** November 2009-June 2010 **Study design:** enriched enrolment randomized withdrawal **Trial duration**: 4 weeks open-label, 12 weeks of therapy of participants randomized to MLN or placebo, double-blind) and 1 week of tapering (double blind)
Participants	**MLN** (N = 100): 96% women, 95.3% white, mean age 54.5 (SD 9.5) years; pain baseline (0-100) 65.4 (SD 13.0) **Placebo** (N = 50): 96% women, 94% white, mean age 54.0 (SD 8.5) years; pain baseline (0-100) 65.7(SD 13.6) **Inclusion criteria:** adults meeting the 1990 ACR criteria for FM who entered directly from a long-term, open-label, flexible-dose, lead-in study in which they received MLN 50 mg/d to 200 mg/d for up to 3.25 years. Prior to this lead-in study, participants had received up to 15 months of treatment with MLN 100 mg/d or 200 mg/d during double-blind studies, resulting in up to 4.5 years of MLN exposure prior to entering into the current discontinuation study. **Exclusion criteria:** significant risk of suicide, history of serious psychiatric disorder, substantial alcohol use or abuse, pregnancy or breastfeeding, cardiovascular disease within the past 12 months, mean systolic BP > 180 mmHg or diastolic BP > 110 mmHg, uncontrolled narrow-angle glaucoma, active liver disease, severe renal impairment and any other medical disorder that might preclude participation as judged by the principal investigator
Interventions	**MLN** 100 or 200 mg/d **Placebo** **Rescue and/or allowed medication**: monoamine oxidase inhibitors, stimulant medications, anorectic agents, daily opiates, sodium oxybate and anesthetic and/or opiate patches were prohibited. Although daily opiates were prohibited, intermittent use was allowed as needed, except during the 7 days before scheduled study visits.
Outcomes	**Pain:** 24-h recall pain intensity (VAS 0-100). Data for mean pain reduction extracted from figures. Time to loss of therapeutic response: < 30% reduction in VAS pain from pre-MLN exposure or worsening of FM requiring alternative treatment: < 50% reduction in VAS pain from pre-MLN exposure or worsening of FM requiring alternative treatment not assessed.

Clauw 2013 *(Continued)*

PGIC much or very much worse from randomization: reported

Fatigue: MFI Total Score (20-100); worsening was defined as a 10-point increase from randomization

Sleep problems: not assessed

HRQoL: FIQ-R total score (0-100). Data extracted from figures

AEs: AEs, vital signs and clinical laboratory tests were monitored for safety. Frequency of nausea reported, of somnolence and insomnia not reported

Depression: FIQ-R depression (0-10): not reported

Anxiety: FIQ-R depression (0-10): not reported

Disability: SF-36 physical summary component score (50-0); worsening was defined as a 6-point decrease from randomization

Sexual function: not assessed

Cognitive disturbances: not assessed

Tenderness: not assessed

Dropout due to lack of efficacy: insufficiently reported (not suited for meta-analysis)

Notes

Conflicts of interest: DJC has received grants and research support from Pfizer Inc and Forest Laboratories. He has been a consultant for and has served on advisory boards for Pfizer Inc, Eli Lilly and Co, Forest Laboratories, Inc, Cypress Bioscience, Inc (now Royalty Pharma), Pierre Fabre Pharmaceuticals, UCB and AstraZeneca. PJM has received research and grant funding as well as consultation fees from Forest Laboratories, Inc, Cypress Bioscience, Inc, Eli Lilly and Co, Pfizer Inc, Allergan, Inc, Wyeth Pharmaceuticals, Jazz Pharmaceuticals and Fralex Therapeutics. In addition to being full-time employees of Forest Research Institute, Inc, a wholly owned subsidiary of the study sponsor (Forest Laboratories, Inc), RHP, JMT and YW hold stock in the parent company.

Funding: Pierre Fabre

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization codes were generated and securely stored by Forest Research Institute, Inc (Jersey City, NJ, USA)
Allocation concealment (selection bias)	Low risk	IVRS and/or web response system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Participant-reported outcomes; no details reported about whether participants and outcome assessors of safety were adequately blinded to intervention.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT by LOCF

Clauw 2013 *(Continued)*

Selective reporting (reporting bias)	High risk	Protocol NCT01014585. Outcomes depression and anxiety not reported
Group similarity at baseline	Low risk	No significant group differences in clinical and demographic variables
Sample size bias	Unclear risk	50-199 participants per treatment arm

Leombruni 2015

Study characteristics	
Methods	**Study setting:** single center (interdisciplinary FM outpatient department); Italy **Study period:** 2011-2012 **Study design:** parallel **Trial duration**: no details on washout period reported; 12 weeks of therapy
Participants	**DLX** (N = 29) **L-carnitine** (N = 22) Total sample: 100% female; ethnicity not reported; mean age 54.0 (SD 8.5) years; duration FM 7.6 (SD 6.8) years. "There were no demographic or clinical differences between the two groups at baseline" **Inclusion criteria:** female adults meeting the 1990 ACR criteria for FM as assessed by an experienced rheumatologist pain intensity > 3 on a VAS **Exclusion criteria:** concomitant DSM-IV TR axis I psychiatric syndrome including mood and anxiety disorders; pain due to trauma; rheumatic disease; autoimmune disease; contraindications to the use of DLX or acetylcarnitine; current antidepressant treatment
Interventions	**DLX** 30 or 60 mg/d **Acetyl-carnitine**: 3x500 mg/d **Rescue and/or allowed medication**: no information provided
Outcomes	**Pain:** VAS 0-10 (current pain); 30% and 50% and more pain relied calculated by imputation method **PGIC much or very much improved**: Clinical Global Impression Improvement: Only average scores reported **Fatigue:** FIQ subscale score not reported **Sleep problems**: not assessed **HRQoL:** FIQ total score not reported **AEs:** "Side effects were assessed by the same psychiatrist". Frequency of nausea, somnolence and insomnia insufficiently reported (not suited for meta-analysis). **Depression:** HADS Depression Subscale 0-21 **Anxiety:** HADS Anxiety Subscale 0-21 **Disability:** SF-36 physical summary component score (100-0) **Sexual function**: not assessed

Leombruni 2015 *(Continued)*

	Cognitive disturbances: not assessed
	Tenderness: not assessed
	Dropout due to lack of efficacy: reported
Notes	**Conflicts of interest**: not reported
	Funding: no details provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Selective reporting (reporting bias)	High risk	No study protocol available. FIQ scores not reported
Group similarity at baseline	Low risk	No significant differences in demographic and clinical variables at baseline
Sample size bias	High risk	< 50 participants per treatment arm

Matthey 2013

Study characteristics

Methods	**Study setting:** single-center study, university hospital, Switzerland
	Study period: September 2006-September 2009
	Study design: parallel
	Trial duration: 1-4 weeks' screening and washout; 7 weeks' therapy; down-titration phase of 3-9 days
Participants	**MLN** (N = 38): 100% women, ethnicity not reported, mean age 48.5 (SD 11.4) years; pain baseline (0-100) 61.2 (SD 14.5)
	Placebo (N = 39): 100% women, ethnicity not reported, mean age 50.9 (SD 11.4) years; pain baseline (0-100) 63.5 (SD 15.1)

Matthey 2013 *(Continued)*

	Inclusion criteria: Women ≥ 18 years old who met the 1990 ACR FMS criteria were included if the following criteria were met: signed informed consent, negative urine pregnancy test at screening and use of adequate contraception or absence of childbearing potential, willingness to withdraw from CNS-active therapies, willingness to discontinue treatment with trigger point injections and anesthetics, and reported baseline weekly recall pain over 40 on a 0–100 mm VAS. **Exclusion criteria:** severe psychiatric illness, current major depressive episode or screening BDI > 25, history of substance abuse, epilepsy, active cardiac disease, severe chronic obstructive pulmonary disease, active liver disease, renal impairment, documented autoimmune disease, current systemic infection, active cancer, active peptic ulcer or inflammatory bowel disease (irritable bowel syndrome excepted), unstable endocrine disorder, pregnancy or breastfeeding, concomitant use of psychotropic drugs (including antidepressants or phytotherapy), sympathicomimetics, long-acting benzodiazepines, anticoagulants, antiepileptic drugs, centrally-acting muscle relaxants, opioids, smoking (> 25 cigarettes a day)
Interventions	**MLN** with stepwise increase starting from 25 mg/d to 200 mg/d **Placebo** **Rescue and/or allowed medication**: no details reported
Outcomes	**Pain:** 1-week recall pain intensity (VAS 0-100). 30% and 50% and more pain reduction rates calculated by imputation method **PGIC much or very much improved**: reported as odds ratio (not suited for meta-analysis) **Fatigue:** MFI Total Score (20-100) **Sleep problems:** MOS Sleep Index I (50-0) **Quality of life:** FIQ total score (0-80) **AEs**: no details reported. Frequency of nausea, somnolence and insomnia not reported. No reports on SAEs **Depression:** BDI -II total score (0-63) **Anxiety:** State-Trait Anxiety Inventory (20-80) **Disability:** FIQ single item (VAS 0-10): not reported **Sexual function**: not assessed **Cognitive disturbances**: not assessed **Tenderness:** pressure pain threshold **Dropout due to lack of efficacy:** reported
Notes	**Conflicts of interest:** each author certifies that he or she, or a member of his or her immediate family, has no commercial association, (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might post a conflict of interest in connection with the submitted manuscript. **Funding:** Pierre Fabre

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list by sponsor

Matthey 2013 *(Continued)*

Allocation concealment (selection bias)	Low risk	Chronological order of the occurring visit 2 by sponsor
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported about whether participants and outcome assessors of safety were adequately blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT by LOCF method
Selective reporting (reporting bias)	High risk	All predefined outcomes of study protocol NCT00757679 except FIQ disability reported
Group similarity at baseline	Low risk	No significant group differences in clinical and demographic variables at baseline
Sample size bias	High risk	< 50 participants per treatment arm

Mease 2009b

Study characteristics	
Methods	**Study setting:** multicenter study with 59 outpatient research centers in USA **Study period:** October 2003-July 2005 **Study design:** parallel **Trial duration:** washout period (weeks 1-4), 2-week baseline period, 27 weeks' therapy (3 weeks' titration, 24 weeks' stable dose); down-titration 3-9 days
Participants	**MLN** 100 mg/d: N = 224: 95.1% women, 95.9% white, mean age 49.9 (SD 10.6) years; pain baseline (0-100) 68.3 (SD 11.5) **MLN** 200 mg/d: N = 441: 95.9% women, 93.4% white, mean age 49.2 (SD 11.0) years; pain baseline (0-100) 69.4 (SD 11.9) b N = 223: 95.5% women, 93.4% white, mean age 49.4 (SD 10.1) years; pain baseline (0-100) 68.3 (SD 11.9) **Inclusion criteria:** 1990 ACR criteria; baseline VAS pain intensity rating between ≥ 50 (0-100 scale) **Exclusion criteria:** severe psychiatric illness; current major depressive episode (as assessed by MINI); significant risk of suicide according to the investigator's judgment; alcohol or other drug abuse; a history of significant cardiovascular, respiratory, endocrine, genitourinary, liver, or kidney disease; autoimmune disease; systemic infection; cancer or current chemotherapy; significant sleep apnoea; active peptic ulcer or inflammatory bowel disease
Interventions	**MLN** 100 mg/d or 200 mg/d **Placebo**

Mease 2009b *(Continued)*

	Rescue medication: hydrocodone up to 60 mg/d
Outcomes	**Pain:** PED 24-h recall pain score (VAS 0-100); missing means and SDs provided on request **PGIC much or very much improved:** Reported (NRS 1-7)* **Fatigue:** MFI total (NRS 20-100); missing SDs reported on request **Sleep problems:** MOS-Sleep Index I (NRS 0-100); missing SDs provided on request **HRQoL:** FIQ total score (VAS 0-100): missing SDs provided on request **AEs:** physical examination, ECGs, and laboratory analysis. AEs were assessed throughout the study based on spontaneous reporting by participants and investigators' observation. Frequency of nausea, somnolence and insomnia reported **Depression:** BDI total score (NRS 0-63): missing means and SDs provided on request **Anxiety:** FIQ (VAS 0-10): not reported **Disability:** SF-36 physical function (0-50): missing means and SDs provided on request **Sexual function:** Arizona Sexual Function Scale (5-50): SD not reported. Data not suited for quantitative analysis. **Cognitive disturbances:** MASQ cognitive function (NRS 38-190) **Tenderness**: not assessed **Dropout due to lack of efficacy:** reported
Notes	*Completer analysis **Conflicts of interest:** Dr. Mease has received research grant support from Pfizer Inc, Cypress Bioscience, Inc., Forest Laboratories, Inc., Eli Lilly and Company, Allergan, Wyeth Pharmaceuticals, Jazz Pharmaceuticals, and Fralex Therapeutics. Dr. Clauw has received grant support from Cypress Bioscience, Inc. and serves as a consultant to Cypress Bioscience, Inc, Forest Laboratories, Inc., Pierre Fabre Médicament, Pfizer Inc, Eli Lilly and Company, Wyeth Pharmaceuticals, and Proctor and Gamble. Dr. Mease was an investigator of this study and a consultant; Dr. Clauw was a consultant for this study. As consultants, Drs. Mease and Clauw were involved in the study design, analysis of results, and preparation of the manuscript. Drs. Gendreau, Rao, and Kranzler are employees of Cypress Bioscience, Inc. Drs. Chen and Palmer are employees of Forest Laboratories, Inc. **Funding:** Forest Research Institute and Cypress Bioscience

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence using an interactive response system (details provided on request)
Allocation concealment (selection bias)	Low risk	Central independent unit (details provided on request)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind (number and appearance of placebo capsules similar-details reported on request)
Blinding of outcome assessment (detection bias)	Low risk	Participant-reported outcomes; participants were adequately blinded to intervention. Blinding of outcome assessors of safety adequately described

Mease 2009b *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation using LOCF for efficacy data. ITT analysis
Selective reporting (reporting bias)	High risk	Standard deviations of outcome 'sexual dysfunction' not reported and not provided on request
Group similarity at baseline	Low risk	No significant differences in demographic and clinical variables at baseline
Sample size bias	Low risk	> 200 participants per treatment arm

Murakami 2015

Study characteristics	
Methods	**Study setting:** multicenter study with 42 outpatient research centers in Japan **Study period:** March 2012-December 2013 **Study design:** parallel **Trial duration:** 1-2 weeks' screening, 14 weeks' treatment, 1 week dose tapering, 1 week follow-up observation
Participants	**DLX** (N = 191): 82% female; mean age 47.8 (SD 12.0) years; ethnicity not reported; 4.2% major depressive disorder; pain baseline (0-10) 6.1 (SD 1.3) **Placebo** (N = 195): 84% female; mean age 49.5 (SD 11.7) years; ethnicity not reported; 3.6% major depressive disorder; pain baseline (0-10) 6.1 (SD 1.3) **Inclusion criteria:** male and female outpatients aged 20-75 years who met the ACR 1990 criteria of FM and had a BPI and average pain score ≥ 4 at visits 1 and 2 **Exclusion criteria:** past DLX treatment; serious or medically unstable disease, clinically significant abnormal laboratory values, or abnormal ECG findings; pain caused by non-FM diseases; poorly controlled thyroid dysfunction; rheumatoid, inflammatory, or infectious arthritis; autoimmune disorders other than thyroid dysfunction; psychiatric disorders other than major depressive disorder within the past year; and suicidal tendencies as assessed using the C-SSRS
Interventions	**DLX:** 20 mg for 1 week, followed by 40 mg for 1 week and then 60 mg for 12 weeks during the treatment phase **Placebo** **Rescue medication**: participants were prohibited from using analgesics and drugs with analgesic effects, including nonsteroidal antiinflammatory drugs, anticonvulsants, pregabalin, neurotropin, anesthetics, opioids, and adrenocorticosteroids. The use of analgesics for up to 3 consecutive days and for up to a total of 10 days was permitted only for the treatment of AEs. Co-administration of acetaminophen at doses up to 1500 mg/d was permitted
Outcomes	**Pain:** BPI average pain score (NRS 0-10) **PGIC much or very much improved:** NRS 1-7; average scores reported; data not suited for data entry **Fatigue:** FIQ subscale fatigue (VAS 0-10)

Murakami 2015 *(Continued)*

Sleep problems: BPI subscale sleep interference (NRS 0-10)

HRQoL: FIQ total score (VAS 0-80)

AEs: safety was assessed on the basis of the presence or absence and incidence of AEs and adverse drug reactions (ADRs) reported during the treatment phase until the end of the follow-up observation phase. Additionally, laboratory tests (hematology, clinical chemistry, and urinalysis), ECG, body weight, and vital signs were measured. The presence or absence of suicidal tendencies was assessed using the C-SSRS. Frequency of nausea, somnolence and insomnia reported

Depression: BDI II total score (NRS 0-63)

Anxiety: FIQ (VAS 0-10)

Disability: SF-36 physical function (0-100)

Sexual function: not assessed

Cognitive disturbances: not assessed

Tenderness: not assessed

Notes	**Conflicts of interest:** HM and TO are employees of Shionogi & Co. Ltd. LA is an employee of Eli Lilly Japan KK, MM, KO, and KN have provided consultancy services and MM and KO received compensation from Shionogi & Co Ltd. for their participation in this study. MM, KO, and KN did not receive any compensation for their input into this study. The authors confirm that there are no non-financial competing interests to declare in relation to this article. **Funding:** Forest Research Institute and Cypress Bioscience

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web-based patient registration system (ACRONET Corp., Tokyo, Japan) with a stochastic minimization procedure
Allocation concealment (selection bias)	Low risk	Blinding was maintained until the end of the study by the person responsible for the study drug assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The drug allocation controller confirmed the study drugs were indiscernible in terms of appearance, packaging, and labeling, and mock titration of placebo pills was also performed to maintain blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant-reported outcomes; participants were adequately blinded to intervention. Blinding of outcome assessors of safety adequately described
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT by BOCF method
Selective reporting (reporting bias)	Low risk	All predefined outcomes of study protocol NCT01552057 reported
Group similarity at baseline	Low risk	No significant group differences in demographic and clinical variables at baseline
Sample size bias	Unclear risk	100-199 participants per treatment arm

NCT00697787

Study characteristics	
Methods	**Study setting:** multicenter study; 27 outpatient research centers, USA **Study period:** 2006-2008 **Study design:** parallel **Trial duration:** 7-30 days' screening, 7 days' single-blind placebo run-in, 8 weeks: study was stopped by the sponsor for "business reasons"
Participants	**Desvenlafaxine** (N =42): 100%female; mean age 47.8 (SD 10.5) years; ethnicity not reported; pain baseline scores not reported **Placebo** (N = 40): 100% female; mean age 46.9 (SD 12.7) years; ethnicity not reported; pain baseline scores not reported **Pregabalin** (N = 43): 100% female; mean age 46.7 (SD 11.7) years; ethnicity not reported; duration of FM and pain baseline not reported **Inclusion criteria:** FM diagnosed according to 1990 ACR criteria **Exclusion criteria:** unstable medical or psychological conditions that would compromise the participant's safety or put the subject at greater risk during study participation. Other painful conditions that may confound the diagnosis or assessment of FM; treatment with other drugs for FM within 14 days of study start or during the study
Interventions	**Desvenlafaxine** 200 mg/d **Pregabalin** 450 mg/d **Placebo** **Rescue medication**: no details reported
Outcomes	**Pain:** pain score (NRS 0-10) across the last 7 days: no 30% and 50% and more reduction rates reported and not calculable **PGIC much or very much improved**: not assessed **Fatigue**: not assessed **Sleep problems**: not assessed **HRQoL**: not assessed **AEs**: no details reported. Frequency of nausea, somnolence and insomnia reported **Depression**: not assessed **Anxiety**: not assessed **Disability**: not assessed **Sexual function**: not assessed **Cognitive disturbances**: not assessed **Tenderness**: not assessed **Dropout due to lack of efficacy:** reported

NCT00697787 *(Continued)*

Notes	**Conflicts of interest**: not reported **Funding:** Wyeth/Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT-analysis by LOCF
Selective reporting (reporting bias)	Low risk	Data reported as outlined in protocol
Group similarity at baseline	High risk	No significant differences in demographic data at baseline; pain baseline not reported
Sample size bias	High risk	< 50 participants per treatment arm

Russell 2008

Study characteristics

Methods	**Study setting:** multicenter study with 38 outpatient research centers in USA and Puerto Rico **Study period:** June 2005-June 2006 **Study design:** parallel **Trial duration**: 1 week screening, 26 weeks' therapy
Participants	**DLX 20/60 mg/d:** N = 79; 97.5% female; 83.5% white; mean age 50.9 (SD 11.4) years; pain baseline (0-10) 6.8 (SD 1.6); 27.9% current major depression **DLX 60 mg/d:** N = 150; 96.7% female; 84.7% white; mean age 51.8 (SD 10.6) years; pain baseline (0-10) 6.5 (SD 1.4); 23.3% current major depression **DLX 120 mg/d:** N = 147; 97.3% female; 82.6% white; mean age 51.0 (SD 10.8) years; pain baseline (0-10) 6.4 (SD 1.6); 23.1% current major depression **Placebo:** N = 144; 95.1% female; 82.6% white; mean age 50.3 (SD 10.9) years; pain baseline (0-10) 6.6 (SD 1.7); 24.3% current major depression

Russell 2008 *(Continued)*

	Inclusion criteria: ACR 1990 criteria; score ≥ 4 on the pain intensity item of the FIQ; age ≥ 18 years; with and without MDD **Exclusion criteria:** any current primary psychiatric diagnosis other than MDD; pain symptoms unrelated to FM that could interfere with interpretation of outcome measures; regional pain syndromes; multiple surgeries or failed back syndrome; a confirmed current or previous diagnosis of rheumatoid arthritis, inflammatory arthritis, or other autoimmune disease; unstable medical or psychiatric disorders; severe liver disease; current pregnancy or breast-feeding; or a history of substance abuse within the past year. Participants who were judged by the investigator to be treatment-refractory or whose response might be compromised by disability compensation issues in the opinion of the investigator were also excluded
Interventions	**DLX** 20/60 mg/d or 60 mg/d or 120 mg/d **Placebo** **Rescue and/or allowed medication:** acetaminophen up to 2 g/d and aspirin up to 325 mg/d
Outcomes	**Pain:** BPI average pain severity (NRS 0-10) **PGIC much or very much improved**: reported **Fatigue:** MFI general fatigue (NRS 4-20) **Sleep problems**: BPI sleep interference (NRS 0-10): not reported **HRQoL:** FIQ score (VAS 0-80) **AEs:** physical examination, ECGs, and laboratory analysis. AEs were assessed throughout the study based on spontaneous reporting by participants. Frequency of nausea, somnolence and insomnia reported **Depression:** BDI-II total score (NRS 0-63): incompletely reported **Sexual function**: not assessed **Cognitive disturbances:** MFI mental fatigue (NRS 4-20) **Global perceived improvement:** PGIC (NRS 1-7) **Tenderness:** mean tender point threshold (kg/cm^2) **Dropout due to lack of efficacy:** reported
Notes	**Conflicts of interest:** at doi:10.1016/j.pain. 2008.02.024. Page only accessible by fees or institutional access **Funding:** Eli Lilly and Company and Boehringer Ingelheim GmbH

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization: computer-generated random sequence using an interactive response system
Allocation concealment (selection bias)	Low risk	Central independent unit (details reported on request)
Blinding of participants and personnel (performance bias)	Low risk	Double blind (number and appearance of placebo capsules similar, details reported on request)

Russell 2008 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant-reported outcomes; participants were adequately blinded to intervention. Blinding of outcome assessors of safety adequately described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation using LOCF for efficacy data. ITT analysis
Selective reporting (reporting bias)	High risk	Outcomes of sleep, anxiety and depression not reported; depression scores only reported in ClinicalStudyResults.org for 20/60 mg DLX
Group similarity at baseline	Low risk	No significant differences in clinical and demographic variables at baseline
Sample size bias	Unclear risk	50-199 participants per treatment arm

Staud 2015

Study characteristics	
Methods	**Study setting:** single-center study, university hospital, USA **Study period:** November 2009-April 2014 **Study design:** Parallel **Trial duration**: 6 weeks
Participants	**MLN** (N = 23): 91% women, ethnicity not reported, mean age 46.9 (SD 11.5) years; pain baseline (0-10) 5.8 (SD 1.8) **Placebo** (N = 23): 96% women, ethnicity not reported, mean age 47.5 (SD 12.0) years; pain baseline (0-10) 5.1 (SD 1.8) **Inclusion criteria:** adults > 18 years; the ability to give informed consent; fulfilment of the 1990 ACR criteria for FM, including widespread pain **Exclusion criteria:** a relevant medical condition besides FM; current participation in another research protocol that could interfere with or influence the outcome measures of the present study; the inability to give informed consent; current use of analgesic drugs, anxiolytic drugs, antidepressants (all participants taking analgesic drugs or antidepressants before enrolment went through the appropriate washout phase before study entry); and previous treatment with MLN; study participants < 30 years of age and those who showed evidence for major depression
Interventions	**MLN** 50 mg twice daily **Placebo** **Rescue and/or allowed medication**: participants were not allowed to take any analgesics during the study except acetaminophen (365 mg ≤ 4 times daily)
Outcomes	**Pain:** daily pain intensity (VAS 0-100). 30% and 50% and more pain reduction rates calculated by imputation method **PGIC much or very much improved**: not assessed **Fatigue: 24- hours recall pain** VAS 0-10by electronic diary

Staud 2015 *(Continued)*

	Sleep problems: not assessed **HRQoL**: not assessed **AEs**: no details of dropout due to AEs and frequency of SAEs reported. Frequency of nausea, somnolence and insomnia insufficiently reported (not suited for meta-analysis) **Depression:** VAS 0-100 **Anxiety:** VAS 0-100 **Disability**: not assessed **Sexual function**: not assessed **Cognitive disturbances**: not assessed **Tenderness:** quantitative sensory testing was performed. Tenderness was not considered as a clinical outcome measure for the intervention. **Dropout due to lack of efficacy:** insufficiently reported (not suited for meta-analysis)
Notes	**Conflicts of interest**: none of the authors has any financial or other relationships that might lead to a conflict of interest. **Funding:** Pierre Fabre

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization performed using Research Randomizer (www.randomizer.org)
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Selective reporting (reporting bias)	High risk	Study protocol NCT01294059 available; no details of dropouts due to AEs and frequency of SAEs reported
Group similarity at baseline	Low risk	No significant differences in clinical and demographic variables at baseline
Sample size bias	High risk	< 50 participants per treatment arm

Vitton 2004

Study characteristics	
Methods	**Study setting:** multicenter study with 12 outpatient research centers in USA **Study period**: not reported **Study design:** parallel **Trial duration:** 1-4 weeks' wash out, 2 weeks' baseline and training, 12 weeks' therapy
Participants	**MLN** once a day (N = 46): 98% women, 82% white, mean age 47.4 (SD 11.6) years; pain baseline scores not reported; 16% current depression **MLN** twice a day (N = 51): 98% women, 89% white, mean age 46.2 (SD 12.2) years; pain baseline scores not reported; 7% current depression **Placebo** (N = 28): 96% women, 79% white, mean age 48.0 (SD 8.4) years; pain baseline scores not reported; 32% current depression **Inclusion criteria:** 1990 ACR criteria; 18-70 years **Exclusion criteria:** severe psychiatric illness excluding depression; significant risk of suicide according to the investigator's judgement; alcohol or other drug abuse; a history of significant cardiovascular, respiratory, endocrine, genitourinary, liver or kidney disease; autoimmune disease; systemic infection; cancer or current chemotherapy; significant sleep apnoea; life expectancy < 1 year; active peptic ulcer or inflammatory bowel disease
Interventions	**MLN** 200 mg/d, dose escalation within 3 weeks **Placebo** **Rescue medication**: hydrocodone up to 60 mg/d
Outcomes	**Pain:** PED 24-h recall pain score (VAS 0-100) **Global perceived improvement**: not assessed **Fatigue:** FIQ VAS 0-10. Data provided on request. OC analysis **Sleep problems:** Jenkins Sleep Survey total score (NRS). Data provided on request. OC analysis **HRQoL:** FIQ total score (VAS 0-80). Data provided on request. OC analysis **AEs:** physical examination, ECGs, and laboratory analysis. AEs were assessed throughout the study based on spontaneous reporting by participants. Frequency of nausea, somnolence and insomnia not reported **Depression:** FIQ VAS 0-10. Data provided on request. OC analysis **Anxiety:** FIQ VAS 0-10. Data provided on request. OC analysis **Disability:** FIQ VAS 0-10. Data provided on request. OC analysis **Sexual function**: not assessed **Cognitive disturbances**: not assessed **Tenderness**: not assessed **Dropout due to lack of efficacy:** reported
Notes	**Conflicts of interest:** 3 authors were employed by Cypress Bioscience, 5 authors were consultants and 3 authors were shareholders for Cypress Bioscience

Vitton 2004 *(Continued)*

Funding: authors were employed by Cypress Bioscience

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence (details provided on request)
Allocation concealment (selection bias)	Low risk	Central independent unit (details provided on request)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind (number and appearance of placebo capsules similar, details reported on request)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant-reported outcomes; participants were adequately blinded to intervention. Blinding of outcome assessors of safety adequately described
Incomplete outcome data (attrition bias) All outcomes	High risk	OC analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported or provided on request
Group similarity at baseline	High risk	Pain baseline scores not reported; higher proportion of participants with depression in placebo group
Sample size bias	High risk	< 50 participants in two treatment arms, 51 in the third arm

ACR: American College of Rheumatology; **AE**: adverse event; **BAI**: Beck Anxiety Inventory; **BDI**: Beck Depression Inventory; **BOCF**: baseline observation carried forward (statistical method); **BP**: blood pressure; **BPI**: Brief Pain Inventory; **bpm**: beats per minute; **C-SSRS**: Columbia-Suicide Severity Rating Scale; **CNS**: central nervous system; **DLX**: duloxetine; **DSM-IV**: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; **ECG**: electrocardiogram; **FIQ**: Fibromyalgia Impact Questionnaire; **FM**: fibromyalgia; **GAD**: generalized anxiety disorder; **HDRS**: Hamilton Depression Rating Scale; **HRQoL**: health-related quality of life; **IVRS**: Interactive Voice Respone System; **ITT**: intention-to-treat analysis; **LOCF**: last observation carried forward (statistical method); **MASQ**: Multiple Ability Self-report Questionnaire; **MDD**: major depressive disorder; **MDHAQ**: Multi-Dimensional Health Assessment Questionnaire; **MFI**: Multidimensional Fatigue Inventory: **MINI**: Mini International Neuropsychiatric Interview; **MLN**: milnacipran; **MMRM**: mixed-effects model repeated measures; **MOS**: Medical Outcomes Study; **NRS**: Numerical rating scale; **NSAID**: non-steroidal anti-inflammatory drug; **OC**: observed cases; **PED**: patient electronic diary; **PGIC**: Patient Global Impression of Change Inventory; **QT**: The Q-T interval represents the time for both ventricular depolarization and repolarization to occur, and therefore roughly estimates the duration of an average ventricular action potential in the ECG; **SAE**: serious adverse effect; **SSR**: Society of Skeletal Radiology; **SSRI**: selective serotonin reuptake inhibitors; **VAS**: visual analog scale

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

Study	Reason for exclusion
Ahmed 2016	RCT with cross-over design with MLN and placebo for 6 weeks each in 19 participants: < 20 participants
Ang 2013	21-week RCT (parallel design) with MLN + CBT (N = 20), MLN + education (N = 19), and placebo + CBT (N = 19)

Study	Reason for exclusion
Branco 2011	1-year extension study, double-blind, randomized, not control arm, of 3 doses of MLN (468 participants)
Chappell 2009b	8-week, open-label period followed by a 52-week, double-blind, that were not placebo-controlled, randomized to 1 or 2 doses of DLX (350 participants)
Dwight 1998	8-week, open trial with venlafaxine in 15 participants
Goldenberg 2010	Not RCT: 6-month extension study, double-blind, randomized,no control arm, of 2 doses of MLN (449 participants)
Hsiao 2007	Not RCT: case report of 1 patient with fibromyalgia, comorbid with premenstrual dysphoric disorder with a low dose of venlafaxine
Mease 2010	Not RCT: 6-month extension phases with no control arm of 2 RCTs with DLX (492 participants)
Natelson 2015	< 20 participants per treatment arm: RCT comparing 100 mg MLN with placebo for 8 weeks
NCT00369343	Data not suited for meta-analysis: randomized, placebo-controlled trial with 696 FM patients on 4 fixed oral doses of DVS SR (50 mg, 100 mg, 150 mg and 200 mg). Interim data analysis indicated that none of the 4 DVS SR treatment groups showed separation from placebo, and that there was a high placebo response rate. The study was discontinued because of the failure of DVS to meet the predefined efficacy criteria (pain reduction, health-related quality of life (FIQ-total score) and PGIC score). Details (means, SDs, absolute numbers) not reported
NCT00725101	No RCT: observational study without control group with 1700 participants
NCT00793520	< 20 participants per study arm: RCT with cross-over design (5 weeks each period) and 1 participant comparing MLN with placebo
NCT01108731	< 20 participants per treatment arm: RCT comparing MLN with placebo in 17 participants each for 8 weeks
NCT01173055	Outcomes (change in pain threshold from baseline to week 6 of treatment, change in diffuse noxious inhibitory control, change in functional magnetic resonance imaging brain activation patterns during pressure stimulation) did not meet inclusion criteria of this review: RCT with cross-over design with 6 weeks in each period comparing MLN and placebo in 22 participants
NCT01234675	< 10 participants per treatment arm: RCT with cross-over design with 6 weeks for each period and 10 participants in MLN and 9 participants in placebo group
NCT01294059	Not RCT: 6-week randomized trial without control group; number of participants not reported
NCT01331109	Not RCT: open-label study with 57 pediatric participants over 53 weeks; no control group
NCT01621191	Not RCT: 50-week extension study of NCT01552057 with DLX and no control arm with 149 participants
Saxe 2012	Study duration < 4 weeks: 2-week randomized, placebo-controlled withdrawal design. Participants who had originally received MLN 100 mg/d for 12 weeks were re-randomized to continue MLN (n = 178) or switch directly to placebo (n = 178); participants originally receiving placebo continued with placebo (n = 359): study duration < 4 weeks
Sayar 2003	Not RCT: 12-week, open trial with venlaxafine in 15 participants with no control arm

Study	Reason for exclusion
Trugman 2014	Only outcome criterion of efficacy was 24-h blood pressure and did not meet the inclusion criteria for this review: RCT comparing 200 mg MLN versus placebo in 321 participants with FM (of whom 50% were classified to be hypertensive at baseline) for 7 weeks
Ziljstra 2002	Study only published as abstract: RCT comparing 75 mg venlafaxine with placebo in 90 participants with FM for 6 weeks

CBT: cognitive behavioral therapy;**DLX**: duloxetine; **DVS SR**: desvenlafaxine sustained release; **FIQ**: Fibromyalgia Impact Questionnaire; **FM**: fibromyalgia; **HRQoL**: health-related quality of life; **MLN**: milnacipran; **PGIC**: Patient Global Impression of Change; **RCT:** randomized controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT00552682

Methods	Pilot, open, randomized clinical trial
Participants	Fibromyalgia in people with HIV 1+; number not reported
Interventions	Duloxetine, dosage and comparator drug not reported
Outcomes	Not reported
Notes	Study completed; no data available in clinicaltrials.gov or Medline

NCT01268631

Methods	Not reported
Participants	Fibromyalgia; number not reported
Interventions	Duloxetine, dosage and comparator drug not reported
Outcomes	Not reported
Notes	The recruitment status of this study is unknown because the information has not been verified recently

DATA AND ANALYSES

Comparison 1. SNRIs versus placebo in parallel and cross-over design trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Self-reported pain relief of 50% or greater	15	6918	Risk Difference (IV, Random, 95% CI)	0.09 [0.07, 0.11]

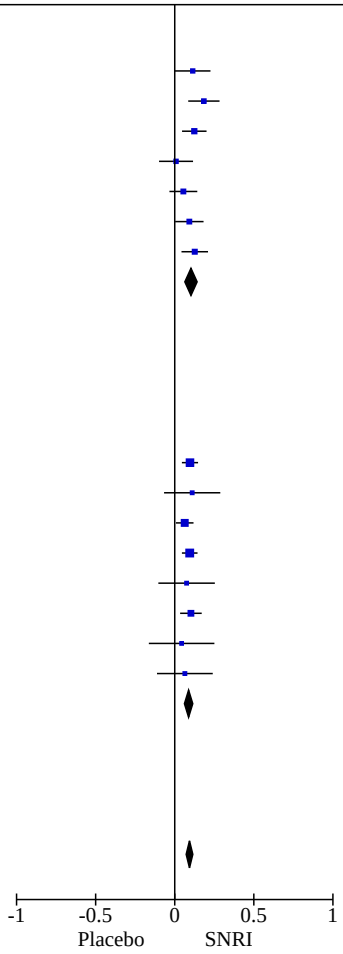
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.1 Duloxetine	7	2582	Risk Difference (IV, Random, 95% CI)	0.10 [0.06, 0.14]
1.1.2 Milnacipran	8	4336	Risk Difference (IV, Random, 95% CI)	0.09 [0.06, 0.11]
1.2 PGIC much or very much improved	6	2918	Risk Difference (M-H, Random, 95% CI)	0.19 [0.12, 0.26]
1.2.1 Duloxetine	1	530	Risk Difference (M-H, Random, 95% CI)	0.35 [0.27, 0.42]
1.2.2 Milnacipran	5	2388	Risk Difference (M-H, Random, 95% CI)	0.15 [0.11, 0.19]
1.3 Withdrawal due to adverse events	15	7029	Risk Difference (IV, Random, 95% CI)	0.07 [0.04, 0.10]
1.3.1 Desvenlafaxine	1	82	Risk Difference (IV, Random, 95% CI)	-0.03 [-0.09, 0.04]
1.3.2 Duloxetine	7	2642	Risk Difference (IV, Random, 95% CI)	0.05 [0.02, 0.07]
1.3.3 Milnacipran	7	4305	Risk Difference (IV, Random, 95% CI)	0.11 [0.07, 0.14]
1.4 Serious adverse events	13	6732	Risk Difference (IV, Random, 95% CI)	-0.00 [-0.01, 0.00]
1.4.1 Desvenlafaxine	1	82	Risk Difference (IV, Random, 95% CI)	0.00 [-0.05, 0.05]
1.4.2 Duloxetine	6	2432	Risk Difference (IV, Random, 95% CI)	-0.00 [-0.01, 0.01]
1.4.3 Milnacipran	6	4218	Risk Difference (IV, Random, 95% CI)	-0.00 [-0.01, 0.01]
1.5 Self-reported fatigue	12	6168	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.18, -0.08]
1.5.1 Duloxetine	5	1954	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.21, -0.03]
1.5.2 Milnacpran	7	4214	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.21, -0.07]
1.6 Self-reported sleep problems	8	4547	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.15, 0.01]
1.6.1 Duloxetine	3	1382	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.31, -0.10]
1.6.2 Milnacipran	5	3165	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.05, 0.10]
1.7 Self-reported health-related quality of life	14	6861	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.25, -0.15]
1.7.1 Duloxetine	7	2604	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.30, -0.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.2 Milnacipran	7	4257	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.25, -0.12]
1.8 Self-reported pain relief of 30% or greater	15	6924	Risk Difference (IV, Random, 95% CI)	0.10 [0.08, 0.12]
1.8.1 Duloxetine	7	2588	Risk Difference (IV, Random, 95% CI)	0.11 [0.07, 0.15]
1.8.2 Milnacipran	8	4336	Risk Difference (IV, Random, 95% CI)	0.10 [0.07, 0.13]
1.9 Self-reported mean pain intensity	16	7014	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.27, -0.17]
1.9.1 Desvenlafaxine	1	82	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.27, 0.59]
1.9.2 Duloxetine	7	2619	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.35, -0.18]
1.9.3 Milncipran	8	4313	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.26, -0.13]
1.10 Self-reported depression	14	6478	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.21, -0.11]
1.10.1 Duloxetine	7	2264	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.34, -0.17]
1.10.2 Milnacipran	7	4214	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.17, -0.05]
1.11 Self-reported anxiety	9	3533	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.21, 0.05]
1.11.1 Duloxetine	4	1403	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.17, 0.04]
1.11.2 Milnacipran	5	2130	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.36, 0.13]
1.12 Self-reported disability	13	6789	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.26, -0.16]
1.12.1 Duloxetine	7	2602	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.37, -0.21]
1.12.2 Milnacipran	6	4187	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.22, -0.10]
1.13 Self-reported cognitive disturbances	8	5444	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.21, -0.10]
1.13.1 Duloxetine	3	1360	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.38, -0.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.13.2 Milnacipran	5	4084	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.18, -0.05]
1.14 Tenderness	5	1444	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.33, -0.09]
1.14.1 Duloxetine	4	1364	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.35, -0.12]
1.14.2 Milnacipran	1	80	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.31, 0.56]
1.15 Withdrawal due to lack of efficacy	14	6924	Risk Difference (IV, Random, 95% CI)	-0.03 [-0.04, -0.02]
1.15.1 Desvenlafaxine	1	82	Risk Difference (IV, Random, 95% CI)	0.07 [-0.02, 0.16]
1.15.2 Duloxetine	7	2642	Risk Difference (IV, Random, 95% CI)	-0.04 [-0.06, -0.02]
1.15.3 Milnacipran	6	4200	Risk Difference (IV, Random, 95% CI)	-0.02 [-0.04, -0.01]
1.16 Nausea	12	6606	Risk Difference (IV, Random, 95% CI)	0.16 [0.14, 0.19]
1.16.1 Desvenlafaxine	1	82	Risk Difference (IV, Random, 95% CI)	0.04 [-0.10, 0.18]
1.16.2 Duloxetine	6	2432	Risk Difference (IV, Random, 95% CI)	0.19 [0.15, 0.22]
1.16.3 Milnacipran	5	4092	Risk Difference (IV, Random, 95% CI)	0.15 [0.12, 0.18]
1.17 Somnolence	7	2514	Risk Difference (IV, Random, 95% CI)	0.05 [0.02, 0.08]
1.17.1 Desvenlafaxine	1	82	Risk Difference (IV, Random, 95% CI)	-0.05 [-0.17, 0.06]
1.17.2 Duloxetine	6	2432	Risk Difference (IV, Random, 95% CI)	0.06 [0.03, 0.09]
1.18 Insomnia	9	5387	Risk Difference (M-H, Random, 95% CI)	0.03 [0.01, 0.04]
1.18.1 Desvenlafaxine	1	82	Risk Difference (M-H, Random, 95% CI)	-0.08 [-0.18, 0.03]
1.18.2 Duloxetine	4	1684	Risk Difference (M-H, Random, 95% CI)	0.04 [0.01, 0.07]
1.18.3 Milnacipran	4	3621	Risk Difference (M-H, Random, 95% CI)	0.03 [0.01, 0.04]

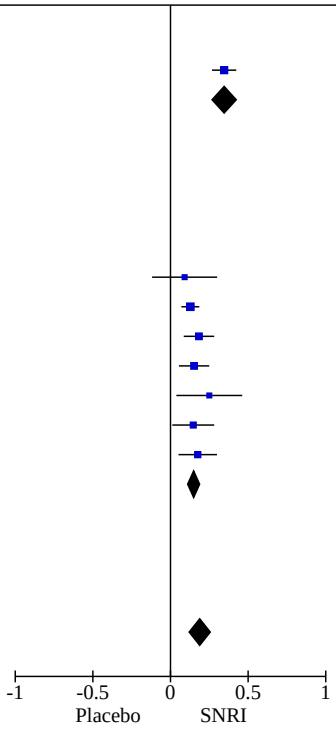
Analysis 1.1. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 1: Self-reported pain relief of 50% or greater

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.1.1 Duloxetine						
Arnold 2004	29	104	17	103	3.5%	0.11 [0.00 , 0.23]
Arnold 2005	95	230	27	118	4.5%	0.18 [0.09 , 0.28]
Arnold 2010a	83	249	52	248	7.3%	0.12 [0.05 , 0.20]
Arnold 2012a	57	155	55	153	3.8%	0.01 [-0.10 , 0.12]
Chappell 2009a	37	158	30	167	5.7%	0.05 [-0.03 , 0.14]
Murakami 2015	66	195	48	195	5.4%	0.09 [0.00 , 0.18]
Russell 2008	126	368	30	139	6.2%	0.13 [0.04 , 0.21]
Subtotal (95% CI)		**1459**		**1123**	**36.4%**	**0.10 [0.06 , 0.14]**
Total events:	493		259			
Heterogeneity: Tau² = 0.00; Chi² = 7.41, df = 6 (P = 0.28); I² = 19%						
Test for overall effect: Z = 5.19 (P < 0.00001)						
1.1.2 Milnacipran						
Arnold 2010b	143	516	92	509	16.8%	0.10 [0.05 , 0.15]
Bateman 2013	20	79	3	21	1.4%	0.11 [-0.07 , 0.29]
Branco 2010	112	430	88	446	14.2%	0.06 [0.01 , 0.12]
Clauw 2008	224	795	75	401	18.0%	0.09 [0.05 , 0.14]
Matthey 2013	10	40	7	40	1.4%	0.08 [-0.10 , 0.25]
Mease 2009b	241	665	58	223	9.4%	0.10 [0.03 , 0.17]
Staud 2015	4	23	3	23	1.0%	0.04 [-0.16 , 0.25]
Vitton 2004	27	97	6	28	1.4%	0.06 [-0.11 , 0.24]
Subtotal (95% CI)		**2645**		**1691**	**63.6%**	**0.09 [0.06 , 0.11]**
Total events:	781		332			
Heterogeneity: Tau² = 0.00; Chi² = 1.44, df = 7 (P = 0.98); I² = 0%						
Test for overall effect: Z = 6.55 (P < 0.00001)						
Total (95% CI)		**4104**		**2814**	**100.0%**	**0.09 [0.07 , 0.11]**
Total events:	1274		591			
Heterogeneity: Tau² = 0.00; Chi² = 9.34, df = 14 (P = 0.81); I² = 0%						
Test for overall effect: Z = 8.74 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%						



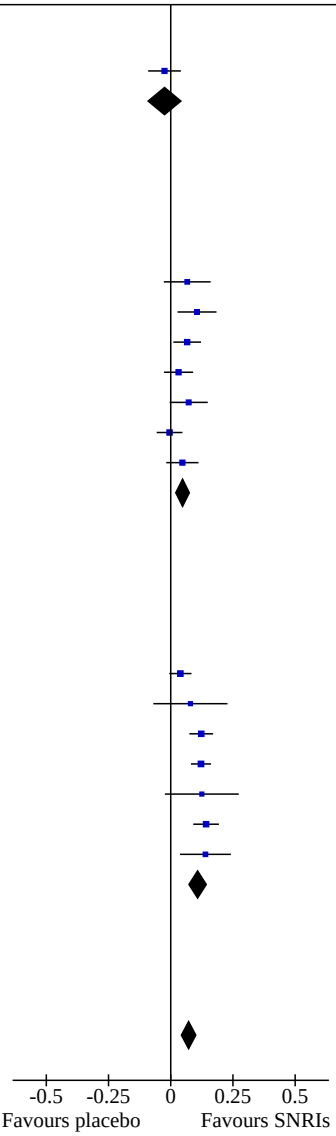
Analysis 1.2. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 2: PGIC much or very much improved

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
1.2.1 Duloxetine						
Arnold 2010a	150	263	60	267	16.1%	0.35 [0.27 , 0.42]
Subtotal (95% CI)		**263**		**267**	**16.1%**	**0.35 [0.27 , 0.42]**
Total events:	150		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.68 (P < 0.00001)						
1.2.2 Milnacipran						
Bateman 2013	26	79	5	21	6.9%	0.09 [-0.12 , 0.30]
Branco 2010	148	443	92	446	17.8%	0.13 [0.07 , 0.19]
Clauw 2008	130	255	47	144	14.3%	0.18 [0.09 , 0.28]
Clauw 2008	127	263	48	145	14.4%	0.15 [0.05 , 0.25]
Matthey 2013	24	40	14	40	6.8%	0.25 [0.04 , 0.46]
Mease 2009b	97	128	44	72	11.3%	0.15 [0.01 , 0.28]
Mease 2009b	186	239	44	73	12.2%	0.18 [0.05 , 0.30]
Subtotal (95% CI)		**1447**		**941**	**83.9%**	**0.15 [0.11 , 0.19]**
Total events:	738		294			
Heterogeneity: Tau² = 0.00; Chi² = 2.35, df = 6 (P = 0.89); I² = 0%						
Test for overall effect: Z = 7.58 (P < 0.00001)						
Total (95% CI)		**1710**		**1208**	**100.0%**	**0.19 [0.12 , 0.26]**
Total events:	888		354			
Heterogeneity: Tau² = 0.01; Chi² = 21.94, df = 7 (P = 0.003); I² = 68%						
Test for overall effect: Z = 5.43 (P < 0.00001)						
Test for subgroup differences: Chi² = 19.60, df = 1 (P < 0.00001), I² = 94.9%						



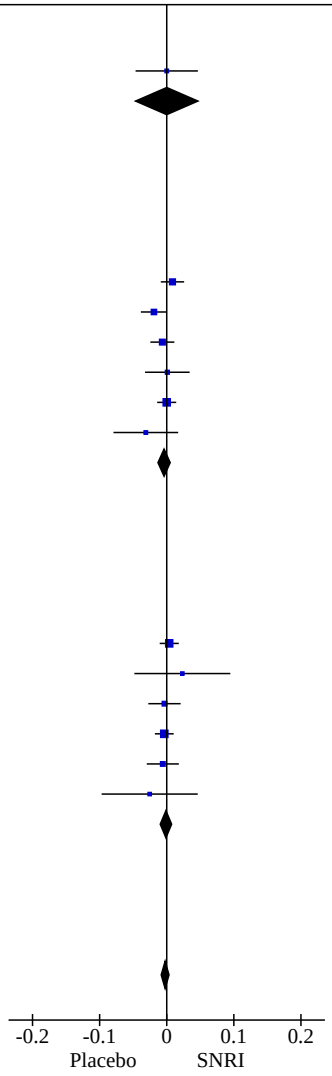
Analysis 1.3. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 3: Withdrawal due to adverse events

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.3.1 Desvenlafaxine						
NCT00697787	0	42	1	40	7.0%	-0.03 [-0.09 , 0.04]
Subtotal (95% CI)		**42**		**40**	**7.0%**	**-0.03 [-0.09 , 0.04]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
1.3.2 Duloxetine						
Arnold 2004	18	104	11	103	5.1%	0.07 [-0.03 , 0.16]
Arnold 2005	52	234	14	120	6.1%	0.11 [0.03 , 0.18]
Arnold 2010a	41	263	24	267	7.8%	0.07 [0.01 , 0.12]
Arnold 2012a	14	155	9	153	7.6%	0.03 [-0.03 , 0.09]
Chappell 2009a	30	162	19	168	6.2%	0.07 [-0.00 , 0.15]
Murakami 2015	14	196	15	197	8.2%	-0.00 [-0.06 , 0.05]
Russell 2008	62	376	17	144	7.1%	0.05 [-0.02 , 0.11]
Subtotal (95% CI)		**1490**		**1152**	**48.2%**	**0.05 [0.02 , 0.07]**
Total events:	231		109			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.27$, df = 6 (P = 0.30); $I^2 = 18\%$						
Test for overall effect: Z = 3.42 (P = 0.0006)						
1.3.3 Milnacipran						
Arnold 2010b	92	516	71	509	8.8%	0.04 [-0.01 , 0.08]
Bateman 2013	15	86	2	21	2.8%	0.08 [-0.07 , 0.23]
Branco 2010	96	435	44	449	8.5%	0.12 [0.07 , 0.17]
Clauw 2008	172	795	38	401	9.1%	0.12 [0.08 , 0.16]
Matthey 2013	8	40	3	40	2.8%	0.13 [-0.02 , 0.27]
Mease 2009b	163	665	23	223	8.2%	0.14 [0.09 , 0.19]
Vitton 2004	17	97	1	28	4.6%	0.14 [0.04 , 0.24]
Subtotal (95% CI)		**2634**		**1671**	**44.8%**	**0.11 [0.07 , 0.14]**
Total events:	563		182			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 12.19$, df = 6 (P = 0.06); $I^2 = 51\%$						
Test for overall effect: Z = 6.09 (P < 0.00001)						
Total (95% CI)		**4166**		**2863**	**100.0%**	**0.07 [0.04 , 0.10]**
Total events:	794		292			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 41.42$, df = 14 (P = 0.0002); $I^2 = 66\%$						
Test for overall effect: Z = 4.88 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 14.54$, df = 2 (P = 0.0007), $I^2 = 86.2\%$						



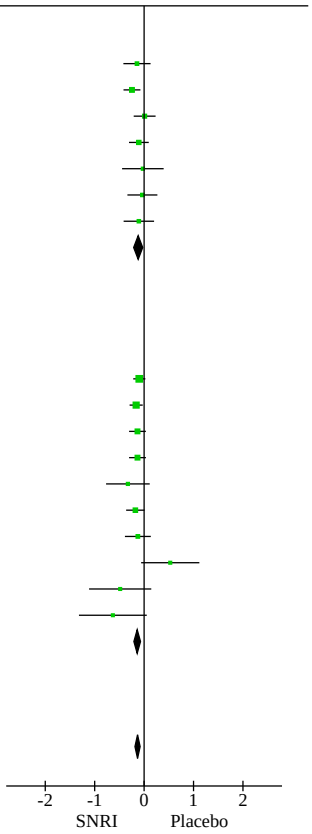
Analysis 1.4. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 4: Serious adverse events

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.4.1 Desvenlafaxine						
NCT00697787	0	42	0	40	1.6%	0.00 [-0.05 , 0.05]
Subtotal (95% CI)		**42**		**40**	**1.6%**	**0.00 [-0.05 , 0.05]**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.4.2 Duloxetine						
Arnold 2005	2	234	0	120	11.1%	0.01 [-0.01 , 0.03]
Arnold 2010a	1	267	6	263	8.8%	-0.02 [-0.04 , 0.00]
Arnold 2012a	0	155	1	153	10.5%	-0.01 [-0.02 , 0.01]
Chappell 2009a	4	162	4	168	3.0%	0.00 [-0.03 , 0.03]
Murakami 2015	1	196	1	194	16.7%	-0.00 [-0.01 , 0.01]
Russell 2008	17	376	11	144	1.4%	-0.03 [-0.08 , 0.02]
Subtotal (95% CI)		**1390**		**1042**	**51.6%**	**-0.00 [-0.01 , 0.01]**
Total events:	25		23			
Heterogeneity: Tau² = 0.00; Chi² = 5.97, df = 5 (P = 0.31); I² = 16%						
Test for overall effect: Z = 0.85 (P = 0.39)						
1.4.3 Milnacipran						
Arnold 2010b	8	516	6	509	16.6%	0.00 [-0.01 , 0.02]
Bateman 2013	2	86	0	21	0.7%	0.02 [-0.05 , 0.09]
Branco 2010	14	431	16	446	5.8%	-0.00 [-0.03 , 0.02]
Clauw 2008	9	795	6	401	17.2%	-0.00 [-0.02 , 0.01]
Mease 2009b	14	665	6	223	5.9%	-0.01 [-0.03 , 0.02]
Vitton 2004	1	97	1	28	0.7%	-0.03 [-0.10 , 0.05]
Subtotal (95% CI)		**2590**		**1628**	**46.8%**	**-0.00 [-0.01 , 0.01]**
Total events:	48		35			
Heterogeneity: Tau² = 0.00; Chi² = 1.64, df = 5 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Total (95% CI)		**4022**		**2710**	**100.0%**	**-0.00 [-0.01 , 0.00]**
Total events:	73		58			
Heterogeneity: Tau² = 0.00; Chi² = 7.78, df = 12 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.82 (P = 0.41)						
Test for subgroup differences: Chi² = 0.20, df = 2 (P = 0.90), I² = 0%						



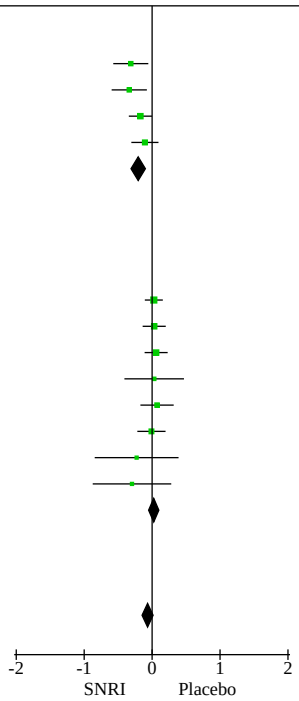
Analysis 1.5. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 5: Self-reported fatigue

Study or Subgroup	SNRI Mean	SNRI SD	SNRI Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.1 Duloxetine								
Arnold 2004	-1.3	2.9	101	-0.88	2.9	103	3.6%	-0.14 [-0.42 , 0.13]
Arnold 2010a	-2.2	3.2	263	-1.4	3.3	267	9.3%	-0.25 [-0.42 , -0.07]
Chappell 2009a	-0.33	3.7	152	-0.37	3.7	162	5.5%	0.01 [-0.21 , 0.23]
Murakami 2015	-1.96	4.7	191	-1.45	4.9	195	6.8%	-0.11 [-0.31 , 0.09]
Russell 2008	-1.79	3.9	79	-1.69	4.1	30	1.5%	-0.03 [-0.45 , 0.40]
Russell 2008	-1.83	4	150	-1.69	4.1	58	3.0%	-0.03 [-0.34 , 0.27]
Russell 2008	-2.12	4	147	-1.69	4.1	56	2.9%	-0.11 [-0.41 , 0.20]
Subtotal (95% CI)			**1083**			**871**	**32.6%**	**-0.12 [-0.21 , -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 3.98, df = 6 (P = 0.68); I² = 0%								
Test for overall effect: Z = 2.58 (P = 0.010)								
1.5.2 Milnacpran								
Arnold 2010b	-4.31	17.5	516	-2.61	17.4	509	18.1%	-0.10 [-0.22 , 0.03]
Branco 2010	-5.94	15.1	430	-3.53	14.8	446	15.4%	-0.16 [-0.29 , -0.03]
Clauw 2008	-5.4	11.9	399	-3.8	12	201	9.4%	-0.13 [-0.30 , 0.04]
Clauw 2008	-5.4	11.9	396	-3.8	12	200	9.4%	-0.13 [-0.30 , 0.04]
Matthey 2013	61	15.9	40	66.2	15.5	40	1.4%	-0.33 [-0.77 , 0.11]
Mease 2009b	-5.8	14	441	-3.4	12.1	148	7.8%	-0.18 [-0.36 , 0.01]
Mease 2009b	-5	12.8	224	-3.4	12.1	75	4.0%	-0.13 [-0.39 , 0.14]
Staud 2015	4.9	2.5	23	3.5	2.7	23	0.8%	0.53 [-0.06 , 1.12]
Vitton 2004	-2	2.6	42	-0.7	2.8	13	0.7%	-0.48 [-1.11 , 0.14]
Vitton 2004	-2.4	2.6	37	-0.7	2.8	11	0.6%	-0.63 [-1.32 , 0.05]
Subtotal (95% CI)			**2548**			**1666**	**67.4%**	**-0.14 [-0.21 , -0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 9.51, df = 9 (P = 0.39); I² = 5%								
Test for overall effect: Z = 4.10 (P < 0.0001)								
Total (95% CI)			**3631**			**2537**	**100.0%**	**-0.13 [-0.18 , -0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 13.60, df = 16 (P = 0.63); I² = 0%								
Test for overall effect: Z = 5.00 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%								



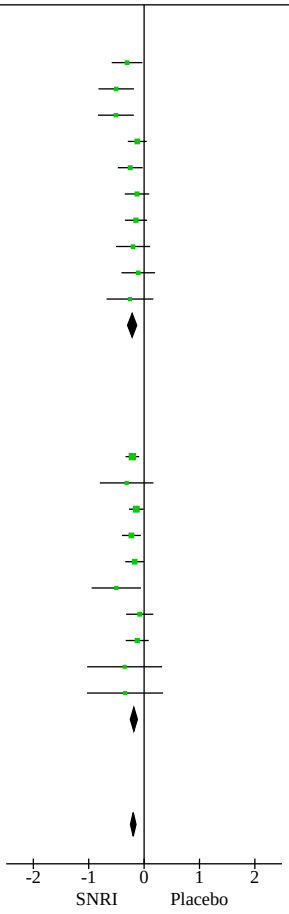
Analysis 1.6. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 6: Self-reported sleep problems

Study or Subgroup	SNRI Mean	SNRI SD	SNRI Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.6.1 Duloxetine								
Arnold 2005	-2.67	3.1	116	-1.71	3	118	7.2%	-0.31 [-0.57 , -0.06]
Arnold 2005	-2.69	3.1	114	-1.71	2.7	118	7.1%	-0.34 [-0.60 , -0.08]
Arnold 2010a	-2	2.9	263	-1.5	2.9	267	12.1%	-0.17 [-0.34 , -0.00]
Murakami 2015	-1.96	4.7	191	-1.45	4.9	195	10.1%	-0.11 [-0.31 , 0.09]
Subtotal (95% CI)			**684**			**698**	**36.5%**	**-0.20 [-0.31 , -0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 2.76, df = 3 (P = 0.43); I² = 0%								
Test for overall effect: Z = 3.79 (P = 0.0001)								
1.6.2 Milnacipran								
Branco 2010	-6.9	20.1	430	-7.4	19.6	446	15.4%	0.03 [-0.11 , 0.16]
Clauw 2008	-2.3	23.1	396	-3	22	200	12.1%	0.03 [-0.14 , 0.20]
Clauw 2008	-1.7	21.9	399	-3	22	201	12.2%	0.06 [-0.11 , 0.23]
Matthey 2013	-52.3	19	40	-52.9	19.8	40	3.0%	0.03 [-0.41 , 0.47]
Mease 2009b	1.7	22.2	441	0.1	20.6	75	7.7%	0.07 [-0.17 , 0.32]
Mease 2009b	-0.1	20.2	224	0.1	20.6	148	9.6%	-0.01 [-0.22 , 0.20]
Vitton 2004	-1.3	3.6	46	-0.5	2.9	13	1.6%	-0.23 [-0.84 , 0.39]
Vitton 2004	-1.3	2.6	51	-0.5	2.9	15	1.8%	-0.30 [-0.87 , 0.28]
Subtotal (95% CI)			**2027**			**1138**	**63.5%**	**0.02 [-0.05 , 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 2.25, df = 7 (P = 0.95); I² = 0%								
Test for overall effect: Z = 0.62 (P = 0.53)								
Total (95% CI)			**2711**			**1836**	**100.0%**	**-0.07 [-0.15 , 0.01]**
Heterogeneity: Tau² = 0.01; Chi² = 16.92, df = 11 (P = 0.11); I² = 35%								
Test for overall effect: Z = 1.61 (P = 0.11)								
Test for subgroup differences: Chi² = 11.92, df = 1 (P = 0.0006), I² = 91.6%								



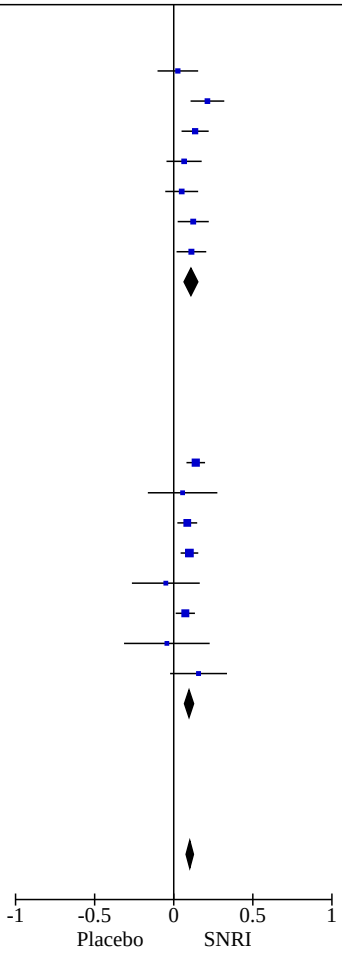
Analysis 1.7. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 7: Self-reported health-related quality of life

Study or Subgroup	SNRI Mean	SNRI SD	SNRI Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.7.1 Duloxetine								
Arnold 2004	-13.46	18.3	101	-7.93	17.5	102	3.2%	-0.31 [-0.58 , -0.03]
Arnold 2005	-16.72	16.6	114	-8.35	16.4	58	2.4%	-0.50 [-0.82 , -0.18]
Arnold 2005	-16.81	16.6	112	-8.35	16.4	57	2.4%	-0.51 [-0.83 , -0.19]
Arnold 2010a	-6	9.7	263	-4.8	9.8	267	8.5%	-0.12 [-0.29 , 0.05]
Arnold 2012a	-14.78	17.6	155	-10.39	17.4	153	4.9%	-0.25 [-0.47 , -0.03]
Chappell 2009a	-7.96	17	153	-5.81	16.5	163	5.1%	-0.13 [-0.35 , 0.09]
Murakami 2015	-18.41	35.5	191	-13.05	37.1	195	6.2%	-0.15 [-0.35 , 0.05]
Russell 2008	-13.86	17	147	-10.42	17.5	56	2.6%	-0.20 [-0.51 , 0.11]
Russell 2008	-12.28	17.6	150	-10.42	17.5	58	2.7%	-0.11 [-0.41 , 0.20]
Russell 2008	-14.77	16.7	79	-10.42	17.5	30	1.4%	-0.26 [-0.68 , 0.17]
Subtotal (95% CI)			**1465**			**1139**	**39.3%**	**-0.22 [-0.30 , -0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 9.53, df = 9 (P = 0.39); I² = 6%								
Test for overall effect: Z = 5.15 (P < 0.00001)								
1.7.2 Milnacipran								
Arnold 2010b	-12.34	24.8	516	-7.12	24.4	509	16.4%	-0.21 [-0.33 , -0.09]
Bateman 2013	-7.77	21	79	-1.38	16.1	21	1.1%	-0.32 [-0.80 , 0.17]
Branco 2010	-14.18	21.4	430	-11.18	20.9	446	14.0%	-0.14 [-0.27 , -0.01]
Clauw 2008	-16.6	20	399	-12	20	201	8.5%	-0.23 [-0.40 , -0.06]
Clauw 2008	-15.4	19.9	396	-12	20	200	8.5%	-0.17 [-0.34 , -0.00]
Matthey 2013	44.1	20.8	40	54.1	18.6	40	1.2%	-0.50 [-0.95 , -0.06]
Mease 2009b	-16.7	21.6	441	-15	20.5	75	4.1%	-0.08 [-0.32 , 0.17]
Mease 2009b	-17.7	22.5	224	-15	20.5	148	5.7%	-0.12 [-0.33 , 0.08]
Vitton 2004	-10.5	14.5	37	-5.4	13.4	11	0.5%	-0.35 [-1.03 , 0.33]
Vitton 2004	-10.3	14.1	33	-5.4	13.4	11	0.5%	-0.35 [-1.03 , 0.34]
Subtotal (95% CI)			**2595**			**1662**	**60.7%**	**-0.19 [-0.25 , -0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 4.60, df = 9 (P = 0.87); I² = 0%								
Test for overall effect: Z = 5.69 (P < 0.00001)								
Total (95% CI)			**4060**			**2801**	**100.0%**	**-0.20 [-0.25 , -0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 14.43, df = 19 (P = 0.76); I² = 0%								
Test for overall effect: Z = 7.74 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%								



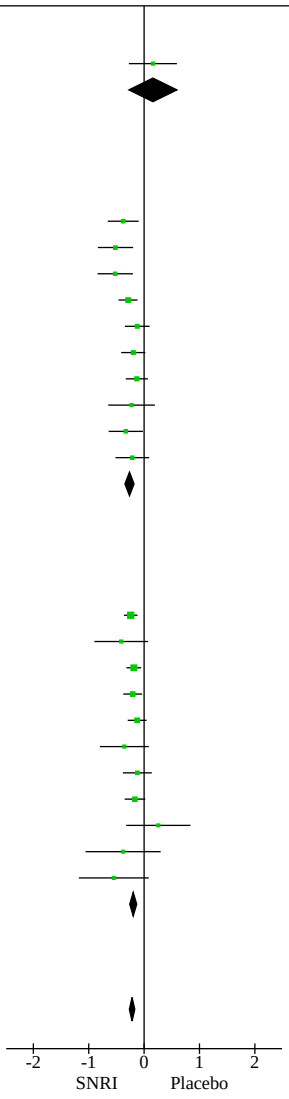
Analysis 1.8. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 8: Self-reported pain relief of 30% or greater

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.8.1 Duloxetine						
Arnold 2004	34	101	32	103	3.2%	0.03 [-0.10 , 0.15]
Arnold 2005	125	230	39	118	4.6%	0.21 [0.11 , 0.32]
Arnold 2010a	119	249	85	248	7.2%	0.14 [0.05 , 0.22]
Arnold 2012a	77	155	66	153	4.3%	0.07 [-0.05 , 0.18]
Chappell 2009a	60	158	55	167	4.9%	0.05 [-0.05 , 0.15]
Murakami 2015	96	191	74	195	5.4%	0.12 [0.02 , 0.22]
Russell 2008	183	376	54	144	6.0%	0.11 [0.02 , 0.21]
Subtotal (95% CI)		**1460**		**1128**	**35.5%**	**0.11 [0.07 , 0.15]**
Total events:	694		405			
Heterogeneity: Tau² = 0.00; Chi² = 7.52, df = 6 (P = 0.28); I² = 20%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
1.8.2 Milnacipran						
Arnold 2010b	230	516	156	509	15.3%	0.14 [0.08 , 0.20]
Bateman 2013	27	79	6	21	1.1%	0.06 [-0.16 , 0.28]
Branco 2010	166	430	134	446	13.4%	0.09 [0.02 , 0.15]
Clauw 2008	307	795	115	401	16.9%	0.10 [0.04 , 0.16]
Matthey 2013	15	40	17	40	1.1%	-0.05 [-0.26 , 0.16]
Mease 2009b	171	665	41	223	14.3%	0.07 [0.01 , 0.13]
Staud 2015	7	23	8	23	0.7%	-0.04 [-0.31 , 0.23]
Vitton 2004	36	97	6	28	1.6%	0.16 [-0.02 , 0.34]
Subtotal (95% CI)		**2645**		**1691**	**64.5%**	**0.10 [0.07 , 0.13]**
Total events:	959		483			
Heterogeneity: Tau² = 0.00; Chi² = 6.11, df = 7 (P = 0.53); I² = 0%						
Test for overall effect: Z = 6.63 (P < 0.00001)						
Total (95% CI)		**4105**		**2819**	**100.0%**	**0.10 [0.08 , 0.12]**
Total events:	1653		888			
Heterogeneity: Tau² = 0.00; Chi² = 13.91, df = 14 (P = 0.46); I² = 0%						
Test for overall effect: Z = 8.66 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%						



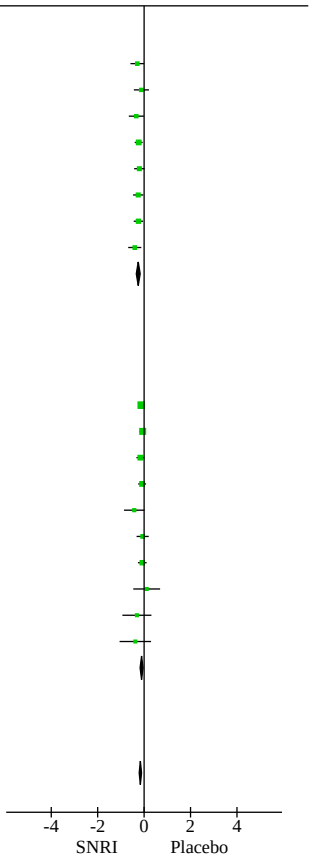
Analysis 1.9. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 9: Self-reported mean pain intensity

Study or Subgroup	SNRI Mean	SNRI SD	SNRI Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.9.1 Desvenlafaxine								
NCT00697787	-1.6	2.4	42	-1.98	2.34	40	1.3%	0.16 [-0.27 , 0.59]
Subtotal (95% CI)			**42**			**40**	**1.3%**	**0.16 [-0.27 , 0.59]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.72 (P = 0.47)								
1.9.2 Duloxetine								
Arnold 2004	-1.83	2.4	100	-0.94	2.3	102	3.1%	-0.38 [-0.66 , -0.10]
Arnold 2005	-2.39	2.4	116	-1.16	2.3	59	2.4%	-0.52 [-0.84 , -0.20]
Arnold 2005	-2.4	2.4	114	-1.16	2.3	59	2.4%	-0.52 [-0.84 , -0.20]
Arnold 2010a	-2.3	2.7	263	-1.5	2.8	267	8.2%	-0.29 [-0.46 , -0.12]
Arnold 2012a	-2.14	2.5	155	-1.83	2.5	153	4.8%	-0.12 [-0.35 , 0.10]
Chappell 2009a	-1.62	2.5	158	-1.13	2.5	167	5.0%	-0.20 [-0.41 , 0.02]
Murakami 2015	-1.38	3.5	191	-0.92	3.5	195	6.0%	-0.13 [-0.33 , 0.07]
Russell 2008	-2	2.5	79	-1.43	2.5	30	1.3%	-0.23 [-0.65 , 0.20]
Russell 2008	-2.26	2.5	147	-1.43	2.5	56	2.5%	-0.33 [-0.64 , -0.02]
Russell 2008	-1.98	2.6	150	-1.43	2.5	58	2.6%	-0.21 [-0.52 , 0.09]
Subtotal (95% CI)			**1473**			**1146**	**38.3%**	**-0.26 [-0.35 , -0.18]**
Heterogeneity: Tau² = 0.00; Chi² = 9.57, df = 9 (P = 0.39); I² = 6%								
Test for overall effect: Z = 6.29 (P < 0.00001)								
1.9.3 Milncipran								
Arnold 2010b	-17.7	27.9	516	-10.76	29.3	509	15.9%	-0.24 [-0.37 , -0.12]
Bateman 2013	-12.3	27.3	79	-1.3	22.6	21	1.0%	-0.41 [-0.90 , 0.07]
Branco 2010	-16.5	24.5	430	-11.97	24.1	446	13.6%	-0.19 [-0.32 , -0.05]
Clauw 2008	-17.4	21.9	396	-13	20	200	8.2%	-0.21 [-0.38 , -0.04]
Clauw 2008	-15.7	22	399	-13	20	201	8.3%	-0.13 [-0.30 , 0.04]
Matthey 2013	39.6	23.1	40	48.3	25.1	40	1.2%	-0.36 [-0.80 , 0.08]
Mease 2009b	53.2	24.6	223	56.2	23.9	75	3.5%	-0.12 [-0.38 , 0.14]
Mease 2009b	52.2	24.4	441	56.2	23.9	148	6.9%	-0.16 [-0.35 , 0.02]
Staud 2015	5.1	2.3	23	4.5	2.3	23	0.7%	0.26 [-0.32 , 0.84]
Vitton 2004	-1.9	2.9	37	-0.8	2.7	11	0.5%	-0.38 [-1.06 , 0.30]
Vitton 2004	-2.3	2.7	42	-0.8	2.7	13	0.6%	-0.55 [-1.18 , 0.08]
Subtotal (95% CI)			**2626**			**1687**	**60.5%**	**-0.20 [-0.26 , -0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 6.73, df = 10 (P = 0.75); I² = 0%								
Test for overall effect: Z = 6.13 (P < 0.00001)								
Total (95% CI)			**4141**			**2873**	**100.0%**	**-0.22 [-0.27 , -0.17]**
Heterogeneity: Tau² = 0.00; Chi² = 20.86, df = 21 (P = 0.47); I² = 0%								
Test for overall effect: Z = 8.70 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.54, df = 2 (P = 0.10), I² = 55.9%								



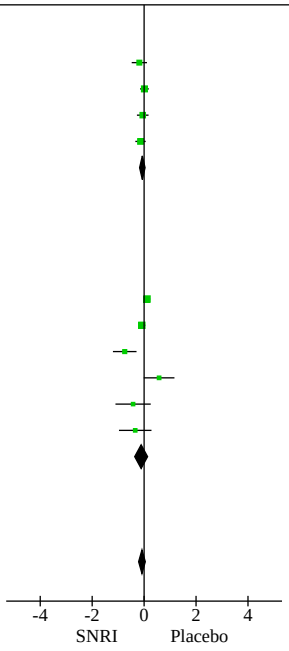
Analysis 1.10. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 10: Self-reported depression

Study or Subgroup	SNRI Mean	SNRI SD	SNRI Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.10.1 Duloxetine								
Arnold 2004	-3.32	8	88	-1.02	7.7	89	2.9%	-0.29 [-0.59 , 0.00]
Arnold 2005	-2.79	4.7	110	-2.24	4.7	54	2.4%	-0.12 [-0.44 , 0.21]
Arnold 2005	-3.79	4.6	111	-2.24	4.7	55	2.4%	-0.33 [-0.66 , -0.01]
Arnold 2010a	-5.5	8.1	263	-3.6	8.2	267	8.8%	-0.23 [-0.40 , -0.06]
Arnold 2012a	-5.47	7.6	155	-3.91	7.6	153	5.1%	-0.20 [-0.43 , 0.02]
Chappell 2009a	-3.42	7.7	154	-1.45	7.8	164	5.2%	-0.25 [-0.47 , -0.03]
Murakami 2015	-4.09	11.6	191	-1.19	11.9	195	6.4%	-0.25 [-0.45 , -0.05]
Russell 2008	-7.26	7	76	-3.91	8.9	139	3.2%	-0.40 [-0.69 , -0.12]
Subtotal (95% CI)			**1148**			**1116**	**36.4%**	**-0.25 [-0.34 , -0.17]**
Heterogeneity: Tau² = 0.00; Chi² = 2.30, df = 7 (P = 0.94); I² = 0%								
Test for overall effect: Z = 5.92 (P < 0.00001)								
1.10.2 Milnacipran								
Arnold 2010b	-2.12	7	516	-1.24	7	509	17.0%	-0.13 [-0.25 , -0.00]
Branco 2010	-0.74	7.5	430	-0.29	7.2	446	14.6%	-0.06 [-0.19 , 0.07]
Clauw 2008	-3.6	8	396	-2.3	8	200	8.8%	-0.16 [-0.33 , 0.01]
Clauw 2008	-3	8	399	-2.3	8	201	8.9%	-0.09 [-0.26 , 0.08]
Matthey 2013	10.8	9.9	40	15	9.7	40	1.3%	-0.42 [-0.87 , 0.02]
Mease 2009b	-2.8	7.8	224	-2.3	8.3	75	3.7%	-0.06 [-0.32 , 0.20]
Mease 2009b	-3	8.9	441	-2.3	8.3	148	7.4%	-0.08 [-0.27 , 0.11]
Staud 2015	2.6	2.7	23	2.3	2.6	23	0.8%	0.11 [-0.47 , 0.69]
Vitton 2004	-1.5	2.9	42	-0.6	2.7	13	0.7%	-0.31 [-0.94 , 0.31]
Vitton 2004	-1.7	2.9	37	-0.6	2.7	11	0.6%	-0.38 [-1.06 , 0.30]
Subtotal (95% CI)			**2548**			**1666**	**63.6%**	**-0.11 [-0.17 , -0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 4.73, df = 9 (P = 0.86); I² = 0%								
Test for overall effect: Z = 3.37 (P = 0.0007)								
Total (95% CI)			**3696**			**2782**	**100.0%**	**-0.16 [-0.21 , -0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 14.23, df = 17 (P = 0.65); I² = 0%								
Test for overall effect: Z = 6.26 (P < 0.00001)								
Test for subgroup differences: Chi² = 7.21, df = 1 (P = 0.007), I² = 86.1%								



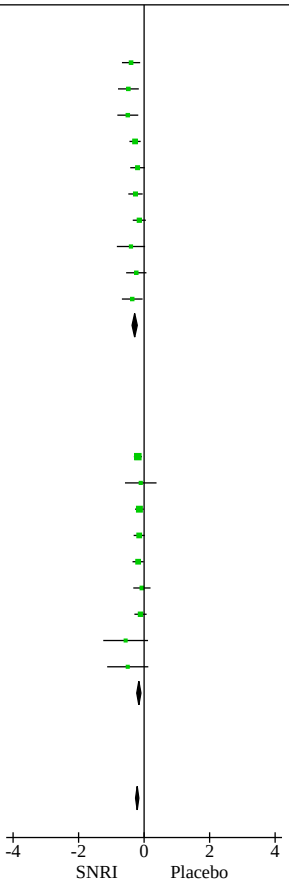
Analysis 1.11. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 11: Self-reported anxiety

Study or Subgroup	SNRI Mean	SNRI SD	SNRI Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.11.1 Duloxetine								
Arnold 2004	-2.6	6.7	93	-1.39	6.4	86	9.8%	-0.18 [-0.48 , 0.11]
Arnold 2010a	-3.1	8.1	263	-3.2	8.2	267	14.8%	0.01 [-0.16 , 0.18]
Arnold 2012a	-3.76	8.5	155	-3.31	8.4	153	12.5%	-0.05 [-0.28 , 0.17]
Murakami 2015	-1.86	4.8	191	-1.18	5	195	13.5%	-0.14 [-0.34 , 0.06]
Subtotal (95% CI)			**702**			**701**	**50.5%**	**-0.07 [-0.17 , 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 1.94, df = 3 (P = 0.58); I² = 0%								
Test for overall effect: Z = 1.28 (P = 0.20)								
1.11.2 Milnacipran								
Arnold 2010b	-0.7	9	516	-1.7	9	509	16.9%	0.11 [-0.01 , 0.23]
Branco 2010	-0.96	11.2	430	0.01	11	446	16.5%	-0.09 [-0.22 , 0.05]
Matthey 2013	38.7	13.6	40	49.1	14	40	5.7%	-0.75 [-1.20 , -0.29]
Staud 2015	3.2	2.7	23	1.7	2.4	23	3.8%	0.58 [-0.01 , 1.17]
Vitton 2004	-1.8	2.9	37	-0.5	3.4	11	3.0%	-0.42 [-1.10 , 0.25]
Vitton 2004	-1.6	3.1	42	-0.5	3.4	13	3.5%	-0.34 [-0.97 , 0.28]
Subtotal (95% CI)			**1088**			**1042**	**49.5%**	**-0.11 [-0.36 , 0.13]**
Heterogeneity: Tau² = 0.05; Chi² = 21.46, df = 5 (P = 0.0007); I² = 77%								
Test for overall effect: Z = 0.90 (P = 0.37)								
Total (95% CI)			**1790**			**1743**	**100.0%**	**-0.08 [-0.21 , 0.05]**
Heterogeneity: Tau² = 0.02; Chi² = 24.12, df = 9 (P = 0.004); I² = 63%								
Test for overall effect: Z = 1.26 (P = 0.21)								
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%								



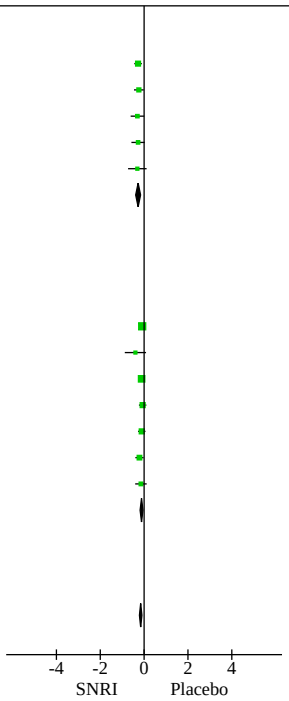
Analysis 1.12. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 12: Self-reported disability

Study or Subgroup	SNRI Mean	SNRI SD	SNRI Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.12.1 Duloxetine								
Arnold 2004	-2.01	2.6	101	-0.95	2.7	102	3.2%	-0.40 [-0.68 , -0.12]
Arnold 2005	-2.57	2.4	116	-1.43	2.3	59	2.5%	-0.48 [-0.80 , -0.16]
Arnold 2005	-2.58	2.3	114	-1.43	2.3	59	2.4%	-0.50 [-0.82 , -0.18]
Arnold 2010a	-2.6	3.2	263	-1.7	3.3	267	8.5%	-0.28 [-0.45 , -0.11]
Arnold 2012a	-2.28	2.5	155	-1.78	2.5	153	4.9%	-0.20 [-0.42 , 0.02]
Chappell 2009a	-1.69	2.5	158	-1.03	2.5	167	5.2%	-0.26 [-0.48 , -0.04]
Murakami 2015	-7.4	29.4	191	-3.04	30.1	195	6.2%	-0.15 [-0.35 , 0.05]
Russell 2008	-2.34	2.4	77	-1.37	2.4	29	1.3%	-0.40 [-0.83 , 0.03]
Russell 2008	-1.98	2.6	144	-1.37	2.4	56	2.6%	-0.24 [-0.55 , 0.07]
Russell 2008	-2.27	2.5	142	-1.37	2.4	54	2.5%	-0.36 [-0.68 , -0.05]
Subtotal (95% CI)			**1461**			**1141**	**39.3%**	**-0.29 [-0.37 , -0.21]**
Heterogeneity: Tau² = 0.00; Chi² = 6.85, df = 9 (P = 0.65); I² = 0%								
Test for overall effect: Z = 7.11 (P < 0.00001)								
1.12.2 Milnacipran								
Arnold 2010b	-1.49	3.2	516	-0.91	2.9	509	16.5%	-0.19 [-0.31 , -0.07]
Bateman 2013	-2.1	6.9	79	-1.43	4.6	21	1.1%	-0.10 [-0.58 , 0.38]
Branco 2010	-1.26	2.3	430	-0.93	2.3	446	14.1%	-0.14 [-0.28 , -0.01]
Clauw 2008	-2.4	6	399	-1.5	6	201	8.6%	-0.15 [-0.32 , 0.02]
Clauw 2008	-2.6	6	396	-1.5	6	200	8.5%	-0.18 [-0.35 , -0.01]
Mease 2009b	-2.99	8.46	223	-2.43	7.74	74	3.6%	-0.07 [-0.33 , 0.20]
Mease 2009b	-3.34	8.42	441	-2.43	7.74	148	7.1%	-0.11 [-0.30 , 0.08]
Vitton 2004	-3.5	5.9	37	0.1	7.5	11	0.5%	-0.56 [-1.25 , 0.12]
Vitton 2004	-3.2	6.2	43	0.1	7.5	13	0.6%	-0.50 [-1.13 , 0.13]
Subtotal (95% CI)			**2564**			**1623**	**60.7%**	**-0.16 [-0.22 , -0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 3.64, df = 8 (P = 0.89); I² = 0%								
Test for overall effect: Z = 4.93 (P < 0.00001)								
Total (95% CI)			**4025**			**2764**	**100.0%**	**-0.21 [-0.26 , -0.16]**
Heterogeneity: Tau² = 0.00; Chi² = 16.49, df = 18 (P = 0.56); I² = 0%								
Test for overall effect: Z = 8.30 (P < 0.00001)								
Test for subgroup differences: Chi² = 6.00, df = 1 (P = 0.01), I² = 83.3%								



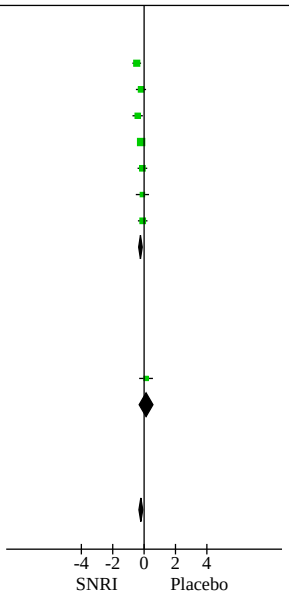
Analysis 1.13. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 13: Self-reported cognitive disturbances

Study or Subgroup	SNRI Mean	SNRI SD	SNRI Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.13.1 Duloxetine								
Arnold 2010a	-2	3.2	263	-1.1	3.3	263	10.5%	-0.28 [-0.45 , -0.10]
Chappell 2009a	-0.99	4.1	153	-0.03	3.9	161	6.3%	-0.24 [-0.46 , -0.02]
Russell 2008	-2.37	4	147	-1.14	4.1	56	3.3%	-0.30 [-0.61 , 0.00]
Russell 2008	-2.29	4.2	150	-1.14	4.1	58	3.4%	-0.27 [-0.58 , 0.03]
Russell 2008	-2.37	3.9	79	-1.14	4.1	30	1.7%	-0.31 [-0.73 , 0.11]
Subtotal (95% CI)			**792**			**568**	**25.2%**	**-0.27 [-0.38 , -0.16]**
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 4 (P = 1.00); I² = 0%								
Test for overall effect: Z = 4.81 (P < 0.00001)								
1.13.2 Milnacipran								
Arnold 2010b	-3.89	17.5	516	-2.36	17.4	509	20.7%	-0.09 [-0.21 , 0.03]
Bateman 2013	-2.39	14.8	79	3.23	10.7	21	1.3%	-0.40 [-0.88 , 0.09]
Branco 2010	-5.88	20.8	430	-3.53	20.3	446	17.7%	-0.11 [-0.25 , 0.02]
Clauw 2008	-3.3	12	399	-2.5	12	201	10.8%	-0.07 [-0.24 , 0.10]
Clauw 2008	-3.8	11.9	395	-2.5	12	200	10.7%	-0.11 [-0.28 , 0.06]
Mease 2009b	-2.68	13.5	441	0.16	12.93	148	8.9%	-0.21 [-0.40 , -0.03]
Mease 2009b	-1.56	11.5	224	0.16	12.93	75	4.5%	-0.14 [-0.41 , 0.12]
Subtotal (95% CI)			**2484**			**1600**	**74.8%**	**-0.12 [-0.18 , -0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 2.90, df = 6 (P = 0.82); I² = 0%								
Test for overall effect: Z = 3.58 (P = 0.0003)								
Total (95% CI)			**3276**			**2168**	**100.0%**	**-0.16 [-0.21 , -0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 8.65, df = 11 (P = 0.65); I² = 0%								
Test for overall effect: Z = 5.51 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.60, df = 1 (P = 0.02), I² = 82.1%								



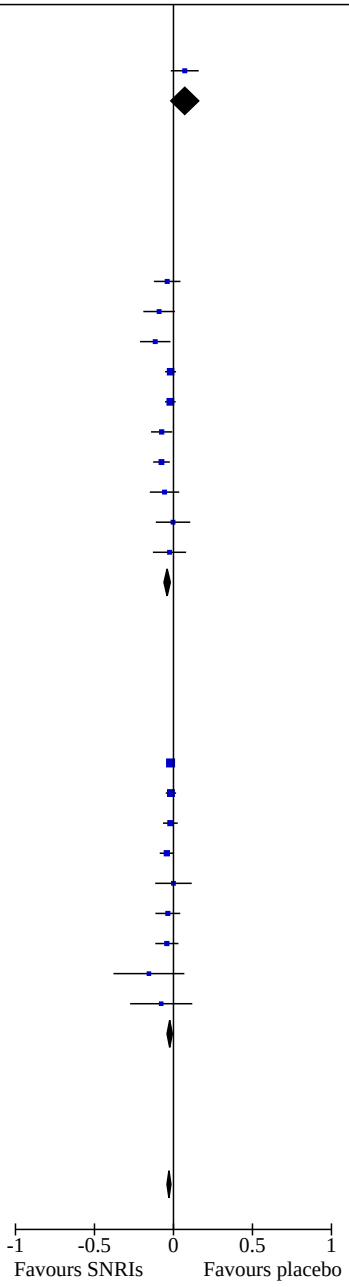
Analysis 1.14. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 14: Tenderness

Study or Subgroup	SNRI Mean	SNRI SD	SNRI Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.14.1 Duloxetine								
Arnold 2004	-0.29	0.7	104	0.04	0.7	103	15.3%	-0.47 [-0.75 , -0.19]
Arnold 2005	-0.22	0.8	111	-0.06	0.8	55	11.8%	-0.20 [-0.52 , 0.12]
Arnold 2005	-0.39	0.8	110	-0.06	0.8	54	11.5%	-0.41 [-0.74 , -0.08]
Chappell 2009a	-0.4	1.1	148	-0.2	1	159	21.1%	-0.19 [-0.41 , 0.03]
Russell 2008	-0.54	1.1	147	-0.42	1.1	56	12.8%	-0.11 [-0.42 , 0.20]
Russell 2008	-0.54	1.1	79	-0.42	1.1	30	7.4%	-0.11 [-0.53 , 0.31]
Russell 2008	-0.52	1.1	150	-0.42	1.1	58	13.2%	-0.09 [-0.39 , 0.21]
Subtotal (95% CI)			**849**			**515**	**93.1%**	**-0.23 [-0.35 , -0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 5.93, df = 6 (P = 0.43); I² = 0%								
Test for overall effect: Z = 4.06 (P < 0.0001)								
1.14.2 Milnacipran								
Matthey 2013	-180.4	74.3	40	-188.9	60.6	40	6.9%	0.12 [-0.31 , 0.56]
Subtotal (95% CI)			**40**			**40**	**6.9%**	**0.12 [-0.31 , 0.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.55 (P = 0.58)								
Total (95% CI)			**889**			**555**	**100.0%**	**-0.21 [-0.33 , -0.09]**
Heterogeneity: Tau² = 0.00; Chi² = 8.32, df = 7 (P = 0.30); I² = 16%								
Test for overall effect: Z = 3.38 (P = 0.0007)								
Test for subgroup differences: Chi² = 2.39, df = 1 (P = 0.12), I² = 58.1%								



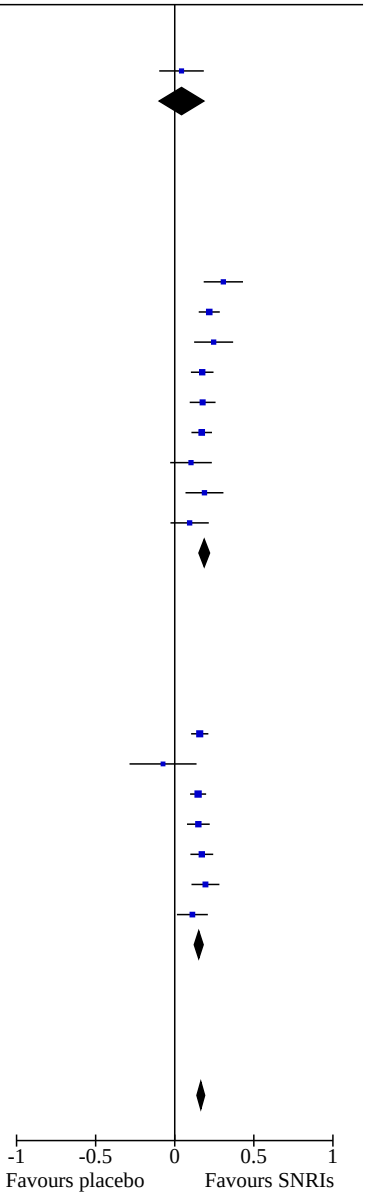
Analysis 1.15. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 15: Withdrawal due to lack of efficacy

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.15.1 Desvenlafaxine						
NCT00697787	3	42	0	40	1.9%	0.07 [-0.02 , 0.16]
Subtotal (95% CI)		**42**		**40**	**1.9%**	**0.07 [-0.02 , 0.16]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
1.15.2 Duloxetine						
Arnold 2004	9	104	13	103	2.1%	-0.04 [-0.12 , 0.04]
Arnold 2005	7	118	9	60	1.5%	-0.09 [-0.19 , 0.01]
Arnold 2005	4	116	9	60	1.6%	-0.12 [-0.21 , -0.02]
Arnold 2010a	9	263	14	267	12.4%	-0.02 [-0.05 , 0.02]
Arnold 2012a	2	155	5	153	13.4%	-0.02 [-0.05 , 0.01]
Chappell 2009a	12	162	25	168	3.3%	-0.07 [-0.14 , -0.01]
Murakami 2015	8	196	23	197	5.4%	-0.08 [-0.13 , -0.02]
Russell 2008	7	147	5	48	1.7%	-0.06 [-0.15 , 0.04]
Russell 2008	8	79	5	48	1.3%	-0.00 [-0.11 , 0.11]
Russell 2008	15	150	6	48	1.4%	-0.02 [-0.13 , 0.08]
Subtotal (95% CI)		**1490**		**1152**	**44.1%**	**-0.04 [-0.06 , -0.02]**
Total events:	81		114			
Heterogeneity: Tau² = 0.00; Chi² = 9.71, df = 9 (P = 0.37); I² = 7%						
Test for overall effect: Z = 3.95 (P < 0.0001)						
1.15.3 Milnacipran						
Arnold 2010b	24	516	33	509	18.7%	-0.02 [-0.05 , 0.01]
Branco 2010	25	435	33	449	14.0%	-0.02 [-0.05 , 0.02]
Clauw 2008	28	401	18	201	6.9%	-0.02 [-0.07 , 0.03]
Clauw 2008	19	396	18	200	7.4%	-0.04 [-0.09 , 0.00]
Matthey 2013	3	40	3	40	1.1%	0.00 [-0.12 , 0.12]
Mease 2009b	26	224	17	112	2.4%	-0.04 [-0.11 , 0.04]
Mease 2009b	49	441	17	111	2.8%	-0.04 [-0.12 , 0.03]
Vitton 2004	3	51	3	14	0.3%	-0.16 [-0.38 , 0.07]
Vitton 2004	3	46	2	14	0.4%	-0.08 [-0.27 , 0.12]
Subtotal (95% CI)		**2550**		**1650**	**54.0%**	**-0.02 [-0.04 , -0.01]**
Total events:	180		144			
Heterogeneity: Tau² = 0.00; Chi² = 3.13, df = 8 (P = 0.93); I² = 0%						
Test for overall effect: Z = 2.83 (P = 0.005)						
Total (95% CI)		**4082**		**2842**	**100.0%**	**-0.03 [-0.04 , -0.02]**
Total events:	264		258			
Heterogeneity: Tau² = 0.00; Chi² = 19.12, df = 19 (P = 0.45); I² = 1%						
Test for overall effect: Z = 4.55 (P < 0.00001)						
Test for subgroup differences: Chi² = 6.51, df = 2 (P = 0.04), I² = 69.3%						



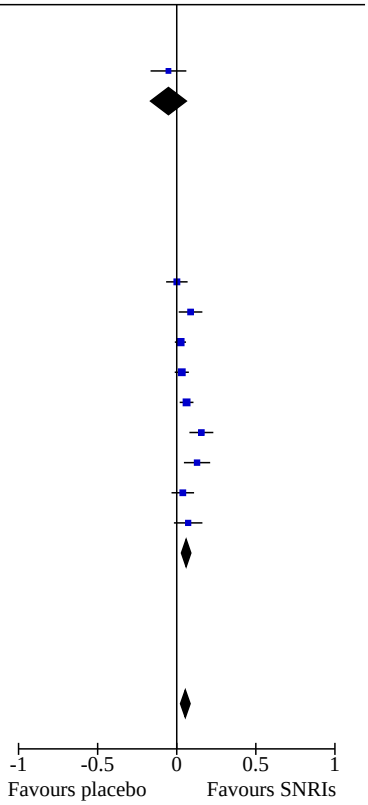
Analysis 1.16. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 16: Nausea

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.16.1 Desvenlafaxine						
NCT00697787	6	42	4	40	2.6%	0.04 [-0.10 , 0.18]
Subtotal (95% CI)		**42**		**40**	**2.6%**	**0.04 [-0.10 , 0.18]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
1.16.2 Duloxetine						
Arnold 2005	52	118	8	60	3.3%	0.31 [0.18 , 0.43]
Arnold 2010a	83	263	26	267	8.5%	0.22 [0.15 , 0.28]
Arnold 2010a	44	116	8	60	3.3%	0.25 [0.12 , 0.37]
Arnold 2012a	33	155	6	153	7.7%	0.17 [0.10 , 0.25]
Chappell 2009a	44	162	16	168	6.4%	0.18 [0.09 , 0.26]
Murakami 2015	42	194	9	196	8.8%	0.17 [0.11 , 0.24]
Russell 2008	18	79	6	48	3.0%	0.10 [-0.03 , 0.23]
Russell 2008	46	147	6	48	3.5%	0.19 [0.07 , 0.31]
Russell 2008	36	150	7	48	3.4%	0.09 [-0.03 , 0.22]
Subtotal (95% CI)		**1384**		**1048**	**47.8%**	**0.19 [0.15 , 0.22]**
Total events:	398		92			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.61$, df = 8 (P = 0.29); $I^2 = 17\%$						
Test for overall effect: Z = 10.95 (P < 0.00001)						
1.16.3 Milnacipran						
Arnold 2010b	189	516	106	509	10.8%	0.16 [0.10 , 0.21]
Bateman 2013	18	85	6	21	1.2%	-0.07 [-0.29 , 0.14]
Branco 2010	112	431	50	446	11.6%	0.15 [0.10 , 0.20]
Clauw 2008	137	399	39	201	7.7%	0.15 [0.08 , 0.22]
Clauw 2008	143	396	38	200	7.6%	0.17 [0.10 , 0.24]
Mease 2009b	177	441	23	111	5.7%	0.19 [0.11 , 0.28]
Mease 2009b	73	224	24	112	4.9%	0.11 [0.01 , 0.21]
Subtotal (95% CI)		**2492**		**1600**	**49.5%**	**0.15 [0.12 , 0.18]**
Total events:	849		286			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.25$, df = 6 (P = 0.40); $I^2 = 4\%$						
Test for overall effect: Z = 10.67 (P < 0.00001)						
Total (95% CI)		**3918**		**2688**	**100.0%**	**0.16 [0.14 , 0.19]**
Total events:	1253		382			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 21.70$, df = 16 (P = 0.15); $I^2 = 26\%$						
Test for overall effect: Z = 13.36 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 5.34$, df = 2 (P = 0.07), $I^2 = 62.5\%$						



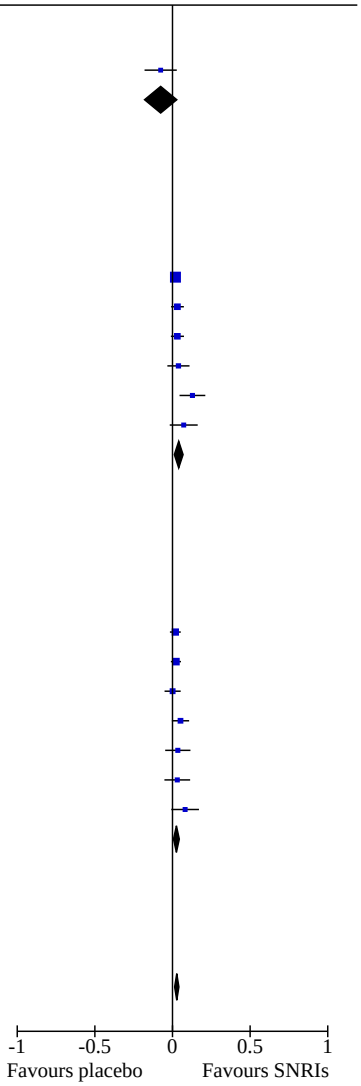
Analysis 1.17. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 17: Somnolence

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.17.1 Desvenlafaxine						
NCT00697787	2	42	4	40	5.2%	-0.05 [-0.17 , 0.06]
Subtotal (95% CI)		**42**		**40**	**5.2%**	**-0.05 [-0.17 , 0.06]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.36)						
1.17.2 Duloxetine						
Arnold 2005	6	118	3	60	9.8%	0.00 [-0.07 , 0.07]
Arnold 2005	14	116	2	60	8.9%	0.09 [0.01 , 0.16]
Arnold 2010a	15	263	9	267	15.4%	0.02 [-0.01 , 0.06]
Arnold 2012a	9	155	4	153	13.7%	0.03 [-0.01 , 0.08]
Chappell 2009a	12	162	2	168	13.9%	0.06 [0.02 , 0.11]
Murakami 2015	51	194	21	196	8.8%	0.16 [0.08 , 0.23]
Russell 2008	25	147	2	48	7.9%	0.13 [0.05 , 0.21]
Russell 2008	12	150	2	48	9.3%	0.04 [-0.03 , 0.11]
Russell 2008	9	79	2	48	7.1%	0.07 [-0.02 , 0.16]
Subtotal (95% CI)		**1384**		**1048**	**94.8%**	**0.06 [0.03 , 0.09]**
Total events:	153		47			
Heterogeneity: Tau² = 0.00; Chi² = 17.36, df = 8 (P = 0.03); I² = 54%						
Test for overall effect: Z = 3.95 (P < 0.0001)						
Total (95% CI)		**1426**		**1088**	**100.0%**	**0.05 [0.02 , 0.08]**
Total events:	155		51			
Heterogeneity: Tau² = 0.00; Chi² = 20.48, df = 9 (P = 0.02); I² = 56%						
Test for overall effect: Z = 3.53 (P = 0.0004)						
Test for subgroup differences: Chi² = 3.52, df = 1 (P = 0.06), I² = 71.6%						



Analysis 1.18. Comparison 1: SNRIs versus placebo in parallel and cross-over design trials, Outcome 18: Insomnia

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
1.18.1 Desvenlafaxine						
NCT00697787	1	42	4	40	1.7%	-0.08 [-0.18 , 0.03]
Subtotal (95% CI)		**42**		**40**	**1.7%**	**-0.08 [-0.18 , 0.03]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.44 (P = 0.15)						
1.18.2 Duloxetine						
Arnold 2010a	5	263	0	263	27.6%	0.02 [0.00 , 0.04]
Arnold 2012a	8	155	3	153	9.2%	0.03 [-0.01 , 0.07]
Chappell 2009a	9	162	4	168	8.8%	0.03 [-0.01 , 0.07]
Russell 2008	12	150	2	48	3.5%	0.04 [-0.03 , 0.11]
Russell 2008	25	147	2	48	2.6%	0.13 [0.05 , 0.21]
Russell 2008	9	79	2	48	2.2%	0.07 [-0.02 , 0.16]
Subtotal (95% CI)		**956**		**728**	**53.9%**	**0.04 [0.01 , 0.07]**
Total events:	68		13			
Heterogeneity: Tau² = 0.00; Chi² = 10.42, df = 5 (P = 0.06); I² = 52%						
Test for overall effect: Z = 2.79 (P = 0.005)						
1.18.3 Milnacipran						
Arnold 2010b	51	516	41	509	11.9%	0.02 [-0.02 , 0.05]
Branco 2010	33	435	24	446	13.3%	0.02 [-0.01 , 0.05]
Clauw 2008	42	399	21	201	6.2%	0.00 [-0.05 , 0.05]
Clauw 2008	62	396	21	200	5.5%	0.05 [-0.00 , 0.11]
Mease 2009b	6	79	2	48	2.7%	0.03 [-0.05 , 0.12]
Mease 2009b	14	150	3	48	2.6%	0.03 [-0.05 , 0.11]
Mease 2009b	21	146	3	48	2.3%	0.08 [-0.01 , 0.17]
Subtotal (95% CI)		**2121**		**1500**	**44.4%**	**0.03 [0.01 , 0.04]**
Total events:	229		115			
Heterogeneity: Tau² = 0.00; Chi² = 3.49, df = 6 (P = 0.74); I² = 0%						
Test for overall effect: Z = 2.66 (P = 0.008)						
Total (95% CI)		**3119**		**2268**	**100.0%**	**0.03 [0.01 , 0.04]**
Total events:	298		132			
Heterogeneity: Tau² = 0.00; Chi² = 15.18, df = 13 (P = 0.30); I² = 14%						
Test for overall effect: Z = 3.93 (P < 0.0001)						
Test for subgroup differences: Chi² = 4.65, df = 2 (P = 0.10), I² = 57.0%						



ADDITIONAL TABLES

Table 1. Subgroup analysis. Efficacy and safety of SNRIs in studies with North American and European participants

Outcome	Number of participants (studies)	Effect size RD (95% CI)	Test for overall effect P value	Heterogeneity I^2 (%)	Test of interaction: effect estimate and P value
Self-reported pain relief 50% or greater					Z = 0.78; P = 0.43

Table 1. Subgroup analysis. Efficacy and safety of SNRIs in studies with North American and European participants *(Continued)*

Only North American participants	3935 (8)	0.10 (0.08 to 0.13)	< 0.001	0	
Only European participants	960 (2)	0.06 (0.01 to 0.12)	0.02	0	
Withdrawal due to adverse events					Z = 1.14; P = 0.25
Only North American participants	3935 (8)	0.08 (0.04 to 0.13)	< 0.0002	71	
Only European participants	960 (2)	0.12 (0.08 to 0.17)	< 0.0001	0	

CI: confidence interval; **RD**: risk difference; **SNRIs**: serotonin and noradrenaline reuptake inhibitors

APPENDICES

Appendix 1. Search strategies and hits retrieved

Randomized controlled trials (RCTs) with serotonin and noradrenaline reuptake inhibitors (SNRIs) in fibromyalgia (updated search 8 August 2017)

Database (access) and date of search	Search strategy and hits retrieved
CENTRAL (the Cochrane Library) 2017, Issue 7	#1 MeSH descriptor Fibromyalgia explode all trees **823** #2 (fibromyalgi$):ti,ab,kw or (fibrositis):ti,ab,kw **62** #3 (#1 OR #2), from 2010 to 2012 **38** #4 (cymbalta):ti,ab,kw or (savella):ti,ab,kw or (ixel):ti,ab,kw or (pristiq):ti,ab,kw or (effexor):ti,ab,kw **31** #5 (desvenlaxafine):ti,ab,kw or (duloxetine):ti,ab,kw or (milnacipran):ti,ab,kw or (venlaxafine):ti,ab,kw**1011** #6 (#4 OR #5), from 2010 to 2017 **106** #7(#3 AND #6) **2**
MEDLINE (PubMed) 8 August 2017	#1 Search Fibromyalgia"[Mesh] OR fibromyalgi*[ti] OR fibrositis[ti] **6497** #2 Search (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT (humans[mh] AND animals[mh])) **3521493** #3 Search cymbalta OR savella OR ixel OR pristiq OR effexor OR desvenlafaxine OR duloxetine OR venlafaxine **6258** # 4 Search ((#1) AND #2) AND #3 Filters: Publication date from 2015/08/01 to 2017/08/07 **7**
Embase via SCOPUS 8 August 2017	(((TITLE-ABS-KEY (**cymbalta**) OR TITLE-ABS-KEY (**savella**) OR TITLE-ABS-KEY (**ixel**) OR TITLE-ABS-KEY (**pristiq**) OR TITLE-ABS-KEY (**effexor**) OR TITLE-ABS-KEY (**desvenlaxafine**) OR TITLE-ABS-KEY (**duloxetine**) OR TITLE-ABS-KEY (**venlaxafine**) AND (((TITLE-ABS-KEY (**fibromyalgia**) OR TITLE-ABS-KEY (**fibrositis**) OR TITLE-ABS-KEY (**fms**))) AND ((TITLE-ABS-KEY (**randomized controlled trial**) OR TITLE-ABS-KEY (**controlled trial**) OR TITLE-ABS-KEY (**placebo**) OR TITLE-ABS-KEY (**single blind**) OR TITLE-ABS-KEY (**double blind**))))) AND (PUBYEAR > **2015**) **18**

(Continued)

US National Institutes of Health 31 November 2015 to 8 August 2017	1 fibromyalgia and desvenlafaxine **0** 2 fibromyalgia and duloxetine **3** 3 fibromyalgia and milnacipran **0** 4 fibromyalgia and venlafaxine **1** 5 SNRI and fibromyalgia **21**
World Health Organization Inception to 8 August 2017	1 fibromyalgia and desvenlafaxine **3** 2 fibromyalgia and duloxetine **10** 3 fibromyalgia and milnacipran **10** 4 fibromyalgia and venlafaxine **1** 5 SNRI and fibromyalgia **0**

RCTs with SNRIs in fibromyalgia (search 30 November 2015)

Database (access) and date of search	Search strategy and hits retrieved
CENTRAL (the Cochrane Library) 2015, Issue 11	#1 fibromyalgi$ or fibrositis:ti,ab,kw (Word variations have been searched) **61** #2 MeSH descriptor: [Fibromyalgia] explode all **675** #3 #1 or #2 **723** #4 cymbalta or savella or ixel or pristiq or effexor or desvenlaxafine or duloxetine or venlaxafine:ti,ab,kw (Word variations have been searched) **816** #5 #3 AND #4 in Trials **31** #6 #5 Publication Year from 2012 to 2015 **7**
MEDLINE (PubMed) 30 November 2015	#1 Search Fibromyalgia"[Mesh] OR fibromyalgi*[ti] OR fibrositis[ti] **5713** #2 Search (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT (humans[mh] AND animals[mh])) **3125777** #3 Search cymbalta OR savella OR ixel OR pristiq OR effexor OR desvenlafaxine OR duloxetine OR venlafaxine **5544** # 4 Search ((#1) AND #2) AND #3 Filters: Publication date from 2012/09/01 to 2015/11/30 **42**
Embase via SCOPUS 30 November 2015	(((TITLE-ABS-KEY (**cymbalta**) OR TITLE-ABS-KEY (**savella**) OR TITLE-ABS-KEY (**ixel**) OR TITLE-ABS-KEY (**pristiq**) OR TITLE-ABS-KEY (**effexor**) OR TITLE-ABS-KEY (**desvenlaxafine**) OR TITLE-ABS-KEY (**duloxetine**) OR TITLE-ABS-KEY (**venlaxafine**) AND (((TITLE-ABS-KEY (**fibromyalgia**) OR TITLE-ABS-KEY (**fibrositis**) OR TITLE-ABS-KEY (**fms**))) AND ((TITLE-ABS-KEY (**randomized controlled trial**) OR TITLE-ABS-KEY (**controlled trial**) OR TITLE-ABS-KEY (**placebo**) OR TITLE-ABS-KEY (**single blind**) OR TITLE-ABS-KEY (**double blind**))))) AND (PUBYEAR > **2011**) **104**
US National Institutes of Health	1 fibromyalgia and desvenlafaxine **1** 2 fibromyalgia and duloxetine **1**

(Continued)

30 November 2015	3 fibromyalgia and milnacipran **2** 3 fibromyalgia and venlafaxine **1** 4 SNRI and fibromyalgia **10**

RCTs with SNRIs in fibromyalgia (updated search 11 September 2012)

Database (access) and date of search	Search strategy and hits retrieved
CENTRAL (the Cochrane Library) 2012, Issue 9	#1MeSH descriptor Fibromyalgia explode all trees 510 #2 (fibromyalgi$):ti,ab,kw or (fibrositis):ti,ab,kw 62 #3 (#1 OR #2), from 2010 to 2012 107 #4 (cymbalta):ti,ab,kw or (savella):ti,ab,kw or (ixel):ti,ab,kw or (pristiq):ti,ab,kw or (effexor):ti,ab,kw 17 #5 (desvenlaxafine):ti,ab,kw or (duloxetine):ti,ab,kw or (milnacipran):ti,ab,kw or (venlaxafine):ti,ab,kw 454 #6 (#4 OR #5), from 2010 to 2012 77 #7 (#3 AND #6) **17**
MEDLINE (PubMed) 11 September 2012	#1"Fibromyalgia"[MeSH] OR fibromyalgi*[ti] OR fibrositis[ti] 6070 #2 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT (humans[mh] AND animals[mh])) 2600091 #3 Search cymbalta OR savella OR ixel OR pristiq OR effexor OR desvenlafaxine OR duloxetine OR milnacipran OR venlafaxine 4353 #4 Search ((#1) AND #2) AND #3 Filters: Publication date from 2010/10/01 to 2012/09/10 **42**
Embase via SCOPUS 11 September 2012	1 (TITLE-ABS-KEY(random) OR TITLE-ABS-KEY(placebo) OR TITLE-ABS-KEY(double-blind)) AND DOCTYPE(ar) AND PUBYEAR > 2009 97115 2 (TITLE-ABS-KEY(expfibromyalgia/) OR TITLE-ABS-KEY(fibrositis) OR TITLE-ABS-KEY(fibromyalgia)) AND DOCTYPE(ar) AND PUBYEAR > 2009 1265 3 (TITLE-ABS-KEY(cymbalta) OR TITLE-ABS-KEY(savella) OR TITLE-ABS-KEY(ixel) OR TITLE-ABS-KEY(pristiq) OR TITLE-ABS-KEY(effexor) OR TITLE-ABS-KEY(desvenlaxafine) OR TITLE-ABS-KEY(duloxetine) OR TITLE-ABS-KEY(venlaxafine) OR TITLE-ABS-KEY(milnacipran)) AND DOCTYPE(ar) AND PUBYEAR > 2009 1051 4 ((TITLE-ABS-KEY(expfibromyalgia/) OR TITLE-ABS-KEY(fibrositis) OR TITLE-ABS-KEY(fibromyalgia)) AND DOCTYPE(ar) AND PUBYEAR > 2009) AND ((TITLE-ABS-KEY(random) OR TITLE-ABS-KEY(placebo) OR TITLE-ABS-KEY(double-blind)) AND DOCTYPE(ar) AND PUBYEAR > 2009) AND ((TITLE-ABS-KEY(cymbalta) OR TITLE-ABS-KEY(savella) OR TITLE-ABS-KEY(ixel) OR TITLE-ABS-KEY(pristiq) OR TITLE-ABS-KEY(effexor) OR TITLE-ABS-KEY(desvenlaxafine) OR TITLE-ABS-KEY(duloxetine) OR TITLE-ABS-KEY(venlaxafine) OR TITLE-ABS-KEY(milnacipran)) AND DOCTYPE(ar) AND PUBYEAR > 2009) **50**
US National Institutes of Health	1 fibromyalgia **401**

(Continued)

11 September 2012	2 fibromyalgia and desvenlafaxine **4**
	3 fibromyalgia and duloxetine **25**
	4 fibromyalgia and milnacipran **27**
	5 fibromyalgia and venlafaxine **0**

RCTs with SNRIs in fibromyalgia (updated search November 2010)

Database (access) and date of search	Search strategy and hits retrieved
CENTRAL	#1MeSH descriptor Fibromyalgia explode all trees 449
(the Cochrane Library)	#2 fibromyalgi* 755
2010, Issue 10	#3 fibrositis 50
	#4 #1 OR #2 OR #3 774
	#5 (#1 OR #2 OR #3), from 2009 to 2010 **137 (69 in clinical trials)**
MEDLINE	#1"Fibromyalgia"[MeSH] OR fibromyalgi*[ti] OR fibrositis[ti] 5248
(PubMed)	#2 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT (humans[mh] AND animals[mh])) 2309479
4 November 2010	#3 #1 AND #2 1682
	#4 (#2) AND #1 Limits: Publication Date from 2009 **312**
Embase	1 exp Fibromyalgia/ 8833
(Ovid)	2 fibromyalgia.ti,ab. 6702
4 November 2010	3 exp Fibromyalgia/ 8833
	4 fibrositis.ti. 271
	5 1 or 2 or 3 or 4 9482
	6 random:.tw. or placebo:.mp. or double-blind:.mp. 776985
	7 5 and 6 1417
	8 limit 7 to yr="2009 -Current" **405**
ClinicalStudyResults.org	1 fibromyalgia 19
31 December 2010	2 fibromyalgia and cymbalta**4**
	3 fibromyalgia and savella or ixel: no search possible
	4 fibromyalgia and pristiq **4**
	5 fibromyalgia and effexor 0

(Continued)

US National Institutes of Health 31 December 2010	1 fibromyalgia 326 2 fibromyalgia and desvenlafaxine **4** 3 fibromyalgia and duloxetine **20** 4 fibromyalgia and milnacipran **20** 5 fibromyalgia and venlafaxine **0**

RCTs with SNRIs in fibromyalgia (initial search February 2009)

Database (access) and date of search	Search strategy and hits retrieved
CENTRAL (the Cochrane Library) 2009, Issue 1	#1MeSH descriptor Fibromyalgia explode all trees 315 #2 fibromyalgi* 512 #3 fibrositis 36 #4 #1 OR #2 OR #3 **526**
MEDLINE (PubMed) 9 February 2009	#1"Fibromyalgia"[MeSH] OR fibromyalgi*[ti] OR fibrositis[ti] 4433 #2 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND humans [mh] 1912816 #3 #1 AND #2 **1316**
Embase (Ovid) 9 February 2009	1 exp Fibromyalgia/ 5537 2 fibromyalgia.ti,ab. 4304 3 exp Fibromyalgia/ 354 4 fibrositis.ti. 122 5 1 or 2 or 3 or 4 6046 6 random:.tw. or placebo:.mp. or double-blind:.mp. 514373 7 5 and 6 **886**

WHAT'S NEW

Date	Event	Description
22 June 2020	Review declared as stable	See Published notes.

HISTORY

Review first published: Issue 1, 2013

Date	Event	Description
4 August 2016	New search has been performed	We added eight new studies but major conclusions are unchanged.
4 August 2016	New citation required but conclusions have not changed	We updated the searches and include eight new studies. This update has six new studies in the analysis of placebo controlled studies with a parallel design (Arnold 2012a; Bateman 2013; Matthey 2013; Murakami 2015; NCT00697787; Staud 2015). One enriched enrolment randomized withdrawal (EERW) trial with placebo control (Mease 2014, secondary report of Clauw 2013) was added into a new comparison of placebo controlled studies with EERW design. Two studies comparing SNRIs to another active drug were added into a new comparison (Leombruni 2015; NCT00697787) of SNRIs versus other active drugs. These studies add 1979 new participants. We performed GRADE assessments and included a 'Summary of findings' table.
21 March 2013	Amended	Minor edits in summary of findings table
14 January 2013	Amended	Revisions to risk of bias tables
23 October 2012	Amended	The protocol 'Antidepressants and centrally active agents for fibromyalgia syndrome' published in 2006 (Nishishinya 2006) has been split into several systematic reviews that will be/have been published as: - Anticonvulsants for fibromyalgia syndrome (Üceyler 2017 b) - Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome (Tort 2012) - Non-steroidal anti-inflammatory drugs (NSAIDs), analgesics and opioid agents for fibromyalgia syndrome - Sedatives and hypnotic agents for fibromyalgia syndrome - Selective serotonin reuptake inhibitors (SNRIs) for fibromyalgia syndrome (Walitt 2015) - Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome (Häuser 2013) - Tricyclic agents for fibromyalgia syndrome

CONTRIBUTIONS OF AUTHORS

WH and PK developed and ran the search. BW and WH selected which studies to include. BW, NÜ, PW and WH extracted data from studies. WH entered data into Review Manager 5 and carried out the analysis. Data entry was checked by BW, NÜ and PW. All authors interpreted the analysis. WH drafted the final review update.

DECLARATIONS OF INTEREST

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

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 (2015, 2016). She received speaker honoraria from Baxalta (2016). She received research grants from Genzyme (2015) and Shire (2017). She received travel grants from Grunenthal (2017).

PK: none known

BW: none known; BW 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 and chronic neuropathic pain. 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 from Grünenthal (2015) on pain management.

SOURCES OF SUPPORT

Internal sources

- Technische Universität München, Germany

  General institutional support

External sources

- New Source of support, Other
- The National Institute for Health Research (NIHR), UK

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the earlier review, the protocol 'Antidepressants and centrally active agents for fibromyalgia syndrome' was split into several systematic reviews (Nishishinya 2006). We added an additional comparison, namely cognitive disturbances. We used a random-effects model for all analysis irrespective of the amount of heterogeneity. We used the GRADE approach for the grading of the quality of the body of evidence.

For this update in 2017, we made the following minor changes:

Background

- We considered recent literature.

Methods/Criteria for considering studies for this review

- We excluded mirtazapine from searches and analysis, because mirtazapine has been classified to another class of antidepressants from serotonin and noradrenaline reuptake inhibitors (SNRIs), namely noradrenergic and specific serotonergic antidepressants (NaSSAs).
- We defined more precisely the criteria of including and excluding studies.
- We included studies with an active drug as comparator.
- We substituted 'pain intensity' with 'patient global impression much or very much improved' as a primary outcome. We reduced the number of primary outcomes from seven to four. Self-reported sleep problems, self-reported health-related quality of life and self-reported fatigue were changed from primary to secondary outcomes. We added number of participants dropping out due to lack of efficacy, and specific adverse events frequently associated with the use of SNRIs (nausea, somnolence, insomnia), as secondary outcomes with regard to the Cochrane Pain, Palliative and Supportive Care template for reviews in fibromyalgia.
- We defined outcomes for studies with an enriched enrolment randomized withdrawal design.
- We included the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) in our search.

Methods/Measures of treatment effect

- We changed from risk ratio to risk difference for categorical variables, because this type of effect size is more meaningful for clinicians.

Methods/Assessment of risk of bias in included studies

- We deleted 'external validity' as a risk of bias and included this item in GRADE assessment within 'indirectness of evidence'.
- We changed the criteria of 'blinding of the outcome assessment' from blinding of the statistician to blinding of the participants for participant-reported outcomes and to blinding of the outcome assessor for outcomes of safety.
- We extended the 'Risk of bias' assessment by two items (selection and sample size bias).
- We changed the methods of screening for publication bias.
- We predefined the criteria for downgrading the quality of evidence for each GRADE item.

Analyses

- We deleted the calculation of intra-group effect sizes (baseline and final treatment) of true drug and placebo on pain and health-related quality of life.
- We added a comparison of SNRIs versus placebo in studies with a randomized withdrawal design.
- We added a comparison of SNRIs versus other active drugs.

Discussion

- We rearranged the sections according to MECIR standards.

Characteristics of included studies

- We added details of the declaration of conflicts of interest and funding.

NOTES

The protocol 'Antidepressants and centrally active agents for fibromyalgia syndrome' published in 2006 (Nishishinya 2006) has been split into several systematic reviews that will be/have been published as:

- Anticonvulsants for fibromyalgia syndrome (Üceyler 2017 b);
- Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome (Tort 2012);
- Non-steroidal anti-inflammatory drugs (NSAIDs) for fibromyalgia (Derry 2017);
- Analgesics and opioid agents for fibromyalgia syndrome;
- Sedatives and hypnotic agents for fibromyalgia syndrome;
- Selective serotonin reuptake inhibitors (SNRIs) for fibromyalgia syndrome (Walitt 2015);
- Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome (Häuser 2013 a)
- Tricyclic agents for fibromyalgia syndrome.

Assessed for updating in 2020

A restricted search in January 2020 did not 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 three 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)

Adrenergic Uptake Inhibitors [*therapeutic use]; Carnitine [therapeutic use]; Cyclopropanes [*therapeutic use]; Desvenlafaxine Succinate [*therapeutic use]; Duloxetine Hydrochloride [*therapeutic use]; Fibromyalgia [*drug therapy]; Milnacipran; Norepinephrine [*metabolism]; Pregabalin [therapeutic use]; Quality of Life; Serotonin Uptake Inhibitors [*therapeutic use]; Syndrome

MeSH check words

Adult; Humans