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Selective serotonin reuptake inhibitors for fibromyalgia syndrome (Review)

Walitt B, Urrútia G, Nishishinya MB, Cantrell SE, Häuser W

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[Intervention Review]

Selective serotonin reuptake inhibitors for fibromyalgia syndrome

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ABSTRACT

Background

Fibromyalgia is a clinically well-defined chronic condition with a biopsychosocial aetiology. Fibromyalgia is characterized by chronic widespread musculoskeletal pain, sleep problems, cognitive dysfunction, and fatigue. Patients often report high disability levels and poor quality of life. Since there is no specific treatment that alters the pathogenesis of fibromyalgia, drug therapy focuses on pain reduction and improvement of other aversive symptoms.

Objectives

The objective was to assess the benefits and harms of selective serotonin reuptake inhibitors (SSRIs) in the treatment of fibromyalgia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 5), MEDLINE (1966 to June 2014), EMBASE (1946 to June 2014), and the reference lists of reviewed articles.

Selection criteria

We selected all randomized, double-blind trials of SSRIs used for the treatment of fibromyalgia symptoms in adult participants. We considered the following SSRIs in this review: citalopram, fluoxetine, escitalopram, fluvoxamine, paroxetine, and sertraline.

Data collection and analysis

Three authors extracted the data of all included studies and assessed the risks of bias of the studies. We resolved discrepancies by discussion.

Main results

The quality of evidence was very low for each outcome. We downgraded the quality of evidence to very low due to concerns about risk of bias and studies with few participants. We included seven placebo-controlled studies, two with citalopram, three with fluoxetine and two with paroxetine, with a median study duration of eight weeks (4 to 16 weeks) and 383 participants, who were pooled together.

All studies had one or more sources of potential major bias. There was a small (10%) difference in patients who reported a 30% pain reduction between SSRIs (56/172 (32.6%)) and placebo (39/171 (22.8%)) risk difference (RD) 0.10, 95% confidence interval (CI) 0.01 to 0.20; number needed to treat for an additional beneficial outcome (NNTB) 10, 95% CI 5 to 100; and in global improvement (proportion of patients

who reported to be much or very much improved: 50/168 (29.8%) of patients with SSRIs and 26/162 (16.0%) of patients with placebo) RD 0.14, 95% CI 0.06 to 0.23; NNTB 7, 95% CI 4 to 17.

SSRIs did not statistically, or clinically, significantly reduce fatigue: standard mean difference (SMD) -0.26, 95% CI -0.55 to 0.03; 7.0% absolute improvement on a 0 to 10 scale, 95% CI 14.6% relative improvement to 0.8% relative deterioration; nor sleep problems: SMD 0.03, 95% CI -0.26 to 0.31; 0.8% absolute deterioration on a 0 to 100 scale, 95% CI 8.3% relative deterioration to 6.9% relative improvement.

SSRIs were superior to placebo in the reduction of depression: SMD -0.39, 95% CI -0.65 to -0.14; 7.6% absolute improvement on a 0 to 10 scale, 95% CI 2.7% to 13.8% relative improvement; NNTB 13, 95% CI 7 to 37. The dropout rate due to adverse events was not higher with SSRI use than with placebo use (23/146 (15.8%) of patients with SSRIs and 14/138 (10.1%) of patients with placebo) RD 0.04, 95% CI -0.06 to 0.14. There was no statistically or clinically significant difference in serious adverse events with SSRI use and placebo use (3/84 (3.6%) in patients with SSRIs and 4/84 (4.8%) and patients with placebo) RD -0.01, 95% CI -0.07 to 0.05.

Authors' conclusions

There is no unbiased evidence that SSRIs are superior to placebo in treating the key symptoms of fibromyalgia, namely pain, fatigue and sleep problems. SSRIs might be considered for treating depression in people with fibromyalgia. The black box warning for increased suicidal tendency in young adults aged 18 to 24, with major depressive disorder, who have taken SSRIs, should be considered when appropriate.

PLAIN LANGUAGE SUMMARY

Selective serotonin reuptake inhibitors (SSRIs) for fibromyalgia

Researchers of the Cochrane Collaboration conducted a review of research about the effects of antidepressants classified as serotonin reuptake inhibitors (SSRIs) on fibromyalgia. After searching for all relevant studies up to June 2014, they found seven studies that compared SSRIs with a fake medication. These studies included a total of 383 people. Most participants were middle-aged women. The SSRIs that they studied were citalopram, fluoxetine and paroxetine. Five studies were each funded by pharmaceutical companies, and two studies were funded by public institutions.

Key results

We are uncertain of the evidence of the outcomes of reduction of pain, sleep problems, fatigue, depression, global improvement (proportion of patients who reported to be much or very much improved), tolerability (dropout rates due to adverse events), and safety (serious adverse events).

Possible side effects of SSRIs may include dry mouth, nausea/vomiting, and sexual dysfunction. Rare complications may include allergies, diseases of the immune system, liver damage, and impairment of a person's ability to drive or operate machinery; serious side effects, such as suicidal thoughts and liver failure, are very rare.

What is fibromyalgia and what are serotonin reuptake inhibitors?

People with fibromyalgia suffer from chronic widespread pain, sleep problems, and fatigue. There is no cure for fibromyalgia at present. Treatments aim at relieving the symptoms and improving health-related quality of life.

Serotonin is a chemical which is produced by the human body and is involved in the experiences of pain, sleep, and mood. Decreased concentrations of serotonin have been reported in people with fibromyalgia. SSRIs are antidepressants that increase the concentration of serotonin in the brain. SSRIs are not approved for use as fibromyalgia treatment, but are approved for depression and anxiety disorder.

Quality of the evidence

The quality of evidence was very low for each outcome. We downgraded the quality of evidence to very low due to concerns about risk of bias and studies with few participants. Therefore we are uncertain whether taking SSRIs for an average of eight weeks improves fibromyalgia symptoms (number of people who reported that their pain was reduced by at least 30%, and number of people reporting a clinically important global improvement in pain intensity, fatigue, sleep problems, and depression).

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SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Selective serotonin reuptake inhibitors (SSRIs) compared with placebo for fibromyalgia

Patient or population: Patients with fibromyalgia

Settings: Outpatient clinical centers

Intervention: SSRIs

Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	SSRI				
Number of patients with at least 30% pain reduction	228 per 1000	333 per 1000 (237 to 429)	RD 0.10 (0.01 to 0.20)	343 (6 studies)	⊕⊕⊕⊕ very low ^{1,2,3}	Absolute risk difference (more patients with at least 30% pain reduction): 10% (95% CI 1% to 20%) Relative per cent improvement: 37% (95% CI 4% deterioration to 98% improvement) NNTB 10 (95% CI 5 to 100)
Number of patients with a clinically important global improvement	160 per 1000	302 per 1000 (220 to 390)	RD 0.14 (0.06 to 0.23)	330 (6 studies)	⊕⊕⊕⊕ very low ^{1,2,3}	Absolute risk difference (more patients with clinically important global improvement): 14% (95% CI 6% to 23%) Relative per cent improvement: 78% (95% CI 17% to 170% improvement) NNTB 7 (95% CI 4 to 17)
Fatigue (lower scores mean less fatigue)	Baseline score control group 7.5 (2.7)*		Mean fatigue score was 0.70 points lower (1.46 lower to 0.08 lower) based on a 0-10 scale	192 (5 studies)	⊕⊕⊕⊕ very low ^{1,2,3}	SMD -0.26 (95% CI -0.55 to 0.03) 7.0% (95% CI 14.6% fewer points to 0.8% fewer points on the fatigue scale) (absolute improvement)

						9.4% relative improvement (95% CI 15.6% relative improvement to 1.1% relative deterioration)
Sleep problems (lower scores mean less sleep problems)	Baseline score control group 68.0 (26.6) **		Mean sleep problems score was 0.80 points higher (8.3 higher to 6.9 lower) based on a 0-100 scale	193 (5 studies)	⊕⊕⊕⊕ very low ^{1,2,3}	SMD 0.03 (95% CI -0.26 to 0.31) 0.08% more (95% CI 8.3% more to 6.9% fewer points) on the sleep problems scale (absolute deterioration) 1.2% relative deterioration (95% CI 10.2% relative improvement to 12.1% relative deterioration)
Depression (lower scores mean less depression)	Baseline score control group 2.5 (2.0) ***		Mean depression score was 0.76 points lower (0.27 lower to 1.38 lower) based on 0-10 scale	244 (6 studies)	⊕⊕⊕⊕ very low ^{1,2,3}	SMD -0.39 (95% CI -0.65 to -0.14) 7.6% (95% CI 2.7% to 13.8%) fewer points on the depression scale (absolute improvement) 30.4% relative improvement (95% CI 11.2% to 52.0% relative improvement) NNTB 13 (95% CI 7 to 37)
Discontinuation due to adverse events	101 per 1000	140 per 1000 (42 to 241)	RD 0.04 (-0.06 to 0.14)	284 (5 studies)	⊕⊕⊕⊕ very low ^{2,3,4}	Absolute risk difference 4% (95% CI 6% less to 14% more discontinuation due to adverse events) Relative per cent deterioration 44% (95% CI 38% improvement to 233% deterioration)
Serious adverse events	48 per 1000	40 per 1000 (-22 to 98)	RD -0.01 (-0.07 to 0.05)	168 (2 studies)	⊕⊕⊕⊕ very low ^{2,3}	Absolute risk difference -1% less (95% CI 7% less to 5% more serious adverse events) Relative per cent improvement 24% (95% CI 83% improvement to 224% deterioration)

CI: confidence interval; NNTB: number needed to treat for an additional beneficial outcome; RD: risk difference; SMD: standard mean difference

GRADE Working Group grades of evidence

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

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

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

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

- 1 > 50% of the participants in low quality studies
 - 2 Patients with inflammatory rheumatic diseases and/ or depressive disorders were excluded in > 50% of participants
 - 3 Total number of patients <400
 - 4 $I^2 > 50\%$
- *Arnold 2002; N = 60 participants (VAS 0-10)
** Goldenberg 1996; N = 31 participants (VAS 0-100)
***Arnold 2002; N = 60 participants (VAS 0-10)

BACKGROUND

Fibromyalgia is a common disorder occurring in all populations across the world. Estimates of the prevalence of fibromyalgia according to the American College of Rheumatology (ACR) 1990 classification criteria in the general European population ranged from 2.1% to 2.9% (Branco 2010) and was 2.0 % in Wichita, USA (Wolfe 1995). The prevalence of fibromyalgia according to the research criteria was 2.1% in the general German (Wolfe 2013) and Japanese population (Nakamura 2014). People with fibromyalgia use a wide range of different types of drugs and non-pharmacological therapies (Bennett 2007; Häuser 2012a; Marschall 2011).

Description of the condition

The disorder is characterized by chronic widespread musculoskeletal pain, which commonly co-exists with cognitive dysfunction, sleep disturbance, and fatigue (Wolfe 2010). Correspondingly, patients often report high disability levels and poor quality of life, along with extensive use of medical care (Haviland 2012; Knight 2013; Marschall 2011). Lacking a specific laboratory test, clinical diagnosis is often based on the ACR 1990 classification (Wolfe 1990), the ACR 2010 preliminary diagnostic criteria (Wolfe 2010), and the 2010 epidemiologic research criteria (Wolfe 2011a; Wolfe 2014). In the past, other criteria had been used to diagnose fibromyalgia (Smythe 1981; Yunus 1981; Yunus 1982; Yunus 1984).

A biopsychosocial model of factors predisposing, triggering and perpetuating fibromyalgia symptoms has been suggested (Sommer 2012). An array of factors have been correlated with fibromyalgia, including genes (Arnold 2013; Lee 2010), life-style factors, such as obesity and physical inactivity (Mork 2010), social disadvantage, psychological and physical stress (van Houdenhove 2005), and sleep disturbances (Mork 2012). Physical and sexual abuse in childhood and adolescence (Häuser 2011), and somatic diseases such as rheumatoid arthritis, often precede the development of fibromyalgia symptoms (Wolfe 2011b). Concomitant psychological disorders, such as depression (Lange 2010) and post-traumatic stress (Häuser 2013a) have a negative impact on the clinical outcome of fibromyalgia. Several biological mechanisms, such as alterations of central pain pathways, hyporeactivity of the hypothalamus-pituitary- adrenal axis, increased systemic pro-inflammatory and reduced anti-inflammatory cytokine profiles, disturbances in the dopaminergic and serotonergic systems, and small fibre pathology have been associated with fibromyalgia. However, none of these mechanisms has been demonstrated to have a causal relationship to fibromyalgia or to be specific for fibromyalgia (Sommer 2012; Üceyler 2013a). The dominant modern pathophysiologic concept views fibromyalgia as the result of alterations in central pain processing, involving alteration of sensory input, its cognitive-emotional appraisal, and reflexive regulation of future sensory input (Bradley 2009). Since specific treatment aimed at altering the pathogenesis is not possible, drug therapy focusing on symptom reduction is widely employed.

Description of the intervention

Serotonin reuptake inhibitors (SSRIs) act on serotonergic neurons in the nervous system. Serotonin is implicated in the mediation of endogenous pain inhibitory mechanisms.

How the intervention might work

Central pain conditions, in which persistent pain occurs in the absence of objective anatomic abnormality, are presumed to respond best to centrally active neuromodulating agents, such as antidepressants and anticonvulsants (Häuser 2012b). Dysfunction of serotonin transmission, which is reported to mediate endogenous analgesic mechanisms via descending inhibitory pain pathways in the central nervous system, may play a role in the pathophysiologic mechanisms of fibromyalgia. Researchers found that levels of metabolites of biogenic amines associated with descending inhibition were lower than normal in at least three fibromyalgia body fluid compartments (Legagneux 2001; Russell 1992). Imbalance or deficiency in serotonin is also associated with other defining symptoms of fibromyalgia, such as fatigue and cognitive deficits (Bradley 2009). Treatment with SSRI increases the functional expression of serotonin and may improve pain, fatigue, and cognitive deficits.

Why it is important to do this review

Anticonvulsants, antidepressants, non-steroidal anti-inflammatory drugs, and opioids are the most frequently used drugs by fibromyalgia patients (Bennett 2007; Häuser 2012a). SSRIs were prescribed in 16% of insurants diagnosed with fibromyalgia in a German statutory health insurance company with seven million insurants between 2008 and 2010 (Marschall 2011). A comprehensive assessment of the potential benefits and risks of SSRIs in fibromyalgia could assist patients and physicians making choices about using medications for fibromyalgia treatment. We continued the Cochrane Reviews of the Cochrane Musculoskeletal Group (CMSG) on centrally acting agents in fibromyalgia (Häuser 2013b; Tort 2012; Üceyler 2013b) with a review on SSRIs.

OBJECTIVES

The objective was to assess the benefits and harms of selective serotonin reuptake inhibitors (SSRIs) in the treatment of fibromyalgia.

METHODS

Criteria for considering studies for this review

Types of studies

We selected all relevant double-blind, randomized controlled trials (RCTs) with a study duration of equal to, or greater than four weeks. We included studies with a parallel or cross-over design. We included studies with a cross-over design if (a) separated data from the two periods were reported, (b) data were presented which excluded statistically significant carry-over effects, or (c) statistical adjustments were carried out in the case of a significant carry-over effect.

Types of participants

Adults (+ 18 years) having a clinical diagnosis of fibromyalgia by any recognized criteria (Smythe 1981; Wolfe 1990; Wolfe 2010; Wolfe 2014; Yunus 1981; Yunus 1982; Yunus 1984).

Types of interventions

We accepted trials comparing SSRIs with placebo or another active drug. We allowed cointerventions, such as non-steroidal anti-

inflammatory drugs, non-opioid analgesics and physical therapy. We considered the following SSRIs in this review: citalopram, fluoxetine, escitalopram, fluvoxamine, paroxetine, and sertraline.

Types of outcome measures

We selected outcomes measures based on the recommendations of the [CMSG 2014](#) and OMERACT ([Mease 2011](#)) for fibromyalgia studies, and on recommendations of best practice in the reporting of systematic reviews in chronic pain ([Moore 2010](#)). In discussion with the CMSG, we modified the recommended CMSG outcomes for fibromyalgia to include fatigue and sleep problems as primary outcomes (and shifted tenderness and physical functioning to secondary outcomes). Along with chronic widespread pain, fatigue and sleep problems are currently considered essential symptoms of fibromyalgia. We chose dichotomous outcomes instead of continuous outcomes for pain and global improvement because a) the distribution of response in chronic pain trials is typically not Gaussian, and b) average changes of pain scores are of very limited utility because they are unrepresentative of the patient experience ([Moore 2010](#)).

Primary outcomes

We used only patient-reported outcomes of symptoms.

1. Number of patients with at least 30% pain reduction rates: If not reported, we calculated responder rates by a validated imputation method ([Furukawa 2005](#)) based on means and standard deviations (SDs) of average pain scores. We preferred single item pain scales (e.g. Visual Analogue Scale (VAS) or numeric rating scales) over composite pain scales, (e.g. McGill Pain Questionnaire).
2. Global improvement: Number of patients with a clinically important global improvement: We preferred proportion of patients who reported to be much or very much improved over investigator-defined composite responder scores. If these outcomes were not available, we used the proportion of patients with a $\geq 25\%$ reduction of the Fibromyalgia Impact Questionnaire (FIQ)FIQ total score. We calculated responder rates by a validated imputation method ([Furukawa 2005](#)) based on means and SDs of average FIQ total scores.
3. Fatigue: We preferred total scores of validated fatigue instruments (e.g. Fatigue Impact Scale) over single item scales (e.g. VAS 0-10).
4. Sleep problems: We preferred total scores of validated sleep problem instruments (e.g. Medical Outcomes Study (MOS) sleep scale) over single item scales (e.g. VAS 0-10).
5. Depression: We preferred total scores of validated depression instruments (e.g. Beck Depression Inventory (BDI)) over single item scales (e.g. VAS 0-10).
6. Tolerability: Discontinuation rates due to adverse events.

7. Safety: Proportion of patients with any serious adverse event.

Secondary outcomes

1. Pain Intensity: We preferred single item pain scales (e.g. VAS or numeric rating scales) over composite pain scales (e.g. McGill Pain Questionnaire).
2. Physical functioning: We preferred total scores of validated instruments (e.g. SF-36 physical function) over single item scales (e.g. VAS 0-10).
3. Anxiety: We preferred total scores of validated anxiety instruments (e.g. AIMS anxiety) over single item scales (e.g. VAS 0-10).
4. Tenderness: We preferred combined scores with dolorimetry (e.g. total myalgic score) over tender point count (preferring dolorimetry over tender point count to thumb pressure).

Search methods for identification of studies

Electronic searches

We ran an electronic search in the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 5), MEDLINE accessed through PubMed (1966 to June 2014), and EMBASE accessed through Elsevier (1946 to June 2014). We ran previous searches in November 2010 and February 2009. The June 2014 search not only updated the search with respect to years of coverage, but also incorporated a stronger and more comprehensive search strategy. Additionally, the June 2014 search provided greater access to EMBASE content (1946 to present versus 1980 to present) than earlier searches. See [Appendix 1](#) for search strategies in all databases and the corresponding number of retrieved results.

Searching other resources

We handsearched bibliographies from reviewed articles and retrieved relevant articles. We contacted content experts for both published and unpublished potential studies.

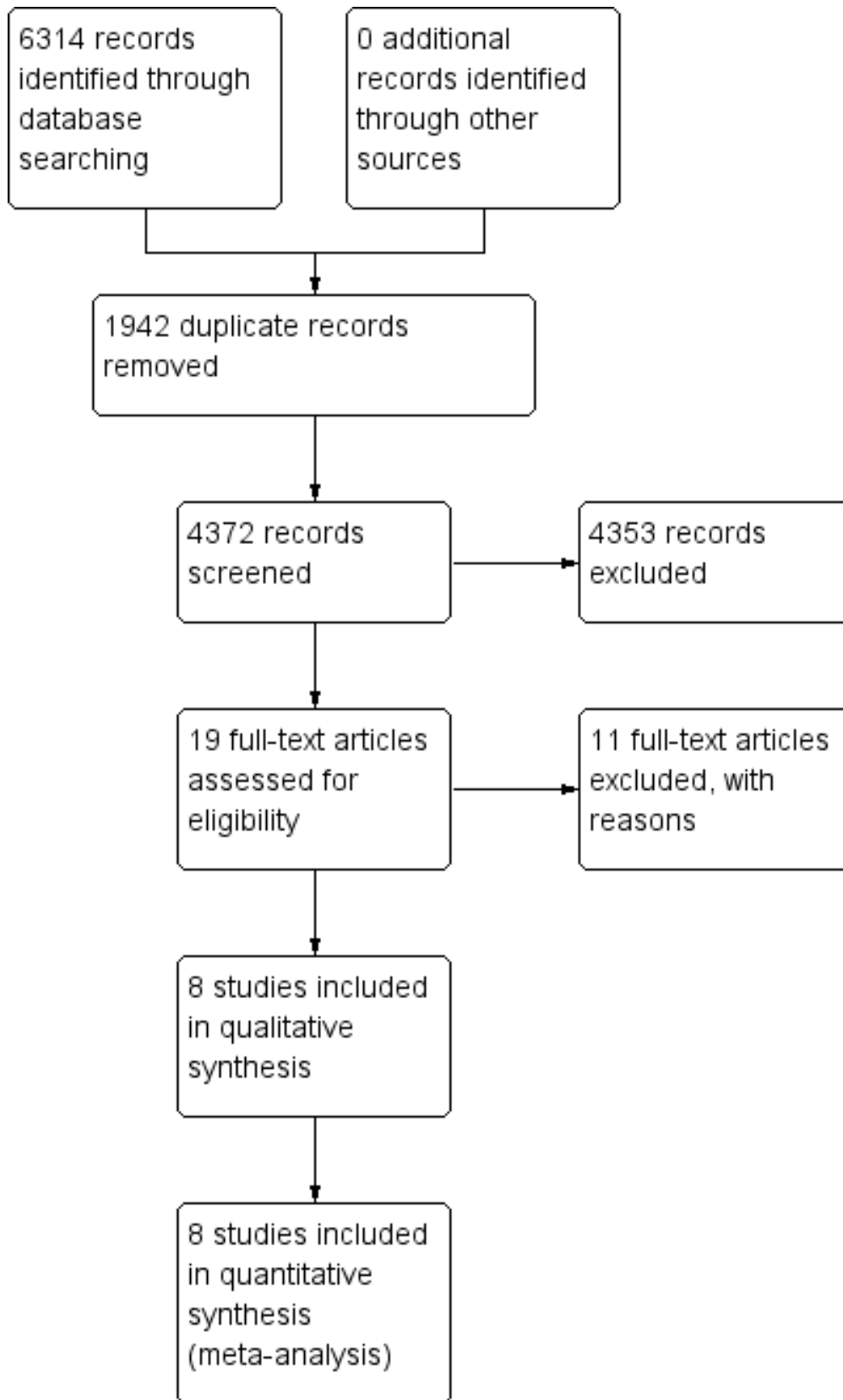
Our search included all languages. We contacted the corresponding authors of identified RCTs when possible for additional information about other relevant studies. We also searched for ongoing trials in relevant databases such as ClinicalTrials.gov (<https://clinicaltrials.gov>) and the metaRegister of controlled trials (<http://www.isrctn.com>).

Data collection and analysis

Selection of studies

Four reviewers (BN, BW, RR, SC) independently scrutinized all the titles and abstracts revealed by the searches and determined which fulfilled the selection criteria. A fifth reviewer (GU) verified that the selection had been properly realized (see [Figure 1](#)).

Figure 1. Study flow diagram.



Data extraction and management

Four review authors (BN, RR, BW, WH) extracted data independently onto a specially designed data extraction form. All data were checked by at least two authors. There were no disagreements in this process. Two authors (BN, WH) entered data into Review Manager ([RevMan 2014](#)) and a third review author (GU) checked them.

Assessment of risk of bias in included studies

Three review authors (BN, GU, WH) independently assessed the risk of bias of each included trial. We resolved disagreements by consensus and, if needed, referral to a fourth review author (BW). For each included study, we assessed risk of bias against key criteria of selection bias, performance bias, detection bias, attrition bias, reporting bias, and funding bias, in accordance with methods recommended by The Cochrane Collaboration ([Higgins 2011](#)). We judged each of these criteria using: low risk of bias; high risk of bias; or unclear (either lack of information or uncertainty over the potential for bias) (see [Appendix 2](#)).

Measures of treatment effect

The effect measures of choice were absolute risk difference (RD) for dichotomous data and standard mean difference (SMD) for continuous data. We selected SMD to enable us to analyze the results of several different measurement scales for a particular outcome as a single outcome estimate. We calculated the numbers needed to treat for an additional beneficial outcome (NNTB) and the numbers needed to treat for an additional harmful outcome (NNTH) for the dichotomous variables by $1/ARR$ (absolute risk reduction) with 95% confidence intervals (CIs).

We used Cohen's categories to evaluate the magnitude of the effect size, calculated by SMD, with Hedge's g of 0.2 = small, 0.5 = medium and 0.8 = large ([Cohen 1988](#)). We labelled $g < 0.2$ to be a "not substantial" effect size. We assumed a minimally important difference if Hedges' g was ≥ 0.2 ([Fayers 2014](#)). We set the threshold for "appreciable benefit" or "appreciable harm" for categorical variables by a NNTB or NNTH < 10 ([Moore 2008](#)).

Unit of analysis issues

In the case of multiple SSRI arms compared with one placebo group, we adjusted the number of participants in the placebo group according to the number of SSRI arms for continuous outcomes.

Assessment of heterogeneity

We assessed heterogeneity using the I^2 statistic. We assumed substantial heterogeneity if I^2 was $> 50\%$ ([Higgins 2011](#)). We assessed clinical heterogeneity by assessing the demographic and clinical characteristics of the study populations.

Assessment of reporting biases

We assessed publication bias using a method designed to detect the amount of unpublished data with a null effect that would be required to make any result clinically irrelevant (usually taken to mean a NNT of 10 or more) ([Moore 2008](#)).

Data synthesis

We undertook each meta-analysis using a random-effects model, using the inverse variance method in Review Manager ([RevMan 2014](#)).

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the overall quality of evidence ([Balslem 2008](#)), defined as the extent of confidence in the estimates of treatment benefits and harms. We made quality ratings separately for each of the eight quality indicators. We defined a study to be of high quality when it fulfilled six to eight of the indicators, to be of moderate quality when it fulfilled three to five of the indicators, and to be of low quality if it fulfilled zero to two of the quality indicators. We downgraded the quality of evidence by one level for each of the following factors that we encountered.

- Limitations of study design: $> 50\%$ of the participants in low quality studies.
- Inconsistency of effect size: $I^2 > 50\%$.
- Indirectness: We assessed whether the question being addressed in this systematic review was different from the available evidence regarding the population in routine clinical care, if patients with inflammatory rheumatic diseases and/or depressive disorders were excluded in $> 50\%$ of participants.
- Imprecision: There was only one trial or when there was more than one trial, the total number was < 400 patients or when 95% CI of the effect size included zero.

We categorized the quality of evidence as follows.

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

We analyzed data in three tiers, according to outcome and freedom from known sources of bias.

The first tier uses data meeting current best standards, where studies report the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of last observation carried forward (LOCF) or other imputation methods for dropouts, report an intention-to-treat (ITT) analysis, last eight or more weeks, have a parallel-group design, and have at least 200 participants (preferably at least 400) in the comparison.

The second tier uses data from at least 200 participants, but where one or more of the above conditions is not met (for example, reporting at least 30% pain intensity reduction, using LOCF or a completer analysis, or lasting four to eight weeks).

The third tier of evidence relates to data from fewer than 200 participants, or where there are expected to be significant problems because, for example, the studies are of very short duration (of less than four weeks), where there is major heterogeneity between studies, or where there are shortcomings in allocation concealment, attrition, or incomplete outcome data ([Moore 2010](#)).

Subgroup analysis and investigation of heterogeneity

We planned to separately analyze data for single SSRIs, for studies of 4 to 12 weeks and >12 weeks duration, and for studies with and without industry sponsorship of the primary outcomes. At least two studies should be available for a valid subgroup analysis.

Sensitivity analysis

We planned to exclude studies in which we extracted data from figures and/or in which we calculated SDs from P values and/or in which we used imputation methods to calculate pain reduction rates.

'Summary of findings' table

We calculated the numbers needed to treat for an additional beneficial outcome (NNTB) or harmful outcome (NNTH) in the 'Summary of findings' table according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For outcomes of continuous variables (fatigue, sleep problems), we calculated the NNTB by $1/ARR$ (absolute risk reduction = % absolute improvement or deterioration).

RESULTS

Description of studies

Results of the search

While initial searches were conducted in 2009 and 2010, we redeveloped our search strategies in June 2014. All search strategies at each time point are available in [Appendix 1](#). In 2014, we ran an electronic search in MEDLINE (accessed through PubMed, 1966 to June 2014), the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 5), and EMBASE (accessed through Elsevier, < 1946 to June 2014). The 2014 search identified 6314 articles. After removing 1942 duplicate citations, this number dropped to 4372 articles. As the search strategy was designed as part of a global search strategy to identify all the RCTs on pharmacological and non-pharmacological treatments for fibromyalgia, many of the obtained references were not related to selective serotonin reuptake inhibitor (SSRI) antidepressants. We excluded 4353 references as they did not fulfill inclusion criteria related to the interventions evaluated in this review. We identified 19 studies potentially related to these interventions, and we obtained the full text for each of them. We excluded 11 studies. See [Characteristics of excluded studies](#) for further details about reasons for exclusion and [Figure 1](#) for a study flow diagram. Therefore, we included eight studies. See [Included studies](#) for full description of studies.

Included studies

One study had a cross-over design (Goldenberg 1996) and seven had a parallel design (Anderberg 2000; Arnold 2002; GSK 2005; Hussain 2010; Norregaard 1995; Patkar 2007; Wolfe 1994).

A total of 383 patients diagnosed with fibromyalgia were randomized. Of them, 42 received citalopram, 77 fluoxetine, 84 paroxetine, and 180 placebo. In a cross-over study, the same 31 patients that received fluoxetine also got amitriptyline, placebo or the combination of both drugs. Sample sizes ranged from 40 to 116 patients, with a mean of 57 patients per study.

Five studies were funded by pharmaceutical companies: Glaxo Smith Kline funded Patkar 2007 and GSK 2005; Eli Lilly and Company funded Arnold 2002 and Wolfe 1994; and H. Lundbeck sponsored Norregaard 1995. The remaining studies were funded by public grants (Anderberg 2000; Goldenberg 1996; Hussain 2010).

Baseline demographic characteristics and risks factors were well balanced in most of the studies. Most patients were females (90% to 100%), except for one study in which 77% of patients were males (GSK 2005). Ages ranged from 42.5 to 52.9 years. All the studies used the American College of Rheumatology (ACR) 1990 classification criteria (Wolfe 1990) to diagnose fibromyalgia. Patients with inflammatory rheumatic disease were explicitly excluded in five studies (Arnold 2002; GSK 2005; Norregaard 1995; Patkar 2007; Wolfe 1994). Three studies did not provide detailed information on this topic (Anderberg 2000; Goldenberg 1996; Hussain 2010). Four studies explicitly excluded patients with major depressive symptoms (Anderberg 2000; Arnold 2002; Norregaard 1995; Patkar 2007). Two studies did not provide detailed information on this topic (Hussain 2010; Wolfe 1994). GSK 2005 explicitly included patients with depressive symptoms.

Four studies were conducted in the US (Arnold 2002; Goldenberg 1996; Patkar 2007; Wolfe 1994), one study was conducted in Asia (Hussain 2010), and the remaining studies were in Europe (Anderberg 2000; GSK 2005; Norregaard 1995).

Two studies had a duration of six weeks (Goldenberg 1996; Wolfe 1994), three studies were eight-weeks long (GSK 2005; Hussain 2010; Norregaard 1995), another two had a duration of 12 weeks (Arnold 2002; Patkar 2007), and one study was 16-weeks long (Anderberg 2000).

Interventions

Two studies compared citalopram with placebo using a flexible dose of 20 to 40 mg/day (Anderberg 2000; Norregaard 1995). Three studies compared fluoxetine with placebo, two of them using a fixed dose of 20 mg/day (Goldenberg 1996; Wolfe 1994) and another one using a flexible dose of 20 to 80 mg/day (Arnold 2002). One study compared paroxetine controlled release flexible (mean dose of 39.1 ± 8.6 mg/day) with placebo (Patkar 2007) and another one compared paroxetine 20 mg/day fixed with placebo (GSK 2005). One study compared fluoxetine 20 mg/day with amitriptyline 25 mg/day and a combination of both with placebo (Goldenberg 1996), and another one compared fluoxetine 20 mg/d fixed with melatonin 5 mg/d fixed (Hussain 2010). Three studies did not report on rescue medication (GSK 2005; Hussain 2010; Norregaard 1995). The remaining studies allowed rescue medication such as acetaminophen, aspirin, non-steroidal anti-inflammatory drugs and codeine.

Outcomes

Pain relief, defined by at least 25% pain reduction, was reported in two studies (Arnold 2002; Patkar 2007). We calculated at least 30% pain reduction rates for all studies.

Global improvement was defined as having at least 25% reduction of the Fibromyalgia Impact Questionnaire (FIQ) total score in two studies (Arnold 2002; Patkar 2007). Anderberg 2000 reported the number of patients with global improvement of well-being. Goldenberg 1996 defined global improvement by an at least 25% reduction of a composite score (pain score, tender point score,

global well-being score, physician global assessment) ranging from 0 to 100. We calculated global improvement by at least 25% reduction rates of global severity (Wolfe 1994), and by at least 25% improvement of general well-being (Norregaard 1995) using an imputation method. We could not calculate global improver scores for the remaining studies as they did not assess global measures of well-being.

Fatigue was measured by a single item Visual Analogue Scale (VAS) in six studies (Anderberg 2000; Arnold 2002; Goldenberg 1996; Hussain 2010; Norregaard 1995; Patkar 2007).

Sleep problems were measured by a single item VAS in four studies (Goldenberg 1996; Hussain 2010; Norregaard 1995; Patkar 2007). One study used the sleep item of the Montgomery Asberg Depression Rating Scale (MADRS) (Anderberg 2000).

Four studies assessed depression using the Beck Depression Inventory (BDI) scale (Goldenberg 1996; Norregaard 1995; Patkar 2007; Wolfe 1994). Anderberg 2000 used the MADRS. GSK 2005 and Hussain 2010 used a single item VAS.

Pain intensity was assessed in all the studies, although using different scales: a VAS (0-3) was used in Wolfe 1994, a VAS (0-10) in Anderberg 2000, Arnold 2002, Hussain 2010, and Norregaard 1995 and a VAS (0-100) in Goldenberg 1996, GSK 2005, and Patkar 2007.

Disease-specific health-related quality of life was measured with the FIQ using different scales: FIQ (0-3) in Anderberg 2000 and Norregaard 1995, and FIQ (0-80) was used by Arnold 2002, Goldenberg 1996 and Patkar 2007.

Physical functioning was assessed by a single item VAS scale of the FIQ in three studies (Anderberg 2000; Arnold 2002; Hussain 2010) and by the Health Assessment Questionnaire (HAQ) in two studies (GSK 2005; Wolfe 1994).

Anxiety was assessed by a single item VAS in four studies (Anderberg 2000; Arnold 2002; GSK 2005; Hussain 2010), and by the AIMS anxiety score in one study (Wolfe 1994).

Tenderness was assessed by the myalgic score (Anderberg 2000; Arnold 2002) and by the tender point count (Norregaard 1995; Wolfe 1994) in two studies each. Wolfe 1994 used dolorimetry.

Risk of bias in included studies

The risk of bias of most items was unclear in all studies: see Figure 2 and Figure 3 for a 'Risk of bias' summary and graph, and Characteristics of included studies for detailed information regarding risk of bias assessments of each study.

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

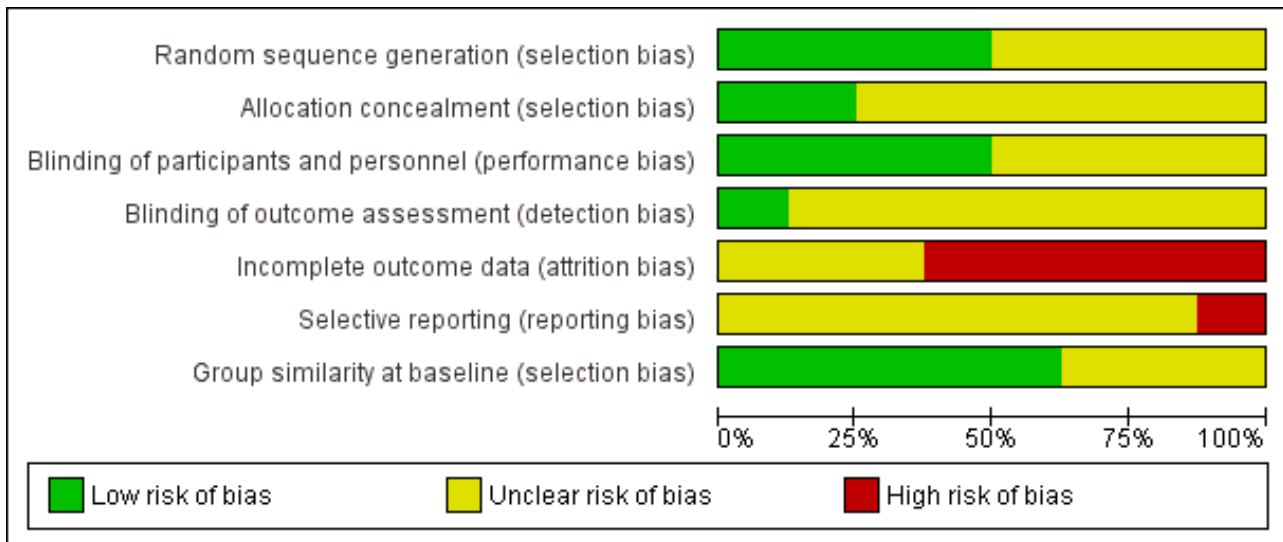


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Group similarity at baseline (selection bias)
Anderberg 2000	+	+	?	?	-	-	?
Arnold 2002	?	?	+	?	?	?	+
Goldenberg 1996	+	?	+	+	-	?	+
GSK 2005	?	?	?	?	-	?	+
Hussain 2010	?	?	?	?	?	?	?
Norregaard 1995	?	?	+	?	-	?	?
Patkar 2007	+	+	+	?	?	?	+
Wolfe 1994	+	?	?	?	-	?	+

Allocation

All studies were randomized. Two studies properly described sequence generation and allocation concealment (Anderberg 2000; Patkar 2007), but no information was provided in other studies

(Arnold 2002; GSK 2005; Hussain 2010). Goldenberg 1996 and Wolfe 1994 described sequence generation, but gave no details regarding allocation concealment. In terms of selection bias, there were no significant differences in demographic and pain parameters at baseline between SSRI and control groups.

Blinding

All studies reported to be "double-blind". However, only four studies reported that all tablets were identical in appearance (Arnold 2002; Goldenberg 1996; Norregaard 1995; Patkar 2007). Only one study provided details of the blinding of the outcome assessor (Goldenberg 1996).

Incomplete outcome data

One study had no dropouts (Hussain 2010). Dropout rates were high across studies (12% to 43%) and most studies also reported a high rate of dropouts in the placebo group (5% to 40%). Intention to treat (ITT) analysis was performed in two studies by last observation carried forward (LOCF) (Arnold 2002; Patkar 2007). Anderberg 2000 and Wolfe 1994 reported some outcomes based on ITT-analysis (LOCF), and some outcomes based on completer analyzes.

Selective reporting

It was not possible to assess selective outcome reporting as we did not have access to the study protocols.

Effects of interventions

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

We analyzed the following effects of interventions separately: SSRIs versus placebo and SSRIs versus other active drugs. The quality of evidence was very low for each outcome. We downgraded the quality of evidence to very low due to concerns about risk of bias and studies with few participants. There was second tier evidence (Moore 2010) of efficacy for comparisons of SSRIs versus placebo in the outcomes: number of patients with an at least 30% pain reduction, number of patients with a clinically important global improvement, depression, and tolerability. There was third tier evidence of efficacy for comparisons of SSRIs with placebo for the remaining outcomes, and for all comparisons of SSRIs with active drug controls.

SSRIs versus placebo

Number of patients with at least 30% pain reduction

We analyzed six studies with 343 participants experiencing pain reduction rates of at least 30%. SSRIs were statistically significantly superior to placebo ($P = 0.04$); RD 0.10, 95% CI 0.01 to 0.20; 56/172 (32.6%) of patients with SSRIs and 39/171 (22.8%) of patients with placebo reported at least 30% pain reduction resulting in a NNTB of 10 (95% CI 5 to 100). The use of SSRIs in fibromyalgia had no appreciable clinical benefit compared to placebo. The quality of evidence was very low (see [Analysis 1.1](#)).

Number of patients with a clinically important global improvement

We analyzed six studies with 330 patients with a clinically important global improvement. SSRIs were statistically significantly superior to placebo ($P = 0.001$); RD 0.14, 95% CI 0.06 to 0.23; 50/168 (29.8%) of patients with SSRIs and 26/162 (16.0%) of patients with placebo reported a clinically important global improvement resulting in a NNTB of 7 (95% CI 4 to 17). The use of SSRIs in fibromyalgia had an appreciable clinical benefit compared to placebo. The quality of evidence was very low ([Analysis 1.2](#)).

Fatigue

We analyzed five studies with 192 participants for reduction of fatigue. SSRIs were not statistically significant superior to placebo ($P = 0.08$) (9.4% relative improvement); SMD -0.26, (95% CI -0.55 to 0.03). The quality of evidence was very low ([Analysis 1.3](#)).

Sleep problems

We analyzed five studies with 193 participants for reduction of sleep problems. SSRIs were not statistically significant superior to placebo ($P = 0.86$) (1.2% relative deterioration); SMD 0.03, 95% CI -0.26 to 0.31. The quality of evidence was very low ([Analysis 1.4](#)).

Depression

We analyzed six studies with 244 participants for reduction of depression scores. SSRIs were statistically and clinically significant superior over placebo ($P = 0.005$) (relative improvement 30.4%); SMD -0.39, 95% CI -0.65 to -0.14. The effect size was small according to Cohen's categories. We could not enter one study into the meta-analysis: paroxetine was not statistically superior ($P = 0.08$) over placebo (Patkar 2007). The quality of evidence was very low ([Analysis 1.5](#)).

Tolerability (discontinuation rates due to adverse events)

We analyzed five studies with 284 participants for discontinuation rates due to adverse events. There was no statistically significant or clinically important difference between SSRIs and placebo ($P = 0.46$); RD 0.04, 95% CI -0.06 to 0.14; 23/146 (15.8%) of patients discontinued treatment in SSRI groups and 14/138 (10.1%) in placebo groups due to adverse events. The quality of evidence was very low ([Analysis 1.6](#)).

Safety (Serious adverse events)

We analyzed two studies with 168 participants for serious adverse events. There was no statistically significant or clinically important difference between SSRIs and placebo ($P = 0.46$); RD -0.01, 95% CI -0.07 to 0.05. Serious adverse events were reported by 3/84 (3.6%) patients with SSRIs and by 4/84 (4.8%) of patients with placebo. The quality of evidence was very low ([Analysis 1.7](#)).

Pain intensity

We analyzed seven studies with 330 participants for reduction in pain intensity. SSRIs were statistically and clinically significantly superior to placebo ($P = 0.03$); SMD -0.37, 95% CI -0.69 to -0.04). The quality of evidence was very low ([Analysis 1.8](#)).

Disease-specific quality of life

We analyzed two studies with 92 participants for improvement in disease-specific quality of life. SSRIs were statistically significant and clinically superior to placebo ($P = 0.001$); SMD -0.70, 95% CI -1.12 to -0.28. The effect size was moderate according to Cohen's categories. We could not enter one study into the meta-analysis; paroxetine was statistically significantly superior over placebo in reducing the FIQ total score (Patkar 2007). The quality of evidence was very low ([Analysis 1.9](#)).

Physical functioning

We analyzed three studies with 117 participants for improvement in physical functioning. SSRIs were not statistically significant or

clinically superior to placebo ($P = 0.65$); SMD -0.06, 95% CI -0.34 to 0.21. The quality of evidence was very low ([Analysis 1.10](#)).

Anxiety

We analyzed four studies with 148 participants for reduction of anxiety scores. SSRIs were not statistically significant or clinically superior to placebo ($P = 0.46$); SMD -0.11, 95% CI -0.44 to 0.21. Two studies were not suited for meta-analysis. We could not enter one study into the meta-analysis; paroxetine was superior to placebo ($P < 0.05$) ([Patkar 2007](#)). Quality of evidence was very low ([Analysis 1.11](#)).

Tenderness

We analyzed four studies with 158 participants for reduction of tenderness. SSRIs were not statistically significant or clinically superior to placebo ($P = 0.14$); SMD -0.23, 95% CI -0.58 to 0.11. We could not enter one study into the meta-analysis; paroxetine was not statistically superior over placebo ([Patkar 2007](#)). The quality of evidence was very low ([Analysis 1.12](#)).

SSRIs versus active drug

Number of patients with an at least 30% pain reduction

We analyzed two studies with 94 participants experiencing pain reduction rates of at least 30%. SSRIs were not statistically significant superior to other active drugs ($P = 0.60$); RD -0.07, 95% CI -0.35 to 0.20 ([Analysis 2.1](#)).

Number of patients with a clinically important global improvement

We analyzed one study with 94 patients with a clinically relevant global improvement. SSRIs were not statistically significant superior to other active drugs ($P = 0.23$); RD 0.13, 95% CI -0.08 to 0.35 ([Analysis 2.2](#)).

Fatigue

We analyzed two studies with 94 participants for reduction of fatigue. SSRIs were not statistically significant superior to other active drugs ($P = 0.32$); SMD 0.21, 95% CI -0.55 to 0.61 ([Analysis 2.3](#)).

Sleep problems

We analyzed two studies with 94 participants for reduction of sleep problems. SSRIs were not statistically superior to other active drugs ($P = 0.13$); SMD 0.31, 95% CI -0.10 to 0.72 ([Analysis 2.4](#)).

Depression

We analyzed two studies with 94 participants for reduction of depression scores. SSRIs were not statistically significant superior to other active drugs ($P = 0.67$); SMD 0.11, 95% CI -0.40 to 0.63 ([Analysis 2.5](#)).

Tolerability (discontinuation rates due to adverse events)

We analyzed two studies with 94 participants for discontinuation rates due to adverse events. There was no statistically significant or clinically important difference between SSRIs and other active drugs ($P = 0.69$); RD 0.01, 95% CI -0.05 to 0.06 ([Analysis 2.6](#)).

Serious adverse events

The two studies did not report on serious adverse events.

Pain intensity

We analyzed two studies with 94 participants for reduction in pain intensity. SSRIs were not statistically significant superior to other active drugs ($P = 0.95$); SMD 0.02, 95% CI -0.28 to 0.51 ([Analysis 2.7](#)).

Disease-specific quality of life

We analyzed one study with 43 participants for improvement of disease-specific quality of life. SSRIs were not statistically significant superior to other active drugs ($P = 0.48$); SMD -0.22, 95% CI -0.82 to 0.38 ([Analysis 2.8](#)).

Physical functioning

We analyzed one study with 51 participants for improvement of physical functioning. SSRIs were not statistically significant superior to other active drugs ($P = 0.11$); SMD -0.46, 95% CI -1.02 to 0.20 ([Analysis 2.9](#)).

Anxiety

We analyzed one study with 51 participants for reduction of anxiety scores. SSRIs were not statistically significant superior to other active drugs ($P = 0.34$); SMD -0.27, 95% CI -0.82 to 0.02 ([Analysis 2.10](#)).

Tenderness

We analyzed one study with 43 participants for reduction of anxiety scores. SSRIs were not statistically significant or clinically superior to other active drugs ($P = 0.32$) SMD 0.31, 95% CI -0.29 to 0.91 ([Analysis 2.11](#)).

Investigation of heterogeneity and subgroup analyses

Placebo-controlled studies: There was low heterogeneity in the outcomes: 30% pain reduction ([Analysis 1.1](#)), global improves ([Analysis 1.2](#)), fatigue ([Analysis 1.3](#)), sleep problems ([Analysis 1.4](#)), depression ([Analysis 1.5](#)), serious adverse events ([Analysis 1.7](#)), disease-related quality of life ([Analysis 1.9](#)), anxiety ([Analysis 1.11](#)), and tenderness ([Analysis 1.12](#)). Heterogeneity was moderate for discontinuation rates due to adverse events ([Analysis 1.6](#)) and high ($I^2 = 51\%$) for pain intensity ([Analysis 1.8](#)). Heterogeneity was due to studies with industry funding ($I^2 = 66\%$). I^2 of pain reduction was 0% in studies without industry funding.

Active drug-controlled studies: There was low heterogeneity in the outcomes: fatigue ([Analysis 2.3](#)), sleep problems ([Analysis 2.4](#)) and discontinuation due to adverse events ([Analysis 2.6](#)). Heterogeneity was moderate for the outcomes: depression ([Analysis 2.5](#)) and physical functioning ([Analysis 2.9](#)). Heterogeneity was high for the outcome of pain reduction of at least 30%. ([Analysis 2.1](#))

There were no statistically significant subgroup differences between the three SSRIs in the comparison to placebo for the outcomes 30% pain reduction ($P = 0.81$; $I^2 = 0\%$) ([Analysis 1.1](#)), global improvement ($P = 1.00$, $I^2 = 0\%$) ([Analysis 1.2](#)), fatigue ($P = 0.61$, $I^2 = 0\%$) ([Analysis 1.3](#)), sleep problems ($P = 0.68$, $I^2 = 0.68$) ([Analysis 1.4](#)), discontinuation rates due to adverse events ($P = 0.09$, $I^2 = 59$) ([Analysis 1.6](#)), pain intensity ($P = 0.20$, $I^2 = 39\%$) ([Analysis 1.8](#)), depression ($P = 0.37$, $I^2 = 0\%$) ([Analysis 1.5](#)), anxiety ($P = 0.58$, $I^2 = 0\%$) ([Analysis 1.11](#)), and tenderness ($P = 0.15$, $I^2 = 0.52$) ([Analysis 1.12](#)).

There were no clinically relevant differences in the demographic and clinical characteristics of the populations of the studies.

There were no statistically significant differences in the primary outcomes in studies with and without industry sponsorship, except for global improvers (Table 1).

Sensitivity analysis

We could not conduct the predefined sensitivity analyzes because less than two studies were available.

Publication bias

To move the NNTB for global improvers from 7 to 10, 140 extra patients would have to be included in entirely negative trials (zero treatment effect).

DISCUSSION

Summary of main results

There is very low quality evidence that the SSRIs, citalopram, fluoxetine, and paroxetine have a small benefit compared with placebo in increasing the number of patients who experience at least 30% pain reduction and 25% global improvement. There was very low quality evidence that SSRIs were superior to placebo in reducing pain intensity and depression. Because of the very low quality of evidence, we are uncertain if there are differences between the SSRIs citalopram, fluoxetine, paroxetine, and placebo in the reduction of sleep problems, fatigue, anxiety, tenderness, improving physical functioning, health-related quality of life, tolerability (dropout rate due to adverse events), and safety (frequency of serious adverse events). It would be inappropriate to suggest a class effect of SSRIs on fibromyalgia symptoms.

Overall completeness and applicability of evidence

The applicability of evidence is strongly limited for the following reasons.

1. The exclusion criteria were strict in most studies; potential participants with other health issues were excluded. Therefore, the study results cannot be applied to people with fibromyalgia complicated by other medical diseases, including inflammatory rheumatic diseases. The study results cannot be applied to people with fibromyalgia and concomitant psychiatric comorbidity (i.e. depression), because no subgroup analysis of people with psychiatric comorbidity were conducted in the studies.
2. Concomitant medications were not allowed in most studies; potential participants using other medications for fibromyalgia symptoms were excluded. In general practice, patients often use SSRIs as part of a multiple-drug regimen, rather than as monotherapy.
3. The majority of the participants were middle-aged women, making it difficult to apply the results to men, seniors and adolescents.
4. Fibromyalgia is a chronic condition, potentially requiring treatment over an entire lifetime. The longest study reviewed only considered improvement at the end of four months. None of the studies reviewed provide any insight into the long-term efficacy of SSRIs for fibromyalgia symptoms.
5. Finally, no SSRI has been approved for fibromyalgia by any drug agency. Some SSRIs (such as the ones included in this review) are approved for anxiety and depressive disorders.

Quality of the evidence

Some of the included studies were published before the publication of the CONSORT statement, which might partly explain their low quality in data reporting (CONSORT 2010). The evidence of the benefits and harms of SSRIs compared to placebo and other active drugs is severely limited by the very low quality of evidence. There is no unbiased evidence that SSRIs are superior to placebo in treating the key symptoms of fibromyalgia, namely pain, fatigue and sleep problems.

Potential biases in the review process

Most studies analyzed were conducted before registers of clinical trials were established. Therefore we might have missed non-published studies with negative results. We used an imputation method for responder analyzes.

Agreements and disagreements with other studies or reviews

Our results are in line with other recent systematic reviews and meta-analyzes (that include the same RCTs) that the SSRIs, citalopram, fluoxetine, and paroxetine offer a small benefit over placebo for the relief of pain and depression, but are not superior to placebo in reducing other key symptoms of fibromyalgia, such as fatigue and sleep problems (Häuser 2009; Häuser 2012b; Sommer 2012). The use of the Cochrane 'Risk of bias' tool and GRADE approach to classify the quality of evidence in our review, point out that all statements on efficacy and harms of SSRIs are based on low quality evidence.

SSRIs were rather well tolerated during the trials; the dropout rate did not differ from placebo in our review. Overall adverse events were quite mild and not highly reported across studies. They were more common in the treatment groups than in the placebo groups, with dry mouth and sexual dysfunction being significantly more reported in the treatment groups. Treatment with SSRIs and serotonin/norepinephrine reuptake inhibitors (SNRIs) is associated with higher rates of sexual dysfunction than with other classes of antidepressants (Clayton 2014). All SSRIs showed similar frequency and range of adverse events, the most common ones being headache, dry mouth, nausea, fatigue, vertigo, sweating, nervousness, and sexual side effects. Nonetheless, Patkar 2007 reported a high percentage of adverse events (65.5% in the treatment group and 58.6% in the placebo one), but only a minority of patients withdrew for this reason. However, a large amount of clinical experience suggests that the safety we report may be overstated. Polypharmacy (the use of multiple medications) is a common issue for fibromyalgia patients. The reviewed trials all administered SSRIs without concomitant central-acting medication therapies. SSRIs have potential drug interactions with tricyclic antidepressants, tramadol, triptans, carbamazepine, alcohol, diuretics, monamine oxidase inhibitors, and zolpidem, all which are often concomitantly used in fibromyalgia treatment. SSRIs also have withdrawal syndromes that are not considered in the studies we reviewed (Fava 2015). Lastly, SSRIs have been linked to increased suicidal tendency, leading the US Food and Drug Administration to issue a black box warning in 2007 (FDA 2007). The review authors suggest that the use of SSRIs in the general population will be more problematic than reflected in the results of this systematic review.

Despite low quality evidence reported here, most clinical practice guidelines recommend the use of SSRIs, mainly fluoxetine, either on its own or in combination with other tricyclic antidepressants. Thus, EULAR recommended the use of fluoxetine (strength of recommendation A) (Carville 2008), the American Society of Pain suggests the use of SSRIs such as fluoxetine, alone or in combination with tricyclics, for pain relief (strength of recommendation B) (Buckhardt 2005). In contrast, the German guideline on fibromyalgia gave only a weak recommendation for the use of SSRIs in patients with fibromyalgia plus depressive and/or anxiety disorder (Sommer 2012). Our review does not support the American Pain Society and EULAR recommendations.

SSRIs did not differ in their modest efficacy, tolerability, and low quality of evidence from amitriptyline and melatonin. This finding is in line with the results of all head-to-head comparisons of SSRIs with amitriptyline (Häuser 2012b) which we did not include in this review due to methodological reasons (see [Excluded studies](#)). As with SSRIs, there is no evidence that is both supportive and unbiased that demonstrates that amitriptyline has a beneficial effect (Moore 2012). A network meta-analysis did not find significant differences between tricyclic agents, SSRIs, SNRIs, and anticonvulsants in reducing pain and limitations of disease-related quality of life (Nüesch 2013). There is no evidence that SSRIs are superior or inferior to other commonly used fibromyalgia treatments.

AUTHORS' CONCLUSIONS

Implications for practice

The total available evidence of the benefits and harms of SSRIs in fibromyalgia is of very low quality. We are uncertain whether taking SSRIs for an average of eight weeks improves fibromyalgia symptoms. Currently, SSRIs are not approved for fibromyalgia by international drug agencies. The US Food and Drug Administration black box warnings for increased suicidal tendency in young adults taking antidepressants should be kept in mind (FDA 2007).

Implications for research

1. A re-analysis of the data using baseline observation carried forward and responder analysis where discontinuation is classified as non-response would allow a more precise estimate of the efficacy of SSRIs in fibromyalgia, likely reducing the effect size of the clinical benefits reported here.
2. Clinical effectiveness trials with antidepressants in fibromyalgia are necessary; they should provide information on the proportion of participants with a moderate or substantial response, with tolerable adverse events and with willingness to continue therapy (Moore 2010).
3. As fibromyalgia is a chronic illness, duration of studies should be substantially longer (at least 48 weeks) to investigate the long-term use and adverse events of antidepressants.
4. Studies should include patients with other comorbidities, such as mood disorders and inflammatory rheumatic diseases.
5. Studies should include patients with different demographics, different disease durations and different severity levels to allow for conclusions to be generalized. Current studies are almost uniformly of middle-aged Caucasian women.
6. The current recommended model for treatment of severe fibromyalgia cases is the utilization of a multidisciplinary approach (Ablin 2013). Future studies should consider SSRI use, both in isolation, as well as part of multidisciplinary programs and multiple drug regimens.

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REFERENCES

References to studies included in this review

Anderberg 2000 {published data only}

Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia—a randomized, double-blind, placebo-controlled study. *European Journal of Pain* 2000;**4**(1):27-35.

Arnold 2002 {published data only}

Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PE Jr. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. *American Journal of Medicine* 2002;**112**(3):191-7.

Goldenberg 1996 {published data only}

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

GSK 2005 {published data only}

GlaxoSmithKline. Treatment of fibromyalgia: a randomized, double blind, placebo-controlled study of paroxetine, a selective serotonin re-uptake inhibitor. Study ID 29060/433. <http://www.gsk-clinicalstudyregister.com/>.

Hussain 2010 {published data only}

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

Norregaard 1995 {published data only}

Norregaard J, Volkmann H, Danneskiold-Samsøe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. *Pain* 1995;**61**(3):445-9.

Patkar 2007 {published data only}

Patkar AA, Masand PS, Krulewicz S, Mannelli P, Peindl K, Beebe KL, et al. A randomized, controlled, trial of controlled release paroxetine in fibromyalgia. *The American Journal of Medicine* 2007;**120**:448-54.

Wolfe 1994 {published data only}

Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. *Scandinavian Journal of Rheumatology* 1994;**23**(5):255-9.

References to studies excluded from this review

Ataoglu 1997 {published data only}

Ataoglu S, Ataoglu A, Erdogan F, Saraç J. Comparison of paroxetine, amitriptyline in the treatment of fibromyalgia. *Turkish Journal of Medical Science* 1997;**27**:535-9.

Cantini 1994 {published data only}

Cantini F, Bellandi F, Niccoli L, Di Munno O. Fluoxetin combined with cyclobenzaprine in the treatment of fibromyalgia. [Italian]. *Minerva Medicine* 1994;**85**(3):97-100.

Cantini 1995 {published data only}

Cantini F, Niccoli L, Bellandi F, Di Munno O. Effectiveness of fluoxetine associated with cyclobenzaprine in the treatment of fibromyalgia: Twelve-months-follow up results. [Italian]. *Reumatismo* 1995;**47**(2):103-8.

Capaci 2002 {published data only}

Capaci K, Hepguler S. Comparison of the effects of amitriptyline and paroxetine in the treatment of fibromyalgia syndrome. *The Pain Clinic* 2002;**14**(3):223-8.

De Vanna 1998 {published data only}

De Vanna M, Ventre L. Fluoxetine and primary fibromyalgic syndrome: A double blind study. [Italian]. *Medicina Psicosomatica* 1998;**43**(2):73-82.

Erhan 2000 {published data only}

Erhan E, Uyar M, Turan S, Yegül I, Tuğlular L, Gökçe, et al. Fluvoxamine versus amitriptyline in the treatment of fibromyalgia. *Agri* 2000;**12**:32-6.

Giordano 1999 {published data only}

Giordano N, Geraci S, Santacroce C, Mattii G, Battisti E, Gennari C. Efficacy and tolerability of paroxetine in patients with fibromyalgia syndrome: A single-blind study. *Current Therapeutic Research, Clinical and Experimental* 1999;**60**(12):696-702.

Gonzalez-Viejo 2005 {published data only}

Gonzalez-Viejo MA, Avellanet M, Hernandez-Morcuende MI. A comparative study of fibromyalgia treatment: ultrasonography and physiotherapy versus sertraline treatment. [French]. *Annales de Réadaptation et de Médecine Physique* 2005;**48**(8):610-5.

Nishikai 2003 {published data only}

Nishikai M, Akiya K. Fluvoxamine therapy for fibromyalgia. *Journal of Rheumatology* 2003;**30**(5):1124.

Ozerbil 2006 {published data only}

Ozerbil O, Okudan N, Gökbel H, Levendoglu F. Comparison of the effects of two antidepressants on exercise performance of the female patients with fibromyalgia. *Clinical Rheumatology* 2006;**25**(4):495-7.

Sencan 2004 {published data only}

Sencan S, Ak S, Karan A, Muslumanoglu L, Ozcan E, Berker E. A study to compare the therapeutic effect of aerobic exercise and paroxetine in fibromyalgia syndrome. *Journal of Back and Musculoskeletal Rehabilitation* 2004;**17**:57-61.

Additional references

Ablin 2013

Ablin J, Fitzcharles MA, Buskila D, Shir Y, Sommer C, Häuser W. Treatment of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines with special emphasis on complementary and alternative therapies.

Evidence-Based Complementary Alternative Medicine 2013 Nov 21 [Epub ahead of print].

Arnold 2013

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

Balshem 2008

Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(4):401-6.

Bennett 2007

Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2,596 people with fibromyalgia. *BMC Musculoskeletal Disorders* 2007;**8**:27.

Bradley 2009

Bradley LA. Pathophysiology of fibromyalgia. *American Journal of Medicine* 2009;**122**(12 Suppl):S22-30.

Branco 2010

Branco JC, Bannwarth B, Failde I, Abello Carbonell J, Blotman F, Spaeth M. Prevalence of fibromyalgia: a survey in five European countries. *Seminars in Arthritis and Rheumatism* 2010;**39**:448-53.

Buckhardt 2005

Buckhardt CS, Goldenberg D, Crofford L, Gerwin R, Gowens S, Jackson K, et al. Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children. Glenview: American Pain Society (APS), 2005.

Carville 2008

Carville SF, Arendt-Nielsen S, Bliddal H, Blotman F, Branco JC, Buskila D, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Annals of Rheumatic Diseases* 2008;**67**(4):536.

Clayton 2014

Clayton AH, Croft HA, Handiwala L. Antidepressants and sexual dysfunction: mechanisms and clinical implications. *Postgraduate Medicine* 2014;**126**:91-9.

CMSG 2014

Cochrane Musculoskeletal Group. Proposed Outcomes for Summary of Findings. <http://musculoskeletal.cochrane.org/proposed-outcomes> 2014.

Cohen 1988

Cohen J. Statistical Power Analysis for the Behavioral Sciences. Vol. 1, Hillsdale: Lawrence Erlbaum Associates, 1988.

CONSORT 2010

Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c869.

Fava 2015

Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. *Psychotherapy Psychosomatics* 2015;**84**:72-81.

Fayers 2014

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

FDA 2007

FDA Proposes New Warnings About Suicidal Thinking, Behavior in Young Adults Who Take Antidepressant Medications. Available from <http://www.fda.gov> (accessed May 2008).

Furukawa 2005

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

Haviland 2012

Haviland MG, Banta JE, Przekop P. Hospitalisation charges for fibromyalgia in the United States, 1999-2007. *Clinical Experimental Rheumatology* 2012;**30**(6 Suppl 74):129-35.

Higgins 2011

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

Häuser 2009

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

Häuser 2011

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

Häuser 2012a

Häuser W, Jung E, Erbslöh-Möller B, Gesmann M, Kühn-Becker H, Petermann F, Langhorst J, Weiss T, Thoma R, Winkelmann A. German fibromyalgia consumer reports. Benefits and harms of fibromyalgia syndrome therapies. [German]. *Schmerz* 2012;**26**(2):150-9.

Häuser 2012b

Häuser W, Wolfe F, Tölle T, Üçeyler N, Sommer C. The role of antidepressants in the management of fibromyalgia syndrome: a systematic review and meta-analysis. *CNS Drugs* 2012;**26**:297-307.

Häuser 2013a

Häuser W, Galek A, Erbslöh-Möller B, Köllner V, Kühn-Becker H, Langhorst J, et al. Posttraumatic stress disorder in fibromyalgia syndrome: prevalence, temporal relationship between

posttraumatic stress and fibromyalgia symptoms, and impact on clinical outcome. *Pain* 2013;**154**(8):1216-23.

Häuser 2013b

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

Knight 2013

Knight T, Schaefer C, Chandran A, Zlateva G, Winkelmann A, Perrot S. Health-resource use and costs associated with fibromyalgia in France, Germany, and the United States. *ClinicoEconomics and Outcomes Research* 2013;**5**:171-180.

Lange 2010

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

Lee 2010

Lee YH, Choi SJ, Ji JD, Song GG. Candidate gene studies of fibromyalgia: a systematic review and meta-analysis. *Rheumatology International* 2010;**32**:417-26.

Legagneux 2001

Legagneux E, Mora JJ, Spreux-Varoquaux O, Thorin I, Herrou M, Alvado G, et al. Cerebrospinal fluid biogenic amine metabolites, plasma-rich platelet serotonin and [3H]imipramine reuptake in the primary fibromyalgia syndrome. *Rheumatology* 2001;**40**(3):290-6.

Marschall 2011

Marschall U, Arnold B, Häuser W. Treatment and healthcare costs of fibromyalgia syndrome in Germany: analysis of the data of the Barmer health insurance (BEK) from 2008-2010. [German]. *Schmerz* 2011;**25**:402-10.

Mease 2011

Mease PJ, Clauw DJ, Christensen R, Crofford LJ, Gendreau RM, Martin SA, et al. OMERACT Fibromyalgia Working Group. Toward development of a fibromyalgia responder index and disease activity score: OMERACT module update. *Journal of Rheumatology* 2011;**38**:1487-95.

Moore 2008

Moore RA, Barden J, Derry S, McQuay HJ. Systematic Reviews in Pain Research: Methodology Refined. Seattle: IASP Press, 2008.

Moore 2010

Moore RA, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al. ACTINPAIN Writing Group of the IASP Special Interest Group on Systematic Reviews in Pain Relief, Cochrane Pain, Palliative and Supportive Care Systematic Review Group Editors. "Evidence" in chronic pain - establishing best practice in the reporting of systematic reviews. *Pain* 2010;**150**(3):386-9.

Moore 2012

Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: [10.1002/14651858.CD008242](https://doi.org/10.1002/14651858.CD008242)]

Mork 2010

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

Mork 2012

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

Nakamura 2014

Nakamura I, Nishioka K, Usui C, Osada K, Ichibayashi H, Ishida M, et al. An epidemiological internet survey of fibromyalgia and chronic pain in Japan. *Arthritis Care and Research* 2014;**66**(7):1093-101.

Nishishinya 2006

Nishishinya MB, Walitt B, Urrútia G, Mease PJ, Rodríguez A, Riera Lizardo RJ, et al. Anti-depressants and centrally active agents for fibromyalgia syndrome. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: [10.1002/14651858.CD006192](https://doi.org/10.1002/14651858.CD006192)]

Nüesch 2013

Nüesch E, Häuser W, Bernardy K, Barth J, Jüni P. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. *Annals of Rheumatic Diseases* 2013;**72**:955-62.

RevMan 2014 [Computer program]

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

Russell 1992

Russell IJ, Vaeroy H, Javors M, Nyberg F. Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositissyndrome and rheumatoid arthritis. *Arthritis and Rheumatism* 1992;**35**:550-6.

Smythe 1981

Smythe HA. Textbook of Rheumatology. 1st Edition. Philadelphia: WB Saunders, 1981.

Sommer 2012

Sommer C, Häuser W, Burgmer M, Engelhardt R, Gerhold K, Petzke F, et al. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. [German]. Etiology and pathophysiology of fibromyalgia syndrome. *Schmerz* 2012;**26**(3):259-67.

Tort 2012

Tort S, Urrútia G, Nishishinya MB, Walitt B. Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: [10.1002/14651858.CD009807](https://doi.org/10.1002/14651858.CD009807)]

van Houdenhove 2005

Van Houdenhove B, Egle U, Luyten P. The role of life stress in fibromyalgia. *Current Rheumatology Reports* 2005;**7**:365-70.

Wolfe 1990

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria, for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis and Rheumatism* 1990;**33**(12):1863-4.

Wolfe 1995

Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis and Rheumatism* 1995;**38**:19-25.

Wolfe 2010

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis and Rheumatism* 2010;**62**(5):600-10.

Wolfe 2011a

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

Wolfe 2011b

Wolfe F, Häuser W, Hassett AL, Katz RS, Walitt BT. The development of fibromyalgia-I: examination of rates and predictors in patients with rheumatoid arthritis (RA). *Pain* 2011;**152**(2):291-9.

Wolfe 2013

Wolfe F, Brähler E, Hinz A, Häuser W. Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population. *Arthritis Care and Research* 2013;**65**:777-85.

Wolfe 2014

Wolfe F. Fibromyalgia research criteria. *Journal of Rheumatology* 2014;**41**:187.

Yunus 1981

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

Yunus 1982

Yunus M, Masi AT, Calabro JJ, Shah IK. Primary fibromyalgia. *American Family Physician* 1982;**25**(5):115-21.

Yunus 1984

Yunus MB. Primary fibromyalgia syndrome: current concepts. *Comprehensive Therapy* 1984;**10**(8):21-8.

Üceyler 2013a

Üceyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Schmid A, et al. Small fibre pathology in patients with fibromyalgia syndrome. *Brain* 2013;**136**:1857-67.

Üceyler 2013b

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

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Anderberg 2000

Methods	<p>Study setting: Single center study in Sweden</p> <p>Study design: Parallel</p> <p>Study duration: (1) duration wash-out not reported, (2) 16 weeks titration and maintenance, (3) no follow-up</p>
Participants	<p>Inclusion criteria: ACR criteria (1990)</p> <p>Exclusion criteria: Patients with severe heart diseases, such as angina pectoris or post-heart infarct, as well as brain infarction, suicidal thoughts or who were seriously depressed (in need of immediate psychiatric care), and who took major or minor tranquilizers, major antidepressants or strong analgesics</p> <p>No separate demographic data for citalopram (N = 20) and Placebo (N = 19) reported; total sample: 100% women, mean age 49 years, race not reported; citalopram pain baseline FIQ subscale 6.6 (SD 2.2); placebo pain baseline FIQ subscale 6.6 (SD 1.9); no FIQ total scores reported</p>
Interventions	<p>Citalopram: 10-40 mg/day p.o. Patients started with either 10 or 20 mg/day for the first week and increased the dose by 10 mg every fifth day up to either 30 or 40 mg/day</p> <p>Placebo: p.o. for 16 weeks</p>

Anderberg 2000 (Continued)

Rescue medication: Paracetamol 500 mg twice daily or acetylsalicylic acid 1g twice daily were allowed

Co-therapies allowed or prohibited: No information provided

Outcomes

At least 30% pain reduction: Calculated by imputation method

Global improvement: Not reported

Fatigue: FIQ subscale VAS 0-10

Sleep problems: Item reduced sleep of the Montgomery Asberg Depression Rating Scale

Drop out due to adverse: Reported

Serious adverse events: Not reported

Depression: FIQ subscale VAS 0-10; total score of Montgomery Asberg Depression Rating Scale not reported

Pain: VAS 0-10

Disease-related quality of life: FIQ total score VAS 0-80 not reported

Physical functioning: FIQ subscale 0-10

Anxiety: FIQ subscale VAS 0-10

Tenderness: Myalgic score

Notes

Adverse effects were more common in the citalopram-treated group as compared to the placebo one. The most commonly seen side effects were headache, nausea, fatigue, vertigo, sweating, sexual side effects and dry mouth. Three patients stopped citalopram treatment after the first dose due to severe nausea and severe dizziness

Funding: Supported by public grants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was made at the medical products agency, and the investigator had a coded list"
Allocation concealment (selection bias)	Low risk	"The code was held secret to the involved investigators and patients until the end of study"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis for most outcomes
Selective reporting (reporting bias)	High risk	FIQ total score and total score of Montgomery Asberg Depression Rating Scale not reported

Anderberg 2000 (Continued)

Group similarity at baseline (selection bias)	Unclear risk	No demographic data of citalopram and placebo group reported
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Arnold 2002

Methods	<p>Study setting: Single center study in US</p> <p>Study design: Parallel</p> <p>Study duration: (1) duration wash-out not reported, (2) 12 weeks titration and maintenance, (3) no follow-up</p>
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Participants	<p>Inclusion criteria: At least 18 years of age and met the ACR criteria (1990)</p> <p>Exclusion criteria: Evidence of traumatic injury, inflammatory rheumatic disease, or infectious or endocrine-related arthropathy; unstable medical illness; a lifetime history of hypomania, mania, psychosis or dementia; alcohol or substance dependence during the past months; substantial risk of suicide; any current Axis I disorder; a score ≥ 10 on the Hamilton Depression Rating Scale (0-17); received any antidepressants within 2 weeks before randomisation; received investigational medications within 3 months before randomisation; previously received fluoxetine for fibromyalgia</p> <p>Fluoxetine: N = 30; Mean age 46 years; 100% women; 90% white; Pain baseline 6.1 (SD 1.9); FIQ total baseline 42 (SD 14)</p> <p>Placebo: N = 30; Mean age 46 years; 100% women; 97% white; Pain baseline 6.0 (SD 1.9); FIQ total baseline 44 (SD 14)</p>
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Interventions	<p>Fluoxetine 10-80 mg p.o. 1/d for 12 weeks. Starting dose of 20 mg. After 2 weeks, the dose could be in 10- to 20-mg increments every 2 weeks to a maximum of 80 mg/d</p> <p>Placebo p.o. 1/d for 12 weeks</p> <p>Rescue medication: Subjects were allowed to continue acetaminophen or NSAID on their usual schedule</p> <p>Co-therapies allowed or prohibited: No information provided</p>
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Outcomes	<p>At least 30% pain reduction: Calculated by imputation method ($\geq 25\%$ pain reduction scores reported)</p> <p>Global improvement: $\geq 25\%$ improvement in FIQ total score</p> <p>Fatigue: FIQ subscale VAS 0-10</p> <p>Sleep problems: Not assessed</p> <p>Depression: FIQ subscale VAS 0-10</p> <p>Drop out due to adverse: Reported</p> <p>Serious adverse events: Not reported</p> <p>Pain: FIQ subscale VAS 0-10</p> <p>Disease-related quality of life: FIQ total score VAS 0-80</p> <p>Physical functioning: FIQ subscale 0-10</p> <p>Anxiety: FIQ subscale VAS 0-10</p> <p>Tenderness: Myalgic score</p>
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Arnold 2002 (Continued)

Notes	<p>High attrition rate (38.3%)</p> <p>Dropouts for any reasons: fluoxetine: 11/30 (36.6%), placebo: 12/30 (40%)</p> <p>The reasons for withdrawal were an adverse effect or event (n = 12), including nervousness, headache, insomnia, nausea, gastrointestinal reflux, increased appetite, decreased appetite or weight loss, fatigue, sedation, anorgasmia, weakness, decreased coordination, decreased concentration, migraine, worsening pain, herniated lumbar disc, fall with muscle strain, ear pain, or diagnosis of breast cancer; lack of efficacy (n = 5); loss to follow-up (n = 4); or for other reasons that were not related to medication (n = 2). There were no significant differences between the treatment groups in the incidence of these events</p> <p>Funding: Supported by an investor initiated grant by Eli-Lilly</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All medication were in identical capsules"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT by LOCF
Selective reporting (reporting bias)	Unclear risk	Insufficient information about the protocol to permit judgment
Group similarity at baseline (selection bias)	Low risk	No significant differences between the two groups in demographic and clinical variables

Goldenberg 1996

Methods	<p>Study setting: Single center study in US</p> <p>Study design: cross-over</p> <p>Study duration: (1) Duration of wash-out not reported, (2) each study period 6 weeks, separated by two weeks of wash-out, (3) no follow-up</p>
Participants	<p>Inclusion criteria: Patients who met ACR criteria (1990). Age within 18-60 years. Willingness to discontinue all central nervous system active medications, nonsteroidal antiinflammatory drugs, and analgesics (other than acetaminophen) for at least 1 week prior to the study. Pain VAS \geq 30, Hamilton Rating Scale \leq 18</p>

Goldenberg 1996 (Continued)

Exclusion criteria: No current or past history of systemic illness (cardiac, kidney, haematological or liver disease)

Total sample (N = 31): Age: 43 (SD 9.1) years; 90% female; 100 white; Pain baseline 68.4 (SD 20.4); FIQ total baseline 57.3 (17.6)

Interventions	<p>Amitriptyline: 25 mg p.o. fixed</p> <p>Fluoxetine : 20 mg p.o. fixed</p> <p>Amitriptyline 25mg + fluoxetine 20 mg p.o.: fixed</p> <p>Placebo: p.o.</p> <p>Rescue medication: acetaminophen</p> <p>Co-therapies allowed or prohibited: no information provided</p>
Outcomes	<p>At least 30% pain reduction: Calculated by imputation method</p> <p>Global improvement: Composite score (global well-being, pain, tender point score, physician global VAS): >= 25% improvement on a 100-point scale</p> <p>Fatigue: VAS 0-100</p> <p>Sleep problems: VAS 0-100</p> <p>Depression: Beck Depression Inventory</p> <p>Drop out due to adverse: Reported</p> <p>Serious adverse events: Not reported</p> <p>Pain: VAS 0-100</p> <p>Disease-related quality of life: FIQ total score VAS 0-80</p> <p>Physical functioning: Not reported</p> <p>Anxiety: Not assessed</p> <p>Tenderness: Tender point score</p>
Notes	<p>High attrition rate (39%); withdrawals for any reason: amitriptyline 1/22 (4.5%), fluoxetine 4/26 (15%), amitriptyline + fluoxetine 5/24 (21%), placebo: 1/20 (5%). No details on adverse events reported.</p> <p>Carry-over effects possible. Authors included a factor for periods effects in the analysis</p> <p>Funding: Public funding</p>
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Low risk The pharmacy assigned patients using randomisation tables
Allocation concealment (selection bias)	Unclear risk No details reported
Blinding of participants and personnel (performance bias)	Low risk "All tablets were identical in appearance"

Goldenberg 1996 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All evaluations were done by a physician who had no prior contact to the patients"
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information about the protocol to permit judgment
Group similarity at baseline (selection bias)	Low risk	Identical demographic and clinical data because of cross-over design

GSK 2005

Methods	Study setting: Single center study, Belgium Study design: Parallel Study duration: (1) duration wash-out not reported, (2) maintenance 8 weeks, (3) no follow-up
Participants	Inclusion criteria: ACR criteria (1990) and having concomitant depressive symptoms. Minimum score of 4 on the VAS for global or pain assessment Exclusion criteria: Patients with known rheumatic or other organic diseases, current treatment with anticoagulants or anti-arrhythmics, current suicidal risk, psychiatric disorders, abusers of alcohol or illicit drugs, abnormalities in haematology, pregnant or lactating women and women of childbearing potential who did not use adequate contraception. Previous prolonged treatment with paroxetine Paroxetine (N = 26): Mean age 44, 73% women, race not reported; pain baseline: 69 (SD 20.4) Placebo (N = 26): mean age 46, 81% women, race not reported, pain baseline 64 (SD 20.4)
Interventions	Paroxetine: 20 mg/day p.o. fixed for 8 weeks Placebo p.o. for 8 weeks Rescue medication: No information provided Co-therapies allowed or prohibited: No information provided
Outcomes	At least 30% pain reduction: Calculated by imputation method Global improvement: Health assessment questionnaire; no baseline values reported Fatigue: Not assessed Sleep: VAS 0-100 Depression: VAS 0-100 Drop out due to adverse: Reported Serious adverse events (considered to be related to study medication): Reported Pain: VAS 0-100 Disease-related quality of life: FIQ total score VAS 0-80

GSK 2005 (Continued)

Physical functioning: Not reported

Anxiety: VAS 0-100

Tenderness: Tender point score not reported

Notes

Dropouts for any reason: paroxetine: 8/26 (31%), placebo: 5/26 (19%)

Adverse effects were common in both groups. The most commonly seen adverse events were infectious illness, gastro-intestinal complaints, headache, and musculoskeletal complaints. Five patients (19%) in the paroxetine group and four (15%) in the placebo group withdrew due to adverse events; one patient (4%) in the placebo group withdrew due to lack of efficacy and three (12%) in the paroxetine group withdrew for other reasons. There were three serious adverse events: one in the paroxetine group (acute depression) and two in the placebo group: stroke and abscess in thigh

Funding: The study was funded by Glaxo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Group similarity at baseline (selection bias)	Low risk	No significant differences between paroxetine and placebo in demographic and clinical parameters

Hussain 2010
Methods

Study setting: Single center study in Iraq

Study design: Parallel

Study duration: (1) Duration of wash-out not reported, (2) maintenance 4 weeks (3) no follow-up

Participants

Inclusion criteria: Primary fibromyalgia (fibromyalgia) according to the ACR criteria

Exclusion criteria: Other marked pathologic disorders that may interfere with the outcome of the study protocol as revealed by the clinical investigation. Patients who were pregnant or breastfeeding were excluded

Hussain 2010 (Continued)

Total sample: Mean age 39 years; 94% female; race not reported; Pain baseline fluoxetine (N = 24) 7.64 (SD 1.8); Pain baseline melatonin (N = 27) 8.33 (SD 1.1)

Interventions	<p>Fluoxetine (N = 24): 20 mg/d p.o. fixed</p> <p>Melatonin (N = 27): 5 mg/d p.o. fixed</p> <p>Rescue medication: No information provided</p> <p>Co-therapies allowed or prohibited: They were not on analgesic, antiinflammatory drugs, or antioxidant therapy including aspirin</p>
Outcomes	<p>At least 30% pain reduction: Calculated by imputation method</p> <p>Global improvement: No imputation method applicable (FIQ total score not reported)</p> <p>Fatigue: VAS 0-10</p> <p>Sleep problems: VAS 0-10</p> <p>Drop out due to adverse: There were no dropouts according to analyzes presented</p> <p>Serious adverse events: Not reported</p> <p>Pain: VAS 0-10</p> <p>Disease-related quality of life: FIQ total score not reported</p> <p>Physical function: VAS 0-10</p> <p>Depression: VAS 0-10</p> <p>Anxiety: VAS 0-10</p> <p>Tenderness: Not assessed</p>
Notes	<p>No details on adverse events reported</p> <p>Funding: Public funding</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	We had insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	We had insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	We had insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	We had insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Probably ITT; no details reported

Hussain 2010 (Continued)

Selective reporting (reporting bias)	Unclear risk	We had insufficient information to permit judgement
Group similarity at baseline (selection bias)	Unclear risk	We had insufficient information to permit judgement

Norregaard 1995

Methods	<p>Study setting: Single center study in Denmark</p> <p>Study design: Parallel</p> <p>Study duration: (1) Duration wash-out not reported, (2) maintenance 8 weeks, (3) no follow-up</p>
Participants	<p>Inclusion criteria: ACR criteria (1990)</p> <p>Exclusion criteria: Cardiovascular, pulmonary or hepatic diseases, glaucoma, were pregnant or lactating, had an earlier diagnosis of endogenous depression or received antidepressant medication or monoamine oxidase inhibitors. If they received opioids other than codeine they had to stop the treatment at least 2 weeks before the trial in order to participate. Two patients were taking a low dose of dextropropoxyphene 2 weeks before the inclusion. They were also excluded if they suffered from inflammatory rheumatological disease or had laboratory tests suggesting other medical diseases.</p> <p>Citalopram (n = 21): Mean age 48 years; gender and race not reported: Pain 6.3 (SD 2); FIQ total score not reported</p> <p>Placebo (n = 21): Mean age 50 years; gender and race not reported: Pain 6.7 (SD 1.9); FIQ total score not reported</p>
Interventions	<p>Citalopram flexible 20-40 mg/day p.o. for 8 weeks</p> <p>Placebo p.o. for 8 weeks</p> <p>Rescue medication: No details reported</p> <p>Co-therapies allowed or prohibited: People were allowed to take usual concomitant medication like acetaminophen, codeine or NSAIDs</p>
Outcomes	<p>At least 30% pain reduction: Calculated by imputation method</p> <p>Global improvement: At least 25% improvement of global well-being (VAS 0-10) calculated by imputation method</p> <p>Fatigue: VAS 0-10</p> <p>Sleep problems: VAS 0-10</p> <p>Depression: Beck Depression Inventory 0-63</p> <p>Drop out due to adverse: Reported</p> <p>Serious adverse events: Not reported</p> <p>Pain: VAS 0-100</p> <p>Disease-related quality of life: FIQ total score VAS 0-80 assessed but not reported</p> <p>Physical functioning: FIQ 0-3</p> <p>Anxiety: Not assessed</p>

Norregaard 1995 (Continued)

Tenderness: Tender points count 0-18

Notes

Total dropouts: 10/42 (24%). Unclear which group they belonged to or reason for dropping out (side-effect or no effect). The reported side effects (dry mouth, nausea/vomiting, fatigue, sleep disturbance, headache) were few and similar in both groups, with no statistically significant differences

Funding: Funding by the manufacturer of the drug (H. Lundbeck)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"22 patients with fibromyalgia were randomised"
Allocation concealment (selection bias)	Unclear risk	Not details reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All tablets were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	No ITT
Selective reporting (reporting bias)	Unclear risk	Insufficient information about the protocol to permit judgment
Group similarity at baseline (selection bias)	Unclear risk	We had insufficient information to permit judgement

Patkar 2007

Methods

Study setting: Two-sites, study in US

Study design: Parallel

Duration: (1) One week single-blind placebo run-in and wash-out; placebo responders ($\geq 25\%$ reduction of FIQ total score) were excluded; (2) 12 weeks maintenance; (3) no follow-up

Participants

Inclusion criteria: 18-65 years of age, who fulfilled ACR criteria (1990). Other inclusion criteria included a Visual Analogue Scale for pain score of ≥ 5 and a Beck Depression Inventory score of ≤ 23 at screening and placebo lead-in visits

Exclusion criteria: Inflammatory disease, unstable medical diseases, psychotic disorders, current depressive or anxiety disorders, substance abuse in the previous 12 months, history of hypersensitivity to paroxetine paroxetine controlled release, involvement in workers compensation or related litigation, or pregnancy

Paroxetine (N = 58): Mean age 48 years; 95% female; race not reported; pain baseline 74.2 (SD 22.7); FIQ total score 53 (SD 8.9)

Patkar 2007 (Continued)

Placebo (N = 58); Mean age 49 years;93% female; race not reported; pain baseline 75.3 (SD 19.8); FIQ total score 49 (SD 12.2)

Interventions	<p>Paroxetine-controlled release: flexible starting at a dose of 12.5 mg/day till 62.5 mg/day p.o. if tolerated</p> <p>Placebo: oral</p> <p>Rescue medication: Acetaminophen up to 4 g/day, ibuprofen up to 1.2 g/day</p> <p>Co-therapies allowed or prohibited: Concomitant medication exclusion included psychotropics, analgesics,muscle relaxants, steroids, and hypnotics</p>
Outcomes	<p>At least 30% pain reduction: Calculated by imputation method; at least 25% pain reduction rates reported</p> <p>Global improvement: FIQ total score >= 50% reduction reported</p> <p>Fatigue: FIQ subscale VAS 0-10 *</p> <p>Sleep problems: Not assessed</p> <p>Drop out due to adverse: Reported</p> <p>Serious adverse events: Reported</p> <p>Pain: VAS 0-100</p> <p>Disease-related quality of life: FIQ total score VAS 0-80 **</p> <p>Depression: Beck Depression Inventory 0-63 ***</p> <p>Anxiety: Beck Anxiety inventory 0-63 ****</p> <p>Tenderness: Tender points count 0-18 *****</p>
Notes	<p>Dropouts due to any reason: Paroxetine: 20 (34.4%), Placebo: 10 (17.4%)</p> <p>Any treatment-emergent adverse event was reported by 38 (65.5%) of the drug and 34 (58.6%) of the placebo groups. Adverse events were cited as the reason for study discontinuation by 4 subjects receiving paroxetine controlled release and 1 subject receiving placebo. Drowsiness, dry mouth, female genital disorders, ejaculatory problems, impotence, anxiety, and blurred vision were reported with ≥ 2 fold frequency with paroxetine controlled release than placebo</p> <p>* Paroxetine was superior to placebo ($P < 0.05$); no means or SD reported</p> <p>** Paroxetine was superior to placebo ($P = 0.02$); no means or SDs reported</p> <p>*** Paroxetine was not superior to placebo ($P = 0.08$); no means or SD reported</p> <p>**** Paroxetine was superior to placebo ($P < 0.05$); no means or SD reported</p> <p>***** Paroxetine was not superior to placebo (no P values reported); no means or SD reported</p> <p>Funding: By manufacturer of the drug (Glaxo Smith Kline)</p>

Risk of bias

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

Patkar 2007 (Continued)

Allocation concealment (selection bias)	Low risk	"The allocation sequence was concealed from the staff before and after assignment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study drug and placebo were identical in appearance and taste"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT with LOCF performed
Selective reporting (reporting bias)	Unclear risk	Insufficient information about the protocol to permit judgment
Group similarity at baseline (selection bias)	Low risk	No significant difference between the two groups in demographic and clinical variables

Wolfe 1994

Methods	Study setting: Single-center study in US Study design: Parallel Study duration: (1) Duration wash-out not reported; (2) maintenance 6 weeks, (3) no follow-up
Participants	Inclusion criteria: ACR criteria (1990), at least 7 of 14 tender points, 21-70 years, VAS pain => 1 (0-3) Exclusion criteria: Other rheumatic disease, previously treated with fluoxetine Fluoxetine (n = 21): Mean age 48 years: 100% female; 100% white; Pain baseline (VAS 0-3) 1.7 (SD 0.48): Placebo (n = 21): Mean age 53 years: 100% female; 95% white; Pain baseline (VAS 0-3) 1.8 (SD 0.81):
Interventions	Fluoxetine: 20 mg, 1/d, p.o., fixed Placebo: 1/d, p.o. Rescue medication: No information provided Co-therapies allowed or prohibited: NSAIDs and acetaminophen were allowed
Outcomes	At least 30% pain reduction: Calculated by imputation method Global improvement: At least 25% reduction of global severity score (VAS 0-100) calculated by imputation method, Fatigue: VAS 0-15 Sleep problems: VAS 0-15 Depression: AIMS Depression: 0-9.9 Drop out due to adverse: Reported Serious adverse events: Not reported Death: Not reported

Wolfe 1994 (Continued)

Pain: VAS 0-3

Disease-related quality of life: Not assessed

Physical functioning: Health assessment questionnaire HAQ 0-3

Anxiety: AIMS Anxiety 0-9.9

Tenderness: Dolorimetry score

Notes

High attrition rate (43%)

The number of total adverse events did not differ between the placebo and fluoxetine groups. Most common adverse event was nausea. Other reported events: rash, headache, diarrhoea, bruising, dyspepsia.

Sample size was calculated but the recruitment did not reach the planned number of patients.

The ITT was only made for depression scores.

Funding: by manufacturer of the drug (Eli Lilly)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment was made by the use of a computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Information not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	No ITT
Selective reporting (reporting bias)	Unclear risk	Insufficient information about the protocol to permit judgment
Group similarity at baseline (selection bias)	Low risk	No significant differences between the groups in demographic and clinical variables

ACR: American College of Rheumatology

FIQ: Fibromyalgia Impact Questionnaire

ITT: intention-to-treat

LOCF: last observation carried forward

NSAID: non-steroidal anti-inflammatory drug

p.o.: by mouth

SD: standard deviation

VAS: visual analogue scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ataoglu 1997	Open trial
Cantini 1994	Open trial
Cantini 1995	Open trial
Capaci 2002	Single-blind trial
De Vanna 1998	Cross-over study with no wash-out period; Outcomes only in graphics
Erhan 2000	Cross-over study with 15 fibromyalgia-patients comparing amitriptyline and fluvoxamine; no wash-out periods reported; no tests of carry over effects conducted
Giordano 1999	Single-blind trial
Gonzalez-Viejo 2005	Compared sertraline versus ultrasonography and physiotherapy
Nishikai 2003	Open trial
Ozerbil 2006	Compared fluoxetine versus amitriptyline, using an outcome not included in our review (VO ² max)/ Wingate anaerobic test)
Sencan 2004	Compared paroxetine with aerobic exercise and transcutaneous electrical nerve stimulation (TENS) placebo

DATA AND ANALYSES
Comparison 1. SSRI versus placebo

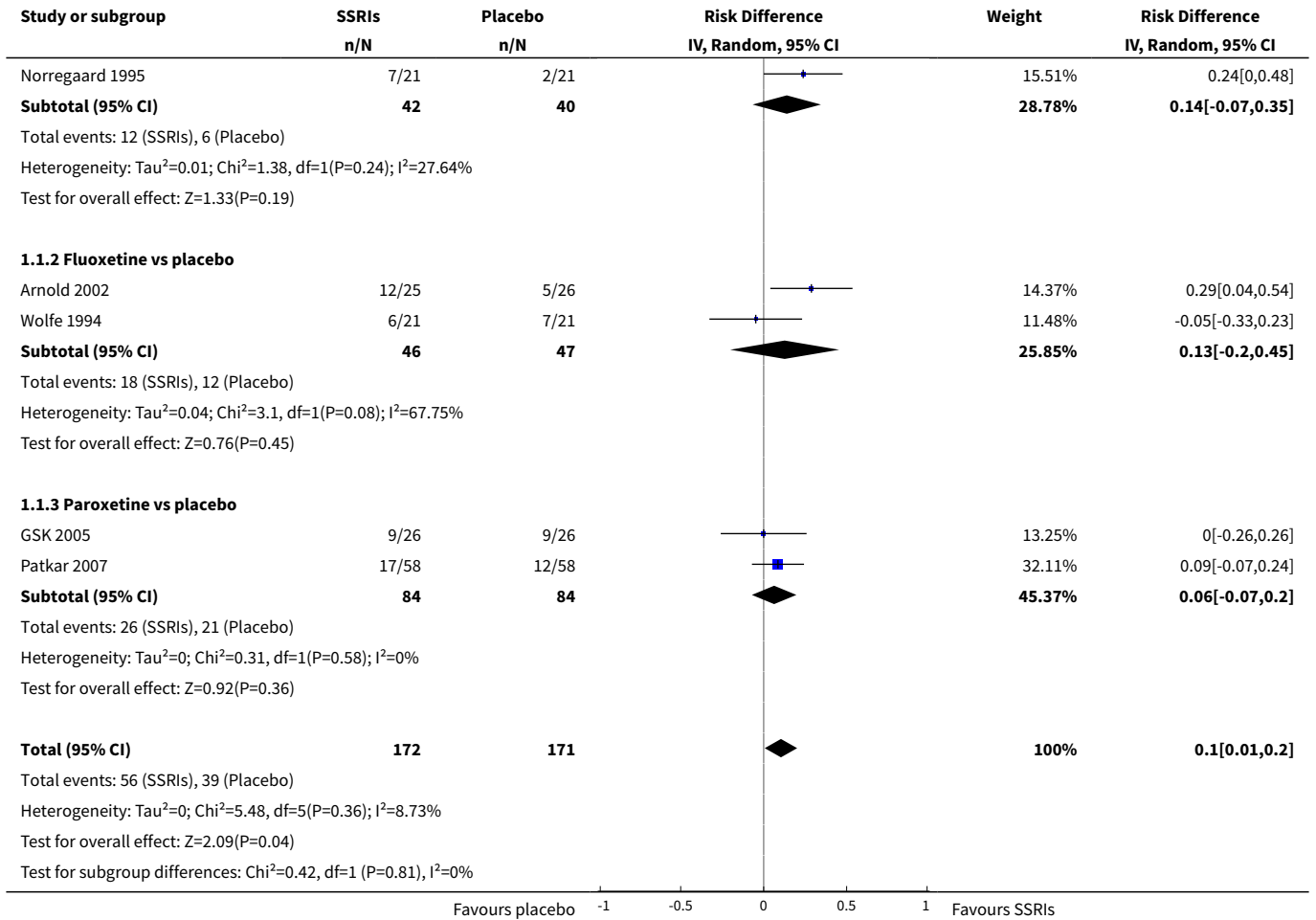
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least 30% pain reduction	6	343	Risk Difference (IV, Random, 95% CI)	0.10 [0.01, 0.20]
1.1 Citalopram vs placebo	2	82	Risk Difference (IV, Random, 95% CI)	0.14 [-0.07, 0.35]
1.2 Fluoxetine vs placebo	2	93	Risk Difference (IV, Random, 95% CI)	0.13 [-0.20, 0.45]
1.3 Paroxetine vs placebo	2	168	Risk Difference (IV, Random, 95% CI)	0.06 [-0.07, 0.20]
2 Global improvement	6	330	Risk Difference (IV, Random, 95% CI)	0.14 [0.06, 0.23]
2.1 Citalopram vs placebo	2	82	Risk Difference (IV, Random, 95% CI)	0.14 [-0.07, 0.34]
2.2 Fluoxetine vs placebo	3	132	Risk Difference (IV, Random, 95% CI)	0.15 [0.02, 0.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Paroxetine vs placebo	1	116	Risk Difference (IV, Random, 95% CI)	0.14 [-0.00, 0.28]
3 Fatigue	2	76	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.62, 0.28]
3.1 Citalopram vs placebo	2	76	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.62, 0.28]
4 Sleep problems	6	309	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.33, 0.12]
4.1 Citalopram vs placebo	2	76	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.51, 0.62]
4.2 Fluoxetine vs placebo	2	65	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.69, 0.30]
4.3 Paroxetine vs placebo	1	52	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.30, 0.79]
4.4 Fluoxetine vs placebo	3	116	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.69, 0.05]
5 Depression	6	244	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.65, -0.14]
5.1 Citalopram vs placebo	2	76	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.59, 0.32]
5.2 Fluoxetine vs placebo	3	116	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-0.93, -0.18]
5.3 Paroxetine vs placebo	1	52	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.99, 0.11]
6 Discontinuation due to adverse events	5	284	Risk Difference (IV, Random, 95% CI)	0.04 [-0.06, 0.14]
6.1 Citalopram vs placebo	1	51	Risk Difference (IV, Random, 95% CI)	0.29 [0.04, 0.54]
6.2 Fluoxetine vs placebo	2	65	Risk Difference (IV, Random, 95% CI)	-0.09 [-0.33, 0.15]
6.3 Paroxetine vs placebo	2	168	Risk Difference (IV, Random, 95% CI)	0.05 [-0.02, 0.12]
7 Serious adverse events	2	168	Risk Difference (IV, Random, 95% CI)	-0.01 [-0.07, 0.05]
7.1 Paroxetine vs placebo	2	168	Risk Difference (IV, Random, 95% CI)	-0.01 [-0.07, 0.05]
8 Pain intensity	7	330	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.69, -0.04]
8.1 Citalopram vs placebo	2	76	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.69, 0.21]

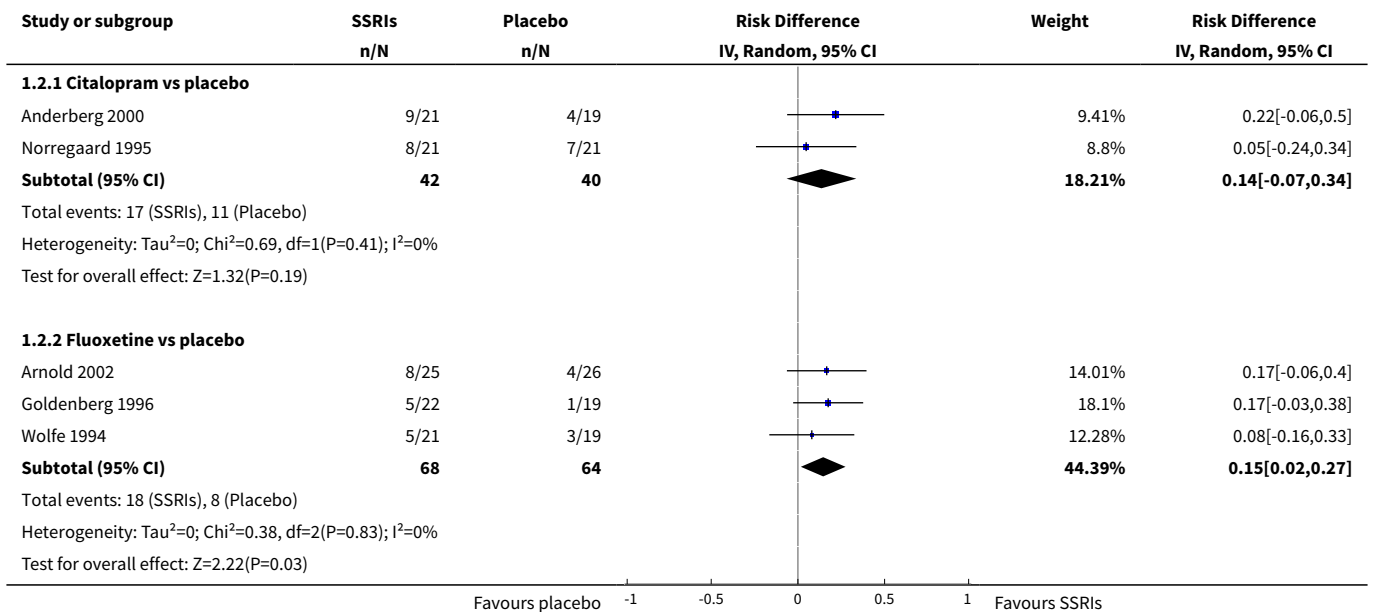
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Fluoxetine vs placebo	3	116	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-1.31, -0.13]
8.3 Paroxetine vs placebo	2	138	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.43, 0.25]
9 Disease-specific quality of life FIQ total score	2	92	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-1.12, -0.28]
9.1 Fluoxetine vs placebo	2	92	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-1.12, -0.28]
10 Physical functioning	5	204	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.34, 0.21]
10.1 Citalopram vs placebo	2	77	Std. Mean Difference (IV, Random, 95% CI)	0.0 [-0.45, 0.45]
10.2 Fluoxetine vs placebo	2	75	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.73, 0.19]
10.3 Paroxetine vs placebo	1	52	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.42, 0.67]
11 Anxiety	4	148	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.44, 0.21]
11.1 Citalopram vs placebo	1	35	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.73, 0.60]
11.2 Fluoxetine vs placebo	2	61	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.84, 0.19]
11.3 Paroxetine vs placebo	1	52	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.45, 0.64]
12 Tenderness	4	158	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.58, 0.11]
12.1 Citalopram vs placebo	1	42	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-1.25, -0.01]
12.2 Fluoxetine vs placebo	3	116	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.47, 0.27]

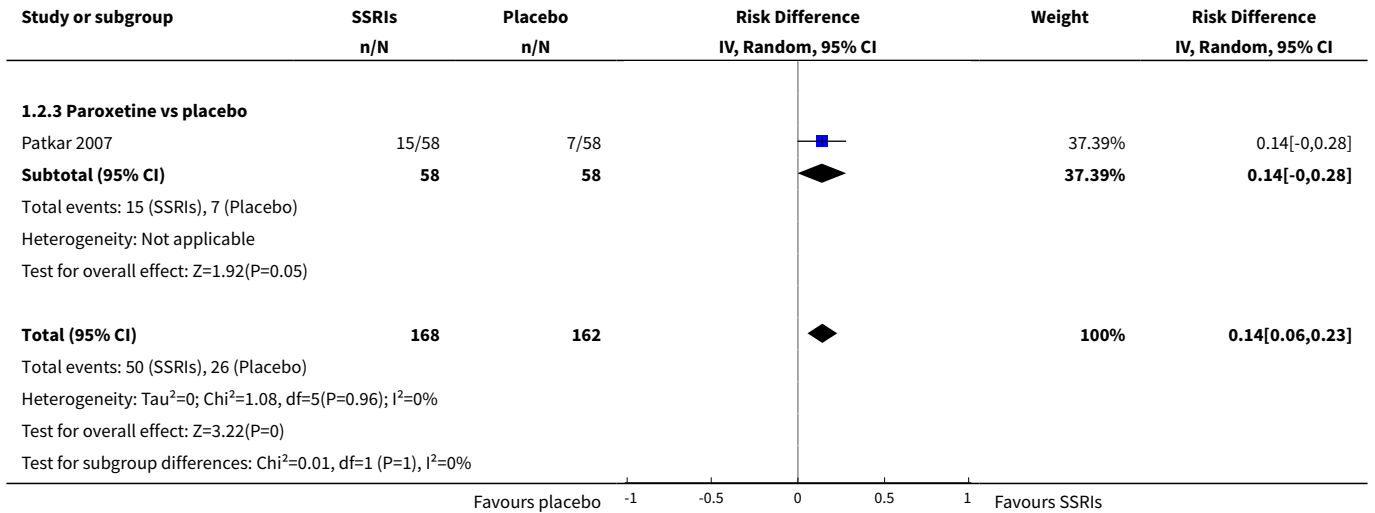
Analysis 1.1. Comparison 1 SSRI versus placebo, Outcome 1 At least 30% pain reduction.

Study or subgroup	SSRIs n/N	Placebo n/N	Risk Difference IV, Random, 95% CI	Weight	Risk Difference IV, Random, 95% CI
1.1.1 Citalopram vs placebo					
Anderberg 2000	5/21	4/19		13.27%	0.03[-0.23,0.29]

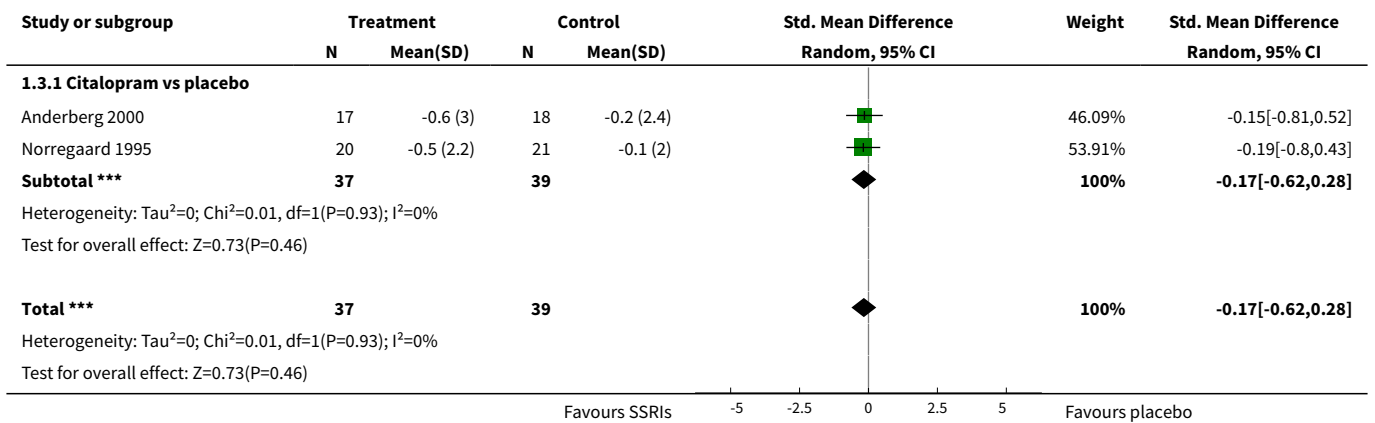


Analysis 1.2. Comparison 1 SSRI versus placebo, Outcome 2 Global improvement.

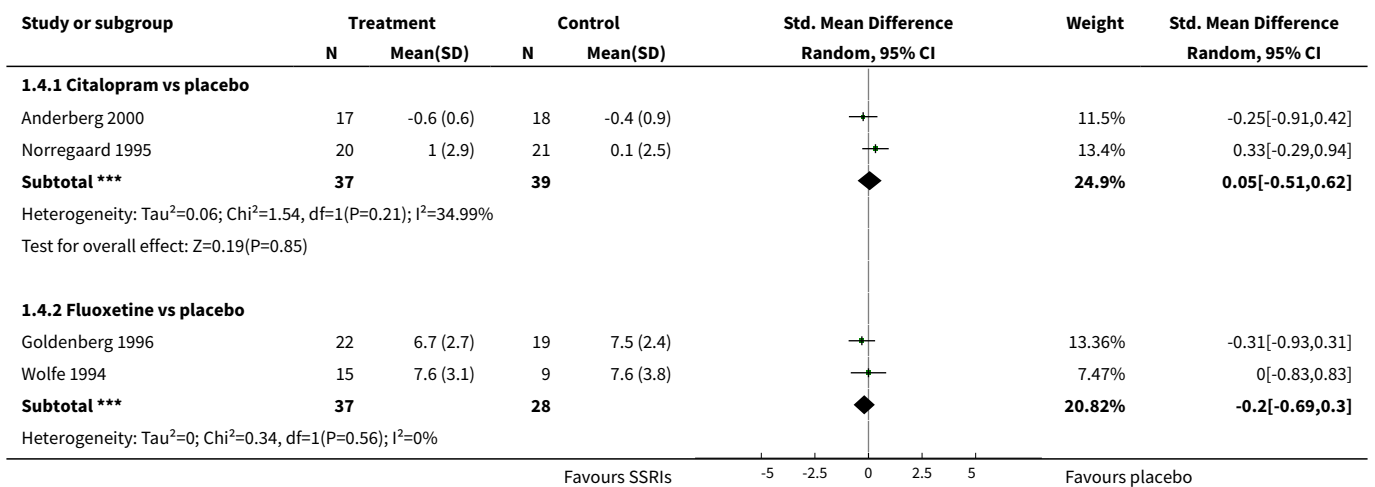


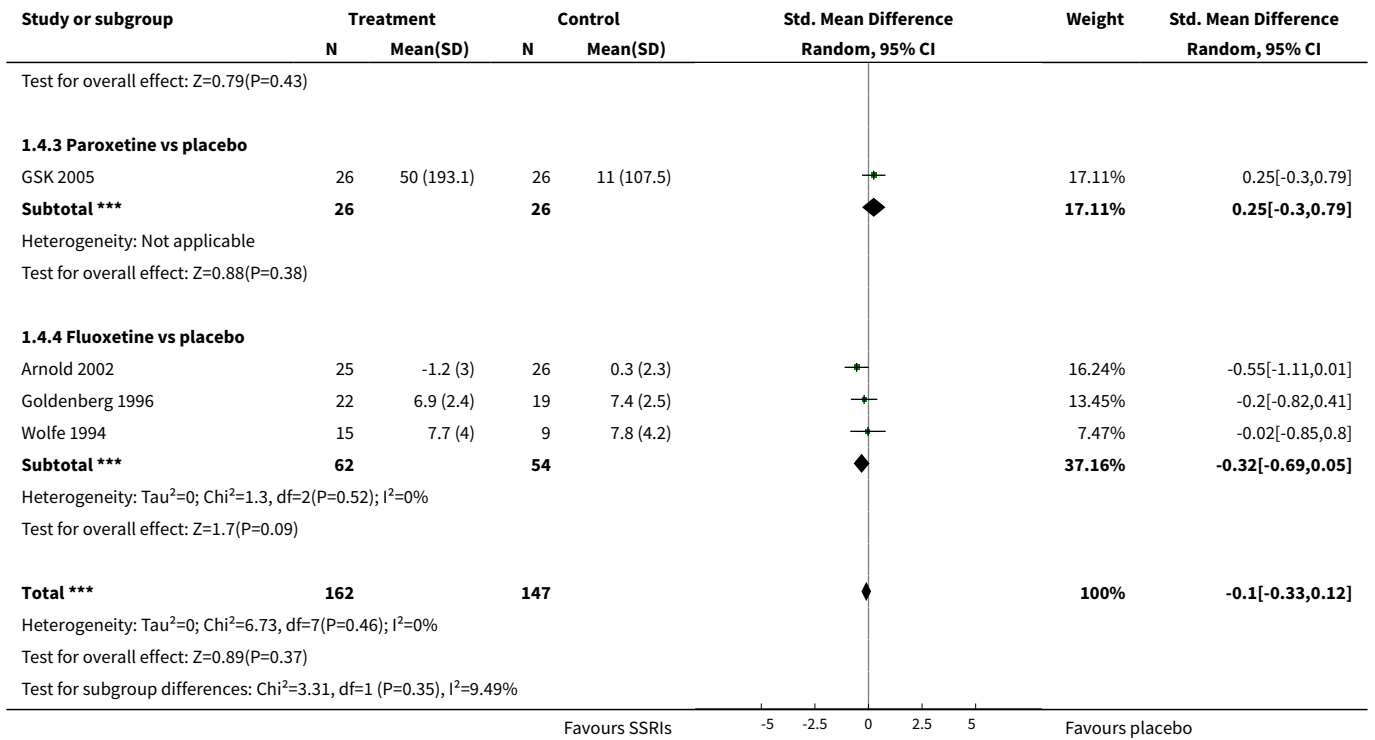


Analysis 1.3. Comparison 1 SSRI versus placebo, Outcome 3 Fatigue.

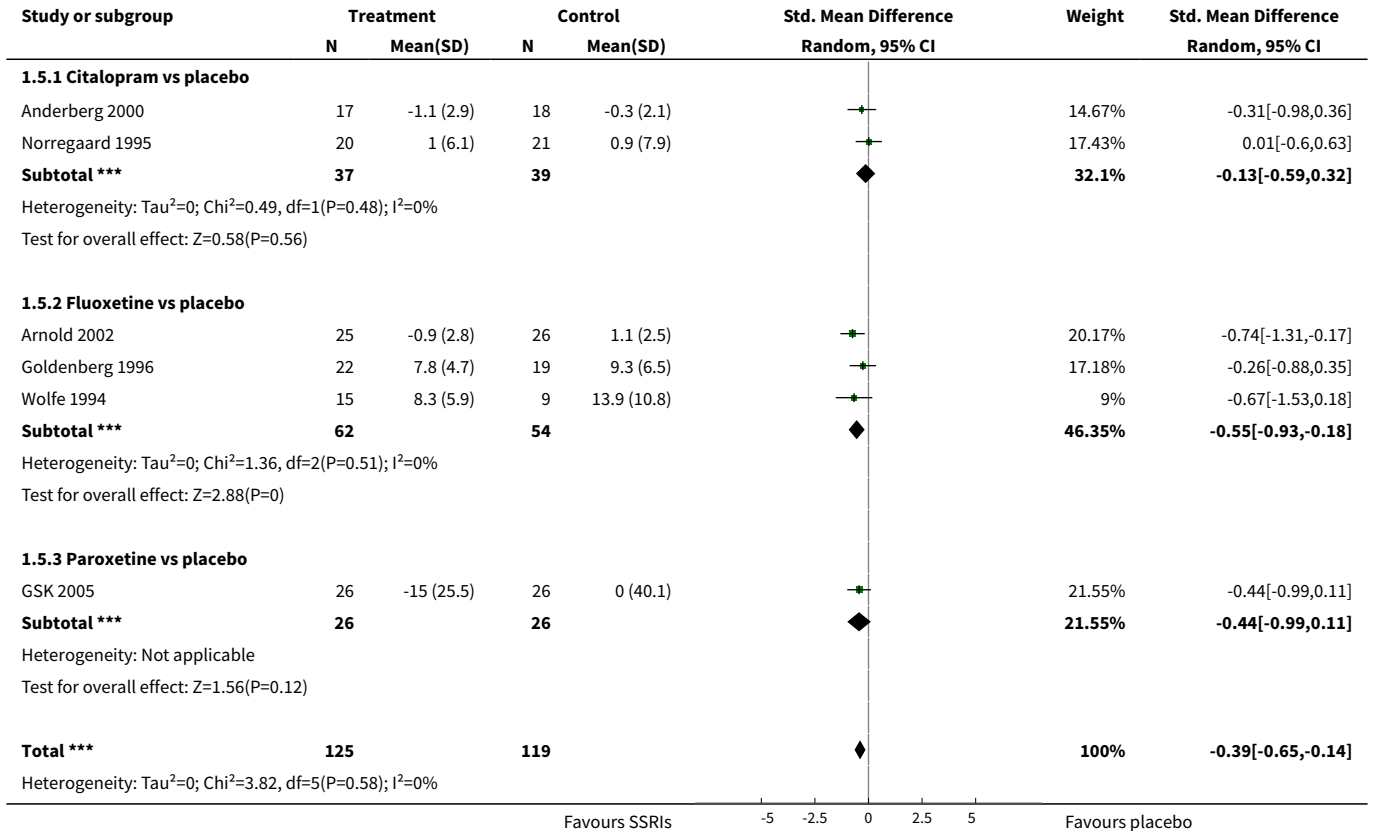


Analysis 1.4. Comparison 1 SSRI versus placebo, Outcome 4 Sleep problems.





Analysis 1.5. Comparison 1 SSRI versus placebo, Outcome 5 Depression.



Study or subgroup	Treatment		Control		Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			

Test for overall effect: $Z=3.02(P=0)$
 Test for subgroup differences: $\text{Chi}^2=1.97, \text{df}=1 (P=0.37), I^2=0\%$

Favours SSRIs -5 -2.5 0 2.5 5 Favours placebo

Analysis 1.6. Comparison 1 SSRI versus placebo, Outcome 6 Discontinuation due to adverse events.

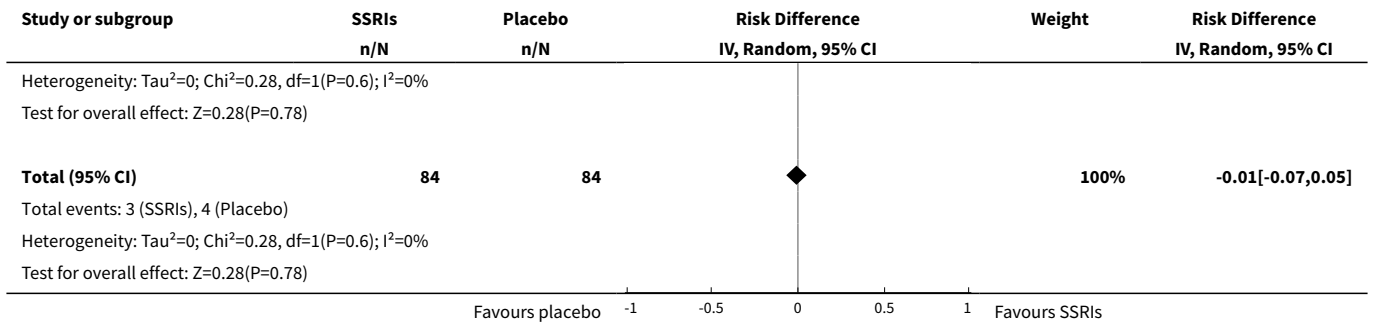
Study or subgroup	SSRIs n/N	Placebo n/N	Risk Difference IV, Random, 95% CI	Weight	Risk Difference IV, Random, 95% CI
Anderberg 2000	12/25	5/26		12.57%	0.29[0.04,0.54]
Subtotal (95% CI)	25	26		12.57%	0.29[0.04,0.54]
Total events: 12 (SSRIs), 5 (Placebo) Heterogeneity: Not applicable Test for overall effect: $Z=2.28(P=0.02)$					
1.6.2 Fluoxetine vs placebo					
Goldenberg 1996	1/22	1/19		26.02%	-0.01[-0.14,0.13]
Wolfe 1994	1/15	3/9		7.93%	-0.27[-0.6,0.07]
Subtotal (95% CI)	37	28		33.95%	-0.09[-0.33,0.15]
Total events: 2 (SSRIs), 4 (Placebo) Heterogeneity: $\text{Tau}^2=0.02; \text{Chi}^2=2.01, \text{df}=1(P=0.16); I^2=50.34\%$ Test for overall effect: $Z=0.75(P=0.46)$					
1.6.3 Paroxetine vs placebo					
GSK 2005	5/26	4/26		16.25%	0.04[-0.17,0.24]
Patkar 2007	4/58	1/58		37.22%	0.05[-0.02,0.13]
Subtotal (95% CI)	84	84		53.48%	0.05[-0.02,0.12]
Total events: 9 (SSRIs), 5 (Placebo) Heterogeneity: $\text{Tau}^2=0; \text{Chi}^2=0.01, \text{df}=1(P=0.91); I^2=0\%$ Test for overall effect: $Z=1.43(P=0.15)$					
Total (95% CI)	146	138		100%	0.04[-0.06,0.14]
Total events: 23 (SSRIs), 14 (Placebo) Heterogeneity: $\text{Tau}^2=0.01; \text{Chi}^2=7.68, \text{df}=4(P=0.1); I^2=47.92\%$ Test for overall effect: $Z=0.74(P=0.46)$ Test for subgroup differences: $\text{Chi}^2=4.85, \text{df}=1 (P=0.09), I^2=58.76\%$					

Favours placebo -1 -0.5 0 0.5 1 Favours SSRIs

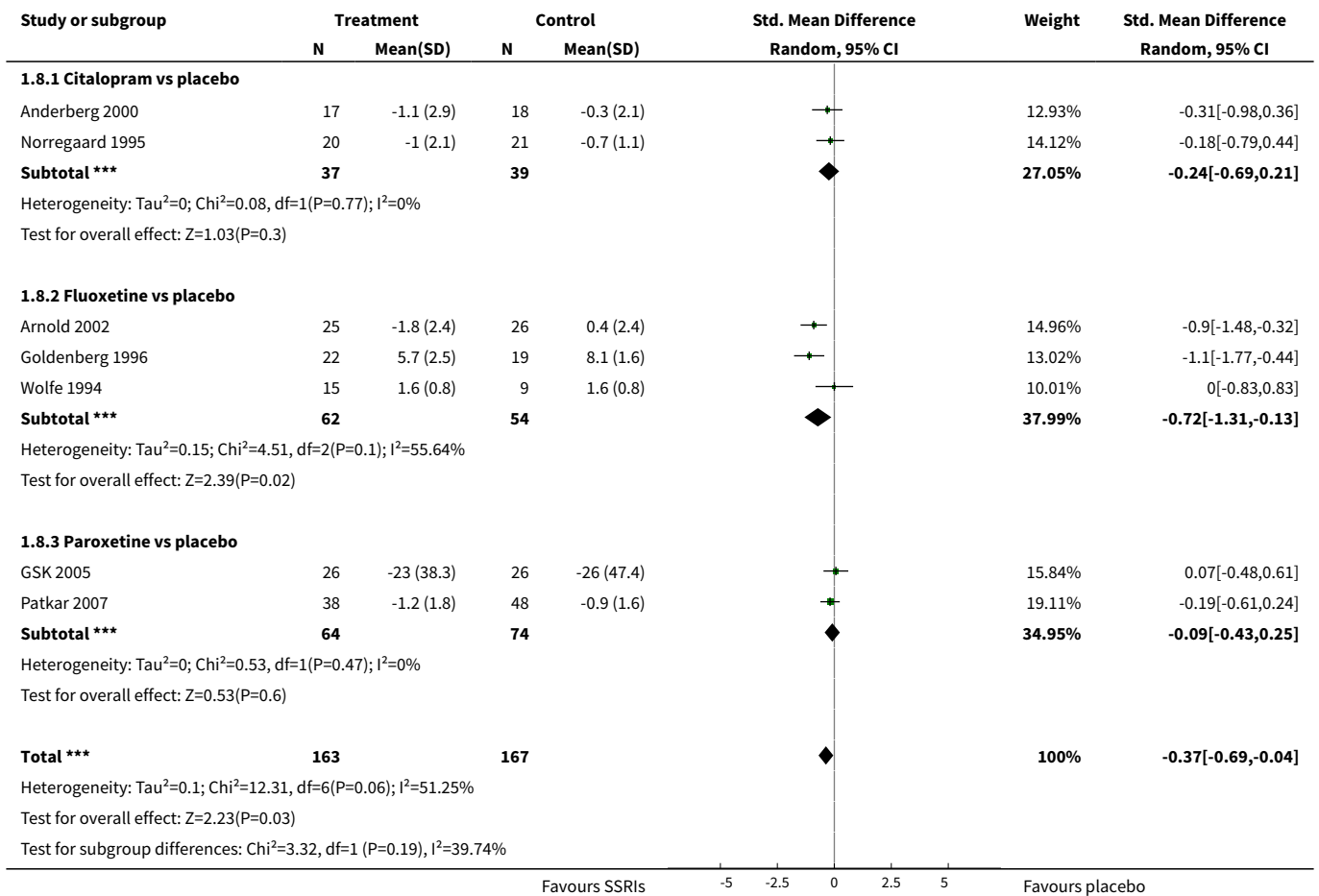
Analysis 1.7. Comparison 1 SSRI versus placebo, Outcome 7 Serious adverse events.

Study or subgroup	SSRIs n/N	Placebo n/N	Risk Difference IV, Random, 95% CI	Weight	Risk Difference IV, Random, 95% CI
GSK 2005	1/26	2/26		21.66%	-0.04[-0.16,0.09]
Patkar 2007	2/58	2/58		78.34%	0[-0.07,0.07]
Subtotal (95% CI)	84	84		100%	-0.01[-0.07,0.05]
Total events: 3 (SSRIs), 4 (Placebo)					

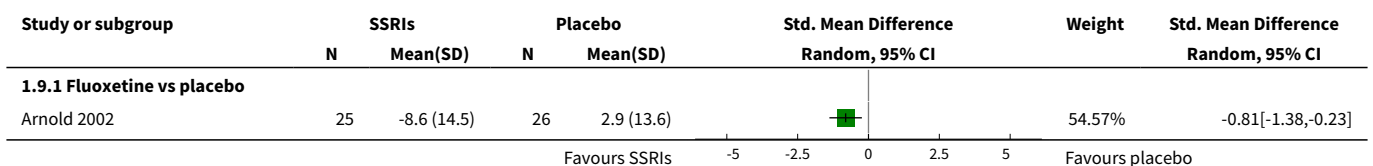
Favours placebo -1 -0.5 0 0.5 1 Favours SSRIs

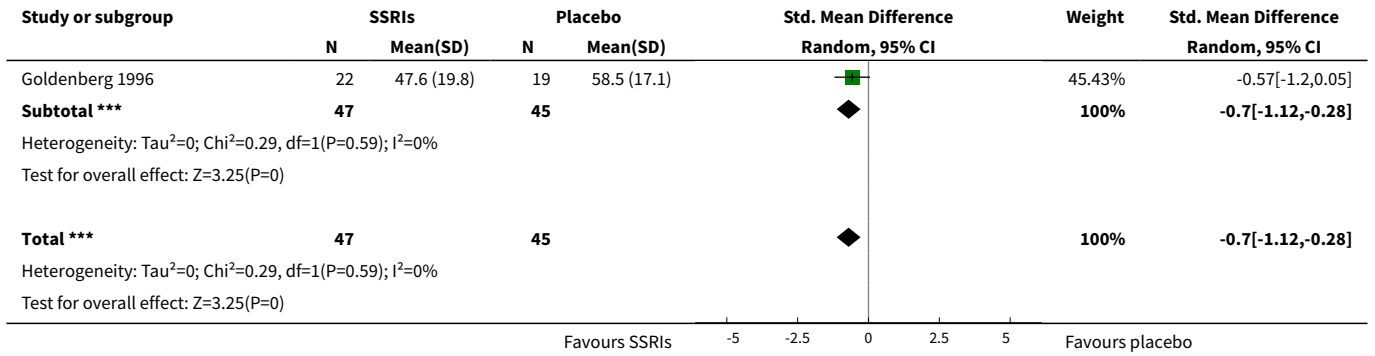


Analysis 1.8. Comparison 1 SSRI versus placebo, Outcome 8 Pain intensity.

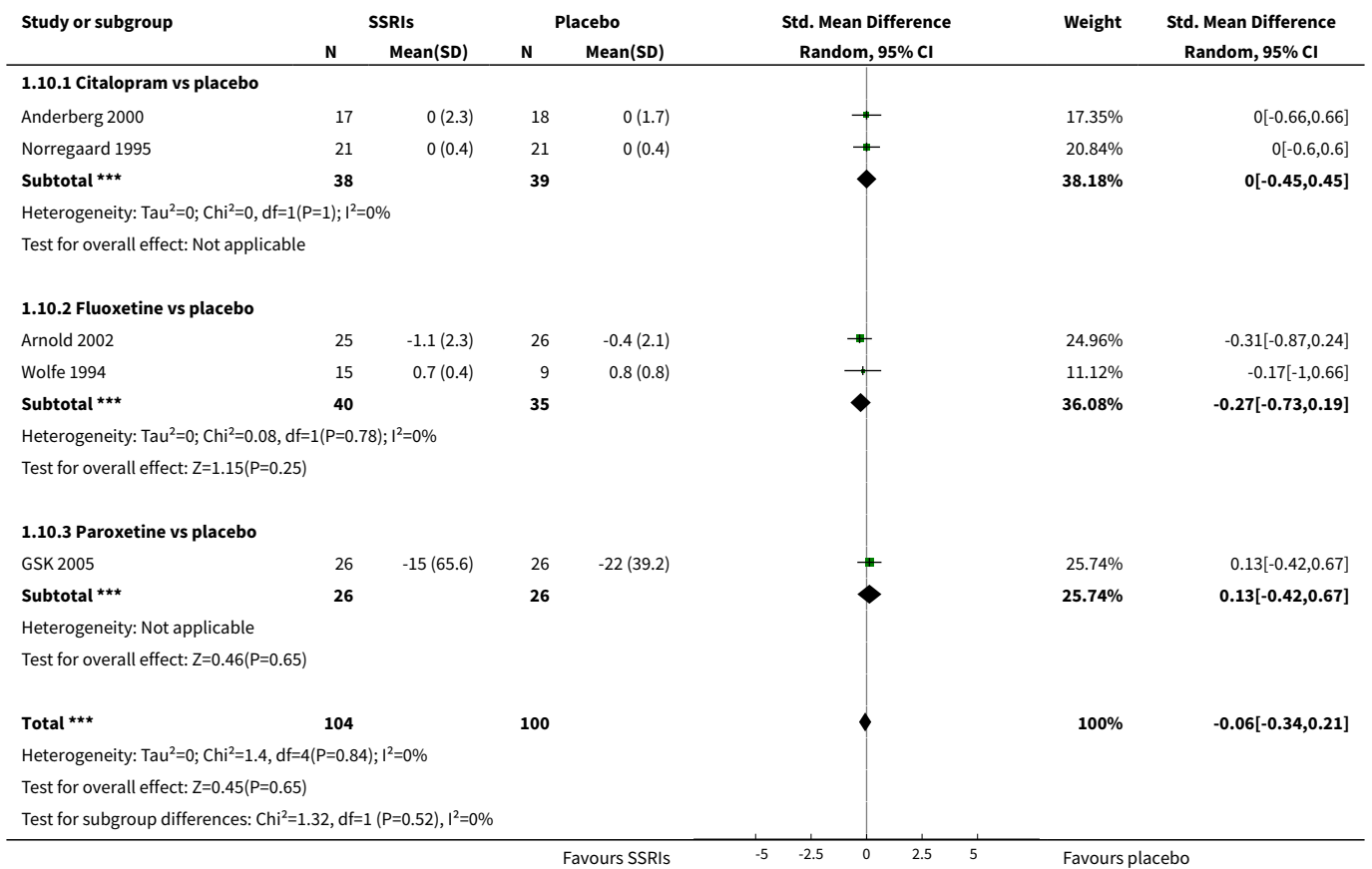


Analysis 1.9. Comparison 1 SSRI versus placebo, Outcome 9 Disease-specific quality of life FIQ total score.

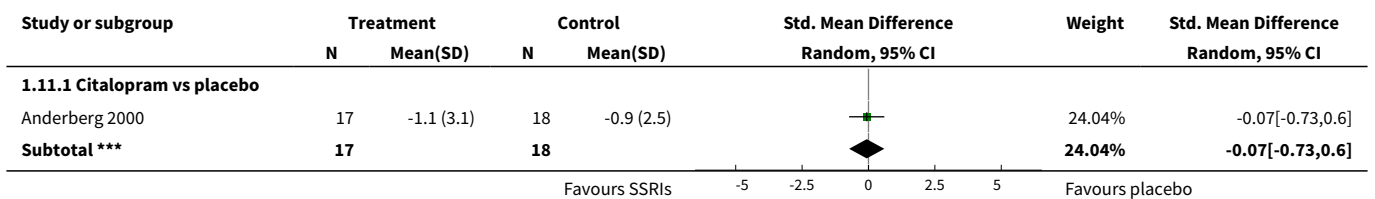


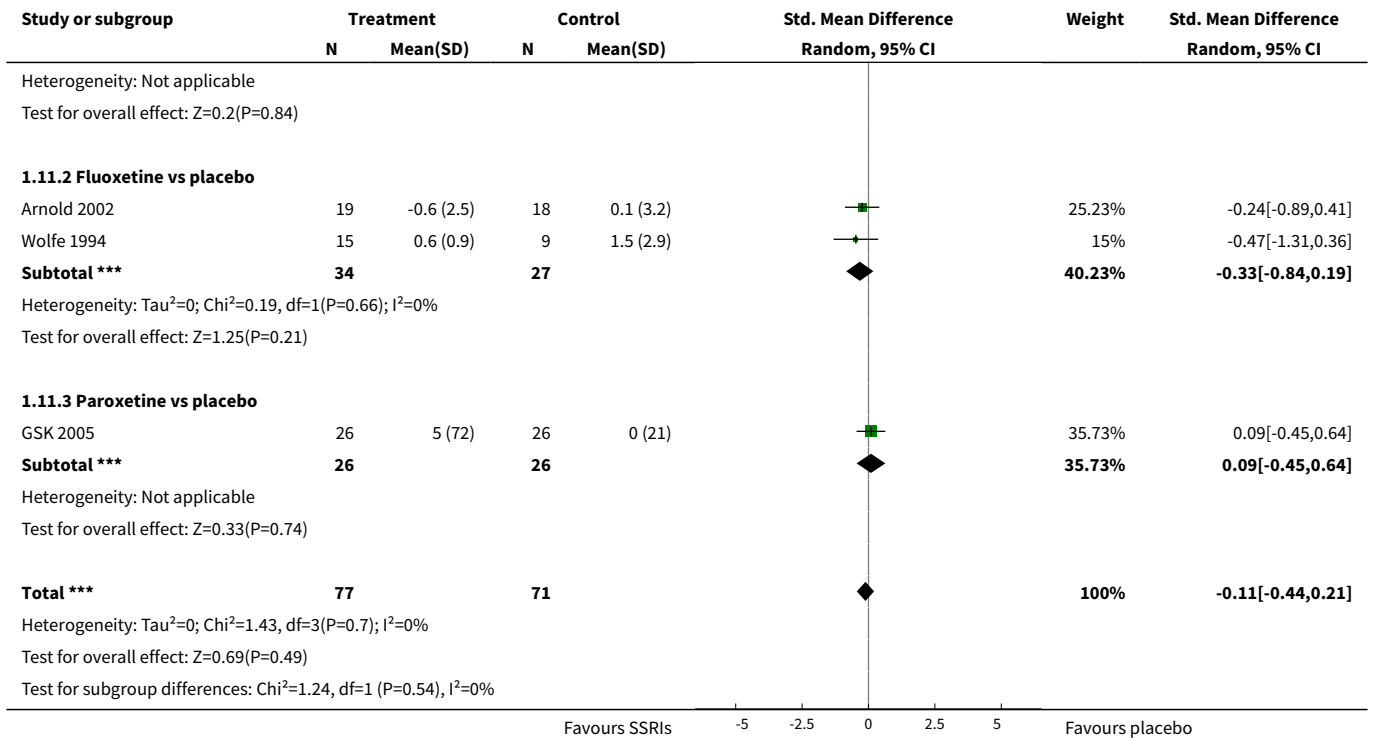


Analysis 1.10. Comparison 1 SSRI versus placebo, Outcome 10 Physical functioning.

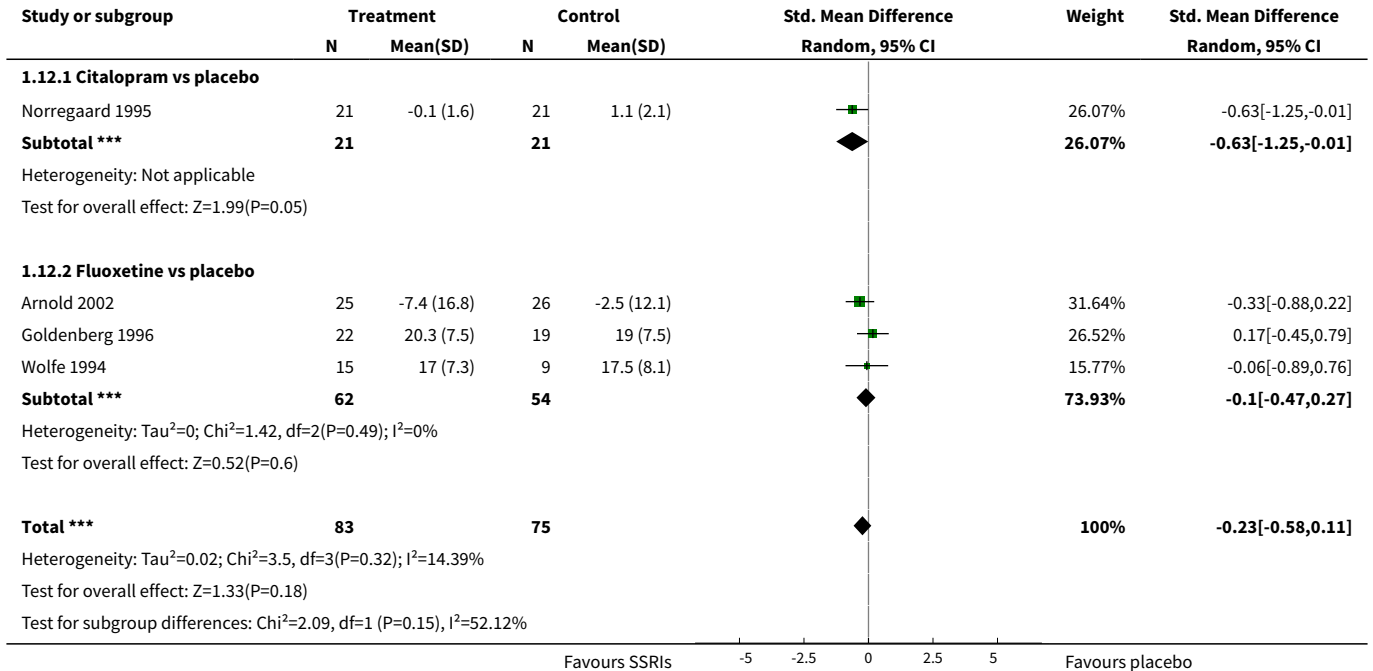


Analysis 1.11. Comparison 1 SSRI versus placebo, Outcome 11 Anxiety.





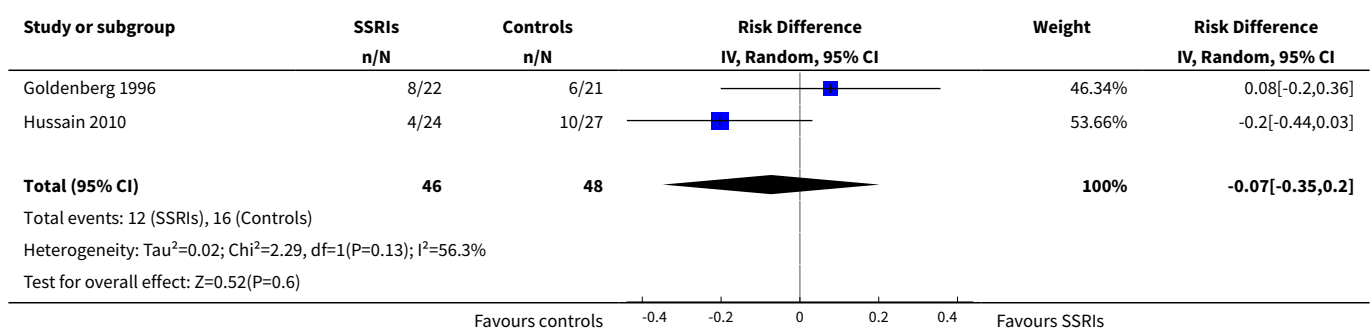
Analysis 1.12. Comparison 1 SSRI versus placebo, Outcome 12 Tenderness.



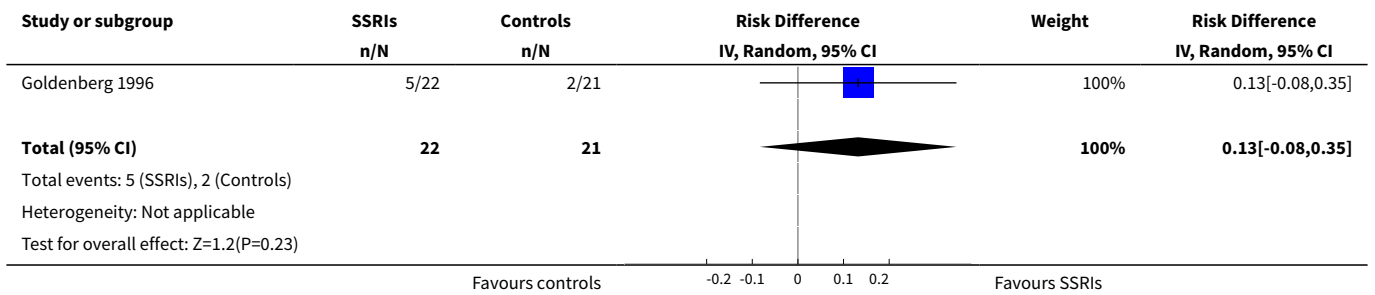
Comparison 2. SSRI versus other drugs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least 30% pain reduction	2	94	Risk Difference (IV, Random, 95% CI)	-0.07 [-0.35, 0.20]
2 Global improvement	1	43	Risk Difference (IV, Random, 95% CI)	0.13 [-0.08, 0.35]
3 Fatigue	2	94	Std. Mean Difference (IV, Random, 95% CI)	0.21 [-0.20, 0.61]
4 Sleep problems	2	94	Std. Mean Difference (IV, Random, 95% CI)	0.31 [-0.10, 0.72]
5 Depression	2	93	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.40, 0.63]
6 Discontinuation due to adverse events	2	94	Risk Difference (IV, Random, 95% CI)	0.01 [-0.05, 0.08]
7 Pain intensity	2	94	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.48, 0.51]
8 Disease-related quality of life	1	43	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.82, 0.38]
9 Physical functioning	1	51	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-1.02, 0.10]
10 Anxiety	1	51	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.82, 0.28]
11 Tenderness	1	43	Std. Mean Difference (IV, Random, 95% CI)	0.31 [-0.29, 0.91]

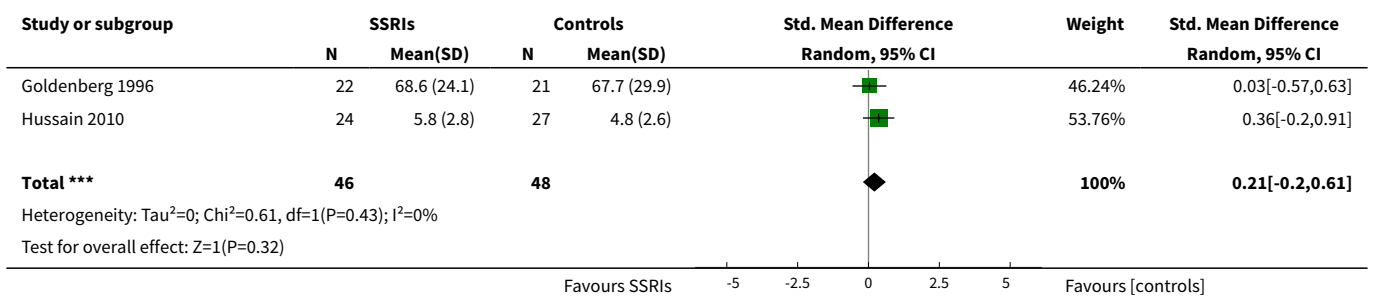
Analysis 2.1. Comparison 2 SSRI versus other drugs, Outcome 1 At least 30% pain reduction.



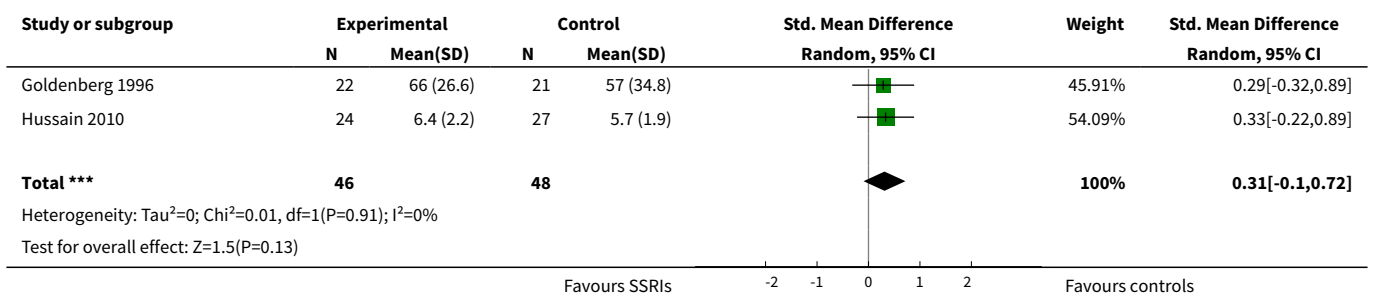
Analysis 2.2. Comparison 2 SSRI versus other drugs, Outcome 2 Global improvement.



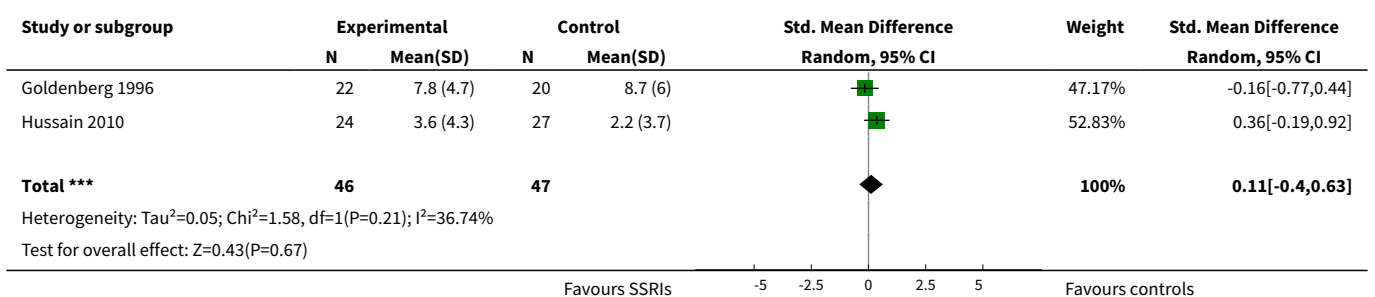
Analysis 2.3. Comparison 2 SSRI versus other drugs, Outcome 3 Fatigue.



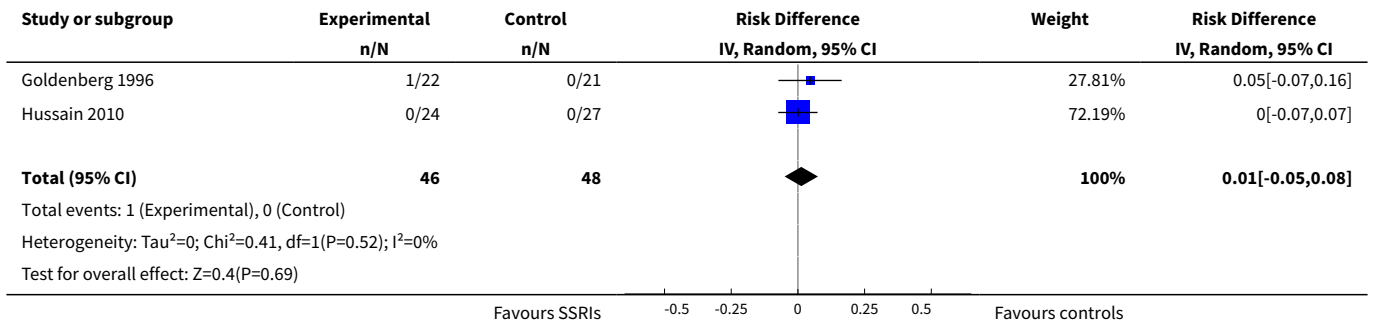
Analysis 2.4. Comparison 2 SSRI versus other drugs, Outcome 4 Sleep problems.



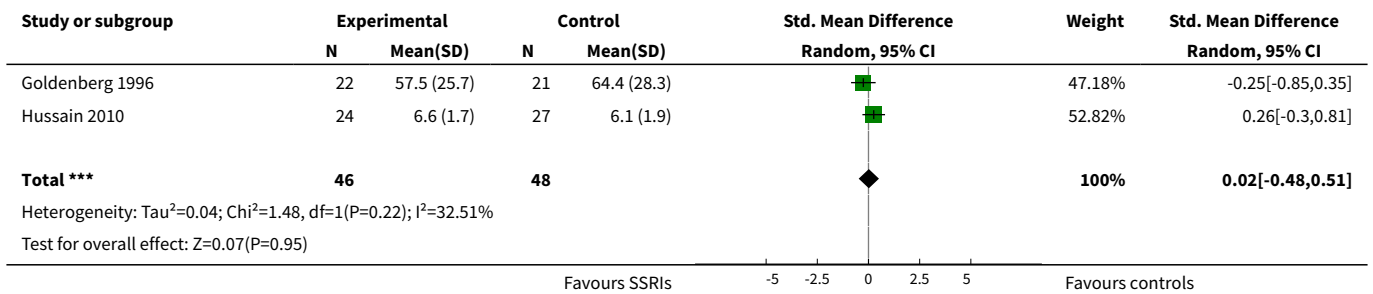
Analysis 2.5. Comparison 2 SSRI versus other drugs, Outcome 5 Depression.



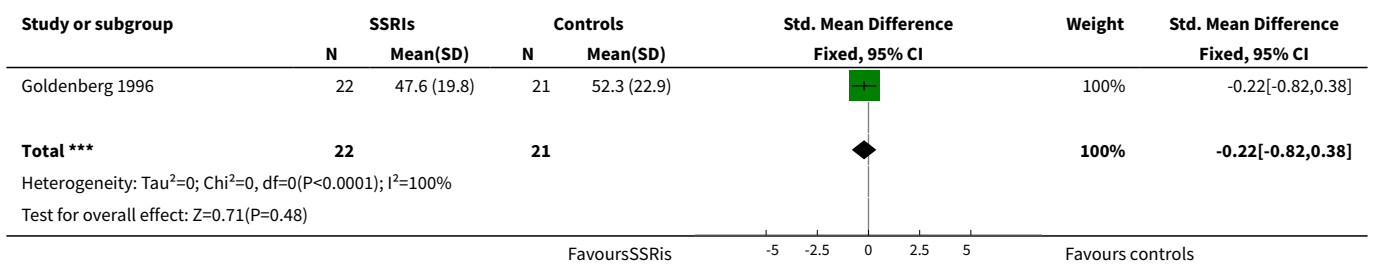
Analysis 2.6. Comparison 2 SSRI versus other drugs, Outcome 6 Discontinuation due to adverse events.



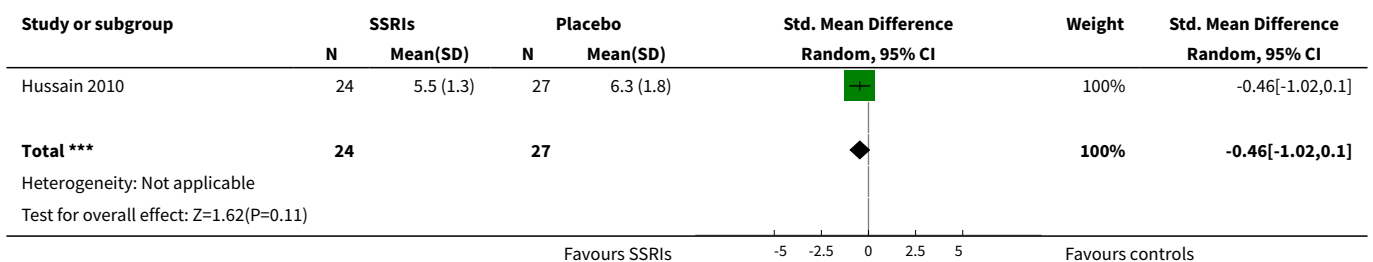
Analysis 2.7. Comparison 2 SSRI versus other drugs, Outcome 7 Pain intensity.



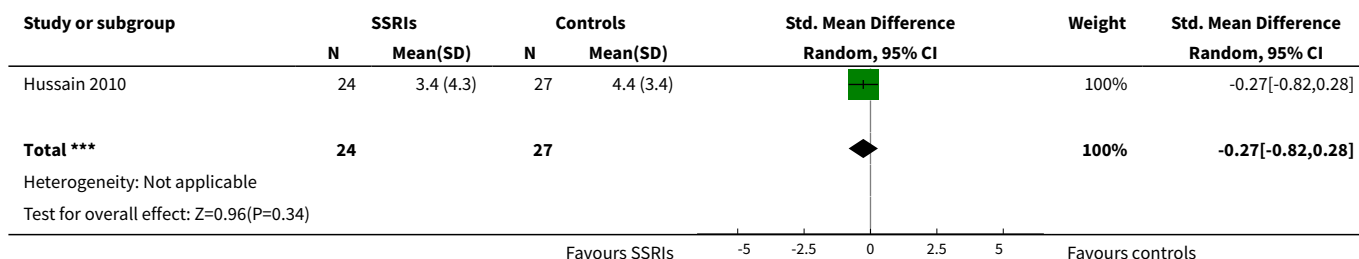
Analysis 2.8. Comparison 2 SSRI versus other drugs, Outcome 8 Disease-related quality of life.



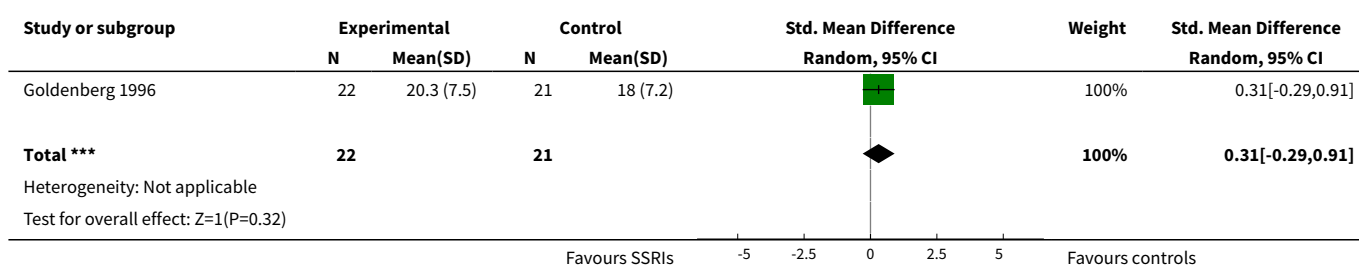
Analysis 2.9. Comparison 2 SSRI versus other drugs, Outcome 9 Physical functioning.



Analysis 2.10. Comparison 2 SSRI versus other drugs, Outcome 10 Anxiety.



Analysis 2.11. Comparison 2 SSRI versus other drugs, Outcome 11 Tenderness.



ADDITIONAL TABLES

Table 1. Subgroup analysis

Outcome title	Number of studies	Number of patients	Effect size (95% CI)	Test for overall effect P value	Heterogeneity I ² (%)
Without industry sponsorship					
01 Number of patients with at least 30% pain reduction	2	82	RD 0.14 (-0.07 to 0.35)	0.19	28
02 Number of patients with a clinically important global improvement	2	82	RD 0.14 (-0.07 to 0.22)	0.17	0
03 Fatigue	2	76	SMD -0.17 (-0.62 to 0.28)	0.46	0
04 Sleep problems	2	76	SMD 0.05 (-0.51 to 0.62)	0.87	35

Table 1. Subgroup analysis (Continued)

05 Dropout due to adverse events	1	61	RD 0.29 (0.04 to 0.54)	0.02	Not applicable
With industry sponsorship					
01 Number of patients with at least 30% pain reduction	4	261	RD 0.09 (-0.04 to 0.22)	0.17	22
02 Number of patients with a clinically important global improvement	4	248	RD 0.14 (0.05 to 0.24)	0.003	0
03 Fatigue	3	117	SMD -0.32 (-0.69 to 0.05)	0.09	0
04 Sleep problems	3	158	SMD -0.24 (-0.60 to 0.13)	0.21	0
05 Dropout due to adverse events	4	233	RD 0.02 (-0.06 to 0.10)	0.64	19

RD: risk difference; SMD: standard mean difference

APPENDICES

Appendix 1. Search strategies and hits retrieved

DATABASE (ACCESS) and date of search	Search strategy and hits retrieved
MEDLINE (PubMed) 1 June 2014	#1 fibromyalgia[mh] #2 fibromyalgi*[tiab] #3 fibrositis[tiab] #4 #1 OR #2 OR #3 8153 #5 randomized controlled trial[pt] #6 controlled clinical trial[pt] #7 randomized[tiab] #8 randomised[tiab] #9 randomly[tiab] #10 randomization[tiab] #11 randomisation[tiab] #12 random allocation[mh] #13 double-blind method[mh] #14 "double blind"[tiab] #15 "double masked"[tiab]

(Continued)

#16 placebo[mh]
 #17 placebo[tiab]
 #18 drug therapy[sh]
 #19 trial[tiab]
 #20 groups[tiab]
 #21 OR/5-20 **3344304**
 #22 animals[mh] NOT (animals[mh] AND humans[mh])
 #23 #21 NOT #22 **2869063**
 #24 #4 AND #23 **2750**

EMBASE

 (Accessed via Elsevier)
 1 June 2014

#1 'fibromyalgia'/exp
 #2 fibromyalgi*: ab,ti
 #3 fibrositis:ab,ti
 #4 #1 OR #2 OR #3 **14,348**
 #5 'controlled clinical trial':de
 #6 'randomized controlled trial':de
 #7 randomized:ab,ti
 #8 randomised:ab,ti
 #9 randomization:ab,ti
 #10 randomisation:ab,ti
 #11 randomly:ab,ti
 #12 randomization:de
 #13 placebo:de
 #14 placebo:ab,ti
 #15 'double blind procedure':de
 #16 double AND blind:ti,ab
 #17 double masked:ti,ab
 #18 trial:ti,ab
 #19 OR/5-18 **1,345,881**
 #20 #4 AND #19 **2,594**

CENTRAL

 Cochrane Central Register of
 Controlled Trials
 Issue 5 of 12, May 2014

#1 MeSH descriptor Fibromyalgia, explode all trees **518**
 #2 fibromyalgi*:ti,ab,kw **933**
 #3 fibrositis:ti,ab,kw **58**
 #4 #1 OR #2 OR #3 **970**

RCTs in fibromyalgia(update November 2010)
Selective serotonin reuptake inhibitors for fibromyalgia syndrome (Review)

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DATABASE (ACCESS) and date of search	Search Strategy and hits retrieved
MEDLINE (PubMed) 4.november.10	#1 "Fibromyalgia"[Mesh] OR fibromyalgi*[ti] OR fibrositis[ti] 5248 #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 #3 #1 AND #2 1682 #4 (#2) AND #1 Limits: Publication Date from 2009 312
CENTRAL (The Cochrane Library) 2010, Issue 10	#1 MeSH descriptor Fibromyalgia explode all trees 449 #2 fibromyalgi* 755 #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)
EMBASE (Ovid) 4.november.10	1 exp Fibromyalgia/ 8833 2 fibromyalgia.ti.ab. 6702 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

RCTs in fibromyalgia (initial search February 2009)

DATABASE (ACCESS) and date of search	Search Strategy and hits retrieved
MEDLINE (PubMed) 9.february.09	#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
CENTRAL (The Cochrane Library)	#1 MeSH descriptor Fibromyalgia explode all trees 315 #2 fibromyalgi* 512

(Continued)

2009, Issue 1	#3 fibrositis 36
	#4 #1 OR #2 OR #3 526
EMBASE	1 exp Fibromyalgia/ 5537
(Ovid)	2 fibromyalgia.ti.ab. 4304
9.february.09	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

Appendix 2. Criteria for risk of bias assessment for RCTs

Criteria for risk of bias assessment for RCTs

1. Random sequence generation (selection bias)

Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence

There is a low risk of selection bias if the investigators describe a random component in the sequence generation process such as: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots or minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).

There is a high risk of selection bias if the investigators describe a non-random component in the sequence generation process such as: sequence generated by odd or even date of birth, date (or day) of admission, hospital or clinic record number; or allocation by judgement of the clinician, preference of the participant, results of a laboratory test or a series of tests, or availability of the intervention.

2. Allocation concealment (selection bias)

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment

There is a low risk of selection bias if the participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; or sequentially numbered, opaque, sealed envelopes.

There is a high risk of bias if participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (for example, a list of random numbers); assignment envelopes were used without appropriate safeguards (for example, if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; or other explicitly unconcealed procedures.

3. Blinding of participants and of personnel/care providers (performance bias)

Performance bias due to knowledge of the allocated interventions by participants and by personnel/care providers during the study

There is a low risk of performance bias if blinding of participants was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

There is a low risk of performance bias if blinding of personnel was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

4. Blinding of outcome assessor (detection bias)

Detection bias due to knowledge of the allocated interventions by outcome assessors of patient reported outcomes

There is low risk of detection bias if the outcome assessor of patient-reported outcomes is not the clinical investigator but a statistician not involved in the treatment of the patients. There is an unclear risk of bias if not details are reported who was the outcome assessor. There is a high risk of bias if the outcome assessor was involved in the treatment of the patients.

5. Incomplete outcome data (attrition bias)

Attrition bias due handling of incomplete outcome data

There is low risk of bias if all randomized patients were reported or analyzed in the group to which they were allocated by randomization and dropouts were analyzed by baseline observation forward method (BOCF). There is an unclear risk of bias if all randomized patients were reported or analyzed in the group to which they were allocated by randomization and dropouts were analyzed by last observation forward method (LOCF). There is a high risk of bias if there was no ITT analysis and only completers were reported.

6. Selective reporting (reporting bias)

Reporting bias due to selective outcome reporting

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.

7. Group similarity at baseline (selection bias)

Bias due to dissimilarity at baseline for the most important prognostic 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.

WHAT'S NEW

Date	Event	Description
6 February 2018	Amended	Minor typographical correction in Figure 1; no changes on data or conclusions

CONTRIBUTIONS OF AUTHORS

SC performed the June 2014 search. BN, GU, BW, SC, and WH were involved in the initial screening of articles. BN, GU, and WH were involved in the data extraction and risk of bias assessment, with the help of BW. BW, GU, SC, and WH wrote the manuscript.

DECLARATIONS OF INTEREST

WH received an honorarium for consulting for study design by Daiichi Sankyo and honoraria for educational lectures by Abbott Germany, MSD Sharp & Dohme and Pfizer.

The other authors have no conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Iberoamerican Cochrane Centre, Spain.

External sources

- Agencia d'Avaluació de Tecnologia i Recerca Mèdiques (146/24/2004), Spain.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol for this review is entitled 'Antidepressants and centrally active agents for fibromyalgia syndrome'. It was published in 2006 (Nishishinya 2006) has been split into several systematic reviews that will be/have been published as:

- Anticonvulsants for fibromyalgia (Üceyler 2013b)
- Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome (Tort 2012)
- Non-steroidal anti-inflammatory drugs (NSAIDs), analgesics and opioids for fibromyalgia
- Sedatives and hypnotic agents for fibromyalgia
- Selective serotonin reuptake inhibitors (SSRIs) for fibromyalgia
- Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome (Häuser 2013b)
- Tricyclic agents for fibromyalgia

The 'clinical relevant tables' and the 'grading system' due to be performed as mentioned in the original protocol have been superseded by the new guidelines for 'Summary of findings' tables, and GRADE, and the new 'Risk of bias' tool for Cochrane reviews.

INDEX TERMS

Medical Subject Headings (MeSH)

Amitriptyline [therapeutic use]; Citalopram [therapeutic use]; Fibromyalgia [*drug therapy]; Fluoxetine [therapeutic use]; Melatonin [therapeutic use]; Musculoskeletal Pain [drug therapy] [etiology]; Paroxetine [therapeutic use]; Randomized Controlled Trials as Topic; Selective Serotonin Reuptake Inhibitors [*therapeutic use]; Syndrome

MeSH check words

Humans