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Antidepressants for pain management in adults with chronic pain: a network meta-analysis (Review)

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Antidepressants for pain management in adults with chronic pain: a network meta-analysis.
Cochrane Database of Systematic Reviews 2023, Issue 5. Art. No.: CD014682.
DOI: 10.1002/14651858.CD014682.pub2.

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[Intervention Review]

Antidepressants for pain management in adults with chronic pain: a network meta-analysis

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: New, published in Issue 5, 2023.

Citation: Birkinshaw H, Friedrich CM, Cole P, Eccleston C, Serfaty M, Stewart G, White S, Moore RA, Phillippo D, Pincus T. Antidepressants for pain management in adults with chronic pain: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2023, Issue 5. Art. No.: CD014682. DOI: 10.1002/14651858.CD014682.pub2.

ABSTRACT

Background

Chronic pain is common in adults, and often has a detrimental impact upon physical ability, well-being, and quality of life. Previous reviews have shown that certain antidepressants may be effective in reducing pain with some benefit in improving patients' global impression of change for certain chronic pain conditions. However, there has not been a network meta-analysis (NMA) examining all antidepressants across all chronic pain conditions.

Objectives

To assess the comparative efficacy and safety of antidepressants for adults with chronic pain (except headache).

Search methods

We searched CENTRAL, MEDLINE, Embase, CINAHL, LILACS, AMED and PsycINFO databases, and clinical trials registries, for randomised controlled trials (RCTs) of antidepressants for chronic pain conditions in January 2022.

Selection criteria

We included RCTs that examined antidepressants for chronic pain against any comparator. If the comparator was placebo, another medication, another antidepressant, or the same antidepressant at different doses, then we required the study to be double-blind. We included RCTs with active comparators that were unable to be double-blinded (e.g. psychotherapy) but rated them as high risk of bias. We excluded RCTs where the follow-up was less than two weeks and those with fewer than 10 participants in each arm.

Data collection and analysis

Two review authors separately screened, data extracted, and judged risk of bias. We synthesised the data using Bayesian NMA and pairwise meta-analyses for each outcome and ranked the antidepressants in terms of their effectiveness using the surface under the cumulative ranking curve (SUCRA). We primarily used Confidence in Meta-Analysis (CINeMA) and Risk of Bias due to Missing Evidence in Network meta-analysis (ROB-MEN) to assess the certainty of the evidence. Where it was not possible to use CINeMA and ROB-MEN due to the complexity of the networks, we used GRADE to assess the certainty of the evidence.

Our primary outcomes were substantial (50%) pain relief, pain intensity, mood, and adverse events. Our secondary outcomes were moderate pain relief (30%), physical function, sleep, quality of life, Patient Global Impression of Change (PGIC), serious adverse events, and withdrawal.

Main results

This review and NMA included 176 studies with a total of 28,664 participants. The majority of studies were placebo-controlled (83), and parallel−armed (141). The most common pain conditions examined were fibromyalgia (59 studies); neuropathic pain (49 studies) and musculoskeletal pain (40 studies). The average length of RCTs was 10 weeks. Seven studies provided no useable data and were omitted from the NMA. The majority of studies measured short-term outcomes only and excluded people with low mood and other mental health conditions.

Across efficacy outcomes, duloxetine was consistently the highest-ranked antidepressant with moderate- to high-certainty evidence. In duloxetine studies, standard dose was equally efficacious as high dose for the majority of outcomes. Milnacipran was often ranked as the next most efficacious antidepressant, although the certainty of evidence was lower than that of duloxetine. There was insufficient evidence to draw robust conclusions for the efficacy and safety of any other antidepressant for chronic pain.

Primary efficacy outcomes

Duloxetine standard dose (60 mg) showed a small to moderate effect for substantial pain relief (odds ratio (OR) 1.91, 95% confidence interval (CI) 1.69 to 2.17; 16 studies, 4490 participants; moderate-certainty evidence) and continuous pain intensity (standardised mean difference (SMD) −0.31, 95% CI −0.39 to −0.24; 18 studies, 4959 participants; moderate-certainty evidence). For pain intensity, milnacipran standard dose (100 mg) also showed a small effect (SMD −0.22, 95% CI −0.39 to 0.06; 4 studies, 1866 participants; moderate-certainty evidence). Mirtazapine (30 mg) had a moderate effect on mood (SMD −0.5, 95% CI −0.78 to −0.22; 1 study, 406 participants; low-certainty evidence), while duloxetine showed a small effect (SMD −0.16, 95% CI −0.22 to −0.1; 26 studies, 7952 participants; moderate-certainty evidence); however it is important to note that most studies excluded participants with mental health conditions, and so average anxiety and depression scores tended to be in the 'normal' or 'subclinical' ranges at baseline already.

Secondary efficacy outcomes

Across all secondary efficacy outcomes (moderate pain relief, physical function, sleep, quality of life, and PGIC), duloxetine and milnacipran were the highest-ranked antidepressants with moderate-certainty evidence, although effects were small. For both duloxetine and milnacipran, standard doses were as efficacious as high doses.

Safety

There was very low-certainty evidence for all safety outcomes (adverse events, serious adverse events, and withdrawal) across all antidepressants. We cannot draw any reliable conclusions from the NMAs for these outcomes.

Authors' conclusions

Our review and NMAs show that despite studies investigating 25 different antidepressants, the only antidepressant we are certain about for the treatment of chronic pain is duloxetine. Duloxetine was moderately efficacious across all outcomes at standard dose. There is also promising evidence for milnacipran, although further high-quality research is needed to be confident in these conclusions. Evidence for all other antidepressants was low certainty. As RCTs excluded people with low mood, we were unable to establish the effects of antidepressants for people with chronic pain and depression. There is currently no reliable evidence for the long-term efficacy of any antidepressant, and no reliable evidence for the safety of antidepressants for chronic pain at any time point.

PLAIN LANGUAGE SUMMARY

How effective are antidepressants used to treat chronic pain and do they cause unwanted effects?

Key messages

• We are only confident in the effectiveness of one antidepressant: duloxetine. We found that a standard dose (60 mg) was effective, and that there is no benefit to using a higher dose.

• We are uncertain about unwanted effects for any antidepressant as the data for this were very poor. Future research should address this.

• In clinical practice for chronic pain, a standard dose of duloxetine may be considered before trying other antidepressants.

• Adopting a person-centred approach is critical. Pain is a very individual experience and certain medications may work for people even while the research evidence is inconclusive or unavailable. Future studies should last longer and focus on unwanted effects of antidepressants.

What is chronic pain?

Chronic pain is pain of any kind that lasts for more than three months. Over one-third of people across the world experience chronic pain. This often affects people's mood and well-being, and their ability to work and carry out daily tasks.

How do antidepressants treat chronic pain?

Antidepressants are medications originally developed to treat depression. Different types of antidepressants work in different ways. Antidepressants that work in the same way are grouped into classes. The most common classes are selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and serotonin-noradrenalin reuptake inhibitors (SNRIs). Research suggests that antidepressants may be effective for pain because the same chemicals that affect mood might also affect pain.

What did we want to find out?

We wanted to find out if antidepressants were effective for managing chronic pain and whether they cause unwanted effects.

What did we do?

We searched for studies that compared any antidepressant with any other treatment for any type of chronic pain (except headache). We compared all the treatments against each other using a statistical method called network meta-analysis. This method allows us to rank the effectiveness of the different antidepressants from best to worst.

What did we find?

We found 176 studies including 28,664 people with chronic pain. These studies investigated 89 different types or combinations of treatment. Studies mainly investigated the effect of antidepressants on three different types of pain: fibromyalgia (59 studies), nerve pain (49 studies), and musculoskeletal pain (e.g. osteoarthritis or low back pain; 40 studies). The most common antidepressant classes investigated were SNRIs (74 studies), TCAs (72 studies), and SSRIs (34 studies). The most common antidepressants investigated were: amitriptyline (a TCA; 43 studies); duloxetine (an SNRI; 43 studies), and milnacipran (an SNRI; 18 studies). Of the 146 studies that reported where their funding came from, pharmaceutical companies funded 72 studies. The average study lasted 10 weeks.

Most of the studies compared an antidepressant with a placebo (which looks like the real medicine but doesn't have any medicine in it), but some studies compared an antidepressant against a different type of medicine, a different antidepressant, a different type of treatment (like physiotherapy), or different doses of the same antidepressant.

Most of the studies in this review reported information on pain relief and unwanted effects. Fewer studies reported on quality of life, sleep, and physical function.

Main results

• Duloxetine probably has a moderate effect on reducing pain and improving physical function. It was the antidepressant that we have the most confidence in. Higher doses of duloxetine probably provided no extra benefits than standard doses. For every 1000 people taking standard-dose duloxetine, 435 will experience 50% pain relief compared with 287 who will experience 50% pain relief taking placebo.

• Milnacipran may reduce pain, but we are not as confident in this result as duloxetine because there were fewer studies with fewer people involved.

• Most studies excluded people with mental health conditions, meaning that participants were already in the 'normal' ranges for anxiety and depression at the beginning of studies. This limited our analysis for mood. Mirtazapine and duloxetine may improve mood, but we are very uncertain about the results.

• We do not know about unwanted effects of using antidepressants for chronic pain; there are not enough data to be certain about the results.

What are the limitations of the evidence?

There are still a number of questions that we were unable to answer:

• Aside from duloxetine and milnacipran, we do not have confidence in the results from any other antidepressant included in this review because there are not enough studies.

• We do not know whether antidepressants are effective at treating pain in the long term. The average length of studies was 10 weeks.

• There was no reliable evidence on the safety of taking antidepressants for chronic pain, both short- and long-term.

• We do not know how effective antidepressants are for people with both chronic pain and depression as the most studies excluded participants with depression and anxiety.

How up to date is this evidence?

This review is up to date to January 2022.

Summary of findings 1. Substantial pain relief summary of findings

Estimates of effects, credible intervals, and certainty of the evidence for substantial pain relief in people with chronic pain

Bayesian network meta-analysis summary of findings table

Patient or population: people with chronic pain

Interventions: desvenlafaxine high dose (≥ 50 mg); duloxetine low dose (< 60 mg), standard dose (60 mg), and high dose (> 60 mg); esreboxetine standard dose (4-8 mg) and high dose (≥ 8 mg); milnacipran standard dose (100 mg) and high dose (> 100 mg); mirtazapine standard dose (30 mg)

Comparator (reference): placebo

Outcome: substantial pain relief (≥ 50% reduction in pain intensity from baseline) as measured on various scales including 0-10 VAS, 0-100 VAS, and the Brief Pain Inventory

Direction: higher is better (i.e. more people reporting substantial pain relief)

Total studies: 42 **Total participants**: 14,626	**Relative effect** **(OR and 95% CI)**	**Anticipated absolute effect (event rate)***			**Certainty of the evidence (CINeMA)**	**Ranking**** **(2.5% to 97.5% credible interval)**	**Interpretation of findings**
		With placebo	**With intervention**	**Difference**			
Duloxetine standard dose RCTs: 16 Participants: 4490	1.91 (1.69 to 2.17)	592/2061 **287 per 1000**	1058/2429 **435 per 1000**	**148 more per 1000**	Moderate[a]	8 (5 to 12)	Equivalent to NNTB of 7.1
Duloxetine high dose RCTs: 14 Participants: 3692	1.91 (1.66 to 2.21)	431/1855 **232 per 1000**	674/1837 **366 per 1000**	**134 more per 1000**	Moderate[a]	8 (5 to 12)	Equivalent to NNTB of 7.4
Milnacipran high dose RCTs: 1 Participants: 384	1.64 (1.04 to 2.58)	38/145 **262 per 1000**	88/239 **368 per 1000**	**106 more per 1000**	Very low[a,b]	11 (4 to 19)	Equivalent to NNTB of 9.4
Esreboxetine standard dose RCTs: 1	1.72 (1.13 to 2.62)	33/275 **120 per 1000**	105/553 **190 per 1000**	**70 more per 1000**	Low[a]	11 (4 to 19)	Equivalent to NNTB of 14

Participants: 828							
Milnacipran standard dose RCTs: 2 Participants: 1298	1.65 (1.28 to 2.13)	130/654 **199 per 1000**	187/644 **290 per 1000**	**91 more per 1000**	Low[a,c]	12 (6 to 18)	Equivalent to NNTB of 11
Mirtazapine standard dose RCTs: 1 Participants: 422	1.30 (0.79 to 2.15)	33/211 **156 per 1000**	41/211 **194 per 1000**	**39 more per 1000**	Low[e]	15 (6 to 21)	Not significantly different from placebo
Duloxetine low dose RCTs: 6 Participants: 1116	1.71 (1.36 to 2.20)	150/523 **287 per 1000**	242/593 **407 per 1000**	**120 more per 1000**	Moderate[a,b,c]	16 (11 to 20)	Equivalent to NNTB of 8.3
Esreboxetine high dose RCTs: 1 Participants: 555	1.29 (0.79 to 2.11)	33/275 **120 per 1000**	42/280 **150 per 1000**	**30 more per 1000**	Very low[a,b]	16 (7 to 22)	Not significantly different from placebo
Desvenlafaxine high dose RCTs: 2 Participants: 870	1.19 (0.83 to 1.70)	51/215 **237 per 1000**	177/655 **270 per 1000**	**33 more per 1000**	Very low[a,b]	17 (11 to 21)	Not significantly different from placebo

Network meta-analysis-summary of findings table definitions

*Anticipated absolute effect. Anticipated absolute effect compares 2 risks by calculating the difference between the risk of the intervention group with the risk of the control group.

** Mean rank and credible intervals are presented.

CI: confidence interval; **CINeMA:** Confidence in Network Meta-Analysis; **NNTB:** number needed to treat for an additional beneficial outcome; **OR:** odds ratio; **RCT:** randomised controlled trial; **VAS:** visual analogue scale

The number of participants for each antidepressant reflects the total number of participants taking the antidepressant or placebo from the studies in the network meta-analysis.

CINeMA grades of confidence in the evidence

High: further research is unlikely to change our confidence in the estimate of effect.

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

Low: 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: we are very uncertain about the estimate.

[a]Downgraded due to within-study bias.
[b]Downgraded due to imprecision in the estimate.
[c]Downgraded due to heterogeneity in the estimate.
[d]Downgraded due to incoherence in the network.
[e]Downgraded due to a small number of trials and participants; we cannot draw reliable conclusions.

Summary of findings 2. Pain intensity summary of findings

Estimates of effects, credible intervals, and certainty of the evidence for pain intensity in people with chronic pain

Bayesian network meta-analysis summary of findings table

Patient or population: people with chronic pain

Interventions: duloxetine low dose (< 60 mg), standard dose (60 mg), and high dose (> 60 mg); milnacipran standard dose (100 mg) and high dose (> 100 mg)

Comparator (reference): placebo

Outcome: change in pain intensity, as measured on multiple scales including 0-10 VAS, 0-100 VAS, Brief Pain Inventory, and the Short-form McGill Pain Questionnaire

Direction: lower is better (i.e. a greater reduction in pain intensity)

Total studies: 50 **Total participants**: 14,926	**Relative effect**	**Anticipated absolute effect (event rate)**			**Certainty of the evidence (CINeMA)**	**Ranking*** (2.5% to 97.5% credible interval)	**Interpretation of findings****
		With placebo	**With intervention**	**Difference**			
Duloxetine high dose RCTs: 14 Participants: 3683	-	-	**-**	**SMD −0.37** (−0.45 to −0.28)	Low[a,b]	9 (8 to 13)	Small to moderate effect
Duloxetine standard dose RCTs: 18 Participants: 4959	-	-	**-**	**SMD −0.31** (−0.39 to −0.24)	Moderate[b]	11 (10 to 15)	Small to moderate effect

Milnacipran high dose RCTs: 2 Participants: 1670	-	-	-	**SMD −0.22** (−0.40 to −0.05)	Low[a,c]	14 (12 to 19)	Small effect
Milnacipran standard dose RCTs: 4 Participants: 1866	-	-	-	**SMD −0.22** (−0.39 to −0.06)	Moderate[a,b]	14 (12 to 20)	Small effect
Duloxetine low dose RCTs: 6 Participants: 1104	-	-	-	**SMD −0.11** (−0.25 to 0.03)	Moderate[a,c]	17 (12 to 21)	Not significantly different from placebo

Network meta-analysis-summary of findings table definitions

*Mean rank and credible intervals are presented.

**SMD interpretation based on clinical judgement and in line with Cohen 1988 and the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022) as small (0.2), moderate (0.5) and large (0.8).

CI: confidence interval; **CINeMA:** Confidence in Network Meta-Analysis; **RCT:** randomised controlled trial; **SMD:** standardised mean difference; **VAS:** visual analogue scale

The number of participants for each antidepressant reflects the total number of participants taking the antidepressant or placebo from the studies in the network meta-analysis.

CINeMA grades of confidence in the evidence

High: further research is unlikely to change our confidence in the estimate of effect.

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

Low: 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: we are very uncertain about the estimate.

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Summary of findings 3. Mood summary of findings

Estimates of effects, credible intervals, and certainty of the evidence of antidepressants on mood in people with chronic pain

Bayesian network meta-analysis summary of findings table

Patient or population: people with chronic pain

Interventions: duloxetine (all doses combined), milnacipran (all doses combined), mirtazapine (all doses combined)

Comparator (reference): placebo

Outcome: change in mood (depression, anxiety, distress) scores as measured on various scales including the Beck Anxiety Inventory, Beck Depression Inventory, SF-36 Mental Component Score, and the SF-36 Mental Health Subscale

Direction: lower is better (i.e. a greater reduction of distress, depression, or anxiety)

Total studies: 38 **Total participants**: 12,985	**Relative effect**	**Anticipated absolute effect (event rate)**			**Certainty of the evidence (CINeMA)**	**Ranking*** **(2.5% to 97.5% credible interval)**	**Interpretation of findings****
		With placebo	**With intervention**	**Difference**			
Mirtazapine RCTs: 1 Participants: 406	-	-	-	**SMD −0.5** (−0.78 to −0.22)	Low[e]	4 (2 to 7)	Moderate effect
Duloxetine RCTs: 26 Participants: 7952	-	-	-	**SMD −0.16** (−0.22 to −0.1)	Moderate[a]	8 (5 to 11)	Small effect
Milnacipran RCTs: 5 Participants: 3109	-	-	-	**SMD −0.13** (−0.26 to 0.01)	Moderate[a,c]	9 (5 to 13)	Not significantly different from placebo

Network meta-analysis-summary of findings table definitions

*Mean rank and credible intervals are presented.

**SMD interpretation based on clinical judgement and in line with Cohen 1988 and the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022) as small (0.2), moderate (0.5) and large (0.8).

CI: confidence interval; **CINeMA:** Confidence in Network Meta-Analysis; **RCT:** randomised controlled trial; **SMD:** standardised mean difference

The number of participants for each antidepressant reflects the total number of participants taking the antidepressant or placebo from the studies in the network meta-analysis.

CINeMA grades of confidence in the evidence

High: further research is unlikely to change our confidence in the estimate of effect.

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

Low: 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: we are very uncertain about the estimate.

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Summary of findings 4. Adverse events summary of findings

Estimates of effects, credible intervals, and certainty of the evidence for adverse events with antidepressants in people with chronic pain

Bayesian network meta-analysis summary of findings table

Patient or population: people with chronic pain

Interventions: amitriptyline standard dose (25-75 mg); desvenlafaxine high dose (> 50 mg); duloxetine low dose (< 60 mg), standard dose (60 mg), and high dose (> 60 mg); milnacipran standard dose (100 mg) and high dose (> 100 mg); mirtazapine standard dose (30 mg)

Comparator (reference): placebo

Outcome: adverse events (as reported per study)

Direction: lower is better (i.e. fewer people reporting adverse events)

Total studies: 93 **Total participants**: 22,558	**Relative effect** **(OR and 95% CI)**	**Anticipated absolute effect (event rate)***			**Certainty of the evidence (GRADE)**	**Ranking**** **(2.5% to 97.5% credible interval)**	**Interpretation of findings**
		With placebo	**With intervention**	**Difference**			
Desvenlafaxine high dose RCTs: 2	1.67 (0.92 to 2.41)	174/220 **791 per 1000**	590/685 **863 per 1000**	**72 more per 1000**	Very low[a,b,c]	30 (16 to 48)	Not significantly different from placebo

Participants: 905							
Mirtazapine standard dose RCTs: 2 Participants: 457	1.70 (0.48 to 2.91)	135/228 **592 per 1000**	162/229 **712 per 1000**	**120 more per 1000**	Very low[b,c]	31 (11 to 52)	Not significantly different from placebo
Duloxetine standard dose RCTs: 20 Participants: 4998	1.88 (1.58 to 2.17)	1259/2164 **582 per 1000**	1883/2834 **723 per 1000**	**142 more per 1000**	Very low[a,b]	33 (24 to 42)	Equivalent NNTH is 7.0
Milnacipran standard dose RCTs: 8 Participants: 2491	1.92 (1.37 to 2.46)	930/1235 **753 per 1000**	1039/1256 **854 per 1000**	**101 more per 1000**	Very low[a,b,c]	33 (20 to 45)	Equivalent NNTH is 10
Duloxetine high dose RCTs: 10 Participants: 4000	1.93 (1.64 to 2.23)	1199/1912 **627 per 1000**	1587/2088 **764 per 1000**	**137 more per 1000**	Very low[a,b]	34 (24 to 43)	Equivalent NNTH is 7.03
Duloxetine low dose RCTs: 6 Participants: 1031	2.03 (1.45 to 2.62)	271/437 **620 per 1000**	325/594 **768 per 1000**	**148 more per 1000**	Very low[a,b]	35 (21 to 47)	Equivalent NNTH is 7.0
Milnacipran high dose RCTs: 7 Participants: 2837	2.44 (1.89 to 2.98)	930/1264 **736 per 1000**	1294/1573 **872 per 1000**	**136 more per 1000**	Very low[a,b]	39 (25 to 50)	Equivalent NNTH is 6.8
Amitriptyline standard dose RCTs: 10 Participants: 997	2.66 (2.14 to 3.19)	250/479 **522 per 1000**	351/518 **744 per 1000**	**222 more per 1000**	Very low[a,b,e]	41 (28 to 51)	Equivalent NNTH is 4.5
Esreboxetine standard dose RCTs: 1 Participants: 783	2.92 (1.90 to 3.93)	85/227 **374 per 1000**	315/556 **636 per 1000**	**262 more per 1000**	Very low[a,b,c,e]	42 (21 to 56)	Equivalent NNTH is 3.8

Network meta-analysis-summary of findings table definitions

* Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

** Mean ranks and credible intervals are presented.

CI: confidence interval; **NNTH:** number needed to treat for an additional harmful outcome; **OR:** odds ratio; **RCT:** randomised controlled trial

The number of participants for each antidepressant reflects the total number of participants taking the antidepressant or placebo from the studies in the network meta-analysis.

GRADE Working Group grades of evidence

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

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

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

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BACKGROUND

Description of the condition

Chronic pain is common in adults internationally, and is defined as pain lasting or recurring for three months or longer (IASP 2019). Chronic pain can be a primary condition or can occur in the context of a disease (Treede 2019).

Chronic pain and its impact on an individual is generally assessed via self-report. It is estimated that about one in five adults worldwide experience pain that is moderate or severe in its intensity and lasts three months or more (Moore 2014), however estimates vary and may be higher. For example, reviews of chronic pain in the UK suggest that between a third and a half of the population experience chronic pain (Fayaz 2016); and a review of chronic low back pain in Africa reported the annual prevalence as 57% (Morris 2018). Some populations are more likely to experience chronic pain: older adults, women, people not in employment due to ill health and disability, and people with comorbidities (Mills 2019). Social circumstances are particularly influential; people in low socio-economic circumstances are not only more likely to experience chronic pain, but also report higher levels of severity and disability (Mills 2019).

The impact of chronic pain is similar across conditions, despite the different aetiologies. Globally, chronic pain accounts for the highest number of years lived with disability, and affects individuals' daily lives, society and healthcare services (Breivik 2006; Rice 2016). Chronic pain accounts for up to one in five general practice consultations each year in Europe, Africa and Asia (European Pain Federation 2016; Jordan 2010; Morris 2018). Chronic pain is also one of the global leading causes for sickness absence and people being unable to work (Bevan 2012; Office for National Statistics 2019).

On an individual level, chronic pain can severely impair a person's quality of life, including physical functioning, mood, sleep, and ability to work outside the home (Breivik 2006). It has also been long-established that chronic pain influences a person's mood; depression is estimated to be three to four times more prevalent in people with chronic pain than those without (Gureje 1998; Sullivan 1992; Tunks 2008). Depression is characterised by persistent feelings of sadness or low mood, loss of pleasure in activities, fatigue, loss of motivation, changes in appetite and having thoughts of suicide or self-harm (American Psychiatric Association 2013). People have reported that experiencing only a few depressive symptoms can be both distressing and disabling; therefore, it is important to address these as effectively as possible (NICE 2009a). Depression and chronic pain are complex to address in both research and clinical practice, as many of the symptoms of chronic pain can overlap with those of depression (for example, fatigue and loss of motivation or pleasure in activities). Furthermore, the content of depressive thoughts and the antecedents of feelings of sadness experienced by people in chronic pain may differ to those experienced in people with depression but without pain. It is important to identify differences in pain-related distress (i.e. individuals with chronic pain experiencing low mood because of their pain) and clinical depression, which may reflect on the prevalence statistics reported above.

Successful treatment of chronic pain can result in significant improvements in quality of life, including anxiety and depression (Goesling 2013; Moore 2010a; Moore 2014). A systematic review identified that for people with fibromyalgia, reductions in pain intensity of 50% or more is associated with self-reports of sleep, fatigue and depression reverting to normative values (Moore 2014). Therefore, efficacious treatment of the pain condition is essential for improvement of both pain and mood, in addition to potential improvements in sleep, physical function and quality of life. There are many different treatments aimed at reducing and managing chronic pain, including analgesic medication, physiotherapy, self-management guidance, exercise, psychological therapy, antidepressants, pain management clinics and surgery. The use of these depends upon the pain condition, severity of pain, individual characteristics, availability of services and national policy and guidelines.

Description of the intervention

Antidepressants are medicines developed and used primarily for the treatment of clinical depression. A network meta-analysis (NMA) of the 21 most common antidepressants has shown that they are efficacious in the treatment of acute major depression, particularly severe depression (Cipriani 2018).

Antidepressants are grouped into different classes based on their chemical structure and presumed mechanism of action. The most common classes are:

- tricyclic antidepressants (TCAs): amitriptyline, desipramine, imipramine, nortriptyline, and others;
- selective serotonin reuptake inhibitors (SSRIs): citalopram, sertraline, fluoxetine, and others;
- serotonin norepinephrine reuptake inhibitors (SNRIs): duloxetine, levomilnacipran, milnacipran, venlafaxine, and others;
- monoamine oxidase inhibitors (MAOIs):
  - irreversible: phenelzine, tranylcipromine, izocarboxazid, and others;
  - reversible: brofaramine, moclobemide, tyrima, and others.

Antidepressants are recommended for first-line treatment of depression, but can also be used 'off-label' in clinical practice to treat other conditions, including chronic pain (British National Formulary 2022a). Prescriptions of antidepressants are relatively common in patients with chronic pain internationally; for example, 12.3% of people with chronic low back pain in Portugal report taking antidepressants for pain relief (Gouveia 2017; Kurita 2012). Recent guidance from the National Institute for Health and Care Excellence (NICE) recommends the use of duloxetine, amitriptyline, fluoxetine, paroxetine, citalopram and sertraline in the management of chronic primary pain (NICE 2020). Amitriptyline and duloxetine are also recommended as first-line treatments for neuropathic pain in primary care (NICE 2019). Both of these guidelines recommend these antidepressants regardless of a person's mood. However, other guidelines contradict this, for example antidepressants can be prescribed for people with a chronic physical health condition only if they are also experiencing moderate to severe depression (NICE 2009b), but they are not recommended at all for the treatment of chronic low back pain (without sciatica; NICE 2017). The NICE guidelines for chronic primary pain recommend antidepressants as the only pharmacological intervention to manage chronic primary pain (NICE 2021).

These guidelines only reviewed the evidence from head-to-head trials, and subsequently recommend six antidepressants with no hierarchy: amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine, or sertraline. Therefore, guidance for clinicians is mixed and unclear. Furthermore, as antidepressants can be prescribed for treating mood or pain, the proportions of antidepressants prescribed to people with chronic pain for the primary aim to reduce pain or improve mood is unknown.

There are also risks in the prescription of antidepressants. Adverse events such as dizziness, headache, nausea, ejaculation disorder, weight loss, tremor, sweating and insomnia, have been found by randomised controlled trials (RCTs) to be more common in people taking antidepressants compared with those taking placebo (Riediger 2017; Sinyor 2020). Use of antidepressants is associated with an increased risk of falls, fractures, all-cause mortality, and stroke in older adults (aged 65 and over), and self-harm and suicide in both younger adults (aged 20 to 64) and older adults (Coupland 2011; Coupland 2015). Antidepressants also increase the risk of onset of seizures (Hill 2015); and the potential for gastrointestinal bleeding with SSRIs is widely recognised (Jiang 2015). Therefore, long-term use of antidepressants for people with chronic pain is expected to be associated with potential for harms at the population level.

How the intervention might work

Antidepressants were originally developed to treat depression. Most antidepressants work by targeting monoamine neurotransmitters associated with mood and emotion and their receptors in the nervous system. These receptors, such as 5-hydroxytryptamine receptors, are activated by many neurotransmitters including serotonin, dopamine, adrenaline and noradrenaline (Harmer 2017). Antidepressants prevent the neurotransmitters from being absorbed into neurons, which prolongs their activity in synapses. The process by which this relieves depression is not fully understood, but research currently focuses on theories of neurochemical changes and neuroplasticity (Harmer 2017). Additionally, depending upon the class, the effect of antidepressants may be delayed, with reported clinical improvement often taking weeks to occur (Harmer 2017; Tylee 2007).

Antidepressants are also often used to manage chronic pain. Antidepressants are reported to offer an analgesic response in people with pain without depression, particularly for neuropathic pain, but also for some people with fibromyalgia, osteoarthritis, and back pain. It is theorised that the body's pain response systems travelling to and from the brainstem involve the noradrenergic neurotransmitters (Taylor 2017). Therefore, by increasing the amount of serotonin and noradrenaline in the nervous system, this may subsequently block pain signals at the peripheral, spinal, and supraspinal levels, reducing perceived pain; particularly in neuropathic pain (Finnerup 2021; Kremer 2018).

Additionally, a part of the brain called the locus coeruleus may have an analgesic effect on pain in the body (Llorca-Torralba 2016). Signals from this part of the brain are sent when the body reacts to a stimulus, such as pain, and noradrenaline is released into the dorsal horn in the spine to block receptors. Animal studies have shown that when pain signals are continuously received, as is the case in chronic pain, this analgesic response lessens over time, and noradrenaline is then not released (Llorca-Torralba 2016; Obata 2017). However, when antidepressants are given, the analgesic response from the locus coeruleus is restored (Alba-Delgado 2012; Llorca-Torralba 2016).

Why it is important to do this review

To date, there have been no NMAs investigating all antidepressants for all chronic pain conditions. There is no evidence comparing classes of antidepressants to each other in the management of chronic pain, as identified by the recent NICE guidelines (NICE 2020). Therefore, in the absence of any one RCT comparing the efficacy and safety of all antidepressants for chronic pain, a NMA is required to assess their relative effectiveness.

Previous Cochrane Reviews have investigated the efficacy of individual antidepressants in improving individual chronic pain conditions, and where possible by dose. There is no high-quality evidence to support or refute the use of amitriptyline, milnacipran, nortriptyline, venlafaxine, desipramine or imipramine for management of neuropathic pain (Derry 2015a; Derry 2015b; Gallagher 2015; Hearn 2014a; Hearn 2014b; Moore 2015), principally because of limited numbers of small studies with some high risks of bias. This is despite amitriptyline being recommended as a first-line treatment for neuropathic pain in primary care in guidelines for the UK, Canada and the International Association for the Study of Pain (Bates 2019; Finnerup 2015; Moulin 2014; NICE 2019). However, there is moderate-quality evidence that duloxetine is efficacious for diabetic peripheral neuropathy at doses of 60 mg and 120 mg (Lunn 2014).

For fibromyalgia, Cochrane Reviews of antidepressants show that there is no unbiased evidence that amitriptyline, desvenlafaxine, venlafaxine or SSRIs are superior to placebo (Walitt 2015; Welsch 2018). There is low-quality evidence that duloxetine and milnacipran have some benefit in improving patients' global impression of change (PGIC) and providing an improvement in pain relief of 30% or more, but no clinical benefit over placebo for improvement in pain relief of 50% or more, health-related quality of life or fatigue (Welsch 2018). Similarly, for mirtazapine, there is evidence for improvement in pain relief of 30% or more, and reduction of mean pain intensity and sleep problems, but this evidence is of low to medium quality, and there is no benefit for improvement in pain relief of 50% or more, PGIC, 20% improvement of health-related quality of life, reduction of fatigue or reduction in negative mood (Welsch 2015).

Only one Cochrane Review has investigated the use of antidepressants for low back pain, and it found no clear evidence to support the use of any antidepressants (Urquhart 2008). A more recent systematic review supports these conclusions (Koes 2018). However, when analysed using the baseline observation carried forward imputation method for missing data, pooled individual patient data analyses of RCTs have shown duloxetine and etoricoxib to be effective in reducing pain for pain conditions including chronic low back pain (Moore 2010b; Moore 2014). These distributions were bimodal; participants generally responded very well or very poorly, with few in between (Moore 2014).

These previous reviews have shown that there is no evidence comparing the data across all antidepressants and pain conditions. Through our review and network meta-analysis, we intend to compare all these antidepressants across pain conditions, and identify whether certain classes or doses of antidepressants are

useful in the management of pain and mood for people with chronic pain, and for certain chronic pain conditions. As antidepressants are also associated with a number of side effects, we will compare the proportion of adverse events occurring with the use of different antidepressants (including different classes of antidepressants, different types of antidepressants, and different dose regimes) within populations living with chronic pain.

There is evidence that people with chronic pain may be experiencing pain-related distress rather than clinical depression, although both conditions can present with similar symptoms (Rusu 2016). The distinction between pain-related distress and depression is particularly important as primary care practitioners are often given contradictory guidance: they are encouraged to better detect depression (Mitchell 2009; Nuyen 2005), whilst avoiding over-medicalisation of distress and thus over-treatment (Dowrick 2013; Mulder 2008). This is important as antidepressants can be prescribed for both the management of pain and mood (e.g. clinical depression) in people with chronic pain. This review aimed to clarify this guidance as, unlike previous reviews in this area, we intended to investigate whether there were differences dependent upon whether the antidepressants were prescribed to primarily treat mood or pain.

OBJECTIVES

To assess the comparative efficacy and safety of antidepressants for adults with chronic pain (except headache) by:

- assessing the efficacy of antidepressants by type, class and dose in improving pain, mood, physical function, sleep, quality of life and PGIC;
- assessing the number of adverse events and serious adverse events for antidepressants by type, class and dose;
- ranking antidepressants for efficacy of treating pain, mood and adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs that compared any antidepressant with any comparator. RCTs are the best design to minimise bias when evaluating the effectiveness of an intervention. We followed the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* for the inclusion of cross-over RCTs, which requires inclusion of this type of study unless there is a justifiable reason not to (McKenzie 2020). The risk in this review was that washout periods between the periods of the study would not be long enough for carry-over effects from the antidepressants or comparators to be sufficiently minimised. Therefore, we only included cross-over trials with washout periods of at least five times the length of the antidepressant half-life (this was calculated individually for each antidepressant).

The most common comparators we anticipated finding in the literature were: the same antidepressant at a different dose; a different antidepressant; placebo (both active and inert); other medications for pain management purposes (e.g. pregabalin, gabapentin); analgesics; psychological therapy (e.g. cognitive behavioural therapy, acceptance and commitment therapy); exercise; physiotherapy; multidisciplinary pain programmes; herbal medicines and nutraceuticals (e.g. St John's Wort); and acupuncture. Where the comparator was a placebo, antidepressant, analgesic or other medication for pain management purposes, these studies were required to be double-blind. We included studies that examined any dose of antidepressants, with a study duration of at least two weeks and minimum of 10 participants per arm. We excluded non-randomised studies, case reports, experimental studies, clinical observations and prevention studies.

Types of participants

We included adults (aged 18 years or older) reporting primary or secondary pain in any part of their body (except headache) as their primary complaint, that matched the International Association for the Study of Pain (IASP) definition of chronic pain (i.e. at least three months' duration; IASP 2019). We included all studies regardless of the severity of participants' chronic pain, although we extracted whether severity was part of the inclusion criteria of the individual studies. We excluded studies where the participants' primary complaint was headache or migraine, as this had been covered in previous Cochrane Reviews (Williams 2020). Although this condition does fit within the IASP criteria, the diagnosis, classification and treatment of primary and secondary headache are often different from that of other pain conditions; and clinical trials are primarily aimed at prevention of further headaches or migraines rather than symptomatic treatment. We included participants with multiple health conditions as long as the chronic pain condition was the focus of the trial.

Types of interventions

Decision set

We included any antidepressant at any dose, for any indication, but used primarily for treatment of people with chronic pain and compared to placebo or active intervention. We included antidepressants grouped into the following classes.

- Tricyclic antidepressants (TCAs): amitriptyline, clomipramine, imipramine, trimipramine, doxepin, desipramine, protriptyline, nortriptyline, dothiepin, lofepramine, and others
- Selective serotonin reuptake inhibitors (SSRIs): fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram, escitalopram, zimelidine and others
- Serotonin-noradrenaline reuptake inhibitors (SNRIs): venlafaxine, milnacipran, duloxetine, and others
- Monoamine oxidase inhibitors (MAOIs):
  - irreversible: phenelzine, tranylcipromine, izocarboxazid, and others;
  - reversible: brofaramine, moclobemide, tyrima, and others
- Other antidepressants
  - Noradrenaline reuptake inhibitors (NARIs): reboxetine, atomoxetine, and others
  - Noradrenaline and dopamine reuptake inhibitors (NDRIs): amineptine, bupropion, and others
  - Noradrenergic and specific serotonergic antidepressants (NaSSAs) including tetracyclic antidepressants (TeCA) such as: mirtazapine, mianserin, maprotiline, and others
  - Serotonin antagonist and reuptake inhibitors (SARIs): trazodone, and others

- Unclassified: agomelatine, vilazodone, and others

We categorised doses of included antidepressants into low, standard, and high doses. These are displayed in Table 1. As the majority of antidepressants are not licensed for pain, we based our judgements on the recommendations of daily doses for clinical depression in the British National Formulary (British National Formulary 2022a). The judgements were made by clinical authors of the review; initially by the clinical pharmacist and then approved by discussion with a psychiatrist and anaesthetist.

Standard doses were the recommended doses for depression in adults. Low doses were those listed as initial doses (where a standard range is specified), the dose for elderly patients, or any dose below the standard dose (where no range was specified). High doses were those listed at the upper range of standard dose ranges, or above the standard dose where no range is specified. Where studies included flexible dosing across multiple categories and did not report mean dose, we labelled them as 'unable to be categorised'.

Supplementary sets

We included studies with any active comparator. We included studies where the antidepressant is combined with another intervention, as long as there was an arm solely for the other intervention, so we were able to isolate the effects of the antidepressant (e.g. antidepressant + drug versus drug). We did not include combination studies where there was no way to isolate the effects of an antidepressant (e.g. antidepressant A + drug versus antidepressant B). For this review we assumed that any participant who met the inclusion criteria was, in principle, equally likely to be randomised to any of the eligible antidepressants; however, we acknowledge there may have been differences in patients' expectations of treatment and outcomes depending upon which antidepressant was studied.

Types of outcome measures

We anticipated that there would be a variety of outcome measures used throughout the literature. Due to the distinction between distress and depression discussed above, this review used the term 'mood' as an outcome, to include depression that is diagnosed, mood that is measured via self-report, and distress.

For pain and mood, where applicable we also dichotomised outcomes into pain relief or improvement of 50% or greater, in line with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidance, to indicate substantial improvement (Dworkin 2008). Where possible, we planned separate NMAs to compare antidepressants to the comparators immediately post-intervention, at short-term follow-up (12 weeks or less post-treatment) and long-term follow up (over 12 weeks post-treatment). Where studies included multiple follow-up time points, we took the most recent time point within each period. If multiple measures were used for the same outcome (e.g. for continuous pain intensity both a 0 to 10 numerical rating scale and the McGill Pain Questionnaire (Melzack 1975) were reported), then we extracted from the most valid, reliable, and widely used measure in the field.

Primary outcomes

- Substantial pain relief: proportion of participants (number and percentage of total and per arm) reporting at least 50% reduction in pain intensity from baseline, irrespective of pain measurement method (e.g. visual analogue scale, numerical rating scale)
- Pain intensity: continuous data from any measures of pain intensity or severity (e.g. visual analogue scale or validated measures such as Brief Pain Inventory)
- Mood: continuous data from any measures of mood (e.g. visual analogue scale, Hospital Anxiety and Depression Scale)
- Adverse events: the proportion of participants (number of percentage of total and per arm) reporting adverse events

Secondary outcomes

- Moderate pain relief: the proportion of participants (number and percentage of total and per arm) reporting at least 30% reduction in pain intensity from baseline, irrespective of pain measurement method (e.g. visual analogue scale, numerical rating scale).
- Physical function: continuous data from any measures of physical movement and disability, e.g. numerical rating scale, SF-36 Physical Component Score)
- Sleep: continuous data from any measures of quality of sleep, including insomnia, restfulness, etc. (e.g. Brief Pain Inventory, Jenkins Sleep Scale)
- Quality of life: continuous data from any measure of quality of life (e.g. numerical rating scale, EQ-5D)
- Patient Global Impression of Change (PGIC): the proportion of participants (number and percentage of total and per arm) reporting "much" and "very much" improved on the PGIC scale, and continuous data from the PGIC scale.
- Serious adverse events: the proportion of participants (number of percentage of total and per arm) reporting serious adverse events).
- Withdrawal: the proportion of participants (number and percentage of total and per arm) withdrawing for any reason.

Search methods for identification of studies

This search was last run on 4 January 2022.

Electronic searches

We searched the following databases, without language restrictions.

- The Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 12) via the Cochrane Library (searched 4 January 2022)
- MEDLINE and MEDLINE In-Process (via OVID) - 1946 to 4 January 2022
- Embase (via OVID) - 1974 to 4 January 2022
- CINAHL (via EBSCO) - 1981 to December 2021
- LILACS (via Birme - 1982 to Dec 2021)
- PsycINFO (via EBSCO)) - 1872 to 4 January 2022
- AMED (via OVID) - 1985 to December 2021

We tailored searches to individual databases. The search strategies used can be found in Appendix 1. The search strategy was

developed by the Cochrane Pain, Palliative and Supportive Care (PaPaS) Review Group's Information Specialist and was independently peer-reviewed. The PaPaS Information Specialist performed the searches.

Searching other resources

We searched ClinicalTrials.govand the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished and ongoing studies. In addition, we searched grey literature, checked reference lists of reviews and retrieved articles for additional studies, and performed citation searches on key articles. We contacted study authors for additional information where necessary.

Data collection and analysis

Selection of studies

Two review authors (HB and CF) independently determined eligibility of each study identified by the search. Review authors independently eliminated studies that clearly did not satisfy inclusion criteria, and obtained full copies of the remaining studies. HB and CF read these studies independently to select relevant studies, and in the event of a disagreement, third and fourth authors adjudicated (TP and CE). We did not anonymise the studies in any way before assessment. We have included a PRISMA flow chart that shows the status of identified studies (Moher 2009), as recommended in *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2022). We included studies in the review irrespective of whether measured outcome data were reported in a 'useable' way. We recorded reasons for exclusion of any ineligible studies at the full-text stage.

Data extraction and management

Two review authors (HB and CF) independently extracted data using a standard piloted form and checked for agreement before entry into Review Manager Web (RevMan Web 2023). In the event of disagreement, third and fourth authors (TP and CE) adjudicated. We collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We collected characteristics of the included studies in sufficient detail to populate the table of 'Characteristics of included studies'. We extracted the following information.

- Study design: authors, publication year and journal, duration, sponsorship, conflicts of interest, aim (pain or emotional functioning), design, number of treatment arms, setting, missing data methods, power calculation used, definition of chronic pain, minimum level of pain for entry, inclusion and exclusion criteria
- Setting
- Participant characteristics: overall number, number in each arm, withdrawal (total, per arm and by sex), type of participant, chronic pain conditions, sex, age, baseline differences
- Intervention: type of antidepressant, class, dose (freeform and dichotomised), route of administration, duration
- Comparator(s): type (e.g. placebo, psychological therapy), description (if placebo medication: active or inert, appearance, taste, smell, titration, number of tablets), type and class (if other antidepressant), doses, route of administration, length, intensity (if physical or psychological comparator)
- Outcomes (data from all time points reported in the study): domain (e.g. pain, physical functioning), measure, measure validation, baseline data, results for each time point, effect sizes
- Adverse events and withdrawals (proportion overall and per arm): any, serious, withdrawal due to adverse event, withdrawal due to lack of efficacy

Assessment of risk of bias in included studies

Two review authors (HB and CF) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), with any disagreements resolved by discussion. We completed a risk of bias table for each included study using the Cochrane risk of bias tool (RoB 1) in Review Manager 5 (Review Manager 2020).

We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as being at:
  - low risk of bias (any truly random process, e.g. random number table; computer random number generator); or
  - unclear risk of bias (method used to generate sequence not clearly stated).
  - We excluded studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We assessed the methods as being at:
  - low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); or
  - unclear risk of bias (method not clearly stated).
  - We will exclude studies that do not conceal allocation (e.g. open list).
- Blinding of participants and personnel (checking for possible performance bias). Due to the inclusion of studies using any comparator, our review will contain both double-blinded RCTs and those studies in which double-blinding is not possible (i.e. RCTs of psychological therapy or acupuncture). In the RCTs that are double-blinded, we assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received in the double-blind trials. We assessed methods as being at:
  - low risk of bias (the study states that it was blinded and describes the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); or
  - unclear risk of bias (the study states that it was blinded but does not provide an adequate description of how this was achieved).
  - Studies in which double-blinding was not possible due to the comparator will be considered to have high risk of bias.
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as being at:

- low risk of bias (the study has a clear statement that outcome assessors were unaware of treatment allocation, and ideally describes how this was achieved);
- unclear risk of bias (the study states that outcome assessors were blind to treatment allocation but it lacks a clear statement on how this was achieved); or
- high risk of bias (the outcome assessment was not blinded).

- Selective reporting (checking for reporting bias). We assessed whether primary and secondary outcome measures were pre-specified and whether these were consistent with those reported. We assessed the methods as being at:
  - low risk of bias (study protocol is available with pre-specified measures);
  - unclear risk of bias (insufficient information available to permit a judgement of high or low risk of bias); or
  - high risk of bias (not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes have been reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review have been reported incompletely so that they cannot be entered in a meta-analysis; the study report failed to include results for a key outcome that would be expected to have been reported for such a study).
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as being at:
  - low risk of bias (no missing outcome data; reasons for missing outcome data are unlikely to be related to the true outcome; missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups; missing data have been imputed using 'baseline observation carried forward' (BOCF) analysis);
  - unclear risk of bias (insufficient reporting of attrition/exclusions to permit a judgement of low or high risk of bias (e.g. number randomised not stated; no reasons for missing data provided; or the study did not address this outcome)); or
  - high risk of bias (the reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; 'as-treated' analysis was done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation; use of 'last observation carried forward' (LOCF) without the addition of any other low risk of bias methods).
- Other bias. We assessed any other potential sources of bias that were not included in the other domains.

We considered studies to be at high risk of bias overall if they met the criteria for high risk of bias in any of the above domains.

Measures of treatment effect

For the outcomes measuring continuous data (pain intensity, mood, physical function, sleep, quality of life, and PGIC continuous), studies reported data as either post-intervention scores (the mean scores at the end of the intervention period) or change scores (mean change from baseline score). We conducted separate analyses for these. As is common in pain management studies, for all outcomes (apart from PGIC) studies used a broad range of scales to measure the outcomes. Therefore, once data were extracted, we converted them into standardised mean difference (SMD) with 95% confidence intervals (CIs). We interpreted SMD as small (0.2), moderate (0.5) and large (0.8), in line with Cohen 1988 and the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a). For outcomes with dichotomous data (substantial pain relief, adverse events, moderate pain relief, PGIC much/very much improved, serious adverse events, and withdrawal), we used odds ratios (OR) with 95% CIs.

Unit of analysis issues

For most RCTs, we did not encounter any unit of analysis complexities as participants were randomised to different study arms, allowing direct analysis. For cross-over RCTs, if the results for the first period (prior to cross-over) were reported, we extracted these in an attempt to avoid cross-over effects. If the results from the first period were not reported then we extracted the final study results, provided there was a sufficient washout period of at least five times the length of the antidepressant half-life (minimum washout period length calculated separately for each antidepressant). The majority of cross-over trials reported the combined effects of both periods (only one study reported first period and second period effects separately), therefore we analysed cross-over trials using these combined effects. Our search did not return any cluster-RCTs that met our inclusion criteria.

Dealing with missing data

For all missing study-level statistical data relevant to our outcomes we first tried to contact the authors of the study. If we could not get the data from the authors, then we followed the guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). If standard deviations were missing then we used the Review Manager calculator (RevMan Web 2023) to calculate these from other data reported in the study. We did not impute any data, but assessed each study's risk of bias due to missing data.

Assessment of heterogeneity

We assessed heterogeneity within the network meta-analyses using the Tau statistic, in line with the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). We assessed heterogeneity using Confidence in Meta-Analysis (CINeMA) software, which calculated the Chi^2 test and the I^2 statistic for each pairwise comparison on each outcome (Nikolakopoulou 2020). As outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*, we interpreted the I^2 statistic as follows (Deeks 2022).

- 0% to 40%: might not be important
- 30% to 50%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

We took into account the magnitude and strength of effects when assessing heterogeneity.

Assessment of the transitivity assumption

We carefully scrutinised transitivity, which is the key underlying assumption of NMA. Transitivity requires studies to be similar on average across all factors that might alter treatment effects other than the intervention comparison being made (Chaimani 2022). To address this, we only included studies with similar clinical populations (i.e. participants reporting pain lasting at least three months; Furukawa 2016). Previous research, combined with review authors' clinical experience and knowledge, identified variables that could potentially influence our primary outcome:

- pain condition;
- age;
- pain intensity at baseline;
- depressive severity at baseline;
- treatment duration; and
- dosing schedule.

We explored the impact of these factors by assessing the indirectness of the network.

The inclusion of placebo and concerns about its potential to violate the transitivity assumption have been highlighted in general (Cipriani 2013), and particularly in depression studies (Rutherford 2009). Therefore, we explicitly compared placebo-controlled studies with those that provide head-to-head evidence as a form of validation of the network.

Assessment of reporting biases

We assessed reporting biases using the Cochrane risk of bias tool (RoB 1) in Review Manager 5 (Review Manager 2020), by checking for study protocols and pre-specified outcomes (as detailed in the Assessment of risk of bias in included studies section). We also used funnel plots for pairwise analyses for antidepressants where more than 10 studies were available, as advised in the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2022). Funnel plots were drawn using ROB-MEN, which is part of CINeMA, and used to assess the significant small study effects via funnel plot asymmetry.

Data synthesis

We undertook separate NMAs for each outcome. NMAs combine information (evidence) from both direct comparisons of interventions within RCTs, and indirect comparisons across studies based on a common placebo comparator (Caldwell 2005; Jansen 2011). Direct comparisons (direct evidence) occur when two or more interventions are compared head to head in a study; in the absence of head-to-head comparisons, interventions can be indirectly compared (indirect evidence).

We analysed the data for all primary and secondary outcomes using Bayesian random-effects NMAs implemented using the R (r-project.org) package multinma (Phillippo 2022). Where dose was included in the network, we categorised them (low, standard, high) and incorporated them as separate nodes. Where a study had multiple arms investigating different doses of the same antidepressant that fall into in the same category (e.g. two different low doses), we did not combine them; by using the multinma package we were able to keep these as separate arms in the analysis.

We fitted random-effects models using broad normal prior distributions for the treatment effects, and study-specific intercepts and a half-normal prior for the heterogeneity standard deviation. We used four chains, each with 2000 iterations and 1000 post-warm up draws per chain.

We explored network connectivity via network plots. In the network plot, for treatment-only models, the nodes represent each intervention. In treatment-dose models, the antidepressant nodes represent the antidepressant and dose (low, standard, high). The colour of the node represents the antidepressant class, and the "nonad" label refers to all interventions that were not an antidepressant. The size of each node represents the combined sample size of participants from all studies investigating that intervention, and the thickness of the lines represents the number of studies for that comparison. The forest plots present the estimates and credible intervals for each intervention in the network, with reference to placebo.

We assessed convergence using the potential scale reduction factor for each parameter, ensured that effective sample sizes were sufficiently large (Vehtari 2021), and verified that there were no divergent transitions (Betancourt 2015). We explored heterogeneity by fitting connected networks for treatment, treatment-dose, class, risk of bias, and condition where network geometry allowed sufficient connectivity (Dias 2013).

We assessed model fit using mean residual deviance, and explored inconsistency through unrelated mean-effect models (UME) and node-splitting where network geometry allowed (Dias 2013a). We used dev-dev plots, which compare residual deviance contributions from each model, to explore inconsistency. The data points are plotted against a line of equality; points on the line fit equally well under either model, whereas points above or below the line indicate better fits for one of the two models (Phillippo 2022). Node-splitting plots present the evidence of direct, indirect, and combined evidence on the same plot to allow comparisons.

We reported effect estimates and cumulative posterior ranks of effect alongside strength of evidence assessment using GRADE (Schünemann 2013).

To rank the treatments for each outcome by probability of best treatment, we used the surface under the cumulative ranking curve (SUCRA) and the mean ranks. We reported relative effects and mean rank of treatments and plotted cumulative rankograms showing the range of rankings of different treatments for each outcome.

We used the deviance information criterion (DIC) to compare the different models for reporting (treatment only, treatment-dose, class and, change score and post-intervention studies for contrast-based models) to assess their parsimony. Substantive differences in DIC (> 5) or models with marginally lower DIC but lower Tau and fewer studies with residual deviance greater than 3 in combination were deemed superior. We selected models to report on the basis of parsimony, minimisation of inconsistency (identified via UME and node-splitting models), residual deviance and heterogeneity (measured as Tau). This approach balanced clinical exploration of results and the risk of overfitting (Dias 2013).

NMA, UME and node-splitting models were implemented in multinma in R (version 4·1.3). Further details of the modelling framework are described by Phillippo 2018; Phillippo 2022.

Subgroup analysis and investigation of heterogeneity

Where data allowed, we performed subgroup analyses for the following factors.

- Class of antidepressant (SSRI, SNRI, TCA, MAOI, etc.)
- Type of pain condition

We used a Bayesian random-effects NMA to account for expected heterogeneity and variation in the data. These methods allowed the uncertainty inherent in the between-study variance component to be reflected in effect estimate precision. We performed these subgroup analyses by building separate models, however this was dependent on the geometry and connectedness of the networks.

Due to sparsity of data, we were unable to perform subgroup analyses for the following factors for any outcome.

- Aim of the study (i.e. whether the intervention is aimed at pain or mood)
  - Only one study had a main aim of addressing mood (Richards 2015)
- Baseline level of depression (none, mild, moderate, severe, as defined by the individual measure criteria)
  - Upon examination, the average scores for the five most commonly used scales (Beck Depression Inventory, Brief Pain Inventory Mood Item, SF-36 Mental Component Score, SF-36 Mental Health Subscale, and Hamilton Depression Rating Scale) were all in the none/minimal ranges.

Sensitivity analysis

We could only undertake analysis by risk of bias judgement (high and not high) for substantial pain relief. We were unable to perform sensitivity analyses for any outcome that compared active placebo to inert placebo, as in total only nine studies used an active placebo.

Summary of findings and assessment of the certainty of the evidence

To assess the certainty of the NMA, we primarily used the CINeMA framework (Nikolakopoulou 2020). In contrast to the NMAs in this review, which were conducted within a Bayesian framework, CINeMA operates within a frequentist framework using the netmeta package in R (Rücker 2017). The CINeMA framework considers the impact of certain issues within NMAs on clinical decision making made from the results. This framework is based on GRADE, and considers the following six domains specific to NMA (Nikolakopoulou 2020).

- Within-study bias (impact of risk of bias in the included studies)
  - CINeMA assesses the impact of risk of bias by combining the study's risk of bias (as judged by the review authors using a risk of bias tool) with its contribution to the network meta-analysis.
- Reporting bias (publication and other reporting biases)
  - Reporting bias in CINeMA is categorised as either 'suspected' or 'undetected'. Suspected reporting bias is when the review methods do not take into account unpublished data, the meta-analysis is based on a small number of positive early findings, or treatments are exclusively studied in industry-funded studies. Undetected reporting bias is when data from unpublished studies has been identified and findings agree, when prospective trial registration has been completed and there are no deviations from protocols, and comparisons of estimates between small and large studies agree.
- Indirectness (relevance to the research question, addressing transitivity)
  - Each study in the NMA is evaluated according to its relevance to the research question. Study-level judgements are combined with the percentage contribution of the study to the network. This approach assesses potential transitivity issues in the NMA.
- Imprecision (the precision of the NMA, by combining direct with indirect evidence)
  - Relevant treatment effects that represent a minimal clinically important difference (MCID) are defined and the range of clinical equivalence is produced (the value of the MCID either side of the line of no effect). CINeMA then compares the treatment effects included in the 95% CI to the range of clinical equivalence. If the 95% CI of a treatment effect crosses the range of clinical equivalence, then it is considered to have major concerns of imprecision. If the 95% CI of a treatment effect only crosses one side of the range of equivalence then there are no concerns of imprecision.
- Heterogeneity (variability in the results of studies)
  - CINeMA accounts for both heterogeneity between studies by comparing the confidence and prediction intervals of a treatment effect. When confidence and prediction intervals indicate the same effect, then there is no evidence of heterogeneity; conversely if a prediction interval leads to a different conclusion than the CIs then there is evidence of heterogeneity.
- Incoherence (agreement between the results of direct and indirect evidence)
  - This is the variation between direct and indirect evidence in the network and also an assessment of transitivity. CINeMA compares the 95% CIs of the estimates of the direct and indirect estimates. If both of these estimates lie on the same side of the range of clinical equivalence, then there are no concerns about incoherence.

The CINeMA framework results in the review authors summarising the judgements across the domains into the four domains of GRADE (high certainty, moderate certainty, low certainty, very low certainty).

For outcomes where we were unable to use CINeMA due to the complexity of the network (adverse events, serious adverse events, and withdrawal), we used GRADE. The GRADE system considers the following five considerations to assess the certainty of the body of evidence for each outcome.

- Serious or very serious study limitations (risk of bias)
- Important or serious inconsistency of results
- Some or major indirectness of evidence
- Serious or very serious imprecision
- Probability of publication bias

The GRADE system results in the assignment of one of the following grades to the evidence.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

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

Two authors (HB and GS) independently interpreted the findings, and collaboratively made the final judgements across all outcomes. To present our findings, we have produced separate summary of findings tables for all outcomes. We have used the template summary of findings tables designed for NMAs (Yepes-Nuñez 2019). Due to the scale of the analyses, we only included antidepressants that had 200 or more participants in total receiving the antidepressant in the write-ups and summary of findings tables. This decision was made to ensure quality and certainty of the final results and conclusions. We based this decision through reference of the tiers of evidence for pain research; Tier 2 uses data from at least 200 participants (Wiffen 2016).

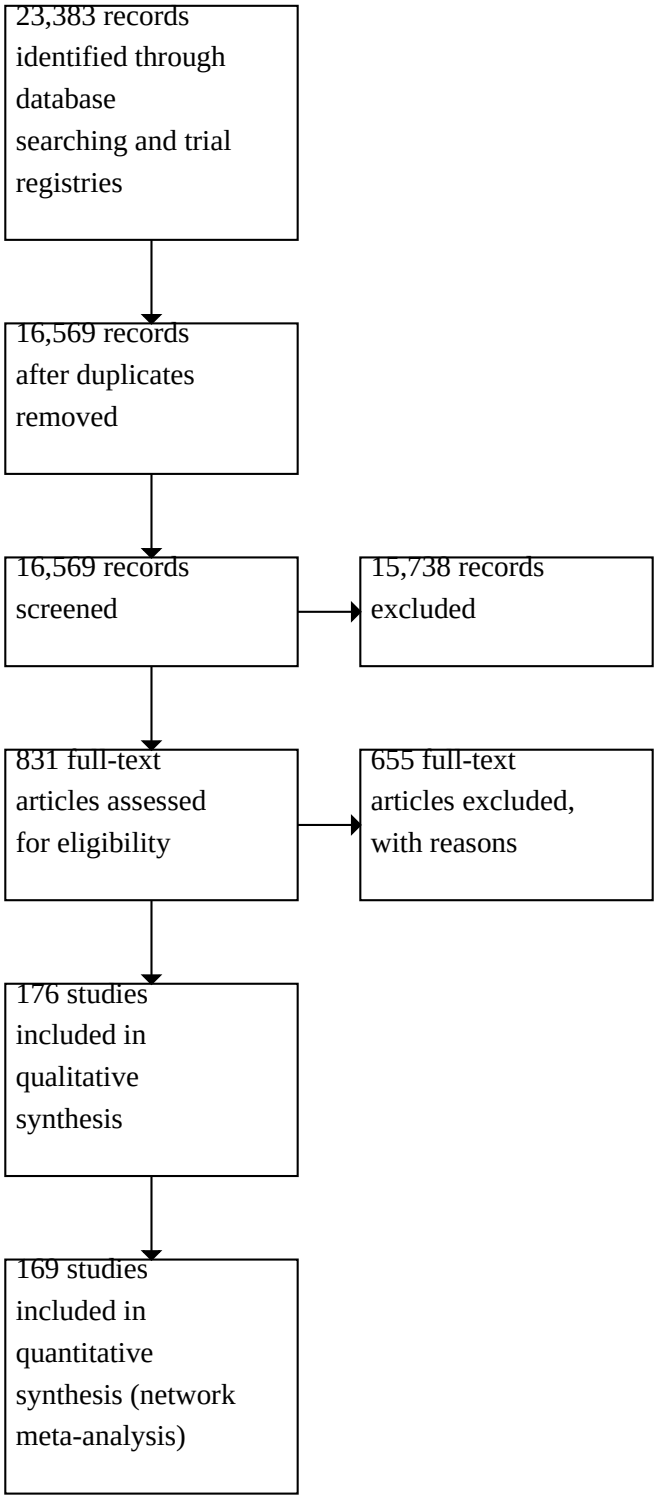
RESULTS

Description of studies

Results of the search

We ran the original search on 6 May 2020, and the top-up search on 4 January 2022. Both searches searched six databases and clinicaltrials.gov. The original search returned 21,569 records, and the top-up search returned 1814 records for a total of 23,383. After removing duplicates, we screened the titles and abstracts of 16,569 records. From this, we excluded 15,738 records, leaving 831 full-text records. After full-text screening, we included 176 studies. The study flow diagram is presented in Figure 1.

Figure 1. PRISMA flow diagram of studies found, screened, and included



Included studies

In total, we included 176 studies in the review, with a total of 28,664 adult participants with a mean age of 50.6 years.

There were a variety of study designs across studies.

- Antidepressant versus placebo (83 studies, e.g. Hudson 2021)
- Antidepressant versus active comparator (22 studies, e.g. Enomoto 2018)
- Antidepressant versus the same antidepressant at different doses versus placebo (17 studies, e.g. Arnold 2012b)
- Antidepressant versus active comparator versus combined antidepressant + active comparator (13 studies, e.g. Ang 2013)
- Antidepressant versus active comparator versus placebo (9 studies, e.g. Rowbotham 2012)
- Antidepressant versus different antidepressant (9 studies, e.g. Kaur 2011)
- Antidepressant versus active comparator versus combined antidepressant + active comparator versus placebo (8 studies, e.g. Gilron 2016)
- Antidepressant versus different antidepressant versus placebo (7 studies, e.g. Heymann 2001)
- Antidepressant versus different antidepressant versus active comparator (4 studies, e.g. Boyle 2012)
- Antidepressant versus the same antidepressant at different doses (2 studies, e.g. Chappell 2009a)
- Antidepressant versus same antidepressants at different doses versus different antidepressant versus different antidepressant at different doses versus placebo (1 study, Atkinson 2007)
- Antidepressant versus different antidepressant versus combined antidepressants versus placebo (1 study, Goldenberg 1996)

Most studies were parallel-arm design (141 studies) compared to cross-over design (35 studies).

Studies mainly included participants with only one type of chronic pain.

- 59 studies included fibromyalgia
- 49 studies included neuropathic pain
- 40 studies included musculoskeletal pain
- Nine studies included primary pain syndromes (not including fibromyalgia) that is, described only as 'somatoform' or 'idiopathic' pain
- Six studies included gastrointestinal pain
- Four studies included non-cardiac chest pain
- Two studies included burning mouth syndrome
- Two studies included visceral pain
- One study included atypical facial pain
- One study included phantom limb pain
- One study included pelvic pain

Two studies included participants with any type of chronic pain.

Most studies were funded by pharmaceutical companies.

- 72 studies were fully funded by pharmaceutical companies.
- Five studies were partially funded by pharmaceutical companies.
- 67 studies were funded through non-pharmaceutical means, mainly government, charity, or institutional funding.
- 32 studies did not report the source of funding.

Most studies had a primary aim of reducing pain.

- 144 studies had a primary aim of reducing pain.
- Two studies had a primary aim of treating mood.
- Eight studies had a primary aim of treating both pain and mood.
- 22 studies had other primary aims (e.g. sleep, other symptoms).

Studies ranged in length from two weeks to nine months, with an average length of 10 weeks.

Only six studies followed up with participants after participants finished taking the study treatment (Creed 2003; Kayiran 2010; NCT00066937; Sencan 2004; Tanum 1996; Zitman 1990). The follow-up time points ranged from four weeks post-treatment to one year post-treatment.

Seven studies with a total of 156 participants provided no useable data and were therefore omitted from the NMAs (Atkinson 2007; Engel 1998; Kalso 1996; Ozerbil 2006; Sarzi Puttini 1988; Tasmuth 2002; Ward 1986).

Of the 176 studies and 28,664 participants, the number of participants receiving each antidepressant (not including combined interventions) are as follows.

- Amitriptyline: 1843 (43 studies)
- Bupropion: 54 (1 study)
- Citalopram: 97 (5 studies)
- Clomipramine: 124 (2 studies)
- Desipramine: 336 (7 studies)
- Desvenlafaxine: 884 (2 studies)
- Dothiepin: 55 (3 studies)
- Doxepin: 30 (2 studies)
- Duloxetine: 6362 (43 studies)
- Escitalopram: 93 (3 studies)
- Esreboxetine: 978 (2 studies)
- Fluoxetine: 277 (11 studies)
- Imipramine: 300 (7 studies)
- Maprotiline: 135 (4 studies)
- Mianserin: 107 (2 studies)
- Milnacipran: 3110 (18 studies)
- Mirtazapine: 255 (2 studies)
- Moclobemide: 42 (1 study)
- Nortriptyline: 374 (7 studies)
- Paroxetine: 422 (9 studies)
- Pirlindole: 50 (1 study)
- Reboxetine: 18 (1 study)
- Sertraline: 91 (3 studies)
- Trazodone: 63 (3 studies)
- Trimipramine: 18 (1 study)
- Venlafaxine: 489 (8 studies)

- Zimeldine: 10 (1 study)

In total, 9854 participants received a placebo across 130 studies.

Excluded studies

We excluded a total of 655 references with reasons throughout the course of this review. The main reasons for exclusion were as follows.

- Duplicate records (including trial registrations): 144 records
- Not chronic pain condition: 71 records
- Not accessible (primarily conference abstracts): 92 records
- Pooled analysis: 50 records
- Open-label: 42 records
- Fewer than 10 participants per arm: 22 records
- Single-blind: 15 records
- Washout period not more than five lengths of antidepressant half-life: 11

Reasons for exclusion other than these are reported in the Characteristics of excluded studies section.

We categorised 15 studies as 'awaiting classification' due to uncertainties regarding blinding or pain duration (Characteristics of studies awaiting classification), and 26 studies are ongoing (Characteristics of ongoing studies).

Risk of bias in included studies

Risk of bias findings from the included studies are shown in Figure 2 and Figure 3. Overall, we rated 116 of 176 studies as 'high risk', and 60 as 'not high risk'. However, of the 60 studies not rated as high risk, 29 had three or more domains rated as 'unclear'.

Figure 2. Risk of bias of included studies by domain

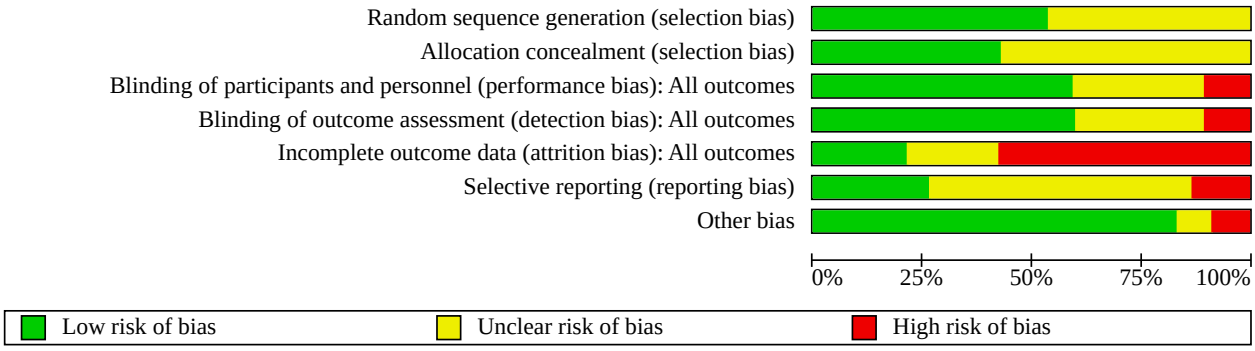


Figure 3. Risk of bias of included studies by study

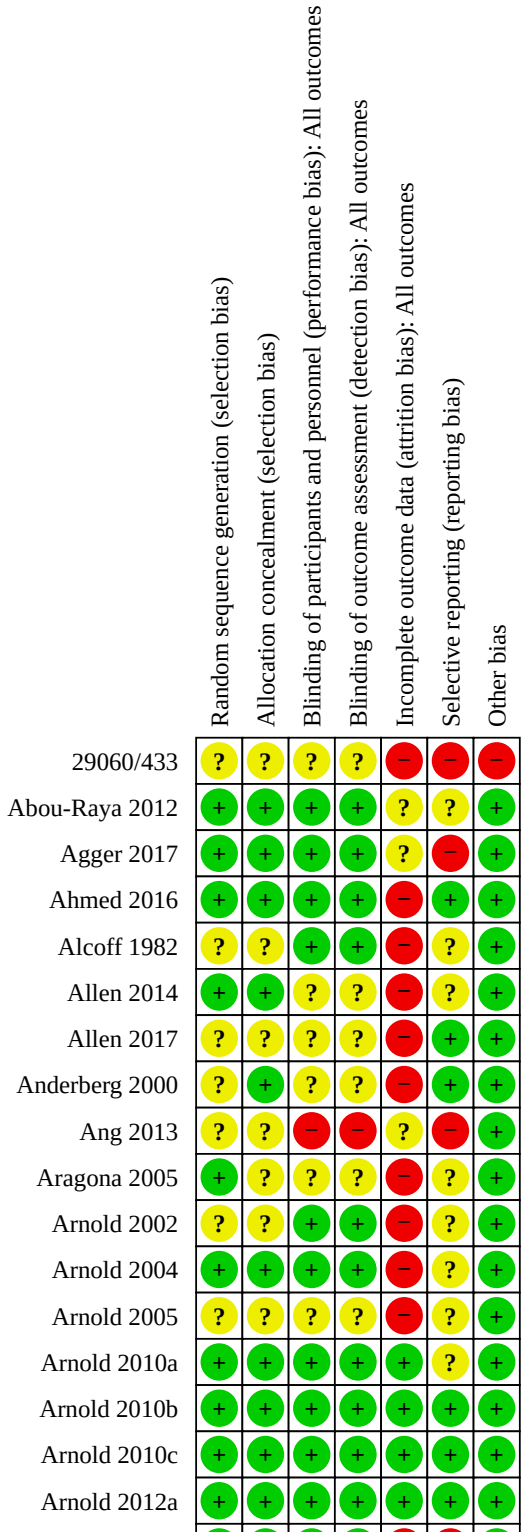


Figure 3. (Continued)

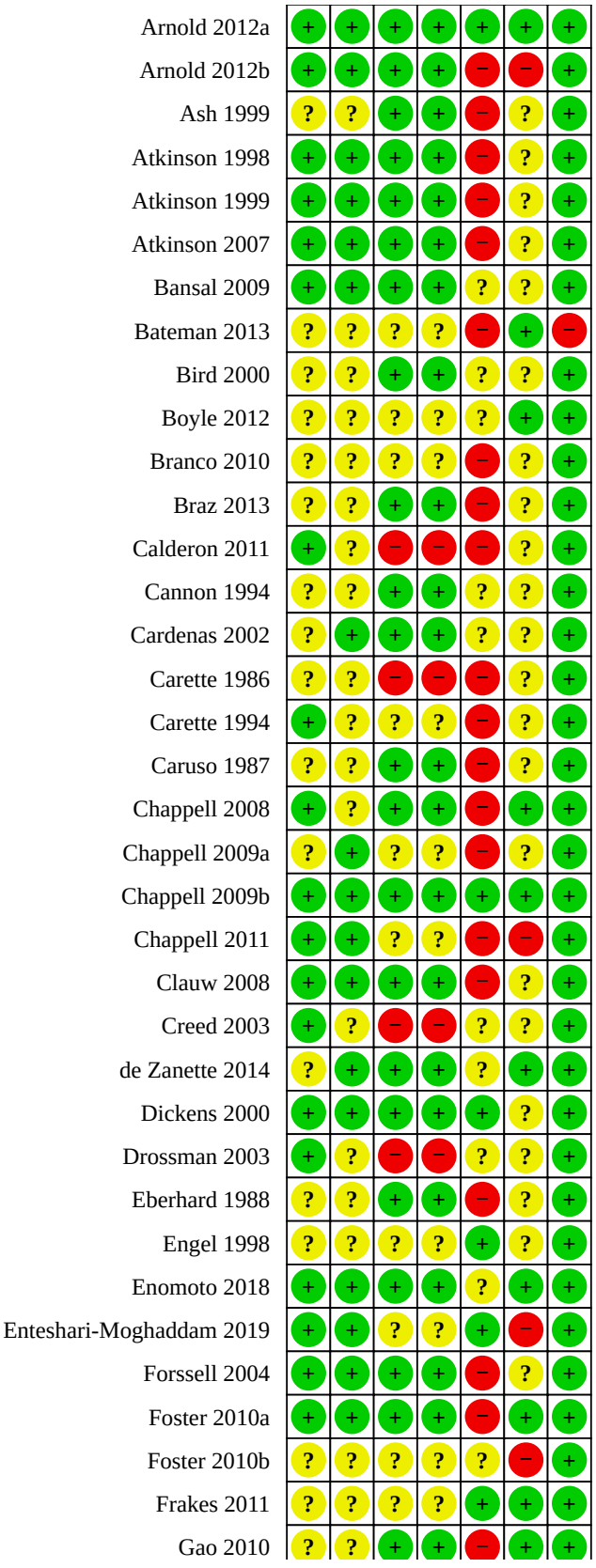
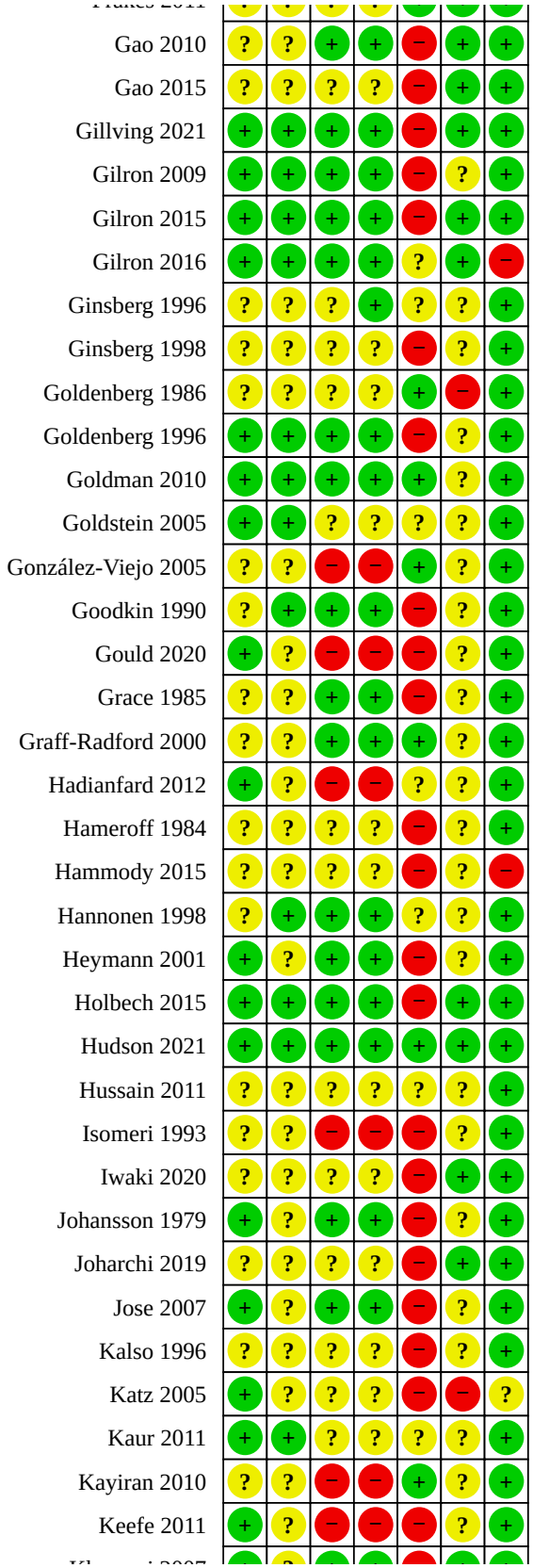


Figure 3. (Continued)



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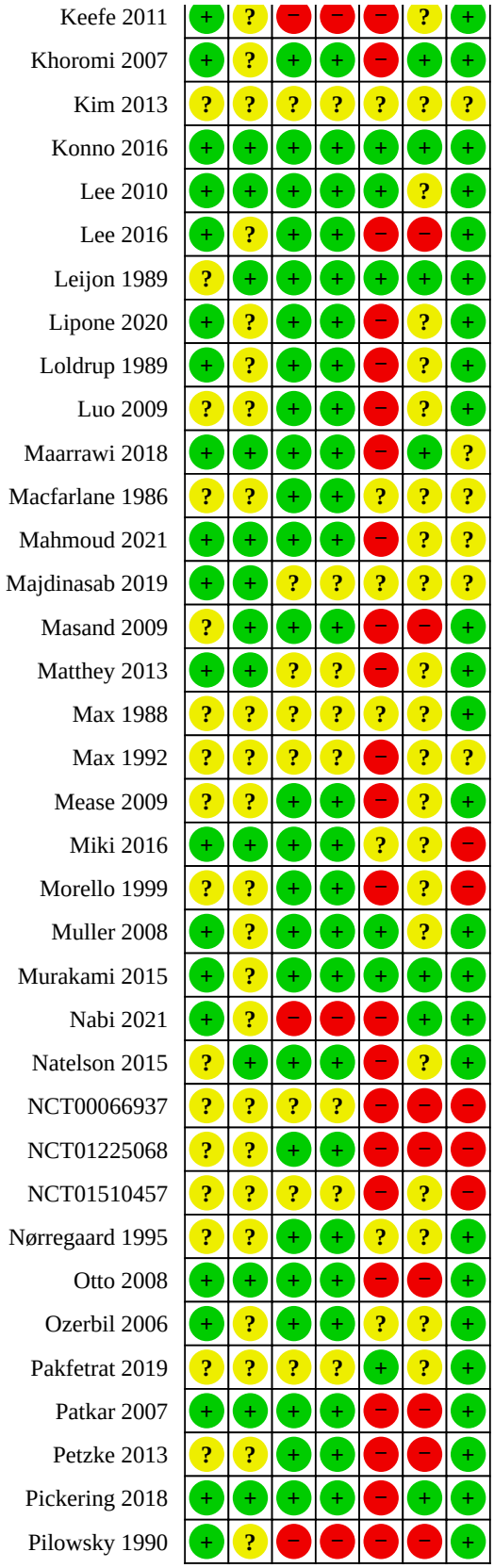

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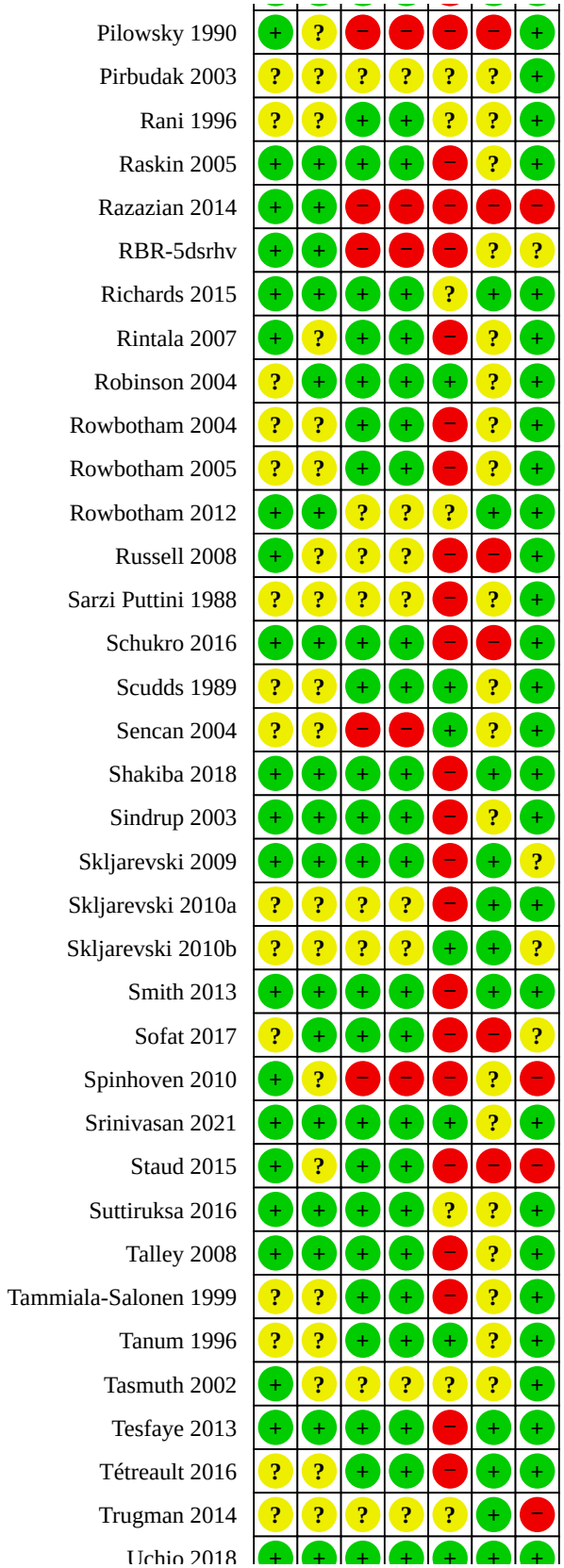

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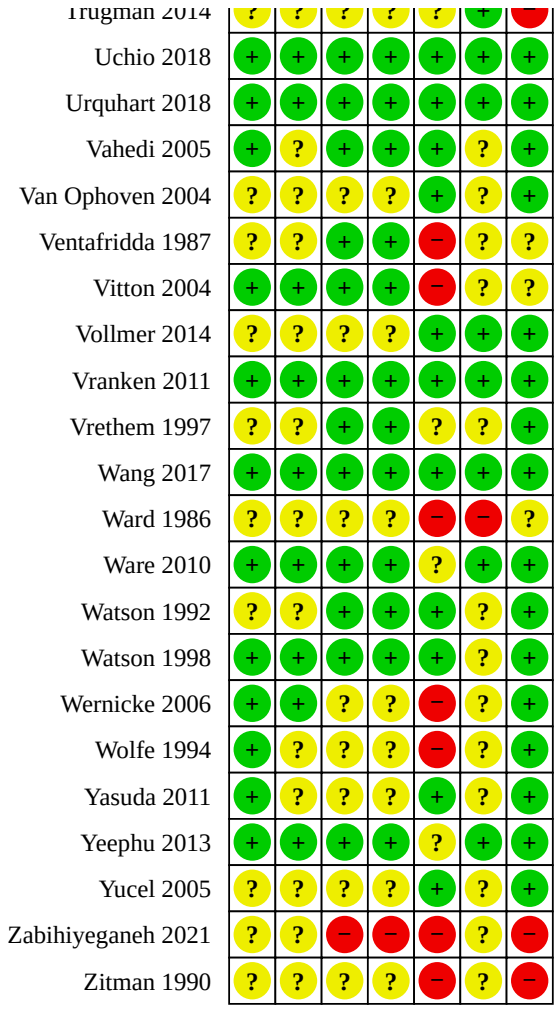


Allocation

We did not assess any studies as high risk of bias for sequence generation or allocation concealment. For sequence generation, we judged 95 studies to be at low risk, and 81 studies as unclear. For allocation concealment, we judged 75 studies to have satisfactory procedures and rated them as low risk and the other 101 studies we rated as unclear. We rated only 64 studies as low risk of bias for both sequence generation and allocation concealment.

Blinding

For this review, we required studies comparing antidepressants with other antidepressants, different doses of the same antidepressant, or other pharmacological interventions to be double-blind. We accepted that some interventions could not be blinded by their nature (e.g. psychological therapy, physiotherapy). These studies were included but judged to be high risk of bias for both blinding of participants, and blinding of outcomes assessors. Seventeen studies were of non-pharmacological interventions and therefore rated high risk of bias for both domains. As this review is focused on pain, all outcomes were self-reported by participants, and therefore judgements were often the same for both domains. In total, we rated 106 studies as low risk for both domains, and 49 studies as unclear for both domains. Low risk of bias was achieved in studies by study drugs appearing identical, having matched or sham dosing schedules across all arms, and using active placebos that mimic the side effects of antidepressants.

Incomplete outcome data

We rated the majority of studies as high risk of bias for incomplete outcome data; 102 studies were high risk. Studies were high risk primarily due to only using the last-observation-carried-forward imputation method, reporting data only on participants who completed the study, or having significantly unequal attrition across arms. We rated 37 studies as low risk of bias; these studies either had no or very little attrition, or used appropriate imputation methods such as baseline-observation-carried-forward or multiple imputation. We rated 37 studies as unclear, due to not clearly specifying missing data methods.

Selective reporting

We could not find protocols or trial registrations for the majority of studies. We rated 108 studies as unclear risk of bias, due to missing protocols or trial registrations published retrospectively, after the study had begun. We rated 44 studies as low risk of bias; outcomes and analyses in the published papers matched

prospective protocols or registrations. We rated 24 studies as high risk of bias. Four of these studies were never published in journal articles, and data were extracted from trials registries (29060/433; NCT00066937; NCT01225068; NCT01510457). For the other studies rated as high risk of bias, there were discrepancies between the protocols and published papers that we judged to be of significant risk of bias (e.g. protocol states that outcomes would be collected that were not reported).

Other potential sources of bias

We did not identify any other sources of bias for 145 studies. We rated 17 studies as unclear risk of bias; primarily due to data not being presented in numerical form, or being reported in a different method to the protocol (e.g. percentage change rather than post-intervention). We rated 14 studies as high risk of bias for the following reasons:

- No published, peer-reviewed articles (29060/433; NCT00066937; NCT01225068; NCT01510457)
- Washout periods and tapering issues (Bateman 2013; Gilron 2016)
- Poor reporting with mistakes in article (Hammody 2015)
- Insufficient power (Morello 1999)
- Significant differences at baseline (Razazian 2014)
- Selection bias prior to participation (Spinhoven 2010)
- Significant differences between published article and trial registry (Trugman 2014; Zabihiyeganeh 2021)
- Using a potential intervention as a placebo (Zitman 1990)

We found some evidence of publication bias in one analysis (duloxetine versus placebo for substantial pain relief), as identified from funnel plots (used to assess small study effects as a proxy for publication bias).

Effects of interventions

See: **Summary of findings 1** Substantial pain relief summary of findings; **Summary of findings 2** Pain intensity summary of findings; **Summary of findings 3** Mood summary of findings; **Summary of findings 4** Adverse events summary of findings

Overview

The following sections detail the results of the NMAs for all outcomes included in the review. Due to the scale of the analysis, we only include antidepressants with more than 200 participants in the write-ups and summary of findings tables. Each outcome has a table listing all the interventions included in the NMA. Antidepressants with fewer than 200 participants, and non-antidepressant interventions are also included in figures for completeness and context.

For all outcomes, we made decisions on which networks to report in this results section. For all outcomes, we considered treatment and treatment-dose networks. For continuous outcomes, we considered both change scores and post-intervention scores networks. For each outcome we have reported the most robust and reliable network. The details of these decisions are reported in Appendix 2. The networks that we have not reported in this manuscript are available in the supplemental file.

The sections are reported in order of primary and secondary outcomes.

Primary outcomes:

- Substantial pain relief
- Pain intensity
- Mood
- Adverse events

Secondary outcomes:

- Moderate pain relief
- Physical function
- Sleep
- Quality of life
- Patient Global Impression of Change (PGIC): proportion of participants reporting "much" and "very much" improved, and continuous scores
- Serious adverse events
- Withdrawal

Primary outcomes

Summary of findings tables are provided for substantial pain relief (Summary of findings 1); pain intensity (Summary of findings 2); mood (Summary of findings 3); and adverse events (Summary of findings 4).

Substantial pain relief (50% reduction)

We report the treatment-dose network for substantial pain relief, as it was the model with the least heterogeneity and had no evidence of inconsistency.

We included 42 RCTs with a total of 14,626 participants (range in study from 47 to 1108). There were 25 different interventions, and some comparisons were informed only by direct evidence from one study. Table 2 shows the number of RCTs and total number of participants for each antidepressant dose included in the analysis. We could not include data from two studies due to disconnected networks. There were no concerns regarding model fit based on residual deviance and convergence diagnostics. The network diagram is presented in Figure 4, and the forest plot in Figure 5.

Figure 4. Substantial pain relief network plot. NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants

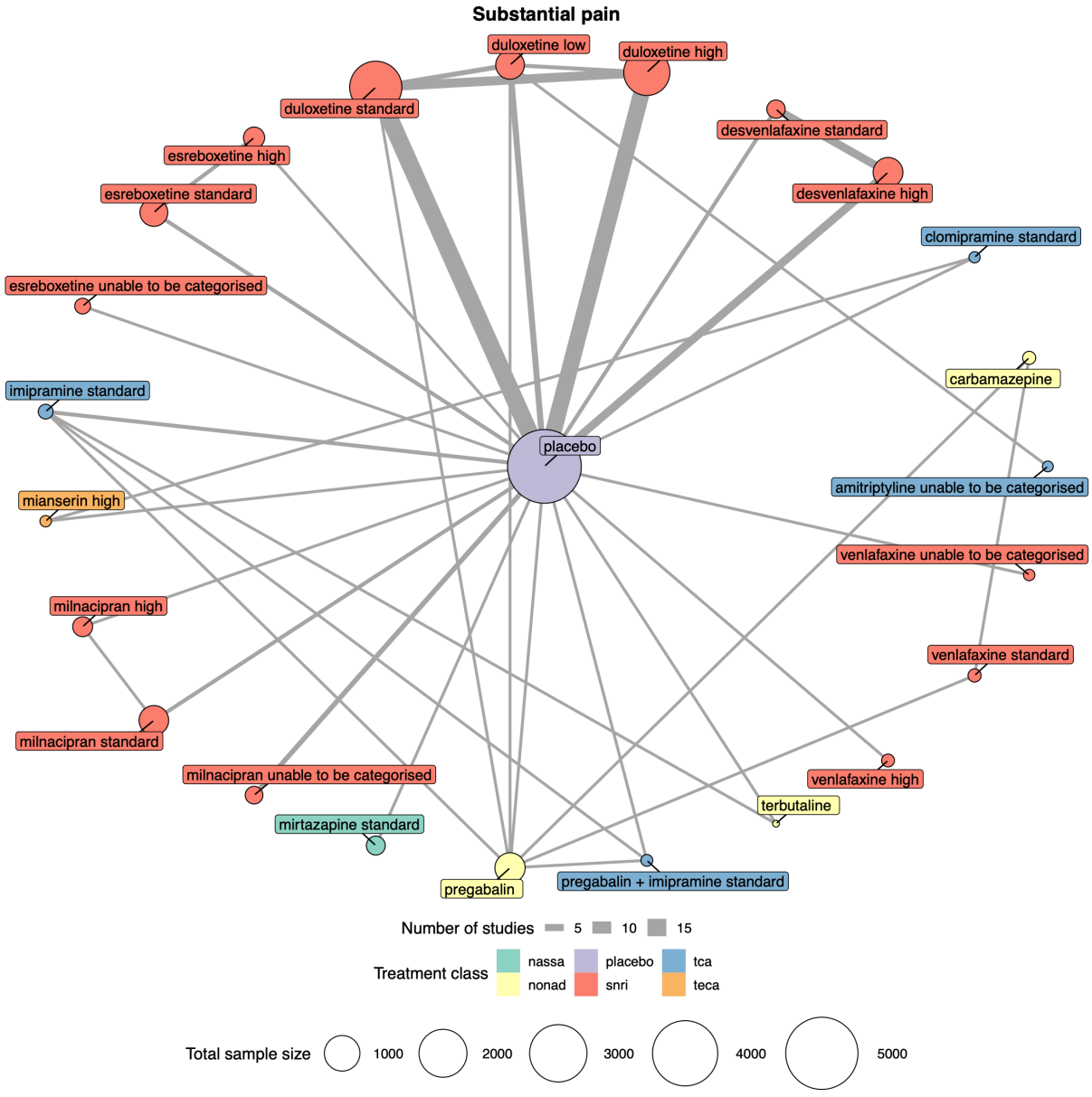
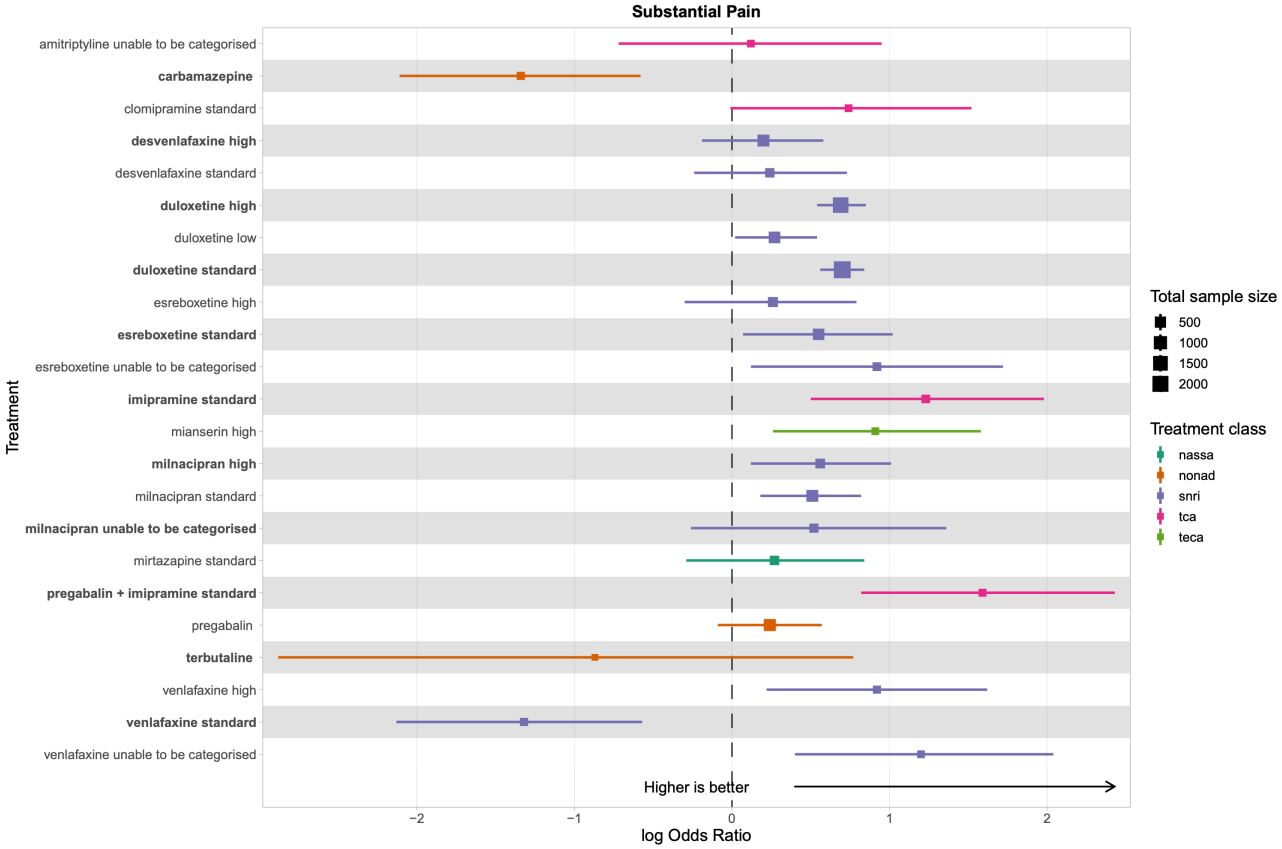


Figure 5. Substantial pain relief forest plot (log odds ratio with credible intervals). NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants



The top-ranked antidepressants for substantial pain relief are shown in Table 3. Duloxetine standard dose and duloxetine high dose were the highest-ranked antidepressants for substantial pain relief, and equally efficacious in comparison to placebo (OR 1.91, 95% CI 1.69 to 2.17 and OR 1.91, 95% CI 1.66 to 2.21, respectively). Milnacipran high dose (OR 1.64, 95% CI 1.04 to 2.58) and esreboxetine standard dose (OR 1.72, 95% CI 1.13 to 2.62) were also equally ranked, but less effective than duloxetine standard dose and duloxetine high dose. Mirtazapine standard dose, esreboxetine high dose, and desvenlafaxine high dose showed no significant difference in comparison to placebo.

A visual representation of the cumulative rankings for every treatment included in the analysis and did not substantially alter interpretation of relative effects or mean rank credible intervals. The unrelated mean-effect model had similar deviance information criteria to the dose-treatment model, with no evidence of inconsistency. We confirmed this with node-splitting models for all nine comparisons where it was possible to compare direct and indirect evidence. The comparison of pregabalin with placebo had the smallest Bayesian P value (P = 0.3) indicative of inconsistency where direct evidence suggests underestimation of the effect of pregabalin based on a single study. These figures are available in the supplemental file. The availability of a consistent evidence-network precluded the need for exploration of transitivity violations.

Exploration of heterogeneity

Despite the risk of over-fitting, we summarise results for multiple models because of the importance of substantial pain as an outcome for patients, clinicians, and overall quality of life. The full results of all models are reported in the supplemental file.

Class

We generated a network by aggregating treatment into classes. The analysis included four antidepressant classes: SNRI, TCA, TeCA, and NaSSA, however we could not draw any reliable conclusions about class differences due to inconsistency and overlapping credible intervals.

Condition

Studies reported substantial pain included neuropathic, fibromyalgia, musculoskeletal, primary, and gastrointestinal pain conditions. However, only neuropathic and fibromyalgia pain conditions had connected networks. We could not derive reliable treatment rankings for neuropathic pain, as the unrelated mean-effect models and node-splitting indicated inconsistency. For fibromyalgia, although the network geometry precluded analysis of inconsistency, esreboxetine, milnacipran, and duloxetine were relatively equally ranked: esreboxetine (mean rank = 2.02, 97.5% credible interval = 1 to 4); milnacipran (mean = 2.30, 97.5% credible interval = 1 to 4); duloxetine (2.48, 97.5% credible interval = 1 to 4).

Risk of bias

We conducted a sensitivity analysis to explore the effect of removing studies at high risk of bias. We rated 15 studies as low risk of bias. The model of the resulting network was unstable with divergent transitions indicating problems with model convergence. Unrelated mean-effects models and the dev-dev plot did not identify inconsistency, but we could not confirm this by node splitting due to network geometry. Results were consistent with the treatment-dose model. The two best-ranked antidepressants were esreboxetine (mean rank = 3.73. 97.5% credible interval = 2 to 7), and duloxetine (mean = 4.64, 97.5% credible interval = 3 to 6).

CINeMA

In addition to fitting multiple models to explore heterogeneity and utilising unrelated mean-effects and node-splitting models to explore inconsistency, we undertook further analysis of pairwise direct evidence and network evidence (excluding multi-arm studies of dose) to facilitate strength of evidence assessment using CINeMA.

The design-by-treatment test showed no inconsistency between direct and indirect evidence (Chi^2 = 14.069, P = 0.296), although duloxetine low dose and desvenlafaxine high dose had high I^2 statistic values (73.6% and 65.8%) indicating heterogeneity. We rated duloxetine low, standard, and high doses as moderate certainty. We rated all other antidepressant doses as low, or very low certainty, primarily due to major concerns regarding studies at high risk of bias, imprecision (estimates crossing zero), and a small number of RCTs and participants contributing to the estimates.

Pain intensity

For pain intensity, we report the change-score treatment-dose network, as it was more robust than the other networks, with low heterogeneity and no indications of inconsistency.

Results

We included 49 RCTs with a total of 14,504 participants (range from 26 to 1191). We removed one study from this analysis due to implausible results (Miki 2016). Twenty-eight studies compared against placebo, nine were studies with a head-to-head comparison with another active comparator, and 12 were dose-comparison studies. There were 21 different interventions, and some comparisons were informed only by direct evidence from one study. Table 4 shows the number of RCTs and total number of participants for each intervention included in the analysis. There were no concerns regarding model fit. The network diagram is presented in Figure 6 and the forest plot in Figure 7.

Figure 6. Pain intensity network diagram. SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants

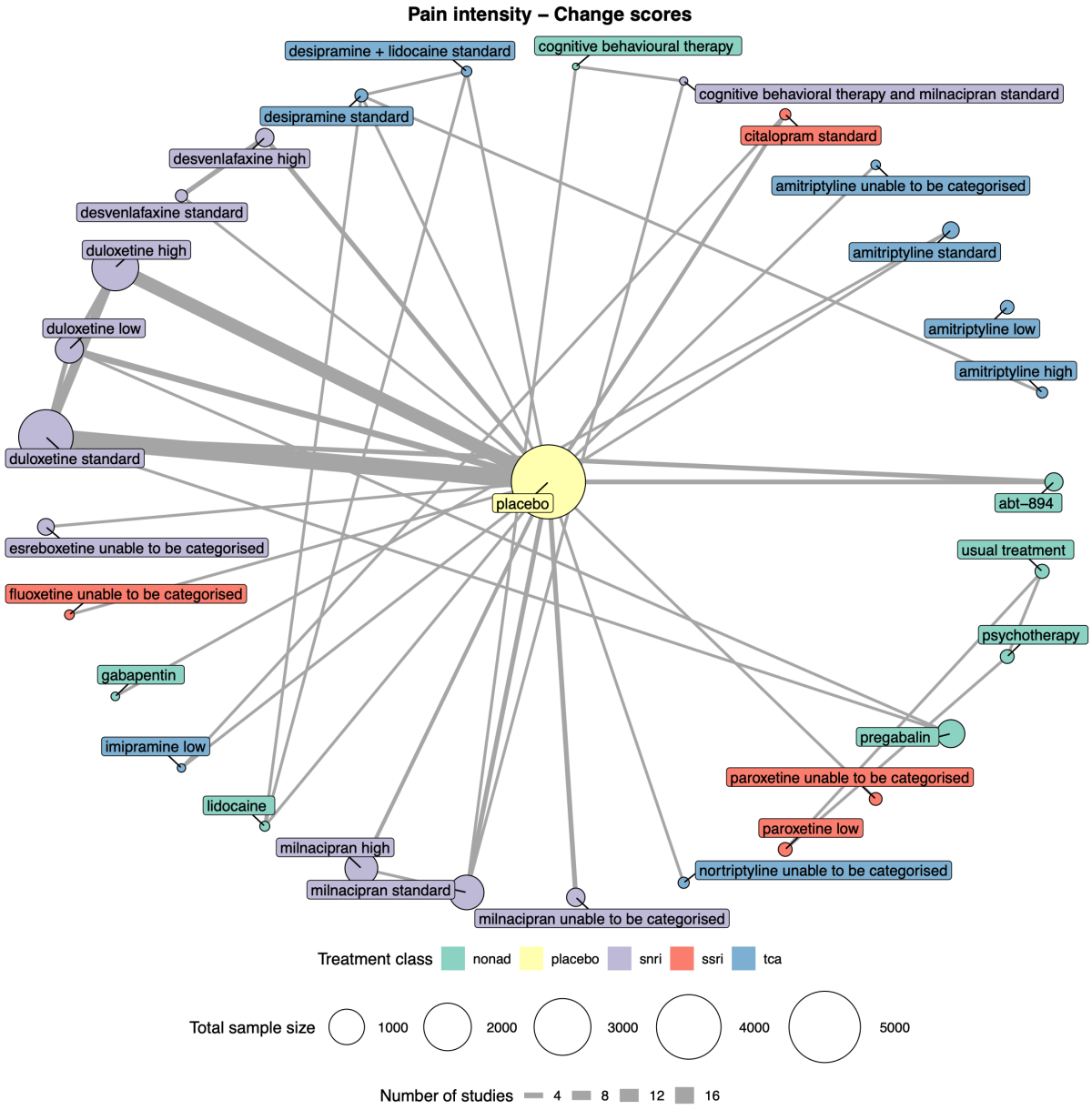
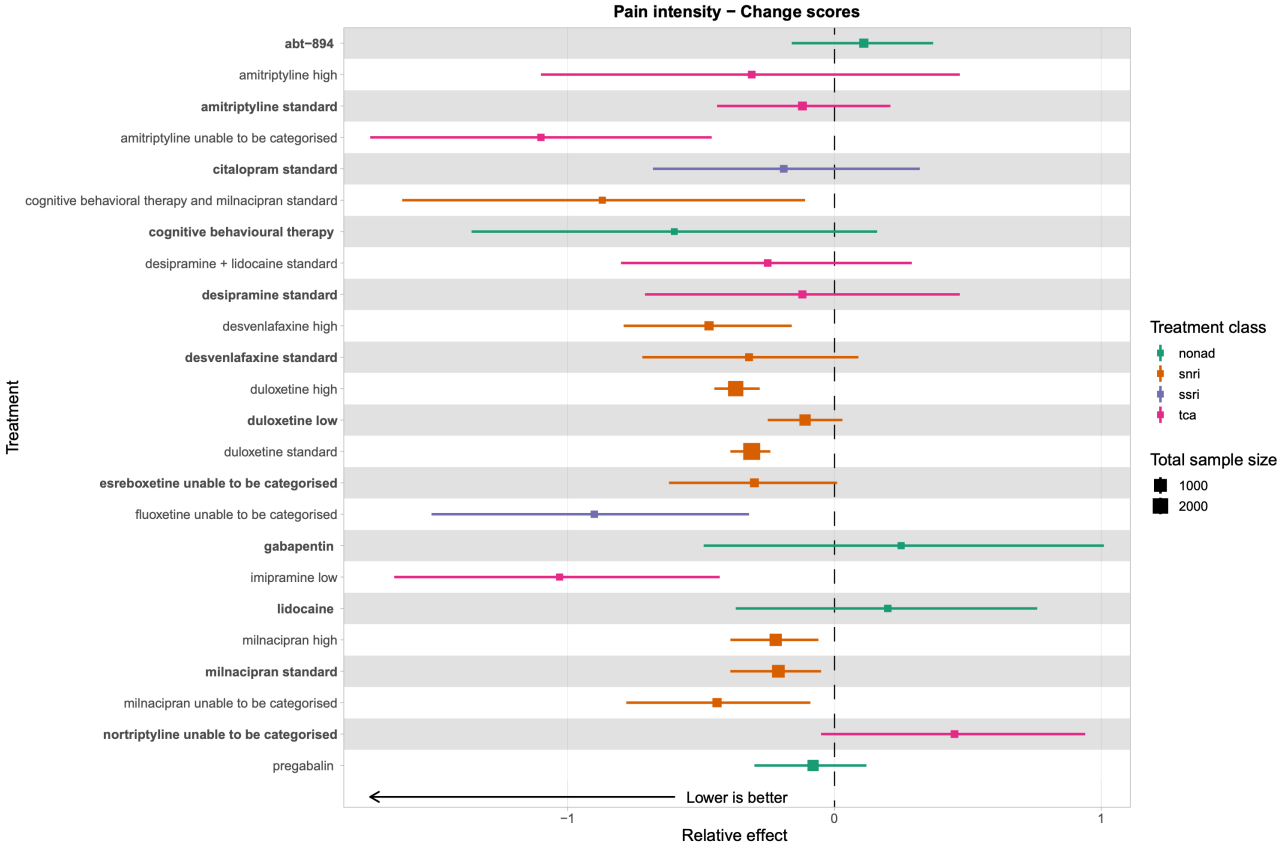


Figure 7. Pain intensity forest plot (standardised mean difference with credible intervals). SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants



Ranking of antidepressants

The top-ranked antidepressants for pain intensity change scores are shown in Table 5. Duloxetine high and standard dose were the highest-ranked antidepressants for pain intensity, with small to moderate effects (SMD −0.37, 95% CI −0.45 to −0.28 and SMD −0.31, 95% CI −0.39 to −0.24, respectively). Milnacipran high and standard doses had a small effect (SMD −0.22, 95% CI −0.40 to −0.05). Duloxetine low dose showed no significant difference in comparison to placebo.

A visual representation of the cumulative rankings for every intervention included in the analysis did not alter interpretation. The unrelated mean-effect model had similar deviance information criteria to the dose-treatment model, with no evidence of inconsistency. We confirmed this with node-splitting models for all nine comparisons where it was possible to compare direct and indirect evidence. The lowest Bayesian P value was for the comparison of duloxetine standard dose compared to duloxetine high dose (0.08). These figures are available in the supplemental files (link provided in Appendix 3).

Condition and risk of bias

We were unable to undertake further NMAs of condition or risk of bias due to small sample sizes, network geometry and the risk of over-fitting, but these were examined in pairwise analyses and network analysis (excluding multi-dose arms) in CINeMA to inform strength of evidence assessment.

CINeMA

The design-by-treatment test showed no inconsistency between direct and indirect evidence (Chi^2 = 8.34; P = 0.82), although duloxetine standard dose and milnacipran standard dose had high I^2 statistic values (65.3% and 67.7%) indicating heterogeneity. We had moderate certainty in the estimates for duloxetine low, standard, and milnacipran standard doses. We rated all other antidepressant doses as low certainty due to major concerns regarding studies at high risk of bias and imprecision (estimates crossing zero).

Mood

For mood, we report the change-score treatment network as this was the most robust and reliable network, with low heterogeneity and no indications of inconsistency.

Results

We included 38 RCTs with a total of 12,985 participants (range from 42 to 1191). Twenty-two studies compared against placebo only, six were multi-arm studies with another active comparator, nine were comparing the same antidepressant in different doses, and one compared two antidepressants together. There were 16 different interventions, and some comparisons were informed only by direct evidence from one study. We rated 23 studies as high risk of bias. At baseline, the average scores for the five most commonly used scales (Beck Depression Inventory, Brief Pain Inventory Mood Item,

SF-36 Mental Component Score, SF-36 Mental Health Subscale, and Hamilton Depression Rating Scale) were all in the none or minimal ranges. We could not include data from one study due to disconnected networks. There were no concerns regarding model fit. An overview of the interventions in the analysis is given in Table 6. The network diagram is presented in Figure 8 and the forest plot is presented in Figure 9.

Figure 8. Mood network diagram. NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants

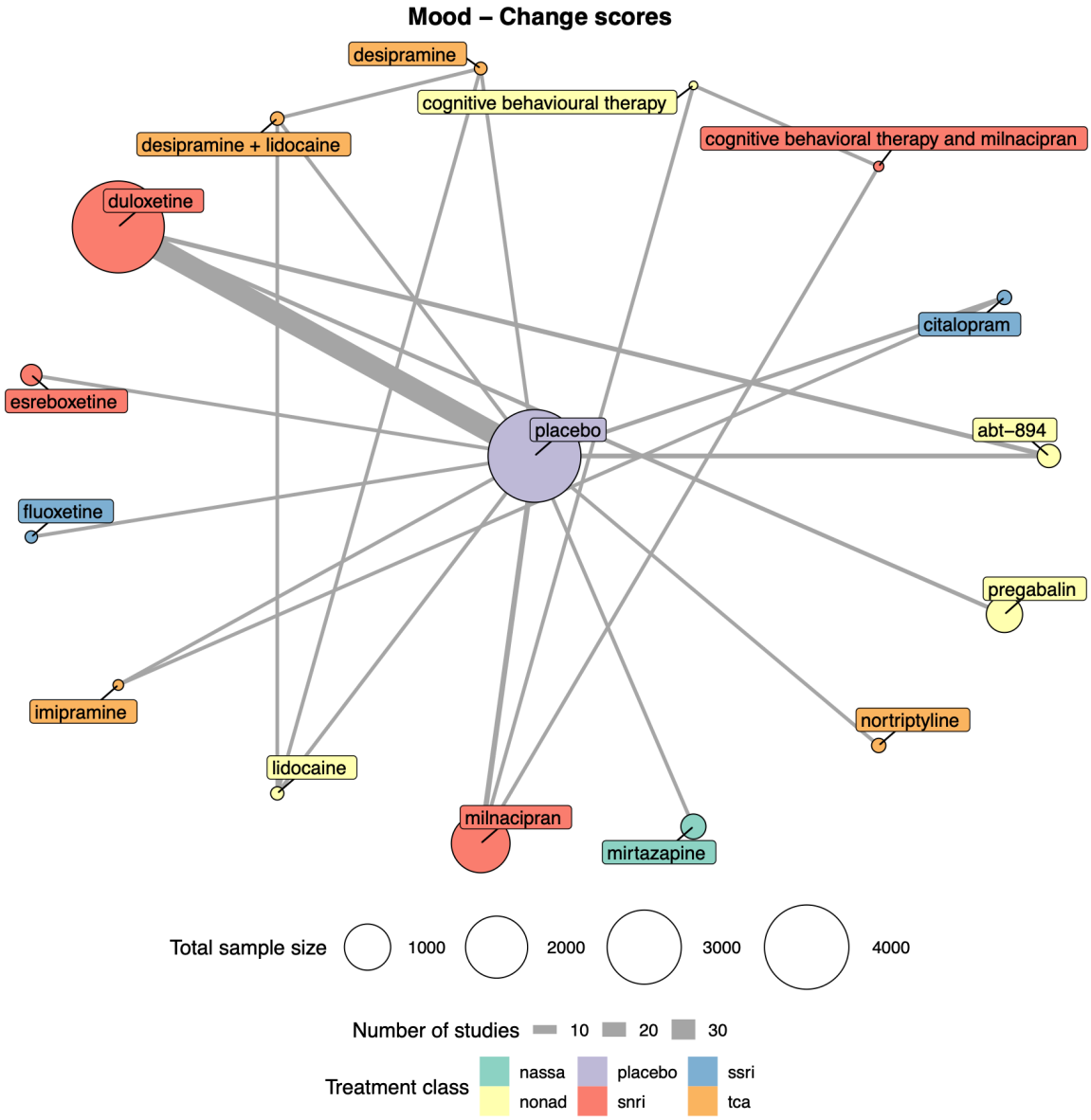
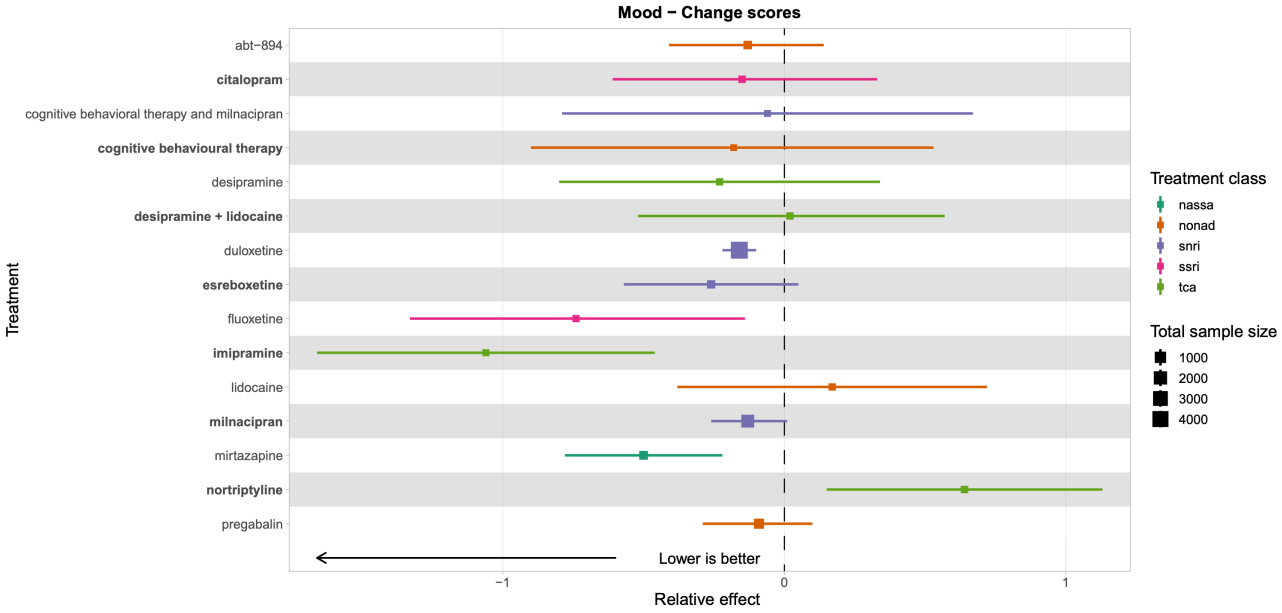


Figure 9. Mood forest plot (standardised mean difference with credible intervals). NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants



Ranking of antidepressants

The top-ranked antidepressants for mood change scores are shown in Table 7. Mirtazapine was the highest-ranked antidepressant for mood with a moderate effect (SMD −0.5, 95% CI −0.78 to −0.22), based on one RCT. Duloxetine and milnacipran were equally ranked. Duloxetine showed very small effects (SMD −0.16, 95% CI −0.22 to −0.1), and milnacipran showed no difference in comparison to placebo.

A visual representation of the cumulative rankings for every intervention included in the analysis did not alter interpretation of the results. This figure is available the supplemental files (link provided in Appendix 3). The unrelated mean effect model had similar deviance information criteria to the dose treatment model, with no evidence of inconsistency.

Class, condition, and risk of bias

We did not undertake further analyses because of small sample sizes, network geometry and the risk of over-fitting but pairwise and NMA (excluding multi-dose study) were performed in CINeMA to inform strength of evidence assessment.

CINeMA

The design-by-treatment test showed no evidence of inconsistency (Chi^2 = 1.83, P = 0.4), and all I^2 statistic values were below 40%, despite the analysis being unable to run node-splitting. We rated both duloxetine and milnacipran as moderate certainty; there were no domains indicating major concern. We rated mirtazapine as having low-certainty evidence, as the estimates were formed from only one study.

Adverse events

For adverse events we report the treatment-dose network. There were similar levels of heterogeneity and inconsistency across networks but we were able to run node-splitting models for treatment dose.

Results

We included 93 RCTs with a total of 22,558 participants. Of all the studies in the network, 47 studies compared antidepressants only against placebo, 27 were multi-arm studies with another active comparator, 15 were dose-comparison studies, and four compared two antidepressants to each other. We rated 62 studies as high risk of bias. There were 60 different interventions, and some comparisons were informed only by direct evidence from one study. We could not include data from one study due to disconnected networks. There were no concerns regarding model fit. Of the 60 interventions included in the network, only nine met the criteria of 200 or more participants to be included in the summary. An overview of all the interventions included in the network is given in Table 8. The network diagram is presented in Figure 10, and the forest plot is presented in Figure 11.

Figure 10. Adverse events network diagram. MAOI_rev: monoamine oxidase inhibitors (reversible); NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; TECA: tetracyclic antidepressants; nonad: non-antidepressants

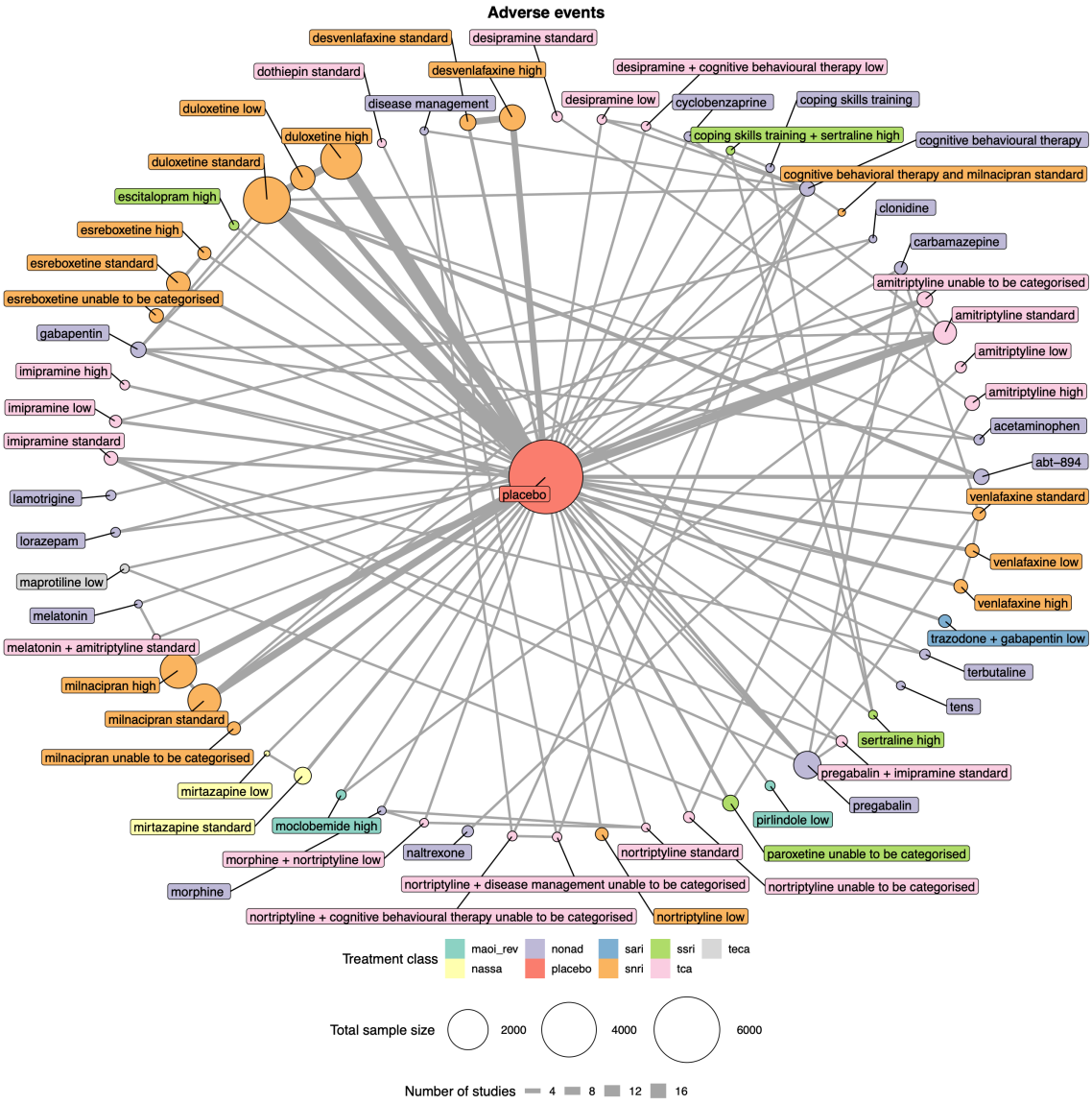
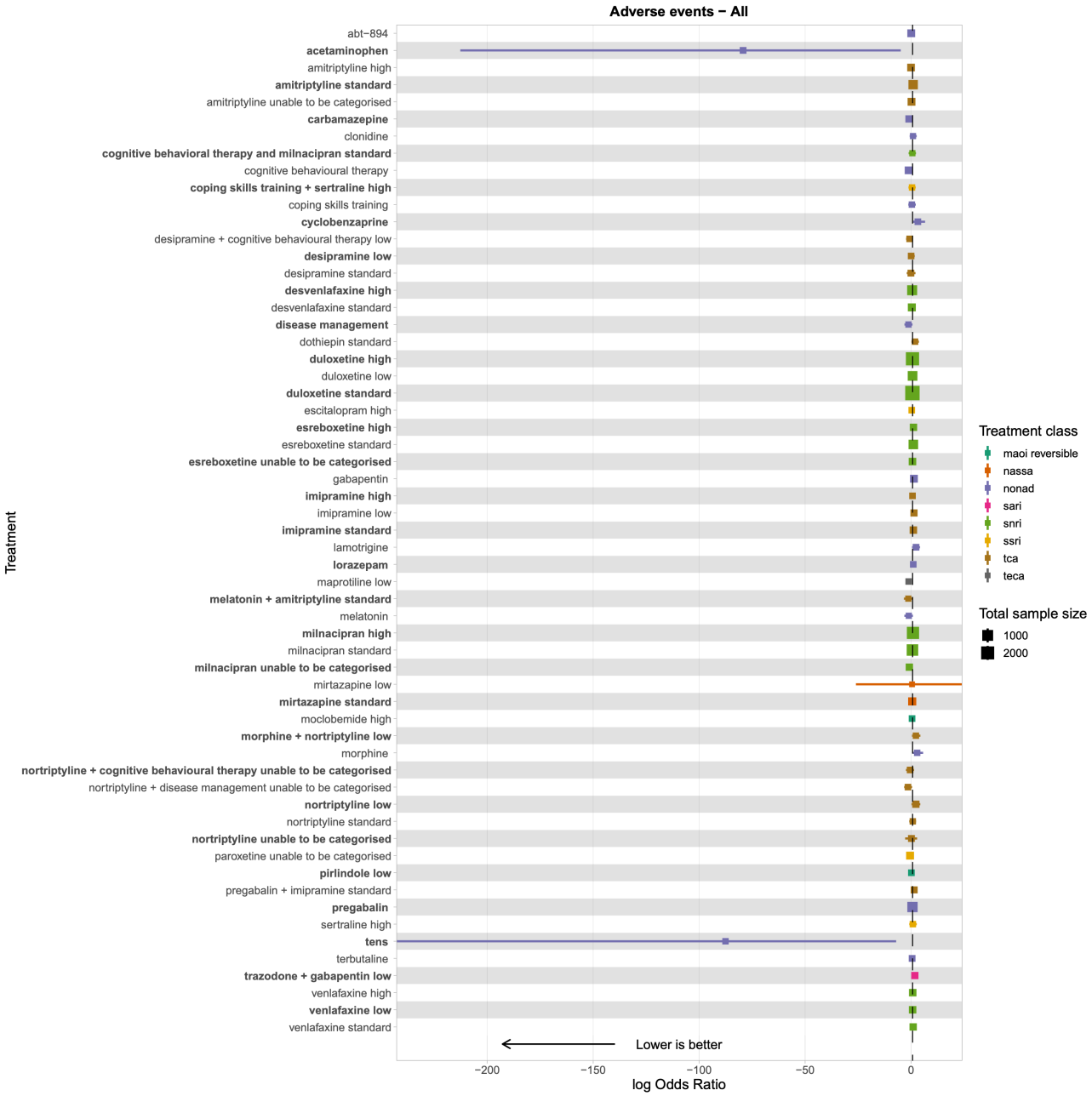


Figure 11. Adverse events forest plot (log odds ratio with credible intervals). MAOI_rev: monoamine oxidase inhibitors (reversible); NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; TECA: tetracyclic antidepressants; nonad: non-antidepressants



Ranking of antidepressants

The ranking of the nine antidepressants with 200 or more participants is given in Table 9. Data for adverse events were sparse, and studies were underpowered. All antidepressants with over 200 participants in the antidepressant arm were closely ranked. Desvenlafaxine and mirtazapine were the highest-ranked antidepressants, with no significant difference compared to placebo (OR 1.67, 95% CI 0.92 to 2.41 and OR 1.70, 95% CI 0.48 to 2.91, respectively). The evidence for both of these antidepressant doses was based on only two studies each. Duloxetine standard dose, milnacipran standard dose, and duloxetine high dose were equally ranked. Duloxetine low dose, milnacipran high dose, amitriptyline standard dose, and esreboxetine standard dose were the lowest-ranked antidepressants, with all odds ratios greater than 2.

A visual representation of the cumulative rankings for every intervention included in the analysis did not alter interpretation. We further investigated inconsistency through unrelated mean-effect models and node-splitting models for all 30 comparisons where it was possible to compare direct and indirect evidence. There was evidence of inconsistency in unrelated mean-effects

models but not node-splitting. These figures are available in the supplemental files (link provided in Appendix 3). However, multiple divergent transition warnings indicate the potential for inconsistency to be poorly estimated in the latter models.

Class, condition, and risk of bias

Our overall model of adverse events is problematic due to divergent transitions, low effective sample sizes and inconsistency in unrelated mean-effects model. We were unable to undertake further exploration of class, condition and risk of bias given the high uncertainty in overall effects.

CINeMA

We were unable to use CINeMA for this outcome due to complexity of the network. Therefore, two review authors (HB and GS) made the judgements based on GRADE and CINeMA domains and the available results. We judged all antidepressants and doses as very low certainty primarily due to concerns with within-study bias, and imprecision in the network.

Secondary outcomes

Moderate pain relief (30% reduction)

For moderate pain relief we report the treatment network as this model had low heterogeneity and no evidence of inconsistency. We present the summary of findings for moderate pain relief in Table 10.

Results

We included 40 RCTs with a total of 14,208 participants (range from 37 to 1025). Twenty studies compared against placebo, eight were multi-arm studies with another active comparator, 11 were dose-comparison studies, and one study compared two antidepressants head to head. There were 17 different interventions, and some comparisons were informed only by direct evidence from one study. We rated 25 studies as high risk of bias. There were no concerns regarding model fit. The network diagram is presented in Figure 12, and the forest plot is presented in Figure 13. An overview of the interventions included in the analysis is given in Table 11.

Figure 12. Moderate pain relief network diagram. NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenalin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants

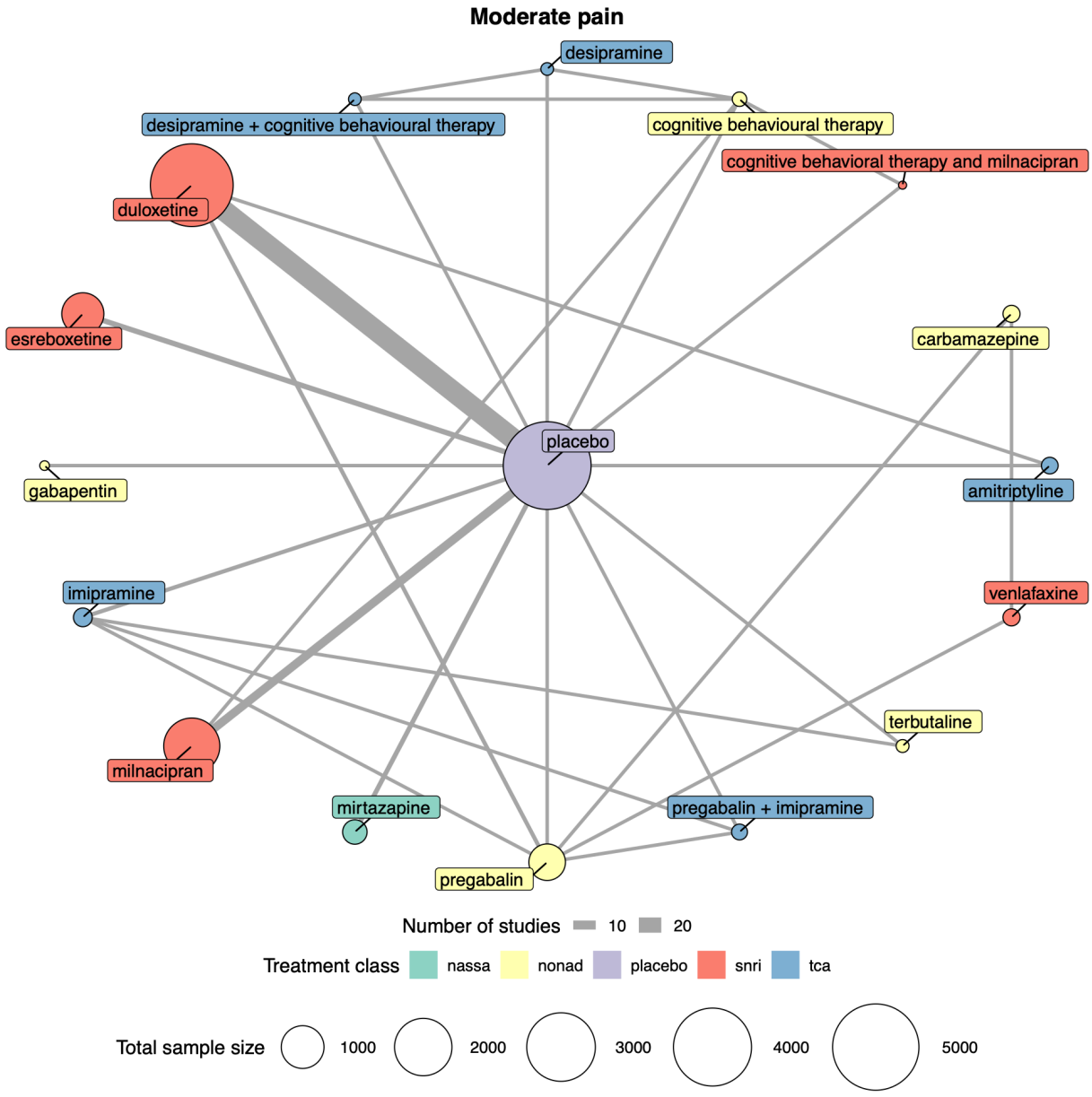
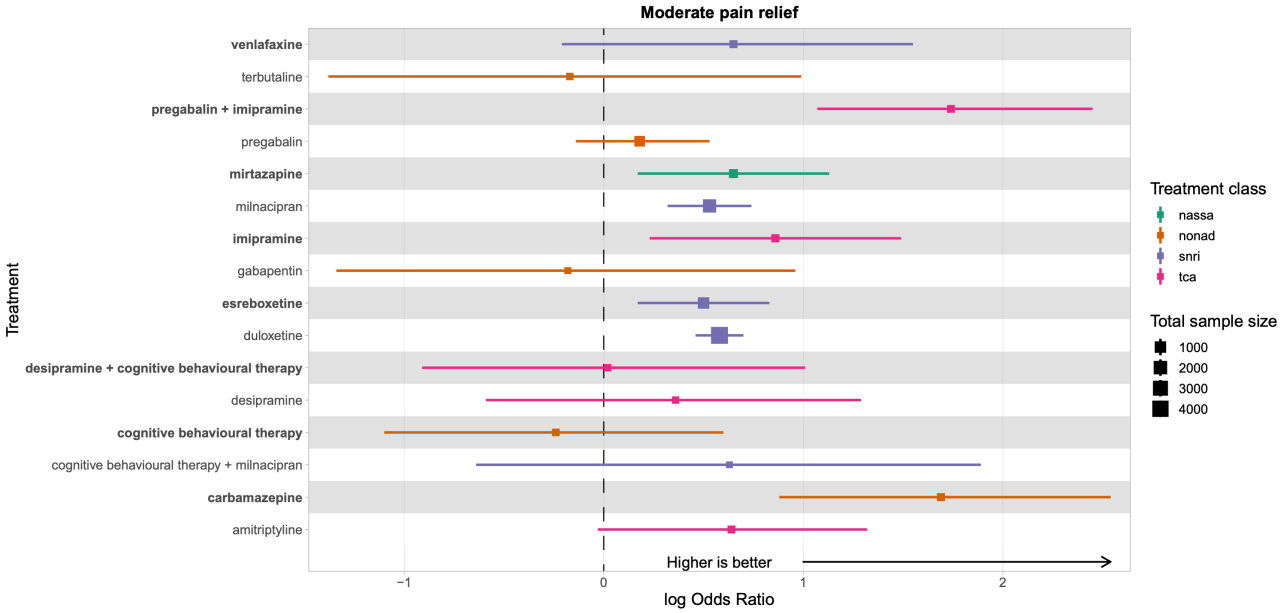


Figure 13. Moderate pain relief forest plot. NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenalin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants



Ranking of antidepressants

The top-ranked antidepressants for moderate pain relief are shown in Table 12. All antidepressants with more than 200 participants in the antidepressant arm showed an effect for moderate pain relief, and were very closely ranked. Mirtazapine was the highest-ranked antidepressant (OR 1.92, 95% CI 1.45 to 2.39), followed by duloxetine (OR 1.79, 95% CI 1.67 to 1.91), milnacipran (OR 1.70, 95% CI 1.48 to 1.92) and esreboxetine (OR 1.65, 95% CI 1.32 to 1.98).

A visual representation of the cumulative rankings for every intervention included in the analysis did not alter interpretation. The unrelated mean-effect model showed no evidence of inconsistency. We confirmed this with node-splitting models for all nine comparisons where it was possible to compare direct and indirect evidence. The comparison of duloxetine and placebo had the lowest Bayesian P value (0.18) with indirect evidence indicative of a larger effect than direct evidence. These figures are available in the supplemental files (link provided in Appendix 3).

Exploration of heterogeneity

We also explored the impact of including dose in the model. There was low heterogeneity (Tau = 0.11), and whilst there was no evidence of inconsistency in unrelated mean-effects and node-splitting models, there were several divergent transitions. The analysis showed similar rankings of antidepressants to the treatment-only model, with mirtazapine, duloxetine, and milnacipran remaining the highest-ranked across doses. The full results of all the analyses are reported in the supplemental files (link provided in Appendix 3).

Class

Three classes were included in the treatment -only analysis: NaSSA, SNRI, and TCA. Only the NaSSA and SNRI classes had over 200 participants in the analyses. SNRI was the highest-ranked class (logOR: 0.56; CrI: 0.45 to 0.60) followed by NaSSA (logOR: 0.67; CrI: 0.11 to 1.23).

Condition and risk of bias

We were unable to undertake further NMAs due to small sample size, network geometry and risk of over-fitting; but pairwise and NMA excluding multi-dose studies were undertaken to inform strength of evidence assessment using CINeMA.

CINeMA

The design-by-treatment test showed no evidence of inconsistency between the direct and indirect evidence in the network ($Chi^2 = 2.65$, P = 0.62), and only esreboxetine had an I^2 statistic value of above 40% (44.6%). We rated duloxetine and milnacipran as moderate certainty, while we downgraded mirtazapine and esreboxetine due to low numbers of studies and participants.

Physical function

For physical function, we report the change-score treatment-dose network as it had lower heterogeneity than other models and no inconsistency. We present the summary of findings for physical function in Table 13.

Results

We included 32 RCTs with a total of 11,760 participants (range from 42 to 1025). Twenty studies compared against placebo, four were head-to-head studies with another active comparator, seven were dose-comparison studies, and one was a direct head-to-head comparison between two different antidepressants. There were 18 different interventions, and some comparisons were informed only by direct evidence from one study. We rated 21 studies as high risk of bias. We did not need to remove any studies due to disconnected networks. There were no concerns regarding model fit. The network diagram is presented in Figure 14, the forest plot of placebo comparisons in Figure 15, and Table 14 shows the number of RCTs and total number of participants for each intervention included in the analysis.

Figure 14. Physical function network diagram. NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants

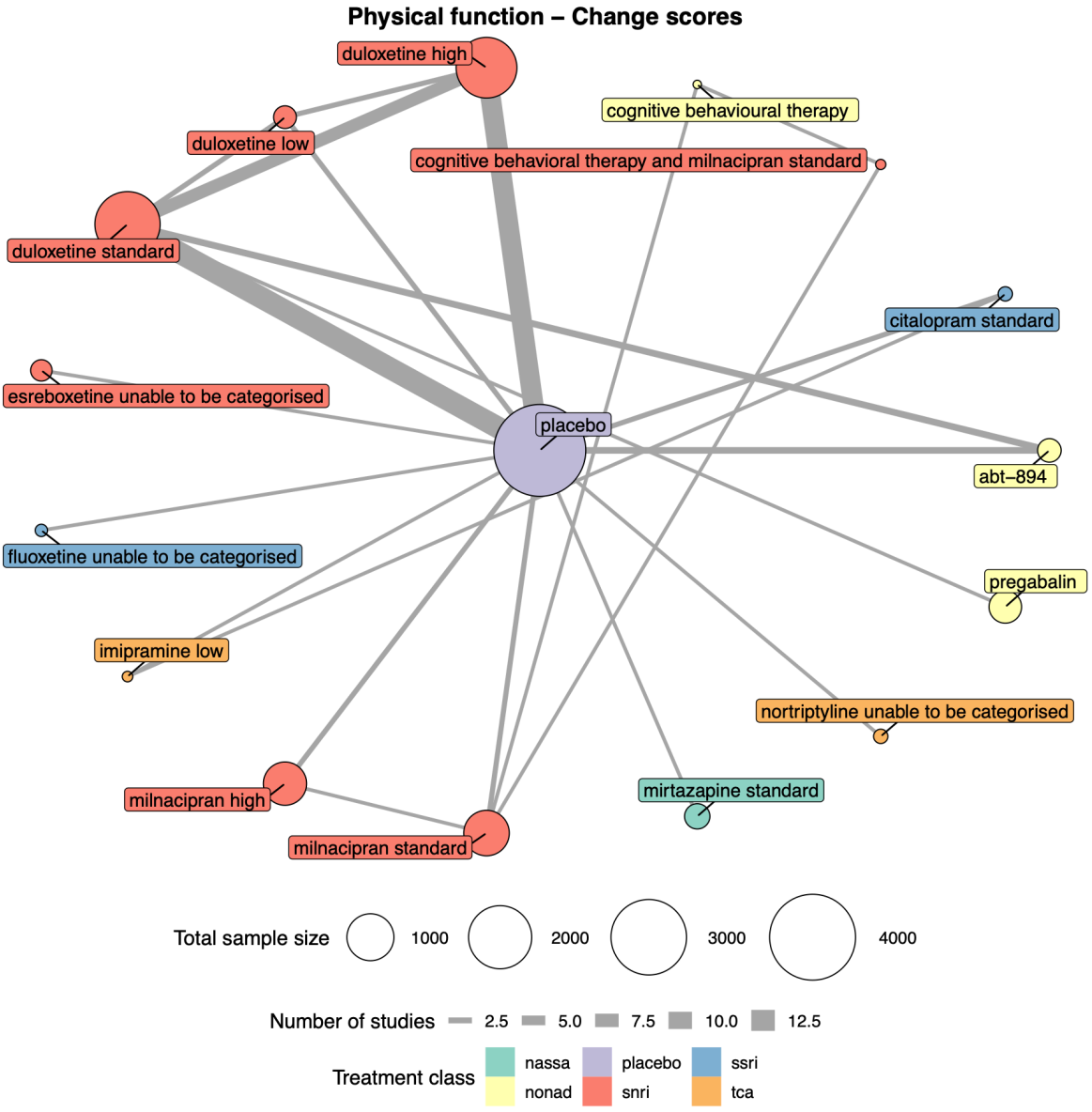
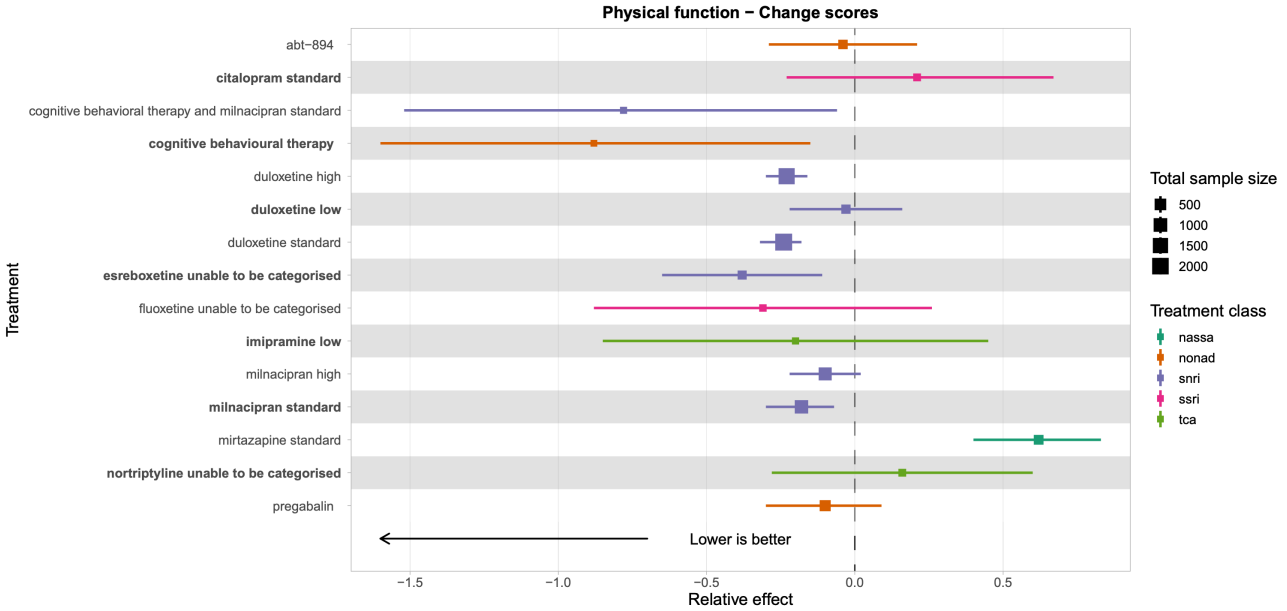


Figure 15. Physical function forest plot (standardised mean difference with credible intervals). NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants



Ranking of antidepressants

The top-ranked antidepressants for physical function change scores are shown in Table 15. Duloxetine standard dose (SMD −0.24, 95% CI −0.32 to −0.18), duloxetine high dose (SMD −0.23, 95% CI 0.30 to 0.16), and milnacipran standard dose (SMD −0.18, 95% CI −0.30 to −0.07) were the highest-ranked antidepressants with small effects. Duloxetine standard dose and duloxetine high doses were equally effective. Milnacipran high dose showed no significant difference compared to placebo (SMD −0.10, 95% CI −0.22 to 0.07). Mirtazapine standard dose was the lowest-ranked antidepressant (SMD 0.62, 95% CI 0.11 to 0.69).

A visual representation of the cumulative rankings for every intervention included in the analysis did not alter interpretation. We performed node-splitting models for all four comparisons where it was possible to compare direct and indirect evidence. The lowest Bayesian P value was for the comparison of duloxetine high dose compared to placebo, where direct evidence showed a larger effect than indirect evidence (P = 0.07). These figures are available in the supplemental files (link provided in Appendix 3).

Class

We included four classes of antidepressants in the analysis: SNRI, SSRI, TCA, and NaSSA, however due to interventions including combinations of drugs, we could not analyse models including class.

Condition and risk of bias

We were unable to undertake further NMAs due to small sample sizes, network geometry and the risk of over-fitting.

CINeMA

The design-by-treatment test showed no evidence of inconsistency between the direct and indirect evidence (Chi^2 = 6.45, P = 0.69), and no antidepressants had an I^2 statistic value of over 40%, although values could not be generated for mirtazapine. We rated duloxetine and milnacipran as moderate certainty, downgraded only due to some concerns with within-study bias. We downgraded esreboxetine and mirtazapine further to low due to the small number of studies and participants included in the analyses.

Sleep

For sleep, we report the change-score treatment-dose network as this was the most robust and reliable model. We present summary of findings for sleep in presented Table 16.

Results

We included 18 RCTs with a total of 6301 participants (range from 42 to 1195). Twelve studies compared against placebo and six were dose-comparison studies. There were eight different interventions, and some comparisons were informed only by direct evidence from one study. We rated nine studies as high risk of bias overall. There were no concerns regarding model fit. The network diagram is presented in Figure 16, the forest plot for placebo comparison is presented in Figure 17, and an overview of all interventions included in the analysis is given in Table 17.

Figure 16. Sleep network diagram. SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors

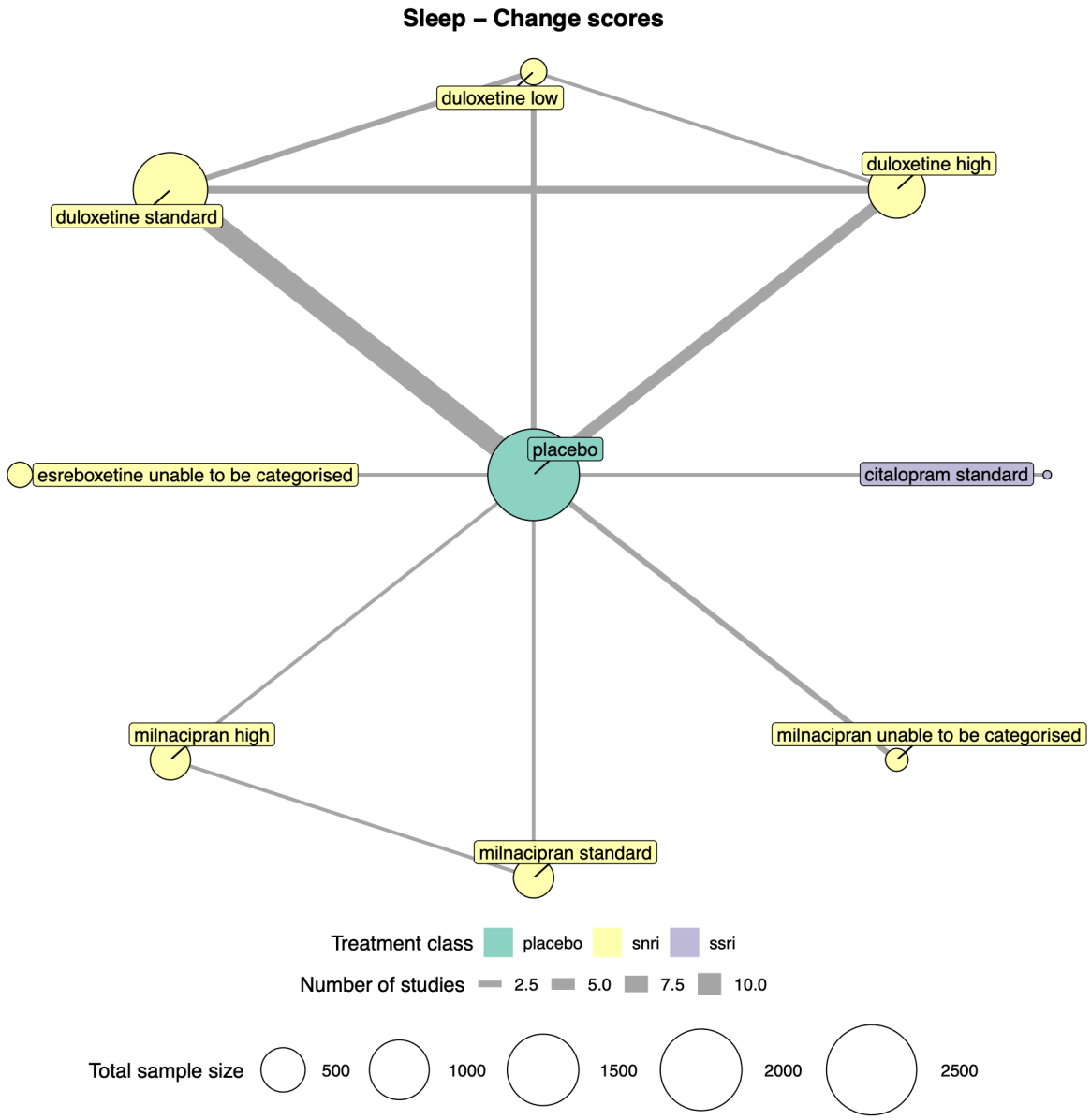
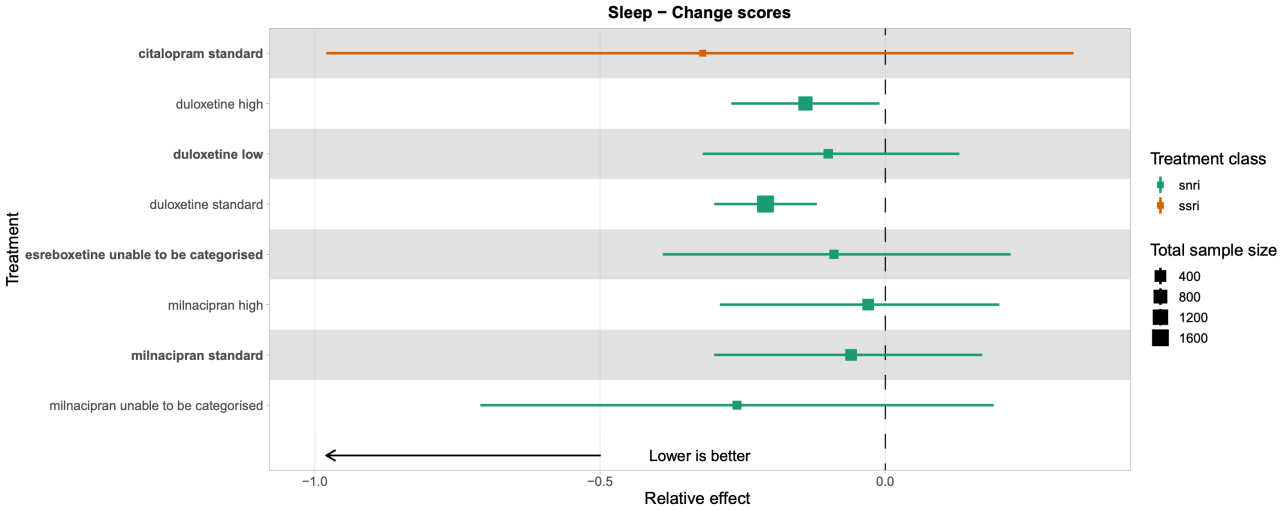


Figure 17. Sleep forest plot (standardised mean difference with credible intervals). SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors



Ranking of antidepressants

The top-ranked antidepressants for sleep are displayed in Table 18. Duloxetine standard and high doses were the highest-ranked antidepressants, and the only antidepressants to show a significant effect when compared to placebo, although the effects were small (standard dose: SMD −0.21, 95% CI −0.30 to −0.12; high dose: SMD −0.14, 95% CI −0.27 to −0.01). Milnacipran standard dose (SMD −0.06, 95% CI −0.30 to 0.17) and high dose (SMD −0.03, 95% CI −0.29 to 0.20) showed no significant difference in comparison to placebo.

A visual representation of the cumulative rankings for every intervention included in the analysis did not alter interpretations. Node-splitting models had divergent transitions and indicated inconsistency for the comparison of high and standard dose duloxetine (P 0.02). We therefore downgraded the strength of evidence for the duloxetine high dose estimate. These figures are available in the supplemental files (link provided in Appendix 3).

Exploration of heterogeneity

Class, condition and risk of bias

Although there were two different classes in the network (SNRI and SSRI), SSRI was only represented by one study using citalopram with 21 participants; therefore only SNRI crossed the threshold of 200 participants. We did not explore condition and risk of bias further using NMA because of concerns about sample size, network geometry and the risk of over-fitting.

CINeMA

The design-by-treatment test showed no evidence of inconsistency between the direct and indirect evidence in the network (Chi^2= 7.39, P = 0.4) despite the concerns identified in node-splitting models. No antidepressants had I^2 statistic values of above 40%, although we could not calculate values for milnacipran high or standard doses. We rated only duloxetine as moderate certainty, downgraded from high due to some concerns about within-study bias and inconsistency from the NMA. We rated duloxetine high dose, milnacipran high dose, and milnacipran standard dose as very low certainty. We downgraded duloxetine high dose due to major concerns regarding within-study bias and incoherence. We downgraded milnacipran standard and high doses due to major concerns regarding within-study bias, and some concerns regarding imprecision, heterogeneity, and inconsistency. Of note, both milnacipran doses analyses were informed by the same study.

Quality of life

For quality of life we report the post-intervention treatment network, as this was the network with the lowest heterogeneity. We present summary of findings for quality of life in Table 19.

Results

We included 19 RCTs with a total of 3103 participants (range from 30 to 998). Five studies compared against placebo, 11 were multi-arm studies with another active comparator, two were direct head-to-head comparisons of different antidepressants, and one was a dose-comparison study. There were 23 different interventions, and some comparisons were informed only by direct evidence from one study. We could not include data from one study due to disconnected networks. We rated 13 studies as high risk of bias overall. There were no concerns regarding model fit. The network diagram is presented in Figure 18 and the forest plot is presented in Figure 19. An overview of the interventions included in the analysis is presented in Table 20.

Figure 18. Quality of life network diagram. SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants

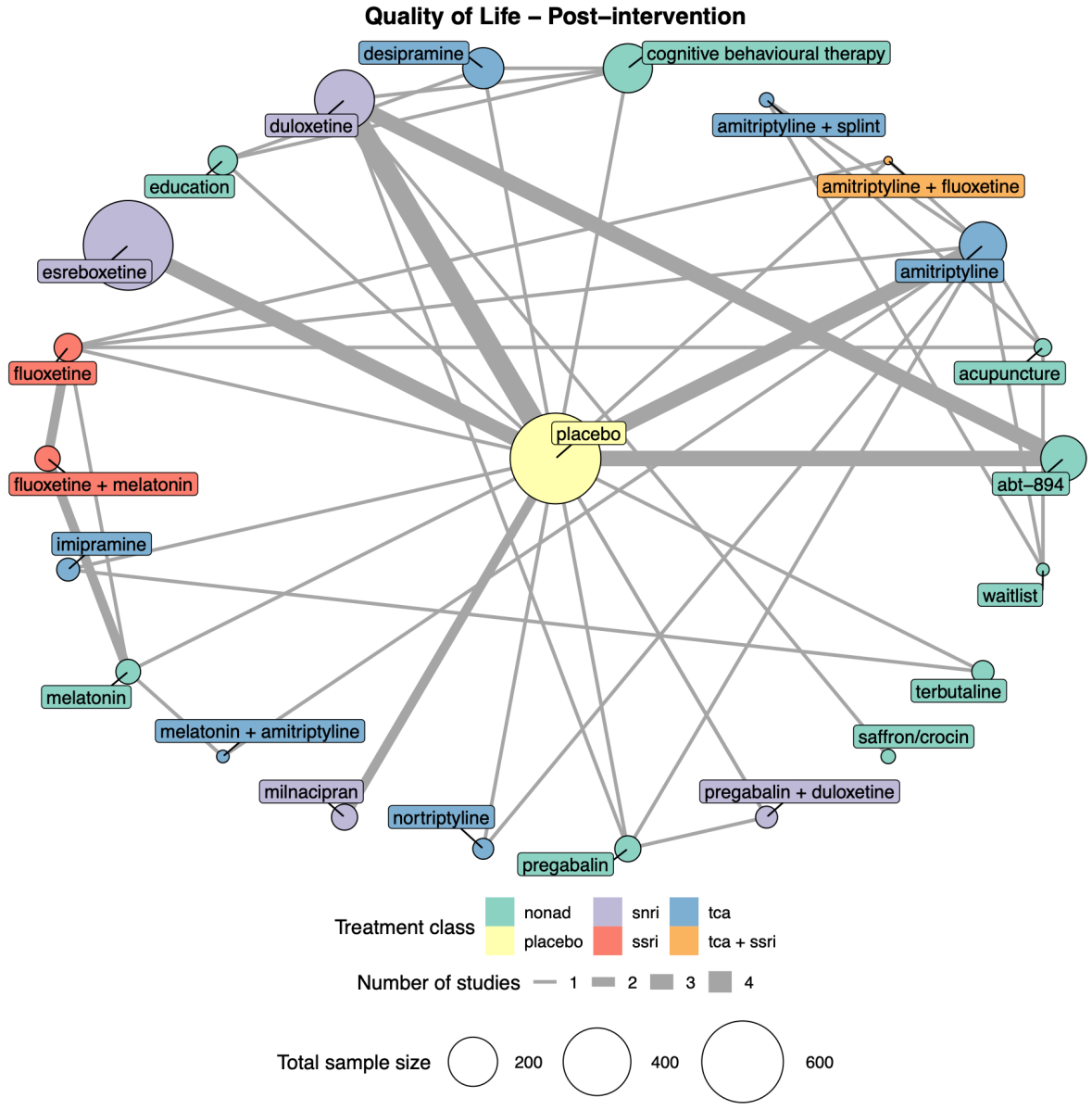
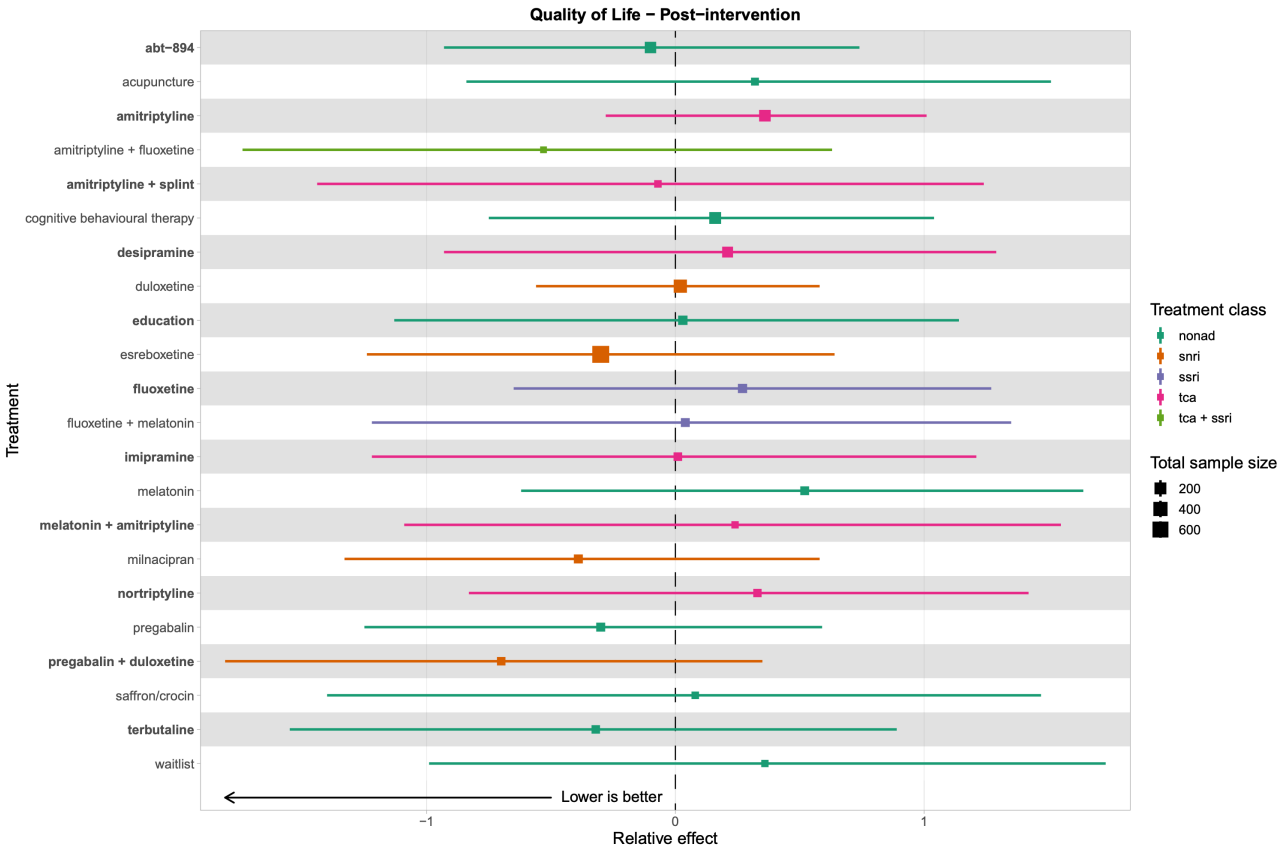


Figure 19. Quality of life forest plot (standardised mean difference with credible intervals). SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants



Ranking of antidepressants

The top-ranked antidepressants for quality of life are displayed in Table 21. Neither esreboxetine nor duloxetine showed a significant difference compared to placebo for quality of life (SMD −0.30, 95% CI −1.24 to 0.64 and SMD 0.02, 95% CI −0.56 to 0.58, respectively).

A visual representation of the cumulative rankings for every intervention included in the analysis did not alter interpretations. Node-splitting models were undertaken for all 13 comparisons where it was possible to compare direct and indirect evidence. The comparison with the lowest Bayesian P value (0.16) was fluoxetine compared to amitriptyline. These figures are available in the supplemental files (link provided in Appendix 3). Unrelated mean-effects models also failed to identify inconsistency.

Exploration of heterogeneity

We explored models including both treatment and dose; this model had higher heterogeneity (Tau = 0.67) and similar residual deviance to that of the treatment-only model.

Class, condition and risk of bias

We were unable to generate meaningful networks including class, condition, and risk of bias. Only one class had antidepressants with over 200 participants (SNRI). Small sample sizes, network geometry and the risk of over-fitting precluded analyses of condition and risk of bias.

CINeMA

The design-by-treatment test showed evidence of significant inconsistency between the direct and indirect evidence in the network (Chi^2 = 80.27, P = 0.00) despite node-splitting and unrelated mean-effect models indicating no concern. The I^2 statistic value for duloxetine showed evidence of heterogeneity (I^2= 67.2%) and could not be calculated for esreboxetine. Therefore, we rated duloxetine as having low-certainty evidence (downgraded due to within-study bias, heterogeneity, and inconsistency) and esreboxetine as very low-certainty evidence (downgraded due to within-study bias, inconsistency, and low numbers of studies).

Patient Global Impression of Change (PGIC)

PGIC was reported in two ways: as a continuous score, and as the proportion of participants scoring one (very much improved) and two (much improved). We include both of these results.

PGIC much and very much improved

For PGIC much and very much improved we report the treatment-dose network as this had low heterogeneity with no inconsistency. We present summary of findings for PGIC much or very much improved in Table 22.

Results

We included 12 RCTs with a total of 6995 participants (range from 43 to 1025). Eight studies compared against placebo and four were

dose-comparison studies. There were nine different interventions, and some comparisons were informed only by direct evidence from one study. We judged seven studies to be high risk of bias. There were no concerns regarding model fit. The network diagram is presented in Figure 20, and the forest plot is presented in Figure 21. An overview of all interventions included in the analysis is given in Table 23.

Figure 20. Patient Global Impression of Change much/very much improved network diagram. SNRI: serotonin noradrenalin reuptake inhibitors

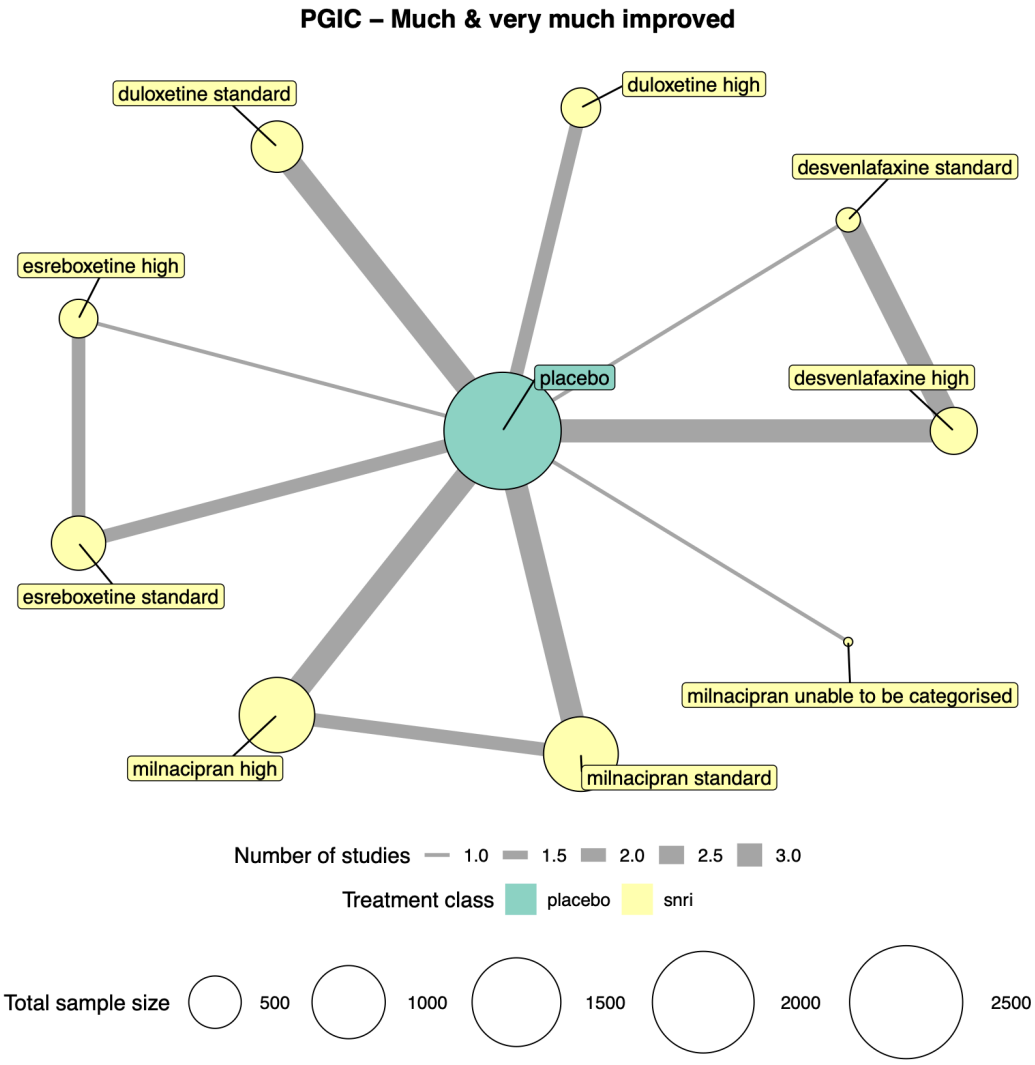
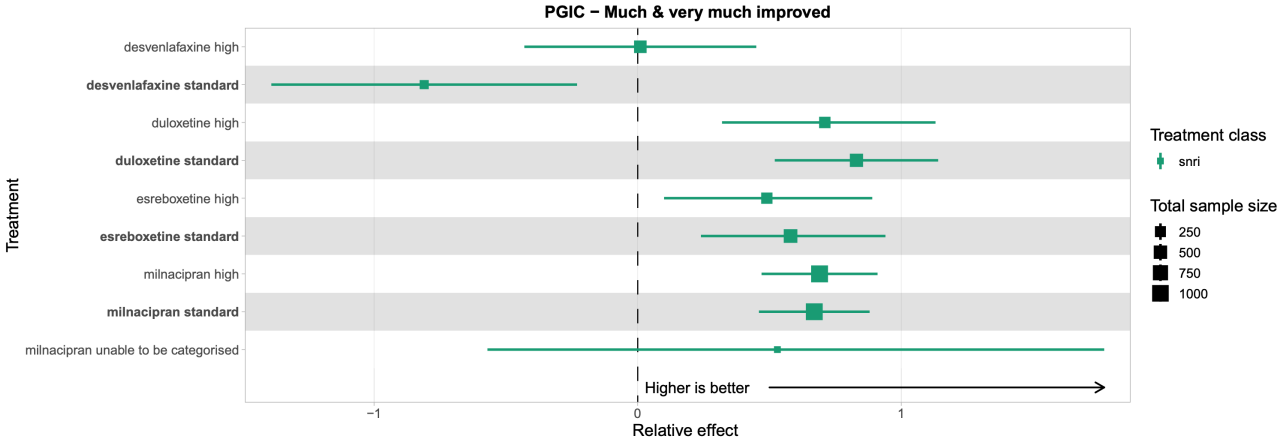


Figure 21. Patient Global Impression of Change much/very much improved forest plot. SNRI: serotonin noradrenalin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants



Ranking of antidepressants

The top-ranked antidepressants for PGIC much and very much improved are presented in Table 24. Duloxetine standard dose was the highest-ranked antidepressant for PGIC much and very much improved, with a large effect (OR 2.29, 95% CI 1.98 to 2.60). Duloxetine high dose (OR 2.03, 95% CI 1.62 to 2.44), milnacipran high dose (OR 1.99, 95% CI 1.77 to 2.21), and milnacipran standard dose (OR 1.95, 95% CI 1.73 to 2.17) were the next highest-ranked antidepressants. Both esreboxetine doses showed a smaller effect (standard: OR 1.79, 95% CI 1.44 to 2.14; high: OR 1.63, 95% CI 1.24 to 2.02), but were among the lowest-ranked antidepressants. Desvenlafaxine high dose showed no significant effects when compared to placebo (OR 1.01, 95% CI 0.58 to 1.44).

A visual representation of the SUCRA rankings for every intervention included in the analysis did not alter interpretation. The unrelated mean-effect model had no evidence of inconsistency. We were only able to compare direct and indirect evidence for milnacipran standard versus milnacipran high dose with a Bayesian P value of 0.66, indicative of no inconsistency. These figures are available the supplemental files (link provided in Appendix 3)..

Exploration of heterogeneity

- **Class, condition and risk of bias:** we were unable to include class, condition, and risk of bias in the models. For class, all the antidepressants included in the model were SNRI. For condition and risk of bias, the sparse network geometry created disconnected networks with small sample sizes and high risk of over-fitting.
- **CINeMA:** the design-by-treatment test showed no evidence of inconsistency (Chi^2 = 0.35, P = 0.84), and no antidepressants had I^2 statistic values of over 40%. We rated the majority of the evidence to be very low certainty, due to within-study bias and low study and participant numbers. We rated milnacipran high dose as low certainty, downgraded due to major concerns of within-study bias. We rated milnacipran and duloxetine standard dose as moderate certainty, only downgraded due to concerns about within-study bias.

PGIC continuous

For PGIC continuous we report the treatment-dose network as it had low heterogeneity and the most clinical utility. We present the summary of findings in Table 25.

Results

We included 24 RCTs with a total of 8415 participants (range from 194 to 804). Twelve studies compared against only placebo, three were multi-arm studies with another active comparator, and nine were dose-comparison studies. There were seven different interventions, and some comparisons were informed only by direct evidence from one study. We judged 15 studies as high risk of bias overall. There were no concerns regarding model fit. The network diagram is presented in Figure 22, and the forest plot of placebo comparisons is presented in Figure 23. An overview of all the interventions included in the analysis is given in Table 26.

Figure 22. Patient Global Impression of Change continuous network diagram. SNRI: serotonin noradrenalin reuptake inhibitors; nonad: non-antidepressants

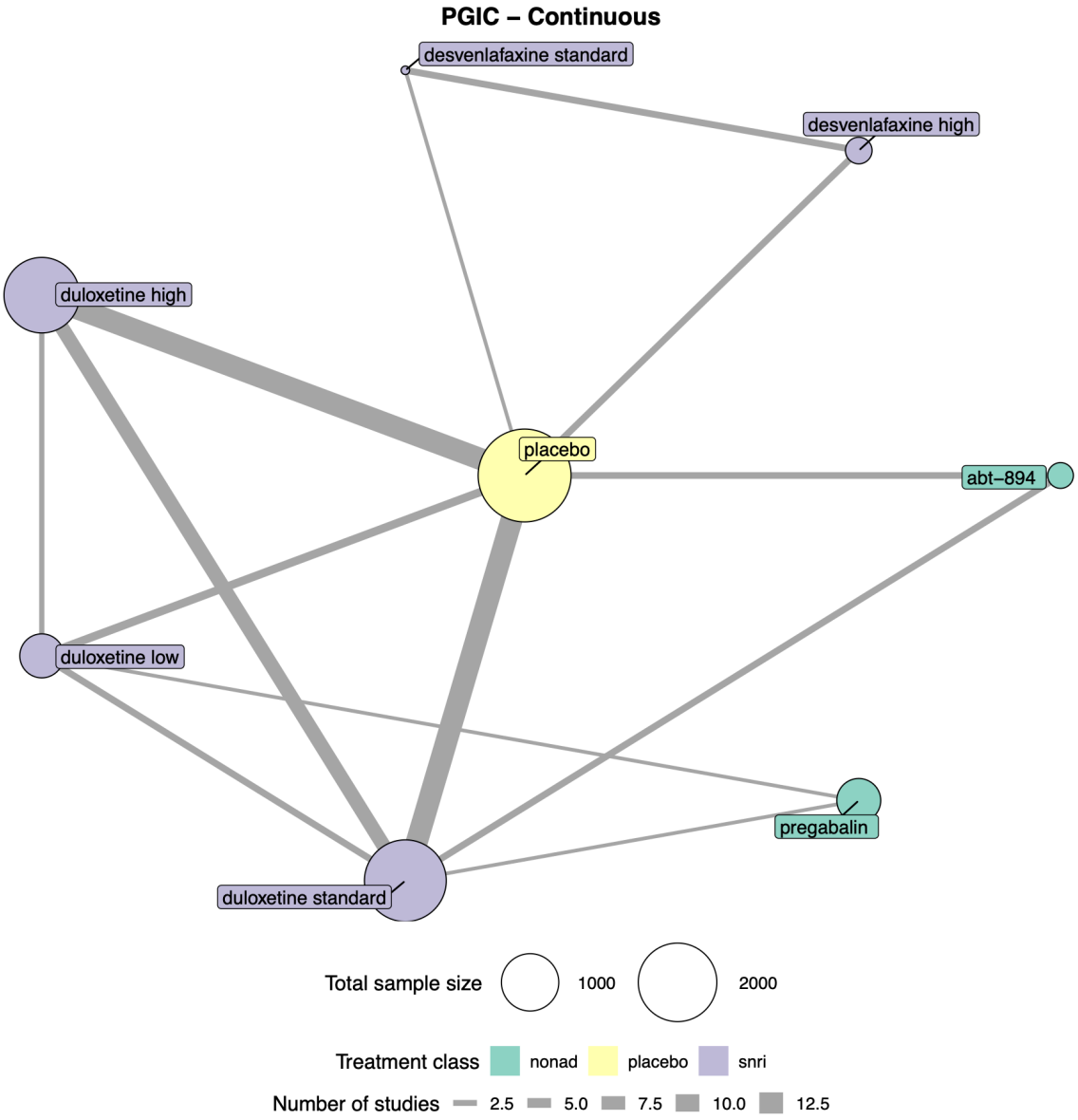
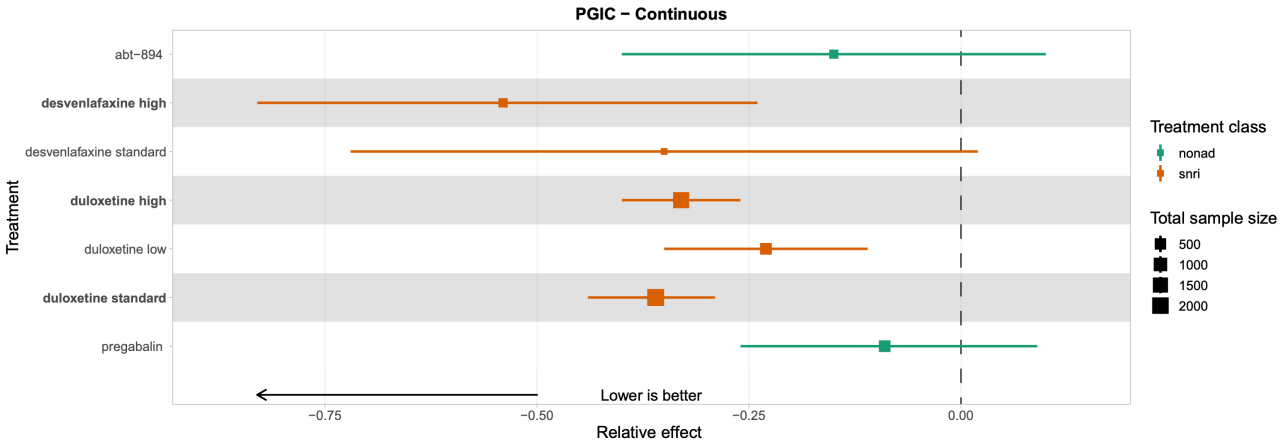


Figure 23. Patient Global Impression of Change continuous forest plot (standardised mean difference with credible intervals). SNRI: serotonin noradrenalin reuptake inhibitors; nonad: non-antidepressants



Ranking of antidepressants

The top-ranked antidepressants for PGIC continuous are presented in Table 27. Duloxetine standard and high doses were the highest-ranked antidepressants, with a small to moderate effect (SMD −0.36, 95% CI −0.44 to −0.29 and SMD −0.33, 95% CI −0.40 to −0.26, respectively). Duloxetine low dose was the lowest-ranked antidepressant with a small effect (SMD −0.23, 95% CI −0.35 to −0.11).

A visual representation of the cumulative rankings for every intervention included in the analysis did not alter interpretations. Both unrelated mean-effect models and node-splitting models showed evidence of inconsistency. The highest Bayesian P value (0.03) suggested that direct evidence overestimated the effectiveness of high-dose duloxetine versus placebo compared to indirect evidence, resulting in strength of evidence downgrading. These figures are available in the supplemental files (link provided in Appendix 3).

Exploration of heterogeneity

- **Class, condition, and risk of bias:** we were unable to run models including class, condition, and risk of bias. We were unable to analyse class as there was only one class present in the network (SNRI). We were unable to analyses condition and risk of bias due to the high risk of over-fitting.
- **CINeMA:** the design-by-treatment test showed no evidence of inconsistency between the direct and indirect evidence in the network (Chi^2 = 14.98, P = 0.13), and no antidepressants had an I^2 statistic value higher than 40%. We rated duloxetine standard and high doses as moderate certainty as a result of incoherence. We downgraded duloxetine low dose to moderate certainty due to some concerns regarding within-study bias in addition to network inconsistency.

Serious adverse events

For serious adverse events we report the treatment-dose model. Both treatment and treatment-dose models had studies with high levels of imprecision; treatment-dose was selected for reporting due to its clinical utility. We present the summary of findings in Table 28.

Results

We included 71 RCTs with a total of 19,304 participants (range from 26 to 1025). Thirty-nine studies compared against placebo, 12 compared against another active comparator, 15 were dose-comparison studies, and four studies compared two different antidepressants against each other. There were 31 different interventions, and some comparisons were informed only by direct evidence from one study. We judged 45 studies as high risk of bias. We could not include data from three studies due to disconnected networks. There were no concerns regarding model fit. The network diagram is presented in Figure 24, and the forest plot of placebo comparisons is presented in Figure 25. An overview of all interventions included in the analysis is given in Table 29.

Figure 24. Serious adverse events network diagram. NARI: noradrenaline reuptake inhibitors; NDRI: Noradrenaline and dopamine reuptake inhibitors; NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenaline reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants

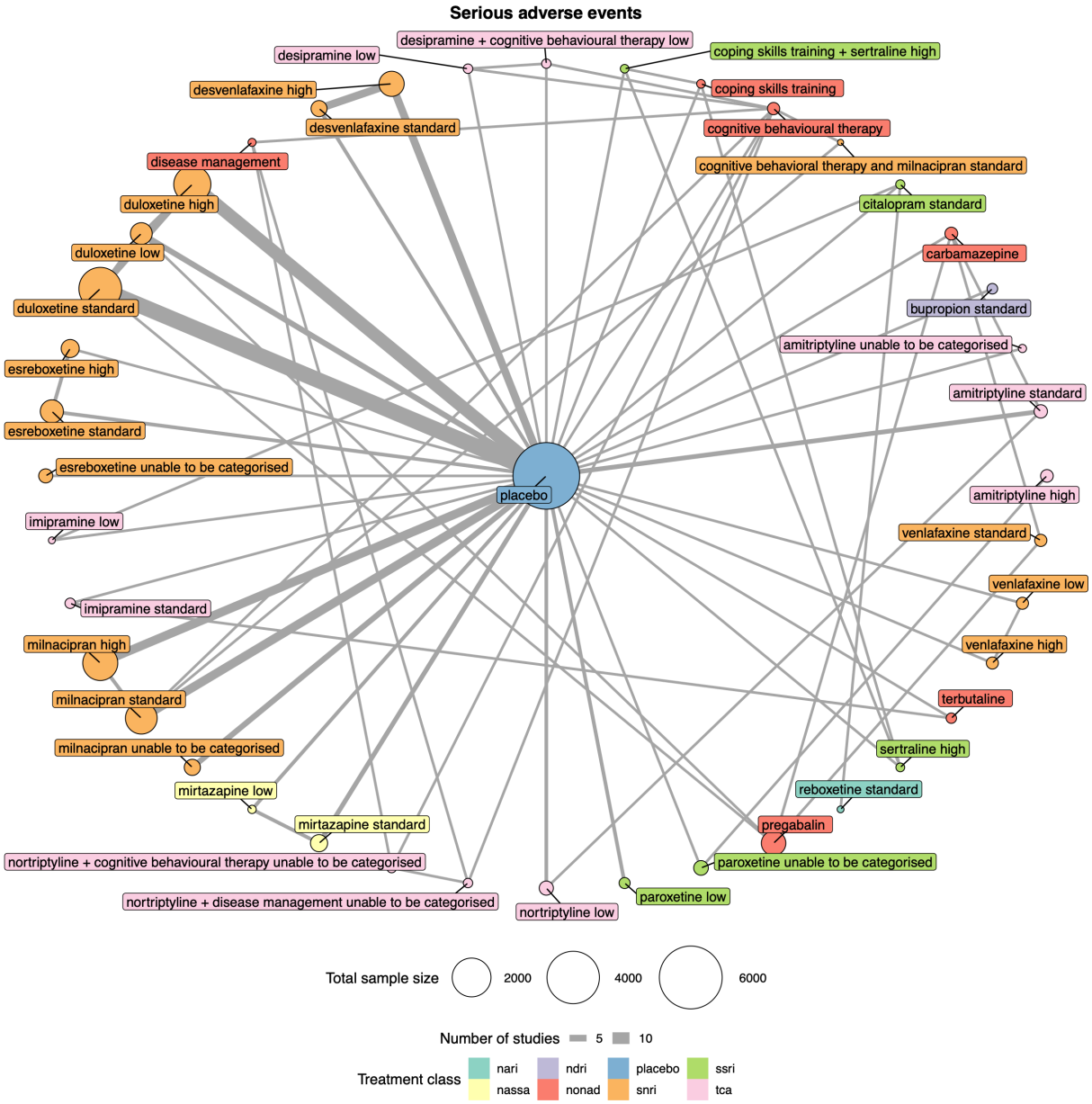
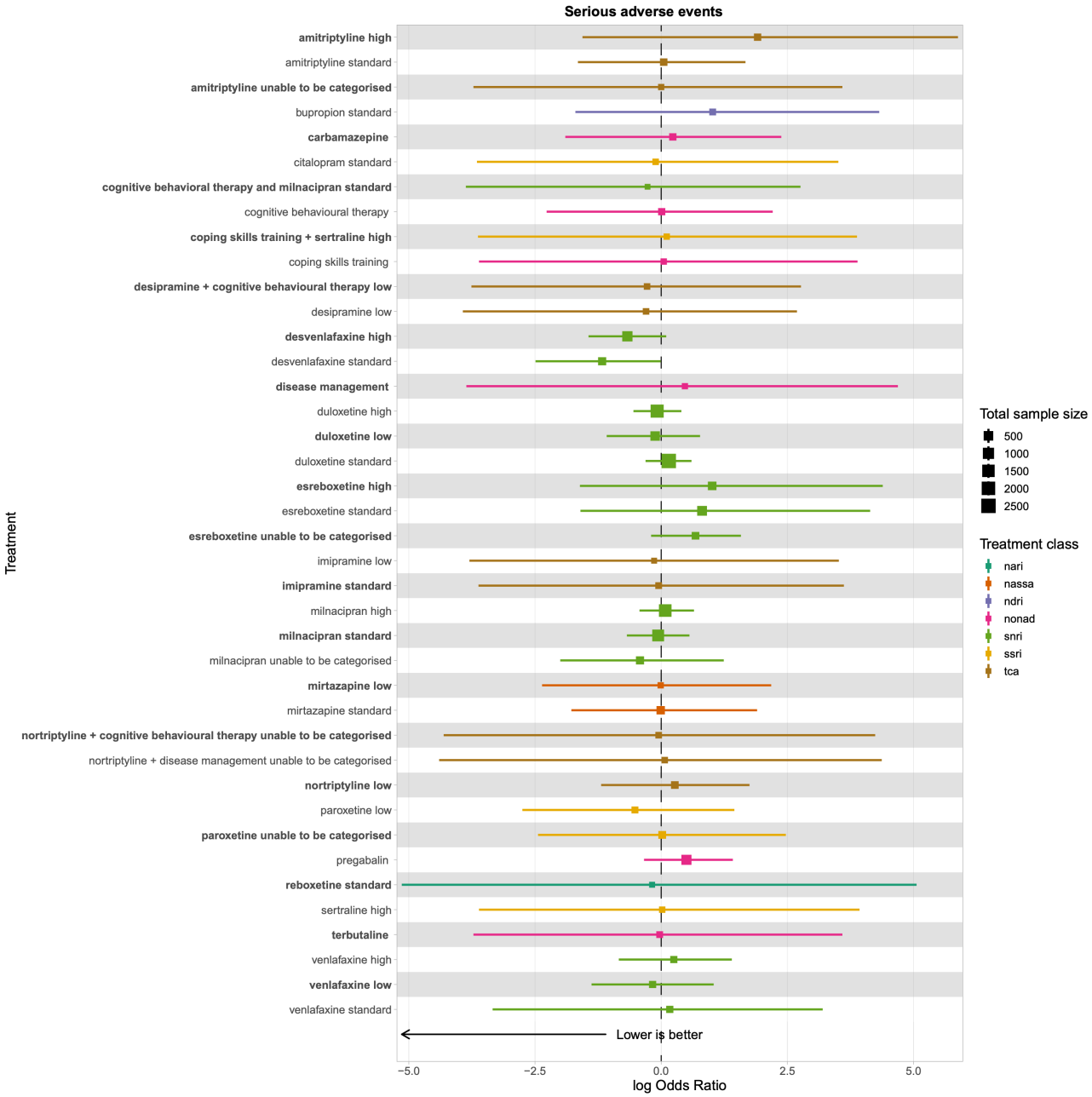


Figure 25. Serious adverse events forest plot (log odds ratio with credible intervals). NARI: noradrenaline reuptake inhibitors; NDRI: Noradrenaline and dopamine reuptake inhibitors; NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenaline reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; nonad: non-antidepressants



Ranking of antidepressants

The top-ranked antidepressants for serious adverse events are displayed in Table 30. Data for serious adverse events were very sparse, and studies were generally underpowered to detect rare events. No antidepressants showed any significant difference when compared with placebo, and the confidence intervals were very wide.

We undertook a visual representation of the cumulative rankings for every intervention included in the analysis. The unrelated mean-effect model had no evidence of inconsistency. We confirmed this with node-splitting models for all 16 comparisons where it was possible to compare direct and indirect evidence. The lowest Bayesian P value (0.07) was for the comparison of pregabalin and low-dose duloxetine. These figures are available in the supplemental files (link provided in Appendix 3).

- **Class, condition, and risk of bias:** we were unable to undertake further analysis of class, condition, or risk of bias in networks due to small sample sizes, network geometry and the risk of over-fitting.

- CINeMA: we were unable to use CINeMA for this outcome due to complexity of the network. Therefore, two review authors (HB and GS) made the judgements based on GRADE and CINeMA domains and the available results. We judged all antidepressants and doses as very low certainty, primarily due to concerns with within-study bias, heterogeneity, and imprecision in the network.

Withdrawal

For withdrawal, we report the treatment network. Although this model has high heterogeneity, we determined that including dose would increase the network complexity to a point where analysis would be infeasible. We present the summary of findings in Table 31.

Results

We included 152 RCTs with a total of 28,120 participants (range from 24 to 1025). Seventy-three studies compared against placebo, 47 were multi-arm studies with another active comparator, 18 were dose-comparison studies, and 14 were head-to-head studies comparing two different antidepressants. There were 77 different interventions, and some comparisons were informed only by direct evidence from one study. We rated 106 studies as high risk of bias. We could not include data from two studies due to disconnected networks. There were no concerns regarding model fit. We present the network diagram in Figure 26, and the forest plot of placebo comparisons in Figure 27. We give an overview of all interventions included in the analysis in Table 32.

Figure 26. Withdrawal network diagram. MAOI_rev: monoamine oxidase inhibitors (reversible); NARI: noradrenaline reuptake inhibitors; NDRI: noradrenaline and dopamine reuptake inhibitors; NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenaline reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; TECA: tetracyclic antidepressants; nonad: non-antidepressants

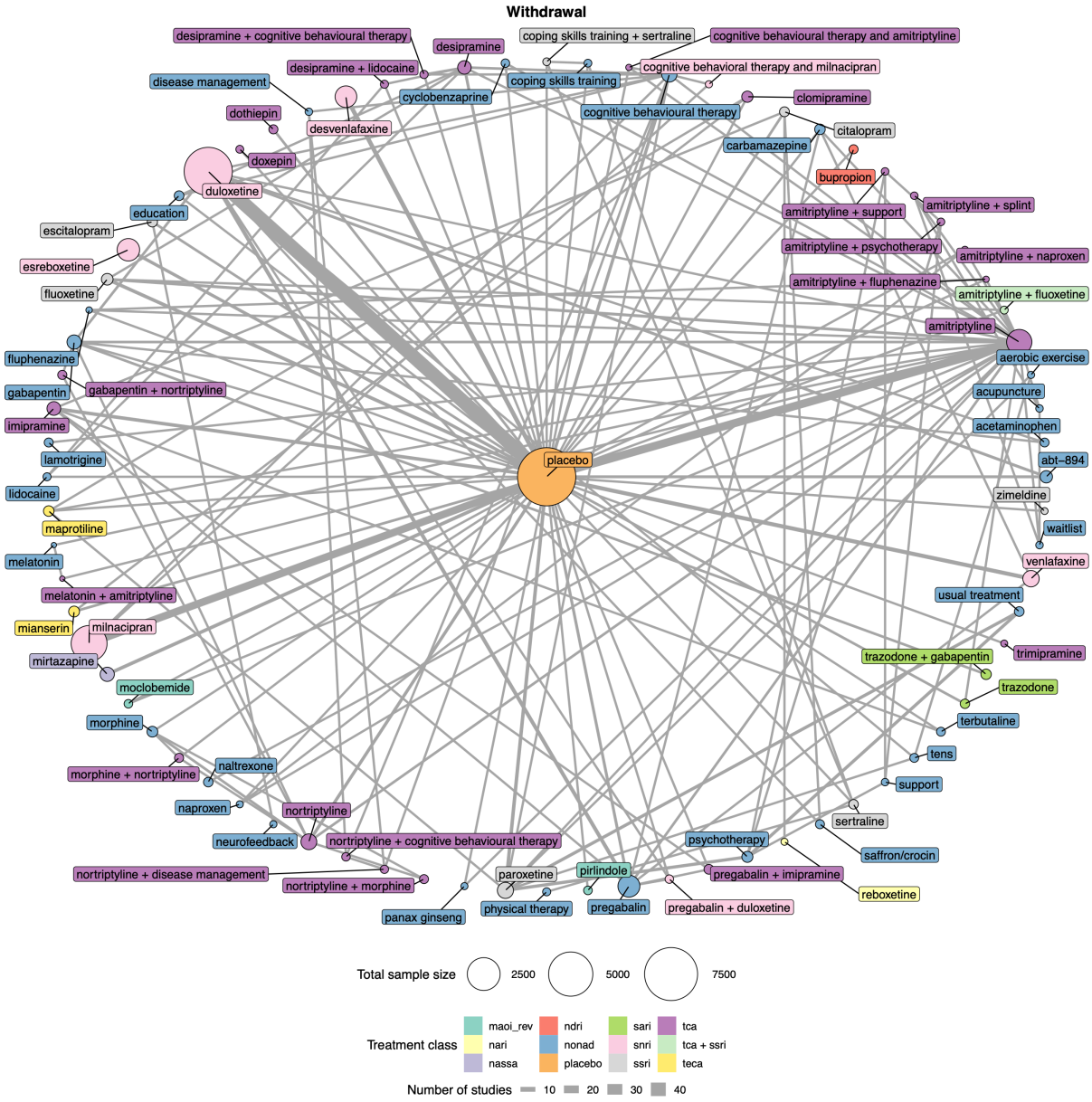
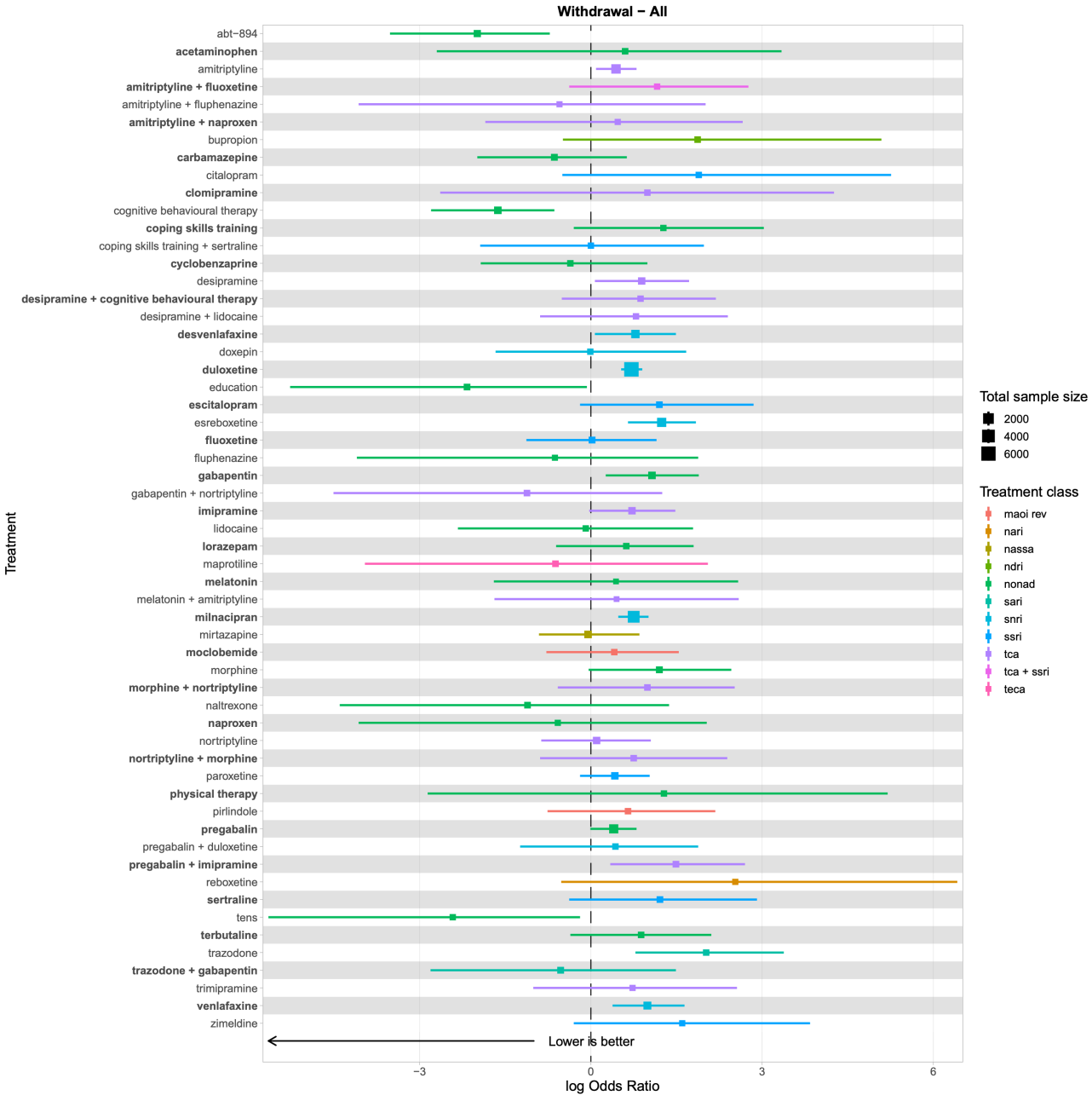


Figure 27. Withdrawal forest plot (log odds ratio with credible intervals). MAOI_rev: monoamine oxidase inhibitors (reversible); NARI: noradrenaline reuptake inhibitors; NDRI: Noradrenaline and dopamine reuptake inhibitors; NASSA: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin noradrenaline reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; TECA: tetracyclic antidepressants; nonad: non-antidepressants



Ranking of antidepressants

The ranking of antidepressants with over 200 participants in order of highest-ranked to lowest-ranked is presented in Table 33. Nortriptyline was the highest-ranked antidepressant. Nortriptyline, mirtazapine, amitriptyline, desvenlafaxine, and venlafaxine all showed no significant difference compared to placebo for withdrawal. Duloxetine, milnacipran, esreboxetine, desipramine, and paroxetine all showed significant effects, ranging from small to moderate.

A visual representation of the cumulative rankings for every intervention included in the analysis is given in the supplemental files (link provided in Appendix 3). We were unable to draw any very reliable conclusions due to all antidepressants having wide, overlapping credible intervals.

Exploration of heterogeneity

Due to the complexity and geometry of the network, we were only able to examine models including class, and were unable to examine condition or risk of bias.

Class

We included 10 classes of antidepressant in the analysis: SNRI, SSRI, TCA, MAOI reversible, NARI, NaSSA, NDRI, SARI, TCA+SSRI, and TeCA. There was slightly higher heterogeneity than the treatment-only model (Tau = 0.33), but no evidence of inconsistency in the unrelated mean effects models. Half of the classes had fewer than 200 participants, leaving SNRI, SSRI, TCA, NaSSA, and TeCA with reliable sample sizes. The rankings of these classes are presented in Table 34.

CINeMA

We were unable to use CINeMA for this outcome due to complexity of the network. Therefore, two review authors (HB and GS) made the judgements based on GRADE and CINeMA domains and the available results. We judged all antidepressants except duloxetine as very low certainty, primarily due to concerns with within-study bias, heterogeneity, and imprecision in the network. We rated duloxetine as low certainty, as the only antidepressant without major concerns due to imprecision.

DISCUSSION

Summary of main results

Overall

We report an NMA of 176 double-blind RCTs that investigated antidepressants for chronic pain. Studies included 28,664 adult participants with a mean age of 50.6 years. The majority of studies investigated antidepressants from three classes: SNRI (74 studies); TCA (72 studies); and SSRI (34 studies). There was a variety of study designs, however the majority of studies were placebo-controlled (83 studies). The remainder compared an antidepressant against an active comparator with no placebo (22 studies) or compared two or more different doses of the same antidepressant with a placebo arm (17 studies). Most studies were parallel-arm design (141 studies) compared to cross-over design (35 studies). Studies mainly included participants with only one type of chronic pain: 59 studies included participants with fibromyalgia; 49 neuropathic pain; 40 musculoskeletal pain; and 26 included participants with other conditions (e.g. gastrointestinal, primary pain conditions, non-cardiac chest pain etc.). Finally, 72 studies were fully funded by pharmaceutical companies. Thirty-two studies did not report the source of funding.

Seven studies, with a total of 156 participants, provided no useable data and were therefore omitted from the NMAs. At the time of writing the review, the majority of antidepressants are not licenced for use in chronic pain. Only amitriptyline and duloxetine are indicated for types of chronic pain in the British National Formulary; amitriptyline for neuropathic pain, and duloxetine for diabetic neuropathy (British National Formulary 2022b; British National Formulary 2022c).

The following results are based on NMA. One study (Vrethem 1997), reported the results separately according to the type of pain condition. This study was stratified into two to include the results for both conditions.

Primary efficacy outcomes

For the primary efficacy outcomes (substantial pain relief, pain intensity, and mood) duloxetine was consistently the highest-ranked antidepressant that had data from over 200 participants in total across studies, and the only antidepressant with robust evidence that showed an effect with moderate-certainty evidence. For substantial pain and pain intensity, standard-dose duloxetine was as efficacious as high-dose duloxetine. For pain intensity and mood, milnacipran also showed reliable effectiveness, with moderate-certainty evidence. At a class level, SNRIs were the only class to have an effect with reliable evidence. For pain intensity, we removed one study that showed improbable effects from the data extracted from the published article (Miki 2016). We emailed the study authors for clarification but received no response.

Secondary efficacy outcomes

Across all the secondary efficacy outcomes (moderate pain relief, physical function, sleep, quality of life, and PGIC) duloxetine and milnacipran were the highest-ranked and most trustworthy antidepressants respectively. Very few other antidepressants included over 200 participants, and those that did were ranked as very low certainty. For both duloxetine and milnacipran, standard doses were as effective as high doses, although effects for both were small.

Safety

We extracted adverse event, serious adverse event, and withdrawal data from the studies included in the review. The data for these outcomes were poor. Although we have reported the ranking of antidepressants in the summary of findings tables, the quality and certainty of this evidence for all antidepressants and doses is very low, and we cannot draw any reliable conclusions from the analyses.

Overall completeness and applicability of evidence

We were able to draw some conclusions about the effectiveness and rankings of antidepressants in the efficacy and safety of treating chronic pain. The evidence is particularly lacking for long-term outcomes and safety data.

Participants

The sample of participants in the included studies was mostly female (68.3%) and had a mean age of 50.6 years. Most studies had a minimum pain intensity inclusion criterion, with 92 studies requiring participants to score 4 or higher on a 0 to 10 scale or equivalent at baseline, and most participants reported experiencing pain for over one year.

Our inclusion criteria for participants was strict, we required the study population to have had pain for three months or longer. If this timeframe was not explicitly reported by the study or required for a diagnosis of the pain condition, then we excluded it. Therefore, we excluded six studies from our full-text screening with a study population described as having a ‘chronic’ pain condition without information regarding duration. This may mean that we excluded other relevant studies, but we believe the number of studies to be affected by this to be minimal.

Interventions

There were 89 different interventions included in the review, 26 of which were antidepressants. We included all interventions that matched the inclusion criteria regardless of dose, formulation, and route of administration. Only four antidepressants were

investigated in over 10 studies. The only antidepressant that had robust studies and evidence is duloxetine, with 43 studies and a total of 11,608 participants randomised. Participants in duloxetine studies accounted for over a third of all the participants included in this review. Milnacipran also showed some reliable evidence across outcomes, with 11 studies and a total of 5083 participants. Forty-three studies, with a total of 3372 participants, investigated amitriptyline, although the certainty of this evidence was very low, and only three studies randomised over 200 participants. Fluoxetine was the fourth antidepressant to be included in more than 10 studies, but the quality and certainty of the evidence was very low, with 11 studies including 630 participants in total. All other antidepressants were included in fewer than 10 studies.

Study designs and comparisons

A variety of study designs were used by studies included in the review. Half the studies included in the review were two-arm, parallel-designed studies comparing antidepressant to placebo (89 out of 176 studies). There were also dose-comparison studies, comparisons against active comparators, combined antidepressant interventions (e.g. antidepressant + psychological therapy), and a number of studies included multiple types of these comparisons. Some of the combined antidepressant comparisons precluded full analysis in the NMA as we were unable to isolate the effects of the antidepressant alone. There were few head-to-head studies comparing two antidepressants with a placebo arm for reference.

The majority of studies provided useable data for the primary efficacy outcomes; 131 studies measured pain intensity, and 87 measured mood. Although these figures represent the majority of studies, it is evident that a large number of studies in chronic pain do not report these key outcomes. In the review, over half of studies did not measure mood, and almost a third did not measure or report pain intensity. Despite the 2005 publication of the IMMPACT guidelines for core outcomes of chronic pain studies (Dworkin 2008), only 44 and 43 studies reported the proportion of participants achieving 50% and 30% pain relief, respectively. For the secondary outcomes, around a third of studies reported physical function, less than a quarter reported sleep, and only a quarter reported quality of life.

All outcomes aside from withdrawal used self-reported measures. There was considerable heterogeneity in the outcome measures used across all outcomes such that SMD was required for the continuous outcomes. Additionally, studies reported a mix of change scores (change in outcome from baseline to post-intervention) and post-intervention scores. As we had to use SMD, this meant that we could not build one NMA that included all data for each outcome; rather we were required to build both change-score and post-intervention-score models and subsequently decide which model to report for each outcome. Typically, larger studies, funded by pharmaceutical companies, reported change scores, whilst smaller studies reported post-intervention scores. Future reviews would benefit from studies reporting both types of scores, so that results can be combined for a holistic evidence synthesis. We found that the data for the safety outcomes were particularly poor; adverse events were reported in various different ways across studies, and studies were often not powered adequately or lasted long enough to detect events.

Mood

As antidepressants are primarily designed and used to manage depression, and low mood is a common comorbidity with chronic pain, we planned to explore their impact upon mood in this analysis in several ways.

First, we planned to undertake a subgroup analysis exploring whether there were any differences in outcomes between studies reporting a main aim of targeting pain compared to those reporting a main aim of targeting mood. We were unable to undertake this analysis as only two studies had a main aim of targeting mood. In contrast, 144 studies had a main aim of targeting pain.

Second, we planned to undertake analyses examining differences in outcomes for studies stratified by levels of depression at baseline (none, mild, moderate, and severe as defined by the diagnostic tools used). The majority of studies excluded participants with diagnoses of major depressive disorder and other mental health conditions. Because of this, baseline measures of depression or anxiety, or both, failed to exceed average scores of mild depression at baseline.

As we were unable to undertake these analyses, we are unable to assess the effect of depression and mood on the outcomes of the NMA, and unable to draw any meaningful conclusions regarding the mood outcome.

Timing

Most of the studies included in this review were of short duration: the average length of the study from baseline to post-intervention was 10 weeks. We planned to undertake analyses at several time points:

- post-intervention (immediately at the end of the treatment period);
- short-term follow-up (< 12 weeks after the treatment had finished);
- long-term follow-up (≥ 12 weeks after the treatment had finished).

We were only able to undertake analyses at the post-intervention time point as only a small number of studies had follow-up periods of any length after the intervention had been completed (6/176 studies). Therefore, we are unable to draw any conclusions regarding the long-term efficacy and safety of using antidepressants for chronic pain.

Ongoing studies

We categorised 26 studies as 'ongoing', which are investigating the following antidepressants.

- Duloxetine (12 studies)
- Amitriptyline (4 studies)
- Citalopram (2 studies)
- Venlafaxine (2 studies)
- Agomelatine (1 study)
- Bupropion (1 study)
- Clomipramine (1 study)
- Fluoxetine (1 study)
- Mianserin (1 study)

- Nortriptyline (1 study)

The ongoing studies are investigating the following pain conditions.

- Neuropathic pain (9 studies)
- Osteoarthritis (6 studies)
- Low back pain (4 studies)
- Chest pain (2 studies)
- Facial pain (2 studies)
- Irritable bowel syndrome (1 study)
- Mastalgia (1 study)
- Phantom limb pain (1 study)

Considering their context, we do not anticipate that the evidence from these studies will have a significant impact on the findings of this review. We consider our results for duloxetine, neuropathic pain, and musculoskeletal pain to be robust - the addition of these results are unlikely to change this. These studies may contribute to conclusions for amitriptyline if the sample sizes are large enough; we were unable to include amitriptyline in the write-up of the review as often there were not more than 200 participants from the studies.

Quality of the evidence

Overall quality

We assessed the quality of the evidence using CINeMA (Nikolakopoulou 2020) (and ROB-MEN (Chiocchia 2021), and GRADE (Schünemann 2013), where appropriate). Across the outcomes, the only antidepressant with consistently robust evidence is duloxetine, followed by milnacipran. We judged all other antidepressants as having low- or very low-certainty evidence. The most common reasons for downgrading comparisons were within-study bias, imprecision in the NMA (wide credible intervals), and small numbers of studies and participants. Additionally, we graded all evidence for safety as very low certainty due to heterogeneity, imprecision, and sparsity of data.

Risk of bias

Overall, the risk of bias for included studies was relatively high. Using RoB 1 resulted in 116 studies being defined as high risk of bias overall. We often downgraded evidence due to within-study bias across antidepressants and outcomes. There are several points relating to risk of bias to be discussed. The common method of deciding the overall rating of a study's risk of bias stipulates that if any one domain is high risk, then the whole study is rated as high risk of bias. As we included studies that compared antidepressants to other active comparators, this included interventions whose designs inherently require participants and study staff to be unblinded (e.g. psychological therapies). To be consistent with other studies in the review, we rated these as high risk of bias for the blinding domains, but it has been recognised previously that these domains are not appropriate for these interventions, and in previous reviews these domains have been omitted (Williams 2020).

Additionally, we found that a number of studies simply do not report the information needed to make a judgement. Of the 60 studies rated as 'not high' risk of bias, over half had three or more domains judged as 'unclear'. Therefore, this raises concerns as to the reporting quality of these studies, an ongoing problem in health research (Pirosca 2022). There is a number of clinical trial reporting guidelines available which these studies have not abided by, which suggests that some of the studies may have been rated as high risk of bias if the correct information had been provided.

Heterogeneity

We found substantial heterogeneity in direct comparisons and entire networks across outcomes when including all doses of each treatment together in the NMAs. Where this was evident, splitting treatments by dose categories removed heterogeneity for most outcomes. Therefore, most of the outcomes were analysed using a split-dose model. Further exploration of heterogeneity by including antidepressant class and pain condition had to be balanced against the risk of over-fitting multiple models (Dias 2013). The decision process for this is discussed within each outcome results section.

Imprecision

Imprecision was a problem across most of our NMAs. Of the 26 different antidepressants included in our review, only four were used in more than 10 studies. Although we included all treatments in each analysis, for each outcome we graded any study with fewer than 200 participants in the antidepressant arms as very low by default and excluded these from the written summaries and summary of findings tables. The remaining networks were generally robust at a network level, but problems remained with network connectivity relying on single studies. Imprecision was a major problem for safety data, particularly adverse events, and serious adverse events, meaning that we cannot be sure of the true effect for these outcomes.

Inconsistency

For each outcome, we used unrelated mean-effect and node-splitting models to assess inconsistency in treatment and split treatment-dose networks. Network geometry was generally adequate to allow both unrelated mean-effect models and node-splitting models to be used to assess discrepancy between direct and indirect evidence. Where discrepancies were identified, we considered the potential for transitivity assumption violations in strength-of-evidence assessments and model choice. On some occasions the distributions of estimates from direct and indirect evidence were wide due to low power, or we were unable to make important comparisons due to an absence of head-to-head studies. In these circumstances, transitivity assumption violations cannot be discounted. In general, there was sufficient evidence to identify discrepancy between direct and indirect evidence - and such discrepancies were rare - especially considering the size of the networks and the potential diversity of participants across pain conditions.

Publication bias

We used ROB-MEN to assess publication bias in the review (Chiocchia 2021). For the primary outcomes, we were only able to produce funnel plots for the duloxetine-placebo comparison as it was the only comparison with over 10 studies. These funnel plots showed some evidence of publication bias, and therefore the comparisons were rated as 'some concerns'. As all other antidepressants tended to report small effects with small numbers of studies and participants, we judged all comparisons to have 'some concerns'.

Potential biases in the review process

We minimised the potential for bias in the review process as much as possible. We published our protocol through the Cochrane Library and followed this for the review process (Birkinshaw 2021). We had an extensive search strategy that included six databases, and also searched clinical trials registries for unpublished and ongoing studies. The chance of a missed study is minimal, and even more minimal is the chance of any missed study having a substantial effect on the overall results.

Two review authors completed screening, data extraction, and risk of bias assessments in duplicate and independently, with all disagreements resolved by discussion. Where possible, we contacted study authors to request missing data, but their response rate was low. Where the study was registered in a clinical trials registry, we collected data that were not reported in the published paper from the results section of the registry.

We used CINeMA (Nikolakopoulou 2020) and ROB-MEN (Chiocchia 2021) to assess our confidence in the results. Two review authors made the final interpretation and judgements in discussion.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the only NMA that has examined all antidepressants for all types of chronic pain; previous reviews in this topic area have focused solely on one pain condition, or one antidepressant, or have examined efficacy by drug, dose, and pain condition. There have been a number of systematic reviews and meta-analyses over the past decade examining antidepressants for different types of pain conditions, the majority of which were Cochrane Reviews.

For neuropathic pain, multiple reviews have shown there is no high-quality or high-certainty evidence for the efficacy of amitriptyline, desipramine, imipramine, milnacipran, nortriptyline, or venlafaxine (Derry 2015a; Derry 2015b; Gallagher 2015; Hearn 2014a; Hearn 2014b; Moore 2015). However, there was moderate-certainty evidence that duloxetine is efficacious for diabetic peripheral neuropathy (Lunn 2014). For fibromyalgia, reviews show that there was no unbiased evidence that amitriptyline, desvenlafaxine, venlafaxine, or SSRIs were better than placebo, but there is low-certainty evidence that duloxetine, milnacipran, and mirtazapine are efficacious (Walitt 2015; Welsch 2018). Finally, for musculoskeletal pain, two reviews found no clear evidence to support the use of antidepressants for low back pain (Koes 2018; Urquhart 2008), though a recent systematic review and meta-analysis showed moderate-certainty evidence for SNRIs for low back pain (Ferreira 2021). The majority of studies in Ferreira and colleagues' review and meta-analysis investigated chronic low back pain, although acute low back pain studies were also included.

Although we were unable to examine the outcomes by condition, our results are broadly in line with previous reviews. We found no high-quality or high-certainty evidence for the efficacy of amitriptyline, desipramine, desvenlafaxine, imipramine, mirtazapine, nortriptyline, or venlafaxine in any of our outcomes. Our review and NMA found that duloxetine had robust evidence and was the highest rated antidepressant for the majority of outcomes. For most outcomes, milnacipran was the second most efficacious antidepressant, although the certainty of evidence ranged between very low and moderate. For outcomes where a treatment-dose model was used, standard and high doses of both duloxetine and milnacipran were equally effective.

AUTHORS' CONCLUSIONS

Implications for practice

For people with chronic pain

Research from randomised controlled trials suggests that duloxetine is more effective than other antidepressants (including amitriptyline) for management of chronic pain. For people with chronic pain considering trying an antidepressant for pain relief, it may be worth trying duloxetine first before other antidepressants. However, it is important to acknowledge that there is no 'one size fits all' with both antidepressants and pain. Adopting a person-centred approach is critical.

For clinicians

Amitriptyline was not among the highest-ranked antidepressants in terms of efficacy for either substantial pain relief or reduction in pain intensity. The evidence suggests that generic duloxetine could be the first option when considering the use antidepressants for chronic pain management. Additionally, for duloxetine there is often no benefit to using a high dose; using a standard dose (60 mg) is often as effective as using a high dose (> 60 mg). We were unable to be certain about the adverse events and harms for any antidepressant, so this is important to consider when prescribing antidepressants for chronic pain.

For policy makers

A full analysis of international guidelines is out of scope, but the National Institute for Health and Care Excellence (NICE) guidelines for the treatment of chronic primary pain recommends antidepressants as the only pharmacological treatment option (NICE 2021). In these guidelines, NICE specifically recommend amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine, or sertraline, with no recommendations regarding dose. Our review and analyses found only moderate- to high-certainty evidence for duloxetine in the management of chronic pain, evidence for amitriptyline, citalopram, fluoxetine, paroxetine or sertraline was low quality and of very low certainty.

For funders of the intervention

Currently, amitriptyline is the most common and first-line antidepressant prescribed for the management of chronic pain; however, there are no large, high-quality studies to support this position. There is also a lack of head-to-head studies where multiple antidepressants are compared in the same study. It is important to recognise that there are no long-term safety data available for any antidepressant used for chronic pain treatment, and that collection and reporting of these data during trials is essential.

Implications for research

General implications

- For all antidepressants aside from duloxetine, there is a lack of high-quality, robust studies to establish effectiveness and safety. Amitriptyline and milnacipran particularly require further research; amitriptyline because it is the most common

antidepressant prescribed for chronic pain management, and milnacipran because it has consistently ranked equivalent or very close to duloxetine.

- Serotonin-noradrenalin reuptake inhibitors (SNRIs) as a class require further research. Duloxetine and milnacipran were consistently the highest-ranked antidepressants across outcomes. Research to identify and explore the mechanisms underpinning the effectiveness of these antidepressants is required.
- The relationship between chronic pain and depression deserves further attention. It is common in studies of analgesics to exclude participants with comorbid mental health disorders such as clinical depression, anxiety, or psychosis. As a consequence, we know nothing of the effects of antidepressants on pain in these populations. Further, depression and anxiety are common consequences of chronic pain, and often co-exist. Although the dosing schedules of anti-depressant medicines are different when prescribed for analgesia rather than depression (typically smaller) there is a possibility of dual effect, but this is not possible to study in these trials.

Design implications

- Longer trials are required: there is no evidence regarding the long-term efficacy or safety of using antidepressants for the treatment of chronic pain. This is critical as it is likely that patients will be prescribed antidepressants for long periods of time, and currently we do not know if there are likely to be any harms related to this.
- Head-to-head trials between antidepressants are required to accurately measure the effects of antidepressants for chronic pain.
- Larger sample sizes: there is no need for small trials; sufficient sizes are required to establish effect.
- There is a need for pragmatic trials with more complex designs to address changes in medication. Pragmatic trial designs that account for individual difference have been recommended for over a decade (Moore 2010c), yet the majority of studies are still designed as two-arm placebo-controlled trials.

Measurement implications

- There is now guidance on the optimal conduct and reporting of clinical trials, and specific guidance on the reporting of pain trials, the Consolidated Standards of Reporting Trials (CONSORT; Schulz 2010), and Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT; Dworkin 2008). These recommendations should be adhered to in order to reduce research waste and efficiently inform clinical decision making.
- Where applicable, both post-intervention and change scores should be reported to enable comprehensive evidence synthesis.
- If trials are reporting responder analyses (e.g. 50% pain relief), then they should also report the continuous data, to reduce the chance of Type 1 errors. Some studies in our review only reported responder analyses and could not be included in the counterpart continuous measures.
- Adverse events should be reported following the CONSORT guidelines, as highlighted many times previously (Edwards 1999; Phillips 2019).

ACKNOWLEDGEMENTS

Cochrane Review Group funding acknowledgement: this project was funded by the National Institute for Health Research (NIHR) via Cochrane Infrastructure funding to Cochrane Pain, Palliative and Supportive Care (PaPaS). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

We acknowledge and thank the NIHR Health Technology Assessment programme (HTA) for funding this review.

We thank Joanne Abbott (Information Specialist for Cochrane PaPaS Review Group) for developing and running the search strategy, and Iris Gordon (Information Specialist for Cochrane Eyes and Vision Review Group) for peer reviewing the search strategy.

We thank the peer reviewers of the protocol Dr Sarah Nevitt, Kevin Pacheco-Barrios MD, Dr Christina Abdel Shaheed, and Prof Amanda C de C Williams, and consumer reviewers Harrison Nelson and Stella O'Brien.

Editorial and peer-reviewer contributions

Cochrane Pain, Palliative and Supportive Care (PaPaS) supported the authors in the development of this review.

The following people conducted the editorial process for this article.

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- Copy-editing (initial copy-edit and final proofread): Denise Mitchell (Cochrane Evidence Production and Methods Directorate)

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CHARACTERISTICS OF STUDIES

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

29060/433

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Country: Belgium
Participants	Pain condition: fibromyalgia Population: people with fibromyalgia and depressive symptoms Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Fibromyalgia meeting ACR criteria • ≥ 4 on 0-10 pain intensity VAS • Concomitant depressive symptoms Exclusion criteria • Physical health comorbidities • Psychiatric disorders Total participants randomised: 52 Age in years (mean): 45 Gender: 12/45 were female Pain duration in years (mean, SD): NR
Interventions	Placebo

29060/433 *(Continued)*

	• n = 26 Paroxetine 20 mg • n = 26 • SSRI • Fixed dose
Outcomes	AEs SAEs Withdrawal
Missing data methods	ITT but no method reported
Funding source	Pharamaceutical: GlaxoSmithKline
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given regarding blinding procedures
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants but unsure of blinding measures
Incomplete outcome data (attrition bias) All outcomes	High risk	Use ITT for primary outcome but don't report imputation method. Completer-only analysis for the secondary outcomes **Attrition** Total: 13/52 (25.0%) Placebo: 5/26 (19.2%) Paroxetine 20 mg: 8/26 (30.8%)
Selective reporting (reporting bias)	High risk	State a number of measures that they will collect but don't report findings for (Abnormal Involuntary Movement Scale, fatigue VAS). No protocol, no publication
Other bias	High risk	Not published - just a scientific summary on GSK registry. Trial ran in 1995 but only posted in 2005

Abou-Raya 2012

Study characteristics	
Methods	Design: parallel Duration: 16 weeks Assessment: baseline and post-intervention Country: Egypt
Participants	Pain condition: knee OA Population: older adults (aged ≥ 65) with knee OA Minimum pain duration: ≥ 40 on 0 -100 scale Inclusion criteria • ACR clinical and radiographic criteria of primary knee OA • Mean knee pain intensity of at least ≥ 40 on 0-100 scale preceding week • Knee pain > 14 days/month during 3 consecutive months preceding enrolment Exclusion criteria • Morbid obesity (BMI > 32 kg/m2), joint inflammatory diseases and or crystal-induced arthropathies, or any other concomitant disease (such as neuropsychiatric disease including cognitive impairment, Alzheimer's disease, Parkinson's disease, cerebrovascular disease, cardiovascular disease, liver and renal disease) • Taking any other antidepressants that could interfere with the evaluation of the intervention Total participants randomised: 288 Age in years (mean, SD): 68.5 (SD NR) Gender: 241/288 were female
Interventions	Duloxetine • 144 participants • 60 mg/day Placebo • 144 participants • Matched to duloxetine
Outcomes	Pain intensity Physical function Mood AE SAE Withdrawal
Missing data methods	ITT but method not specified

Abou-Raya 2012 *(Continued)*

Funding source	Non-pharmaceutical: sponsored by University of Alexandria, Egypt
Conflicts of interest	Author conflicts of interest NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised by a clinical pharmacist using a computerised random number list.
Allocation concealment (selection bias)	Low risk	Allocation was concealed in sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, and placebo was identical to duloxetine.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	States ITT but no imputation method reported **Attrition:** Total: 34/288 (11.8%) Placebo: 13/144 (9.0%) Duloxetine 60 mg: 21/144 (14.6%)
Selective reporting (reporting bias)	Unclear risk	Protocol registered retrospectively: https://clinicaltrials.gov/show/NCT01425827 2011: Pain is the only stated outcome in the trial registry
Other bias	Low risk	No other sources of bias were identified.

Agger 2017

Study characteristics

Methods	Design: parallel Duration: 15 weeks Assessment: baseline and post-intervention (15 weeks) Country: Denmark
Participants	Pain condition: multiorgan bodily distress syndrome (including fibromyalgia, IBS, and non-cardiac chest pain) Population: adults aged 20-50 with a diagnosis of chronic multi-organ bodily distress syndrome

Agger 2017 *(Continued)*

	Minimum pain duration: no Inclusion criteria • A diagnosis of chronic (i.e. minimum 2 years) multi-organ bodily distress syndrome, which requires functional somatic symptoms from at least 3 of 4 bodily systems, leading to moderate or severe impairment in daily living • The diagnosis was established by a medical doctor after a thorough physical and psychological assessment including diagnostic interview (Schedules for Clinical Assessment in Neuropsychiatry), physical examination, blood test, ECG, and a close review of all medical records Exclusion criteria • Lifetime diagnosis of psychosis, mania, or depression with psychotic symptoms • Concurrent severe psychiatric disorder demanding treatment—e.g. current depressive episode • Undergoing concomitant treatment with antidepressants, anticonvulsants, analgesics, or other medication with pain-relieving properties were excluded, unless this medication could be discontinued • Imipramine treatment in sufficient dosage within the past year; known hypersensitivity to or intolerance of imipramine; abuse of alcohol, narcotics, or illicit drugs; physical comorbidity that would make imipramine inappropriate, including arrhythmias, epilepsy, hepatic insufficiency; absence of use of contraception for female participants; pregnancy and breastfeeding; and use of medication that would interact with imipramine Total participants randomised: 139 Age in years (mean, SD): NR Gender: 94/139 were female
Interventions	Imipramine • 70 participants • Flexible dose, 25-75 mg/day depending on tolerance Placebo • 68 participants • Matched dosing schedule
Outcomes	AE Withdrawal
Missing data methods	ITT but imputation method NR
Funding source	Non-pharmaceutical: The Research Clinic for Functional Disorders, Aarhus University Hospital, Denmark
Conflicts of interest	JLA, AS, LKG, JSJ, and PKF declare no competing interests. TSJ reports personal fees from Pfizer and Mundipharma, outside the submitted work.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation code was generated by a trained, but independent employee at the hospital pharmacy at Aarhus University Hospital through a web--based system.

Agger 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	Coded (numbered) packs of study drug and matched placebo were produced according to the randomisation schedule by the hospital pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study, with medications over-encapsulated by the hospital pharmacy to ensure identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT but no imputation method given **Attrition:** Total: 21/139 (15.1%) Placebo: 15/68 (22.1%) Imipramine 25-75 mg: 13/70 (18.6%)
Selective reporting (reporting bias)	High risk	Published article reports slightly different registered outcomes to those mentioned in the protocol: https://clinicaltrials.gov/ct2/show/NCT01518634 They registered they will measure VAS for pain and the FIC checklist but do not report VAS and use a different checklist.
Other bias	Low risk	No other sources of bias were identified.

Ahmed 2016

Study characteristics	
Methods	Design: cross-over Duration: 6 weeks Assessment: baseline and post-intervention (6 weeks) Country: USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia and clinically significant sleep disturbance Inclusion criteria • Adults with fibromyalgia as defined by ACR 1990 criteria • Clinically significant sleep disturbance, defined as subjective complaint of maintaining sleep at least 3 times per week for at least 1 month Exclusion criteria • Liver disease, blood disorder, autoimmune disease, endocrine, cardiovascular, hypertension, renal, hepatic, gastrointestinal, or neurological disorder, active peptic ulcer or inflammatory bowel disease, significant sleep apnoea, periodic leg movement disorder (PLMD) or restless legs syndrome (RLS), uncontrolled glaucoma

Ahmed 2016 *(Continued)*

	• Any form of severe psychiatric illness, moderate to severe depression, including significant risk of suicide Total participants randomised: 19 Age in years (mean, SD): 49.2 Gender: 17/19 were female
Interventions	Milnacipran • 19 participants • Fixed dose of 100 mg/day • 50 mg taken twice daily (morning and evening) Placebo • 19 participants • Matching dose schedule
Outcomes	Sleep Quality of life Pain intensity AE SAE Withdrawal
Missing data methods	LOCF
Funding source	Pharmaceutical: Forest Research Institute, New Jersey, USA
Conflicts of interest	Authors indicated no other financial conflicts of interest
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers were used for enrollment and allocation to sequence (1:1): milnacipran → placebo or placebo → milnacipran
Allocation concealment (selection bias)	Low risk	The investigator, clinical staff, participants, and the study sponsor were blinded to sequence allocation. A noninvolved staff member generated the random allocation sequence and kept an electronic copy in a secure location.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drug was supplied as masked tablets of milnacipran and matching placebos.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes self-reported by blinded participants

Ahmed 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Only use LOCF and unbalanced dropout **Attrition:** Total: 4/19 (21.1%) Placebo: 1/19 (5.5%) Milnacipran 100 mg: 3/19 (16.7%)
Selective reporting (reporting bias)	Low risk	Trial registered prospectively: https://clinicaltrials.gov/show/NCT01234675 Study outcomes reported match those in the protocol
Other bias	Low risk	No other sources of bias were identified

Alcoff 1982

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention (8 weeks) Country: USA
Participants	Pain condition: low back pain Population: adults with chronic low back pain Inclusion criteria • Low back pain for at least 6 weeks if first episode, or ≥ 2 prior episodes lasting at least 2 weeks with a current episode of a minimum of 2 weeks' duration Exclusion criteria NR, but the following potential participants were excluded: • 1 person had a persistent diastolic blood pressure reading of > 90 mm Hg • 1 person had ECG changes consistent with an old myocardial infarction Total participants randomised: 50 Age in years (mean, SD): NR Gender: 24/50 were female Pain duration (categorical): < 2 years (n = 8), 2–4 years (n = 6), > 4 years (n = 14)
Interventions	Imipramine • 28 participants • Fixed dose of 150 mg/day Placebo • 22 participants

Alcoff 1982 *(Continued)*

- Identical appearance and dosing to imipramine

Outcomes	Withdrawal
Missing data methods	NR
Funding source	Non-pharmaceutical: the Bureau of Medicine and Surgery, Department of the Navy, Clinical Investigation Program, USA
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not enough information - just says 'randomly assigned'
Allocation concealment (selection bias)	Unclear risk	Only the pharmacist knew the treatment allocation, but unclear how this was allocated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo was identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data methods NR and unequal attrition between arms **Attrition:** Total: 9/50 (18.0%) Placebo attrition: 2/22 (9.1%) Imipramine 150 mg: 7/28 (25.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias identified

Allen 2014

Study characteristics

Methods	Design: parallel Duration: 13 weeks Assessment: baseline and post-intervention (13 weeks)

Allen 2014 *(Continued)*

	Country: USA
Participants	Pain condition: diabetic peripheral neuropathy Population: adults with diabetic peripheral neuropathy Inclusion criteria • Male and female outpatients with diabetes, stable and optimised glycaemic control for at least 3 months before the study • Clinically and/or neurophysiologically diagnosed painful diabetic distal symmetric sensorimotor polyneuropathy affecting primarily the lower extremities, and symptoms that included chronic paraesthesias, dysaesthesias, hyperaesthesia, hyperalgesia, or allodynia or some combination of these symptoms in the lower extremities for > 6 months • A score of ≥ 3 on the physical examination portion of the MNSI at screening and baseline • An average pain score of at least 4 (where 0 = no pain and 10 = worst possible pain) on the NRS for symmetrical neuropathic pain in the feet and legs, based on the last 7 daily scores recorded before randomisation Exclusion criteria • Any previous treatment with desvenlafaxine or previous treatment with venlafaxine that could not be tolerated, had a history of drug allergies that the investigator believed would put the patient at risk, had significant asymmetrical neuropathic signs and symptoms or a neuropathy that was not due to diabetes, had other pain or any condition that may have confounded interpretation of symptoms in the lower leg and/or feet, or had suffered foot ulcers or amputation affecting all or part of a foot or toes • Peripheral vascular disease manifested by ischaemic claudication; MDD; evidence of significant risk of suicide or self-harm; uncontrolled hypertension; symptoms of orthostatic hypotension; raised intraocular pressure; elevated total cholesterol or triglycerides; unstable renal disease (creatinine clearance, 50 mL/min); gastrointestinal disease or surgery known to interfere with the absorption or excretion of drugs; current major illness or clinically important medical disease that might put the patient at risk during the study; history of any of the following: seizure disorder; neoplastic disorder within 5 years; myocardial infarction within 6 months; stroke or transient ischaemic attack within 3 years; narrow angle glaucoma; or clinically important abnormalities on screening physical examination, ECG, laboratory evaluation, or urine drug screen Total participants randomised: 412 Age in years (mean, SD): 60.3 (SD NR) Gender: 108/412 were female Pain duration: NR
Interventions	Desvenlafaxine 50 mg • 63 participants • Fixed dose of 50 mg/day Desvenlafaxine 100 mg • 87 participants • Fixed dose of 100 mg/day Desvenlafaxine 200 mg • 99 participants • Fixed dose of 200 mg/day Desvenlafaxine 400 mg • 69 participants

Allen 2014 *(Continued)*

	• Fixed dose of 400 mg/day Placebo • 90 participants
Outcomes	Pain intensity 50% pain reduction PGIC AE SAE Withdrawal
Missing data methods	LOCF
Funding source	Pharmaceutical: sponsored by Wyeth, company now owned by Pfizer
Conflicts of interest	Rob Allen, is a former Pfizer employee currently working as an independent consultant. Suna Barlas, is a Pfizer employee. Uma Sharma, is a former Pfizer employee and currently works at MMS Holdings Inc.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blinding of all patients and site personnel to treatment allocation was ensured by using a computerised randomisation/enrollment system to assign participant numbers and study drug package numbers
Allocation concealment (selection bias)	Low risk	Study drug package numbers were produced by the computer-randomised system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear as to whether placebo was identical to desvenlafaxine medication
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes by participants, but unclear blinding procedures regarding medication appearance
Incomplete outcome data (attrition bias) All outcomes	High risk	LOCF and unbalanced attrition across arms **Attrition:** Total: 107/412 (30.0%) Placebo: 15/90 (16.7%) Desvenlafaxine 50 mg: 12/63 (19.0%) Desvenlafaxine 100 mg: 18/87 (20.7%) Desvenlafaxine 200 mg: 31/99 (31.3%) Desvenlafaxine 400 mg: 27/69 (39.1%)

Allen 2014 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The 2 stated in the protocol are reported in the paper, but the article also reports other outcomes that were not included in the protocol.
Other bias	Low risk	No other sources of bias identified

Allen 2017

Study characteristics	
Methods	Design: parallel Duration: 15 weeks (intended to be 27 weeks but terminated early) Assessment: baseline, study termination (15 weeks) Country: USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Inclusion criteria • fibromyalgia diagnosis according to the ACR 1990 diagnostic criteria, including widespread pain for > 3 months with at least 11 of 18 defined tender points on examination at screening and baseline. • Average pain score of ≥ 4 on the 0-10 NRS Exclusion criteria • Previous treatment with desvenlafaxine, a history of intolerance of venlafaxine, or a history of drug allergies, pregnancy or breastfeeding, history of seizure disorder, neoplastic disorder within 5 years, myocardial infarction within 6months, stroke or transient ischaemic attack within 3 years, narrow-angle glaucoma, or clinically important abnormalities on screening • The presence of a clinically important medical disease, presence or history of psychotic, bipolar, or major depressive disorder, alcohol or drug abuse/dependence, or evidence of significant risk of suicide or self -harm Total participants randomised: 697 Age in years (mean, SD): NR Gender: NR Pain duration: NR
Interventions	Desvenlafaxine 50 mg • 136 participants • fixed dose of 50 mg/day Desvenlafaxine 100 mg • 139 participants • fixed dose of 100 mg/day Desvenlafaxine 200 mg • 142 participants • fixed dose of 200 mg/day

Allen 2017 *(Continued)*

	Desvenlafaxine 400 mg • 149 participants • fixed dose of 400 mg/day Placebo • 130 participants
Outcomes	Pain intensity 50% pain reduction PGIC AE SAE Withdrawal
Missing data methods	LOCF
Funding source	Pharmaceutical: Wyeth Research, now incorportated into Pfizer
Conflicts of interest	Rob Allen, MD, is a former Pfizer employee currently working as an independent consultant. Suna Barlas, PhD, is a Pfizer employee. Uma Sharma, PhD, is a former Pfizer employee and currently works at MMS Holdings Inc.
Notes	Study terminated early (at 15 weeks instead of 27 weeks) due to interim efficacy analysis not meeting the preplanned efficacy criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not enough information - just says 'randomly assigned'
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on matching appearance or dosing schedules of antidepressants and placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes by participants, but blinding information unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	Study terminated, so missing data from all time points past 15 weeks. LOCF. Very high attrition across all arms before study termination. **Attrition:** Total: 445/697 (63.8%) Placebo: 84/130 (67.7%) Desvenlafaxine 50 mg: 87/136 (66.0%)

Allen 2017 *(Continued)*

		Desvenlafaxine 100 mg: 81/140 (62.0%) Desvenlafaxine 200 mg: 100/142 (76.0%) Desvenlafaxine 400 mg: 93/149 (67.0%)
Selective reporting (reporting bias)	Low risk	Protocol stated the interim analyses
Other bias	Low risk	Study terminated early, but this was due to interim efficacy analyses not meeting the prespecified criteria.

Anderberg 2000

Study characteristics	
Methods	Design: parallel Duration: 16 weeks Assessment: baseline and post-intervention Country: Sweden
Participants	Pain condition: fibromyalgia Population: women with fibromyalgia Minimum pain duration: no Inclusion criteria • Diagnosis of fibromyalgia fulfilling the ACR criteria (1990) Exclusion criteria • Patients with any severe heart diseases, such as angina pectoris or post-heart infarction, or other severe heart diseases, as well as brain infarction, suicidal thoughts or who were seriously depressed (in need of immediate psychiatric care) • Patients taking major or minor tranquillisers, major antidepressants or strong analgesics Total participants randomised: 40 Age in years (mean, SD): 48.6 (7.5) Gender: 40/40 were female Pain duration: 11.9 (7.0) years average duration of fibromyalgia
Interventions	Citalopram • 30-40 mg/ day • Flexibly dosed • Titrated from 10/20 mg to 30/40 mg in 5 mg doses every 5 days Placebo • Inert • Matched dosing schedule
Outcomes	AE

Anderberg 2000 *(Continued)*

	Withdrawal
Missing data methods	ITT but no method reported
Funding source	The study was supported by grants from H. Lundbeck AB, the Söderström Königska Foundation, the Swedish Association of Physicians, the Märta and Nicke Nasvell Foundation, the Swedish Health Insurance System, the Uppsala County Council and 'Förenade Liv' Mutual Group Life Insurance Company, Stockholm, Sweden and the Swedish Medical Research Council (21X-9523)
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Low risk	Randomisation was made at a separate agency, and the investigator had a coded list. Included patients were given consecutive code numbers.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given regarding appearance of placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough information given
Incomplete outcome data (attrition bias) All outcomes	High risk	Unequal attrition, states ITT but no method given **Attrition:** Total: 5/40 (12.5%) Placebo: 1/19 (5.26%) Citalopram 30-40 mg: 4/21 (19.1%)
Selective reporting (reporting bias)	Low risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Ang 2013

Study characteristics

Methods	Design: parallel Duration: 21 weeks Assessment: baseline and post-intervention (21 weeks)

Ang 2013 *(Continued)*

	Country: USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: ≥ 4 out of 10 Inclusion criteria • People aged 18- 65 with a diagnosis of fibromyalgia made by a rheumatologist matching the ACR criteria. On stable doses of current medication for at least 4 weeks • Have a weekly average pain intensity score as recorded by wristwatch monitor of ≥ 4 out of 10, and report that fibromyalgia limits ability to perform daily activities. Exclusion criteria • Uncontrolled hypertension; history of heart disease, glaucoma, or hepatitis; diagnosis of peripheral neuropathy; diagnosed with another major rheumatic conditions (i.e. RA, systemic lupus erythematosus, scleroderma and other connective tissue diseases) BMI of > 34; frequent thoughts of suicide or self-harm; currently pregnant or planning to become pregnant, or breastfeeding; diagnosis of schizophrenia or bipolar disorder; currently taking fluoxetine, paroxetine, citalopram, sertraline, escitalopram, venlafaxine, mirtazapine or duloxetine; currently participating in other pain research; have been previously enrolled in any study or class that includes CBT or education to help control pain or stress related to fibromyalgia Total participants randomised: 58 Age in years (mean, SD): 46.59 (10.39) Gender: 54/58 were female Pain duration: average duration since fibromyalgia of 12.07 (10.04) years
Interventions	CBT • 8 telephone-delivered therapy sessions from baseline to week 9, with a companion handbook for home practice. • Inert placebo pill to match antidepressant doses CBT + milnacipran • Milnacipran 100 mg/day combined with 8 weekly telephone-delivered therapy sessions from baseline to week 9, with a companion handbook for home practice • Milnacipran doses titrated over 8 days until participants were taking 50 mg twice a day. Milnacipran + education • Milnacipran 100 mg/day combined with 8 weekly telephone general pain education sessions delivered from baseline to week 9 • Milnacipran doses titrated over 8 days until participants were taking 50 mg twice a day.
Outcomes	Pain intensity Moderate pain relief Physical function Quality of life Depression AEs

Ang 2013 *(Continued)*

	SAEs Withdrawal
Missing data methods	NR
Funding source	National Institute of Arthritis and Musculoskeletal and Skin Diseases (Grant number: 1R21AR056046-01A2). The authors thank Forest Research Institute for providing the active drug and placebo.
Conflicts of interest	Authors state no conflicts of interest to declare
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Does not report how the participants were randomised - just says "participants were randomised to one of the three treatment arms".
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	The professionals delivering the CBT and education sessions are authors on the paper, and would have been unblinded to participant selection
Blinding of outcome assessment (detection bias) All outcomes	High risk	Participants likely to identify which psychological therapy group they were in, and study authors did not report participants' identification of group assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing data methods reported **Attrition:** Total: 9/58 (15.5%) CBT: 4/19 (21.1%) CBT + milnacipran: 3/20 (15.0%) Education + milnacipran: 2/19 (10.5%)
Selective reporting (reporting bias)	High risk	Stated in the protocol that they would measure participants' identification of group assignment but NR.
Other bias	Low risk	No other sources of bias were identified

Aragona 2005

Study characteristics

Methods	Design: parallel Duration: 8 weeks

Aragona 2005 *(Continued)*

	Assessment: baseline and post-intervention Country: Italy
Participants	Pain condition: somatoform DSM-IV-TR pain disorder Population: people with somatoform DSM-IV-TR pain disorder Minimum pain intensity: no Inclusion criteria • People with DSM-IV-TR pain disorder as assessed by clinicians. Pain had to have no direct, organic explanation, and participants had to have presence of psychological factors that could have influenced consent/clinical course of pain. Exclusion criteria • Pregnancy • Medical conditions of clinical importance • Diagnosis of another mental health condition Total participants randomised: 35 Age in years (mean, SD): NR Gender: 21/35 were female Pain duration: NR
Interventions	Citalopram • Fixed dose of 40 mg/day (2 x 20 mg doses) • Titrated over 4 days • SSRI Reboxetine • Fixed dose of 8 mg/day (2 x 4 mg doses) • Titrated over 4 days • NaRI
Outcomes	Pain intensity Depression AEs SAEs Withdrawal
Missing data methods	LOCF
Funding source	NR
Conflicts of interest	NR
Notes	
Risk of bias	

Aragona 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned using random tables
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given regarding appearance of medications
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given regarding appearance of medications
Incomplete outcome data (attrition bias) All outcomes	High risk	Used LOCF as imputation method, high attrition **Attrition:** Total: 6/35 (17.1%) Citalopram 40 mg: 6/17 (35.3%) Reboxetine 8 mg: 9/18 (50.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Arnold 2002

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: women with fibromyalgia Minimum pain intensity: no Inclusion criteria • Aged over 18 and meeting the ACR 1990 criteria for fibromyalgia Exclusion criteria • Evidence of traumatic injury, inflammatory rheumatic disease, or infectious or endocrine-related arthropathy; clinically unstable medical illness; a history of seizure, head trauma, or stroke; a lifetime history of hypomania, mania, psychosis, or dementia; alcohol or substance dependence during the

Arnold 2002 *(Continued)*

	past 6 months; a substantial risk of suicide; any current Axis I diagnosis; or a score of ≥ 10 on the 17-item Hamilton Depression Rating Scale. • Received monoamine oxidase inhibitors, tricyclics, lithium, SSRIs, or other antidepressants within 2 weeks before randomisation; received investigational medications within 3 months before randomisation; or previously received fluoxetine for fibromyalgia Total participants randomised: 60 Age in years (mean, SD): 46 (11) Gender: 46/46 were female Pain duration: average duration of fibromyalgia was 11 (9) years
Interventions	Fluoxetine • SSRI • Flexibly dosed depending upon tolerance and improvement: starting dose 20 mg/day, maximum dose 80 mg/day • Mean dose was 45 mg/day Placebo • Inert • Identical capsules to fluoxetine, with matched titration process
Outcomes	Pain intensity Quality of life Depression Physical function Withdrawal
Missing data methods	LOCF
Funding source	Pharmaceutical: Eli Lilly
Conflicts of interest	NR, but authors in other papers have declared conflicts of interest regarding involvement with Eli Lilly
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not enough information - just says that participants were 'randomly assigned'
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules and titration process
Blinding of outcome assessment (detection bias)	Low risk	Self-reported outcomes from blinded participants

Arnold 2002 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition and used LOCF **Attrition:** Total: 23/60 (38.3%) Placebo: 12/30 (40.0%) Fluoxetine 10- 30 mg: 11/30 (36.7%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Arnold 2004

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention (12 weeks) Country: USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia with and without MDD Minimum pain intensity: ≥ 4 out of 10 Inclusion criteria • ≥ 8 years of age and met the ACR criteria for fibromyalgia • Score ≥ 4 on the pain intensity item of the Fibromyalgia Impact Questionnaire (with 10 indicating very severe pain) at visits 1 and 2 • Have an educational level and degree of understanding that allowed them to communicate intelligibly. Exclusion criteria • Pain from traumatic injury or structural or regional rheumatic disease; RA, inflammatory arthritis, or autoimmune disease; unstable medical or psychiatric illness; current dysthymia, which is more treatment-resistant than major depression, or primary psychiatric disorder other than MDD; substance abuse in the last year; history of psychosis; pregnancy or breastfeeding; unacceptable contraception in those of childbearing potential; or involvement in disability reviews that might compromise treatment response • Use of an investigational drug within 30 days; prior participation in a study of duloxetine; severe allergic reactions to multiple medications; intolerance to 3 psychoactive drugs or 1 SSRI; and failure to respond to 2 adequate regimens of 2 different classes of antidepressants for depression or fibromyalgia Total participants randomised: 207 Age in years (mean, SD): Gender: 184/200 were female

Arnold 2004 *(Continued)*

	Pain duration: NR
Interventions	Duloxetine • SNRI • Fixed dose of 120 mg/day, 2 x 60 mg doses • Forced titration from 20 mg/day to 120 mg/day over 2 weeks Placebo • Inert • Identical dosing strategy to duloxetine
Outcomes	Pain intensity Quality of life Physical function Mood PGIC AEs Withdrawal
Missing data methods	Mixed-effects model and LOCF
Funding source	Pharmaceutical - Eli Lilly
Conflicts of interest	Drs Crofford and Arnold have received consulting fees or honoraria in the last 2 years from Eli Lilly and Company (DrCrawford USD 10,000, Dr Arnold USD 10,000). In addition to the authors employed by Eli Lilly and Company listed above, Dr Goldstein's wife is employed by Eli Lilly and Company
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment to treatment groups was determined by a computer-generated random sequence.
Allocation concealment (selection bias)	Low risk	Participants were allocated using an interactive voice response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matched appearance and dosing schedule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition, unequal reasons for dropout, used LOCF **Attrition:** Total: 83/207 (40.1%)

Arnold 2004 *(Continued)*

		Placebo: 37/103 (35.9%) Duloxetine 120 mg: 46/104 (44.2%)
Selective reporting (reporting bias)	Unclear risk	Trial registration was retrospective.
Other bias	Low risk	No other sources of bias were identified.

Arnold 2005

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: women with fibromyalgia, with and without MDD Minimum pain intensity: ≥ 4 out of 10 Inclusion criteria • Female outpatients aged ≥ 18 who met the criteria for primary fibromyalgia as defined by the ACR • Had a score of ≥ 4 on the average pain severity item of the Brief Pain Inventory at randomisation Exclusion criteria • Pain from traumatic injury or structural or regional rheumatic disease; RA, inflammatory arthritis, or autoimmune disease; unstable medical or psychiatric illness; current primary psychiatric diagnosis other than MDD, a primary anxiety disorder within the past year (specific phobias allowed); substance abuse within the past year; serious suicide risk; pregnancy or breastfeeding. • Women who, in the opinion of the investigator, were treatment refractory or may have had an involvement in disability reviews that might compromise treatment response; severe allergic reactions to multiple medications; or prior participation in a study of duloxetine Total participants randomised: 354 Age in years (mean, SD): 49.6 (10.9) Gender: 354/354 were female Pain duration: NR
Interventions	Duloxetine 60 mg • SNRI • Fixed dose of 60 mg/day Duloxetine 120 mg • SNRI • Fixed dose of 120 mg/day, titrated from 60 mg/day over 3 days Placebo

Arnold 2005 *(Continued)*

	• Inert
Outcomes	Pain intensity Quality of life Physical function Mood Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	LOCF
Funding source	Pharmaceutical - Eli Lilly
Conflicts of interest	NR, but have declared COIs in other papers with this sponsor/funder
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information regarding randomisation procedures given
Allocation concealment (selection bias)	Unclear risk	No information regarding allocation concealment given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information regarding matched dose schedules or identical appearance of medications given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, uncertain about blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition and significantly different reasons for dropout between groups. Used LOCF **Attrition:** Total: 138/354 (39.0%) Placebo: 52/121 (43.0%) Duloxetine 60 mg: 41/117 (35.0%) Duloxetine 120 mg: 45/115 (39.1%)

Arnold 2005 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Arnold 2010a

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention (8 weeks) Country: USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: ≥ 40 on 0-100 VAS Inclusion criteria • People aged ≥ 18 meeting the ACR criteria for fibromyalgia (widespread pain for at least 3 months, and pain in at least 11 of 18 specific tender point sites) • Score of ≥ 40 on 100 mm ViAS of the Short Form McGill Pain Questionnaire Exclusion criteria • Other severe pain conditions; severe hepatic impairment; any inflammatory musculoskeletal disorder; rheumatic disease; active infection; untreated endocrine disorder; previous or current significant psychiatric disorder; severe depression (in the investigator's judgement); serious suicide risk; seizure disorder; uncontrolled narrow-angle glaucoma; recurrent syncope or evidence of low blood pressure; symptomatic postural hypotension; significant or unstable medical or psychological conditions; pregnancy, use of an unacceptable mode of contraception, or breastfeeding; or involvement in disability claims, civil litigation, or workman's compensation claims for fibromyalgia • Exclusions based on concomitant medications or treatments included tender-point injections and use of fluoxetine or opioids within 30 days before the study; use of thioridazine or inhibitors of cytochrome P450 3A4 within 14 days before the study; use of muscle relaxants, antidepressants, anticonvulsants, oral steroids, mexiletine, dopamine agonists, long-acting benzodiazepines, acupuncture, or TENS within 7 days before the study; and use of diphenhydramine or melatonin within 1 day before the study. Total participants randomised: 268 Age in years (mean, range): 50 (20-84) Gender: 239/268 were female Pain duration in years (mean, range): 7 (0-46.8)
Interventions	Esreboxetine • SNRI • Initial dose 2 mg/day, titrated to individual tolerability by 2 mg/day to a maximum of 8 mg/day Placebo

Arnold 2010a *(Continued)*

	• Inert • Matched appearance
Outcomes	Pain intensity Quality of life Sleep Mood Physical function Moderate pain relief Substantial pain relief PGIC AEs SAEs
Missing data methods	LOCF
Funding source	Pharmaceutical - Pfizer
Conflicts of interest	Dr Arnold has received grants/research support from Allergan, Boehringer Ingelheim, Cypress Biosciences Inc., Forest Laboratories Inc., Eli Lilly and Company, Pfizer Inc., Sanofi-Aventis, and Wyeth Pharmaceuticals. She has been a consultant for Allergan, AstraZeneca, Boehringer Ingelheim, Cypress Biosciences, Forest Laboratories, Eli Lilly and Company, Organon, Pfizer, sanofi-aventis, Sepracor, Takeda, Theravance, Inc., DCB, Vivus, Inc., and Wyeth. She has served on speakers' bureaus for Forest Laboratories, Eli Lilly and Company, and Pfizer. Drs Chatamra, Hirsch, and Stoker were employees of Pfizer at the time of the study. They have indicated that they have no other conflicts of interest with regard to the content of this article.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation to treatment groups was performed according to a computer-generated randomisation code.
Allocation concealment (selection bias)	Low risk	Allocation was managed through a centralised telerandomisation system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo matched appearance and dose
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Equal attrition (20%), LOCF supplemented by BOCF **Attrition:**

Arnold 2010a *(Continued)*

		Total: 55/267 (20.5%) Placebo: 27/133 (20.3%) Esreboxetine: 27/134 (20.1%)
Selective reporting (reporting bias)	Unclear risk	Some changes in what were secondary or primary outcomes, not 100% lining up with protocol but primary outcome remains the same
Other bias	Low risk	No other sources of bias were identified.

Arnold 2010b

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention (12 weeks) Country: USA and Canada
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: ≥ 40 on 0-100 VAS Inclusion criteria • People aged 18-70 who met the ACR 1990 criteria for fibromyalgia • Patients were required to have a raw score of 4 on the physical function domain of the Fibromyalgia Impact Questionnaire at screening and a mean VAS pain score of between 40 and 90 on the electronic patient experience diary 24-hour recall pain report (0-100 VAS) during the 14-day baseline period Exclusion criteria • Other rheumatic or medical conditions that displayed symptoms similar to fibromyalgia; previous exposure to milnacipran; treatment with an investigational drug within 30 days of screening; BDI score > 25 at screening or baseline; current major depressive episode as determined by the MINI; significant risk of suicide according to the investigator's judgement or the results of the MINI or the BDI; lifetime history of psychosis, hypomania, or mania, substance abuse; other severe psychiatric illness as determined by investigator judgement; history of behaviour that would, in the investigator's judgement, prohibit compliance for the duration of the study; active or pending disability claim; worker's compensation claim, or litigation; pregnancy or breastfeeding; unacceptable contraception method; active or unstable medical illness • Concomitant treatments considered to be criteria for exclusion included digitalis; centrally acting medications for fibromyalgia; TENS; biofeedback; tender and trigger point injections; acupuncture; and anaesthetic or narcotic patches Total participants randomised: 1025 Age in years (mean, SD): NR Gender: 977/1025 were female Pain duration in years (mean): 10.8
Interventions	Milnacipran

Arnold 2010b *(Continued)*

- n = 516
- SNRI
- 100 mg/day, forced titration over 6 weeks

Placebo

- n = 509
- Inert
- Matched appearance and dosing schedule

Outcomes	Pain intensity Physical function Mood Quality of life Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	BOCF
Funding source	Pharmaceutical - Forest Laboratories
Conflicts of interest	Dr Arnold has received consulting fees, speaking fees, and/or honoraria from Cypress Bioscience, Wyeth, Boehringer Ingelheim, Allergan, Takeda, UCB, Theravance, AstraZeneca, and Sanofi-Aventis (less than USD 10,000 each) and from Eli Lilly, Pfizer, and Forest Laboratories (> USD 10,000 each) and has received research support from Eli Lilly, Cypress Bioscience, Wyeth, Boehringer In-gelheim, Allergan, Forest Laboratories, and Pfizer. Drs R. M. Gendreau and J. F. Gendreau own stock or stock options in Cypress Bioscience. Drs Palmer and Wang own stock or stock options in Forest Laboratories.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation assignment by computer code in blocks of 4
Allocation concealment (selection bias)	Low risk	Assignment to treatment groups was conducted centrally (i.e. at the study level) using an interactive voice response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo appearance and matched dosing schedule
Blinding of outcome assessment (detection bias)	Low risk	Self-reported outcomes from blinded participants

Arnold 2010b *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar attrition across both arms, BOCF used for imputation **Attrition:** Total: 309/1025 (30.1%) Placebo: 150/509 (29.5%) Milnacipran 100 mg: 159/516 (30.8%)
Selective reporting (reporting bias)	Low risk	Trial registered prospectively on clinicaltrials.gov
Other bias	Low risk	No other sources of bias were identified.

Arnold 2010c

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention (12 weeks) Country: USA and Puerto Rico
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: ≥ 4 out of 10 Inclusion criteria • Aged ≥ 18, met the criteria for fibromyalgia as defined by the ACR • Scored ≥ 4 on the average pain item of the Brief Pain Inventory Short Form at visit 1 and visit 2. Exclusion criteria • Current or diagnosed within the past year with any primary psychiatric disorder other than MDD or GAD defined by the DSM-IV; clinically judged to be at serious risk of suicide; had any unstable medical illness that was likely to require intervention or hospitalisation; pain symptoms unrelated to fibromyalgia that could interfere with interpretation of outcome measures; regional pain syndromes; multiple surgeries or failed back syndrome; a confirmed current or previous diagnosis of RA, inflammatory arthritis, or other autoimmune disease; severe liver disease; pregnant or breastfeeding; or history of substance abuse within the past year • Treated with an adequate trial of duloxetine and did not respond or could not tolerate duloxetine; were judged by the opinion of the investigator to be treatment-refractory in fibromyalgia; or those in whom treatment response might be compromised by disability compensation issues Total participants randomised: 530 Age in years (mean, SD): 50.2 (11.1) Gender: 494/530 were female Pain duration in years: NR

Arnold 2010c *(Continued)*

Interventions	Duloxetine • n = 263 • SNRI • 3 doses depending on patient tolerability: 60 mg/day, 90 mg/day, or 120 mg/day • Mean dose 81.7 mg/day Placebo • n = 267 • Inert • Identical appearance
Outcomes	Pain intensity Mood Physical function Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	LOCF and MMRM
Funding source	Pharmaceutical - Lilly USA LLC
Conflicts of interest	Dr Mease has received grants/research support from Eli Lilly and Company; Pfizer, Inc; Cypress Bioscience, Inc; Forest Laboratories, Inc; Allergan; Fralex; and Boehringer Ingelheim. He has been a consultant for Eli Lilly and Company; Pfizer, Inc; Cypress Bioscience, Inc; Forest Laboratories, Inc; Allergan; Fralex; Boehringer Ingelheim; Pierre Fabre; and Wyeth; and he is on the Speakers Bureau of Pfizer, Inc. Dr Arnold has received grants/research support from Eli Lilly and Company; Pfizer, Inc; Cypress Bioscience, Inc; Boehringer Ingelheim; and Forest Laboratories, Inc, and received honoraria as a consultant to Eli Lilly and Company; Pfizer, Inc; Cypress Bioscience, Inc; Boehringer Ingelheim; Forest Laboratories, Inc; Allergan; Takeda; UCB Inc.; Theravance; AstraZeneca; Sanofi-Aventis; and Grunenthal. Drs Mohs, Ahl, Gaynor, and Wohlreich are all employees and stockholders in Eli Lilly andCompany. Dr Wang is a former employee of Lilly USA, LLC.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Allocation was managed using an Interactive Voice Response System.

Arnold 2010c *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Good blinding procedures, identical appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	HIgh attrition but equal, ITT with LOCF and BOCF **Attrition:** Total: 167/530 (31.5%) Placebo: 80/267 (30.0%) Duloxetine 60-120 mg: 87/263 (33.1%)
Selective reporting (reporting bias)	Low risk	Trial registered prospectively and all outcomes reported
Other bias	Low risk	No other sources of bias were identified.

Arnold 2012a

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention (12 weeks) Country: USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: ≥ 4 out of 10 Inclusion criteria • People aged ≥ 18 who met the ACR 1990 criteria for primary fibromyalgia • Patients with MDD or GAD were included Exclusion criteria • Prior treatment with duloxetine; prior participation in a duloxetine study; a history of substance abuse within the past year; a primary psychiatric disorder other than MDD or GAD within the last year; a history of psychosis or bipolar disorder; clinically judged to be at risk of suicide; pregnant or breast-feeding; pain symptoms unrelated to fibromyalgia that could interfere with interpretation of outcome measures; regional pain syndromes; failed back syndrome; chronic localized pain related to any past surgery, and a confirmed current or previous diagnosis of RA; inflammatory arthritis, or infectious arthritis; or an autoimmune disease • Patients who, in the opinion of the investigator, were judged to be treatment-refractory or whose response might be compromised by disability compensation, or had an unstable medical condition were also excluded

Arnold 2012a *(Continued)*

	Total participants randomised: 308 Age in years (mean): 51 Gender: 95.2% were female Pain duration in years (mean): 6.5
Interventions	Duloxetine • n = 155 • SNRI • Fixed dose of 30 mg/day (participants with MDD whose depression worsened during the trial had their dose increased to 60 mg/day) Placebo • n = 153 • Inert • Matched appearance to duloxetine
Outcomes	Pain intensity Mood Quality of life Moderate pain relief Substantial pain relief PGIC Adverse SAE Withdrawal
Missing data methods	LOCF and BOCF
Funding source	Pharmaceutical - Eli Lilly
Conflicts of interest	B.A.P. and S.Z. are full time employees and stockholders at Eli Lilly and Company. L.M.A. has received grants from and/or is a consultant for Eli Lilly and Company, Pfizer Inc, Cypress Bioscience Inc, Forest Laboratories, Boehringer Ingelheim, Novartis, Takedo, Grunenthal and Daiichi Sankyo
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Aloocation was managed using an interactive voice response system.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind with placebo identical appearance to duloxetine

Arnold 2012a *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition and reasons for withdrawal similar across groups. Mix of methods for missing data including LOCF and BOCF **Attrition:** Total: 77/308 (25.0%) Placebo: 31/110 (28.2%) Duloxetine 30 mg: 29/121 (23.9%)
Selective reporting (reporting bias)	Low risk	Trial registered prospectively, outcomes match those predefined
Other bias	Low risk	No other sources of bias were identified.

Arnold 2012b

Study characteristics	
Methods	Design: parallel Duration: 14 weeks Assessment: baseline and post-intervention Country: USA and Canada
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: ≥ 40 out of 100 Inclusion criteria • People aged ≥ 18 who met the ACR 1990 criteria for primary fibromyalgia • Score of ≥ 40 mm on 100 mm VAS for pain intensity Exclusion criteria • Comorbid physical and mental health conditions excluded Total participants randomised: 1122 Age in years (mean, range): 50 (19-84) Gender: 1009/1122 were female Pain duration in years (mean, range): 7 (0-55)
Interventions	Esreboxetine 4 mg • n = 245 • SNRI

Arnold 2012b *(Continued)*

	• Fixed dose Esreboxetine 8 mg • n = 254 • SNRI • Fixed dose Esreboxetine 10 mg • n = 255 • SNRI • Fixed dose Placebo • n = 255 • Identical appearance • Inert
Outcomes	Pain intensity Physical function Mood Quality of life Moderate pain relief Substantial pain relife PGIC AEs SAEs Withdrawal
Missing data methods	LOCF with BOCF as a sensitivity analysis on pain outcomes
Funding source	Pharmaceutical - Pfizer
Conflicts of interest	Dr Arnold has received consulting fees from Eli Lilly, Cypress Bioscience, Forest Laboratories, Takeda, AstraZeneca, Sanofi-Aventis, Grunenthal, Johnson & Johnson, and Daiichi Sankyo (less than USD 10,000 each) and from Pfizer (> USD 10,000); she has received research grants from Eli Lilly, Pfizer, Cypress Bioscience, Boehringer Ingelheim, Forest Laboratories, Novartis, and Takeda. Dr Hirsch owns stock or stock options in AstraZeneca. Dr Sanders owns stock or stock options in Pfizer and AstraZeneca. Drs Ellis and Hughes own stock or stock options in Pfizer.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were then randomised, according to a computer-generated pseudorandom code, in a 1:1:1:1 ratio

Arnold 2012b *(Continued)*

Allocation concealment (selection bias)	Low risk	A centralised telerandomisation system was used to manage the allocation of treatment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients received esreboxetine or matching placebo once daily in the form of round, light grey tablets; all of the tablets were identical in appearance, to preserve blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout across arms and significant differences in rates between placebo and intervention arms **Attrition:** Total: 406/1122 (36.2%) Placebo: 76/278 (27.3%) Esreboxetine 4 mg: 103/277 (37.2%) Esreboxetine 8 mg: 111/284 (39.1%) Esreboxetine 10 mg: 108/283 (38.2%)
Selective reporting (reporting bias)	High risk	Primary outcomes were switched on the trial registry. Protocol states they will collect and report HADS, SDI, and Sleep Interference but not published
Other bias	Low risk	No other sources of bias were identified.

Ash 1999

Study characteristics	
Methods	Design: parallel Duration: 10 weeks Assessment: baseline and post-intervention Country: UK
Participants	Pain condition: RA Population: women with RA and depression Minimum pain intensity: NR Inclusion criteria: • Patients with definite or classical RA as diagnosed per the ARA criteria • Aged between 18 and 70 • Scored a) > 7 on the depression or anxiety subscales of HADS, b) total score of > 11 on HADS scale, or c) considered to be depressed on clincial assessment Exclusion criteria • Experiencing an acute flare in RA symptoms

Ash 1999 *(Continued)*

	• Taking oral steroids, antidepressants, or had received a steroid injection in the previous month Total participants randomised: 48 Age in years (mean, SD): NR Gender: 48/48 were female Pain duration in years (mean, SD): NR
Interventions	Dothiepin • n = 25 • TCA • Flexible dosing dependent on tolerability and side-effects Placebo • n = 23 • Identical appearance • Inert
Outcomes	Pain intensity Mood Physical function Withdrawal
Missing data methods	ITT but does not state imputation methods
Funding source	Pharmaceutical - Boots
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States random allocation but no method given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind with identical appearing antidepressants and placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Over 40% of participants did not compelte the study due to lack of effect or intolerable side effects. **Attrition:**

Ash 1999 *(Continued)*

		Total: 21/48 (43.75%) Placebo: 10/23 (43.5%) Dothiepin 75 to 150 mg: 11/25 (44.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Atkinson 1998

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: low back pain Population: men with chronic low back pain Minimum pain intensity: NR Inclusion criteria • Aged between 21 and 65 • Had low back pain (T-6 or below) present for daily basis for at least 6 months Exclusion criteria • Comorbid physical or mental health condition Total participants randomised: 78 Age in years (mean, SD): 47.13 (10.65) Gender: 0/78 were female Pain duration in years (mean, SD): 14.81 years
Interventions	Nortriptyline: • n = 38 • TCA • Forced titration to maximum tolerated dose between 25 mg and 100 mg Placebo: • n = 40 • Identical appearance • Inert
Outcomes	Pain intensity Physical function

Atkinson 1998 *(Continued)*

	Mood Quality of life AEs Withdrawal
Missing data methods	ITT, but no methods of imputation given
Funding source	Non-pharmaceutical: United States Department of Veteran's Affairs and the National Institutes of Health
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned using a random number table
Allocation concealment (selection bias)	Low risk	Randomisation performed by research pharmacist not involved in any other aspects of the trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded with identical appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	26% of participants withdrew. LOCF imputation only. **Attrition:** Total: 21/78 (26.9%) Placebo: 11/40 (27.5%) Nortriptyline 25 to 100 mg: 10/38 (26.3%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found.
Other bias	Low risk	No other sources of bias were identified.

Atkinson 1999

Study characteristics

Methods	Design: parallel Duration: 8 weeks

Atkinson 1999 *(Continued)*

	Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: low back pain Population: adults with low back pain Minimum pain intensity: NR Inclusion criteria • Aged between 21 and 65 • Low back pain (at T-6 or below) present daily for at least 6 months Exclusion criteria • Comorbid physical and mental health conditions Total participants randomised: 103 Age in years (mean, SD): NR Gender: 40/103 were female Pain duration in years (mean, SD): 14.5 (11.1)
Interventions	Maprotiline 50-150 mg • n = 33 • TeCA • Fixed doses of 50 mg, 100 mg, or 150 mg depending on tolerability Paroxetine 10 to 30 mg • n = 34 • SSRI • Fixed doses of 10 mg, 20 mg, or 30 mg depending on tolerability Placebo (diphenhydramine 37.5 mg) • n = 36 • Identical appearance and matched dosing • Active placebo - antihistamine
Outcomes	Pain intensity AEs Withdrawal
Missing data methods	ITT using LOCF
Funding source	Non-pharmaceutical: funded by the United States Department of Veterans Affairs and the National Institutes of Health
Conflicts of interest	NR
Notes	
Risk of bias	

Atkinson 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a random number table
Allocation concealment (selection bias)	Low risk	Randomisation was performed by a research pharmacist not otherwise involved in the trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, active placebo, all capsules had identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT using LOCF. Unequal dropout across arms **Attrition** Total: 29/103 (28.2%) Maprotiline 50-150 mg: 13/33 (39.4%) Paroxetine 10-30 mg: 12/34 (35.3%) Placebo: 4/36 (11.1%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found. Only report data for primary outcome despite collecting post-intervention data for other outcomes
Other bias	Low risk	No other sources of bias were identified

Atkinson 2007

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: low back pain Population: adults with low back pain Minimum pain intensity: NR Inclusion criteria • Aged 21-65 • Low back pain (T-6 or below) present on a daily basis for at least 6 months Exclusion criteria

Atkinson 2007 *(Continued)*

	• Comorbid physical and mental health conditions Total participants randomised: 121 Age in years (mean, SD): NR Gender: NR Pain duration in years (mean, SD): NR
Interventions	Placebo (benzotropine mesylate 0.5 mg) • n = 26 • Identical • Active placebo - anticholinergic • Fixed dose of 0.5 mg Desipramine 50 mg • n = 17 • TCA • Fixed dose Desipramine 100 mg • n = 17 • TCA • Fixed dose Desipramine 150 mg • n = 18 • TCA • Fixed dose Fluoxetine 20 mg • n = 14 • SSRI • Fixed dose Fluoxetine 40 mg • n = 14 • SSRI • Fixed dose Fluoxetine 60 mg • n = 15 • SSRI • Fixed dose
Outcomes	No useable data provided
Missing data methods	ITT with LOCF
Funding source	Non-pharmaceutical: US Department of Veterans Affairs
Conflicts of interest	NR

Atkinson 2007 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a computerised random number generator
Allocation concealment (selection bias)	Low risk	Randomisation was completed by a research pharmacist not involved in other aspects of the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, double-dummy design, no significant difference in participants guessing allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition:** Total: 38/121 (31.4%) Attrition by arm NR
Selective reporting (reporting bias)	Unclear risk	Only 1 outcome prespecified in protocol. Do not perform their original analysis
Other bias	Low risk	No other sources of bias were identified.

Bansal 2009

Study characteristics

Methods	Design: cross-over Duration: 5 weeks Assessment: baseline and post-intervention Country: India
Participants	Pain condition: diabetic peripheral neuropathy Population: adults with diabetic peripheral neuropathy Minimum pain intensity: ≥ 50 on 0-100 VAS Inclusion criteria • Aged 18-75 • Painful diabetic neuropathy for at least 1 month • Pain rating of 50 on 0-100 VAS

Bansal 2009 *(Continued)*

	Exclusion criteria • Comorbid physical and mental health conditions (aside from diabetes) Total participants randomised: 51 Age in years (median, range): 54.5 (48-61) Gender: 25/44 completers were female Pain duration in months (mean, IQR): 12 (3-24)
Interventions	Pregabalin • Anticonvulsant • Flexible dosing • Mean dose of 218 mg/day Amitriptyline • TCA • Flexible dosing • Mean dose of 16 mg/day
Outcomes	Pain intensity PGIC Withdrawal
Missing data methods	ITT but no method of imputation reported
Funding source	Funding: NR
Conflicts of interest	No conflicts of interest to declare
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a random number table
Allocation concealment (selection bias)	Low risk	Blinding and randomisation were carried out by an independent person unrelated to the study, while drug administration and patient assessment were carried out by the investigator.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, identical appearing tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias)	Unclear risk	States ITT but no method of imputation reported **Attrition:**

Bansal 2009 *(Continued)*

All outcomes		Total: 7/51 (13.7%) Amitriptyline 10-50 mg: 3/25 (12.0%) Pregabalin 75-300 mg: 4/26 (15.4%)
Selective reporting (reporting bias)	Unclear risk	Trial registration, but registered retrospectively
Other bias	Low risk	No other sources of bias were identified.

Bateman 2013

Study characteristics	
Methods	Design: parallel Duration: 10 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: people with fibromyalgia who did not respond to duloxetine Minimum pain intensity: VAS pain score ≥ 40 mm/100 mm Inclusion criteria • Diagnosis of fibromyalgia • Pain intensity of ≥ 40/100 • Dissatisfaction with duloxetine after 6 weeks Exclusion criteria • Comorbid physical and mental health conditions Total participants randomised: 107 Age in years (mean): 48.6 Gender: 92/107 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 21 • Matched dosing schedule • Inert Milnacipran 50-200 mg • n = 86 • SNRI • Flexible dosing
Outcomes	Pain intensity

Bateman 2013 *(Continued)*

	Quality of life Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical - Forest Laboratories Inc.
Conflicts of interest	LB has received research support and speaker fees from Forest Laboratories, Inc. and Forest Research Institute, Inc. RHP, JMT, and YL are full-time employees of Forest Research Institute, Inc., a wholly owned subsidiary of Forest Laboratories, Inc., and hold stock in the parent company. This study was supported by Forest Laboratories, Inc. The authors thank Allan Spera at Forest Research Institute, Inc. for his contributions to the study and development of this paper. The authors also thank Mildred Bahn at Prescott Medical Communications Group (Chicago, IL, USA) for medical writing assistance supported by Forest Research Institute, Inc.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Included small placebo arm to ensure blinding, matched dosing schedule but no information given regarding appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF and high attrition **Attrition** Total: 45/107 (42.1%) Placebo: 10/21 (47.6%) Milnacipran 50-200 mg: 35/86 (40.7%)
Selective reporting (reporting bias)	Low risk	Primary measures match those listed prospectively in trial registry

Bateman 2013 *(Continued)*

Other bias	High risk	Placebo group spent first week still taking duloxetine while active drug group had no down taper between taking duloxetine and milnacipran

Bird 2000

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Countries: UK, Ireland, Germany, Italy, and Belgium
Participants	Pain condition: RA Population: adults with RA and depression Minimum pain intensity: NR Inclusion criteria • Aged 18-70 • RA for > 1 year • Diagnosis of mild, moderate, or severe depression • Had a total MADRS score of ≥ 16 Exclusion criteria • Severe comorbid physical conditions Total participants randomised: 191 Age in years (mean): 54.8 Gender: 150/191 were female Pain duration in years (mean, SD): NR
Interventions	Paroxetine 20-40 mg • n = 94 • SSRI • Flexible dosing based on efficacy Amitriptyline 75-150 mg • n = 97 • TCA • Flexible dosing based on efficacy
Outcomes	Mood PGIC AEs SAEs

Bird 2000 *(Continued)*

	Withdrawal
Missing data methods	ITT but imputation method not specified
Funding source	Pharmaceutical - educational grant from SmithKline Beecham
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded - double-dummy dosing schedule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	States ITT but no information regarding imputation method given **Attrition** Total: 37/191 (19.4%) Paroxetine 20-40 mg: 18/95 (18.9%) Amitriptyline 75-150 mg: 20/105 (19.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Boyle 2012

Study characteristics

Methods	Design: parallel Duration: 4 weeks Assessment: baseline and post-intervention Country: UK
Participants	Pain condition: diabetic peripheral neuropathy

Boyle 2012 *(Continued)*

	Population: adults with diabetic peripheral neuropathy Minimum pain intensity: NR Inclusion criteria • Adults with a diagnosis of diabetic peripheral neuropathy for > 1 year • Score > 12 on the Leeds Assessment of Neuropathic Symptoms and Signs Scale Exclusion criteria • Severe physical health condition • Comorbid mental health condition Total participants randomised: 83 Age in years (mean, SD): 65.1 (8.9) Gender: 26/83 were female Pain duration in years (mean, SD): NR
Interventions	Pregabalin 600 mg • n = 27 • Anticonvulsant • Forced titration to fixed dose Amitriptyline 75 mg • n = 28 • TCA • Forced titration to fixed dose Duloxetine 120 mg • n = 28 • SNRI • Forced titration to fixed dose
Outcomes	Pain intensity Sleep Physical function Mood Withdrawal
Missing data methods	ITT but imputation methods not specified
Funding source	Pharmaceutical - Pfizer
Conflicts of interest	This study was funded by an investigator-led research grant, which was awarded by Pfizer Ltd. J.B. received an honorarium to present the research findings internally to a Pfizer consultancy board. D.K.received consultancy fees and honoraria from Eli Lilly, Novo Nordisk, Abbott Diabetes Care, and Roche, companies providing medicine and monitoring equipment used by participants in this study. No other potential conflicts of interest relevant to this article were reported.
Notes	

Boyle 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not specified
Allocation concealment (selection bias)	Unclear risk	Procedure for allocation not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Matched dosing, but no information given regarding appearance of tablets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported pain outcomes, but not enough information regarding blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data methods: NR **Attrition** Total: 18/83 (21.7%) Pregabalin 300 mg: 5/27 (18.5%) Amitriptyline 75 mg: 4/28 (14.3%) Duloxetine 120 mg: 0/28 (0.0%)
Selective reporting (reporting bias)	Low risk	Pre-registered protocol lists primary outcomes
Other bias	Low risk	No other sources of bias were identified.

Branco 2010

Study characteristics

Methods	Design: parallel Duration: 17 weeks Assessment: baseline and post-intervention Country: Czech Republic, Denmark, Finland, France, Germany, Italy, Norway, Poland, Portugal, Romania, Spain, Sweden, UK
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: baseline VAS pain intensity rating between 40 and 90 (0-100 scale) Inclusion criteria • Aged 18-70 • Diagnosed with fibromyalgia as per the ACR criteria

Branco 2010 *(Continued)*

	• Raw score ≥ 3 on physical function component of the FIQ • Baseline VAS pain intensity rating between 40 and 90 (0-100 scale) Exclusion criteria • Severe mental health conditions • Comorbid physical health conditions Total participants randomised: 884 Age in years (mean): 48.4 Gender: 826 were female Pain duration in years (mean): 9.5
Interventions	Placebo • n = 449 • Matched dosing and identical appearance • Inert Milnacipran 200 mg • n = 435 • SNRI • Forced titration to fixed dose
Outcomes	Pain intensity Quality of life Physical function Mood PGIC AEs SAEs Withdrawal
Missing data methods	ITT with LOCF, and BOCF sensitivity analyses
Funding source	Pharmaceutical - Pierre Fabre Medicament, France
Conflicts of interest	Dr Branco has received grant support as an investigator and consultant for Pierre Fabre Medicament. Drs Zachrisson and Perrot have served as speakers and consultants for Pierre Fabre Medicament. Dr Mainguy is an employee and shareholder of Pierre Fabre Medicament. Medical writing assistance provided by Prescott Medical Communications Group was supported by Pierre Fabre Medicament.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified

Branco 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Matched dosing but no information regarding appearance of drugs
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF and BOCF as sensitivity analysis. More dropouts in antidepressant arm related to side-effects **Attrition** Total: 206/882 (23.3%) Placebo: 79/449 (17.6%) Milnacipran 200 mg: 127/435 (29.2%)
Selective reporting (reporting bias)	Unclear risk	Primary outcome matches trial registry, but secondary outcomes not listed
Other bias	Low risk	No other sources of bias were identified.

Braz 2013

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: Brazil
Participants	Pain condition: fibromyalgia Population: women with fibromyalgia Minimum pain intensity: NR Inclusion criteria • Women aged 21-60 • Fibromyalgia diagnosed as per the ACR criteria Exclusion criteria • Physical health comorbidity • Use of TCA in the previous 3 months Total participants randomised: 52 Age in years (mean): 43.2

Braz 2013 *(Continued)*

	Gender: 52/52 were female Pain duration in months (mean): 43.8
Interventions	Placebo • n = 17 • Identical appearance • Inert Amitriptyline 25 mg • n = 16 • TCA • Fixed dose with no titration Panax ginseng 100 mg • n = 19 • Plant extract • Fixed dose with no titration
Outcomes	Withdrawal
Missing data methods	Completer-only analysis
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation procedure not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, drugs identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported measures completed by blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer-only analysis, unequal attrition **Attrition** Total: 14/52 (26.9%) Placebo: 4/17 (23.5%) Amitriptyline 25 mg: 3/16 (18.8%)

Braz 2013 *(Continued)*

		Panax ginseng 100 mg: 7/19 (36.8%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Calderon 2011

Study characteristics	
Methods	Design: parallel Duration: 7 weeks Assessment: baseline, post-intervention, follow-up (4 weeks after post-intervention) Country: Brazil
Participants	Pain condition: orofacial pain Population: women with temporomandibular disorders Minimum pain intensity: ≥ 40 mm on a 0-100 mm VAS Inclusion criteria • Women aged between 17 and 55 • Orofacial pain for > 6 months • Pain occurring daily or almost daily • Pain ≥ 40 on a 0-100 mm VAS Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 47 Age in years (mean, range): 35.6 (17-52) Gender: 47/47 were female Pain duration in months (mean, range): 72.35 (6-384)
Interventions	Placebo • n = 13 • Inert Placebo + CBT • n = 11 • Inert placebo • Weekly 90-min CBT sessions for 7 weeks Amitriptyline 25 mg • n = 11 • TCA • Fixed dose with no titration

Calderon 2011 *(Continued)*

	Amitriptyline 25 mg + CBT • n = 12 • TCA - antidepressant • Weekly 90-min CBT sessions for 7 weeks
Outcomes	Withdrawal
Missing data methods	Completer-only analysis
Funding source	Non-pharmaceutical - Ministry of Education in Brazil
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using the website www.randomization.com
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to nature of CBT group participants cannot be blinded. When comparing the placebo versus amitriptyline group(s) there was no description of whether pills were matched.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	No clear explanation of reasons for withdrawal and from which group, not clear on handling missing data or group sizes in outcomes **Attrition** Total: 10/47 (21.3%) Placebo: 2/13 (15.4%) CBT: 2/11 (18.2%) Amitriptyline 25 mg: 2/11 (18.2%) CBT + amitriptyline 25 mg: 4/12 (33.3%)
Selective reporting (reporting bias)	Unclear risk	No trial registration or protocol found
Other bias	Low risk	No other sources of bias were identified.

Cannon 1994

Study characteristics	
Methods	Design: parallel Duration: 3 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: non-cardiac chest pain Population: adults with non-cardiac chest pain Minimum pain intensity: NR Inclusion criteria • People with chest pain and normal coronary angiograms • Psychiatric conditions included Exclusion criteria • NR Total participants randomised: 60 Age in years (mean, range): 50 (29-72) Gender: 40/60 were female Pain duration in months (mean, range): 53 (3-175)
Interventions	Placebo • n = 20 • Inert • Matched dosing schedule and identical capsules Clonidine 0.2 mg • n = 20 • Anti-hypertensive • Fixed dose of 0.2 mg/day • Forced titration over 1 week Imipramine 50 mg • n = 20 • TCA • Fixed dose of 50 mg/day • Forced titration over 1 week
Outcomes	AEs
Missing data methods	NR
Funding source	Funding: NR
Conflicts of interest	NR

Cannon 1994 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation procedure not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, matched dosing schedules and identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given regarding dropout or missing data analyses - could be that everyone completed the trial but NR **Attrition** NR
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Cardenas 2002

Study characteristics

Methods	Design: parallel Duration: 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: pain resulting from spinal cord injury Population: adults with persistent pain from spinal cord injury Minimum pain intensity: average of ≥ 3 out of 10 over the last month Inclusion criteria • Aged 18-65 • Spinal cord injury > 6 months ago • Pain for at least 3 months • Average pain rating of ≥ 3 out of 10 over the last month

Cardenas 2002 *(Continued)*

	Exclusion criteria • Comorbid physical and mental health conditions Total participants randomised: 84 Age in years (mean): 41.5 Gender: 17/84 were female Pain duration in months (mean): 168.3
Interventions	Placebo (benztropine mesylate 0.5 mg) • n = 40 • Active placebo - anticholinergic • Identical appearance • Fixed dose Amitriptyline 10-125 mg • n = 44 • TCA • Flexible titration based on efficacy and tolerance
Outcomes	Pain intensity Mood Physical function AEs Withdrawal
Missing data methods	ITT but no imputation method specified
Funding source	Non-pharmaceutical - National Institutes of Health
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Low risk	Random assignment to treatment group and provision of medication was done by the University of Washington Medical Center Pharmacy Investigational Drug Services.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, active placebo, identical appearance
Blinding of outcome assessment (detection bias)	Low risk	Self-reported outcomes from blinded participants

Cardenas 2002 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Low levels of dropout, not significantly different across both arms. ITT analysis but no imputation method specified **Attrition** Total: 11/84 (13.1%) Benzotropine mesylate 0.5 mg: 3/40 (7.5%) Amitriptyline 10-125 mg: 8/44 (18.2%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Carette 1986

Study characteristics	
Methods	Design: parallel Duration: baseline and post-intervention Assessment: 9 weeks Country: Canada
Participants	Pain condition: primary fibrositis/fibromyalgia Population: people with fibromyalgia Minimum pain intensity: NR Inclusion criteria • Widespread pain lasting > 3 months • Local tenderness at 12 out of 14 specified sites Exclusion criteria • History of heart conditions • Treated with amitriptyline in the previous year Total participants randomised: 70 Age in years (mean): 41 Gender: 54/70 were female Pain duration in months (mean): 84
Interventions	Placebo • n = 36 • Identical appearance • Inert Amitriptyline 10-50 mg

Carette 1986 *(Continued)*

- n = 34
- TCA
- Forced titration to fixed doses dependent upon tolerability

Outcomes	Pain intensity AEs Withdrawal
Missing data methods	Completer analysis only
Funding source	Non-pharmaceutical - Arthritis Grant
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Although the study used double-blind procedures, the authors noted that 70% of the amitriptyline participants experienced side effects that, in some cases, unblinded participants and research staff.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from participants who may have been unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only **Attrition** Total: 11/70 (15.7%) Placebo: 4/32 (11.1%) Amitriptyline 10-50 mg: 7/27 (20.6%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Carette 1994

Study characteristics

Methods	Design: parallel

Carette 1994 *(Continued)*

	Duration: 25 weeks Assessment: baseline and post-intervention Country: Canada
Participants	Pain condition: fibromylagia Population: adults with fibromyalgia Minimum pain intensity: ≥ 4 on a 0-10 VAS Inclusion criteria • Adults with a diagnosis of fibromyalgia as per the ACR criteria • Score of ≥ 4 on at least 1 of two 0-10 VAS, one evaluating pain, one evaluating fibromyalgia symptoms Exclusion criteria • History of cardiac conditions • Previous treatment with amitriptyline or cyclobenzaprine Total participants randomised: 208 Age in years (mean): 44.9 Gender: 199/208 were female Pain duration in months (mean): 92.6
Interventions	Placebo • n = 42 • Inert Amitriptyline 25-50 mg • n = 84 • TCA • Forced titration to fixed doses • 25 mg/day for 12 weeks, then 50 mg/day for 12 weeks Cyclobenzaprine 20-30 mg • n = 82 • Muscle relaxant • Forced titration to fixed doses • 20 mg/day for 12 weeks, then 30 mg/day for 12 weeks
Outcomes	Pain intensity Physical function Mood AEs Withdrawal
Missing data methods	ITT but no imputation methods stated

Carette 1994 *(Continued)*

Funding source	Partly pharmaceutical - supported by grants from the Canadian Arthritis Society and Merck Frosst Canada
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a random number table
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Matched dosing but no information on appearance. Not enough information about physician blinding as there were some physician-reported measures.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Mostly self-reported outcomes from participants. Not enough information regarding blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	Do not clearly report reasons for withdrawal and numbers between groups. State ITT but no methods specified **Attrition** Total: 52/208 (25.0%) Placebo: 14/84 (33.3%) Amitriptyline 50 mg: 14/82 (16.7%) Cyclobenzaprine 20-30 mg: 24/42 (29.3%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Caruso 1987

Study characteristics

Methods	Design: parallel Duration: 8 weeks Assessment: baseline, week 2, week 4, post-intervention Country: Italy
Participants	Pain condition: fibromyalgia

Caruso 1987 *(Continued)*

	Population: adults with fibromyalgia Minimum pain intensity: NR Inclusion criteria • Aged 25-65 • Affected by fibromyalgia Exclusion criteria: NR Total participants randomised: 60 Age in years (mean): 46 Gender: 52/60 were female Pain duration in years (mean): 5.7
Interventions	Placebo • n = 30 • Identical appearance and matched dosing • Inert Dothiepin 75 mg • n = 30 • TCA • Fixed dose
Outcomes	AEs Withdrawal
Missing data methods	NR
Funding source	Funding: NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomsiation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind with matched dosing and identical appearance of tablets
Blinding of outcome assessment (detection bias)	Low risk	Self-reported outcomes by blinded participants

Caruso 1987 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only **Attrition** Total: 8/60 (13.3%) Placebo: 4/30 (13.3%) Dothiepin 75 mg: 4/30 (13.3%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Chappell 2008

Study characteristics	
Methods	Design: parallel Duration: 27 weeks Assessment: baseline and post-intervention Country: USA, Germany, Spain, Sweden, UK
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: none Inclusion criteria • Adults with fibromyalgia diagnosed as per the ACR criteria • With or without MDD Exclusion criteria • Severe physical health comorbidity Total participants randomised: 330 Age in years (mean, SD): 50.5 (10.7) Gender: 308/330 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 168 • Inert Duloxetine • n = 162 • SNRI

Chappell 2008 *(Continued)*

- Blind forced titration to fixed doses dependent upon efficacy for pain relief
- Mean dose at end of trial was 113.4 mg/day

Outcomes	Pain intensity Quality of life Mood Physical function Moderate pain relief Substantial pain relief PGIC AEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharamaceutical - Eli Lilly and Boehringer Ingelheim GmbH
Conflicts of interest	Drs Chappell, Detke, and D'Souza are employees and stockholders of Eli Lilly and Company. Dr Wiltse is a former employee of Eli Lilly and Company. Dr Spaeth is a consultant to Allergan, Eli Lilly, Jazz, and Pierre Fabre Medicament, and is on the speaker bureaus of Eli Lilly and Pierre Fabre Medicament. Dr Bradley is a consultant for Eli Lilly, Pfizer, and Forest; has received grant/research support from the National Institutes of Health, the Agency for Healthcare Research and Quality, Eli Lilly, Pfizer, and the American Fibromyalgia Syndrome Association; has received honoraria from Eli Lilly, Pfizer, Forest, and the Society for Women's Health Research; is a member of the speaker/advisory board for Pfizer; and has received royalties from UpToDate Rheumatology.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment to treatment groups was determined by a computer-generated random sequence within each study centre, stratified by MDD status
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical appearance tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Significant difference in participants withdrawing due to lack of efficacy (higher in placebo). Uses ITT with LOCF **Attrition** Total: 126/330 (38.2%)

Chappell 2008 *(Continued)*

		Placebo: 65/168 (38.7%) Duloxetine 60-120 mg: 61/162 (37.7%)
Selective reporting (reporting bias)	Low risk	Outcomes match those listed in trial registration record
Other bias	Low risk	No other sources of bias were identified.

Chappell 2009a

Study characteristics	
Methods	Design: parallel Duration: 8 weeks open-label, 52 weeks double-blind Assessment: baseline and post-intervention Country: Argentina, Australia, Brazil, Canada, Mexico, Poland, Taiwan, USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Adults with fibromyalgia that met the ACR criteria • ≥ 4 on 0-10 BPI pain item for 2 consecutive visits Exclusion criteria • Physical health comorbidity • Suicide risk (scoring ≥ 2 on item 9 of the BDI-II) Total participants randomised in double-blind phase: 307 Age in years (mean, SD): 49 (11.07) Gender: 335/350 were female (including those in the open-label phase) Pain duration in years (mean, SD): NR
Interventions	Duloxetine 60 mg • n = 104 • SNRI • Titrated to fixed dose of 60 mg over 8-week open-label phase • Continued on fixed 60 mg dose for 52-week double-blind phase Duloxetine 120 mg • n = 203 • SNRI • Titrated to fixed dose of 60 mg over 8-week open-label phase, then increased to 120 mg fixed dose for double-blind phase
Outcomes	Pain intensity

Chappell 2009a *(Continued)*

	Quality of life Physical function Sleep Mood PGIC AEs SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical - Eli Lilly and Co and Boehringer Ingelheim
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation procedure not specified
Allocation concealment (selection bias)	Low risk	Patients were allocated using an interactive voice response system that was accessed via telephone by each investigator.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind but not enough information on medication i.e. appearance or number of tablets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but not enough information regarding blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Use ITT with LOCF. Similar but significant attrition rates in both arms **Attrition** Total: 112/307 (36.5%) Duloxetine 60 mg: 33/104 (31.7%) Duloxetine 120 mg: 79/203 (38.9%)
Selective reporting (reporting bias)	Unclear risk	Protocol not very detailed, report matched domains but did not register measures and time points, etc
Other bias	Low risk	No other sources of bias were identified.

Chappell 2009b

Study characteristics	
Methods	Design: parallel Duration: 13 weeks Assessment: baseline and post-intervention Country: USA, Puerto Rico, Romania
Participants	Pain condition: knee OA Population: adults aged ≥ 40 with knee OA Minimum pain intensity: ≥ 4 on 24-h 0-10 VAS Inclusion criteria • Adults aged ≥ 40 with knee OA matching ACR criteria • Pain ≥ 14 days a month for 3 months prior to study entry • Mean score of ≥ on 24-h average pain score (0-10) on first 2 study visits Exclusion criteria • Comorbid physical and mental health conditions • Previous exposure to duloxetine Total participants randomised: 231 Age in years (mean): 62.3 Gender: 151/231 were female Pain duration in years (mean): 9
Interventions	Placebo • n = 120 • Identical in appearance, smell, and taste • Matched dosing • Inert Duloxetine • n = 111 • SNRI • Fixed dose of 60 mg for 6 weeks, then re-randomised to fixed dosage of 60 mg or 120 mg for weeks 7-13
Outcomes	Pain intensity Sleep Quality of life Mood Physical function Moderate pain relief Substantial pain relief PGIC

Chappell 2009b *(Continued)*

	AEs SAEs Withdrawal
Missing data methods	ITT with LOCF, and MMRM
Funding source	Pharmaceutical - Eli Lilly
Conflicts of interest	NR, but authors are employed by Eli Lilly and declare CoIs in other papers.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Participants were allcoated using an Interactive Voice Response System (IVRS).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, matched dosing and identical appearance, smell, and taste of capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT with LOCF, BOCF, and MMRM **Attrition** Total: 58/231 (25.1%) Placebo: 24/120 (20.0%) Duloxetine 60-120 mg: 34/111 (30.6%)
Selective reporting (reporting bias)	Low risk	Outcomes and procedures match those listed prospectively in trial registration
Other bias	Low risk	No other sources of bias were identified.

Chappell 2011

Study characteristics

Methods	Design: parallel Duration: 13 weeks Assessment: baseline and post-intervention

Chappell 2011 *(Continued)*

	Country: USA, Canada, Greece, Russia, Sweden
Participants	Pain condition: knee OA Population: adults aged ≥ 40 with knee OA Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Adults aged ≥ 40 with knee OA matching ACR criteria • Pain ≥ 14 days a month for 3 months prior to study entry • Mean score of ≥ on 24-h average pain score (0-10) on first 2 study visits Exclusion criteria • Comorbid physical and mental health conditions Total participants randomised: 256 Age in years (mean): 62.5 Gender: 196/256 were female Pain duration in years (mean): 7.4
Interventions	Placebo • n = 128 • Inert • Matched dosing Duloxetine • n = 128 • SNRI • Fixed dose of 60 mg for 6 weeks, then titrated to fixed dosage of 120 mg for weeks 7-13 dependent on 30% pain relief
Outcomes	Pain intensity Physical function Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	ITT with LOCF, sensitivity analysis of primary outcome with BOCF and modified-BOCF
Funding source	Pharmaceutical - Eli Lilly
Conflicts of interest	This study was sponsored by Eli Lilly and Company, Indianapolis, IN, USA. Drs Chappell, Skljarevski, Desaiah, Liu-Seifert, and Ms Zhang are employees and stockholders of Eli Lilly and Company. Drs Be-

Chappell 2011 *(Continued)*

	lenkov and Brown were participating investigators in the conduct of this study and received funding from Eli Lilly and Company.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment to treatment was determined by a computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Participants were allocated using an interactive voice response system to ensure blinding.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind and matched dosing, but don't mention drug appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rates may be influenced by group allocation: "Significantly more patients in the duloxetine group (n = 24, 18.8%) discontinued from the study due to adverse events (P = 0.002) than patients in the placebo group (n = 7, 5.5%)." Used LOCF, BOCF, mBOCF, ITT to handle/impute missing data **Attrition** Total: Placebo: 17/128 (13.3%) Duloxetine 60-120 mg: 35/128 (27.3%)
Selective reporting (reporting bias)	High risk	Data not presented on outcomes that were non-significant
Other bias	Low risk	No other sources of bias were identified.

Clauw 2008

Study characteristics

Methods	Design: parallel Duration: 15 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: ≥ 40 on 0-100 VAS

Clauw 2008 *(Continued)*

	Inclusion criteria • Aged 18-70 with a diagnosis of fibromyalgia as per ACR • ≥ 40 on 0-100 pain intensity VAS • ≥ 4 on physical function component of FIQ Exclusion criteria • Current physical or mental health condition • Previous exposure to milnacipran Total participants randomised: 1207 Age in years (mean): 50.2 Gender: 1151/1207 were female Pain duration in years (mean): 9.7
Interventions	Placebo • n = 405 • Inert • Matched dosing with identical appearance Milnacipran 100 mg • n = 401 • SNRI • Fixed dose, titrated over 6 days • Sham escalation to match 200 mg arm Milnacipran 200 mg • n = 401 • SNRI • Fixed dose, titrated over 6 days
Outcomes	Pain intensity Moderate pain relief Physical function Mood Quality of life Sleep PGIC AEs SAEs Withdrawal
Missing data methods	ITT with LOCF and BOCF
Funding source	Pharmaceutical - Forest Research Institute, Inc. and Cypress Bioscience, Inc.

Clauw 2008 *(Continued)*

Conflicts of interest	This research was financially supported by Forest Research Institute, Inc., Jersey City, New Jersey, and Cypress Bioscience, Inc., San Diego, California. The study drug was manufactured by Pierre Fabre Medicament, Boulogne, France. Drug supply and data collection were managed by Forest Research Institute. The study was designed and conducted under the supervision of Drs Gendreau, Palmer, and Clauw. The manuscript was prepared with the editorial assistance of Prescott Medical Communications Group, Chicago, Illinois, under the supervision of Dr Clauw. Dr Clauw has received grant support from Cypress Bioscience, Inc., and serves as a consultant to Cypress Bioscience, Forest Laboratories, and Pierre Fabre Medicament, all of which are involved in the development of milnacipran for fibromyalgia. He also acts as a consultant to Eli Lilly and Company, Pfizer Inc., Procter & Gamble, and Wyeth Pharmaceuticals. He has owned stock in Cypress Bioscience. Dr Mease has received research grant support from Allergan, Inc.; Cypress Bioscience; Forest Laboratories; Fralex Therapeutics Inc.; Jazz Pharmaceuticals; Eli Lilly; Pfizer; and Wyeth. Drs Palmer and Wang are employees of Forest Research Institute and own stock in Forest Laboratories. Dr Gendreau is an employee of Cypress Bioscience and owns stock in that company.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation lists for each site were generated by a computer program.
Allocation concealment (selection bias)	Low risk	Assignments made via an interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, matched dosing, and identical appearance of tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition rates, did not adhere to the mentioned plan with handling and reporting missing data **Attrition** Total: Placebo: 115/405 (28.4%) Milnacipran 100 mg: 137/401 (34.2%) Milnacipran 200 mg: 144/401 (35.9%)
Selective reporting (reporting bias)	Unclear risk	Trial registration available but did not specify outcome measures - just outcomes
Other bias	Low risk	No other sources of bias were identified.

Creed 2003

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline, post-intervention, follow-up 1 year post-intervention Country: UK
Participants	Pain condition: IBS Population: adults with IBS Minimum pain intensity: Inclusion criteria • Aged 18-65 • Rome I criteria for IBS • Severe abdominal pain, defined as > 59 on a VAS Exclusion criteria • Psychotic disorder, severe personality disorder, active suicidal ideation • Consumed > 50 units of alcohol per week Total participants randomised: 257 Age in years (mean): 43.3 Gender: 205/257 were female Pain duration in years (mean, SD): NR
Interventions	Psychotherapy • n = 85 • Psychodynamic interpersonal therapy • 8 sessions of 3 months Paroxetine 20 mg/day • n = 86 • SSRI • Fixed dose Usual treatment • n = 86 • Usual treatment - patients continued to be seen either by their gastroenterologist and/or general practitioner, using whatever management was deemed appropriate throughout the 15 months of the study.
Outcomes	Pain intensity Physical function Mood Withdrawal

Creed 2003 *(Continued)*

Missing data methods	ITT, data imputed using SOLAS (data imputation software)
Funding source	Non-pharmaceutical - Medical Research Council and UK North West Regional Health Authority Research and Development Directorate
Conflicts of interest	F Creed has consultancy links with Lilly. He has received payment for sitting on an advisory panel. All other authors declare that they have no competing interests.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by a computer-generated series of random numbers.
Allocation concealment (selection bias)	Unclear risk	When patients had been assessed and accepted into the trial, they were then allocated to a treatment group by the trial administrator using the next slot on the appropriate randomisation list.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and researchers unable to be blinded to due to nature of psychotherapy
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unequal attrition. State ITT and data imputed by SOLAS - but no explanation given **Attrition** Total: 69/257 (26.8%) Psychotherapy: 26/85 (30.6%) Paroxetine 20 mg: 32/86 (37.2%) Usual treatment: 11/86 (12.8%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

de Zanette 2014

Study characteristics

Methods	Design: parallel Duration: 6 weeks Assessment: baseline and post-intervention

de Zanette 2014 *(Continued)*

	Country: Brazil
Participants	Pain condition: fibromyalgia Population: women with fibromyalgia Minimum pain intensity: ≥ 50 on 0-100 VAS Inclusion criteria • Women with fibromyalgia matching ACR criteria • Pain intensity of ≥ 50 on 0-100 VAS Exclusion criteria • Physical health comorbidities • BMI > 35 Total participants randomised: 63 Age in years (mean): 48.9 Gender: 63/63 were female Pain duration in years (mean, SD): NR
Interventions	Melatonin 10 mg • n = 21 • Hormone • Identical appearance • Double-dummy to match combined arm Amitriptyline 25 mg • n = 21 • TCA • Fixed dose, no titration • Double-dummy to match combined arm Melatonin 10 mg + amitriptyline 25 mg • n = 21 • Hormone and TCA antidepressant • Fixed doses, no titration
Outcomes	Pain intensity Quality of life Sleep AEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Non-pharmaceutical - multiple Brazilian governmental agencies
Conflicts of interest	The authors declare that there are no financial or other relationships that might lead to CoIs involving any of the following arrangements: financial relationship to the work, employees of a company, consul-

de Zanette 2014 *(Continued)*

	tants for a company, stockholders of the company, members of a speakers' bureau or any other form of financial compensation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods: NR
Allocation concealment (selection bias)	Low risk	Sealed, sequentially numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy trial, identical appearance of tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	States ITT but no method of imputation specified. Low attrition **Attrition** Total: 6/63 (9.5%) Melatonin 10 mg: 2/21 (9.5%) Amitriptyline 25 mg: 2/21 (9.5%) Melatonin + amitriptyline: 2/21 (9.5%)
Selective reporting (reporting bias)	Low risk	Outcomes match those listed on trial registration
Other bias	Low risk	No other sources of bias were identified.

Dickens 2000

Study characteristics

Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Country: UK
Participants	Pain condition: low back pain Population: adults with chronic low back pain and depression Minimum pain intensity: NR

Dickens 2000 *(Continued)*

	Inclusion criteria • Aged 18-65 • Chronic low back pain for > 6 months • Significant depressive symptoms as measured with the MADRS scale • Significant disability in daily living tasks as measured by the ODI Exclusion criteria • Any other significant physical or mental health condition Total participants randomised: 98 Age in years (mean, SD): 45.2 (10.2) Gender: 53/98 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 48 • Inert • Identical in appearance to antidepressant Paroxetine 20 mg • n = 44 • SSRI • Fixed dose
Outcomes	Pain intensity Physical function Mood
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: SmithKline Beecham
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation of order of treatment allocation was achieved using a computer-generated randomisation list in which treatments were balanced.
Allocation concealment (selection bias)	Low risk	Sequentially numbered treatment packs containing the medication were held in and distributed by the hospital pharmacy. The packs were allocated to consecutive participants in strict sequential order.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, appearance of both placebo and antidepressant was identical

Dickens 2000 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT with LOCF, but very low dropout **Attrition** Total: 6/98 (6.1%) Attrition per arm NR
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Drossman 2003

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA and Canada
Participants	Pain condition: functional bowel disorders Population: women with moderate to severe functional bowel disorders Minimum pain intensity: NR Inclusion criteria • Women aged 18-70 • Moderate to severe abdominal pain with or without altered bowel habit (functional bowel disorder) for at least 2 days per week for 6 months Exclusion criteria • Serious physical health conditions • Schizophrenia or bipolar disorder • Previous use of desipramine Total participants randomised: 431 Age in years (mean, SD): 38.6 (12.0) Gender: 431/431 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 71 • Inert • Matched dosing

Drossman 2003 *(Continued)*

	Desipramine 150 mg • n = 144 • TCA • Flexible dosing based on tolerability and efficacy CBT • n = 144 • 12 weekly hour-long sessions of CBT Education • n = 71 • 12 weekly hour-long pain education sessions involving reviewing symptom diaries and educational materials from a book on functional bowel disorders
Outcomes	Pain intensity Quality of life Withdrawal
Missing data methods	ITT but imputation method not specified
Funding source	Non-pharmaceutical: supported by a research grant from the National Institutes of Health (RO1-DK49334).
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by computer
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to be double-blinded across all study arms due to the nature of CBT
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	States ITT but method not specified **Attrition** Total: 123/431 (28.5%) Placebo: 16/72 (22.2%) Desipramine 150 mg: 49/144 (34.0%)

Drossman 2003 *(Continued)*

		CBT: 33/144 (22.9%) Education: 25/71 (35.2%)
Selective reporting (reporting bias)	Unclear risk	Protocol registered but no outcome measures listed
Other bias	Low risk	No other sources of bias were identified

Eberhard 1988

Study characteristics	
Methods	Design: parallel Duration: 6 weeks Assessment: baseline and post-intervention Country: Sweden
Participants	Pain condition: idiopathic pain syndromes Population: adults with idiopathic pain syndromes Minimum pain intensity: NR Inclusion criteria • Fulfilled diagnosis of idiopathic pain syndromes according to criteria given by Williams and Spitzer (1982), comparable to somatoform pain disorder in DSM-III R Exclusion criteria • Major depressive disorder and other psychiatric illnesses Total participants randomised: 70 Age in years (mean, SD): 50.3 (12.5) Gender: 51/70 were female Pain duration in years (range): 0.5-28
Interventions	Maprotiline 25-150 mg • n = 30 • TeCA • Flexible dosing dependent upon efficacy and tolerability • Mean dose = 100 mg/day Clomipramine 25-150 mg • n = 40 • TCA • Flexible dosing dependent upon efficacy and tolerability • Mean dose = 97.2 mg/day
Outcomes	Pain intensity

Eberhard 1988 *(Continued)*

	Mood Withdrawal
Missing data methods	None - completer-only analysis
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information regarding sequence generation given
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical appearing tablets with matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only **Attrition** Total: 18/70 (25.7%) Maprotiline 25-150 mg: 5/30 (16.7%) Clomipramine 25-150 mg: 13/40 (32.5%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias identified

Engel 1998

Study characteristics

Methods	Design: cross-over Duration: 15 weeks (6 weeks per cross-over period) Assessment: baseline and post-intervention Country: USA

Engel 1998 *(Continued)*

Participants	Pain condition: pelvic pain Population: women with chronic pelvic pain Minimum pain intensity: no Inclusion criteria • Aged 18-50 • Pelvic pain persisting for ≥ 3 months Exclusion criteria • Laparoscopy within the last 3 months Total participants randomised: 25 Age in years (mean, SD): 29.0 (7.2) Gender: 25/25 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 25 • Inert Sertraline 100 mg • n = 25 • SSRI • Fixed dose, 50 mg taken twice daily
Outcomes	No useable data were able to be extracted from the study.
Missing data methods	Completer analysis only
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding procedures
Blinding of outcome assessment (detection bias)	Unclear risk	Self-reported outcomes but unsure of blinding procedures

Engel 1998 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Completer analysis but low dropout **Attrition** Total: 2/25 (8%) Attrition per arm NR
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias identified

Enomoto 2018

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: Japan
Participants	Pain condition: peripheral diabetic neuropathy Population: adults with peripheral diabetic neuropathy Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Aged 20-80 • Diagnosed with peripheral diabetic neuropathy • ≥ 4 on 0-10 pain intensity VAS Exclusion criteria • Poor glycemic control • Mental health conditions including MDD Total participants randomised: 303 Age in years (mean, SD): 59.6 (9.03) Gender: 83/303 were female Pain duration in years (mean, SD): 4.59 (4.25)
Interventions	Pregabalin 300-600 mg • n = 151 • Anticonvulsant • Matched dosing to antidepressant arm • Forced titration dependent upon efficacy • Mean dose 348.7 mg/day

Enomoto 2018 *(Continued)*

	Duloxetine 40-60 mg • n = 152 • SNRI • Forced titration dependent upon efficacy • Mean dose 42.5 mg/day
Outcomes	Pain intensity Quality of life Mood Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	MMRM
Funding source	Pharmaceutical: Eli Lilly Japan
Conflicts of interest	HE, SF, MT and AY are employees of Eli Lilly Japan K.K. AN is an employee of Shionogi & Co. Ltd., and MF, MI and TT are employees and minor stockholders of Shionogi & Co. Ltd. LA is an employee of Eli Lilly Turkey. SF and LA hold shares in Eli Lilly and Company. HY reports speaking fees from Nippon Boehringer Ingelheim Co. Ltd., Eli Lilly Japan K.K., Shionogi & Co. Ltd., Sanwa Kagaku Kenkyusyo Co. Ltd., and Sumitomo Dainippon Pharma Co. Ltd., and consulting fees from Shionogi & Co.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were assigned to duloxetine or pregabalin in a 1:1 ratio via a computer-generated random sequence.
Allocation concealment (selection bias)	Low risk	Patients were assigned via a computer-generated random sequence using an interactive web response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, study drugs were identical in appearance and followed a matched dosing schedule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In the statistical analysis plan in their protocol they mention they will handle missing data and impute using LOCF and BOCF but this is not mentioned anywhere in the paper. State MMRM **Attrition**

Enomoto 2018 *(Continued)*

		Total: 36/303 (11.9%) Pregabalin 300-600 mg: 21/151 (13.9%) Duloxetine 40-60 mg: 15/152 (9.9%)
Selective reporting (reporting bias)	Low risk	All outcomes prospectively listed on clinicaltrials.gov before trial started
Other bias	Low risk	No other sources of bias were identified

Enteshari-Moghaddam 2019

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline to post-intervention Country: Iran
Participants	Pain condition: knee OA Population: adults with moderate-severe knee OA Minimum pain intensity: ≥ 5 on 0-10 VAS Inclusion criteria • Aged 45-75 • ≥ 5 on 0-10 VAS for pain intensity • ≥ 48 on WOMAC scale • Radiographic evidence of OA Exclusion criteria • Physical health comorbidities Total participants randomised: 150 Age in years (mean): 54.4 Gender: 110/150 were female Pain duration in years (mean): 8.44
Interventions	Paracetamol 2000 mg • n = 50 • Forced titration to fixed dose Duloxetine 60 mg • n = 50 • SNRI • Forced titration to fixed dose Gabapentin 600 mg

Enteshari-Moghaddam 2019 *(Continued)*

- n = 50
- Anticonvulsant
- Forced titration to fixed dose

Outcomes	AEs Withdrawal
Missing data methods	All participants completed the trial
Funding source	Non-pharmaceutical: Ardabil University of Medical Sciences
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using random number blocks.
Allocation concealment (selection bias)	Low risk	Participants were allocated to an arm using sealed, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind but does not report blinding procedures
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes by participants, but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the trial **Attrition:** none
Selective reporting (reporting bias)	High risk	Do not report quality of life as stated in protocol
Other bias	Low risk	No other sources of bias were found

Forssell 2004

Study characteristics

Methods	Design: cross-over Duration: 4 weeks Assessment: baseline to post-intervention Country: Finland
Participants	Pain condition: atypical facial pain

Forssell 2004 *(Continued)*

	Population: adults with atypical facial pain Minimum pain intensity: ≥ 3 on 0-10 scale Inclusion criteria • No clear pathology or somatic findings explaining the facial pain • ≥ 3 on 0-10 pain intensity scale Exclusion criteria • Cardiac, hepatic, or renal disease Total participants randomised: 30 Age in years (median, range): 52 (38-66) Gender: 12/30 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 30 • Inert • Matched dosing schedule and identical appearance to antidepressants Venlafaxine 37.5-70 mg • n = 30 • SNRI • Flexible dosing based on tolerability
Outcomes	Pain intensity Mood Withdrawal
Missing data methods	Completer analysis only
Funding source	Non-pharmaceutical: funded by Helsinki University Central Hospital Research Fund
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind with identical appearance and matched dosing schedules

Forssell 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer-only analysis **Attrition** Total: 10/30 (33.3%) Venlafaxine 37.5-70 mg: 6/30 (20.0%) Placebo: 4/30 (13.3%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Foster 2010a

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: vulvodynia Population: women with vulvodynia Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Aged 18-50 • 3 continuous months of insertional (entryway) dyspareunia, pain, or both with tampon insertion • Mean score ≥ 4 out of 10 on NRS of pain intensity Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 133 Age in years (mean): 30.4 Gender: 133/133 were female Pain duration in years (range): 4.4-6.5
Interventions	Placebo • n = 33 • Inert • Placebo tablet and cream to match intervention arms

Foster 2010a *(Continued)*

- Matched dosing for antidepressant
- Placebo cream for lidocaine

Lidocaine 5% cream

- n = 33
- Topical local anaesthetic
- Participants also took placebo tablet to match antidepressant arm

Desipramine 150 mg

- n = 33
- TCA
- Fixed dose with forced titration
- Participants also used placebo cream to match lidocaine arm

Desipramine 150 mg and lidocaine 5% cream

- n = 34
- Combined intervention
- Fixed dose of antidepressant with forced titration

Outcomes	Pain intensity Mood Withdrawal
Missing data methods	ITT with LOCF
Funding source	Non-pharamaceutical: supported by grant RO-1 HD040123-05 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health
Conflicts of interest	The study authors did not report any potential CoIs.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using permuted block randomisation scheme by means of a computer-based random numbers generator.
Allocation concealment (selection bias)	Low risk	Drug assignments were determined by the Department of Biostatistics.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical-appearing pills and creams, matched dosing with active drug treatment for both tablets and creams
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF. 4 x higher number of dropouts in desipramine+lidocaine arm than placebo **Attrition**

Foster 2010a *(Continued)*

		Total: 21/133 (15.8%) Placebo: 2/33 (6.1%) Lidocaine 5%: 5/33 (15.2%) Desipramine 150 mg: 6/33 (18.2%) Desipramine 150 mg + lidocaine 5%: 6/34 (17.7%)
Selective reporting (reporting bias)	Low risk	All outcomes listed prospectively on clinicaltrials.gov
Other bias	Low risk	No other sources of bias were identified.

Foster 2010b

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA and Canada
Participants	Pain condition: Interstitial Cystitis/Painful Bladder Syndrome Population: people with painful bladder pain with no prior treatment experience for IC/PBS. Minimum pain intensity: ≥ 3 on 0-10 VAS Inclusion criteria • ≥ 3 on 0-10 pain intensity VAS • ≥ 3 on 0-10 symptom score of abnormal urinary frequency VAS • No prior significant treatment for IC/PBS Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 271 Age in years (median): 38 Gender: 216/271 were female Pain duration in years (mean): 6.4
Interventions	Placebo • n = 136 • Inert • Matched dosing schedule Amitriptyline 25-75 mg • n = 135 • TCA

Foster 2010b *(Continued)*

	• Flexible dosing based on tolerability
Outcomes	Pain intensity AEs Withdrawal
Missing data methods	ITT but do not specify missing data methods
Funding source	Non-pharmaceutical: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), collaborator: University of Pennsylvania
Conflicts of interest	Dr Foster reports having no conflicts. Dr Hanno reports Astellas, Pfizer, and Trillium. Dr Nickel reports receiving consulting fees from Merck, Glaxo-Smith-Kline, Pfizer, Ortho Women's Health, Farr Labs, Watson, Medtronic, NeurAxon, Genyous Biomed and research support from Merck, Glaxo-Smith Kline, Allergan, Watson, Pfizer and American Medical Systems. Dr C. Yang reports Medtronic. Dr Chai reports Pfizer and Allergan. Dr Kusek reports holding stock in deCode Genetics. No other potential COI relevant to this manuscript was reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind but no information given regarding study drug appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	State ITT but no imputation methods specified **Attrition** Total: 40/271 (14.8%) Placebo: 17/136 (12.5%) Amitriptyline 25-75 mg: 23/135 (17.0%)
Selective reporting (reporting bias)	High risk	Primary outcome reported according to protocol, not all secondary outcomes reported. Added new outcomes into the outcome measures under methods but never report the outcome for these.
Other bias	Low risk	No other sources of bias were identified.

Frakes 2011

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline to post-intervention Country: USA and Puerto Rico
Participants	Pain condition: knee OA Population: adults over 40 with OA who have not responded to NSAIDs Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria: • Aged ≥ 40 • Met ACR diagnostic criteria for knee OA • Knee pain for at least 14 days/month in the 3 months preceding study • Use of oral NSAIDs for knee pain on most days Exclusion criteria • Physical health comorbidities Total participants randomised: 524 Age in years (mean, SD): 61 (9.2) Gender: 299/524 were female Pain duration in years (mean, SD): 9.5 (8.9)
Interventions	Placebo • n = 260 • Inert Duloxetine 60-120 mg • n = 264 • SNRI • Forced titration to fixed doses • At week 3 of active treatment, participants who had a mean average pain severity rating of at least 4 during the previous week had a blinded dose escalation to 120 mg/day.
Outcomes	Pain intensity Moderate pain relief Substantial pain relief Physical function Mood Sleep PGIC AEs

Frakes 2011 *(Continued)*

	SAEs Withdrawal
Missing data methods	ITT, modified ITT, BOCF, LOCF, MMRM
Funding source	Pharmaceutical: Eli Lilly
Conflicts of interest	"At the time this manuscript was written, E.P.F., R.C.R., and M.M.W. were full-time employees of Eli Lilly and/or one of its subsidiaries and were minor stockholders of Eli Lilly and Company. M.C.H. currently receives research support from the National Institutes of Health; is a consultant for Abbott Laboratories, Amgen, Astra-Zeneca Pharmaceutical Co., Bioiberica S.A., Bristol Myers Squibb Company, Covidien, Eli Lilly and Company, EMD Serono, Inc., Genentech/Roche, Iroko Pharmaceuticals, Merck & Co. Inc., NiCox S.A., Pfizer Inc., Pozen Inc., Rand Corporation, Smith & Nephew, TransPharma Medical Ltd, and UCB Inc.; is a member or chair of DSMB, National Eye Institute, Novartis Pharma A.G., Savient Pharmaceuticals Inc., and Stryker Biotech LLC; and is a member of the medical advisory board and owns stock in Theralogixx, LLC. TDB is a full-time employee of i3 Data Services, a division of InVentiv Health Company. She was contracted by Eli Lilly for writing services. CMRO peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods were not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures were not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind but no information on drug appearance and dosing schedules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants but unsure of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT with LOCF, BOCF, and mBOCF **Attrition** Total: 136/524 (30.0%) Placebo: 61/260 (23.5%) Duloxetine 60-120 mg: 75/264 (28.4%)
Selective reporting (reporting bias)	Low risk	All outcomes reported match those registered prospectively on clincaltrials.gov
Other bias	Low risk	No other sources of bias were identified.

Gao 2010

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: China
Participants	Pain condition: diabetic peripheral neuropathy Population: adults with diabetic peripheral neuropathy Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • ≥ 4 on 0-10 pain intensity VAS • Daily pain for ≥ 6 months • 3 on the clinical portion of the MNSI Exclusion criteria • Unstable glycemic control, any other medical condition that could compromise participation • Risk for suicide Total participants randomised: 215 Age in years (mean): 59.3 Gender: 14/215 were female Pain duration in years (mean): 3.2
Interventions	Placebo • n = 109 • Inert • Matched to antidepressant Duloxetine 60 to 120 mg • n = 106 • SNRI • Flexible dosing dependent on efficacy and tolerance
Outcomes	Pain intensity Sleep Mood Quality of life Moderate pain relief Substantial pain relief PGIC AEs

Gao 2010 *(Continued)*

	SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: Eli Lilly and Boehringer Ingelheim Pharmaceuticals
Conflicts of interest	Drs Vladimir Skljarevski, Durisala Desaiah, Zhang Shu-yu, and Zhang Qi are employees and stockholders of Eli Lilly and Company. All other authors from China were the investigators and received funding from Eli Lilly and Company for conducting this study.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind with identical placebo and matched dosing schedule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 36/215 (16.7%) Placebo: 17/109 (15.6%) Duloxetine 60-120 mg: 19/106 (17.9%)
Selective reporting (reporting bias)	Low risk	All outcomes registered prospectively on clinicaltrials.gov
Other bias	Low risk	No other sources of bias identified

Gao 2015

Study characteristics

Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention

Gao 2015 *(Continued)*

	Country: China
Participants	Population: adults with diabetic peripheral neuropathy Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • ≥ 4 on 0-10 pain intensity VAS • Daily pain for ≥ 6 months • 3 on the clinical portion of the MNSI Exclusion criteria • Unstable glycemic control, any other medical condition that could compromise participation • Mental health conditions Total participants randomised: 405 Age in years (mean, SD): 61.4 (9.5) Gender: 223/405 were female Pain duration in years (mean, SD): 3.3 (3.6)
Interventions	Placebo • n = 202 • Inert • Matched dosing Duloxetine 60 mg • n = 203 • SNRI • Fixed dose with forced titration
Outcomes	Pain intensity Physical function Sleep Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	MMRM, ITT with LOCF
Funding source	Pharmaceutical: Eli Lilly
Conflicts of interest	Drs Gao, Guo, Han, Li, Yang, and Qu have no conflicts of interest. Drs Due~nas, Yue, Wang, Skljarevski, and Raskin are employees and minor shareholders of Eli Lilly

Gao 2015 *(Continued)*

Notes

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind but no information regarding study drugs appearance etc
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 56/405 (13.2%) Placebo: 26/202 (12.9%) Duloxetine 60 mg: 30/203 (14.8%)
Selective reporting (reporting bias)	Low risk	All outcomes listed prospectively to trial on clinicaltrials.gov
Other bias	Low risk	No other sources of bias were identified

Gillving 2021

Study characteristics	
Methods	Design: Denmark Duration: 5 weeks Assessment: baseline and post-intervention Country: cross-over
Participants	Pain condition: painful polyneuropathy of any aetiology Population: people with painful polyneuropathy Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria: • Polyneuropathy for > 6 months • Polyneuropathy diagnosis confirmed by clinical signs

Gillving 2021 *(Continued)*

	Exclusion criteria: • Physical health comorbidities • ≥ 20 on the BDI Total participants randomised: 51 Age in years (median, range): 59 (20-76) Gender: 22/51 were female Pain duration in years (median, range): 40 (10-156)
Interventions	Placebo • n = 38 • Inert • Matched appearance to intervention drugs, and matched dosing Terbutaline 5-15 mg • n = 41 • b2-agonist • Flexible dosage dependent on whether participants were metabolisers and ≥ 70 years of age • Mean dose: 14.4 mg/day Imipramine 30-150 mg • n = 44 • TCA • Flexible dosing dependent on whether participants were metabolisers and ≥ 70 years of age • Mean dose: 85.1 mg/day
Outcomes	Pain intensity Quality of life Sleep Substantial pain relief Moderate pain relief AEs SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Non-pharmaceutical: grants from Danish Regions (Grant no. 14/217) and the Research Foundation of Odense University Hospital. S.S. Gylfadottir was funded by a grant from the Novo Nordic Foundation (Grant no. 14OC0011633).
Conflicts of interest	The study authors have no conflicts of interest to declare
Notes	
Risk of bias	

Gillving 2021 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised through a computer-generated randomisation list.
Allocation concealment (selection bias)	Low risk	Participants were consecutively allocated to the next available randomisation number. The study drugs were packed in containers marked with a randomisation number and treatment period by the hospital pharmacy. Sealed, opaque envelopes containing the treatment sequence for each participant were present at the study sites for emergency situations.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs and double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 12/51 (23.5%) Placebo: 3/51 (5.9%) Terbutaline 5-15 mg: 5/51 (9.8%) Imipramine 30-150 mg: 4/51 (7.8%)
Selective reporting (reporting bias)	Low risk	Trial registered prospectively and outcomes matched those registered
Other bias	Low risk	No other sources of bias were identified

Gilron 2009

Study characteristics	
Methods	Design: cross-over Duration: 6 weeks Assessment: baseline and post-intervention Country: Canada
Participants	Pain condition: neuropathic pain from diabetic peripheral neuropathy or post-herpetic neuralgia Population: adults with diabetic polyneuropathy or post-herpetic neuralgia Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • diagnoses of either diabetic peripheral neuropathy or post-herpetic neuralgia • ≥ 4 on 0-10 pain intensity VAS

Gilron 2009 *(Continued)*

	Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 56 Age in years (median, range): diabetic peripheral: 61 (53-69); post-herpetic: 68 (65-73) Gender: 21/56 were female Pain duration in years (median, range): diabetic peripheral: 5.2 (3.4); post-herpetic: 2.8 (4.3)
Interventions	Gabapentin ≤ 3600 mg • n = 51 • Anticonvulsant • Flexible dosing dependent on tolerability • Double-dummy design Nortriptyline ≤ 100 mg • n = 51 • TCA • Flexible dosing dependent on tolerability • Double-dummy design Nortriptyline ≤ 100 mg and gabapentin ≤ 3600 mg • n = 51 • Combined intervention: TCA + anticonvulsant • Flexible dosing dependent on tolerability • Double-dummy design
Outcomes	Pain intensity Sleep Mood Physical fucntion SAEs Withdrawal
Missing data methods	ITT but no method specified
Funding source	Non-pharmaceutical: Canadian Institutes of Health Research (grant numbers MCT-69422 and MSH-55041)
Conflicts of interest	IG has received honoraria for consulting or being a member of an advisory board, or both for Pfizer. RLH has received research grant support from Pfizer. All other authors declare that they have no conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Gilron 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	Participants were randomised using computer randomisation of the 3 sequences in blocks of 3.
Allocation concealment (selection bias)	Low risk	A trial pharmacist prepared a concealed allocation schedule, and the pharmacist had no further involvement in the trial. Patients were assigned in turn to the next consecutive number, and the corresponding series of study drugs was dispensed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF, unequal dropout **Attrition** Total: 11/56 (19.6%) Gabapentin ≤ 3600 mg: 8/56 (14.3%) Nortriptyline ≤ 100 mg: 1/56 (1.8%) Gabapentin ≤ 3600 mg + nortriptyline ≤ 100 mg: 2/56 (3.6%)
Selective reporting (reporting bias)	Unclear risk	Can't find global pain relief reported in study (was stated in prospective ISRCTN registration). In the protocol, the Profile of Mood State questionnaire was listed as a secondary outcome but it is NR.
Other bias	Low risk	No other sources of bias identified

Gilron 2015

Study characteristics	
Methods	Design: cross-over Duration: 6 weeks Assessment: baseline to post-intervention Country: Canada
Participants	Pain condition: any chronic neuropathic pain Population: adults with chronic peripheral neuropathic pain Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Peripheral neuropathy for at least 6 months • ≥ 4 on 0-10 pain intensity VAS Exclusion criteria

Gilron 2015 *(Continued)*

	• Physical or mental health comorbidities Total participants randomised: 52 Age in years (median, range): 66 (49-80) Gender: 14/52 were female Pain duration in years (mean, SD): 6.1 (6.4)
Interventions	Morphine ≤ 100 mg • n = 52 • Analgesic • Flexible dosing dependent on tolerability • Mean dose: 65.4 mg/day Nortriptyline • n = 52 • TCA • Flexible dosing dependent on tolerability • Mean dose: 83.9 mg/day Nortriptyline and morphine • n = 52 • Combined intervention: TCA and analgesic • Flexible dosing dependent on tolerability • Mean dose: 60.2 mg/day
Outcomes	Pain intensity Mood Sleep Moderate pain relief Substantial pain relief Withdrawal
Missing data methods	NR
Funding source	Part funded by pharmaceutical: "This work was supported by CIHR (Canadian Institutes of Health Research) Grant #MCT-94187 and a CIHR-Pfizer Rx&D Collaborative Research Investigator Program (CIHR Grant #MSH-55041)."
Conflicts of interest	I. Gilron has received support from Adynxx, TARIS Biomedical, AstraZeneca, Pfizer, and Johnson & Johnson and has received grants from the Canadian Institutes of Health Research, Physicians' Services Incorporated Foundation, and Queen's University. R. R. Holden has received research funding from the Canadian Institutes of Health Research, the Social Sciences and Humanities Research Council of Canada, the American Foundation for Suicide Prevention, and Queen's University. A. C. Jackson has received grants from the Canadian Institutes of Health Research, Research Manitoba (formerly the Manitoba Health Research Council), and the University of Manitoba. The remaining authors have no conflicts of interest to declare.
Notes	

Risk of bias

Gilron 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using computer randomisation of the 3 sequences in blocks of 3.
Allocation concealment (selection bias)	Low risk	A trial pharmacist prepared a concealed allocation schedule, and the pharmacist had no further involvement in the trial. Patients were assigned in turn to the next consecutive number, and the corresponding series of study drugs was dispensed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Unequal attrition across arms, states ITT but no imputation methods specified **Attrition** Total: 16/52 (30.8%) Morphine: 9/52 (17.3%) Nortriptyline ≤ 100 mg: 2/52 (3.9%) Nortriptyline + morphine: 7/52 (13.5%)
Selective reporting (reporting bias)	Low risk	All outcomes prospectively reported on ISRCTN.com
Other bias	Low risk	No other sources of bias were identified

Gilron 2016

Study characteristics	
Methods	Design: cross-over Duration: 6 weeks Assessment: baseline and post-intervention Country: Canada
Participants	Pain condition: fibromyalgia Population: people with fibromyalgia Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Aged 18-70 • Fibromyalgia that matches the ACR criteria • ≥ 4 on 0-10 pain intensity VAS

Gilron 2016 *(Continued)*

	Exclusion criteria • Physical health comorbidity • Severe mood disorder Total participants randomised: 41 Age in years (median, range): 56 (20-71) Gender: 36/41were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 41 • Inert • Identical appearance and matched dosing schedule • Double-dummy design Pregabalin ≤ 450 mg • n = 41 • Anticonvulsant • Forced titration to maximum tolerated dose or ceiling dose • Double-dummy design Duloxetine ≤ 120 mg • n = 41 • SNRI • Forced titration to maximum tolerated dose or ceiling dose • Double-dummy design Pregabalin ≤ 450 mg + duloxetine ≤ 120 mg • n = 41 • Anticonvulsant + SNRI • Forced titration to maximum tolerated dose or ceiling dose • Double-dummy design
Outcomes	Pain intensity Quality of life Physical function Mood Sleep Withdrawal
Missing data methods	NR
Funding source	Part funded by pharmaceutical: "This work was supported by CIHR (Canadian Institutes ofHealth) Grant CIHR-MOP-106489 and a CIHR-Pfizer R&D Collaborative Research Investigator Program (CIHR Grant MSH-55041)."
Conflicts of interest	I. Gilron has received support from Adynxx, Taris Biomedical, Astra Zeneca, Pfizer, and Johnson & Johnson and has received grants from the Canadian Institutes of Health Research, Physicians' Services In-

Gilron 2016 *(Continued)*

	corporated Foundation, and Queen's University. L. E. Chaparro received a John J. Bonica Training Fellowship from the International Association for the Study of Pain and also financial support from the Queen's University Department of Anesthesiology and Perioperative Medicine. R. R. Holden has received research funding from the Canadian Institutes of Health Research, the Social Sciences and Humanities Research Council of Canada, the American Foundation for Suicide Prevention, and Queen's University. R. Milev has received financial support and research grants from CIHR, Ontario Brain Institute, Ontario Mental Health Foundation, Lundbeck, Lilly, Sunovion, BMS, Otsuka, Pfizer, Paladin, and Merck. T. Towheed has received financial support from Abbvie and Bristol-Meyers-Squibb and research funding from the Canadian Institutes of Health Research. D. D. Shore. and S. Walker received no external financial support.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using computer randomisation of the 3 sequences in blocks of 3.
Allocation concealment (selection bias)	Low risk	A trial pharmacist prepared a concealed allocation schedule, and the pharmacist had no further involvement in the trial. Patients were assigned in turn to the next consecutive number, and the corresponding series of study drugs was dispensed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, matched dosing schedule and double dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on missing data methods **Attrition** Total: 8/41 (19.5%) Placebo: 1/41 (2.4%) Pregabalin ≤ 450 mg: 1/41 (2.4%) Duloxetine ≤ 120 mg: 3/41 (7.32%) Pregabalin ≤ 450 mg + duloxetine ≤ 120 mg: 4/41 (9.76%)
Selective reporting (reporting bias)	Low risk	Everything as reported in prospectively registered protocol
Other bias	High risk	Taper and washout period were combined, only 1 day complete washout. They state that "primary analysis revealed no significant effects of sequence or carryover, but effects of period and treatment were significant".

Ginsberg 1996

Study characteristics

Ginsberg 1996 *(Continued)*

Methods	Design: parallel Duration: 8 weeks Assessment: baseline, 4 weeks (halfway point), post-intervention Country: Belgium
Participants	Pain condition: fibromyalgia Population: people with fibromyalgia Minimum pain intensity: no Inclusion criteria • Fibromyalgia meeting the ACR 1990 criteria • History of widespread pain for at least 3 months • Pain in at least 11 of 18 specific tender points Exclusion criteria • Physical health comorbidities Total participants randomised: 51 Age in years (mean): 46 Gender: 38/51 were female Pain duration in years (mean): 3.2
Interventions	Placebo • n = 22 (completers) • Inert • Identical appearance and matched dosing schedule Amitriptyline 25 mg • n = 24 (completers) • TCA • Fixed dose with no titration
Outcomes	Pain intensity Sleep AEs Withdrawal
Missing data methods	ITT but no information regarding imputation methods given
Funding source	NR
Conflicts of interest	NR
Notes	
Risk of bias	

Ginsberg 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given, just says patients were "randomised"
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, identical study drugs and matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	State ITT but no imputation methods reported **Attrition** Total: 6/51 (11.8%) Placebo: 3/25 (12.0%) Amitriptyline 25 mg: 3/26 (11.5%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias identified

Ginsberg 1998

Study characteristics	
Methods	Design: parallel Duration: 4 weeks Assessment: baseline and post-intervention Country: Belgium
Participants	Pain condition: fibromyalgia Population: people with fibromyalgia Minimum pain intensity: no Inclusion criteria • Aged between 18 and 75 • Fibromyalgia meeting the ACR 1990 criteria • History of widespread pain for at least 3 months • Pain in at least 11 of 18 specific tender points Exclusion criteria

Ginsberg 1998 *(Continued)*

	• Physical health comorbidities Total participants randomised: 100 Age in years (mean): 39.8 Gender: 85/100 were female Pain duration in months (mean): 34.7
Interventions	Placebo • n = 50 • Inert • Matched dosing Pirlindole 150 mg • n = 50 • Reversible MAOI • Fixed dose
Outcomes	Pain intensity Mood AEs Withdrawal
Missing data methods	NR
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind, but no information regarding study drugs' appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only. Unclear with number randomised, completer analysis and no clear explanation of when and who withdrew. **Attrition**

Ginsberg 1998 *(Continued)*

		Total: 39/100 (39.0%) Placebo: 22/44 (50.0%) Pirlindole 150 mg: 17/45 (37.8%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias identified

Goldenberg 1986

Study characteristics	
Methods	Design: parallel Duration: 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Fibromyalgia matching criteria reported by Yunus 1983 • At least 3 months' duration • ≥ 4 on 0-10 pain intensity VAS Exclusion criteria • History of peptic ulcer disease or cardiac arrhythmias Total participants randomised: 62 Age in years (mean, range): 43.8 (21-69) Gender: 59/62 were female Pain duration in years (mean, range): 3.5 (0.25-20)
Interventions	Amitriptyline 50 mg + naproxen 1000 mg • n = NR • Combined intervention: TCA + NSAID • Fixed doses Placebo + naproxen 1000 mg • n = NR • NSAID • Fixed dose • Double-dummy design

Goldenberg 1986 *(Continued)*

	Amitriptyline 50 mg + placebo • n = NR • TCA • Fixed dose • Double-dummy design Placebo + placebo • n = NR • Double dummy to match intervention arms
Outcomes	Withdrawal
Missing data methods	Completer analysis
Funding source	Partly pharmaceutical: supported by grants from the Arthritis Foundation, Multipurpose Arthritis Center grant no. AM-20613, and a clinical investigator grant from Syntex Co.
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-dummy design, but no information on study drug appearance and dosing
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completer analysis but very low dropout **Attrition** Total: 4/62 (6.5%) Attrition per arm NR
Selective reporting (reporting bias)	High risk	Only present the data for the groups that had significant differences. No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Goldenberg 1996

Study characteristics	
Methods	Design: cross-over Duration: 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: ≥ 30 on 0-100 VAS Inclusion criteria • Aged 18-60 • Fibromyalgia that matches ACR criteria • ≥ 30 on 0-100 pain intensity VAS Exclusion criteria • Physical health comorbidities • Depression: ≥ 18 on Hamilton Rating Scale for Depression Total participants randomised: 31 Age in years (mean, SD): 43.2 (9.1) Gender: 28/31 were female Pain duration/fibromyalgia symptoms in months (mean, SD): 72.6 (48.1)
Interventions	Placebo • Inert • Double-dummy design = 2 tablets per day Amitriptyline 25 mg + placebo • TCA • Fixed dose • Double-dummy design Fluoxetine 20 mg + placebo • SSRI • Fixed dose • Double-dummy design Amitriptyline 25 mg + fluoxetine 20 mg • Combined intervention: TCA + SSRI • Fixed doses • Double dummy design
Outcomes	Pain intensity Quality of life

Goldenberg 1996 *(Continued)*

	Sleep
	Mood
	Withdrawal
Missing data methods	Completer analysis only
Funding source	Non-pharmaceutical: Lot Page Fund, Newton-Wellesley Hospital, Newton
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a table of random numbers
Allocation concealment (selection bias)	Low risk	Randomisation and allocation was performed in the hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical tablets and double-dummy to match dosing schedules across groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer-only analysis, unequal attrition across arms and high overall dropout **Attrition** Total: 12/31 (38.7%) Placebo: 1/31 (3.2%) Amitriptyline 25 mg: 1/31 (3.2%) Fluoxetine 20 mg: 4/31 (12.9%) Amitriptyline 25 mg + fluoxetine 20 mg: 5/31 (16.1%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Goldman 2010

Study characteristics

Methods	Design: parallel

Goldman 2010 *(Continued)*

	Duration: 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: arm pain Population: people with persistent arm pain from repetitive use Minimum pain intensity: ≥ 3 on 0-10 VAS Inclusion criteria • Adults with persistent arm pain that had lasted for at least 3 weeks • ≥ 3 on 0-10 pain intensity VAS Exclusion criteria • Physical health conditions that may affect arm pain Total participants randomised: 118 Age in years (mean): 37.5 Gender: 66/118 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 59 • Inert • Identical appearance to antidepressant arm • Matched dosing Amitriptyline 25 mg • n = 59 • TCA • Fixed dose • If participants complained of side effects during the study, the physician could reduce the dose by half or more
Outcomes	Pain intensity Sleep Mood AEs SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Non-pharmaceutical: "This study was supported by Grants 1RO1 AT 00402-01 and 1K24 AT 004095 from the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health, USA"

Goldman 2010 *(Continued)*

Conflicts of interest	"No author had or now has any financial interest in any for-profit organisation related to the treatment of patients with repetitive strain injuries or related disabling conditions. Dr Rose Goldman sometimes serves as a paid expert witness, independent medical examiner, and/or consultant in workers' compensation and disability cases that might involve musculoskeletal problems and repetitive strain injuries."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a permuted block randomisation design
Allocation concealment (selection bias)	Low risk	Participants were allocated using assignments sealed in sequentially numbered opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs and matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT with LOCF but low attrition **Attrition** Total: 12/118 (10.2%) Placebo: 4/59 (6.8%) Amitriptyline 25 mg: 8/59 (13.6%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Goldstein 2005

Study characteristics

Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: painful diabetic neuropathy Population: people with painful diabetic neuropathy

Goldstein 2005 *(Continued)*

	Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Daily pain due to diabetic polyneuropathy present for at least 6 months • ≥ 4 on 0-10 pain intensity VAS • ≥ 3 on MNSI Exclusion criteria • Physical health comorbidities • Mental health comorbidies, including a diagnosis of MDD Total participants randomised: 457 Age in years (mean, SD): 60.1 (10.9) Gender: 176/457 were female Pain duration in years (mean, SD): 3.7 (3.8)
Interventions	Placebo • n = 115 • Inert Duloxetine 20 mg • n = 115 • SNRI • Fixed dose Duloxetine 60 mg • n = 114 • SNRI • Fixed dose Duloxetine 120 mg • n = 113 • SNRI • Fixed dose
Outcomes	Pain intensity Physical function Quality of life Mood Substantial pain relief PGIC Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: Eli Lilly and Company and PRN Consulting

Goldstein 2005 *(Continued)*

Conflicts of interest	Authors are employees and/or stockholders of Eli Lilly and Company. David J. Goldstein, MD, PhD, is a consultant for Eli Lilly and Company
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a computer-generated random sequence.
Allocation concealment (selection bias)	Low risk	Participants were allocated using an Interactive Voice Response System.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given on blinding procedures in regard to medication, although reported as double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT with LOCF **Attrition** Total: 113/457 (24.7%) Placebo: 28/115 (24.4%) Duloxetine 20 mg: 24/115 (20.9%) Duloxetine 60 mg: 28/114 (24.6%) Duloxetine 120 mg: 33/113 (29.2%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

González-Viejo 2005

Study characteristics

Methods	Design: parallel Duration: physical therapy 3 weeks; sertraline 24 weeks Assessment: baseline and post-intervention Country: Spain
Participants	Pain condition: fibromyalgia Population: women with fibromyalgia

González-Viejo 2005 *(Continued)*

	Minimum pain intensity: no Inclusion criteria • Fibromyalgia as per the ACR criteria • Duration ≥ 6 months Exclusion criteria • Hypertension and pregnancy • Use of antidepressants for at least 4 weeks Total participants randomised: 70 Age in years (mean, SD): 47.5 (4) Gender: 70/70 were female Pain duration in years (mean, SD): NR
Interventions	Physical therapy • n = 34 • 15 sessions over 3 weeks • Participants received physiotherapy treatment, learning and practicing physiotherapy exercises for the cervical spine. They also received ultrasonography (1 W/cm2) on painful points in the cervical area. Sertraline 50 mg • n = 36 • SSRI • 24 weeks • Fixed dose
Outcomes	Pain intensity Sleep Withdrawal
Missing data methods	All participants completed the trial
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias)	High risk	Unable to be double-blind due to the nature of interventions

González-Viejo 2005 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the trial **Attrition** None
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Goodkin 1990

Study characteristics	
Methods	Design: parallel Duration: 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: low back pain Population: adults with low back pain Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Minmum of 1 year of back pain or 2 prior episodes low back pain of at least 2 weeks in duration with a current episode of at least 2 weeks • ≥ 4 on 0-10 pain intensity VAS Exclusion criteria • ≥ 4 additional pain sites • Physical and mental health comorbidities Total participants randomised: 42 Age in years (mean, SD): 53.6 (12.9) Gender: 16/42 were female Pain duration in years (mean, SD): 20.3 (16.0)
Interventions	Placebo • n = 20 • Inert • Identical appearance and taste, and matched dosing schedule

Goodkin 1990 *(Continued)*

	Trazodone ≤ 600 mg • n = 22 • SARI • Forced titration to maximum tolerable dose • Mean dose: 201 mg/day
Outcomes	Pain intensity Physical function Mood Withdrawal
Missing data methods	ITT with LOCF
Funding source	Partly funded by pharmaeutical: "This work was supported by NIH grants MH18764 and MH16744 and NIMH Mental Health Clinical Research Center grant MH41115, a grant from the Procter and Gamble Company, a grant from the Stanford University Health Sciences Research and Development Fund, and a grant from the Western Research and Development Office of the Veterns Administration."
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Low risk	Participants were randomised to either trazodone or placebo groups by the Stanford University pharmacist who never interacted with participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical appearance of study drugs and matched dosing schedule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 13/42 (31.0%) Placebo: 4/20 (20.0%) Trazodone ≤ 600 mg: 9/22 (40.9%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Gould 2020

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: low back pain Population: adults with low back pain Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Aged 18-70 • Non-specific low back with a duration of least ≥ 6 months • ≥ 4 on a 0-10 pain intensity VAS Exclusion criteria • Current physical or mental health comorbidities Total participants randomised: 142 Age in years (mean, SD): 55.8 (11.7) Gender: 15/142 were female Pain duration in years (mean, SD): NR
Interventions	Placebo (benzotropine mesylate 0.125 mg) • n = 33 • Active placebo • Fixed dose Desipramine • n = 38 • TCA • Flexible dosage dependent upon patient metabolism Placebo (benzotropine mesylate 0.125 mg) + CBT • n = 34 • Combined intervention: active placebo pill + CBT • Fixed dose of 0.125 mg • 6 CBT appointments over the course of 8 weeks Desipramine + CBT • n = 37 • Combined intervention: TCA + CBT • Flexible dosage dependent upon patient metabolism • 6 CBT appointments over the course of 8 weeks

Gould 2020 *(Continued)*

Outcomes	Pain intensity Physical function Moderate pain relief AEs SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Non-pharmaceutical: VA Office of Research and Development Collaborator: University of California, San Diego
Conflicts of interest	The study authors have no conflicts of interest to declare
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	To minimise the risk of bias in treatment assignment, randomisation using a random number generator (www.randomizer.org) was conducted by a VA San Diego Healthcare System Clinical Research Pharmacy (author S.D.F.), who alone held the key
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Double-blinding across all arms not possible due to the nature of CBT
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF. Attrition unequal across arms **Attrition** Total: Placebo: 9/33 (27.3%) Desipramine 20-60 mg: 11/38 (29.0%) Placebo + CBT: 7/34 (20.6%) Desipramine 20-60 mg + CBT: 16/37 (43.2%)
Selective reporting (reporting bias)	Unclear risk	Mention in published paper that other outcomes were measured and reported in the protocol (which they don't seem to be) and that they were NR in the publication as it was not in keeping with the study hypothesis/aim

Gould 2020 *(Continued)*

Other bias	Low risk	No other sources of bias were identified

Grace 1985

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline, 4 weeks, 8 weeks, and post-intervention Country: Canada
Participants	Pain condition: RA Population: adults with RA Minimum pain intensity: no Inclusion criteria • Patients with 'definite' or 'classical' RA, as defined by the ACR criteria Exclusion criteria: NR Total participants randomised: 36 Age in years (mean, range): 58 (27-76) Gender: 29/36 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 18 • Inert • Identical appearance to antidepressants Amitriptyline 50-75 mg • n = 18 • TCA • Flexible doses dependent upon tolerability
Outcomes	Withdrawal
Missing data methods	Completer-only analysis
Funding source	NR
Conflicts of interest	NR
Notes	
Risk of bias	

Grace 1985 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical tablets with matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only **Attrition** Total: 8/36 (22.2%) Placebo: 4/18 (22.2%) Amitriptyline 50-75 mg: 4/18 (22.2%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Graff-Radford 2000

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline to post-intervention Country: USA
Participants	Pain condition: post-herpetic neuralgia Population: adults with post-herpetic neuralgia Minimum pain intensity: no Inclusion criteria • Post-herpetic neuralgia for at least 6 months Exclusion criteria: NR Total participants randomised: 50 Age in years (mean, SD): 72.9 (10.1)

Graff-Radford 2000 *(Continued)*

	Gender: 22/50 were female Pain duration in months (mean, SD): 33.4 (29.5)
Interventions	Amitriptyline ≤ 200 mg • n = 11 • TCA • Flexible dose dependent upon tolerability • Double-dummy design Amitriptyline ≤ 200 mg + fluphenazine ≤ 3 mg • n = 12 • Combined intervention: TCA + antipsychotic • Flexible doses dependent upon tolerability Fluphenazine ≤ 3 mg • n = 13 • Antipsychotic • Flexible dose dependent upon tolerability Placebo (glycopyrrolate) • n = 13 • Active placebo • Flexible dose dependent upon tolerability • Double-dummy design
Outcomes	Pain intensity Mood Withdrawal
Missing data methods	Completer analysis only
Funding source	Non-pharmaceutical: "This study was supported by a grant from the National Institute of Health/National Institute of Dental Research (1RO3DE10086-01)"
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical appearing study drugs, double-dummy design

Graff-Radford 2000 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completer analysis but only 1 person withdrew **Attrition** Total: 1/50 (2.0%) Amitriptyline 12.5-200 mg: 1/12 (8.3%) Amitriptyline 12.5-200 mg + fluphenazine 1-3 mg: 0/12 (0.0%) Fluphenazine 1-3 mg: 0/13 (0.0%) Placebo: 0/13 (0.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Hadianfard 2012

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline, 2 weeks, 4 weeks, post-intervention, follow-up (10 months post-intervention) Country: Iran
Participants	Pain condition: fibromyalgia Population: women ≤ 65 with fibromyalgia Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Women aged 20-65 • Diagnosed with fibromyalgia as per ACR criteria • ≥ 4 on 0-10 pain intensity scale Exclusion criteria • Significant physical and mental health comorbidities Total participants randomised: 30 Age in years (mean): 44 Gender: 30/30 were female Pain duration in months (mean): 81.2
Interventions	Acupuncture

Hadianfard 2012 *(Continued)*

	• n = 15 • 2 weeks of 3 sessions (weekly) lasting for 30 min in each session Fluoxetine 20 mg • n = 15 • SSRI • Fixed dose
Outcomes	Pain intensity Quality of life Mood Physical function
Missing data methods	ITT but methods not specified
Funding source	Non-pharmaceutical: Shiraz University of Medical Sciences research project No. 88-5035
Conflicts of interest	"We declare no conflict of interest. This article is from Shiraz University of Medical Sciences research project No. 88-5035"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a computer-generated random sequence of the numbers
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded. Lead author was the acupuncturist
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	States ITT but no imputation methods reported **Attrition** NR
Selective reporting (reporting bias)	Unclear risk	Protocol registered retrospectively
Other bias	Low risk	No other sources of bias were identified.

Hameroff 1984

Study characteristics	
Methods	Design: parallel Duration: 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: chronic cervical and/or lumbar spine pain Population: adults with chronic cervical and/or lumbar spine pain and depression Minimum pain intensity: no Inclusion criteria • Patients with chronic cervical and/or lumbar spine pain and co-existing clinical depression • Pain for at least 2 months Exclusion criteria: NR Total participants randomised: 60 Age in years (mean): 48.7 Gender: 28/60 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 30 • Inert Doxepin ≤ 300 mg • n = 30 • TCA • Flexible dose dependent upon tolerability and effficacy
Outcomes	Withdrawal
Missing data methods	NR
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information, just says "patients were randomly assigned to one of two treatment groups"

Hameroff 1984 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Says double-blind but no information regarding procedures
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	Only report completer analysis. 50% more dropout in placebo arm than intervention **Attrition** Total: 9/60 (15.0%) Placebo: 6/30 (20.0%) Doxepin ≤ 300 mg: 3/30 (10.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Hammody 2015

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline, week 4, week 8, post-intervention Country: Iraq
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: no Inclusion criteria • Patients with fibromyalgia fulfilling the Wolfe 2010 criteria Exclusion criteria • Inflammatory conditions and cardiovascular problems Total participants randomised: 123 Age in years (mean, SD): NR Gender: NR

Hammody 2015 *(Continued)*

	Pain duration in years (mean, SD): NR
Interventions	Pregabalin 75 mg • n = 62 • Anticonvulsant • Fixed dose, no titration Amitriptyline 25 mg • n = 61 • TCA • Fixed dose, no titration
Outcomes	Pain intensity Quality of life
Missing data methods	NR
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind, but no information regarding blinding procedures
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition, analysis of per-protocol population **Attrition** Total: 45/123 (36.6%) Attrition per arm NR
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	High risk	Poorly reported - mistakes throughout document, figures not really adding up and tables wrongly titled

Hannonen 1998

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: Finland
Participants	Pain condition: fibromyalgia Population: women with fibromyalgia Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Women aged 18-65 • Fulfilling ACR criteria for fibromyalgia • ≥ 4 out of 0-10 for pain, general health, sleep, and fatigue Exclusion criteria • Severe physical health problems, major depression, psychosis, obsessive compulsive disorder Total participants randomised: 130 Age in years (mean): 48.7 Gender: 130/130 were female Pain duration in years (mean): 8.2
Interventions	Placebo • n = 45 • Inert • Double-dummy design Moclobemide 450-600 mg • n = 43 • Reversible MAOI • Flexible dose dependent upon efficacy • Double-dummy design Amitriptyline 25-37.5 mg • n = 42 • TCA • Flexible dose dependent upon efficacy • Double-dummy design
Outcomes	Pain intensity Sleep Mood

Hannonen 1998 *(Continued)*

	Physical function AEs Withdrawal
Missing data methods	States ITT but no methods reported
Funding source	Partly supported by pharmaceutical: "The financial support by Roche Oy, Finland, is gratefully acknowledged."
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods NR
Allocation concealment (selection bias)	Low risk	The randomisation was organised centrally with sequentially numbered envelopes consisting of blocks of 6
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, study drugs were identical, double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	States ITT but no methods reported **Attrition** Total: 38/130 (29.2%) Moclobemide 450-600 mg: 13/43 (30.2%) Amitriptyline 25-37.5 mg: 10/42 (23.8%) Placebo: 15/45 (33.3%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias identified

Heymann 2001

Study characteristics

Methods	Design: parallel Duration: 8 weeks

Heymann 2001 *(Continued)*

	Assessment: baseline and post-intervention Country: Brazil
Participants	Pain condition: fibromyalgia Population: women with fibromyalgia Minimum pain intensity: no Inclusion criteria • Women with fibromyalgia meeting the ACR criteria Exclusion criteria • Physical health comorbidities • Use of nortriptyline or amitriptyline at any point Total participants randomised: 118 Age in years (mean): 50.5 Gender: 118/118 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 40 • Inert • Identical tablets, matched dosing Amitriptyline 25 mg • n = 40 • TCA • Fixed dose Nortriptyline 25 mg • n = 38 • TCA • Fixed dose
Outcomes	Quality of life SAEs Withdrawal
Missing data methods	Completer analysis
Funding source	NR
Conflicts of interest	NR
Notes	
Risk of bias	

Heymann 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using random number tables
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, all study drugs were identical in appearance and packaging
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Much higher attrition in the placebo group than intervention groups. No missing data methods; report only completer analysis **Attrition** Total: 12/118 (10.2%) Amitriptyline 25 mg: 3/40 (7.5%) Nortriptyline 25 mg: 2/38 (5.3%) Placebo: 7/40 (17.5%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Holbech 2015

Study characteristics	
Methods	Design: cross-over Duration: 5 weeks Assessment: baseline and post-intervention Country: Denmark
Participants	Pain condition: polyneuropathy Population: adults with polyneuropathy Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Aged 20-85 • Polyneuropathy for > 6 months • Median pain rating of ≥ 4 on 0-10 scale

Holbech 2015 *(Continued)*

	Exclusion criteria • Pain other than polyneuropathy Total participants randomised: 73 Age in years (mean, range): 59.3 (29-82) Gender: 28/73 were female Pain duration in months (mean, range): 63.5 (9 -24)
Interventions	Placebo • Inert • Double-dummy design Pregabalin 300 mg • Anticonvulsant • Fixed dose • Patients > 70 years were given a lower dose (150 mg) • Double-dummy design Imipramine 75 mg • Antidepressant • Fixed dose • Patients > 70 years were given a lower dose (25 mg) • Double-dummy design Pregabalin 300 mg + imipramine 75 mg • Combined anticonvulsant and antidepressant • Fixed doses • Patients > 70 years were given lower doses (pregabalin 150 mg and imipramine 25 mg) • Double-dummy design
Outcomes	Moderate pain relief Substantial pain relief AEs Withdrawal
Missing data methods	ITT with LOCF and per-protocol analysis
Funding source	Partly funded by pharmaceutical: "This was an investigator-initiated trial supported by Pfizer with a grant of USD 52080 (grant no: WS368802). The trial was also supported by a grant from Odense University Hospital."
Conflicts of interest	F. W. Bach reports to have been compensated as an Investigator in clinical trials on neuropathic pain sponsored by Pfizer and Grunenthal. N. B. Finnerup reports personal fees from Pfizer, grants and personal fees from Grunenthal, personal fees from Astellas, personal fees from Norpharma, grants from EU/EFPIA; outside the submitted work. T. S. Jensen reports to be on Advisory Board for Pfizer, Grunenthal, and Orion. The other authors have no conflicts of interest to declare.
Notes	

Holbech 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised through a computer-generated randomisation list.
Allocation concealment (selection bias)	Low risk	Participants were allocated using sealed, opaque envelopes containing the treatment sequence. The randomisation plan was generated by a person at the hospital pharmacy at Odense University Hospital, who was not otherwise involved in the conduct of the trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical appearing study drugs, double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 23/70 (32.9%) Placebo: 5/73 (6.9%) Pregabalin 300 mg: 5/73 (6.9%) Imipramine 75 mg: 4.73 (5.5%) Pregabalin 300 mg + imipramine 75 mg: 9/73 (13.0%)
Selective reporting (reporting bias)	Low risk	All outcomes reported prospectively on clinicaltrials.gov
Other bias	Low risk	No other sources of bias were identified

Hudson 2021

Study characteristics	
Methods	Design: parallel Duration: 14 weeks Assessment: baseline and post-intervention Country: New Zealand
Participants	Pain condition: knee OA Population: people with knee OA on a stable analgesic regime Minimum pain intensity: ≥ 20 out of 50 on WOMAC pain subscale Inclusion criteria

Hudson 2021 *(Continued)*

- Primary knee OA defined according to ACR classification criteria
- ≥ 20 out of 50 on WOMAC pain subscale
- Stable analgesic regime for 2 months before study entry

Exclusion criteria

- Prior joint replacement on study knee
- Sensitivity to nortriptyline or other TCAs
- Cardiovascular conditions
- Bipolar disorder

Total participants randomised: 205

Age in years (mean): 64.5

Gender: 87/205 were female

Pain duration in years (mean): 7.6

Interventions	Placebo • n = 103 • Inert • Identical appearance and matched dosing schedule Nortriptyline ≤ 100 mg • n = 102 • TCA • Flexible dosing dependent upon efficacy and tolerability • Mean dose: 55.8 mg/day
Outcomes	Pain intensity Physical function Mood AEs SAE Withdrawal
Missing data methods	Imputation using multivariate normal multiple imputation
Funding source	Non-pharmaceutical: project grant from the Health Research Council of New Zealand (reference number: 14/152).
Conflicts of interest	The authors have declared no competing interests
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised with a 1:1 allocation, computer-generated randomisation list with blocks of varying size (1-4) was prepared by the study statistician (https://cran.r-project. org/web/packages/blockrand/index.html).

Hudson 2021 *(Continued)*

Allocation concealment (selection bias)	Low risk	The contracted pharmacist will determine which group of participants, A or B, will be allocated to receive nortriptyline. The study medication (nortriptyline or identical placebo) will be packaged in identical containers. Each container will be pre-labelled (by the study pharmacist contracted to provide the study medication) with a study identifier according to randomisation schedule.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identically appearing study drugs, matched dosing schedules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very low dropout with no data collection at follow- up (4/205). Multiple imputation for missing data **Attrition** Total: 4/205 (2.0%) Placebo: 1/103 (1.0%) Nortriptyline 25-100 mg: 3/102 (2.9%)
Selective reporting (reporting bias)	Low risk	Published trial protocol: https://trialsjournal.biomedcentral.com/track/pdf/10.1186/s13063-015-0961-1.pdf. All outcomes reported or reasons for no further analysis given. Although there was an error collecting data at baseline for the first 24 participants, this was reported and accounted for in the analysis.
Other bias	Low risk	No other sources of bias were identified.

Hussain 2011

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Country: Iraq
Participants	Pain condition: fibromyalgia Population: people aged between 18-65 with early diagnosed fibromyalgia Minimum pain intensity: no Inclusion criteria • Aged 18-65 • Primary fibromyalgia diagnosed as per ACR criteria Exclusion criteria

Hussain 2011 *(Continued)*

	• Other pathologic disorders that would interfere with the study Total participants randomised: 101 Age in years (mean, SD): 38.8 Gender: 95/101 were female Pain duration in years (mean, SD): NR
Interventions	Melatonin 5 mg + placebo • n = 27 • Hormone • Fixed dose • Double-dummy design Fluoxetine 20 mg + placebo • n = 24 • SSRI • Fixed dose • Double-dummy design Fluoxetine 20 mg + melatonin 3 mg • n = 27 • Combined intervention: SSRI + hormone • Fixed doses Fluoxetine 20 mg + melatonin 5 mg • n = 23 • Combined intervention: SSRI + hormone • Fixed doses
Outcomes	Pain intensity Quality of life Mood Physical function
Missing data methods	NR
Funding source	Non-pharmaceutical: the present data were abstracted from PhD theses submitted to the Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad. "The authors gratefully thank the College of Pharmacy for supporting the project."
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified

Hussain 2011 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-dummy dosing used, but no information given regarding appearance of capsules. Also no information regarding AEs given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but uncertain of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on withdrawal. No missing data methods reported
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Isomeri 1993

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: Finland
Participants	Pain condition: fibromyalgia Population: people with fibromyalgia Minimum pain intensity: no Inclusion criteria • Patients fulfilling the diagnostic criteria of Yunus 1983 for primary fibromyalgic syndrome Exclusion criteria • Other diseases causing pain Total participants randomised: 51 Age in years (mean): 43.7 Gender: 39/51 were female Pain duration in years (mean): 7.9
Interventions	Physiotherapy and amitriptyline 25 mg • n = 17 • Combined intervention: physiotherapy + TCA

Isomeri 1993 *(Continued)*

- Fixed dose of 25 mg
- Conventional physiotherapy consisting of light muscle stretching exercises only

Physical fitness training

- n = 17
- Cardiovascular fitness training

Physical fitness training and amitriptyline 25 mg

- n = 17
- Combined intervention: physical fitness training + TCA
- Physical fitness training of increasing strenuousness and amitriptyline 25 mg in the evenings
- Fixed dose

Outcomes	Withdrawal
Missing data methods	NR
Funding source	Non-pharmaceutical: supported by grants from the Rheumatism Research Foundation
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods NR
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not able to be double-blinded due to nature of interventions. Doesn't mention sham dosing or placebo for group not receiving amitriptyline
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer-only analysis, no information given about withdrawal reasons **Attrition** Total: 6/51 (11.8%) Physiotherapy + amitriptyline 25 mg: 1/17 (5.9%) Physical fitness training: 2/17 (11.8%) Physical fitness training + amitriptyline 25 mg: 3/17 (17.7%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found

Isomeri 1993 *(Continued)*

Other bias	Low risk	No other sources of bias were identified.

Iwaki 2020

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: Japan
Participants	Pain condition: pain in Parkinson's disease Population: adults with Parkinson's disease experiencing associated pain Minimum pain intensity: no Inclusion criteria • Aged ≥ 20 with diagnosed Parkinson's disease • Pain associated with Parkinson's disease Exclusion criteria • Evidence of clinically significant disease • Suicidal risk Total participants randomised: 47 Age in years (mean): 68.0 Gender: 25/47 were female Pain duration in years (mean): 2.3
Interventions	Placebo • n = 23 • Inert • Matched dosing Duloxetine 40 mg • n = 23 • SNRI • Fixed dose
Outcomes	Pain intensity Mood SAEs Withdrawal
Missing data methods	Not specified

Iwaki 2020 *(Continued)*

Funding source	Pharmaceutical: funding was provided by Ehime University under a contract with Shionogi & Co. Ltd (pharmaceutical company).
Conflicts of interest	The authors have no COI to report
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods NR
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blinded but no information on appearance of study drugs
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but uncertain of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	Much higher attrition in antidepressant arm than placebo. Unsure of imputation methods used **Attrition** Total: 9/46 (19.6%) Placebo: 2/23 (8.7%) Duloxetine 40 mg: 7/23 (30.4%)
Selective reporting (reporting bias)	Low risk	Outcomes match those in protocol
Other bias	Low risk	No other sources of bias were identified

Johansson 1979

Study characteristics

Methods	Design: parallel Duration: 4 weeks Assessment: baseline and post-intervention Country: Sweden
Participants	Pain condition: chronic pain conditions Population: people hospitalised at the Department of Neurology, University of Umeå with chronic pain syndromes

Johansson 1979 *(Continued)*

	Minimum pain intensity: no Inclusion criteria • Pain syndromes of at least 6 months with a stable course • All possibilities of active treatment tried Exclusion criteria: NR Total participants randomised: 40 Age in years (range): 25-65 Gender: 23/40 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 20 • Inert • Matched dosing schedule Zimelidine 200 mg • n = 20 • SSRI • Fixed dose with forced titration
Outcomes	Pain intensity Withdrawal
Missing data methods	Completer analysis
Funding source	NR
Conflicts of interest	NR
Notes	Zimelidine has been banned worldwide due to serious, sometimes fatal, cases of central and/or peripheral neuropathy known as Guillain-Barré syndrome and due to a peculiar hypersensitivity reaction involving many organs including skin exanthema, flu-like symptoms, arthralgias, and sometimes eosinophilia. Additionally, zimelidine was found to cause an increase in suicidal ideation and/or attempts among depressive patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were then according to a randomisation list given tablets of identical form, color and taste, containing either Zimelidine 25 mg or a placebo according to a fixed dose regimen"
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, matched dosing and appearance of study drugs

Johansson 1979 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	HIgh attrition in Zimeldine arm. Reported compeleter analysis only, with no missing data methods **Attrition** Total: 8/20 (40.0%) Placebo: 3/11 (27.3%) Zimeldine 200 mg: 5/9 (55.6%)
Selective reporting (reporting bias)	Unclear risk	No protocol found
Other bias	Low risk	No other sources of bias were identified.

Joharchi 2019

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline, 4 weeks, 8 weeks, post-intervention Country: Iran
Participants	Pain condition: diabetic peripheral neuropathy Population: type 2 diabetic adults aged ≥ 40 and ≤ 65 with diabetic peripheral neuropathic pain Minimum pain intensity: ≥ 40 on 0-100 VAS Inclusion criteria • Aged 40-65 • Diabetes duration ≥ 5 years • Diabetic peripheral neuropathy diagnosis • Diabetic peripheral neuropathy severity ≥ 40 on 100 VAS with a duration of ≥ 12 months Exclusion criteria • Severe physical and mental health comorbidities Total participants randomised: 180 Age in years (mean): 54.48 Gender: 109/180 were female Pain duration in years (mean): 3.8
Interventions	Duloxetine 30-60 mg • n = 90

Joharchi 2019 *(Continued)*

- SNRI
- Flexible dose dependent upon efficacy and tolerability
- Mean dose: 42.5 mg/day

Pregabalin 150-300 mg

- n = 90
- Anticonvulsant
- Flexible dose dependent upon efficacy and tolerability
- Mean dose: 235.5 mg/day

Outcomes	Pain intensity AEs Withdrawal
Missing data methods	Completer analysis
Funding source	Non-pharmaceutical: part of a PhD project - financially supported by “Research Department of theS-chool of Medicine Shahid Beheshti University of Medical Sciences(SBUMS)” (Grant No 13/587).
Conflicts of interest	The authors declare that they have no COI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified: Just states "randomly divided into 2 groups"
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Used "similar" capsules but participants in pregabalin arm took 2 capsules a day compared to 1 a day for duloxetine
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from blinded participants, unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	Higher attirition in duloxetine group than pregabalin, completer analysis only **Attrition** Total: 36/180 (20.0%) Duloxetine 30-60 mg: 24/90 (26.7%) Pregabalin 150-300 mg: 12/90 (13.3%)
Selective reporting (reporting bias)	Low risk	Protocol registered prospectively to study with outcome measures
Other bias	Low risk	No other sources of bias were identified.

Jose 2007

Study characteristics	
Methods	Design: cross-over Duration: 6 weeks Assessment: baseline, 2 weeks, 4 weeks, post-intervention Country: India
Participants	Pain condition: diabetic peripheral neuropathy Population: adults with type 2 diabetes and diabetic peripheral neuropathy Minimum pain intensity: ≥ 50 on 0-100 scale Inclusion criteria • Aged 18-75 with painful diabetic neuropathy • Painful diabetic neuropathy for at least 1 month and having pain of > 50% as assessed by 0-100 scale Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 75 Age in years (median, range): 56 (50-62) Gender: 30/75 were female Pain duration in years (median, range): 12 (4-24)
Interventions	Lamotrigine 50-200 mg • Anticonvulsant • Flexible dosing dependent upon efficacy and tolerability • Identical tablets to amitriptyline Amitriptyline 10-50 mg • TCA • Flexible dosing dependent upon efficacy and tolerability • Identical tablet to lamotrigine
Outcomes	Pain intensity AEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	NR
Conflicts of interest	None declared
Notes	

Jose 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using random number tables by block randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation procedure unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, study drugs appeared identical and matched dosing schedules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Use ITT and LOCF. Unequal attrition across arms - 100% of participants who completely dropped out did so from the 1st period in one intervention arm. **Attrition** Total: 7/53 (13.2%) Lamotrigine 50-200 mg: 0/53 (0.0%) Amitriptyline 10-50 mg: 7/53 (13.2%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Kalso 1996

Study characteristics

Methods	Design: cross-over Duration: 4 weeks Assessment: baseline, 2 weeks, post-intervention Country: Finland
Participants	Pain condition: cancer-related neuropathic pain Population: women with chronic neuropathic pain following treatment for breast cancer Minimum pain intensity: no Inclusion criteria • Moderate-severity neuropathic pain following treatment for breast cancer Exclusion criteria: NR

Kalso 1996 *(Continued)*

	Total participants randomised: 20 Age in years (median, range): 56 (39-72) Gender: 20/20 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • Inert • Matched dosing to antidepressant Amitriptyline 100 mg • TCA • Forced titration to maximum tolerated dose or 100 mg/day
Outcomes	The article reported no useable data
Missing data methods	Completer-only analysis
Funding source	Non-pharmaceutical: The study was supported by the Academy of Finland (E.K., T.T.), the Paulo Foundation, Finland (E.K.) and the Centre for International Mobility (T.T.).
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind and matched dosing but doesn't specify other blinding procedures
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer-only analysis. Withdrawal information doesn't specify in which period the participants withdrew **Attrition** Total: 5/20 (25.0%) Attrition per arm NR
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found

Kalso 1996 *(Continued)*

Other bias	Low risk	No other sources of bias were identified.

Katz 2005

Study characteristics	
Methods	Design: cross-over Duration: 7 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: low back pain Population: adults with chronic low back pain Minimum pain intensity: no Inclusion criteria • ≥ 18 years and chronic low back pain for ≥ 3 months Exclusion criteria • Any other significant physical or mental health comorbidity Total participants randomised: 54 Age in years (mean, SD): 50.6 (10.7) Gender: 26/54 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • Inert • Matched dosing schedule Bupropion 300 mg • NDRI • Fixed dose with forced titration
Outcomes	Pain intensity SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Partly funded by pharmaceutical: "Supported in part by an investigator-initiated research grant from GlaxoSmithKline"
Conflicts of interest	Supported in part by an investigator-initiated research grant from GlaxoSmithKline to R.H.D., who has also received research support, consulting fees, or lecture honoraria in the past year from Abbott Laboratories, Eli Lilly & Co., Endo Pharmaceuticals, EpiCept Corporation, NeurogesX, Novartis Pharmaceu-

Katz 2005 *(Continued)*

	ticals, Organon, Ortho-McNeil Pharmaceutical, Pfizer, Purdue Pharma, Ranbaxy Corporation, Reliant Pharmaceuticals, Renovis, and UCB Pharma.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a computer-generated list of random numbers.
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind and used same dosing for placebo as intervention but no information given regarding other blinding procedures
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants but uncertain of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 14/54 (25.9%) Placebo: 5/54 (9.3%) Bupropion 300 mg: 9/54 (16.7%)
Selective reporting (reporting bias)	High risk	"Several other health-related quality-of-life measures of physical and emotional functioning were administered, but these data were not analyzed because of the absence of significant beneficial effects on the pain intensity and relief outcome measures."
Other bias	Unclear risk	Participants tapering off of bupropion reported having AEs from reducing the medication, which could have lasted the washout period, but this is not explored further in the article.

Kaur 2011

Study characteristics

Methods	Design: cross-over Duration: 6 weeks Assessment: baseline and post-intervention Country: India
Participants	Pain condition: diabetic peripheral neuropathy Population: adults with type 2 diabetes and diabetic peripheral neuropathy

Kaur 2011 *(Continued)*

	Minimum pain intensity: ≥ 50 on 0-100 VAS Inclusion criteria • Aged 18-75 • diabetic peripheral neuropathy for at least 1 month • ≥ 50 on 0-100 pain intensity VAS Exclusion criteria • Clinically significant physical or mental health comorbidities Total participants randomised: 65 Age in years (median, IQR): 52.5 (48.2–62) Gender: 31/65 were female Pain duration in years (median IQR): 8 (6–36)
Interventions	Amitriptyline 10-50 mg • TCA • Flexible titration with fixed doses: started at 10 mg, with optional titration every 2 weeks to 25 mg, and then 50 mg Duloxetine 20-60 mg • SNRI • Flexible titration with fixed doses: started at 20 mg, with optional titration every 2 weeks to 40 mg, and then 60 mg
Outcomes	Moderate pain relief Substantial pain relief
Missing data methods	Unclear regarding methods
Funding source	NR
Conflicts of interest	No potential conflicts of interest relevant to this study were reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using computer-generated randomisation of blocks of 4
Allocation concealment (selection bias)	Low risk	The drug packets were administered to patients serially according to the patient's reporting sequence.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Says double-blind but no information given regarding procedure e.g. appearance of tablets
Blinding of outcome assessment (detection bias)	Unclear risk	Self-reported outcomes by participants but not enough information given regarding blinding

Kaur 2011 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear reporting of withdrawals and analysis. State ITT analysis but only including those 58 who completed the study **Attrition** Total: 7/65 (10.8%) Attrition per arm NR
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Kayiran 2010

Study characteristics	
Methods	Design: parallel Duration: 4 or 8 weeks Assessment: baseline, 2 weeks (mid-intervention), 4 weeks (post-intervention for neurofeedback), 8 weeks (post-intervention for escitalopram), week 16 (follow-up), week 24 (follow-up) Country: Turkey
Participants	Pain condition: fibromyalgia Population: women aged 16-49 with fibromyalgia Minimum pain intensity: no Inclusion criteria • Aged 16-49 • Meet the ACR criteria for fibromyalgia Exclusion criteria • Cardiovascular problems Total participants randomised: 40 Age in years (mean): 32.1 Gender: 40/40 were female Pain duration in years (mean): 4.8
Interventions	Neurofeedback • n = 20 • 5 x 30-min sessions per week • "Patients were seated on a comfortable armchair in front of a computer screen where they can involve in the selected computer game during treatment sessions. It was explained to participants to be relaxed and concentrated on the computer game and try to widen the river which is seen on the monitor as a game. Whenever the patients could be successful on widening the river then they enhanced SMR

Kayiran 2010 *(Continued)*

	activity and decreased theta activity relative to pre-feedback baseline measures. By this way rewards (points and auditory beeps) were gained and so their scores were increased." Escitalopram 10 mg • n = 20 • SSRI • Fixed dose
Outcomes	Pain Mood Withdrawal
Missing data methods	NR
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods NR
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Can't be double-blind due to neurofeedback intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes but participants weren't blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Methods NR but low attrition **Attrition** Total: 4/40 (10.0%) Neurofeedback: 2/20 (10.0%) Esciptalopram 10 mg: 2/20 (10.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Keefe 2011

Study characteristics	
Methods	Design: parallel Duration: 34 weeks Assessment: baseline, 10 weeks, post-intervention Country: USA
Participants	Pain condition: non-cardiac chest pain Population: people who had presented to medical care with complaints of non-cardiac chest pain Minimum pain intensity: no Inclusion criteria • Presented for medical care with complaints of chest pain in the previous 6 months • Aged 18-85 • No clinical explanation for chest pain Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 115 Age in years (mean, SD): 48 (12) Gender: 77/115 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 28 • Inert • Sham dosing to match antidepressant arms Sertraline ≤ 200 mg • n = 30 • SSRI • Flexible dose over first 10 weeks dependent on efficacy • After the initial 10 weeks of treatment, the dose level was stabilised for the remaining 24 weeks of the study Coping skills training + placebo • n = 29 • Placebo • Sham dosing to match antidepressant arms • Coping skills training was delivered in 5, 60-min individual sessions held bi-weekly for 10 weeks and 6, 30-min individual follow-up sessions held monthly for 6 months. Sertraline ≤ 200 mg + coping skills training • n = 28 • Combined intervention: SSRI + coping skills training • Sham dosing to match antidepressant arms

Keefe 2011 *(Continued)*

- Coping skills training was delivered in 5, 60-min individual sessions held bi-weekly for 10 weeks and 6, 30-min individual follow-up sessions held monthly for 6 months.

Outcomes	Pain intensity Mood Physical function AEs SAEs Withdrawal
Missing data methods	ITT but no method specified
Funding source	Non-pharmaceutical: "This study was supported by a grant from NIMH (R01 MH63429)"
Conflicts of interest	The authors on this manuscript report no COI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a randomisation table
Allocation concealment (selection bias)	Unclear risk	Allocation procedure NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to be double-blind across all arms due to the nature of coping skills training intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	More participants withdrew from the coping skills training+sertraline arm than other arms. Did not report missing data methods **Attrition** Total: Placebo: 6/28 (21.4%) Sertraline ≤ 200 mg: 5/30 (16.7%) Coping skills training: 8/29 (28.0%) Coping skills training + sertraline ≤ 200 mg: 12/28 (42.9%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Khoromi 2007

Study characteristics	
Methods	Design: cross-over Duration: 9 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: chronic lumbar root pain Population: people with lumbar radiculopathy Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Evidence of lumbar radiculopathy, including pain in one or both buttocks or legs for ≥ 3 months for at least 5 days a week • Average leg pain of at least 4/10 for the past month on a NRS of 0–10 where 0 represents no pain and 10 represents the worst possible pain Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 55 Age in years (median, range): 53 (19-65) Gender: 25/55 were female Pain duration in years (median, range): 5 (0.3-37)
Interventions	Placebo (benzotropine ≤ 1 mg) • Active placebo • Identical to antidepressant • Dosing the same as intervention arms: ranged from 0.25-1 mg a day Morphine ≥ 15 and ≤ 90 mg • Opioid • Forced titration to maximum tolerated dose • Mean dose: 62 ± 29 mg/day Nortriptyline ≥ 25 and ≤ 100 mg • TCA • Forced titration to maximum tolerated dose • Mean dose: 84 ± 24.44 mg/day Morphine ≥ 15 and ≤ 90 mg + nortriptyline ≥ 25 and ≤ 100 mg • Combined intervention: opioid + TCA • Forced titration to maximum tolerated doses • Mean doses: morphine, 49 ± 27 mg/day plus nortriptyline, 55 mg ± 33.18 mg/day
Outcomes	Pain intensity

Khoromi 2007 *(Continued)*

	Mood Physical function AEs Withdrawal
Missing data methods	Completer-only analysis
Funding source	Non-pharmaceutical: "This study was supported by an intramural grant from the National Institute of Dental and Craniofacial Research."
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned by random numbers within blocks of four to 1 of 4 treatment sequences specified by a Latin square.
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical appearing study drugs, sham dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer-only analysis. High attrition overall **Attrition** Total: 27/55 (49.1%) Placebo: 9/55 (16.4%) Morphine 15-90 mg: 9/55 (16.4%) Nortriptyline 25-100 mg: 3/55 (5.5%) Morphine 15-90 mg + nortriptyline 25-100 mg: 6/55 (10.9%)
Selective reporting (reporting bias)	Low risk	All outcomes registered prospectively on clinicaltrials.gov
Other bias	Low risk	No other sources of bias were identified.

Kim 2013

Study characteristics

Kim 2013 *(Continued)*

Methods	Design: cross-over Duration: 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: no Inclusion criteria • Diagnosed with fibromyalgia by their rheumatologist or physician, with confirmation of the diagnosis by ACR criteria Exclusion criteria • Severe physical and mental health comorbidities (except depression) Total participants randomised: 20 Age in years (mean, SD): 47.6 (9.1) Gender: 18/20 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • Inert Milnacipran 12.5-200 mg • SNRI • Forced titration to maximum tolerated dosage
Outcomes	AEs SAEs
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: "This study was supported by Forest Laboratories through an Investigator-Initiated Award."
Conflicts of interest	"Dr Marks has served as a consultant to Forest, Dey, Gilead, and TTK; has received grant/research support from Bristol-Myers Squibb, Dov, Eli Lilly, Endo, GlaxoSmithKline, Janssen, Johnson & Johnson, Pfizer, Saegis, Sepracor, and Somaxon; and has served on the speakers or advisory boards of Alkermes, Bristol-Myers Squibb, Dey, Pfizer, and Sunovion. Dr Masand has served as a consultant to Forest, Lundsbeck, Merck, Pfizer, and Sunovion; has received grant/research support from Forest; has received honoraria from or served on the speakers or advisory boards of Forest, GlaxoSmithKline, Merck, Pfizer, and Sunovion; and is a stock shareholder in Global Medical Education. Dr Millet has received grant/research support from Forest. Dr Keefe has served as a consultant to Abbvie, Akebia, Amgen, Asubio, BiolineRx, Biomarin, Boehringer-Ingelheim, Eli Lilly, EnVivo, Lundbeck, Merck, Mitsubishi, Novartis, Otsuka, Pfizer, Roche, Shire,

Kim 2013 *(Continued)*

Sunovion, Takeda, and Targacept; has received grant/research support from Feinstein Institute for Medical Research, GlaxoSmithKline, National Institute of Mental Health, PsychoGenics, Research Foundation for Mental Hygiene, and Singapore Medical Research Council; is a stock shareholder in NeuroCog Trials; and has received royalties from the Brief Assessment of Cognition in Schizophrenia (BACS) and MATRICS Battery (BACS Symbol Coding).

Dr Patkar has served as a consultant to Dey, Forest, Gilead, and TTK; has received grant/research support from Dey, Duke Endowment, Envivo, Forest, Janssen, Lundbeck, National Institutes of Health (National Institute on Drug Abuse/National Institute on Alcohol Abuse and Alcoholism), Pfizer, Shire, Sunovion, and Titan; and has served on the speakers or advisory boards of Alkermes, BristolMyers Squibb, Dey, Pfizer, and Sunovion.

Dr Kim and Mss Rele and Yerramsetty report no conflicts of interest related to the subject of this article.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Says double-blinded but no specific information given regarding identical medication
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes by participants but not enough information regarding blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors state that the same 20 participants completed both phases of study (20) but LOCF numbers are 31. Not clear about ITT, imputation or handling of missing data **Attrition** Not clearly reported, unable to establish total attrition and attrition per arm
Selective reporting (reporting bias)	Unclear risk	Protocol lists pain, fatigue and cognition prospectively but doesn't mention any of the secondary measures. A lot of missing outcomes
Other bias	Unclear risk	Data NR in numerical forms - all secondary outcomes are classified e.g. "transient change" which has no interpretation

Konno 2016

Study characteristics

Methods

Design: parallel

Duration: 14 weeks

Assessment: baseline and post-intervention

Konno 2016 *(Continued)*

	Country: Japan
Participants	Pain condition: low back pain Population: adults aged 20-80 with chronic low back pain Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Outpatients of age 20 to < 80 years who had low back pain persisting for at least 6 months • Used NSAIDs for at least 14 days per month for an average of 3 months before the start of the study and for at least 14 days during the 1-month period before the start of the study • Pain intensity ≥ 4 on 0-10 scale Exclusion criteria • Low back surgery, current invasive treatment for low back pain • Depression and suicidal risk Total participants randomised: 458 Age in years (mean): 58.9 Gender: 237/458 were female Pain duration in years (mean): 10.1
Interventions	Placebo • n = 226 • Inert • Identical appearance to duloxetine Duloxetine 60 mg • n = 232 • SNRI • Fixed dose, forced titration
Outcomes	Pain intensity Sleep Quality of life Physical function Mood Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	MMRM and LOCF, BOCF as sensitivity analysis for pain

Konno 2016 *(Continued)*

Funding source	Pharmaceutical: Shionogi & Co. Ltd., Eli Lilly Japan K.K., and Eli Lilly and Company funds were received in support of this work.
Conflicts of interest	Relevant financial activities outside the submitted work: consultancy, employment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a stochastic minimisation procedure
Allocation concealment (selection bias)	Low risk	An "investigator in charge of blinding" randomly assigned participants to a treatment arm based on an assignment table. This assignment table was sealed and was inaccessible to all parties until after the clinical report was finalised.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs and matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rates. Mixture of analyses for primary outcome including MMRM, LOCF and BOCF. Results were the same across all missing data analyses. **Attrition** Total: 49/458 (10.7%) Placebo: 26/226 (11.5%) Duloxetine 60 mg: 23/232 (9.9%)
Selective reporting (reporting bias)	Low risk	All outcomes were prospectively registered on clinicaltrials.gov
Other bias	Low risk	No other sources of bias were identified

Lee 2010

Study characteristics	
Methods	Design: cross-over Duration: 4 weeks Assessment: baseline and post-intervention Country: South Korea
Participants	Pain condition: functional chest pain

Lee 2010 *(Continued)*

	Population: adults aged 20-29 with functional chest pain Minimum pain intensity: no Inclusion criteria • At least 3 episodes per week of unexplained midline chest pain, for a minimum of 3 months Exclusion criteria • Serious physical or mental health comorbidities Total participants randomised: 50 Age in years (mean, SD): 23.5 (1.9) Gender: 6/50 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • Inert • Identical capsules • Matched to active drug arm (1 capsule in the evening) Venlafaxine 75 mg • SNRI • Fixed dose
Outcomes	Pain intensity Mood Physical function AEs Withdrawal
Missing data methods	Unclear
Funding source	Not financially supported
Conflicts of interest	No potential competing interests
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated random list
Allocation concealment (selection bias)	Low risk	Allocation was concealed using a sealed opaque envelope technique
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, study drugs had identical appearance and matched dosage

Lee 2010 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completer analysis but low attrition **Attrition** Total: 4/25 (16.0%) Placebo: 3/25 (12.0%) Venlafaxine 75 mg: 1/25 (4.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Lee 2016

Study characteristics	
Methods	Design: cross-over Duration: 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: RA Population: adults aged ≥ 24 with RA in ≥ 5 body pain sites Minimum pain intensity: ≥ 4 on the BPI short form, ≥ 5 on the Regional Pain Scale Inclusion criteria • ≥ 4 on the BPI short form, ≥ 5 on the Regional Pain Scale • Diagnosis of RA Exclusion criteria • Serious physical and mental health comorbidities • Depression included as long as there was no history of suicide or significant risk of suicide attempt as assessed by the BDI Total participants randomised: 43 Age in years (mean): 54.0 Gender: 25/43 were female Pain duration in years (mean, SD): 11.29
Interventions	Placebo: • Inert

Lee 2016 *(Continued)*

- Identical in appearance to the milnacipran tablets
- Sham dosing to match milnacipran

Milnacipran 100 mg

- SNRI
- Fixed dose
- If participants couldn't tolerate dose: decreased to highest tolerable dose

Outcomes	Pain intensity Moderate pain relief AEs SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: "This work was conducted with support from Forest Research Institute, NIH-NIAMS K23AR057578, NIH-NIAMS K24 AR055989, Harvard Catalyst"
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised via a random number generator, with 4 participants per block.
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, study drugs had identical appearance and matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Says they will use ITT and LOCF, but only report results from completers **Attrition** Total: 9/41 (22.0%) Placebo: 3/41 (7.3%) Milnacipran 100 mg: 6/41 (14.6%)
Selective reporting (reporting bias)	High risk	Outcomes stated in the methods section of the paper are NR. Protocol changed on clinicaltrials.gov to remove some outcomes

Lee 2016 *(Continued)*

Other bias	Low risk	No other sources of bias were identified.

Leijon 1989

Study characteristics	
Methods	Design: cross-over Duration: 4 weeks Assessment: baseline, week 1, week 2, week 3, post-intervention Country: Sweden
Participants	Pain condition: central post-stroke pain Population: adults with central post-stroke pain Minimum pain intensity: no Inclusion criteria • an unequivocal stroke episode • the patient should seek remedy for constant or intermittent pain, which started after the stroke Exclusion criteria: • Pain of nociceptive, peripheral neuropathic or psychogenic origin • Known contraindication to both amitriptyline and carbamazepine Total participants randomised: 15 Age in years (mean, range): 66 (53-74) Gender: 3/15 were female Pain duration in months (mean, range): 54 (11-154)
Interventions	Placebo • Inert • Identical tablets to intervention arms • Double-dummy technique Amitriptyline 75 mg • TCA • Fixed dose with forced titration Carbamazepine 800 mg • Anticonvulsant • Fixed dose with forced titration
Outcomes	Pain intensity PGIC AEs SAEs

Leijon 1989 *(Continued)*

	Withdrawal
Missing data methods	NR
Funding source	Non-pharmaceutical: "The study was supported by grants from the County Council of Ostergotland and the Swedish Association of the Neurologically Disabled"
Conflicts of interest	None reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given apart from "randomised"
Allocation concealment (selection bias)	Low risk	Separate pharmacy team performed randomisation and allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, study drugs had identical appearance and matched dosing. Investigators were also blinded - separate neurologists were consulted for side-effects.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data methods, but only 1 person withdrew **Attrition** Total: 1/15 (6.7%) Placebo: 0/15 (0.0%) Amitriptyline 75 mg: 0/15 (0.0%) Carbamazepine 800 mg: 1/14 (7.1%)
Selective reporting (reporting bias)	Low risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Lipone 2020

Study characteristics

Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention

Lipone 2020 *(Continued)*

	Country: Czech Republic, Hungary, and Poland
Participants	Pain condition: painful diabetic neuropathy Population: people with painful diabetic neuropathy Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Aged 18-75 • painful diabetic neuropathy manifesting with distally distributed neuropathic pain • ≥ 4 on 0-10 pain intensity scale Exclusion criteria • Other pain conditions, general physical conditions (glaucoma, hisotry of seizures, etc), and significant mental disorders Total participants randomised: 142 Age in years (mean): 62.7 Gender: 68/142 were female Pain duration in years (mean, SD): NR
Interventions	Placebo + gabapentin 2400 mg • n = 48 • Placebo + anticonvulsant • Gabapentin open-label, placebo identical to trazodone Trazodone 30 mg + gabapentin 2400 mg • n = 43 • Combined intervention: SARI antidepressant + anticonvulsant • Fixed dose • Gabapentin in open-label condition Trazodone 60 mg + gabapentin 2400 mg • n = 51 • Combined intervention: SARI antidepressant + anticonvulsant • Fixed dose • Gabapentin in open-label condition
Outcomes	Pain intensity Substantial pain relief AEs SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: "This study was sponsored by Angelini Pharma S.p.A. (S. Palomba, Pomezia, Rome, Italy)."

Lipone 2020 *(Continued)*

Conflicts of interest	Giorgio Cruccu received personal fees for advisory boards or consultancy from Angelini, Grunenthal, and Lilly, and personal fees for educational activity by PTS Global Services. Andrea Truini received honoraria for speaking at symposia or research financial supports from Alpha-Sigma, Angelini Pharma, Epitech, FB Health, Pfizer, and Grunenthal. Edvard Ehler has no conflicts of interest that are directly relevant to the content of this study; however, his institution received a fee for conducting the clinical trial from Angelini Pharma S.p.A. Marcin Nastaj and Ilona Palka-Kisielowska received principal investigator fees from Angelini Pharma S.p.A. Fabrizio Calisti, Agnese Cattaneo, Alessandro Comandini, Alessandra Del Vecchio, Giorgio Di Loreto, Paola Lipone, and Ilena Pochiero are full-time employees of Angelini Pharma S.p.A.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised in a 1:1:1 ratio to the 3 parallel groups, based on a computer-generated sequence
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blinding was maintained throughout all treatment periods by using a TRZ [trazodone] solution matching PLB [placebo] solution and the same dosing regimen for all groups in terms of timing and number of drops."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 38/142 (26.8%) Gabapentin 2400 mg: 13/48 (27.1%) Trazodone 30 mg + gabapentin 2400 mg: 10/43 (23.3%) Trazodone 60 mg + gabapentin 2400 mg: 15/51 (29.4%)
Selective reporting (reporting bias)	Unclear risk	Do not report a lot of the secondary outcomes clearly, the baseline or the post-intervention, these are also NR in the trial registry
Other bias	Low risk	No other sources of bias were identified.

Loldrup 1989

Study characteristics

Methods	Design: parallel Duration: 6 weeks Assessment: baseline and post-intervention

Loldrup 1989 *(Continued)*

	Country: Denmark
Participants	Pain condition: idiopathic pain syndromes: (a) tension headache, (b) burning mouth syndrome (oral dysaesthesia), (c) abdominal pain (gastroscopy negative for ulcer), and (d) low back pain Population: people with idiopathic pain syndromes Minimum pain intensity: no Inclusion criteria • Pain from 1 of the 4 conditions listed above Exclusion criteria • Physical health comorbidities • Excluded severe psychiatric conditions but included depression and anxiety Total participants randomised: 253 Age in years (median, range): 51.0 (17-80) Gender: 185/253 were female Pain duration in years (median, range): 60.0 (6-636)
Interventions	Placebo • n = 87 • Inert Clomipramine 75-150 mg • n = 84 • Fixed dose of either 75 mg or 150 mg dependent upon side effects • Mean dose: 125 mg/day Mianserin 30-60 mg • n = 82 • Fixed dose of either 30 mg or 60 mg dependent upon side effects • Mean dose: 45 mg/day
Outcomes	Substantial pain Withdrawal
Missing data methods	Completer analysis only
Funding source	Non-pharmaceutical: "This study was financially supported by: Danish Medical Research Council, Danish Medical Research Council-Region-III, Kleins legat, Geerd Jorgensens fond, Lundbeck Fonden, Mimi and Victor Larsens Fond, Danish Dental Association (FUT-foundation), Bryde Nielsen Fond, P. Carl Petersens Fond, Ciba Geigy A/S, and Organon."
Conflicts of interest	"Per Bech has occasionally over the past 3 years until August 2008 received funding from and been speaker or member of advisory boards for pharmaceutical companies with an interest in drug treatment of affective disorders (Astra-Zeneca, Lilly, H. Lundbeck A/S, Lundbeck Foundation, Organon). All other authors declare that they have no conflicts of interests."
Notes	

Loldrup 1989 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised by use of random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs and dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only **Attrition** Total: 75/253 (29.6%) Placebo: 15/87 (17.2%) Clomipramine 75-100 mg: 28/84 (33.3%) Mianserin 30-60 mg: 28/82 (34.2%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Luo 2009

Study characteristics

Methods	Design: parallel Duration: 8 weeks Assessment: baseline, week 1, week 2, week 4, post-intervention Country: China
Participants	Pain condition: persistent somatoform pain disorder Population: people aged 18-65 with persistent somatoform pain disorder Minimum pain intensity: no Inclusion criteria • Outpatients meeting the ICD-10 diagnostic criteria for persistent somatoform pain disorder with > 6 months' duration

Luo 2009 *(Continued)*

	Exclusion criteria • Coexisting depressive symptoms that occurred prior to pain • Severe and unstable physical illnesses Total participants randomised: 80 Age in years (mean, SD): 40.96 (12.69) Gender: 46/80 were female Pain duration in months (mean, SD): 21.02 (9.02)
Interventions	Placebo • n = 40 • Inert • Identical capsules and matched dosing schedule Fluoxetine 20 mg • n = 40 • SSRI • Fixed dose, no titration
Outcomes	Pain intensity
Missing data methods	ITT with LOCF
Funding source	Non-pharmaceutical: "This research was supported by Shanghai Science and Technology Committee."
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, matched dosing schedule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** No withdrawal data reported

Luo 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Maarrawi 2018

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Country: Lebanon
Participants	Pain condition: chronic neck pain Population: people with chronic neck pain Minimum pain intensity: no Inclusion criteria • Chronic neck pain for > 15 days/month during at least 3 consecutive months Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 332 Age in years (mean, SD): 44.23 (11.39) Gender: 190/332 were female Pain duration in years (mean, SD): 15.4 (4.86)
Interventions	Placebo • n = 166 • Inert • Identical appearance and matched dosing Amitriptyline 5 mg • n = 166 • TCA • Fixed dose, no titration
Outcomes	Pain intensity
Missing data methods	Completer-only analysis
Funding source	Non-pharmaceutical: "This study was supported by the Council of Research of the Saint Joseph University of Beirut – Lebanon (FM201)"
Conflicts of interest	No conflicts of interest

Maarrawi 2018 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised via the block randomisation method, computer-generated via www.randomization.com)
Allocation concealment (selection bias)	Low risk	Randomisation was centralised by a staff nurse (who had never seen the patient) not otherwise involved in the study and noted the group of each participant next to the number assigned to him. The same staff nurse delivered the corresponding medication to each patient.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, study drugs were identical with matched dosing schedule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer-only analysis. Withdrawal rate rate was ~17% **Attrition** Total: 58/332 (17.5%) Placebo: 25/166 (15.1%) Amitriptyline 5 mg: 33/166 (19.9%)
Selective reporting (reporting bias)	Low risk	All outcomes match up with those prospectively registered on clinicaltrials.gov
Other bias	Unclear risk	Unclear reporting in the publication, especially in relation to sample size and withdrawal

Macfarlane 1986

Study characteristics

Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: Canada
Participants	Pain condition: RA Population: adults with RA and elevated self-reported depression Minimum pain intensity: no Inclusion criteria

Macfarlane 1986 *(Continued)*

- 'Definite' or 'classical' RA as defined by the ARA
- All of the patients had a score exceeding 50 on the 'self-rating depression scale' described by Zung 1965

Exclusion criteria: NR

Total participants randomised: 36

Age in years (mean, SD): 59.15

Gender: 27/36 were female

Pain duration in years (mean, SD): NR

Interventions	Placebo • n = 18 • Inert • Identical tablets Trimipramine 75 mg • n = 18 • TCA • Fixed titration schedule to 75 mg, but if participants experienced side effects they could reduce the dose
Outcomes	Pain intensity Mood Withdrawal
Missing data methods	NR
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants

Macfarlane 1986 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on handling missing data, report 9 participants withdrew in the text but 10 in the table **Attrition** Total: 9/36 (25.0%) Placebo: 4/18 (22.2%) Trimipramine 25-75 mg: 5/18 (27.8%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Unclear risk	Not a lot of information on methods, short publication so not enough information to assess whether a further risk of bias exists

Mahmoud 2021

Study characteristics	
Methods	Design: parallel Duration: 16 weeks Assessment: baseline and post-intervention Country: Egypt
Participants	Pain condition: neck pain Population: adults with chronic neck pain Minimum pain intensity: no Inclusion criteria • Chronic neck pain for > 15 days per month and lasting at least 3 months Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 80 Age in years (mean): 46.6 Gender: 52/80 were female Pain duration in years (mean, SD): NR
Interventions	Amitripyline 5 mg • n = 40 • TCA • Fixed dose Amitripyline 10 mg • n = 40 • TCA

Mahmoud 2021 *(Continued)*

	• Fixed dose
Outcomes	Pain intensity Withdrawal
Missing data methods	Completer-only analysis
Funding source	Non-pharmaceutical: "This work was funded in part by Fayoum University Hospitals (Fayoum, Egypt) and by the authors' personal resources."
Conflicts of interest	The authors declare that there are no conflicts of interest regarding the publication of this paper.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation using a randomisation table created by a computer software program
Allocation concealment (selection bias)	Low risk	Participants were allocated using sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind with identical study drugs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only **Attrition** Total: 10/80 (12.5%) Amitriptyline 5 mg: 5/40 (12.5%) Amitriptyline 10 mg: 5/40 (12.5%)
Selective reporting (reporting bias)	Unclear risk	Outcomes published match trial registry though retrospectively registered
Other bias	Unclear risk	Confusing reporting of primary outcome. In the text, it says that neck pain (as measured by the Neck Pain Driving Index) decreased by 71.9% ± 13.4% in the 10 mg group, which was greater than the decrease in the 5 mg group (47.3% ± 17.3%). However in the figure it says that the decreases were 48.3% for 5 mg and 68.2% for 10 mg.

Majdinasab 2019

Study characteristics

Majdinasab 2019 *(Continued)*

Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Country: Iran
Participants	Pain condition: painful diabetic peripheral polyneuropathy Population: adults with painful diabetic peripheral polyneuropathy Minimum pain intensity: ≥ 40 on 0-100 VAS Inclusion criteria • Aged between 18-75 • Painful diabetic peripheral poly-neuropathy from 1 month to 5 years • ≥ 40 on 0-100 pain intensity VAS Exclusion criteria • Severe illness in vital organs • Using medication to treat pain Total participants randomised: 104 Age in years (mean): 60.3 Gender: 50/104 were female Pain duration in years (mean): 3.75
Interventions	Gabapentin 300-900 mg • n = 52 • Anticonvulsant • Flexible dose depending on tolerability • Identical appearance to duloxetine Duloxetine 30-60 mg • n = 52 • SNRI • Flexible dose depending on tolerability
Outcomes	Pain intensity Sleep AEs Withdrawal
Missing data methods	NR
Funding source	Non-pharmaceutical: "This study was funded by Ahvaz Jundishapur University of Medical Sciences (grant number IR.AJUMS.REC.1395.78)"

Majdinasab 2019 *(Continued)*

Conflicts of interest	Dr Nastaran Majdinasab, Dr Hossein Kaveyani, and Dr Mojgan Azizi have received research grants from Ahvaz Jundishapur University of Medical Sciences (grant number IR.AJUMS.REC.1395.78). The authors report no other conflicts of interest in this work.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using the 4 block randomised method (equalised 4-blocks).
Allocation concealment (selection bias)	Low risk	"The medications of this study were first made similar to each other by a doctor who had no role in the collection and analysis of data and then sufficient amounts were packed into packets A and B and were given to the researcher."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Used identical drugs and placebos and packets but: "Before the commencement of the study, the side effects of the medications were explained to the patients " could then allow participants to know what they're experiencing and which medication it comes from.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Method of missing data not specified **Attrition** Total: 16/104 (15.4%) Gabapentin 300-900 mg: 11/52 (21.2%) Duloxetine 30-60 mg: 5/52 (9.6%)
Selective reporting (reporting bias)	Unclear risk	Protocol registered retrospectively
Other bias	Unclear risk	Errors in publication between tables

Masand 2009

Study characteristics

Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: IBS Population: adults aged 18-75 with IBS Minimum pain intensity: no

Masand 2009 *(Continued)*

	Inclusion criteria • Confirmed diagnosis of IBS by use of Rome II diagnostic criteria for over 1 year Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 72 Age in years (mean): 49.0 Gender: 63/72 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 36 • Inert • Dosing matched to antidepressant arm Paroxetine 12.5-50 mg • n = 36 • SSRI • Forced titration to maximum tolerated dose
Outcomes	SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: This study was supported by a collaborative research grant from GlaxoSmithKline.
Conflicts of interest	Dr Masand is a consultant for Bristol-Myers Squibb Company, Cephalon, Inc., Eli Lilly and Company, Forest Pharmaceutical Laboratories Inc., GlaxoSmithKline, Janssen Pharmaceutica, Jazz Pharmaceuticals, Organon, Inc., Pfizer Inc., U.S. Pharmaceuticals Group., Targacept Inc., and Wyeth Pharmaceuticals. He is on the speaker's bureau of Astra-Zeneca, Bristol-Myers Squibb Company, Forest Pharmaceutical Laboratories, Inc., GlaxoSmithKline, Janssen Pharmaceutica, Pfizer Inc., U.S. Pharmaceuticals Group., and Wyeth Pharmaceuticals. He has received research support from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Cephalon, Inc.., Eli Lilly and Company, Forest Pharmaceutical Laboratories Inc., GlaxoSmithKline, Ortho McNeil Pharmaceutical, Inc., Janssen Pharmaceutica, and Wyeth Pharmaceuticals, and is an employee of i3CME. Dr Patkar is a consultant for Bristol-Myers Squibb Company, GlaxoSmithKline, and Reckitt Benckiser; he is on the speaker's bureau of Bristol-Myers Squibb Company, GlaxoSmithKline, and Reckitt Benckiser, and has received research support from National Institutes of Health, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Forest Pharmaceuticals, Inc., GlaxoSmithKline, Janssen Pharmaceutica, McNeil Consumer and Specialty Inc., Organon, Inc., Jazz Pharmaceuticals, and Pfizer Inc., U.S. Pharmaceuticals Group. Dr Pae has received research support from GlaxoSmithKline. Mr. Krulewicz is an employee of GlaxoSmithKline and owns common stock in the company.
Notes	
Risk of bias	

Masand 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not described
Allocation concealment (selection bias)	Low risk	Participants were allocated using an Interactive Voice Response System
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, matching drug appearance and identical dosing schedules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 14/72 (19.4%) Placebo: 8/36 (22.2%) Paroxetine 12.5-50 mg: 6/36 (16.7%)
Selective reporting (reporting bias)	High risk	Trial registry lists quality of life and IBS symptoms as outcomes but these are NR. Beck Depression Index and Beck Anxiety Index are NR for all participants, divided into samples with or without history of anxiety and depression.
Other bias	Low risk	No other sources of bias were identified

Matthey 2013

Study characteristics	
Methods	Design: parallel Duration: 7 weeks Assessment: baseline and post-intervention Country: Switzerland
Participants	Pain condition: fibromyalgia Population: adult women with fibromyalgia Minimum pain intensity: ≥ 40 on 0-100 VAS Inclusion criteria • Women who met the ACR fibromyalgia criteria • Pain intensity of ≥ 40 on 0-100 VAS at baseline Exclusion criteria • Physical and mental health comorbidities

Matthey 2013 *(Continued)*

	Total participants randomised: 80 Age in years (mean): 49.7 Gender: 80/80 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 39 • Inert Milnacipran 100-200 mg • n = 40 • SNRI • Flexible dosing to 100 mg, 150 mg, or 200 mg per day based on tolerability
Outcomes	Pain intensity Quality of life Physical function Mood Sleep Withdrawal
Missing data methods	ITT wit h LOCF
Funding source	Pharmaceutical: This trial was supported by a grant from Pierre Fabre Médicament.
Conflicts of interest	"Each author certifies that he or she, or a member of his or her immediate family, has no commercial association, (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might post a COI in connection with the submitted manuscript."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list was computer-generated.
Allocation concealment (selection bias)	Low risk	Allocation of treatments was done by the investigator according to the chronological order of the occurring visit 2
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	State double-blind but not enough information about study drug appearance and dosing
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding procedures

Matthey 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF, high attrition **Attrition** Total: 37/80 (46.3%) Placebo: 16/40 (40.0%) Milnacipran 100-200 mg: 21/40 (52.5%)
Selective reporting (reporting bias)	Unclear risk	No changes to protocol, but it's registered 2 years after trial start
Other bias	Low risk	No other sources of bias were identified.

Max 1988

Study characteristics	
Methods	Design: cross-over Duration: each cross-over period was 6 weeks Assessment: baseline and post-cross-over period Country: USA
Participants	Pain condition: post-herpetic neuralgia Population: adults with post-herpetic neuralgia Minimum pain intensity: no Inclusion criteria • Daily pain, persisting at least 3 months after a segmental herpes zoster eruption Exclusion criteria • Another type of pain as severe • Depression Total participants randomised: 58 Age in years (median, range): 72 (25-86) Gender: 27/58 were female Pain duration in months (median, range): 19 months (3 months-25 years)
Interventions	Placebo • Inert - lactose • "Placebo (PLAC) is given only during the first period, because both amitriptyline (AMI) and lorazepam (LOR) have prominent side effects. We predicted that patients given placebo following one of those drugs would immediately recognize this inert treatment. The design permitted a comparison of AMI, LOR, and PLAC during the first treatment period." Amitriptyline 12.5-150 mg • TCA

Max 1988 *(Continued)*

	• Forced titration to maximum tolerable dose in first 3 weeks, then held at that dose for final 3 weeks Lorazepam 0.5-6 mg • Benzodiazepine • Forced titration to maximum tolerable dose in first 3 weeks, then held at that dose for final 3 weeks
Outcomes	AEs
Missing data methods	Unclear
Funding source	Non-pharmaceutical: from the Neurobiology and Anaesthesiology Branch, National Institute of Dental Research (Drs Max, Gracely, Smoller, and Dubner). and the Nursing Department, Clinical Center (Ma. Schnfer and Me. Culnane), National Institutes of Health, Bethesda, MD
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Says double-blind but no information about this was given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information regarding missing data reported. 41 completed both of the treatment periods for their group, but authors report data on 58
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias identified

Max 1992

Study characteristics

Methods	Design: cross-over Duration: each cross-over period was 6 weeks Assessment: baseline and post-cross-over period

Max 1992 *(Continued)*

	Country: USA
Participants	Pain condition: diabetic peripheral neuropathy Population: type 1 or 2 diabetic adults with diabetic peripheral neuropathy Minimum pain intensity: no Inclusion criteria • Daily pain of at least moderate severity, the quality and location of which were consistent with the peripheral neuropathy Exclusion criteria • Other pain as severe as the diabetic peripheral neuropathy • Depression • Cardiovascular conditions Total participants randomised: 54 Age in years (median, range): 58 (20-84) Gender: 21/54 were female Pain duration in years (median, range): 3 (0.5-12)
Interventions	Desipramine 12.5-150 mg • TCA • Forced titration to highest tolerated dose • Mean dose 111 mg/day (SD 39) Amitriptyline 12.5-150 mg • TCA • Forced titration to highest tolerated dose • Mean dose 105 mg/day (SD 37)
Outcomes	Pain intensity AEs
Missing data methods	Completer-only analysis
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified

Max 1992 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind but no information regarding procedures e.g. study drug appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding process
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only **Attrition** Total: 16/54 (29.6%) Attrition per arm NR
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Unclear risk	Complicated trial design between 2 studies. Of the 54 participants in the desipramine vs amitriptyline study only 29 were randomised into it.

Mease 2009

Study characteristics	
Methods	Design: parallel Duration: 27 weeks Assessment: baseline, 15 weeks, post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: ≥ 50 on 0-100 scale Inclusion criteria • Aged 18-70 with fibromyalgia meeting ACR criteria • Pain intensity of ≥ 50 on 0-100 scale Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 888 Age in years (mean, SD): 49.5 Gender: 849/888 were female Pain duration in years (mean, SD): 5.6
Interventions	Placebo

Mease 2009 *(Continued)*

- n = 223
- Inert
- Identical appearance and matched dosing

Milnacripran 100 mg

- n = 224
- SNRI
- Fixed dose

Milnacripran 200 mg

- n = 441
- SNRI
- Fixed dose

Outcomes	Pain intensity Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	ITT with LOCF, sensitivity analyses with BOCF
Funding source	Pharmaceutical: supported by Forest Laboratories, Inc., New York, New York, and CypressBioscience, Inc., San Diego, California, USA
Conflicts of interest	Dr Mease has received research grant support from Pfizer Inc, Cypress Bioscience, Inc., Forest Laboratories, Inc., Eli Lilly and Company, Allergan, Wyeth Pharmaceuticals, Jazz Pharmaceuticals, and Fralex Therapeutics. Dr Clauw has received grant support from Cypress Bioscience, Inc. and serves as a consultant to Cypress Bioscience, Inc, Forest Laboratories, Inc., Pierre Fabre Medicament, Pfizer Inc, Eli Lilly and Company, Wyeth Pharmaceuticals, and Proctor and Gamble. Dr Mease was an investigator of this study and a consultant; Dr Clauw was a consultant for this study. As consultants, Drs Mease and Clauw were involved in the study design, analysis of results, and preparation of the manuscript. Drs Gendreau, Rao, and Kranzler are employees of Cypress Bioscience, Inc. Drs Chen and Palmer are employees of Forest Laboratories, Inc
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified

Mease 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind with study drugs identical and matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Very high attrition rate, especially for the high-dose milnacipran. Use a mix of imputation methods including LOCF, BOCF and completers, but not all of the data for this are presented in the paper **Attrition** Total: 376/888 (42.3%) Placebo: 78/223 (35.0%) Milnacipran 100 mg: 96/224 (42.9%) Milnacipran 200 mg: 202/441 (45.8%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Miki 2016

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: Japan
Participants	Pain condition: fibromyalgia Population: Japanese adults aged between 20-64 with fibromyalgia Minimum pain intensity: ≥ 40 on 0-100 scale Inclusion criteria • Japanese adults aged between 20 and 64 years who met the ACR diagnostic criteria for fibromyalgia • Pain intensity ≥ 40 on 0-100 scale Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 430 Age in years (mean): 45.2 Gender: 347/430 were female

Miki 2016 *(Continued)*

	Pain duration in years (mean): 4.4
Interventions	Placebo • n = 215 • Inert • Identical appearance to mirtazapine with matched dosing Mirtazapine 30 mg • n = 215 • NaSSA • Fixed dose
Outcomes	Pain intensity Mood Quality of life Physical function Moderate pain relief Substantial pain relief AEs Severe AEs Withdrawal
Missing data methods	NR
Funding source	Pharmaceutical: funded by Meiji Seika Pharma Co, Ltd.
Conflicts of interest	The authors have no conflicts of interest to declare. K. Miki, M. Murakami, H. Oka, K. Osada received honorarium from Meiji Seika Pharma Co, Ltd. K. Onozawa and S. Yoshida are employees of Meiji Seika Pharma Co, Ltd.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was done by a computer-generated allocation sequence
Allocation concealment (selection bias)	Low risk	Allocation was delivered by a telephone randomisation service (randomisation manager) not involved in participant recruitment or treatment to ensure allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs with matched dosing
Blinding of outcome assessment (detection bias)	Low risk	Self-reported outcomes from blinded participants

Miki 2016 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT but methods not specified **Attrition** Total: 48/430 (11.2%) Placebo: 23/215 (10.7%) Mirtazapine 30 mg: 25/215 (11.6%)
Selective reporting (reporting bias)	Unclear risk	Protocol published prospectively but no outcomes specified apart from "amount of change from baseline"
Other bias	High risk	Pain intensity change scores reported in the paper do not seem to be correct. When calculated into SMD, an SMD of over 4 resulted, which is improbable. Emailed study authors for clarification but no response, and no correction found.

Morello 1999

Study characteristics	
Methods	Design: cross-over Duration: cross-over periods were 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: diabetic peripheral neuropathy Population: type 1 and 2 diabetic veterans with diabetic peripheral neuropathy pain Minimum pain intensity: no Inclusion criteria • Chronic daily pain for > 3months, during which both the quality and location were consistent with diabetic peripheral neuropathy pain, as diagnosed by a neurologist Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 25 Age in years (mean, SD): 60.4 (10.8) Gender: 1/25 were female Pain duration in years (mean, SD): 5.7 (4.2)
Interventions	Gabapentin 900-1800 mg • Anticonvulsant • Flexible dosing dependent upon tolerance • Mean dose after titration: 1565 mg/day

Morello 1999 *(Continued)*

	Amitriptyline 25-75 mg • TCA • Flexible dosing dependent upon tolerance • Mean dose after titration: 59 mg/day
Outcomes	Pain intensity AEs Withdrawal
Missing data methods	Completer analysis only
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind medications, same dosing schedules and appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer-only analysis **Attrition** Total: 4/25 (16.0%) Gabapentin 900-1800 mg: 2/25 (8.0%) Amitriptyline 25-75 mg: 2/25 (8.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	High risk	Post hoc power analysis and report needing sample of 280 to detect effect, they have 25 participants randomised

Muller 2008

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: South Africa
Participants	Pain condition: multisomatoform disorder Population: people aged 18-65 with somatoform symptoms and medically unexplained symptoms Minimum pain intensity: no Inclusion criteria • Aged 18-65 • Multisomatoform disorder defined as ≥ 3 bothersome medically unexplained symptoms within the past month, together with a history of ≥ 1 somatoform symptoms for at least 2 years Exclusion criteria • Current or past psychotic disorder, any unstable mental illness, suicide risk Total participants randomised: 51 Age in years (mean, SD): 39.6 Gender: 46/51 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 26 • Inert • Identical apprearance and matched dosing Escitalopram 10-20 mg • SSRI • Flexible dose according to tolerability
Outcomes	Pain intensity Mood Physical function Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: this study was funded by H. Lundbeck A/S
Conflicts of interest	At the time this study was conducted, Professor Stein, Professor Seedat and Dr Muller were funded by the Medical Research Council of South Africa
Notes	

Muller 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned via computer-generated randomisation lists
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, with study drugs identical and matched dosing schedule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT and LOCF, but only 1 person withdrew **Attrition** Total: 1/51 (2.0%) Placebo: 0/26 (0.0%) Escitalopram 10-20 mg: 1/25 (4.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Murakami 2015

Study characteristics

Methods	Design: parallel Duration: 14 weeks Assessment: baseline and post-intervention Country: Japan
Participants	Pain condition: fibromyalgia Population: adults aged 20-75 with fibromyalgia Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Outpatients aged between 20 and 75 years who met the ACR 1990 criteria for fibromyalgia • Pain intensity of ≥ 4 on 0-10 scale Exclusion criteria

Murakami 2015 *(Continued)*

	• Severe or unstable disease, psychiatric disorders other than major depressive disorder within the last year Total participants randomised: 393 Age in years (mean, SD): 48.7 (11.9) Gender: 321/393 were female Pain duration in years (mean): 5.6
Interventions	Placebo • n = 197 • Inert • Identical appearance and matched dosing schedule Duloxetine 60 mg • n = 196 • SNRI • Forced titration to fixed dose
Outcomes	Pain intensity Mood Sleep Quality of life Physical function PGIC AEs SAEs Withdrawal
Missing data methods	ITT with LOCF, MMRM, and sensitivity analyses using BOCF and WOCF
Funding source	Pharmaceutical: Shionogi & Co. Ltd., Eli Lilly Japan K.K., and Eli Lilly & Company provided funding for the study
Conflicts of interest	HM and TO are employees of Shionogi & Co. Ltd. LA is an employee of Eli Lilly Japan K.K. MM, KO, and KN have provided consultancy services and MM and KO received compensation from Shionogi & Co. Ltd. for their participation in this study. MM, KO, and KN did not receive any compensation for their input into this study. The authors confirm that there are no non-financial competing interests to declare in relation to this article.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were assigned randomly to receive duloxetine or placebo in a 1:1 ratio, using a web-based patient registration system (ACRONET Corp., Tokyo, Japan) with a stochastic minimisation procedure.

Murakami 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, study drugs had identical appearance, packaging, and labelling, matched dosing schedule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although there was attrition, sensitivity analyses of the primary outcomes with LOCF, BOCF, and WOCF showed no signficiant differences. **Attrition** Total: 78/393 (19.9%) Placebo: 48/198 (24.4%) Duloxetine 60 mg: 30/196 (15.3%)
Selective reporting (reporting bias)	Low risk	All outcomes listed prospectively on clinicaltrials.gov
Other bias	Low risk	No other sources of bias were identified.

Nabi 2021

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline, 4 weeks, post-intervention Country: Iran
Participants	Pain condition: painful diabetic neuropathy Population: adults with type I or type II diabetes and a diagnosis of diabetic peripheral neuropathic pain Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Diabetic peripheral neuropathic pain for at least 6 months diagnosed according to the MNSI scale • Pain intensity of ≥ 4 on 0-10 scale Exclusion criteria • Hepatic, heart, or renal failure; uncontrolled hypertension; psychological disorders; epilepsy; other neuropathies Total participants randomised: 72 Age in years (mean, SD): 57.71 (7.43)

Nabi 2021 *(Continued)*

	Gender: 29/72 were female Pain duration in months (mean, SD): 22.46 (9.52)
Interventions	TENS • n = 30 • TENS • For 4 weeks, sessions every other day. Then, twice a week for 3 months Duloxetine - 60 mg • n = 42 • SNRI • Fixed dose with forced titration
Outcomes	Pain intensity AEs Withdrawal
Missing data methods	Completer analysis only - 12 participants discontinued treatment due to intolerability and were replaced with new cases.
Funding source	Study was not financially supported
Conflicts of interest	The study authors reported no conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using http://www.graphpad.com/quickcalcs/index.cfm.
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to be blinded due to the nature of TENS
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only. 12 participants dropped out, all in the duloxetine arm due to side effects. Participants who dropped out were replaced with new participants, and their data not analysed. **Attrition** Total: 12/72 (16.7%) TENS: 0/30 (0.0%)

Nabi 2021 *(Continued)*

		Duloxetine 60 mg: 12/42 (28.6%)
Selective reporting (reporting bias)	Low risk	Trial registered prospectively and outcomes match
Other bias	Low risk	No other sources of bias were identified.

Natelson 2015

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: adults aged 18-68 with fibromyalgia Minimum pain intensity: no Inclusion criteria • Fibromyalgia meeting the ACR criteria • > 10 of 18 tender points, points were considered tender if they were reported to be ≥ 2 on a pain intensity VAS from 0-10 reported by patients Exclusion criteria • Severe physical and mental health comorbidities Total participants randomised: 34 Age in years (mean, SD): 46.8 Gender: 33/34 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 17 • Inert • Identical appearance and matched dosing schedule Milnacipran 100 mg • n = 17 • SNRI • Forced titration to fixed dose
Outcomes	Pain intensity AEs SAEs

Natelson 2015 *(Continued)*

	Withdrawal
Missing data methods	Completer-only analysis
Funding source	Part funded by pharmaceutical: "This work was supported by a Forest Laboratories Investigator-initiated grant to B.H.N., and, in part, by National Institutes of Mental Health (NIMH) grant R01 MH100005 to D.C.S."
Conflicts of interest	"J.D.C. has been a speaker for Pfizer, Forest, Bristol Myers Squibb, Glaxo Smith Kline, Eli Lilly, and Sunovion. He has received grants from Pfizer Pharmaceuticals, GSK, Corcept, and Neurocrine. There were no other conflicts of interest in doing this research. This work was supported by a Forest Laboratories Investigator-initiated grant to B.H.N., and, in part, by National Institutes of Mental Health (NIMH) grant R01 MH100005 to D.C.S. The sources of funding had no involvement in any of the aspects of running this study, analyzing the data, or preparing this manuscript."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Low risk	Mount Sinai Beth Israel Pharmacy dispensed the drug or placebo according to the randomisation list in sequential order.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, with identical study drugs and matched dosage schedule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer-only analysis **Attrition** Total: 8/34 (23.5%) Placebo: 4/17 (23.5%) Milnacipran 100 mg: 4/17 (23.5%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

NCT00066937

Study characteristics

Methods	Design: parallel

NCT00066937 *(Continued)*

	Duration: 8 weeks Assessment: baseline, post-intervention, 3-month follow-up, 6-month follow-up Country: USA
Participants	Pain condition: temporomandibular joint disorders Population: adults aged 18-65 with temporomandibular joint disorders Minimum pain intensity: no Inclusion criteria • Age 18-65 • Pain ≤ 3 months duration due to temporomandibular joint disorder Exclusion criteria • Severe physical and mental health co-morbidities Total participants randomised: 140 Age in years (mean, SD): 37.2 (11.5) Gender: 28/140 were female Pain duration in years (mean, SD): NR
Interventions	Placebo (benztropine mesylate) + CBT • n = 38 • Active placebo + CBT • Flexible titration: benztropine titrated up from 0.125 mg every night at bedtime to a maximum dose of 0.750 mg every night at bedtime based on treatment response and side effect profile • 6 in-person, individual sessions of CBT for pain management Nortriptyline + CBT • n = 41 • TCA + CBT • Flexible titration: nortriptyline titrated up from 25 mg every night at bedtime to a maximum dose of 150 mg every night at bedtime based on treatment response and side effect profile • 6 in-person, individual sessions of CBT for pain management Placebo (benztropine mesylate) + management • n = 24 • Active placebo + management • Flexible titration: benztropine titrated up from 0.125 mg every night at bedtime to a maximum dose of 0.750 mgevery night at bedtime based on treatment response and side effect profile • 6 in-person, individual sessions of temporomandibular joint disorder disease management Nortriptyline + management • n = 37 • TCA + management • Flexible titration: nortriptyline titrated up from 25 mg every night at bedtime to a maximum dose of 150 mg every night at bedtime based on treatment response and side effect profile • 6 in-person, individual sessions of temporomandibular joint disorder disease management
Outcomes	Pain intensity

NCT00066937 *(Continued)*

	Mood AEs SAEs Withdrawal
Missing data methods	Completer analysis
Funding source	Non-pharmaceutical: Johns Hopkins University. Collaborator: National Institute of Dental and Craniofacial Research (NIDCR)
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although there are matched active placebos/interventions there is not enough information to determine blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer-only analysis **Attrition** Total: 24/140 (17.1%) CBT: 5/38 (13.2%) Nortriptyline 25-150 mg + CBT: 3/41 (7.3%) Disease management: 5/24 (20.8%) Nortriptyline 25-150 mg + disease management: 11/37 (29.7%)
Selective reporting (reporting bias)	High risk	Changed primary outcome from physical and psychosocial function to "pain"
Other bias	High risk	Not published, all information and data extracted from trial registration: https://clinicaltrials.gov/ct2/show/study/NCT00066937

NCT01225068

Study characteristics	
Methods	Design: parallel Duration: 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: low back pain Population: adults aged 18-70 with chronic neuropathic low back pain Minimum pain intensity: ≥ 50 on 0-100 scale Inclusion criteria • Aged 18-70 • Low back pain for a minimum of 6 months with radiation to leg or buttocks • ≥ 50 on 0-100 scale Exclusion criteria • Significant other medical disease and major psychiatric disorders excluded Total participants randomised: 40 Age in years (mean, SD): 47.7 (10.3) Gender: 21/40 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 20 • Inert • Identical appearance and matched dosing schedule Milnacipran 100-200 mg • n = 20 • SNRI • Flexible dose: 100-200 mg/day
Outcomes	AEs SAEs Withdrawal
Missing data methods	Completer analysis
Funding source	Partly funded by pharmaceutical: sponsor: Northwestern University; Collaborators: Forest Laboratories; Shirley Ryan Ability; Lab Best Practice
Conflicts of interest	NR
Notes	

NCT01225068 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs with matched dosing schedules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer-only analysis **Attrition** Total: 5/40 (12.5%) Placebo: 1/20 (5.0%) Milnacipran 100-200 mg: 4/20 (20.0%)
Selective reporting (reporting bias)	High risk	Originally had lots of outcome measures listed: effect size of outcome measures, VAS pain, BPI, McGill Pain Questionnaire and Physical Activity measurement), but only VAS pain reported
Other bias	High risk	Not published. All info and results extracted from trial registration: https://clinicaltrials.gov/ct2/show/study/NCT01225068

NCT01510457

Study characteristics

Methods	Design: parallel Duration: approximately 8 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: knee OA Population: adults with knee OA Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Confirmed knee OA • Chronic pain for ≥ 6 months

NCT01510457 *(Continued)*

	• Average pain rating of worse knee is ≥ 4 on a 0-10 scale Exclusion criteria • Severe or untreated psychiatric disorder (e.g. depression, anxiety) • Severe ongoing or unaddressed medical conditions Total participants randomised: 46 Age in years (mean, SD): 56 (8) Gender: 23/46 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 17 • Inert • Identical appearance and matched dosing Milnacipran 100 mg-200 mg • n = 29 • SNRI • Forced titration to fixed doses
Outcomes	Pain intensity Mood Physical function AEs SAEs Withdrawal
Missing data methods	Completer analysis only
Funding source	Pharmaceutical: Forest Laboratories
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinded procedures, but 0 placebo participants reported AEs and 34% of milnacipran participants did report AEs, somewhat unblinding

NCT01510457 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, unsure of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer-only analysis **Attrition** Total: 8/46 (17.4%) Placebo: 5/17 (29.4%) Milnacipran 100-200 mg: 3/29 (10.3%)
Selective reporting (reporting bias)	Unclear risk	As we're using all outcomes from trial they report all registered outcomes BUT they first posted the trial in 2012, the trial started in 2010.
Other bias	High risk	Not published - trial registry report only

Nørregaard 1995

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Country: Denmark
Participants	Pain condition: fibromyalgia Population: people with fibromyalgia Minimum pain intensity: no Inclusion criteria • Fulfilled the ACR criteria for fibromyalgia during the last year Exclusion criteria • Severe physical and mental health comorbidities Total participants randomised: 43 Age in years (mean, SD): 49 Gender: NR Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 21 • Inert • Identical appearance and sham dosing Citalopram 20-40 mg

Nørregaard 1995 *(Continued)*

- n = 21
- SSRI
- Forced titration to fixed dose depending on response: started on 20 mg a day for 4 weeks (1 tablet), and then if participants did not report 2-point improvement then they were upped to 40 mg (2 tablets)

Outcomes	Pain intensity Mood Physical function Sleep
Missing data methods	ITT but methods NR
Funding source	Pharmaceutical: "This work was supported by funding from H. Lundbeck A/S."
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs with sham dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	State ITT but no methods specified **Attrition** Total: 10/43 (23.3%) Attrition per arm NR
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Otto 2008

Study characteristics

Otto 2008 *(Continued)*

Methods	Design: cross-over Duration: 5 weeks Assessment: baseline and post-intervention Country: Denmark
Participants	Pain condition: polyneuropathy Population: adults aged 20-80 with chronic polyneuropathy Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Symptoms of polyneuropathy within at least 6 months, diagnosis confirmed by physical examination • Pain intensity ≥ 4 on 0-10 scale Exclusion criteria • Other pain conditions and severe physical comorbidities Total participants randomised: 48 Age in years (median, range): 62 (37–74) Gender: 12/48 were female Pain duration in months (median, range): 48 (8–180)
Interventions	Placebo • Inert • Identical appearance and matched dosing Escitalopram 20 mg • SSRI • Fixed dose
Outcomes	Pain intensity Sleep Mood AEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Partly pharmaceutical: Odense University Hospital The work behind this study was supported by unrestricted grants from H. Lundbeck A/S and Gruenenthal GmbH and a grant from the Danish Clinical Intervention Research Academy.
Conflicts of interest	This was an investigator-initiated study and neither company was responsible for the creation of the study protocol, the data analysis, data interpretation, or writing of the manuscript.
Notes	

Otto 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment to treatment sequence was random via a computer-generated randomisation code with a block size of 4.
Allocation concealment (selection bias)	Low risk	The randomisation plan was generated by a person in the hospital pharmacy at Odense University Hospital who was not involved in the conduct of the trial. The study drugs were packed in boxes marked with randomisation number and treatment period by the hospital pharmacy. Patients were enrolled by the investigators and, after the baseline period, numbered consecutively by the investigators and treated with the study drugs with the corresponding randomisation number. Sealed opaque envelopes with the treatment sequence for each patient for emergency situations were present at the study sites.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs with matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 10/41 (24.4%) Placebo: 4/41 (9.8%) Escitalopram 20 mg: 6/41 (14.6%)
Selective reporting (reporting bias)	High risk	Some outcomes mentioned prospectively on clinicaltrials.gov NR e.g. different subtypes of pain and quality of life
Other bias	Low risk	No other sources of bias were identified

Ozerbil 2006

Study characteristics

Methods	Design: cross-over Duration: 2 weeks Assessment: baseline and post-intervention Country: Turkey
Participants	Pain condition: fibromyalgia Population: adult women aged 20-60 with fibromyalgia Minimum pain intensity: no Inclusion criteria

Ozerbil 2006 *(Continued)*

	• Aged 20-60 • Fibromyalgia according to ACR classification Exclusion criteria • Current or past history of systemic illness, including cardiac, renal, haematologic, or hepatic disease Total participants randomised: 15 Age in years (mean, SD): NR Gender: 15/15 were female Pain duration in years (mean, SD): NR
Interventions	Amitriptyline 25 mg + placebo • TCA + placebo • Fixed dose • Double-dummy design Fluoxetine 20 mg + placebo • SSRI + placebo • Fixed dose • Double-dummy design
Outcomes	The study provided no useable data
Missing data methods	NR
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using randomisation tables
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, dummy dosing technique and identical tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researcher blinding - not enough information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information regarding missing data or withdrawal given

Ozerbil 2006 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias identified

Pakfetrat 2019

Study characteristics	
Methods	Design: parallel Duration: 11 weeks Assessment: baseline, 3 weeks, 7 weeks, post-intervention Country: Iran
Participants	Pain condition: burning mouth syndrome Population: people with burning mouth syndrome Minimum pain intensity: ≥ 5 on 0-10 VAS Inclusion criteria • Daily deep bilateral burning sensation in the mouth for at least 4-6 months, persistent or increased burning intensity throughout the day • Pain intensity ≥ 5 on 0-10 VAS Exclusion criteria • Severe physical and mental health comorbidities Total participants randomised: 47 Age in years (mean): 50.9 Gender: 32/47 were female Pain duration in years (mean, SD): NR
Interventions	Crocin (saffron) 30 mg • n = 26 • Plant extract • Fixed dose • Identical appearance to citalopram Citalopram 20 mg • n = 21 • SSRI • Fixed dose
Outcomes	Pain intensity Mood Withdrawal

Pakfetrat 2019 *(Continued)*

Missing data methods	No participants withdrew
Funding source	Non-pharmaceutical: "We are thankful to the Vice Chancellor of Mashhad University of Medical Sciences for providing financial support for this study".
Conflicts of interest	"The authors declare that they have no conflict of interest in this research."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation methods not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Mention similar package and pill appearance but citalopram is being taken once daily and saffron twice daily so it's not completely identical in dosing schedule.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of participants who completed self reported measures is unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants withdrew
Selective reporting (reporting bias)	Unclear risk	Could not access trial registration
Other bias	Low risk	No other sources of bias were identified

Patkar 2007

Study characteristics

Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: people aged 18-65 with fibromyalgia and depression Minimum pain intensity: ≥ 5 on 0-10 scale Inclusion criteria

Patkar 2007 *(Continued)*

	• People aged 18-65, who fulfilled ACR diagnostic criteria for fibromyalgia • VAS for pain score of ≥ 5 out of 10 • BDI score of ≤ 23 Exclusion criteria • Unstable medical conditions and psychotic disorders, severe depression or anxiety Total participants randomised: 116 Age in years (mean, SD): 48.5 Gender: 109/116 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 58 • Inert • Identical in appearance and taste Paroxetine 12.5-62.5 mg • n = 58 • SSRI • Forced titration to maximum tolerated dose • Mean dose 39.1 (8.6) mg/day
Outcomes	Pain intensity AEs SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: this work was supported by a Collaborative Research Grant from GlaxoSmithKline
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation (1:1) was determined by the Investigational Drug Service through a computer-generated sequence.
Allocation concealment (selection bias)	Low risk	The trial staff obtained the randomisation assignment over the phone at screening. The allocation sequence was concealed from the staff before and after assignment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, study drugs identical

Patkar 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF. Double the number of people withdrew from intervention arm than placebo **Attrition** Total: 30/116 (25.9%) Placebo: 10/58 (17.2%) Paroxetine 12.5-62.5 mg: 20/58 (34.5%)
Selective reporting (reporting bias)	High risk	Differs from protocol, though primary outcome remains the same In the protocol on clinicaltrials.gov it says that they will report change from baseline in BDI/BAI, but they do not.
Other bias	Low risk	No other sources of bias were identified.

Petzke 2013

Study characteristics	
Methods	Design: parallel Duration: 13 weeks Assessment: baseline and post-intervention Country: UK, Sweden, and Germany
Participants	Pain condition: fibromyalgia Population: right-handed women, 18–55 years of age, with fibromyalgia Minimum pain intensity: ≥ 40 on 0-100 VAS Inclusion criteria • Right-handed women, 18–55 years of age, who met the 1990 ACR diagnostic criteria for fibromyalgia • ≥ 40 on 0-100 pain intensity VAS Exclusion criteria • Severe psychiatric illness and other severe or unstable physical health conditions Total participants randomised: 92 Age in years (mean, SD): 44.2 Gender: 92/92 were female Pain duration in years (mean, SD): 11.1
Interventions	Placebo • n = 46 • Inert

Petzke 2013 *(Continued)*

	• Identical appearance with matched dosing Milnacipran 200 mg • n = 46 • SNRI • Fixed dose, participants who could not tolerate dose were withdrawn
Outcomes	AEs SAEs Withdrawal
Missing data methods	MMRM for pain, NR for other outcomes
Funding source	Pharmaceutical: this study (EudraCT # 2004-004249-16) was financed and performed in collaboration with the pharmaceutical company Pierre Fabre.
Conflicts of interest	This study (EudraCT # 2004-004249-16) was financed and performed in collaboration with the pharmaceutical company Pierre Fabre. There are no other conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs with matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Mix of different methods used for missing data. More participants discontinued in intervention arm due to AEs than placebo arm **Attrition** Total: 22/92 (23.9%) Placebo: 8/46 (17.4%) Milnacipran: 13/46 (28.3%)
Selective reporting (reporting bias)	High risk	Lots of outcomes reported in the EudraCT registration recorded at baseline and 12 weeks that are NR in the results on there or published papers.
Other bias	Low risk	No other sources of bias were identified

Pickering 2018

Study characteristics	
Methods	Design: parallel Duration: 4 weeks Assessment: baseline and post-interventions Country: France
Participants	Pain condition: fibromyalgia Population: adult women with fibromyalgia Minimum pain intensity: no Inclusion criteria • Fibromyalgia meeting ACR criteria Exclusion criteria • Physical or mental health comorbidities Total participants randomised: 54 Age in years (mean, SD): 46.7 (10.6) Gender: 54/54 were female Pain duration in months (mean): 71.9
Interventions	Placebo • n = 25 • Inert • Matched dosing Milnacipran 100 mg • n = 29 • SNRI • Fixed dose
Outcomes	Pain intensity Moderate pain relief AEs SAEs Withdrawal
Missing data methods	Completer analysis only
Funding source	Non-pharmaceutical: "We thank the Apicil foundation for their financial support"
Conflicts of interest	The study authors report no conflicts of interest in this work.

Pickering 2018 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation sequence was generated using random blocks.
Allocation concealment (selection bias)	Low risk	Treatment allocation followed a predefined randomisation plan and was conducted by a person independent from the protocol.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs with matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only **Attrition:** Total: 6/54 (11.1%) Placebo: 1/29 (3.5%) Milnacipran 100 mg: 5/25 (20.0%)
Selective reporting (reporting bias)	Low risk	Study protocol published: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4393595/ All outcomes matched those published
Other bias	Low risk	No other sources of bias were identified.

Pilowsky 1990

Study characteristics

Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: Australia
Participants	Pain condition: chronic, intractable 'psychogenic' pain Population: patients with chronic, intractable ‘psychogenic’ pain Minimum pain intensity: no Inclusion criteria • Complaint of pain for at least 1 month, which is not responding adequately to appropriate treatment

Pilowsky 1990 *(Continued)*

	• Absence of objective evidence for the presence of any significant organic disease sufficient to explain the presence or severity of the pain experience and degree of disability • Impairment of functioning by at least 25% taking into account biological, personal, social, occupational and recreational aspects Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 129 Age in years (mean): 42.26 Gender: 80/129 were female Pain duration in years (mean, SD): NR
Interventions	Amitriptyline + pyschotherapy • n = 26 • Combined intervention: TCA + psychotherapy • Amitriptyline: flexibly dosed up to 150 mg/day • Psychotherapy: 12 weekly, 45-minute psychotherapy sessions focusing on "facing inner conflicts" that were theorised to be causing physical pain Amitriptyline + support • n = 26 • TCA • Amitriptyline: flexibly dosed up to 150 mg/day • Support to 'match' psychotherapy: 6 x 2-weekly. 15-minute sessions that focused on the physical symptoms, effects and side effects of medication Placebo + psychotherapy • n = 26 • Inert placebo • Psychotherapy: 12 weekly, 45-minute psychotherapy sessions focusing on "facing inner conflicts" that were theorised to be causing physical pain Placebo + support • n = 24 • Inert placebo • Support to 'match' psychotherapy: 6 x 2-weekly, 15-minute sessions that focused on the physical symptoms, effects and side effects of medication
Outcomes	Pain intensity Withdrawal
Missing data methods	Completer analysis
Funding source	Non-pharmaceutical: "We are indebted to the National Health and Medical Research Council who provided generous support for the conduct of this study."
Conflicts of interest	NR
Notes	

Pilowsky 1990 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to 1 of 4 treatment groups with the use of a table of random numbers.
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of blinding procedures between psychotherapy/support and amitriptyline/placebo.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Very different intervention experience for those undergoing psychotherapy versus simple support. Triallists attempt to control for effects of contact in therapy by having clincian support, but participants would be aware of their intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only. Original numbers of participants in arms not given, and withdrawal only given in percentages. No reasons given for withdrawal **Attrition** Total: 28/129 (21.7%) Amitriptyline ≤ 150 mg + psychotherapy: 6/26 (24%) Amitriptyline ≤ 150 mg + support: 7/26 (25%) Psychotherapy: 5/26 (19%) Support: 7/24 (31%)
Selective reporting (reporting bias)	High risk	Some outcome measures mentioned in the methods don't seem to be reported in the results section (e.g. McGill pain questionnaire). No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Pirbudak 2003

Study characteristics

Methods	Design: parallel Duration: 9 months Assessment: baseline, 2 weeks, 6 weeks, 3 months, 6 months, post-intervention Country: Turkey
Participants	Pain condition: low back pain Population: people aged > 35 years with chronic low back pain Minimum pain intensity: no

Pirbudak 2003 *(Continued)*

	Inclusion criteria • Chronic low back pain of at least 3 months' duration not responding to other modalities of conservative management Exclusion criteria • Severe clinical ailments such as cardiac disease and chronic renil failure Total participants randomised: 92 Age in years (mean, SD): 49.1 Gender: 62/92 were female Pain duration in months (median, range): 16.5 (6-48)
Interventions	Epidural injection + placebo • n = 46 • Inert placebo • Epidural injection consisted of 10 mL of betamethasone dipropionate (10 mg) + betamethasone sodium phosphate (4 mg) + bupivacaine (0.25%). Injections were repeated at the end of the 2nd week if the improvement was partial and at the end of the 6th week if there was still incomplete recovery from pain. • Participants took placebo tablets for 9 months in addition to the injection. Epidural injection + amitriptyline (10-50 mg) • n = 46 • TCA • Amitriptyline flexibly dosed between 10 and 50 mg/day depending upon tolerance • Epidural injection consisted of 10 mL of betamethasone dipropionate (10 mg) + betamethasone sodium phosphate (4 mg) + bupivacaine (0.25%). Injections were repeated at the end of the 2nd week if the improvement was partial and at the end of the 6th week if there was still incomplete recovery from pain. Participants took amitriptyline tablets for 9 months in addition to the injection.
Outcomes	Pain intensity Physical function
Missing data methods	Unclear
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified

Pirbudak 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Says double-blinded, but doesn't specify information about the medication
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing data methods and no withdrawal data reported, seems like all participants completed but unclear
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Rani 1996

Study characteristics	
Methods	Design: parallel Duration: 4 weeks Assessment: baseline, week 1, week 2, week 3, post-intervention Country: India
Participants	Pain condition: chronic pain syndrome Population: 27 presented with low back pain, 16 with OA, 8 with fibromyalgia, and 8 with RA Minimum pain intensity: ≥ 60 on 0-100 VAS Inclusion criteria • People with chronic pain syndrome • Pain intensity ≥ 60 on 0-100 VAS • Poor response to NSAIDs after 1 month Exclusion criteria • Severe physical health comorbidities Total participants randomised: 59 Age in years (mean, SD): 40 Gender: 36/59 were female Pain duration in months (mean): 25.3
Interventions	Placebo • n = 18 • Inert • Identical appearance

Rani 1996 *(Continued)*

	Amitriptyline 25 mg • n = 20 • TCA • Fixed dose Fluoxetine 20 mg • n = 21 • SSRI • Fixed dose
Outcomes	Pain intensity Withdrawal
Missing data methods	Unclear
Funding source	Pharmaceutical: supported by Natco Pharma Limited, India
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs with matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of missing data handling/impute methods, it seems like no participants dropped out but this is unclear
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Raskin 2005

Study characteristics

Raskin 2005 *(Continued)*

Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: "Worldwide"
Participants	Pain condition: diabetic peripheral neuropathic pain Population: type 1 or 2 diabetic adults with diabetic peripheral neuropathic pain Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Pain due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes mellitus. The pain had to begin in the feet and with relatively symmetrical onset • Present for ≥ 6 months • Pain intensity ≥ 4 on 0-10 scale Exclusion criteria • Serious or unstable illness, medical or psychological condition that might compromise participation in the study, diagnosis of MDD, dysthymia, GAD Total participants randomised: 348 Age in years (mean, SD): 58.8 (10.1) Gender: 186/348 were female Pain duration in years (mean, SD): 4.3 (4.2)
Interventions	Placebo • n = 116 • Inert • Identical appearance and matched dosing Duloxetine 60 mg • n = 116 • SNRI • Fixed dose Duloxetine 120 mg • n = 116 • SNRI • Fixed dose
Outcomes	Pain intensity Mood Sleep Moderate pain relief Substantial pain relief PGIC

Raskin 2005 *(Continued)*

	AEs
	SAEs
	Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: funded by Eli Lilly
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment to treatment groups was determined by a computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Allocation to treatment groups using an Interactive Voice Response System
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs with matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF. Significantly more people in the duloxetine 120 mg arm dropped out due to AE than other arm **Attrition** Total: 52/348 (14.9%) Placebo: 16/116 (13.8%) Duloxetine 60 mg: 15/116 (12.9%) Duloxetine 120 mg: 21/116 (18.1%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Razazian 2014

Study characteristics

Methods	Design: parallel
	Duration: 4 weeks

Razazian 2014 *(Continued)*

	Assessment: baseline, 2 days, 7 days, 14 days, 1 week post-intervention Country: Iran
Participants	Pain condition: diabetic polyneuropathy Population: adults with diabetic polyneuropathy referred to diabetic clinic Minimum pain intensity: ≥ 40 on 0-100 scale Inclusion criteria • Diagnosis of metabolically stable type 1 or 2 diabetes with diabetic polyneuropathy according to the Boulton 2005 criteria • History of neuropathic pain for at least 3 months • Pain intensity of ≥ 40 on 0-100 scale Exclusion criteria • Any other pain condition, severe medical conditions including severe depression and psychotic disorders Total participants randomised: 257 Age in years (mean, SD): 56.3 (10.4) Gender: 156/257 were female Pain duration in months (mean, SD): 23.5 (2.5)
Interventions	Carbamazepine 400 mg • n = 85 • Anticonvulsant • Fixed dose Pregabalin 150 mg • n = 86 • Anticonvulsant • Fixed dose Venlafaxine 150 mg • n = 86 • SNRI • Fixed dose
Outcomes	Moderate pain relief Substantial pain relief Sleep Mood AEs SAEs Withdrawal
Missing data methods	NR

Razazian 2014 *(Continued)*

Funding source	Non-pharmaceutical: Kermanshah Univesity Of Medical Science
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised via a computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Investigators and participants were blinded to the treatments by preprinted medication code labels.
Blinding of participants and personnel (performance bias) All outcomes	High risk	States double-blind but drugs not identical and dosage schedule differs between participants: venlafaxine taken as tablet twice daily, pregabalin as capsule once daily and carbamazepine twice daily as tablet
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from participants, but not strict blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	No methods for dealing with missing data specified, think they present completer analysis. **Attrition** Total: 33/257 (12.8%) Carbamazepine 400 mg: 7/85 (8.2%) Pregabalin 150 mg: 9/86 (10.5%) Venlafaxine 150 mg: 17/86 (19.8%)
Selective reporting (reporting bias)	High risk	Protocol not very clear, mention reporting 30th day as outcome time point but in article it's the 35th day. Did not mention work interference as outcome but have included it in paper, mention primary outcome will be measured with "PPI" and VAS but seems that PPI NR in article. Protocol registered on IRCT while recruiting participants, only 2 outcomes specified.
Other bias	High risk	Significant difference in VAS pain between groups at baseline

RBR-5dsrhv

Study characteristics

Methods	Design: parallel Duration: 16 weeks Assessment: baseline and post-intervention Country: Brazil

RBR-5dsrhv *(Continued)*

Participants	Pain condition: temporomandibular pain Population: women aged 18-59 with chronic temporomandibular pain Minimum pain intensity: intensity of muscle pain ≥ 7 on a 0-10 VAS Inclusion criteria • Women between 18 and 59 with chronic temporomandibular pain • Intensity of muscle pain ≥ 7 on a 0-10 VAS Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 96 Age in years (mean): 35.9 Gender: 96/96 were female Pain duration in years (mean, SD): NR
Interventions	Waitlist • n = 24 • Participants kept on a waiting list for 4 months and instructed not to receive any other treatment for temporomandibular pain with telephone calls every 2 weeks Amitriptyline 10 mg • n = 24 • TCA • Fixed dose Amitriptyline 10 mg + splint • n = 24 • Combined intervention: TCA + splint • Amitriptyline = fixed dose • Use of an occlusal plaque stabiliser without occlusal guide during sleep Acupuncture • n = 24 • Weekly acupuncture performed by acupuncturist dental surgeons, totaling 16 sessions, with needling time of 20 min
Outcomes	Pain intensity Mood Quality of life Sleep Withdrawal
Missing data methods	Completer-only analysis
Funding source	Non-pharmaceutical: thanks the CAPES scholarship for fund

RBR-5dsrhv *(Continued)*

Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised by means of random numbers generated by computer
Allocation concealment (selection bias)	Low risk	The randomisation of patients in the 4 groups was carried out by means of opaque and sealed envelopes encoded by 'A', 'B', 'C' or 'D', prepared by a researcher without contact with the other procedures.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind the participants and the clinicians due to the nature of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only. Unequal attrition - many more participants withdrew from the acupuncture group than the other groups. **Attrition** Total: 18/96 (18.75%) Waitlist: 3/24 (12.5%) Amitriptyline 10 mg: 3/24 (12.5%) Amitriptyline 10 mg + splint: 1/24 (4.2%) Acupuncture: 11/24 (45.8%)
Selective reporting (reporting bias)	Unclear risk	Trial was registered on the Brazilian Registry of Clinical Trials after completion.
Other bias	Unclear risk	Extracted from a doctoral thesis translated from Portuguese - can't find published papers

Richards 2015

Study characteristics

Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: pain from spinal cord injury

Richards 2015 *(Continued)*

	Population: adults aged 18-64 with spinal cord injury and dysthymia/major depression Minimum pain intensity: no Inclusion criteria • At least 1 month post-spinal cord injury • Meeting DSM-IV criteria for major depression or dysthymia Exclusion criteria • Physical health comorbidities • History of schizophrenia or bipolar disorder; suicidal risk Total participants randomised: 123 Age in years (mean, SD): 40 (11) Gender: 31/123 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 59 • Inert • Identical appearance and matched dosing Venlafaxine 37.5 - 225 mg • n = 64 • SNRI • Flexible dosing dependent upon efficacy and tolerability
Outcomes	Substantial pain relief Mood Withdrawal
Missing data methods	NR
Funding source	Non-pharmaceutical: the contents of this article were developed under a grant from the Department of Education, National Institute on Disability and Rehabilitation Research (grant no. H133A060107).
Conflicts of interest	Supported by Pfizer in the form of study drug (0600B1-4439). Study authors report no CoIs.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated by the study biostatistician
Allocation concealment (selection bias)	Low risk	Drug allocation handled by outside pharmacy "The investigational drug service at the lead center (University of Washington) trained and coordinated pharmacists at all sites, provided randomisation logs, and supplied active and placebo drug encapsulated into blinded study drug A and B."

Richards 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data methods not specified **Attrition** Total: 29/123 (23.6%) Placebo: 14/59 (23.7%) Venlafaxine 37.5-300 mg: 15/64 (23.4%)
Selective reporting (reporting bias)	Low risk	Outcomes as listed on the main trial registration (https://clinicaltrials.gov/ct2/show/study/NCT00592384)
Other bias	Low risk	No other sources of bias were identified.

Rintala 2007

Study characteristics	
Methods	Design: cross-over Duration: each cross-over period was 8 weeks Assessment: baseline and post-cross-over period Country: USA
Participants	Pain condition: chronic neuropathic pain following spinal cord injury Population: adults with a spinal cord injury at least 12 months ago with chronic neuropathic pain Minimum pain intensity: ≥ 5 on 0-10 scale Inclusion criteria • Aged 18-70 • Spinal cord injury occurred at least 12 months before entering the study • At least 1 chronic (6 months) pain component characteristic of neuropathic pain • At least 1 neuropathic pain component rated as at least 5 on a 0-10 scale Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 38 Age in years (completers; mean, SD): 42.6 (12.6) Gender (completers): 2/38 were female

Rintala 2007 *(Continued)*

	Pain duration in years (completers; mean, SD): 7.3 (7.7)
Interventions	Gabapentin ≤ 3600 mg • Anticonvulsant • Forced titration to maximum tolerated dose • Matched dosing schedule Amitriptyline ≤ 150 mg • TCA • Forced titration to maximum tolerated dose • Matched dosing schedule Placebo (diphenhydramine ≤ 75 mg) • Active placebo - antihistamine • Forced titration to fixed dose • Matched dosing schedule
Outcomes	Pain intensity Moderate pain relief Withdrawal
Missing data methods	Completer-only analysis
Funding source	Non-pharmaceutical: supported by the Department of Veterans Affairs, Veterans Health Administration, Rehabilitation Research and Development Service (grant no. B2573R)
Conflicts of interest	"No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the author(s) or upon any organisation with which the author(s) is/are associated"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The order of this assignment within the sets of 6 was based on a table of random numbers, and varied from set to set.
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matched dosing regime, active comparator used as placebo, and identical capsules for medication
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only. High levels of attrition **Attrition**

Rintala 2007 *(Continued)*

		Total: 16/38 (42.1%) Gabapentin ≤ 3600 mg: 12/38 (31.6%) Amitriptyline ≤ 150 mg: 10/38 (26.3%) Placebo: 13/38 (34.2%) As this is a cross-over study, some participants only withdrew from one period of the study, not the study as a whole, therefore, the numbers of participants withdrawing per arm does not match the total numbers of participants withdrawing.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias identified

Robinson 2004

Study characteristics	
Methods	Design: parallel Duration: 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: phantom/residual limb pain Population: amputees with chronic phantom limb/residual limb pain Minimum pain intensity: ≥ 2 on 0-10 scale Inclusion criteria • Aged 18-65 • Amputation > 6 months before enrollment, pain for at least 3 months, and average pain rating in the last month of at least 2 on a scale of 0-10 Exclusion criteria • Cardiovascular disease or seizures Total participants randomised: 39 Age in years (mean, SD): 44.9 Gender: 5/20 were female Pain duration in years (mean, SD): NR
Interventions	Placebo (benztropine mesylate 0.5 mg) • n = 19 • Active placebo • Identical appearance Amitriptyline

Robinson 2004 *(Continued)*

- n = 20
- TCA
- Maximum dose: 125 mg/day. Titration: week 1: 10 mg/day, week 2, 25 mg/d; week 3, 50 mg/d; week 4, 75 mg/d; week 5, 100 mg/d; and week 6, 125 mg/day. Dosages were increased by study nurse each week until pain relief or tolerance

Outcomes	Pain Mood Physical function Withdrawal
Missing data methods	ITT but no methods specified
Funding source	Non-pharmaceutical: supported by the National Institutes of Health, National Institute of Child Health and Human Development, National Institute of Neurological Disorders and Stroke (grant no. 1PO1 HD/NS33988)
Conflicts of interest	"No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the authors(s) or upon any organisation with which the author(s) is/are associated."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Low risk	Provision of medication was done by the Harborview Medical Center Pharmacy Investigational Drug Services. Medication was provided to each participant on a weekly basis by the study nurse or by mail for participants who lived far from the study center. A 7-day supply of medication was provided to each participant each week in identical gelatin capsules placed in a plastic holder (Mediset), so that study personnel and participants were blind to medication assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study medication
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data methods reported, but low withdrawal **Attrition** Total: 2/39 (5.1%) Placebo: 0/19 (0.0%) Amitriptyline ≤ 125 mg: 2/20 (10.0%)

Robinson 2004 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Outcomes not registered in protocol and protocol registered retrospectively
Other bias	Low risk	No other sources of bias were identified

Rowbotham 2004

Study characteristics	
Methods	Design: parallel Duration: 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: diabetic peripheral neuropathy Population: type 1 or 2 diabetic adults with diabetic peripheral neuropathy Minimum pain intensity: ≥ 40 on 0-10 scale Inclusion criteria • Metabolically stable type 1 or 2 diabetes were eligible if they had symptomatic peripheral neuropathy due only to diabetes and daily pain at moderate intensity for at least 3 months Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 245 Age in years (mean): 59 Gender: 99/245 were female Pain duration in weeks (mean): 252.6
Interventions	Placebo • n = 81 • Inert • Identical appearance, double-dummy design Venlafaxine 75 mg • n = 82 • SNRI • Fixed dose Venlafaxine 150/225 mg • n = 82 • SNRI • Flexible dose: 150 mg/day - 225 mg/day depending on clinical response and tolerance.
Outcomes	Substantial pain relief

Rowbotham 2004 *(Continued)*

	AEs SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: support for this study was provided by Wyeth Research, Collegeville, Pennsylvania.
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded bottles and capsules, identical dosing schedules between groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 43/245 (17.6%) Placebo: 12/81 (14.8%) Venlafaxine 75 mg: 13/82 (15.9%) Venlafaxine 150-225 mg: 18/82 (22.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Rowbotham 2005

Study characteristics

Methods	Design: parallel Duration: 6 weeks

Rowbotham 2005 *(Continued)*

	Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: post-herpetic neuralgia Population: people aged > 40 with post-herpetic neuralgia Minimum pain intensity: no Inclusion criteria • Over the age of 40 were eligible if they had well-established post-herpetic neuralgia (defined as pain present > 3 months after healing of the skin rash) Exclusion criteria • Any pain condition with greater severity than the post-herpetic neuralgia. Depression included and measured at baseline by a psychologist Total participants randomised: 47 Age in years (mean, range): 72 (40-84) Gender: 27/47 were female Pain duration in months (mean, range): 42 (3-168)
Interventions	Desipramine 25-150 mg • n = 15 • TCA • Flexible dose • Mean dose taken: 93 mg/day Amitriptyline 25-150 mg • n = 17 • TCA • Flexible dose • Mean dose taken: 77 mg/day Fluoxetine 10-60 mg • n = 15 • SSRI • Flexible dose • Mean dose taken: 44 mg/day
Outcomes	Withdrawal
Missing data methods	ITT but no methods
Funding source	Non-pharmaceutical: supported by NIH program project grant NINDS 21445 and NINDS K24 NS02164
Conflicts of interest	NR
Notes	
Risk of bias	

Rowbotham 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods NR
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Says modified ITT but doesn't mention imputation method. Higher attrition in the fluoxetine arm than other arms **Attrition** Total: 9/47 (19.2%) Desipramine 25-150 mg: 2/15 (13.3%) Amitriptyline 25-150 mg: 2/17 (11.8%) Fluoxetine 10-60 mg: 5/15 (33.3%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry found
Other bias	Low risk	No other sources of bias were identified.

Rowbotham 2012

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Country: USA, Canada, France, Germany, Italy, Mexico, Puerto Rico
Participants	Pain condition: diabetic peripheral neuropathy Population: diabetic adults with diabetic peripheral neuropathic pain Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • 18-75 years of age with a diagnosis of diabetes mellitus • Painful distal symmetric diabetic polyneuropathy for P6 months and a score of ≥ 3 on the physical assessment portion of the MNSI at the screening visit • An average score ≥ 4 during the 7 days before the baseline visit on the 24-hour average pain scale

Rowbotham 2012 *(Continued)*

	Exclusion criteria • Cardiovascular and mental health conditions excluded Total participants randomised: 280 Age in years (mean, SD): NR Gender: 128/280 were female Pain duration in years (mean): 4.68
Interventions	Placebo • n = 51 • Inert Duloxetine 60 mg • n = 57 • SNRI • Fixed dose ABT-894 2 mg • n = 61 • Neuronal nicotinic acetylcholine receptor agonist • Fixed dose ABT-894 4 mg • n = 56 • Neuronal nicotinic acetylcholine receptor agonist • Fixed dose ABT-894 8 mg • n = 55 • Neuronal nicotinic acetylcholine receptor agonist • Fixed dose
Outcomes	Pain intensity Physical function Mood Quality of life PGIC AEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: Abbott Laboratories: AbbVie (prior sponsor, Abbott)
Conflicts of interest	These studies were sponsored by Abbott Laboratories. Dr Rowbotham has served as a consultant to Abbott, Adynxx, Afferent Pharmaceuticals, Allergan, Arcion, Bristol Meyers Squibb, Cardiome, Flexion, Kyowa Hakko Kirin, Neurotherapeutics Pharma, NuvoResearch, Xenon, Xenoport, and Zalicus. Dr Stacey has received grant support from NeurogesX and Pfizer, and has served as a consultant to As-

Rowbotham 2012 *(Continued)*

	traZeneca, Boehringer Ingelheim, Endo Pharmaceuti-cals, NeurogesX, and Pfizer. Dr Arslanian has no conflicts of interest to declare. Dr Zhou is an employee of Abbott. Drs Nothaft, Duan, Best, and Pritchett are employees of Abbott and hold Abbott stock and stock options.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised 1:1 to each treatment arm using a randomisation schedule that was generated before study start.
Allocation concealment (selection bias)	Low risk	Patients were allocated to each treatment arm via an interactive voice response system.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clear on blinding procedures regarding study drug appearance and dosing
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but unsure of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	States ITT but no methods reported **Attrition** Total: 43/280 (15.4%) Placebo: 7/51 (13.7%) Duloxetine 60 mg: 13/57 (22.8%) ABT-894 2 mg: 8/61 (13.1%) ABT-894 4 mg: 8/56 (14.3%) ABT-894 8 mg: 7/55 (12.7%)
Selective reporting (reporting bias)	Low risk	Everything as listed in the protocol
Other bias	Low risk	No other sources of bias were identified.

Russell 2008

Study characteristics

Methods	Design: parallel Duration: 28 weeks Assessment: baseline, 3 months, post-intervention Country: USA and Puerto Rico
Participants	Pain condition: fibromyalgia

Russell 2008 *(Continued)*

	Population: adults with fibromyalgia with or without MDD Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Outpatients at least 18 years of age who met criteria for fibromyalgia as defined by the ACR criteria • Score ≤ 4 on the average pain severity item of BPI • Patients with or without current MDD were included Exclusion criteria • Physical health comorbidities • Any current primary psychiatric diagnosis other than MDD Total participants randomised: 520 Age in years (mean, SD): 51.02 (10.87) Gender: 492/520 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 144 • Inert • Matched dosing Duloxetine 20 mg then 60 mg • n = 79 • SNRI • Forced titration to fixed dose Duloxetine 60 mg • n = 150 • SNRI • Forced titration to fixed dose Duloxetine 120 mg • n = 147 • SNRI • Forced titration to fixed dose
Outcomes	Pain intensity Quality of life Physical function Mood Moderate pain relief Substantial pain relief PGIC AEs SAEs

Russell 2008 *(Continued)*

	Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: this work was sponsored by Eli Lilly and Company and Boehringer Ingelheim GmbH.
Conflicts of interest	Drs Chappell, Detke, Kajdasz, Walker, and Wohlreich are employees and stockholders of Eli Lilly and Company. Drs Arnold, Mease, Russell, and Smith were Principal Investigators at sites conducting the trial. Their sites received funds for participating in the research study. Dr Arnold has received grants/research support from Eli Lilly and Company, Pfizer Inc, Cypress Biosciences Inc, Wyeth Pharmaceuticals, Sanofi-Aventis, Boehringer Ingelheim, Allergan, and Forest; she has been a consultant for Eli Lilly and Company, Pfizer Inc, Cypress Biosciences Inc, Wyeth Pharmaceuticals, Sanofi-Aventis, Boehringer Ingelheim, Sepracor, Forest Laboratories Inc, Allergan, Vivus Inc, and Organon; and she is on the Speakers Bureau of Eli Lilly and Company and Pfizer, Inc. Dr Mease has received grants/research support from Eli Lilly and Company, Pfizer Inc, Cypress Bioscience, Forest, Allergan, Fralex, and Boehringer Ingelheim; he has been a consultant for Eli Lilly and Company, Pfizer Inc, Cypress Bioscience, Forest, Allergan, Fralex, Boehringer Ingelheim, Pierre Fabre, and Wyeth; and he is on the Speakers Bureau of Pfizer Inc. Dr Russell has received grants/research support from the National Institutes of Health, RGK Foundation of Austin Texas, The National Fibromyalgia Association, Autoimmune Technologies, LLC, New Orleans, Louisiana, LKB World (Southern France), Pfizer Central Research, Eli Lilly and Company, Orphan Medical/Jazz, Grutnenthal GmbH, Allergan, and Schwarz; and he is on medical advisory boards of Pfizer Inc, Eli Lilly and Company, Jazz Pharmaceutical, Gruenthal GmbH, and Allergan. Dr Smith has received grants/research support from Abbott, Allergan, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Johnson and Johnson, Merck, Ortho-McNeil, Pfizer Inc, Minster, Novartis, Novo Nordisk, Orexigen, Shionogi, Schwarz, Vernalis, and Wyeth; he has been a consultant or on advisory boards of Allergan, Eli Lilly and Company, was previously on a medical advisory board for Eli Lilly and Compant, GlaxoSmithKline and Merck.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment to treatment groups was determined by a computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	All participants only took 1 dose daily to maintain blinding. No information about appearance, taste etc. Possibly some participants in the 20/60 arm would become unblinded with the increase in dose.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes but unsure of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF. High attrition **Attrition** Total: 24/520 (46.7%) Placebo: 72/144 (50.0%) Duloxetine 20 mg then 60 mg: 35/79 (44.3%) Duloxetine 60 mg: 68/150 (45.3%)

Russell 2008 *(Continued)*

		Duloxetine 120 mg: 68/147 (46.3%)
Selective reporting (reporting bias)	High risk	Not completely clear in all outcome measures to be used - only domains - in the protocol. In the trial registry results submitted by study authors: they show they've measured the same outcomes with multiple scales (Hamilton Depression Rating Scale and BDI-II) have also measured further outcomes like BPI interference but do not report these. Have reported significant results in the trial report.
Other bias	Low risk	No other sources of bias were identified.

Sarzi Puttini 1988

Study characteristics	
Methods	Design: parallel Duration: 4 weeks Assessment: baseline and post-intervention Country: Italy
Participants	Pain condition: RA Population: adults with RA and with or without depression Minimum pain intensity: ≥ 50 on 0-100 scale Inclusion criteria • Classical or definite active RA, diagnosed according to the ARA criteria • Pain intensity ≥ 50 on 0-100 scale Exclusion criteria: NR Total participants randomised: 60 Age in years (mean, SD): NR Gender: 52/60 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 30 • Inert Dothiepin 75 mg • n = 30 • TCA • Fixed dose
Outcomes	Study provided no useable data
Missing data methods	Completer analysis

Sarzi Puttini 1988 *(Continued)*

Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation methods not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Says matched dosing schedules but not other information given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants but unsure of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only **Attrition** Total: 10/60 (16.7%) Attrition per arm NR
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Schukro 2016

Study characteristics

Methods	Design: cross-over Duration: 4 weeks Assessment: baseline and post-intervention Country: Austria
Participants	Pain condition: chronic low back pain with a neuropathic component Population: adults with chronic low back pain with a neuropathic component Minimum pain intensity: ≥ 5 on 0-10 scale Inclusion criteria

Schukro 2016 *(Continued)*

	• Aged 18-80 • Chronic low back and leg pain (> 6-month duration) and VAS score > 5cm on a 10-cm VAS scale Exclusion criteria • Mild depression present for > 12 months (defined as ≥ 10 points in the BDI) and severe coexisting diseases Total participants randomised: 41 Age in years (mean, SD): 57.9 (13.4) Gender: 21/41 were female Pain duration in months (mean, SD): 18 (6–70)
Interventions	Placebo • Inert • Identical appearance to duloxetine and matched dosing Duloxetine ≤ 120 mg • SNRI • Fixed dose
Outcomes	Pain intensity Physical function Mood Substantial pain relief AEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Non-pharmaceutical: this study was supported by the Medical Scientific Fund of the Mayor of the City of Vienna, Vienna, Austria
Conflicts of interest	The study authors declare no competing interests.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer-assisted and stratified according to age and sex.
Allocation concealment (selection bias)	Low risk	Study drugs and placebo were packaged in blue opaque capsules, which were manufactured by the hospital pharmacy of the Medical University of Vienna, and administered according to the assignment code, which was held by an independent study nurse.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, identical study drugs with matched dosing

Schukro 2016 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF. High attrition **Attrition** Total: 20/41 (48.8%) Placebo: 6/41 (14.6%) Duloxetine 120 mg: 6/41 (14.6%) 7 participants dropped out after randomisation but before starting to take study medication, and 1 participant dropped out between study periods. Therefore the total withdrawal is 20, while only 12 participants' withdrawal can be attributed to an arm.
Selective reporting (reporting bias)	High risk	Says in protocol registered on clinicaltrials.gov that participant data from the BDI will be collected at screening, week 4 and week 10, but in the paper it was only used as a screening tool.
Other bias	Low risk	No other sources of bias were identified.

Scudds 1989

Study characteristics	
Methods	Design: cross-over Duration: 4 weeks per cross-over period Assessment: baseline and post-cross-over period Country: Canada
Participants	Pain condition: fibrositis (fibromyalgia) Population: adults with fibromyalgia Minimum pain intensity: no Inclusion criteria • widespread muscular aching lasting at least 3 months • a non-restorative sleep pattern • morning stiffness and fatigue • localised tenderness at ≥ 12 of 14 specific sites Exclusion criteria • Severe physical health comorbidities • Amitriptyline use in previous year Total participants randomised: 39 Age in years (completers; mean, SD): 39.9 (10.2)

Scudds 1989 *(Continued)*

	Gender (completers): 32/39 were female Pain duration in years (completers; mean, SD): 5.1 (4.6)
Interventions	Placebo • Inert • Identical appearance to amitriptyline and matched dosing Amitriptyline 50 mg • TCA • Fixed dose
Outcomes	Withdrawal
Missing data methods	Completer-only analysis
Funding source	Non-pharmaceutical: "Supported in part by The Arthritis Society Studentship S-198 to R.A. Scudds and NSERC Grant AO 392 10"
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completer analysis but low dropout **Attrition** Total: 3/39 (7.7%) Placebo: 2/39 (5.13%) Amitriptyline 50 mg: 1/39 (2.6%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Sencan 2004

Study characteristics	
Methods	Design: parallel Duration: 6 weeks Assessment: baseline, post-intervention, follow-up (6 months) Country: Turkey
Participants	Pain condition: fibromyalgia Population: women aged 18-50 with fibromyalgia Minimum pain intensity: no Inclusion criteria • fibromyalgia patients between ages 18–50, diagnosed by the ACR criteria Exclusion criteria • Physical health comorbidities Total participants randomised: 60 Age in years (mean): 34.5 Gender: 60/60 were female Pain duration in years (mean): 5.4
Interventions	Aerobic exercise • n = 20 • Aerobic exercises 3 times a week for 6 weeks, each exercise period lasted for 40 minutes Paroxetine 20 mg • n = 20 • SSRI • Fixed dose Placebo TENS • n = 20 • Placebo TENS with electrodes applied on the 2 most painful tender points for 20 minutes, 3 times a week for 6 weeks
Outcomes	Pain intensity Mood
Missing data methods	No participants withdrew
Funding source	NR
Conflicts of interest	NR
Notes	

Sencan 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants unable to be blinded due to the nature of interventions
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants withdrew during the trial period
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Shakiba 2018

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline, 4 weeks, post-intervention Country: Iran
Participants	Pain condition: fibromyalgia Population: adults aged 18-60 with fibromyalgia Minimum pain intensity: ≥ 40 on 0-100 scale Inclusion criteria • Aged 18-60 years who were diagnosed with fibromyalgia based on ACR criteria Exclusion criteria • Psychiatric disorders other than depressive disorders, serious medical conditions, other pain/inflammatory conditions Total participants randomised: 54 Age in years (mean): 41.98

Shakiba 2018 *(Continued)*

	Gender: 34/54 were female Pain duration in years (mean, SD): NR
Interventions	Saffron 15 mg • n = 27 • Plant extract • Identical appearance to duloxetine Duloxetine 30 mg • n = 27 • SNRI • Fixed dose
Outcomes	Pain intensity Mood Quality of life Withdrawal
Missing data methods	ITT with LOCF
Funding source	Non-pharmaceutical: "This study was supported by Tehran University of Medical Sciences (TUMS) through a grant to Prof. Shahin Akhondzadeh (Grant number 31842)."
Conflicts of interest	"The authors of this manuscript declare that they have no COI. TUMS had no role in the design, conduct, data collection, analysis, data interpretation, manuscript preparation, review, final approval, or decision to submit this paper for publication."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation to either saffron or the duloxetine arm, was carried out in a 1:1 ratio through computerised random number generation by an independent person.
Allocation concealment (selection bias)	Low risk	Treatment allocation concealment was achieved using sequentially numbered sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Saffron capsules were identical to duloxetine in shape, size, texture, odour, and colour. Medications were distributed by an independent investigational drug pharmacist.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	State that they use ITT with LOCF, but then the n in tables is completers **Attrition** Total: 8/54 (14.8%)

Shakiba 2018 *(Continued)*

		Saffron 15 mg: 4/27 (14.8%) Duloxetine 30 mg: 4/27 (14.8%)
Selective reporting (reporting bias)	Low risk	Outcomes listed prospectively: https://en.irct.ir/trial/940
Other bias	Low risk	No other sources of bias were identified

Sindrup 2003

Study characteristics	
Methods	Design: cross-over Duration: each cross-over period lasted 4 weeks Assessment: baseline, post-cross-over period Country: Denmark
Participants	Pain condition: polyneuropathy Population: adults aged 20-70 with painful polyneuropathy Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Aged 20-70 • Symptoms compatible with polyneuropathy present for > 6 months, polyneuropathy diagnosis confirmed by nerve conduction studies • Pain intensity median ≥ 4 on 0-10 scale Exclusion criteria • Other pain conditions and severe terminal illness Total participants randomised: 40 Age in years (mean, range): 56 (31-69) Gender: 9/40 were female Pain duration in months (mean, range): 51 (6-300)
Interventions	Placebo • Inert • Identical appearance and matched dosing • Double-dummy design Venlafaxine 225 mg • SNRI • Fixed dose, forced titration Imipramine 150 mg • TCA

Sindrup 2003 *(Continued)*

- Fixed dose, forced titration

Outcomes	AEs
Missing data methods	Completer analysis
Funding source	Non-pharmaceutical: supported by the Danish National Research Council (NASTRA grant no. 42820) and the local research foundation at Odense University Hospital.
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment to one of the 6 possible treatment sequences was random via a computer-generated randomisation code.
Allocation concealment (selection bias)	Low risk	"The study drugs were packed in boxes marked with patient number and treatment period. After the baseline period, the patients were numbered consecutively and were treated with the study drugs with the corresponding randomisation number. Sealed envelopes with treatment sequence for each patient were present at the study sites for emergency situations."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy technique, matching study drugs and package appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 7/40 (17.5%) Not clear in which arm withdrawals occurred
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Skljarevski 2009

Study characteristics

Methods	Design: parallel Duration: 13 weeks Assessment: baseline and post-intervention

Skljarevski 2009 *(Continued)*

	Country: USA and Argentina
Participants	Pain condition: low back pain Population: adult patients with non-radicular chronic low back pain Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Clinical diagnosis of chronic low back pain with pain present on most days for ≥ 6 months • Pain intensity ≥ 4 on 0-10 scale Exclusion criteria • Surgery or invasive procedures to treat low back pain • Major depressive disorder Total participants randomised: 404 Age in years (mean, SD): 53.9 (14.1) Gender: 232/404 were female Pain duration in years (mean, SD): 11.7 (11.4)
Interventions	Placebo • n = 117 • Inert • Identical in smell, taste and appearance to duloxetine • Matched dosing across all arms Duloxetine 20 mg • n = 59 • SNRI • Fixed dose Duloxetine 60 mg • n = 116 • SNRI • Fixed dose Duloxetine 120 mg • n = 112 • SNRI • Fixed dose
Outcomes	Pain intensity Sleep Physical function Quality of life Mood PGIC

Skljarevski 2009 *(Continued)*

	Moderate pain relief
	Substantial pain relief
	AEs
	SAEs
	Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: study design, funding and drugs were supplied by Eli Lilly and Company.
Conflicts of interest	Authors V. Skljarevski, M. Ossanna, H. Liu-Seifert, Q. Zhang, A. Chappell, S. Iyengar and M. Detke are or were at the time of submission employees of Eli Lilly and Company and may be minor shareholders.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned by a computer-generated random sequence.
Allocation concealment (selection bias)	Low risk	Participants were allocated using an Interactive Voice Response System.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition with significantly more missing in higher dose arm due to AEs. Use ITT and LOCF **Attrition** Total: 137/404 (33.9%) Placebo: 35/117 (29.9%) Duloxetine 20 mg: 16/59 (27.1%) Duloxetine 60 mg: 36/116 (31.0%) Duloxetine 120 mg: 50/112 (44.6%)
Selective reporting (reporting bias)	Low risk	Primary outcomes specified prospectively on clincialtrials.gov along with data not presented in paper
Other bias	Unclear risk	Some baseline differences in important variables: pain history but not imbalanced in a way which favours treatment

Skljarevski 2010a

Study characteristics	
Methods	Design: parallel Duration: 13 weeks Assessment: baseline and post-intervention Country: Brazil, France, Germany, Mexico, and Netherlands
Participants	Pain condition: low back pain Population: adults with chronic low back pain Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Chronic low back pain as the primary painful condition; pain must have been present in lower back (T-6 or below) for most days for the past 6 months or longer with a weekly mean of 24-hour average pain score of ≥ 4 out of 10 at baseline Exclusion criteria • Any other pain condition, current depression, psychiatric conditions Total participants randomised: 236 Age in years (mean): 51.5 Gender: 144/236 were female Pain duration in years (mean): 9.2
Interventions	Placebo • n = 121 • Inert • Sham matched dosing using same criteria as duloxetine arm Duloxetine 60-120 mg • n = 115 • SNRI • Participants who did not meet reponse criteria (30% pain relief) had their doses uptitrated blindly.
Outcomes	Pain intensity Mood Physical function Quality of life Sleep PGIC Moderate pain relief Substantial pain relief AEs

Skljarevski 2010a *(Continued)*

	SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: Eli Lilly and Company
Conflicts of interest	Drs Skljarevski, Desaiah, Liu-Seifert, Zhang, Chappell, and Iyengar are employees and stockholders of Eli Lilly and Company. Dr Detke was a full-time employee and a major stock holder of Eli Lilly andCompany until March 2009 and is currently a full-time employee and a major stock holder of Medavante Corporation. Dr Atkinson serves on Lilly Pain Advisory Board. Dr Backonja serves on Lilly Pain Advisory Board and in addition performed clinical trials and received research funding from Allergan, Astellas, Johnson and Johnson, Lilly,Merck, NeurogesX, and Pfizer Corporate/Industry and Foundation funds were received in support of this work. One or more of the author(s) has/have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this manuscript: e.g., honoraria, gifts, consultancies, royalties, stocks, stock options, decision-making position.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified; only mention voice centralised system for allocating participants to higher dose, not when randomising and allocating all sample
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double blind, matched dosing but no information on study drug appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, but uncertain of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF. Some data are not the same in the protocol and the paper: more AEs reported on clinicaltrials.gov than in the paper. Participants did have significant differences as to why they have missing data: duloxetine group had significantly more withdrawals due to AEs. **Attrition** Total: 54/236 (22.9%) Placebo: 23/121 (19.0%) Duloxetine 60-120 mg: 31/115 (27.0%)
Selective reporting (reporting bias)	Low risk	All outcomes match those registered on clinicaltrials.gov
Other bias	Low risk	No other sources of bias identified

Skljarevski 2010b

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: Germany, Netherlands, Poland, Russia, Spain and USA
Participants	Pain condition: low back pain Population: adults with chronic low back pain Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Outpatients with chronic low back pain as their primary painful condition present on most days for at least 6 months and a rating of ≥ 4 on BPI pain intensity item Exclusion criteria • Low back surgery in previous year • Major depressive disorder and other psychiatric disorders excluded Total participants randomised: 401 Age in years (mean): 54.1 Gender: 246/401 were female Pain duration in years (mean): 8.3
Interventions	Placebo • n = 203 • Inert Duloxetine 60 mg • n = 198 • SNRI • Fixed dose
Outcomes	Pain intensity Sleep Mood Physical function Quality of life Moderate pain relief Substantial pain relief PGIC AEs

Skljarevski 2010b *(Continued)*

	SAEs Withdrawal
Missing data methods	ITT with LOCF, BOCF for sensitivity analyses of primary outcome
Funding source	Pharmaceutical: Eli Lilly and Company
Conflicts of interest	Drs Skljarevski and Desaiah, Ms Zhang, and Ms Alaka are employees of Eli Lilly and Company and hold company stocks. Drs Palacios, Miazgowski, and Patrick were study investigators and received funding from Eli Lilly and Company, Indianapolis, Indiana. These external authors had access to the data relevant to this manuscript.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind but no information on study drug appearance or matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reprorted outcomes from participants, but uncertain of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used ITT with LOCF but for primary outcome used BOCF and mBOCF for sensitivity analysis. Results using all methods of imputation were significant. **Attrition** Total: 98/401 (24.4%) Placebo: 47/203 (23.2%) Duloxetine 60 mg: 51/198 (25.8%)
Selective reporting (reporting bias)	Low risk	Published outcomes match protocol
Other bias	Unclear risk	In the trial registry they've registered 2 research sites in Brazil but have just not mentioned it anywhere after, no reason for excluding those centres stated

Smith 2013

Study characteristics

Smith 2013 *(Continued)*

Methods	Design: cross-over Duration: cross-over periods were 5 weeks Assessment: baseline and post-cross-over period Country: USA
Participants	Pain condition: neuropathic pain caused by chemotherapy Population: adults aged ≥ 25 with cancer and neuropathic pain after completing chemotherapy Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • At least grade 1 sensory pain based on the National Cancer Institute Common Terminology Criteria for AEs version 3.0 grading scale, for at least 3 months after completing chemotherapy • Average pain intensity ≥ 4 on 0-10 scale • Any cancer diagnosis Exclusion criteria • Severe depression, suicidal ideation, bipolar disease, alcohol abuse, a major eating disorder • Markedly abnormal renal or liver function tests Total participants randomised: 231 Age in years (mean, SD): 59 (10.5) Gender: 138/231 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 116 • Inert • Sham dosing to match duloxetine arm Duloxetine 60 mg • n = 115 • SNRI • Forced titration to fixed doses
Outcomes	Pain intensity Moderate pain relief Substantial pain relief Quality of life SAEs Withdrawal
Missing data methods	Completer analysis
Funding source	Non-pharmaceutical: This study was supported by grant CA31946 from the NCI Division of Cancer Prevention, the Alliance Statistics and Data Center, and the Alliance Chairman

Smith 2013 *(Continued)*

Conflicts of interest	"Disclosures: all authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Smith reported receiving support from CALGB/Alliance for travel to meetings. Dr Paskett reported institutional support from CALGB/Alliance for travel to meetings. Dr Ahles reported receiving support from CALBG/Alliance for travel to meetings. Dr Fadul reported pending institutional grants from Genentech. Dr Gilman reported institutional and direct grants pending from the NCI [National Cancer Institute]. No other financial disclosures were made."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation, provided by the CALGB/Alliance Statistical Center, was stratified by neurotoxic drug class (taxanes vs platinums) and by pain risk (high risk vs no risk). A computer-generated kit number was used to order the blinded study drug from a distribution center."
Allocation concealment (selection bias)	Low risk	"A computer-generated kit number was used to order the blinded study drug from a distribution center. Drug labels were applied to the capsule bottles at the distribution center before being mailed to study sites; thus, all patients and personnel were blinded to the treatment assignment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs with matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Mention ITT and imputation, but only report completer analysis **Attrition** Total: 33/230 (14.3%) Placebo: 12/111 (10.8%) Duloxetine 60 mg: 21/109 (19.3%)
Selective reporting (reporting bias)	Low risk	Outcomes match those on prospective trial registration on clinicaltrials.gov
Other bias	Low risk	No other sources of bias were identified.

Sofat 2017

Study characteristics

Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention

Sofat 2017 *(Continued)*

	Country: UK
Participants	Pain condition: hand OA Population: adults aged 40–75 with hand OA Minimum pain intensity: ≥ 5 on 0-10 scale Inclusion criteria • Aged 40-75 • Fulfilling the ACR criteria for the diagnosis of hand OA • Receiving usual care for hand OA including paracetamol (acetaminophen) and/or NSAIDs Exclusion criteria • History of depression and current uncontrolled depression/anxiety as scored by HADS excluded Total participants randomised: 65 Age in years (mean, SD): NR Gender: 52/65 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 22 • Inert • Identical appearance and matched dosing to intervention arms Pregabalin 300 mg • n = 22 • Anticonvulsant • Fixed dose, forced titration Duloxetine 60 mg • n = 21 • SNRI • Fixed dose, forced titration
Outcomes	Pain intensity Physical function Mood Withdrawal
Missing data methods	ITT with LOCF
Funding source	Non-pharmaceutical: "This work was supported by The Rosetrees' Trust, grant number M11-F1, by the UK National Institute of Health (NIHR) Clinical Research Network and an NIHR Clinical Academic Fellowship to MR"
Conflicts of interest	Disclosure: the authors report no conflicts of interest in this work.
Notes	

Sofat 2017 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Low risk	The random allocation sequence, with a block size of nine, was generated by the manufacturer and implemented through sequentially numbered containers.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 13/65 (20.0%) Placebo: 3/22 (13.6%) Pregabalin 300 mg: 5/22 (22.7%) Duloxetine 60 mg: 5/21 (23.8%)
Selective reporting (reporting bias)	High risk	2 protocols found registed, which have different primary outcomes. The protocol was submitted 2.5 years after recruitment started.
Other bias	Unclear risk	Small baseline difference in groups "prior analgesic use", there was slightly less paracetamol (acetaminophen) use at baseline before enrollment in the duloxetine group than in the pregabalin and placebo groups, but for other NSAIDs and opiates, analgesic use was similar in all 3 groups.

Spinhoven 2010

Study characteristics

Methods	Design: parallel Duration: 16 weeks Assessment: baseline, mid-intervention, post-intervention Country: Netherlands
Participants	Pain condition: non-cardiac chest pain Population: adult cardiology outpatients with a diagnosis of non-cardiac chest pain Minimum pain intensity: no Inclusion criteria

Spinhoven 2010 *(Continued)*

	• Aged between 18 and 75 • Non-cardiac chest pain as main presenting complaint; non-cardiac chest pain occurring at least once a week, or at least once per month if accompanied by severe psychological distress Exclusion criteria • Physical and mental health comorbidities (except panic disorder) Total participants randomised: 69 Age in years (mean): 55.9 Gender: 32/69 were female Pain duration in years (mean): 5.4
Interventions	Placebo • n = 23 • Inert • Matched dosing Paroxetine 10-40 mg • n = 23 • SSRI • Forced titration to maximum tolerated dose CBT • n = 23 • Psychological therapy • CBT was based on a tested treatment protocol and consisted of a minimum of 6 to a maximum of 12 sessions of 45–60 minutes. The number of sessions depended on the severity of symptoms and speed of recovery.
Outcomes	Pain intensity Mood Withdrawal
Missing data methods	ITT with LOCF
Funding source	Partly funded by pharmaceutical: supported by a grant of the Dutch Heart Foundation (grant nr. 1998B209) and an unconditional educational grant of Glaxo Smith Kline.
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using random permuted blocks with a length of 6.
Allocation concealment (selection bias)	Unclear risk	States allocation by pharmacists not involved in trial, but procedure not specified

Spinhoven 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding across arms not possible due to nature of CBT intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF and unequal attrition **Attrition** Total: 11/69 (15.9%) Placebo: 4/23 (17.4%) Paroxetine 10-40 mg: 7/23 (30.4%) CBT: 0/23 (0.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	High risk	Selection bias: 379 (80%) of patients approached refused participation due to potential of being put on paroxetine

Srinivasan 2021

Study characteristics	
Methods	Design: cross-over Duration: cross-over periods lasted 6 weeks Assessment: baseline and post-cross-over period Country: India
Participants	Pain condition: painful diabetic neuropathy Population: adults aged 18-75 with type 2 diabetes and painful diabetic neuropathy Minimum pain intensity: ≥ 50 on 0-100 scale Inclusion criteria • Diabetic neuropathic pain present for at least 1 month • Mean pain intensity of > 50% by patient assessment by VAS Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 67 Age in years (mean, SD): 49 (4) Gender: 32/67 were female

Srinivasan 2021 *(Continued)*

	Pain duration in years (mean, SD): 28 (6)
Interventions	Naltrexone 4-8 mg • Opioid receptor antagonist • Identical appearance to amitriptyline • Flexible dosing between 2 mg and 4 mg • Mean dose: 3.84 mg/day Amitriptyline 10-50 mg • TCA • Flexible dosing between 25 mg and 50 mg • Mean dose: 24.02 mg/day
Outcomes	PGIC AEs Withdrawal
Missing data methods	ITT with multiple imputation
Funding source	Non-pharmaceutical: postgraduate Institute of Medical Education and Research
Conflicts of interest	The authors have no COI pertaining to this study. The authors are thankful to M/s. Sun Pharmaceutical Industries Limited, Mumbai (India), and M/s. Wockhardt Pharmaceuticals, Mumbai (India), for providing the pure naltrexone active pharmaceutical ingredient and amitriptyline tablets, respectively, for this study.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation codes were generated by a random block randomisation method using the “random allocation software.”
Allocation concealment (selection bias)	Low risk	"The blinding and allocation concealment was maintained by labeling the container with the serial numbers provided for each randomisation code by a person not related to the trial. The drugs were dispensed by an investigator who was neither involved in screening nor involved in evaluating the end points of the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical appearance and dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Multiple imputation techniques (multivariate imputation by chained equations) was used to deal with the missing values for ITT. Low dropouts, balanced across arms **Attrition**

Srinivasan 2021 *(Continued)*

		Total: 7/67 (10.5%) Naltrexone 2-4 mg: 2/67 (3.0%) Amitriptyline 25-50 mg: 5/67 (7.5%)
Selective reporting (reporting bias)	Unclear risk	Trial registered retrospectively
Other bias	Low risk	No other sources of bias were identified.

Staud 2015

Study characteristics	
Methods	Design: parallel Duration: 6 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia Minimum pain intensity: ≥ 4 on 0-10 VAS Inclusion criteria • Fulfill the 1990 ACR criteria for fibromyalgia including widespread pain Exclusion criteria • Significant comorbidities: MDD, anxiety disorders and other chronic illnesses Total participants randomised: 61 Age in years (mean, SD): NR Gender: 56/61 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 30 • Inert • Identical appearance and matched dosing Milnacipran 100 mg • n = 31 • SNRI • Fixed dose
Outcomes	Pain intensity Mood

Staud 2015 *(Continued)*

	Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: This study was supported by an investigator-initiated grant from Forest Laboratories. All study drugs were provided by Forest Laboratories.
Conflicts of interest	Funded by an investigator-initiated grant from Forest Laboratories. All study drugs were provided by Forest Laboratories. The sponsors of this trial had no role in planning and implementing the study, and in the analysis of the data. They were not involved in the writing of this report. None of the authors have any financial or other relationships that might lead to a COI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using Research Randomizer (http://www.randomizer.org/)
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs with matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Similar attrition in both arms, report that they will use LOCF for missing data but then state that as "missing data did not result in different conclusions, we report only the results of uncorrected analyses", so completer analysis. **Attrition** Total: 26/62 (41.9%) Placebo: 5/23 (21.7%) Milnacipran 100 mg: 6/23 (26.1%) 15 participants (8 milnacipran, 7 placebo) withdrew post-randomisation prior to receiving study medication, so were not included in the arm-specific totals above. No reasons were given for the withdrawals of these 15 participants.
Selective reporting (reporting bias)	High risk	Protocol only lists mechanical and heat hyperalgesia and clinical pain as outcomes. Doesn't specify how these will be collected or the other measures used in the study.
Other bias	High risk	Create a second baseline essentially: a lot of participants withdrew after randomisation and so the authors ignore that in final analysis and only include those who came back for a second study visit.

Suttiruksa 2016

Study characteristics	
Methods	Design: parallel Duration: 13 weeks Assessment: baseline, 5 weeks, 9 weeks, post-intervention Country: Thailand
Participants	Pain condition: fibromyalgia Population: Thai adults with fibromyalgia Minimum pain intensity: ≥ 40 on 0-100 VAS Inclusion criteria • Patients of Thai ethnicity who were ≥ 18 years with a diagnosis of fibromyalgia as defined by the ACR criteria • Moderate pain: ≥ 40 on 0-100 VAS Exclusion criteria • Substance abuse and comorbid inflammatory rheumatic diseases Total participants randomised: 40 Age in years (mean): 44.7 Gender: 40/40 were female Pain duration in years (mean): 3.5
Interventions	Placebo • n = 13 • Inert • Identical appearance and matched dosing Mirtazapine 15 mg • n = 13 • NaSSA • Fixed dose, forced titration Mirtazapine 30 mg • n = 14 • NaSSA • Fixed dose, forced titration
Outcomes	Pain intensity Mood Physical function SAEs Withdrawal

Suttiruksa 2016 *(Continued)*

Missing data methods	ITT but no methods specified
Funding source	Non-pharmaceutical: This work was supported by the Office of theHigher Education Commission, Thailand through a grant in the program "Strategic Scholarships for Frontier Research Network for the PhD Program, Thai Doctoral degree".
Conflicts of interest	The authors declare that there is no COI in this research.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The patients were allocated using a block size of 3 in a ratio of 1:1:1 with parallel assignment to 1 of 3 groups, using a pharmacy-controlled randomisation process with a random number table.
Allocation concealment (selection bias)	Low risk	Sequentially numbered identical containers that were administered serially
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT but no methods specified **Attrition** Total: 8/40 (20.0%) Placebo: 3/13 (23.1%) Mirtazapine 15 mg: 2/13 (15.4%) Mirtazapine 30 mg: 3/14 (21.4%)
Selective reporting (reporting bias)	Unclear risk	Trial protocol registered online is for multiple studies (https://clinicaltrials.gov/ct2/show/NCT00919295)
Other bias	Low risk	No other sources of bias were identified

Talley 2008

Study characteristics

Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention

Talley 2008 *(Continued)*

	Country: Australia
Participants	Pain condition: IBS Population: people with IBS Minimum pain intensity: ≥ 3 on 0-10 scale Inclusion criteria • Diagnosis of IBS following specialist consultation • Pain intensity of ≥ 3 on 0-10 scale Exclusion criteria • Major uncontrolled physical or mental health conditions Total participants randomised: 51 Age in years (mean, SD): NR Gender: NR Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 16 • Inert • Identical appearance • Double-dummy design Imipramine 50 mg • n = 18 • TCA • Fixed dose, forced titration Citalopram 40 mg • n = 17 • SSRI • Fixed dose, forced titration
Outcomes	Pain intensity Mood Physical function SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Non-pharmaceutical: this work was supported by the National Health and Medical Research Council of Australia (Dr Talley, PI).
Conflicts of interest	NR
Notes	

Talley 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised to one of the 3 treatment arms using a computer-generated random list.
Allocation concealment (selection bias)	Low risk	Concealed allocation was assured by a central drug distribution from the hospital pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF. Very unequal attrition between arms, high attrition for imipramine **Attrition** Total: 17/51 (33.3%) Placebo: 3/16 (18.8%) Imipramine 50 mg: 9/18 (50.0%) Citalopram 40 mg: 5/17 (29.4%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Tammiala-Salonen 1999

Study characteristics

Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Country: Finland
Participants	Pain condition: burning mouth syndrome Population: women with burning mouth syndrome Minimum pain intensity: ≥ 30 on 0-100 VAS Inclusion criteria • Daily, or almost daily, oral burning pain that had lasted ≥ 6 months • Moderate pain intensity: ≥ 30 on 0-100 VAS

Tammiala-Salonen 1999 *(Continued)*

	Exclusion criteria: NR Total participants randomised: 37 Age in years (mean, range): 58.6 (39-71) Gender: 37/37 were female Pain duration in years (mean, range): 2.8, (6 months-20 years)
Interventions	Placebo • n = 19 • Inert • Identical appearance to trazodone and matched dosing Trazodone 200 mg • n = 18 • SARI • Fixed dose, forced titration
Outcomes	Withdrawal
Missing data methods	Completer analysis
Funding source	Non-pharmaceutical: the study was supported by the Finnish Dental Society.
Conflicts of interest	NR
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only. Unequal attrition - more participants withdrew due to AEs in the intervention arm than the placebo arm **Attrition** Total: 9/37 (24.3%) Placebo: 2/19 (10.5%)

Tammiala-Salonen 1999 *(Continued)*

		Trazodone 200 mg: 7/18 (38.9%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Tanum 1996

Study characteristics	
Methods	Design: parallel Duration: 7 weeks Assessment: baseline, 3 weeks, post-intervention, follow-up (4 weeks after taper) Country: Norway
Participants	Pain condition: functional gastrointestinal disorder Population: adults aged 18-70 functional gastrointestinal disorder Minimum pain intensity: no Inclusion criteria: • Aged between 18 and 70 years of age and have a diagnosis of functional gastrointestinal disorder established by a gastroenterologist • Continuous or chronic intermittent gastrointestinal pain and distress, located in the upper and/or lower gastrointestinal tract, had to be present during at least the past 12 months. The symptoms had to be present more days in a week than not, and if there were symptom-free intervals, they could not exceed 5 days in a row. Exclusion criteria • Severe physical comorbidity; depression, mood and affective disorders Total participants randomised: 49 Age in years (mean): 37.3 Gender: 32/49 were female Pain duration in years (mean, SD): 8.3 (9.2)
Interventions	Placebo • n = 22 • Inert • Identical appearance and matched dosing Mianserin • n = 25 • TeCA • Fixed dose, forced titration
Outcomes	Pain intensity

Tanum 1996 *(Continued)*

	Substantial pain relief Withdrawal
Missing data methods	ITT with LOCF
Funding source	Non-pharmaceutical: the study was on request supported by an educational grant from NV Organon, Oss, The Netherlands
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT with LOCF, but low attrition **Attrition** Total: 2/49 (4.1%) Placebo: 0/22 (0.0%) Mianserin 120 mg: 2/27 (7.4%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias identified

Tasmuth 2002

Study characteristics

Methods	Design: cross-over Duration: cross-over periods were 4 weeks Assessment: baseline and post-cross-over period

Tasmuth 2002 *(Continued)*

	Country: Finland
Participants	Pain condition: neuropathic pain following breast cancer treatment Population: women with neuropathic pain following treatment of breast cancer Minimum pain intensity: moderate severity (no numerical scale) Inclusion criteria • Neuropathic pain after treatment for breast cancer. The pain had to be in the anterior chest wall and/or axilla and/or median upper arm in an area with sensory disturbances. • The pain had to be at least moderate in severity. Exclusion criteria • Free of relapses or metastases of the breast cancer and free from clinically overt cardiac, renal or hepatic disease Total participants randomised: 15 Age in years (mean, range): 55 (37-72) Gender: 15/15 were female Pain duration in months (mean, range): 20 (18-26)
Interventions	Placebo • Inert • Matched dosing Venlafaxine ≤ 75 mg • SNRI • Flexible titration to highest possible dose: dose was increased by 18.75 mg every week to the highest tolerable dose or ceiling (75 mg)
Outcomes	The study provided no useable data
Missing data methods	NR
Funding source	Non-pharmacetucal: financial support was received from the Helsinki University Central Hospital Research Funds.
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Hospital pharmacy performed the randomisation using computer-generated numbers
Allocation concealment (selection bias)	Unclear risk	States that hospital pharmacy performed randomisation but not how this was allocated

Tasmuth 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind, matched dosing, but no information regarding appearance of study drugs
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes by blinded participants, but unsure of blinding methods
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Low attrition, but not explained fully (i.e. during which period dropout happened) **Attrition** Total: 2/15 (13.3%) Attrition per arm NR
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Tesfaye 2013

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline to post-intervention Country: Australia, Canada, Croatia, France, Germany, Greece, Italy, South Korea, Mexico, Netherlands, Poland, Spain, Sweden, Switzerland, Turkey, UK
Participants	Pain condition: diabetic neuropathy Population: adults with diabetes type 1 or 2 and diabetic neuropathy Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Pain due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes mellitus, beginning in the feet in a relatively symmetrical fashion • Daily pain should have been present for at least 3 months and the diagnosis had to be confirmed by a score of ≥ 3 on the MNSI at screening • 24-hour average pain severity of ≥ 4 on BPI Exclusion criteria • Any suicidal risk as judged by the investigator or as defined by a score of ≤ 2 on item 9 of the BDI II Total participants randomised: 811 Age in years (mean): 61.7 Gender: 356/804 were female

Tesfaye 2013 *(Continued)*

	Pain duration in years (mean, SD): NR
Interventions	Duloxetine 60 mg • n = 401 • SNRI • Fixed dose, forced titration Pregabalin 300 mg • n = 403 • Anticonvulsant • Fixed dose, forced titration • Identical capsules to duloxetine
Outcomes	Pain intensity Physical function Mood Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: The sponsor, Eli Lilly & Company (Indianapolis, IN, USA), was involved in study design, in the collection, analysis, and interpretation of data, in the writing of the manuscript, and in the decision to submit the paper for publication.
Conflicts of interest	The sponsor, Eli Lilly & Company (Indianapolis, IN, USA), was involved in study design, in the collection, analysis, and interpretation of data, in the writing of the manuscript, and in the decision to submit the paper for publication. Stefan Wilhelm, Alexander Schacht, and Vladimir Skljarevski own stock in and are Lilly employees. Alberto Lledo, former Lilly employee, owns Lilly stocks. Solomon Tesfaye, Thomas T√∂lle, Didier Bouhassira, Giorgio Cruccu, and Rainer Freynhagen have received economic compensation for participation in the Lilly EU Pain Advisory Board. Solomon Tesfaye declares having received honoraria for invited lectures from Eli Lilly & Company and Pfizer Inc. Thomas Tolle reports consultancy and invited lectures for Grunenthal, Mundipharma, Biogen Idec, Hexal, Pfizer Inc., Janssen-Cilag, Astellas, Pharmaleads, Boehringer-Ingelheim, Eli Lilly & Company, and Esteve. Didier Bouhassira has served on the Speakers,Äô Bureau for Eli Lilly & Company, Pfizer Inc., and Astellas, and has worked as a consultant to Eli Lilly & Company, Pfizer Inc., Sanofi-Aventis, SanofiPasteur-MSD, Astra Zeneca, and Astellas and has received research support from Pfizer Inc. Giorgio Cruccu has received fees for advisory boards and for lectures by Astellas, Eli Lilly & Company, and Pfizer Inc. Rainer Freynhagen has received consultancy and speaker fees in the past 12 months from Astellas, Epionics, Grunenthal, Forrest Research, HRA, Eli Lilly & Company, and Pfizer. All authors have made substantial contribution to conception and design of the COMBO-DN study, or analysis or interpretation of the data or revising the manuscript critically for important intellectual content. Alberto Lledo was responsible for generating the primary hypothesis of the study and reviewed

Tesfaye 2013 *(Continued)*

	the manuscript critically. Solomon Tesfaye, Thomas Tolle, Didier Bouhassira, Giorgio Gruccu, and Rainer Freynhagen were involved in the early conception of the study, the selection of the primary and secondary objectives and the final review of the manuscript. Alexander Schacht was responsible for building the final statistical plan. Stefan Wilhelm and Alexander Schacht were responsible for data collection and extraction and completion of the final study report. Solomon Tesfaye and Stefan Wilhelm wrote the primary version of the manuscript and Vladimir Skljarevski reviewed the manuscript critically with regard to interpretation of the data.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"At the start of the initial therapy period, patients were randomised in a 1:1:1:1 ratio to 4 parallel groups stratified by site, based on a computer-generated sequence"
Allocation concealment (selection bias)	Low risk	Participants were allocated using a centralised interactive voice response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 138/811 (17.1%) Pregabalin 300 mg: 70/403 (17.4%) Duloxetine 60 mg: 68/401 (17.0%)
Selective reporting (reporting bias)	Low risk	Outcomes match trial registration
Other bias	Low risk	No other sources of bias identified

Trugman 2014

Study characteristics

Methods	Design: parallel Duration: 7 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: fibromyalgia

Trugman 2014 *(Continued)*

	Population: adults with fibromyalgia Minimum pain intensity: no Inclusion criteria • Aged 18-70 years of age, who met the 1990 ACR criteria for fibromyalgia Exclusion criteria • Excluded major conditions, those with history of hypertension were included. Excluded active or unstable mental illness Total participants randomised: 321 Age in years (mean): 49.2 Gender: 264/321 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 110 • Inert • "matched" Milnacipran • n = 210 • SNRI • Fixed dose, forced titration
Outcomes	AEs SAEs Withdrawal
Missing data methods	Unclear
Funding source	Pharmaceutical: The study was sponsored by Forest Laboratories Inc. in collaboration with Cypress Bioscience Inc. (acquired by Royalty Pharma).
Conflicts of interest	J.M.T., R.H.P. and Y.M. are all full-time employees with Forest Research Institute Inc., a wholly owned subsidiary of Forest Laboratories Inc. CMRO peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods NR
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR

Trugman 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear blinding of study drugs, says "matched" but no other information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, uncertain of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear missing data methods **Attrition** Total: 75/321 (23.4%) Placebo: 25/111 (22.5%) Milnacipran 200 mg: 50/210 (23.8%)
Selective reporting (reporting bias)	Low risk	Primary outcomes match those registered prospectively on clinicaltrials.gov
Other bias	High risk	Outcomes extracted from published paper, but these are very different to what's registered in the trial registry results

Tétreault 2016

Study characteristics	
Methods	Design: parallel Duration: 16 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: knee OA Population: adults aged 45-80 with knee OA Minimum pain intensity: ≥ 5 on 0-10 scale Inclusion criteria • Diagnosed by a clinician for knee OA, fulfilled ACR criteria, and had knee pain for at least 1 year • Knee pain intensity of at least 4/10 Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 40 Age in years (mean, SD): 58.7 (7.6) Gender: 21/40 were female Pain duration in years (mean, SD): 10.54 (9.1)

Tétreault 2016 *(Continued)*

Interventions	Placebo • n = 21 • Inert • Identical appearance to duloxetine, matched dosing Duloxetine 60 mg • n = 19 • SNRI • Fixed dose, forced titration
Outcomes	Pain intensity Physical function Mood AEs SAEs
Missing data methods	Completer-only analysis
Funding source	Partly pharmaceutical: Eli Lilly Pharmaceuticals (IIT number: F1J-US-XO61). This research was also partially supported by grants from National Institute of Neurological Disorders and Stroke, ninds.nih.gov (NS035115), and National Center for Complementary and Integrative Health, nccih.nih.gov (AT007987) of the US National Institutes of Health. PT was supported by postdoctoral fellowships from the Canadian Institutes of Health Research (CIHR), cihr-irsc.gc.ca.
Conflicts of interest	No financial or other relationships that might lead to a COI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only **Attrition** Total: 21/60 (35.0%)

Tétreault 2016 *(Continued)*

		Attrition per arm NR
Selective reporting (reporting bias)	Low risk	Outcomes match those in the protocol
Other bias	Low risk	No other sources of bias identified

Uchio 2018

Study characteristics	
Methods	Design: parallel Duration: 14 weeks Assessment: baseline and post-intervention Country: Japan
Participants	Pain condition: knee OA Population: adults aged 40-80 with chronic knee pain due to OA Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Outpatients aged 40 to < 80 years were eligible if they had experienced pain for ≥ 14 days/month during the 3-month period before Visit 1 • BPI-Severity average pain score of ≥ 4 • Patients needed to satisfy the ACR criteria for idiopathic knee OA Exclusion criteria • Physical and mental health comorbidities Total participants randomised: 354 Age in years (mean): 65.9 Gender: 274/354 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 176 • Inert • Identical appearance to duloxetine Duloxetine 60 mg • n = 177 • SNRI • Fixed dose, forced titration
Outcomes	Pain intensity Sleep

Uchio 2018 *(Continued)*

	Quality of life Mood Physical function Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	ITT with LOCF and BOCF
Funding source	Pharmaceutical: Eli Lilly and Company and Shionogi
Conflicts of interest	TT is an employee of and owns stock in Shionogi Co. Ltd. HE, SF, NS, and HT are employees of Eli Lilly Japan K.K. SF and HE own stock in Eli Lilly and Company. YU has been a member of a Board of Directors and Speakers' Bureau and had a consulting role with Eli Lilly Japan K.K.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised participants an Interactive Web Response System and stochastic minimisation method
Allocation concealment (selection bias)	Low risk	Participants were allocated using an Interactive Web Response System
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical capsules for study drugs, matched doses
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition. Missing data were imputed using the LOCF, BOCF, or the modified BOCF. These findings were consistent for all missing data imputation methods. **Attrition** Total: 31/354 (8.8%) Placebo: 14/176 (8.0%) Duloxetine 60 mg: 17/178 (10.0%)
Selective reporting (reporting bias)	Low risk	Some results for outcomes (BDI, Patient Global Assessment of Illness) reported on clinicaltrials.gov but not in the paper

Uchio 2018 *(Continued)*

Other bias	Low risk	No other sources of bias were identified.

Urquhart 2018

Study characteristics	
Methods	Design: parallel Duration: 24 weeks Assessment: baseline, 3 months, post-intervention Country: Australia
Participants	Pain condition: low back pain Population: people aged 18-75 with chronic non-specific low back pain Minimum pain intensity: no Inclusion criteria • Aged 18–75 years with chronic, nonspecific low back pain lasted > 3 months Exclusion criteria • Current physical or mental health comorbidities • Previously diagnosed depression Total participants randomised: 146 Age in years (mean, SD): 54.8 (13.7) Gender: 53/146 were female Pain duration in years (mean): 14.3
Interventions	Placebo (benzotropine mesylate 1 mg) • n = 74 • Active placebo • Identical appearance, matched dosing Amitriptyline 25 mg • n = 72 • TCA • Fixed dose, no titration
Outcomes	Pain intensity Physical function Mood Quality of life AEs Withdrawal

Urquhart 2018 *(Continued)*

Missing data methods	ITT using multiple imputation with chained equations
Funding source	Non-pharmaceutical: "This work was supported by theNational Health and Medical Research Council(NHMRC, Australia, ID 1024401). Drs Urquhart, Wluka, and Wang are recipients of NHMRC Career Development Fellowships (Clinical Level 1 No.1011975; Clinical Level 2 No. 1063574; Clinical Level1 No. 1065464, respectively)"
Conflicts of interest	None reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was based on computer-generated random numbers prepared by a statistician who had no involvement in trial conduct."
Allocation concealment (selection bias)	Low risk	"The use of a central allocation that involved pharmacy-controlled randomisation ensured that the allocation could not be accessed by research personnel."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, active placebo, identical appearance, matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Uses multiple imputation by chained equations, presents comparisons with no multiple imputation **Attrition** Total: 28/146 (19.2%) Placebo: 15/74 (20.3%) Amitriptyline 25 mg: 13/72 (18.1%)
Selective reporting (reporting bias)	Low risk	Matches protocol. Explains why Descriptor Differential Scale is NR (participants had difficulty filling it in)
Other bias	Low risk	No other sources of bias

Vahedi 2005

Study characteristics

Methods	Design: parallel Duration: 12 weeks Assessment: baseline, post-intervention, follow-up (4 weeks post-intervention) Country: Iran

Vahedi 2005 *(Continued)*

Participants	Pain condition: IBS Population: people with pain and constipation-predominant IBS Minimum pain intensity: no Inclusion criteria • People with pain and constipation-predominant IBS as defined by the Rome II criteria were included Exclusion criteria • Physical and severe mental health comorbidities Total participants randomised: 44 Age in years (mean, SD): 34.9 (10.0) Gender: 27/44 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 22 • Inert • Identical appearance to fluoxetine, matched dosing Fluoxetine 20 mg • n = 22 • SSRI • Fixed dose
Outcomes	Withdrawal
Missing data methods	No participants withdrew
Funding source	Non-pharmaceutical: This study was supported by a grant from the Digestive Disease Research Center of Tehran University of Medical Sciences.
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned according to a computer-generated randomisation table
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, matched dosing

Vahedi 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants withdrew
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Van Ophoven 2004

Study characteristics	
Methods	Design: parallel Duration: 16 weeks Assessment: baseline and post-intervention Country: Germany
Participants	Pain condition: interstitial cystitis Population: adults with interstitial cystitis Minimum pain intensity: Inclusion criteria • People meeting the symptom criteria of the National Institute of Diabetes, Digestive and Kidney Diseases for interstitial cystitis Exclusion criteria • Previous or current intake of amitriptyline Total participants randomised: 50 Age in years (mean, SD): NR Gender: 44/50 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 25 • Inert • Identical appearance and matched dosing Amitriptyline ≤ 100 mg • n = 25 • TCA • Flexible dose and self-titration until satisfactory relief of symptoms, doses of 25 mg, 50 mg, 75 mg, or 100 mg

Van Ophoven 2004 *(Continued)*

	• Mean dose = 52 mg/day
Outcomes	Pain intensity AEs SAEs Withdrawal
Missing data methods	NR
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods NR
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Identical study medication, amitriptyline arm could self-titrate, no information given about whether this was matched for placebo arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, uncertain of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completer-only analysis, but ≤ 5% dropout **Attrition** Total: 2/50 (4.0%) Placebo: 1/25 (4.0%) Amitriptyline ≤ 100 mg: 1/25 (4.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified.

Ventafridda 1987

Study characteristics

Methods	Design: parallel

Ventafridda 1987 *(Continued)*

	Duration: 15 days Assessment: baseline and post-intervention Country: Italy
Participants	Pain condition: chronic pain syndromes from deafferentation and with oncological pain with deafferentation component Population: adults aged 34-79 with cancer pain and other painful syndromes with deafferentation component Minimum pain intensity: no Inclusion criteria • Chronic pain from: phantom limb, cancer, post-herpetic neuralgia, traumatic nerve lesion, post-radiation nerve lesion • Pain lasting at least 6 months Exclusion criteria • Glaucoma, myasthenia, hypertrophic prostate, serious cardiopathia and stomach ulcer Total participants randomised: 45 Age in years (range) 34-79 Gender: NR Pain duration in years (mean, SD): NR
Interventions	Amitriptyline 75 mg • n = 22 • TCA • Fixed dose, forced titration over 3 days Trazodone 225 mg • n = 23 • SARI • Fixed dose, forced titration over 3 days • Identical appearance to amitriptyline
Outcomes	Withdrawal
Missing data methods	Completer-only analysis
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods NR

Ventafridda 1987 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical appearance of study drugs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis with ~30% dropout **Attrition** Total: 14/45 (31.1%) Amitriptyline 75 mg: 4/22 (18.2%) Trazodone 225 mg: 10/23 (43.5%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Unclear risk	Unclear - data other than withdrawal not presented in any useable way, no tables only figures

Vitton 2004

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: adults aged 18-70 with fibromyalgia Minimum pain intensity: ≥ 10 on a 20-point logarithmic pain scale (Gracely scale) Inclusion criteria • Aged between 18 and 70 years, met the ACR 1990 research criteria for fibromyalgia • Pain intensity of ≥ 10 on a 20-point logarithmic pain scale (Gracely scale) Exclusion criteria • Severe psychiatric illness (apart from depression) and a history of severe physical health problems Total participants randomised: 125 Age in years (mean, SD): 47.0 (11.1) Gender: 122/125 were female

Vitton 2004 *(Continued)*

	Pain duration in years (mean, SD): 4.1 (4.2) years
Interventions	Placebo • n = 28 • Inert • Identical appearance, matched dosing • Double-dummy design Milnacipran ≤ 200 mg (one dose) • n = 46 • SNRI • Flexible titration to maximum tolerated dose • Taken in 1 dose Milnacipran ≤ 200 mg (2 doses) • n = 51 • SNRI • Flexible titration to maximum tolerated dose • Taken in 2 doses (1 dose each, morning and evening)
Outcomes	Pain intensity Sleep Moderate pain relief Substantial pain relief PGIC SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: supported by Cypress Biosciences, San Diego, California
Conflicts of interest	Drs M.Gendreau, J. Gendreau, and J. Kranzler are employees of Cypress Biosciences. Drs Clauw, Gracely, and Williams are paid consultants for and shareholders in Cypress Biosciences. Drs Mease and Thorn are consultants for Cypress Biosciences.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a randomisation table.
Allocation concealment (selection bias)	Low risk	Participants were allocated using an automated telephone response system.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, identical study drugs, matched dosing, double-dummy design

Vitton 2004 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 35/125 (28.0%) Placebo: 7/28 (25.0%) Milnacipran 200 mg: 14/46 (30.4%) Milnacipran 400 mg: 14/51 (27.5%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Unclear risk	Imbalance in prevalence of depression at baseline but no further information on whether controlled for or which group had more/less

Vollmer 2014

Study characteristics	
Methods	Design: parallel Duration: 6 weeks Assessment: baseline and post-intervention Country: Belgium, Canada, Poland and the USA
Participants	Pain condition: central neuropathic pain due to multiple sclerosis Population: adults with multiple sclerosis experiencing chronic neuropathic pain Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Central neuropathic pain due to multiple sclerosis • ≥ 4 on the daily 24-hour average pain score • Diagnosis of multiple sclerosis at least 1 year prior to study • Daily pain for ≥ 3 months Exclusion criteria • Majority of psychiatric disorders (except depression and anxiety) and other pain conditions Total participants randomised: 239 Age in years (mean): 51.8 Gender: 179/239 were female Pain duration in years (mean): 6.9

Vollmer 2014 *(Continued)*

Interventions	Placebo • n = 121 • Inert • Matched dose Duloxetine 60 mg • n = 118 • SNRI • Fixed dose, titrated over 7 days
Outcomes	Pain intensity Quality of life Mood Sleep Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	ITT with LOCF and BOCF as sensitivity analysis
Funding source	Pharmaceutical: Eli Lilly and Company
Conflicts of interest	Dr Robinson was a full-time employee and shareholder of Eli Lilly and Company at the time this study was conducted. Dr Robinson is a current employee of AbbVie. Author TLV is a consultant and/or advisory board member with Lilly and has received grants from and is involved in research supported by Lilly. Authors RCR and SKM are current employees and/or stockholders of Lilly.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods NR
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, matched doses, but no information regarding study drugs appearance etc
Blinding of outcome assessment (detection bias)	Unclear risk	Self-reported outcomes from participants, unclear regarding blinding procedures

Vollmer 2014 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT with LOCF, BOCF for sensitivity analysis of primary outcome - no significant differences. Low attriton **Attrition** Total: 30/239 (12.6%) Placebo: 12/121 (9.9%) Duloxetine 60 mg: 18/118 (15.3%)
Selective reporting (reporting bias)	Low risk	All outcomes pre-specified on clinicaltrials.gov prospectively.
Other bias	Low risk	No other sources of bias identified

Vranken 2011

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Country: Netherlands
Participants	Pain condition: neuropathic pain caused by spinal cord injury or stroke Population: people with severe neuropathic pain caused by spinal cord injury or stroke Minimum pain intensity: ≥ 6 on 0-10 scale Inclusion criteria • Severe neuropathic pain caused by lesion or dysfunction in the central nervous system • Pain persisting for ≥ 6 months • Pain intensity of ≥ 6 on 0-10 scale Exclusion criteria • Known history of significant hepatic, renal, or psychiatric disorder; using antidepressants for treatment of depression Total participants randomised: 48 Age in years (mean, SD): NR Gender: NR Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 24 • Inert • Identical appearance to duloxetine

Vranken 2011 *(Continued)*

	• Sham dosing matching duloxetine arm procedure Duloxetine 60-120 mg • n = 24 • SNRI • Flexible dosing of 1-2 capsules of 60 mg a day. Patients started with 1 capsule per day and were titrated at a 1-week interval; if relief was insufficient (> 1.8 on a VAS) then participants were given 2 capsules to take.
Outcomes	Pain intensity Quality of life Physical function Mood PGIC Withdrawal
Missing data methods	State ITT but no methods
Funding source	Non-pharmaceutical: "Academic Medical Center": assuming the author's institution: Medical Center Alkmaar
Conflicts of interest	There are no conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using computerised random sampling (clorandm.exe)
Allocation concealment (selection bias)	Low risk	At baseline each coded medication bottle was supplied by the hospital pharmacist to the blinded treating physician.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, sham dosing of placebo to match intervention arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition. State ITT but do not report methods **Attrition** Total: 4/48 (8.3%) Placebo: 1/24 (4.2%) Duloxetine 60-120 mg: 3/24 (12.5%)

Vranken 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	Matches what's registered in protocol: https://www.trialregister.nl/trial/1125
Other bias	Low risk	No other sources of bias were identified.

Vrethem 1997

Study characteristics	
Methods	Design: cross-over Duration: each cross-over period lasted 4 weeks Assessment: baseline, mid-intervention (8-14 days), post-cross-over period Country: Sweden
Participants	Pain condition: polyneuropathy (diabetic and non-diabetic) Population: adults with painful polyneuropathy. 19 had diabetic polyneuropathy, 18 had non-diabetic polyneuropathy Minimum pain intensity: no Inclusion criteria • Daily moderate or severe polyneuropathic pain for at least 6 months Exclusion criteria • Patients with other neurologic diseases were excluded. Total participants randomised: 37 Age in years (range): 35-83 Gender: 19/37 were female Pain duration in years (range): 6-168
Interventions	Placebo • Inert • Identical appearance • Double-dummy design Amitriptyline 75 mg • TCA • Fixed dose, forced titration Maprotiline 75 mg • TeCA • Fixed dose, forced titration
Outcomes	Pain intensity
Missing data methods	NR

Vrethem 1997 *(Continued)*

Funding source	Non-pharmaceutical: This work was supported by grants from The Medical Research Council, project no. 9058, The Swedish Association of Neurologically Disabled, The County Council of Ostergotland, and The University Hospital of Linkoping
Conflicts of interest	NR
Notes	This study reported results separately for participants with and without neuropathic pain caused by diabetes. Therefore, in the NMA we separated the study into 2 to include the 2 sets of results for both populations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods NR
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No clear information regarding withdrawal, no information regarding missing data methods **Attrition** Total: 4/37 (10.8%) Attrition per arm NR
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Wang 2017

Study characteristics

Methods	Design: parallel Duration: 13 weeks Assessment: baseline and post-intervention Country: China
Participants	Pain condition: knee or hip OA

Wang 2017 *(Continued)*

	Population: adults aged ≥ 40 with knee or hip OA Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Outpatients of at least 40 years who meet clinical and radiographic criteria for the diagnosis of OA of the knee or hip Exclusion criteria • Physical health comorbidities • All psychiatric conditions including current MDD excluded Total participants randomised: 407 Age in years (mean): 60.5 Gender: 311/407 were female Pain duration in years (mean): 7.99
Interventions	Placebo • n = 202 • Inert • Identical and matched dosing Duloxetine 60 mg • n = 205 • SNRI • Fixed dose, forced titration
Outcomes	Pain intensity Physical function Mood Sleep Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	MRMM, ITT with LOCF
Funding source	Pharmaceutical: Eli Lilly and Company
Conflicts of interest	Drs Guochun Wang, LiQi Bi, Xiangpei Li, Zhijun Li, Dongbao Zhao, Jinwei Chen, and Dongyi He had no conflicts of interest to report. Drs Hector Due nas, Li Yue, Chia-Ning Wang, and Vladimir Skljarevski, are employees and minor shareholders of Eli Lilly and Company.

Wang 2017 *(Continued)*

Notes

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS)."
Allocation concealment (selection bias)	Low risk	"The IWRS was used to assign investigational product packages to each patient throughout this study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs, matched dosing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low levels of attrition. Used ITT with both MMRM and LOCF **Attrition** Total: 65/407 (16.0%) Placebo: 26/202 (12.9%) Duloxetine 60 mg: 39/205 (19.0%)
Selective reporting (reporting bias)	Low risk	All outcomes match those registered prospectively on clinicaltrials.gov.
Other bias	Low risk	No other sources of bias were identified.

Ward 1986

Study characteristics	
Methods	Design: parallel Duration: 4 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: low back pain Population: adults with chronic low back pain and diagnosed with depressive mood (major affective disorder, unipolar depression, dysthymic disorder) Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Hamilton Depression Rating Scale scores of ≥ 18 and were diagnosed as having major affective disorder, unipolar depression or dysthymic disorder

Ward 1986 *(Continued)*

	• Stable, chronic low back pain lasting ≥ 6 months, for ≥ 40% of waking hours, with an average severity of ≥ 4 on a scale of 0 (no pain) to 10 (worst pain imaginable) Exclusion criteria • Candidate for back surgery Total participants randomised: NR Age in years (mean): 40.2 Gender: 17/35 were female Pain duration in years (mean, SD): NR
Interventions	Doxepin • TCA • Flexible dosing: started at 50 mg/day • Mean dose: 188 mg/day Desipramine • TCA • Flexible dosing: started at 50 mg/day • Mean dose: 173 mg/day
Outcomes	Study reports no useable data
Missing data methods	Completer analysis
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods NR
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given regarding blinding procedures
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes by participants but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only. Do not report number of participants randomised, reasons for dropouts, from which arms, etc.

Ward 1986 *(Continued)*

Selective reporting (reporting bias)	High risk	No protocol or trial registration found. Didn't plan to combine data from both arms until they found no significant differences between arms.
Other bias	Unclear risk	Combined data from both arms in the paper

Ware 2010

Study characteristics	
Methods	Design: cross-over Duration: each cross-over period lasted 2 weeks Assessment: baseline and post-cross-over period Country: Canada
Participants	Pain condition: fibromyalgia Population: adults with fibromyalgia and self-reported chronic insomnia Minimum pain intensity: no Inclusion criteria • People with a diagnosis of fibromyalgia who had self-reported chronic insomnia Exclusion criteria • Severe physical comorbidities and psychotic disorders Total participants randomised: 32 Age in years (mean, SD): 49.5 (11.2) Gender: 26/32 were female Pain duration in years (mean, SD): NR
Interventions	Nabilone 0.5-1.0 mg • Synthetic cannabinoid • Flexible titration: started at 0.5 mg/day for the first week, physician assessed and if patient could benefit from higher dose the dose was doubled for the second week to 1 mg/day. Amitriptyline 10-20 mg • TCA • Flexible titration: started at 10 mg/day for the first week, physician assessed and if patient could benefit from higher dose the dose was doubled for the second week to 20 mg/day.
Outcomes	SAEs
Missing data methods	Unclear
Funding source	Pharmaceutical: supported by an unrestricted grant from Valeant (Canada) Inc.
Conflicts of interest	MAW and MAF have received honoraria from Valeant Canada for CME activities. YS and LJ have no conflicts to declare.

Ware 2010 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation schedule was prepared (ralloc procedure, Stata version 8.0, Houston, TX) using randomly assigned block sizes ranging from 2 to 8."
Allocation concealment (selection bias)	Low risk	"The schedule was kept by the study pharmacist away from the investigators. Study subjects were consecutively assigned to treatment order by the study nurse based on the randomisation schedule. A coded script was given to the subject with instructions on the use of the allocated treatment. The subject then collected the medication from the study pharmacy and began taking the medication the same night."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical opaque capsules for both nabilone and amitriptyline
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear - no missing data methods reported **Attrition** Total: 3/32 (9.4%) Attrition per arm NR
Selective reporting (reporting bias)	Low risk	All outcomes are prespecified in protocol on clinicaltrials.gov
Other bias	Low risk	No other sources of bias identified

Watson 1992

Study characteristics

Methods	Design: cross-over Duration: each cross-over period lasted 5 weeks Assessment: baseline and post-cross-over period Country: Canada
Participants	Pain condition: post-herpetic neuralgia Population: adults with post-herpetic neuralgia Minimum pain intensity: pain of at least moderate severity (disagreeable, unpleasant, uncomfortable) for at least one half of the day; no numerical values Inclusion criteria

Watson 1992 *(Continued)*

	• Pos-therpetic neuralgia of > 3 months' duration • Pain of at least moderate severity (disagreeable, unpleasant, uncomfortable) for at least one half of the day Exclusion criteria • cardiac disease, seizure disorder, severe depression with voiced suicidal intent requiring urgent management, presence of another significant pain problem, previous brain damage due to head injury, stroke or other causes, alcoholism Total participants randomised: 35 Age in years (median, range): 71 (55-85) Gender: 17/35were female Pain duration in months (median, range): 14 months (4 months-7 years)
Interventions	Amitriptyline • TCA • Flexible titration schedule: start with 12.5 mg/day if > 65 years old or 25 mg/day if < 65 • Median dose at week 5: 100 mg/day (range: 37.5-150 mg) • Double-dummy design due to different colour/shape of amitriptyline and maprotiline Maprotiline • TCA • Flexible titration schedule: start with 12.5 mg/day if > 65 years old or 25 mg/day if < 65 • Median dose at week 5 was 100 mg/day (range: 50-150 mg) • Double-dummy design due to different colour/shape of amitriptyline and maprotiline
Outcomes	Withdrawal
Missing data methods	Unclear
Funding source	Non-pharmaceutical: The study was funded by Physicians' Services Incorporated (PSI) Grant PSI: 88-17.
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods NR
Allocation concealment (selection bias)	Unclear risk	Allocation procedures NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy design
Blinding of outcome assessment (detection bias)	Low risk	Self-reported outcomes by blinded participants

Watson 1992 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Completer analysis but very low dropout **Attrition** Total: 3/35 (8.6%) Amitriptyline 37.5-150 mg: 2/35 (5.7%) Maprotiline 50-150 mg: 1/35 (2.9%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found. Lots of measures mentioned in the methods have no data given in results, just a sentence description
Other bias	Low risk	No other sources of bias were identified

Watson 1998

Study characteristics	
Methods	Design: cross-over Duration: each cross-over period lasted 5 weeks Assessment: baseline and post-cross-over period Country: Canada
Participants	Pain condition: post-herpetic neuralgia Population: adults with post-herpetic neuralgia Minimum pain intensity: pain of at least moderate severity (disagreeable, unpleasant, uncomfortable) for at least one half of the day; no numerical values Inclusion criteria • Post-herpetic neuralgia of > 3 months' duration • Pain of at least moderate severity (disagreeable, unpleasant, uncomfortable) for at least one half of the day Exclusion criteria • Cardiac disease, seizure disorder, severe depression with voiced suicidal intent requiring urgent management, presence of another significant pain problem, previous brain damage due to head injury, stroke or other causes, alcoholism Total participants randomised: 33 Age in years (mean, SD): NR Gender: NR Pain duration in months (median): 13 months
Interventions	Nortriptyline • TCA • Flexible dose: 10-160 mg

Watson 1998 *(Continued)*

	• Flexible titration: started on 10 mg/day if > 65 years old or 20 mg/day if < 65 years old. Depending on efficacy and tolerability, the dose was increased by 10 mg/day every 3-5 days for the first 3 weeks. • Identical blue capsules Amitriptyline • TCA • Flexible dose: 10-160 mg • Flexible titration: started on 10 mg/day if > 65 years old or 20 mg/day if < 65 years old. Depending on efficacy and tolerability, the dose was increased by 10 mg/day every 3-5 days for the first 3 weeks. • Identical blue capsules
Outcomes	AEs Withdrawal
Missing data methods	Unclear
Funding source	NR
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Individuals were randomised by telephone at another site by computer.
Allocation concealment (selection bias)	Low risk	The sequence was concealed in sequential, numbered, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes by blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data methods unclear, but only 1 participant withdrew **Attrition** Total: 2/33 (6.1%) Amitriptyline 10-160 mg: 1/33 (3.0%) Nortriptyline 10-150 mg: 1/33 (3.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Wernicke 2006

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: USA
Participants	Pain condition: diabetic peripheral neuropathic pain Population: type 1 and 2 diabetic adults with diabetic peripheral neuropathic pain Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • diabetic peripheral neuropathic pain caused by type 1 or type 2 diabetes mellitus. The pain had to begin in the feet and with relatively symmetrical onset. • Daily pain must have been present for at least 6 months, and the diagnosis was to be confirmed by a score of at least 3 on the MNSI • Pain intensity of ≥ 4 on BPI pain severity item Exclusion criteria • Physical health comorbidities • Any DSM-IV diagnosis of MDD, dysthymia, GAD, alcohol or eating disorders Total participants randomised: 334 Age in years (mean, SD): 60.7 (10.6) Gender: 130/334 were female Pain duration in years (mean, SD): 3.8 (4.4)
Interventions	Placebo • n = 108 • Inert Duloxetine 60 mg • n = 114 • SNRI • Fixed dose, no titration Duloxetine 120 mg • n = 112 • SNRI • Fixed dose, forced titration over 3 days
Outcomes	Pain intensity Mood Quality of life Physical function

Wernicke 2006 *(Continued)*

	Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Pharmaceutical: research for this study was funded by Eli Lilly and Company
Conflicts of interest	"Authors (J.F.W., D.N.D., A.W., S.I., J.R.) are employees and stockholders of Eli Lilly and Company. P.T. and Y.L.P. are former employees of Eli Lilly and Company. J.F.W., Y.L.P., P.T., and J.R. hold equity in Eli Lilly and Company in excess of USD 10,000."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment to a treatment group was determined by a computer-generated random sequence.
Allocation concealment (selection bias)	Low risk	Participants were allocated using an interactive voice response system (IVRS).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding procedures for study drugs, appearance, dosing etc
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, uncertain of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 86/334 (25.8%) Placebo: 23/108 (21.3%) Duloxetine 60 mg: 29/114 (25.4%) Duloxetine 120 mg: 34/112 (30.4%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias were identified

Wolfe 1994

Study characteristics	
Methods	Design: parallel Duration: 6 weeks Assessment: baseline, 3 weeks, post-intervention Country: USA
Participants	Pain condition: fibromyalgia Population: women aged 21-70 with fibromyalgia Minimum pain intensity: ≥ 1 on a 0-3 VAS Inclusion criteria • Patients with fibromyalgia who had at least 7 of 14 tender points, widespread pain according to the definition of the 1990 ACR criteria for the classification of fibromyalgia, and a pain score ≥ 1 on a 0-3 VAS Exclusion criteria: NR Total participants randomised: 42 Age in years (mean): 50.5 Gender: 42/42 were female Pain duration in years (mean, SD): 12.8
Interventions	Placebo • n = 21 • Inert Fluoxetine 20 mg • n = 21 • SSRI • Fixed dose
Outcomes	Pain intensity Sleep Physical function Mood Withdrawal
Missing data methods	Completer-only analysis (but ITT with LOCF for depression?)
Funding source	Pharmaceutical: supported by a grant from Lilly Research Laboratories, Inc, Indianapolis, IN, USA
Conflicts of interest	NR
Notes	
Risk of bias	

Wolfe 1994 *(Continued)*

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	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding procedures reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants, uncertain of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	High risk	Seem to only report completer analysis for each time point (with possible ITT and LOCF for depression?). Imbalanced withdrawal between groups (double in placebo compared to fluoxetine). **Attrition** Total: 18/42 (42/9%) Placebo: 12/21 (57.1%) Fluoxetine 20 mg: 6/21 (28.6%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias identified

Yasuda 2011

Study characteristics	
Methods	Design: parallel Duration: 12 weeks Assessment: baseline and post-intervention Country: Japan
Participants	Pain condition: diabetic neuropathic pain Population: adults aged 20-80 with diabetic neuropathic pain Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Sustained pain for ≥ 6 months as a result of distal symmetric polyneuropathy caused by type 1 or type 2 diabetes mellitus • Pain intensity of ≥ 4 on 0-10 scale Exclusion criteria

Yasuda 2011 *(Continued)*

	• Physical health comorbidities that could interact with neuropathic pain • Psychiatric diseases, such as mania, bipolar disorder, depression, anxiety disorders and eating disorders, or patients with history of these diseases that needed any pharmacotherapy during the past year Total participants randomised: 339 Age in years (mean, SD): 60.8 (10.0) Gender: 82/339 were female Pain duration in years (mean, SD): 4.3 (4.1)
Interventions	Placebo • n = 167 • Inert • Matched dosing Duloxetine 40 mg • n = 86 • SNRI • Fixed dose, forced titration over 2 weeks Duloxetine 60 mg • n = 86 • SNRI • Fixed dose, forced titration over 2 weeks
Outcomes	Pain intensity Mood Sleep Moderate pain relief Substantial pain relief PGIC AEs SAEs Withdrawal
Missing data methods	MMRM, LOCF
Funding source	Pharmaceutical: This study is financially supported by Shionogi & Co.Ltd., Eli Lilly Japan K.K., and Eli Lilly and Company.
Conflicts of interest	The study authors have no COI to declare.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Yasuda 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Before randomisation, an assigning table was prepared using Create Key Code 3.3. Patients were randomly assigned to duloxetine 40 or 60 mg or placebo groups in a 1:1:2 ratio by stochastic minimisation allocation taking into account the following 4 factors: (i) weekly mean of 24-h average pain score at baseline < or ‡6; (ii) duration of diabetic neuropathy < or ‡2 years; (iii) type 1 or type 2 diabetes mellitus; and (iv) each study center."
Allocation concealment (selection bias)	Unclear risk	Allocation procedure not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Says double-blind but procedures not specified. No information on drug or packaging concealment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF, MMRM. Low attrition **Attrition** Total: 44/339 (13.0%) Placebo: 17/167 (10.2%) Duloxetine 40 mg: 13/86 (15.1%) Duloxetine 60 mg: 14/86 (16.3%)
Selective reporting (reporting bias)	Unclear risk	Did not include depression outcome in publication, other than that, everything lines up with protocol
Other bias	Low risk	No other sources of bias were identified.

Yeephu 2013

Study characteristics	
Methods	Design: parallel Duration: 13 weeks Assessment: baseline and post-intervention Country: Thailand
Participants	Pain condition: fibromyalgia Population: Thai adults with fibromyalgia Minimum pain intensity: ≥ 40 on 0-100 scale Inclusion criteria • Adult outpatients, aged ≥ 18 years, descended from Thai parents, met fibromyalgia criteria as defined by the ACR criteria • Pain intensity of ≥ 40 on 0-100 scale

Yeephu 2013 *(Continued)*

	Exclusion criteria • Physical health comorbidities • Severe or unstable physical or psychiatric conditions were excluded Total participants randomised: 40 Age in years (mean, SD): 44.66 (10.77) Gender: 40/40 were female Pain duration in years (mean, SD): 3.44 (2.71)
Interventions	Placebo • n = 13 • Inert • Identical appearance to mirtazapine Mirtazapine 15 mg • n = 13 • NaSSA • Fixed dose, forced titration Mirtazapine 30 mg • n = 14 • NaSSA • Fixed dose, forced titration
Outcomes	Moderate pain relief PGIC AEs SAEs Withdrawal
Missing data methods	ITT with LOCF, BOCF
Funding source	Non-pharmaceutical: This study was supported by a scholarship from the Commission on Higher Education Staff Development Project for the Joint PhD Program in Biopharmaceutical Sciences, Thailand.
Conflicts of interest	Study authors reported no conflicts of interest.
Notes	Same study as Suttiruksa 2016 - however different outcomes were reported in the two papers.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The patients were allocated using a block size of 3 in a ratio of 1:1:1 with parallel assignment to 1 of 3 groups using a pharmacy-controlled randomisation process.
Allocation concealment (selection bias)	Low risk	Participants were allocated with sequentially numbered identical containers.

Yeephu 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical study drugs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcomes from blinded participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	State that they use LOCF and BOCF measures, but don't present the numbers of participants in each of these analyses. Low attrition rates across all arms. **Attrition** Total: 8/40 (20.0%) Placebo: 3/13 (23.1%) Mirtazapine 15 mg: 2/13 (15.4%) Mirtazapine 30 mg: 3/14 (21.4%)
Selective reporting (reporting bias)	Low risk	All outcomes in protocol reported either in this article or Suttiruksa 2016
Other bias	Low risk	No other sources of bias were identified

Yucel 2005

Study characteristics	
Methods	Design: parallel Duration: 8 weeks Assessment: baseline and post-intervention Country: Turkey
Participants	Pain condition: neuropathic pain of any cause Population: people aged between 20 and 70 with neuropathic pain Minimum pain intensity: ≥ 4 on 0-10 scale Inclusion criteria • Aged between 20 and 70 years, having symptoms compatible with neuropathic pain present for a period > 6 months • Pain intensity of ≥ 4 on 0-10 scale Exclusion criteria • Pain other than neuropathic pain, pain presumably of mixed origin, exclude majority psychiatric illness Total participants randomised: 60 Age in years (mean): 50.2

Yucel 2005 *(Continued)*

	Gender: 33/60 were female Pain duration in years (mean, SD): NR
Interventions	Placebo • n = 20 • Inert Venlafaxine 75 mg • n = 20 • SNRI • Fixed dose Venlafaxine 150 mg • n = 20 • SNRI • Fixed dose
Outcomes	AEs SAEs Withdrawal
Missing data methods	Completer-only analysis
Funding source	Pharmaceutical: This study was supported by a grant from Wyeth Ilaclari A.S., Istanbul, Turkey.
Conflicts of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Says double-blinded but no information regarding blinding procedures given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes from participants but unsure of blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only report completer analysis, but very low attrition **Attrition** Total: 5/60 (8.3%)

Yucel 2005 *(Continued)*

		Placebo: 1/20 (5.0%) Venlafaxine 75 mg: 1/20 (5.0%) Venlafaxine 150 mg: 3/20 (15.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	Low risk	No other sources of bias identified

Zabihiyeganeh 2021

Study characteristics	
Methods	Design: parallel Duration:10 weeks Assessment: baseline and post-intervention Country: Iran
Participants	Pain condition: fibromyalgia Population: women aged 18-65 with fibromyalgia Minimum pain intensity: no Inclusion criteria • Women aged 18-65 with a definitive diagnosis of fibromyalgia Exclusion criteria • Presence of co-morbid conditions affecting the serum cytokine levels, including RA, OA, metabolic disorders, infection, etc. • Severe psychiatric disorders; severe depression or anxiety (BDI score 30-63) Total participants randomised: 128 Age in years (mean): 42.5 Gender: 128/128 were female Pain duration in years (mean): 3.9
Interventions	CBT • n = 64 • Psychological therapy • Traditional face-to-face CBT was implemented based on the Beck and Ellis method, which was organised by Free 2007. The CBT was offered in twice-weekly sessions over 10 weeks. Each session lasted 2 h. Duloxetine 60 mg • n = 64 • SNRI • Fixed dose, forced titration

Zabihiyeganeh 2021 *(Continued)*

Outcomes	Pain intensity Quality of life AEs Withdrawal
Missing data methods	ITT with LOCF
Funding source	Non-pharmaceutical: This study was funded by Iran University of Medical Sciences under the Grant code of 32415.
Conflicts of interest	The study authors declare that they have no confict of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear - state that was perfomed via a random number list, but also that participants were allocated depending upon order of referral: "the frst 64 random numbers were assigned to the CBT group, and the following 64 random numbers were assigned to the duloxetine group"
Allocation concealment (selection bias)	Unclear risk	Allocation methods unclear (see random sequence generation)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to be blinded due to nature of CBT intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes from unblinded participants
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT with LOCF **Attrition** Total: 23/128 (18.0%) CBT: 12/64 (18.8%) Duloxetine 60 mg: 11/64 (17.2%)
Selective reporting (reporting bias)	Unclear risk	Prospectively registered protocol (https://en.irct.ir/trial/24406). Primary outcomes match but secondary outcomes (FIQ, Widespread Pain Index) not registered, no plan of analysis
Other bias	High risk	In the protocol they state a third group, a control group with no treatment, but this isn't mentioned anywhere in the paper.

Zitman 1990

Study characteristics	
Methods	Design: parallel Duration: 6 weeks Assessment: baseline, 2 weeks, post-intervention, follow-up (6 weeks post-intervention) Country: Netherlands
Participants	Pain condition: chronic pain of various origins Population: adults aged 30-60 with chronic pain of various origins Minimum pain intensity: no Inclusion criteria • Aged 30-60 • Any chronic pain for > 6 months Exclusion criteria • No serious mental disease requiring other medication and/or higher doses of antidepressants • No organic disease in which antidepressants are contraindicated Total participants randomised: 49 Age in years (mean, SD): 45.2 (1.3) Gender: 20/49 were female Pain duration in years (mean, SD): 5.1 (3.4)
Interventions	Placebo (riboflavin 15 mg) • n = 24 • Active placebo: vitamin B2 • Fixed dose Amitriptyline 75 mg + placebo (riboflavin 15 mg) • n = 25 • Combined: TCA + vitamin B • Tablets containing amitriptyline + riboflavin • Fixed doses
Outcomes	Pain intensity Mood Withdrawal
Missing data methods	Completer analysis
Funding source	NR
Conflicts of interest	NR
Notes	

Zitman 1990 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not specified
Allocation concealment (selection bias)	Unclear risk	Allocation procedures not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Says double-blind but no information given regarding appearance of tablets etc. Also the 12-week follow-up was open-label and participants could choose what they wanted.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes, but unsure of blinding conditions
Incomplete outcome data (attrition bias) All outcomes	High risk	No missing data methods given, completer analysis only **Attrition** Total: 10/49 (20.4%) Placebo: 4/24 (16.7%) Amitriptyline 75 mg: 6/25 (24.0%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found
Other bias	High risk	A lot of imbalances at baseline. Authors class vitamin B as a placebo, but this could have a beneficial effect on mood.

ACR: American College of Rheumatology; **AE:** adverse events; **ARA:** American Rheumatism Association; **BAI:** Beck Anxiety Inventory; **BDI:** Beck Depression Inventory; **BMI:** body mass index; **BOCF:** baseline observation carried forward; **BPI:** Brief Pain Inventory; **CBT:** cognitive behavioural therapy; **CoI:** conflict of interest; **DMS-IV:** *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; **DSM-IV-TR:***Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*; **ECG:** electrocardiogram; **FIC:** functional impairment checklist; **FIQ:** Fibromyalgia Impact Questionnaire; **FM:** fibromyalgia; **GAD:** generalised anxiety disorder; **HADS:** Hospital Anxiety and Depression Scale; **IBS:** irritable bowel syndrome; **ICD-10:***International Classification of Diseases 10th Revision*; **IQR:** interqurtile range; **ITT:** intention-to-treat; **LOCF:** last observation carried forward; **MADRS:** Montgomery–Åsberg Depression Rating Scale; **MAOI:** monoamine oxidase inhibitors; **mBOCF:** mean baseline observation carried forward; **MDD:** major depressive disorder; **MINI:** Mini International Neuropsychiatric Interview; **MMRM:** mixed models for repeated measures; **MNSI:** Michigan Neuropathy Screening Instrument; **NaRI:** noradrenaline reuptake inhibitors; **NaSSA:** noradrenergic and specific serotonergic antidepressant; **NR:** not reported; **NRS:** numerical rating scale; **NSAID:** non-steroidal anti-inflammatory drug; **OA:** osteoarthritis; **ODI:** Oswestry Disability Index; **PGIC:** Patient Global Impression of Change; **RA:** rheumatoid arthritis; **SAE:** serious adverse events; **SARI:** serotonin antagonist and reuptake inhibitors; **SD:** standard deviation; **SDI:** Sleep Disorders Inventory; **SNRI:** serotonin-noradrenalin reuptake inhibitors; **SSRI:** selective serotonin reuptake inhibitors; **TCA:** tricyclic antidepressants; **TeCA:** tetracyclic antidepressants; **TENS:** transcutaneous electrical nerve stimulation; **VAS:** visual analogue scale; **WOCF:** worst observation carried forward; **WOMAC:** Western Ontario and McMaster Universities Osteoarthritis pain scale

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

Study	Reason for exclusion
Amelin 1991	One combined arm, no comparator
Amr 2010	Prevention not treatment
Arnold 2014	All participants currently taking antidepressants
Avan 2018	Not chronic pain
Beaumont 1980	Study invalidated - paper describes an attempt at a trial of clomipramine and a matching placebo which failed
Braak 2011	Condition does not meet chronic pain criteria
Carette 1995	Cross-over trial - no washout period
ChiCTR-TRC-12001968	Pain inclusion criteria not met
ChiCTR-TRC-12001969	Pain inclusion criteria not met
ChiCTR2000030195	Pain treatment/prevention post-surgery
Chitsaz 2009	Pain inclusion criteria not met
CTRI/2015/05/005791	Pain inclusion criteria not met
Daghaghzadeh 2015	Pain inclusion criteria not met
Dinat 2015	Not chronic pain
Ehrnrooth 2001	Not chronic pain
EUCTR2005-005555-17-NL	Study terminated due to insufficient clinical response
EUCTR2006-003656-38-GB	Study was prematurely ended, but no reason given
EUCTR2006-005506-32-DK	Trial registration says prematurely ended, but no reason given
EUCTR2009-013061-26-FI	Study prematurely ended due to poor recruitment
EUCTR2016-003146-89-GB	No antidepressant-only arm
EUCTR2017-003307-21-NL	Pain inclusion criteria not met
EUCTR2018-000133-12-GB	No antidepressant-only arm
EUCTR2019-003437-42-DK	Study terminated but reason not given
Farshchian 2018	Not chronic pain
Frank 1988	Washout period not > 5 half-lifes of antidepressant
Gardela 1991	Not chronic pain
Gelijkens 2014	Not chronic pain

Study	Reason for exclusion
Ghadir 2011	Pain inclusion criteria not met
Goldenberg 2010	Participants re-randomised partway through study
Gomez-Perez 1985	No antidepressant-only arm, just a combined arm
Greenbaum 1987	Pain inclusion criteria not met
Henry 2018	Not chronic pain
IRCT201506171647N4	Pain inclusion criteria not met
IRCT20170829035966N1	Pain inclusion criteria not met
IRCT20191210045685N1	Treatment/prevention of pain post-surgery
ISRCTN16086699	Pain inclusion criteria not met
ISRCTN63671932	Pain inclusion criteria not met
Kaosombatwattana 2015	Pain inclusion criteria not met
Kautio 2008	Not chronic pain
Khalilian 2021	Pain inclusion criteria not met
Khosrawi 2018	Not chronic pain
Kieburtz 1998	Not chronic pain
Kishore-Kumar 1990	Washout period not > 5 half-lifes of antidepressant
Kreiter 2021	Pain inclusion criteria not met
Kroenke 2006	Pain inclusion criteria not met
Kuiken 2003	Pain inclusion criteria not met
Kvinesdal 1984	Cross-over study - no washout period
Ladabaum 2010	Pain inclusion criteria not met
Lara Muñoz 1986	Effect of amitriptyline on the pain relief provided by other analgesics, not the effect of amitriptyline itself
Li 2019	Pain inclusion criteria not met
Matsuoka 2019a	Not chronic pain
Max 1987	Cross-over study - no washout period
Max 1991	Cross-over study - no washout period
McQuay 1992	Cross-over study - no washout period

Study	Reason for exclusion
Mishra 2012	Not chronic pain
NCT00006157	Pain inclusion criteria not met
NCT00189059	Study terminated but reason not given
NCT00191919	Somatic symptoms of depression, not chronic pain condition
NCT00283842	Study terminated for business reasons
NCT00592384	Pain inclusion criteria not met
NCT00610909	Pain inclusion criteria not met
NCT00619983	Study terminated due to poor recruitment
NCT00625833	Study terminated due to insufficient clinical response
NCT00696787	Study terminated by sponsor
NCT00754793	Study terminated due to poor recruitment
NCT00945945	Study invalidated - study drugs were mislabelled, participants who were supposed to receive placebo actually received duloxetine and vice versa.
NCT01116531	Study withdrawn
NCT01173055	Experimental pain
NCT01268709	Pain inclusion criteria not met
NCT01288937	Study terminated due to poor recruitment
NCT01359514	Pain prevention rather than treatment
NCT01359826	Principle Investigator left institution and unable to locate any study documents
NCT01377038	Study withdrawn due to funding issues
NCT01451606	Study terminated due to poor recruitment
NCT01471379	Terminated due to recruitment difficulties
NCT01579279	Study terminated but no reason given
NCT01869907	Pain inclusion criteria not met
NCT01910259	Pain inclusion criteria not met
NCT02650544	Pain inclusion criteria not met
NCT02970591	No specific antidepressant, just "optimised management", which could include an antidepressant option
NCT03364075	Study terminated due to recruitment issues

Study	Reason for exclusion
NCT03522207	Study terminated due to short-staffing
NCT04747314	Antidepressant arm is not one single antidepressant, it's a mixture
Nickel 2005	No antidepressant only arm, just a combined arm
Panerai 1990	Cross-over study - no washout period
Parker 2003	No antidepressant-only arm
Parkman 2013	Pain inclusion criteria not met
Pilowsky 1982	Cross-over study - no washout period
Pilowsky 1995	All participants received antidepressant
Poulsen 1987	Unable to determine trial length
Raja 2002	Participants could take different antidepressants/comparators, no comparisons per drug
Rajagopalan 1998	Pain inclusion criteria not met
Saxe 2009	Results from discontinuation phase of trial
Seddighnia 2020	Pain inclusion criteria not met
Selvarajah 2018	No antidepressant-only arm
Semenchuk 2001	No washout period
Strauss 2019	Not chronic pain
Tadyon Najafabadi 2019	Pain inclusion criteria not met
Tondlova 2002	Not chronic pain
van Houdenhove 1992	Washout period not > 5 half-lifes of natidepressant
Varia 2000	Not chronic pain
Vork 2018	Pain inclusion criteria not met
Wang 2014	Pain inclusion criteria not met

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

ACTRN12620000656932

Methods	Double-blind, parallel-arm, placebo-controlled RCT
Participants	Unclear from trial registration whether this is acute or chronic pain Inpatients and outpatients with diagnoses of cancer and neuropathic pain (probable or definite neuropathic pain by IASP criteria)

ACTRN12620000656932 *(Continued)*

	Pain related to cancer with a worst pain score of ≥ 4 on BPI item 3 (worst pain intensity) score in the past 24 h Neuropathic Pain on LANSS ≥ 12 Taking stable regular analgesics within 72 hours before commencing on the study. Target: 160
Interventions	Duloxetine 30/day orally for 7 days, then increase to 60 mg/day for 7 days, then downward titrate to 30 mg/day for 7 days Pregabalin 50/day orally for 3 days, 150 mg/day for 4 days, then 300 mg/day for 7 days, then downward titration to 150 mg/day for 4 days, and 50 mg/day for 3 days
Outcomes	Pain intensity Anxiety Depression Daily opioid use
Notes	

Brown 2015

Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT
Participants	Patients with multiple sclerosis n = 38
Interventions	Duloxetine Placebo
Outcomes	Pain PGIC Depression Quality of life Sleep
Notes	Unable to ascertain pain duration, unsure if chronic

Chandra 2006

Methods	Double-blind, parallel, head-to-head, 2-arm RCT 9 weeks
Participants	Adult PHN patients 8 weeks of postherpetic neuralgia pain after healing of rash

Chandra 2006 *(Continued)*

	Pain intensity of at least 40 mm on a 100 mm VAS at screening and at randomisation
	Average pain score of at least 4 on the Likert scale during the baseline week
	n = 70
Interventions	Gabapentin
	Nortriptyline
	Flexibly dosed to maximum tolerated dose
Outcomes	Pain intensity
	Sleep
Notes	Unable to ascertain pain duration - not sure if chronic

Cánovas Martínez 2009

Methods	Parallel RCT
	3 months
Participants	60 patients with severe neuropathic pain (VAS > 6)
Interventions	Duloxetine
	Placebo
Outcomes	Pain intensity
	Symptom relief
Notes	Unable to ascertain blinding

Di 2019

Methods	Parallel, 2-arm RCT
Participants	Patients with severe cancer pain and depression
	n = 46
Interventions	Oxycontin + amitriptyline
	Oxycontin
Outcomes	Cancer pain
	Depression
Notes	Unable to ascertain blinding
	Unable to ascertain pain duration - unclear if chronic

Hammack 2002

Methods	Double-blind, placebo-controlled, cross-over, RCT
Participants	Patients who had received CDDP (cisplatin) chemotherapy, and have had painful paresthaesiae for at least 1 month attributed to CDDP neuropathy. n = 51
Interventions	Nortriptyline 100 mg Placebo
Outcomes	Pain Sleep Quality of life AEs
Notes	Unable to ascertain pain duration - inclusion criteria only says at least 1 month

Jia 2006

Methods	Double-blind, placebo-controlled, double-dummy, parallel, 2-arm RCT 2 weeks
Participants	Patients with painful peripheral diabetic neuropathy n = 132
Interventions	Carbamazepine 0.2 mg Venlafaxine 50 mg
Outcomes	Pain intensity Quality of life Mood Sleep AEs
Notes	Unable to establish pain duration, unsure if chronic

Keskinbora 2006

Methods	Double-blind, comparative, parallel, 2-arm RCT 4 weeks
Participants	Patients with neuropathic pain

Keskinbora 2006 *(Continued)*

	n = 46
Interventions	Gabapentin Amitriptyline
Outcomes	Pain sensations Satisfaction
Notes	States chronic pain, but no duration reported in article, so unable to confirm chronic

Riesner 2008

Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT 8 weeks
Participants	People with knee and hip OA
Interventions	Fluvoxamine 50-150 mg Placebo
Outcomes	Pain WOMAC total score PGIC AEs
Notes	Unable to ascertain pain duration, unsure if chronic

Salehifar 2020

Methods	Double-blind, comparative, parallel, 2-arm RCT 6 weeks
Participants	Patients with breast cancer who had a ≥ grade 1 neuropathy and who had score ≥ 4 neuropathic pain severity based on the VAS
Interventions	Pregabalin 150 mg Duloxetine 60 mg
Outcomes	Pain Sensory neuropathy grade
Notes	Unable to ascertain pain duration - unclear if chronic

Shabbir 2011

Methods	Parallel, 3-arm RCT
Participants	Patients with peripheral diabetic neuropathy for at least 6 months duration, an average pain score ≥ 4 (on an 11-point, Likert-like NRS; 0 = "no pain" to 10 = "worst possible pain") over a 7-day baseline period
Interventions	Amitriptyline Pregabalin Placebo Flexibly dosed depending upon tolerance
Outcomes	Pain intensity 50% pain relief
Notes	Unable to ascertain blinding

Shlay 1998

Methods	Comparative RCT
Participants	Patients with HIV- associated, symptomatic, lower-extremity peripheral neuropathy n = 250
Interventions	Acupuncture Amitriptyline 75 mg Placebo
Outcomes	Pain intensity
Notes	Unable to establish pain duration, unsure if chronic

Taghizadeh 2020

Methods	Comparative, 2-arm RCT 12 weeks
Participants	Women with mastalgia n = 62
Interventions	Fluoxetine Tamoxifen
Outcomes	Pain intensity
Notes	Unable to ascertain blinding, and duration of pain

Xu 2006

Methods	Comparative, 2-arm RCT 4 weeks
Participants	Patients with primary fibromyalgia syndrome n = 46
Interventions	Amitriptyline 25 mg ~ 50 mg Paroxetine 10 mg ~ 20 mg
Outcomes	Pain intensity AEs
Notes	Unable to ascertain blinding

Zakerkish 2017

Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT 6 weeks
Participants	Patients with diabetic peripheral neuropathy n = 134
Interventions	Duloxetine 30-60 mg Placebo
Outcomes	Pain intensity 50% pain relief AEs
Notes	Unable to establish pain duration, unclear if chronic

AE: adverse event; **BPI:** Brief Pain Inventory; **IASP:** International Association for the Study of Pain; **LANSS:** Leeds Assessment of Neuropathic Symptoms and Signs; **NRS:** numeric rating scale; **OA:** osteoarthritis; **PGIC:** Patient Global Impression of Change; **RCT:** randomised controlled trial; **VAS:** visual analogue scale; **WOMAC:** Western Ontario and McMaster Universities Osteoarthritis pain scale

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

ACTRN12619000878178

Study name	A randomised controlled trial of venlafaxine to treat patients with knee osteoarthritis pain
Methods	Double-blind, parallel-arm, placebo-controlled, 2-arm RCT
Participants	• Age 40-80 years • Knee pain for ≥ 14 days of each month for > 3 months • Significant knee pain on most days (defined as a VAS > 40 mm) on 100 mm VAS pain

ACTRN12619000878178 *(Continued)*

	• Meet ACR clinical criteria for knee OA confirmed by a rheumatologist
Interventions	Venlafaxine; 75 mg daily for 4 weeks and then increase to 150 mg daily for next 8 weeks Placebo
Outcomes	Pain intensity Physical function Quality of life painDETECT score Anxiety Pain catastrophising Pain disability Depression Responders (using OMERACT-OARSI criteria)
Starting date	20 June 2019
Contact information	Dr Feng Pan Menzies Institute for Medical Research 17 Liverpool Street Hobart Tasmania 7000 Australia Feng.Pan@utas.edu.au
Notes	

ACTRN12619001082190

Study name	Venlafaxine compared to duloxetine for the treatment of osteoarthritis pain: A double-blind, randomised, non-inferiority trial
Methods	Double-blind, parallel arm, antidepressant head-to-head, 2-arm RCT
Participants	Men and women at least 40 years old who have radiographic evidence of knee OA and meet the ACR clinical criteria for the diagnosis of knee OA A history of knee pain for > 14 days of each month for ≥ 3 months A BPI average pain rating of at least 4/10 at the time of initial screening Target: 146
Interventions	Venlafaxine 75 mg for 1 week, then 150 mg for 7 weeks Duloxetine 30 mg for 1 week, then 60 mg for 7 weeks
Outcomes	Pain intensity Anxiety

ACTRN12619001082190 *(Continued)*

	Depression Physical function Quality of life PGIC Moderate pain relief (30% reduction) Substantial pain relief (50% reduction)
Starting date	6 August 2019
Contact information	Dr David Rice Waitemata Pain Services, Level 10, North Shore Hospital, 124 Shakespeare Road, Takapuna, Auckland 0622, New Zealand david.rice@aut.ac.nz
Notes	

Ammitzboll 2021

Study name	A mechanism based proof of concept study of the effects of duloxetine in the treatment of patients with osteoarthritic knee pain
Methods	Double-blind, crossover, placebo-controlled, 2-arm trial
Participants	Men and women between 40 and 75 years of age Patients with knee OA based on disease diagnostic criteria Self-reported pain intensities ≥ 5 cm on a 0-10 cm VAS when asked to assess the worst pain within the last 24 hours Knee pain for at least 14 days per month for the last 3 months before study entry
Interventions	Patients will be randomised to 1 of 2 treatment sequences: • Sequence 1: 20 mg duloxetine every day for 1 week, 40 mg duloxetine every day for 1 week, 60 mg duloxetine every day for 10 weeks, 40 mg duloxetine every day for 1 week, 20 mg duloxetine every day for 1 week, followed by 14 weeks of corresponding placebo • Sequence 2: 14 weeks of placebo followed by 20 mg duloxetine every day for 1 week, 40 mg duloxetine every day for 1 week, 60 mg duloxetine every day for 10 weeks, 40 mg duloxetine every day for 1 week and 20 mg duloxetine every day for 1 week The 2 treatment periods of 14 weeks each are separated by a washout period of 2 weeks and include a 2-week titration period.
Outcomes	Pressure Pain Threshold
Starting date	13 January 2020
Contact information	Kristian Kjær Petersen, Aalborg University
Notes	

ChiCTR1900027038

Study name	Synergistic analgesia of duloxetine in phantom limb pain of amputees from bone tumors: a randomized controlled trial
Methods	Unclear on blinding or chronic pain from trial registration Placebo-controlled, 2-arm, RCT
Participants	Bone tumour patients, phantom limb pain after amputation Aged 18-65 Target: 120
Interventions	Duloxetine 60 mg Placebo
Outcomes	Pain intensity
Starting date	29 October 2019
Contact information	Shuang Jiang 44 Xiaoheyan Road, Dadong District, Shenyang, Liaoning, China 110042 jiangshuang@cancerhosp-ln-cmu.com
Notes	

CTRI/2018/10/015944

Study name	A comparative evaluation of duloxetine and gabapentin in painful diabetic neuropathy: a randomised control trial
Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT 12 weeks
Participants	• Patients of either sex with type 2 diabetes mellitus, aged 18 -75 years, who were on stable glucose-lowering medications during the preceding month and who had painful diabetic neuropathy for at least1 month • Had a pain score of > 50%, as assessed by VAS Target: 86
Interventions	Duloxetine 60 mg daily Gabapentin 300 mg daily
Outcomes	Pain intensity Diabetic neuropathy symptom score
Starting date	22 October 2018
Contact information	Dr Sameer Khasbage

CTRI/2018/10/015944 *(Continued)*

	Department of Pharmacology Basni 2 AIIMS Jodhpur Rajasthan 342005 Jodhpur, Rajasthan, India samkhasbage@gmail.com
Notes	

CTRI/2018/10/015983

Study name	Effectiveness of vitamin D as a supplement with conventional therapy in the treatment of diabetic peripheral neuropathy - a randomized controlled clinical trial
Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT 3 months
Participants	• Patients with diabetic peripheral neuropathy • Both male and female patients > 18 years • Patients who are willing to give written informed consent Target: 80
Interventions	Amitriptyline 25 mg Vitamin D
Outcomes	Vitamin D levels Pain intensity Quality of life
Starting date	10 October 2018
Contact information	Dr Melvin George Department of Pharmacology SRM Medical College Hospital and Research Centre SRM Institute of Science and Technology (SRMIST) Kattankulathur 603203 Kancheepuram, Tamil Nadu, India melvingeorge2003@gmail.com
Notes	

CTRI/2021/02/031068

Study name	A randamized double-blind comparative study evaluating the efficacy of a combination of pregabalin and duloxetine versus pregabalin alone and the modulation of mRNA expression of PPARG and Akt genes in patients of painful diabetic peripheral neuropathy
Methods	Unclear blinding from trial registration 2-arm, combination vs antidepressant-only RCT 12 weeks

CTRI/2021/02/031068 *(Continued)*

Participants	• Male or female patients ≥ 18 years of age with pain due to diabetic peripheral neuropathy caused by type -I or II diabetes mellitus for at least 3 months with confirmed diagnosis on MNSI with score ≤ 3 at the time of screening • Patients must have average pain severity of ≥ 4/10 on NRS • BPI-Modified short form ≥ 4 • Patients should have stable glycaemic control with HbA1C < 12% Target: 60
Interventions	Combination of tablet pregabalin 75 mg and tablet duloxetine 30 mg pregabalin 75 mg twice a day orally
Outcomes	Sleep Pain Physical function Modulation of mRNA expression of PPARG and Akt gene
Starting date	08 February 2021
Contact information	Dr Ashok Kumar Department of Anaesthesia and Critical Care, second floor University College of Medical Sciences and GTB Hospital, Dilshad Garden, Delhi 110095 East, Delhi, India profashoksaxena2@gmail.com
Notes	

CTRI/2021/03/031875

Study name	Efficacy of duloxetine in patients with central post-stroke pain: a randomised double blind placebo controlled study
Methods	Double-blind, placebo-controlled, parallel, 2-arm, RCT 4 weeks
Participants	• Positive history of haemorrhagic or ischaemic stroke with lesion in the unilateral brain region proved by computed tomography or magnetic resonance imaging of the brain • Presence of spontaneous or stimulated pain in the affected side, which could be smaller or the same in size as the sensory impairment area, fulfilling the mandatory criteria proposed by Klit 2009 • Patients with moderate to severe pain (NRS score of ≥ 4) are included Target: 82
Interventions	Duloxetine: 30 mg in the night every day and followed up at 2 weeks if no response, i.e. decrease in NRS score < 2 then the dose is doubled and again followed up after 2 weeks Placebo: the similar appearing placebo tablets are given at night every day and followed up at 2 weeks, if no response, i.e. decrease in NRS score < 2 the dose is doubled and again followed up after 2 weeks
Outcomes	Pain intensity

CTRI/2021/03/031875 *(Continued)*

	Disability PGIC
Starting date	10 March 2021
Contact information	Dr Rameshwar Nath Chaurasiya Department of Neurology, Institue of Medical Sciences, Banaras Hindu University, 221005 Varanasi, Uttar Pradesh, India goforrameshwar@gmail.com
Notes	

EUCTR2019-000243-27-DK

Study name	The effect of bupropion in peripheral neuropathic pain. A randomized, double-blind, placebo-controlled study
Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT
Participants	• Age > 18 years • Peripheral neuropathic pain for > 3 months • Pain score at least 4 and not higher than 9 on NRS 0-10 points Target: 90
Interventions	Bupropion 150 mg Placebo
Outcomes	Pain intensity Pain modulation PGIC Neuropathic pain symptoms Suicide ideation
Starting date	28 January 2019
Contact information	Neuromuscular Clinic J.B.Winsløws Vej 4 5000 Odense Denmark soeren.sindrup@rsyd.dk
Notes	

EUCTR2019-000324-17-GB

Study name	Amitriptyline at low-dose and titrated for irritable bowel syndrome as second-line treatment (the ATLANTIS study): a double-blind placebo-controlled trial - the ATLANTIS study

EUCTR2019-000324-17-GB *(Continued)*

Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT
Participants	Unclear about pain chronicity from trial registration • A diagnosis of IBS (of any subtype of stool pattern (diarrhoea, constipation, mixed) in their primary care record, and fulfilling the Rome IV criteria • Ongoing symptoms, defined as an IBS severity scoring system (IBS-SSS) score of = 75 at screening Target: 518
Interventions	Amitriptyline 10 mg Placebo
Outcomes	IBS symptoms Anxiety Depression Quality of life Health care use Ability to work
Starting date	07 November 2019
Contact information	Dr Heather Cook CTRU, University of Leeds LS2 9JT Leeds United Kingdom Atlantis@leeds.ac.uk
Notes	

EUCTR2019-001202-14-NL

Study name	CiPA Trial: effect of citalopram on chest pain in patients with achalasia
Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT 6 weeks
Participants	Diagnosed with achalasia type 1 or 2, confirmed by high-resolution manometry Recurrent chest pain • Midline chest pain or discomfort that is not of burning quality • At least 3 episodes per week of unexplained chest pain, for a minimum of 3 months Target: 68
Interventions	Citalopram Placebo
Outcomes	Pain intensity and frequency

EUCTR2019-001202-14-NL *(Continued)*

	Quality of life Anxiety Depression AEs
Starting date	18 April 2019
Contact information	Research Team Meibergdreef 9 1105 AZ Amsterdam Netherlands j.m.schuitenmaker@amc.uva.nl
Notes	

EUCTR2021-002288-24-NL

Study name	Effect of citalopram on chest pain in patients with functional chest pain - Ci-FCP
Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT 12 weeks
Participants	• Minimum age: 18 years • Functional chest pain according to Rome IV criteria • Ruled out cardiac origin of chest pain • Symptoms of chest pain for at least 6 months • Frequency of symptoms at least once a week Target: 52
Interventions	Citalopram Placebo
Outcomes	Reduction in chest pain Chest pain severity and frequency Quality of life Depression Anxiety AEs
Starting date	27 July 2021
Contact information	Research Team Meibergdreef 9 1105 AZ Amsterdam Netherlands t.kuipers1@amsterdamumc.nl
Notes	Potentially linked to Euctr 2019?

IRCT20110413006186N13

Study name	A comparison of the effectiveness of transcutaneous electrical nerve stimulation and duloxetine on diabetic peripheral neuropathic pain
Methods	Parallel, 2-arm RCT
Participants	Patients with type I or II diabetes mellitus, with diabetic neuropathic pain Resistant to usual drug treatments, at least for 6 months Minimum Pain Rating ≥ 4 based on NRS Target: 60
Interventions	TENS Duloxetine 60 mg
Outcomes	Pain intensity
Starting date	22 June 2019
Contact information	Dr Bahram Naderi Nabi Poursina Hospital 4193713189 Rasht Iran (Islamic Republic of) naderi_bahram@yahoo.com
Notes	

IRCT20200205046381N1

Study name	Comparing the analgesic effect of fluoxetine and vitamin E with vitamin E only in mastalgia due to fibrocystic breast disease
Methods	Double-blind, double-dummy, parallel, 2-arm RCT 8 weeks
Participants	• Unclear pain duration from trial registry • Women 20-50 years old with fibrocystic breast disease-induced mastalgia • Women with mastalgia criterion ≥ 4 on the VAS scale • Women whose pain lasts > 5 days per month Target: 70
Interventions	Vitamin E + fluoxetine: 600 units of vitamin E daily and 10 mg of fluoxetine Vitamin E: 600 units of vitamin E and placebo daily
Outcomes	Pain intensity
Starting date	20 March 2020
Contact information	Sheida Shabanian Hajar Hospital of Shahrekord University of Medical Sciences, Parastar street, Shahrekord, Iran 818718791 Shahrekord Iran (Islamic Republic of)

IRCT20200205046381N1 *(Continued)*

	shabanian@skums.ac.ir
Notes	

IRCT20200620047852N1

Study name	Comparing the analgesic effect of agomelatin versus placebo in combination with pregabalin in patients with chronic low back pain: a randomized, double-blinded study
Methods	Double-blind, double-dummy, parallel, 2-arm RCT
Participants	• Patients with chronic low back pain without an indication for surgery • Chronic low back pain = low back pain for at least 3 months (almost every day) • Patients aged between 18-60
Interventions	Pregabalin 75mg twice daily + agomelatine 25 mg Pregabalin 75 mg twice daily + placebo
Outcomes	Pain Anxiety Depression Quality of life Disability
Starting date	06 July 2020
Contact information	Shayan Amiri No 24, First West Street, 24 Metres Boulvard, Saadat Abad, Tehran, Iran, 1998667133 Tehran, Iran (Islamic Republic of) Amiri.shayan23@gmail.com
Notes	

NCT00981149

Study name	Duloxetine for treatment of painful temporomandibular joint disorder
Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT 6 weeks
Participants	n = 24 Unclear whether chronic pain from trial registration • Patients with chronic temporomandibular joint disorder pain of 2 weeks' duration • Pain score of ≥ 4 on the baseline VAS (0-10) • Aged 18-65

NCT00981149 *(Continued)*

Interventions	Duloxetine 30 mg Placebo
Outcomes	Pain intensity
Starting date	May 2009
Contact information	
Notes	

NCT03249558

Study name	Effect of combined morphine and duloxetine on chronic pain
Methods	Double-blind, combination + double-dummy, parallel, 3-arm RCT 10 weeks
Participants	• 18-70 years old • Chronic neck or back pain for at least 3 months • VAS ≥ 5 Target: 135
Interventions	Morphine 60 mg + duloxetine 60 mg Morphine 60 mg + placebo Duloxetine 60 mg + placebo
Outcomes	Opioid dose Pain intensity
Starting date	01 February 2018
Contact information	Karina de Sousa kdesousa1@mgh.harvard.edu
Notes	

NCT03324035

Study name	Treatment of neuropathic pain in leprosy: a randomized double blind controlled study
Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT
Participants	• Presence of spontaneous pain of medium intensity in the last 24 hours with a minimum value of 4 in 10 on a numerical scale, with a maximum of 10 points (summed pain questionnaire) • Duration of pain of at least 6 months

NCT03324035 *(Continued)*

	• Presence of neuropathic pain "pure" or of clearly dominant character (no other pain, or pain associated unimportant) • Pain due to leprosy confirmed by clinical examination and/or appropriate electrophysiological examination n = 102
Interventions	Amitriptyline, flexible doses varying from 25-75 mg Placebo, flexible doses from 1-3 capsules
Outcomes	30% pain relief Pain intensity Neuropathic pain symptoms Quality of life AEs
Starting date	01 March 2017
Contact information	Daniel Ciampi Araujo de Andrade, MD, PhD, Principal Investigator, Pain Center coordinator, Department of Neurology, University of Sao Paulo, São Paulo, Brazil, University of Sao Paulo
Notes	

NCT04704453

Study name	Phase II randomized controlled study aiming to evaluate the interest of Qutenza in patients with head and neck cancer in remission and with sequelae neuropathic pain
Methods	Double-blind, parallel, 2-arm RCT 9 months
Participants	Unclear pain duration from trial registration • Head and neck cancer in remission: absence of clinical or radiological signs of progression at least 3 months after specific treatments • Pain of the cervico-facial sphere persisting for > 3 months after surgical and/or radiotherapy treatment • Peripheral neuropathic character of pain objectified to a score ≥ 4/10 on the DN (Douleur Neuropathique) 4 questionnaire • Pain whose average intensity over the last 24 hours is assessed on the numerical scale as ≥ 2/10 Target: 130
Interventions	Capsaïcin patch (Qutenza) 8% Amitriptyline flexibly dosed 25-75 mg
Outcomes	Pain intensity Neuropathic pain symptoms Quality of life

NCT04704453 *(Continued)*

	AEs
Starting date	28 April 2021
Contact information	Antoine Boden 05 31 15 57 91 boden.antoine@iuct-oncopole.fr
Notes	

NCT04727502

Study name	Comparison of duloxetine versus pregabalin in post-mastectomy pain syndrome: a randomized controlled trial
Methods	Double-blind, comparative, parallel, 2-arm RCT 12 weeks
Participants	Patients with 3 months of chronic neuropathic pain after breast surgery Target: 70
Interventions	Duloxetine 30 mg Pregabalin 150 mg
Outcomes	Pain intensity
Starting date	20 December 2020
Contact information	Mohamed Abdel Wadod, MD +201006645981 m_wadod@yahoo.com
Notes	

PACTR202001764151121

Study name	Efficacy of clomipramine for chronic lumbar radicular pain: a randomized clinical trial
Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT
Participants	• Male and female participants • Aged 20-80 years • Chronic lumbar radicular pain whatever the aetiology, defined as pain lumbosacral radicular radiating into the leg below the knee, which had been present for > 3 months • VAS pain= 6/10 • Pain which was not improved by NSAIDs, analgesics and physical treatment

PACTR202001764151121 *(Continued)*

	Target: 62
Interventions	Clomipramine Placebo
Outcomes	Pain intensity Neuropathic pain symptoms Walking Disability Anxiety Depression
Starting date	27 May 2019
Contact information	Redouane Abouqal Faculty of Medicine and Pharmacy, Impasse Souissi, Rabat, Morocco Redouane.abouqal@yahoo.fr
Notes	

RBR-6pqx4n

Study name	Efficacy of duloxetine in chronic temporomandibular disorder: a randomized clinical trial
Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT 12 weeks
Participants	Temporomandibular disorder Presence of pain for at least 3 months
Interventions	Duloxetine 60 mg Placebo
Outcomes	Pain intensity Sleep Psychosocial profile Mechanical somatosensory profile
Starting date	01 October 2018
Contact information	Dyna Mara Araújo Oliveira Ferreira Al. Octávio Pinheiro Brisola, 9-75 17012-901 Bauru Brazil dyna.mara@hotmail.com

RBR-6pqx4n *(Continued)*

Notes	

Reckziegel 2017

Study name	Imaging pain relief in osteoarthritis (IPRO): protocol of a double-blind randomised controlled mechanistic study assessing pain relief and prediction of duloxetine treatment outcome
Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT
Participants	Chronic knee pain with radiographically defined OA changes (Kellgren Lawrence ≥ grade 2) Aged ≥ 35 n = 77
Interventions	Duloxetine 60 mg Placebo
Outcomes	Experimental pain Functional magnetic resonance imaging
Starting date	December 2014
Contact information	University of Nottingham - School of Medicine - Radiological Sciences Nottingham, Nottinghamshire, United Kingdom, NG7 2UH
Notes	

TCTR20190303001

Study name	A comparison of analgesic efficacy between amitriptyline and mianserin in chronic low back pain patients: a randomized double-blind controlled trial
Methods	Double-blind, placebo-controlled, parallel, 2-arm RCT
Participants	• 18 - 65 years old • Chronic low back pain for > 3 months with NRS > 4 Target: 60
Interventions	Amitriptyline 10-50 mg Mianserin 10-50 mg
Outcomes	Pain intensity Quality of life
Starting date	01 November 2018
Contact information	Suratsawadee Wangnamthip

TCTR20190303001 *(Continued)*

	Bangkok Noi 10700 Bangkok Thailand suratsawadee.wang@gmail.com
Notes	

TCTR20210311009

Study name	Comparison effectiveness of nortriptyline and placebo in the treatment of chronic osteoarthritis knee
Methods	Uncertain of blinding from trial registry
Participants	• OA knee as ACR criteria with Kellgren-Lawrence II, III • 3 months of clinical pain • WOMAC pain score > 20 points Target: 200
Interventions	Nortriptyline 25 mg Placebo
Outcomes	WOMAC total score Pain intensity
Starting date	29 May 2019
Contact information	Krittamuk Ompornnuwat 681 Samsen road, Vajira hospital, 20300 10300 Dusit Thailand krittamuk@nmu.ac.th
Notes	

Wluka 2021

Study name	Knee osteoarthritis pain study (KOPS)
Methods	Double-blind, parallel arm, placebo controlled 2-arm RCT 12 weeks
Participants	Adults aged 40-75 with knee OA as defined by the ACR clinical and radiographic criteria Pain intensity of ≥ 30 on 0-100 pain scale
Interventions	Amitriptyline 25 mg Placebo
Outcomes	Pain intensity WOMAC total score

Wluka 2021 *(Continued)*

	Moderate pain relief (30% reduction) Substantial pain relief (50% reduction)
Starting date	07 July 2015
Contact information	Mrs Aruna Kartik Department of Epidemiology and Preventive Medicine, Monash University, Alfred Hospital, Commercial Road, Melbourne, VIC 3004, Australia jointstudy@monash.edu
Notes	

ACR: American College of Rheumatology; **AE:** adverse event; **BPI:** Brief Pain Inventory; **IBS:** irritable bowel syndrome; **MNSI:** Michigan Neuropathy Screening Instrument; **NRS:** numeric rating scale; **NSAID:** non-steroidal anti-inflammatory drug; **OA:** osteoarthritis; **OMERACT-OARSI:** Outcome Measures in Rheumatology-Osteoarthritis Research Society International; **PGIC:** Patient Global Impression of Change; **RCT:** randomised controlled trial; s; **TENS:** transcutaneous electrical nerve stimulation; **VAS:** visual analogue scale;

ADDITIONAL TABLES

Table 1. Antidepressant dose categorisation

Antidepressant	Total daily dosage		
	Low	Standard	High
Amitriptyline	< 25 mg	25-75 mg	> 75 mg
Bupropion	n/a[a]	150-300 mg	> 300 mg
Citalopram	< 20 mg	20 mg	40 mg
Clomipramine	< 30 mg	30-150 mg	> 150 mg
Desipramine	< 100 mg	100-200 mg	> 200 mg
Desvenlafaxine	n/a[b]	50 mg	> 50 mg
Dothiepin (dosulepin)	< 75 mg	75-150 mg	> 150 mg
Doxepin	< 75 mg	75-150 mg	> 150 mg
Duloxetine	< 60 mg	60 mg	> 60 mg
Escitalopram	< 10 mg	10 mg	20 mg
Esreboxetine	n/a[c]	4-8 mg	> 8 mg
Fluoxetine	< 20 mg	20-40 mg	> 40 mg
Imipramine	< 75 mg	75-150 mg	> 150 mg
Nortriptyline	< 75 mg	75-100 mg	> 100 mg

Table 1. Antidepressant dose categorisation *(Continued)*

Maprotiline	150 mg	300 mg	> 300 mg
Mianserin	< 30 mg	30-40 mg	> 40 mg
Milnacipran	< 100 mg	100 mg	> 100 mg
Mirtazapine	< 30 mg	30 mg	> 30 mg
Moclobemide	150 mg	300 mg	600 mg
Paroxetine	< 20 mg	20 mg	50 mg
Pirlindole	< 225 mg	225-300 mg	> 300 mg
Reboxetine	< 8 mg	8 mg	> 8 mg
Sertraline	n/a[d]	50 mg	> 50 mg
Trazodone	< 150 mg	150-300 mg	> 300 mg
Trimipramine	< 75 mg	75-150 mg	> 150 mg
Venlafaxine	< 75 mg	75-150 mg	> 150 mg
Zimelidine	< 300 mg	300 mg	> 300 mg

[a]Lowest dose form is 150 mg.
[b]Desvenlafaxine is not available in UK, lowest dose form is 50 mg.
[c]Esreboxetine is not available in UK, and no doses lower than 4 mg have been used in trials.
[d]50 mg is both the initial and standard dose, no recommendations of lower doses in the British National Formulary.

Table 2. Substantial pain - overview of interventions in the NMA

Treatment	RCTs	Participants
Antidepressants with ≥ 200 participants		
Desvenlafaxine high dose	2	655
Duloxetine low dose	6	593
Duloxetine standard dose	15	2429
Duloxetine high dose	14	1837
Esreboxetine standard dose	1	553
Esreboxetine high dose	1	280
Milnacipran standard dose	2	644
Milnacipran high dose	1	239
Mirtazapine standard dose	1	211

Table 2. Substantial pain - overview of interventions in the NMA *(Continued)*

Antidepressants with < 200 participants (excluded from summaries)		
Amitriptyline dose unable to be categorised	1	58
Clomipramine standard dose	1	62
Desvenlafaxine standard dose	2	194
Esreboxetine dose unable to be categorised	1	133
Imipramine standard dose	2	113
Mianserin high dose	2	89
Imipramine + pregabalin standard dose	1	69
Venlafaxine standard dose	1	86
Venlafaxine high dose	1	82
Venlafaxine dose unable to be categorised	1	64
Non-antidepressant interventions (excluded from summaries)		
Carbamazepine	1	85
Pregabalin	4	678
Terbutaline	1	39

RCT: randomised controlled trial

Participant numbers reflect the total number of participants receiving the antidepressant.

Table 3. Top-ranked antidepressants for substantial pain relief

Antidepressant	Odds ratio (95% CI)	Mean rank	Credible intervals	
			2.5%	97.5%
Duloxetine standard dose	1.91 (1.69 to 2.17)	8.3	5	12
Duloxetine high dose	1.91 (1.66 to 2.21)	8.5	5	12
Milnacipran high dose	1.64 (1.04 to 2.58)	10.9	4	19
Esreboxetine standard dose	1.72 (1.13 to 2.62)	11.0	4	19

Table 3. Top-ranked antidepressants for substantial pain relief *(Continued)*

Milnacipran standard dose	1.65 (1.28 to 2.13)	11.8	6	18
Mirtazapine standard dose	1.30 (0.79 to 2.15)	15.4	6	21
Duloxetine low dose	1.71 (1.36 to 2.20)	15.7	11	20
Esreboxetine high dose	1.29 (0.79 to 2.11)	15.7	7	22
Desvenlafaxine high dose	1.19 (0.83 to 1.70)	16.8	11	21

CI: confidence interval

Table 4. Overview of interventions in pain intensity change-score analysis

Treatment	RCTs	Participants
Antidepressants with ≥ 200 participants		
Duloxetine low dose	6	560
Duloxetine standard dose	18	2727
Duloxetine high dose	14	1925
Milnacipran standard dose	4	943
Milnacipran high dose	2	823
Antidepressants with < 200 participants (excluded from summaries)		
Amitriptyline high dose	1	38
Amitriptyline low dose	1	70
Amitriptyline standard dose	2	130
Amitriptyline dose unable to be categorised	1	24
Citalopram standard dose	2	38
Desipramine standard dose	2	59
Desipramine standard dose + lidocaine	1	30
Desvenlafaxine standard dose	1	49

Table 4. Overview of interventions in pain intensity change-score analysis *(Continued)*

Desvenlafaxine high dose	1	175
Esreboxetine dose unable to be categorised	1	133
Fluoxetine dose unable to be categorised	1	25
Imipramine low dose	1	18
Milnacipran dose unable to be categorised	2	176
Nortriptyline dose unable to be categorised	1	38
Paroxetine low dose	1	74
Paroxetine dose unable to be categorised	1	58
Non-antidepressant interventions (excluded from summaries)		
ABT-894	1	170
Cognitive behavioural therapy	1	15
Gabapentin	1	19
Lidocaine	1	27
Pregabalin	2	550
Psychotherapy	1	74
Usual treatment	1	79

RCT: randomised controlled trial

Participant numbers reflect the total number of participants receiving the antidepressant.

Table 5. Top-ranked antidepressants for pain intensity change scores

	Standardised mean difference (95% CI)	Mean rank	Credible intervals	
			2.5%	97.5%
Duloxetine high dose	-0.37 (-0.45 to -0.28)	9.3	8	13
Duloxetine standard dose	-0.31 (-0.39 to -0.24)	11.1	10	15
Milnacipran high dose	-0.22 (-0.40 to -0.05)	14.0	12	19
Milnacipran standard dose	-0.22	14.2	12	20

Table 5. Top-ranked antidepressants for pain intensity change scores *(Continued)*

	(-0.39 to -0.06)			
Duloxetine low dose	-0.11 (-0.25 to 0.03)	17.0	12	21

CI: confidence interval

Table 6. Overview of interventions in mood change-score analysis

Treatment	RCTs	Participants
Antidepressants with ≥ 200 participants		
Duloxetine	26	4837
Milnacipran	5	1753
Mirtazapine	1	204
Antidepressants with < 200 participants (excluded from summaries)		
Citalopram	2	38
Desipramine	1	27
Desipramine + lidocaine	1	32
Esreboxetine	1	126
Fluoxetine	1	25
Imipramine	1	18
Milnacripran + cognitive behavioural therapy	1	17
Nortriptyline	1	38
Paroxetine	1	59
Non-antidepressant interventions (excluded from summaries)		
ABT-894	1	166
Cognitive behavioural therapy	1	15
Pregabalin	2	548
Psychotherapy	1	58
Usual treatment	1	63

RCT: randomised controlled trial

Table 7. Top-ranked antidepressants for mood change-score analysis

	Standardised mean difference (95% CI)	Mean rank	Credible intervals	
			2.5%	97.5%
Mirtazapine	−0.5 (−0.78 to −0.22)	3.7	2	7
Duloxetine	−0.16 (−0.22 to −0.1)	8.0	5	11
Milnacipran	−0.13 (−0.26 to 0.01)	8.9	5	13

CI: confidence interval

Table 8. Overview of interventions in adverse event treatment-dose analysis

Treatment	RCTs	Participants
Antidepressants with ≥ 200 participants		
Amitriptyline standard dose	10	518
Desvenlafaxine high dose	2	685
Duloxetine high dose	15	2088
Duloxetine low dose	6	594
Duloxetine standard dose	20	2834
Esreboxetine standard dose	1	556
Milnacipran high dose	7	1573
Milnacipran standard dose	8	1256
Mirtazapine standard dose	1	229
Antidepressants with < 200 participants (excluded from summaries)		
Amitriptyline low dose	1	67
Amitriptyline standard dose + melatonin	1	21
Amitriptyline high dose	2	150
Amitriptyline dose unable to be categorised	5	175
Desipramine low dose	1	38

Table 8. Overview of interventions in adverse event treatment-dose analysis *(Continued)*

Desipramine low dose + cognitive behavioural therapy	1	37
Desipramine standard dose	1	54
Desvenlafaxine standard dose	2	199
Dothiepin standard dose	1	30
Escitalopram high dose	1	41
Esreboxetine high dose	1	107
Esreboxetine dose unable to be categorised	1	134
Imipramine low dose	2	85
Imipramine standard dose	2	121
Imipramine standard dose + pregabalin	1	69
Imipramine high dose	1	40
Maprotiline low dose	1	33
Milnacipran standard dose + cognitive behavioural therapy	1	20
Milnacipran dose unable to be categorised	2	105
Mirtazapine low dose	1	13
Moclobemide high dose	1	43
Nortriptyline low dose	1	99
Nortriptyline low dose + morphine	1	28
Nortriptyline standard dose	1	28
Nortriptyline dose unable to be categorised	2	61
Nortriptyline dose unable to be categorised + cognitive behavioural therapy	1	41
Nortriptyline dose unable to be categorised + disease management	1	37
Paroxetine unable to be categorised	3	186
Pirlindole low dose	1	45
Sertraline high dose	1	30
Sertraline high dose + coping skills training	1	28
Trazadone low dose + gabapentin	1	94
Venlafaxine low dose	3	123

Table 8. Overview of interventions in adverse event treatment-dose analysis *(Continued)*

Venlafaxine standard dose	2	106
Venlafaxine high dose	2	122
Non-antidepressant interventions (excluded from summaries)		
ABT-894	1	172
Acetaminophen (paracetamol)	1	50
Carbamazepine	2	99
Clonidine	1	20
Cognitive behavioural therapy	4	155
Coping skills training	1	29
Cyclobenzaprine	1	42
Disease management	1	24
Gabapentin	4	175
Lamotrigine	1	46
Lorazepam	1	41
Melatonin	1	21
Morphine	1	28
Naltrexone	1	67
TENS	1	30
Terbutaline	1	51

RCT: randomised controlled trial; **TENS:** transcutaneous electrical nerve stimulation

Participant numbers reflect the total number of participants receiving the antidepressant.

Table 9. Top-ranked antidepressants for adverse events analysis

	Odds ratio (95% CI)	Mean rank	Credible intervals	
			2.5%	97.5%
Desvenlafaxine high dose	1.67 (0.92 to 2.41)	30.4	16	48
Mirtazapine standard dose	1.70 (0.48 to 2.91)	31.1	11	52

Table 9. Top-ranked antidepressants for adverse events analysis *(Continued)*

Duloxetine standard dose	1.88 (1.58 to 2.17)	32.7	24	42
Milnacipran standard dose	1.92 (1.37 to 2.46)	33.2	20	45
Duloxetine high dose	1.93 (1.64 to 2.23)	33.5	24	43
Duloxetine low dose	2.03 (1.45 to 2.62)	35.0	21	47
Milnacipran high dose	2.44 (1.89 to 2.98)	38.9	25	50
Amitriptyline standard dose	2.66 (2.14 to 3.19)	41.0	28	51
Esreboxetine standard dose	2.92 (1.90 to 3.93)	41.5	21	56

CI: confidence interval

Table 10. Moderate pain summary of findings

Estimates of effects, credible intervals, and certainty of the evidence for moderate pain relief in people with chronic pain

Bayesian network meta-analysis summary of findings table

Patient or population: people with chronic pain

Interventions: mirtazapine, duloxetine, milnacipran. all doses were combined for each antidepressant.

Comparator (reference): placebo

Outcome: moderate pain relief (defined as 30% reduction in pain intensity from baseline to post-intervention; measured on a range of scales including 0-10 VAS, 0-100 VAS, and hort-form McGill Pain Questionnaire

Direction: Higher is better (i.e. more people reporting moderate pain relief)

Total studies: 40 **Total participants**: 14,208	**Relative effect (OR and 95% CI)**	**Anticipated absolute effect (event rate)***			**Certainty of the evidence (CINeMA)**	**Ranking** (2.5% to 97.5% credible interval)	**Interpretation of findings**
		With placebo	**With intervention**	**Difference**			
Mirtazapine RCTs: 2 Participants: 462	1.92 (1.45 to 2.39)	70/224 **313 per 1000**	112/238 **466 per 1000**	**154 more per 1000**	Low[e]	7 (3 to 13)	Equivalent NNTB is 6.5
Duloxetine RCTs: 24 Participants: 7833	1.79 (1.67 to 1.91)	1324/3271 **405 per 1000**	2469/4562 **549 per 1000**	**144 more per 1000**	Moderate[a]	7 (4 to 11)	Equivalent NNTB is 6.9
Milnacipran RCTs: 7 Participants: 3056	1.7 (1.48 to 1.92)	347/1128 **308 per 1000**	825/1928 **430 per 1000**	**123 more per 1000**	Moderate[a]	8 (4 to 12)	Equivalent NNTB is 8.1
Esreboxetine RCTs: 2 Participants: 1374	1.65 (1.32 to 1.98)	107/409 **262 per 1000**	356/965 **369 per 1000**	**107 more per 1000**	Low[a,e]	9 (4 to 13)	Equivalent NNTB is 9.3

Network meta-analysis-summary of findings table definitions

Table 10. Moderate pain summary of findings *(Continued)*

* Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

** Mean rank and credible intervals are presented.

CI: confidence interval; **CINeMA:** Confidence in Network Meta-Analysis; **NNTB:** number needed to treat for an additional beneficial outcome; **OR:** odds ratio; **RCT:** randomised controlled trial; **VAS:** visual analogue scale

The number of participants for each antidepressant reflects the total number of participants taking the antidepressant or placebo from the studies in the network meta-analysis.

CINeMA grades of confidence in the evidence

High: further research is unlikely to change our confidence in the estimate of effect.

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

Low: 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: we are very uncertain about the estimate.

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[a]Downgraded due to within-study bias.
[b]Downgraded due to imprecision in the estimate.
[c]Downgraded due to heterogeneity in the estimate.
[d]Downgraded due to incoherence in the network.
[e]Downgraded due to a small number of trials and participants; we cannot draw reliable conclusions.

Table 11. Overview of all interventions in the moderate pain relief analysis

Treatment	RCTs	Participants
Antidepressants with ≥ 200 participants		
Duloxetine	24	4562
Esreboxetine	2	965
Milnacipran	7	1928
Mirtazapine	2	238
Antidepressants with < 200 participants (excluded from summaries)		
Amitriptyline	2	80
Desipramine	1	37
Desipramine + cognitive behavioural therapy	1	37
Imipramine	2	113
Imipramine + pregabalin	1	69
Venlafaxine	1	86
Non-antidepressant interventions (excluded from summaries)		
Carbamazepine	2	85
Cognitive behavioural therapy	2	53
Gabapentin	1	22
Pregabalin	4	680
Terbutaline	1	39

RCT: randomised controlled trial

Participant numbers reflect the total number of participants receiving the antidepressant.

Table 12. Top-ranked antidepressants moderate pain relief

	Odds ratio (95% CI)	Mean rank	Credible intervals	
			2.5%	97.5%
Mirtazapine	1.92 (1.45 to 2.39)	6.9	3	13
Duloxetine	1.79	7.4	4	11

Table 12. Top-ranked antidepressants moderate pain relief *(Continued)*

	(1.67 to 1.91)			
Milnacipran	1.7 (1.48 to 1.92)	8.2	4	12
Esreboxetine	1.65 (1.32 to 1.98)	8.7	4	13

CI: confidence interval

Table 13. Physical function summary of findings

Estimates of effects, credible intervals, and certainty of the evidence of antidepressants on physical function in people with chronic pain

Bayesian network meta-analysis summary of findings table

Patient or population: people with chronic pain

Interventions: duloxetine standard dose (60 mg) and high dose (> 60 mg); milnacipran standard dose (100 mg) and high dose (> 100 mg); mirtazapine standard dose (30 mg)

Comparator (reference): placebo

Outcome: change in physical function (lower scores are better) from a range of measures, including Fibromyalgia Impact Questionnaire and the SF-36

Direction: lower is better (i.e. a greater improvement in physical function and disability)

Total studies: 32 **Total participants**: 11,760	**Relative effect**	**Anticipated absolute effect (event rate)**			**Certainty of the evidence (CINeMA)**	**Ranking***	**Interpretation of findings****
		With placebo	**With intervention**	**Difference**		**(2.5% to 97.5% credible interval)**	
Duloxetine standard dose RCTs: 15 Participants: 3887	-	-	-	**SMD −0.24** (−0.32 to −0.18)	High	6 (3 to 8)	Small effect
Duloxetine high dose RCTs: 13 Participants: 3503	-	-	-	**SMD −0.23** (−0.30 to −0.16)	Moderate[a]	6 (2 to 9)	Small effect
Milnacipran standard dose RCTs: 3 Participants: 1840	-	-	-	**SMD −0.18** (−0.30 to −0.07)	Moderate[a]	7 (4 to 11)	Small effect
Milnacipran high dose RCTs: 2 Participants: 1670	-	-	-	**SMD −0.1** (−0.22 to 0.07)	Very low[a,c]	9 (6 to 13)	Not significantly different from placebo
Mirtazapine standard dose	-	-	-	**SMD 0.62**	Very low[e]	16	Moderate to large effect

Table 13. Physical function summary of findings *(Continued)*

RCTs: 1	(0.11 to 0.69)	(15 to 16)
Participants: 204		

Network meta-analysis-summary of findings table definitions

** Mean rank and credible intervals are presented.

**SMD interpretation based on clinical judgement and in line with Cohen 1988 and the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2022) as small (0.2), moderate (0.5) and large (0.8).

CI: confidence interval; **CINeMA:** Confidence in Network Meta-Analysis; **RCT:** randomised controlled trial; **SMD:** standardised mean difference; **VAS:** visual analogue scale

The number of participants for each antidepressant reflects the total number of participants taking the antidepressant or placebo from the studies in the network meta-analysis.

CINeMA grades of confidence in the evidence

High: further research is unlikely to change our confidence in the estimate of effect.

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

Low: 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: we are very uncertain about the estimate.

[a]Downgraded due to within-study bias.
[b]Downgraded due to imprecision in the estimate.
[c]Downgraded due to heterogeneity in the estimate.
[d]Downgraded due to incoherence in the network.
[e]Downgraded due to a small number of trials and participants; we cannot draw reliable conclusions.

Table 14. Overview of all interventions in the physical function analysis

Treatment	RCTs	Participants
Antidepressants with ≥ 200 participants		
Duloxetine high dose	13	1831
Duloxetine standard dose	14	2157
Milnacipran high dose	2	823
Milnacipran standard dose	3	930
Mirtazapine standard dose	1	204
Antidepressants with < 200 participants (excluded from summaries)		
Citalopram standard dose	2	38
Duloxetine low dose	2	150
Esreboxetine dose unable to be categorised	1	126
Fluoxetine	1	25
Imipramine	1	18
Milnacipran standard + cognitive behavioural therapy	1	17
Nortriptyline dose unable to be categorised	1	38
Paroxetine low dose	1	59
Non-antidepressant interventions (excluded from summaries)		
ABT-894	1	166
Cognitive behavioural therapy	1	15
Pregabalin	1	401
Psychotherapy	1	58
Usual treatment	1	63

RCT: randomised controlled trial

Participant numbers reflect the total number of participants receiving the antidepressant.

Table 15. Top-ranked antidepressants for physical function change-score analysis

	Standardised mean difference (95% CI)	Mean rank	Credible intervals	
			2.5%	97.5%

Table 15. Top-ranked antidepressants for physical function change-score analysis *(Continued)*

Duloxetine standard	−0.24 (−0.32 to −0.18)	5.5	3	8
Duloxetine high	−0.23 (−0.30 to −0.16)	6.0	2	9
Milnacipran standard	−0.18 (−0.30 to −0.07)	7.3	4	11
Milnacipran high	−0.10 (−0.22 to 0.07)	9.5	6	13
Mirtazapine standard	0.62 (0.11 to 0.69)	15.9	15	16

CI: confidence interval

Table 16. Sleep summary of findings

Estimates of effects, credible intervals, and certainty of the evidence of antidepressants on sleep in people with chronic pain

Bayesian network meta-analysis summary of findings table

Patient or population: people with chronic pain

Interventions: duloxetine standard dose (60 mg) and high dose (> 60 mg); milnacipran standard dose (100 mg) and high dose (> 100 mg)

Comparator (reference): placebo

Outcome: change in sleep as measured on various scales, primarily Brief Pain Inventory Sleep Item

Direction: lower is better (i.e. greater improvement in sleep compared to baseline)

Total studies: 18 **Total participants**: 6301	**Relative effect**	**Anticipated absolute effect (event rate)**			**Certainty of the evidence (CINeMA)**	**Ranking*** **(2.5% to 97.5% credible interval)**	**Interpretation of findings****
		With placebo	**With intervention**	**Difference**			
Duloxetine standard RCTs: 11 Participants: 2615	-	-	-	**SMD −0.21** (−0.30 to −0.12)	Moderate[a,d]	3 (1 to 6)	Small effect
Duloxetine high RCTs: 6 Participants: 1494	-	-	-	**SMD −0.14** (−0.27 to −0.01)	Very low[a,c,d]	4 (2 to 7)	Small effect
Milnacipran standard RCTs: 1 Participants: 799	-	-	-	**SMD −0.06** (−0.30 to 0.17)	Very low[a,c,d,e]	6 (2 to 9)	Not significantly different from placebo
Milnacipran high RCTs: 1 Participants: 797	-	-	-	**SMD −0.03** (−0.29 to 0.20)	Very low[a,c,d,e]	7 (2 to 9)	Not significantly different from placebo

Network meta-analysis-summary of findings table definitions

* Mean rank and credible intervals are presented.

Table 16. Sleep summary of findings *(Continued)*

**SMD interpretation based on clinical judgement and in line with Cohen 1988 and the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2022) as small (0.2), moderate (0.5) and large (0.8).

CI: confidence interval; **CINeMA:** Confidence in Network Meta-Analysis; **RCT:** randomised controlled trial; **SMD:** standardised mean difference

The number of participants for each antidepressant reflects the total number of participants taking the antidepressant or placebo from the studies in the network meta-analysis.

CINeMA grades of confidence in the evidence

High: further research is unlikely to change our confidence in the estimate of effect.

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

Low: 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: we are very uncertain about the estimate.

[a]Downgraded due to within-study bias.
[b]Downgraded due to imprecision in the estimate.
[c]Downgraded due to heterogeneity in the estimate.
[d]Downgraded due to incoherence in the network.
[e]Downgraded due to a small number of trials and participants; we cannot draw reliable conclusions.

Table 17. Overview of all interventions in the sleep analysis

Treatment	RCTs	Participants
Antidepressants with ≥ 200 participants		
Duloxetine standard dose	11	1640
Duloxetine high dose	6	891
Milnacipran standard dose	1	398
Milnacipran high dose	1	396
Antidepressants with < 200 participants (excluded from summaries)		
Citalopram standard dose	1	21
Duloxetine low dose	1	141
Esreboxetine unable to be categorised	1	126
Milnacipran unable to be categorised	1	97

RCT: randomised controlled trial

Participant numbers reflect the total number of participants receiving the antidepressant.

Table 18. Top-ranked antidepressants for sleep change-score analysis

	Standardised mean difference (95% CI)	Mean rank	Credible intervals	
			2.5%	97.5%
Duloxetine standard	−0.21 (−0.30 to −0.12)	3.0	1	6
Duloxetine high	−0.14 (−0.27 to −0.01)	4.4	2	7
Milnacipran standard	−0.06 (−0.30 to 0.17)	6.0	2	9
Milnacipran high	−0.03 (−0.29 to 0.20)	6.6	2	9

CI: confidence interval

Table 19. Quality of life summary of findings

Estimates of effects, credible intervals, and certainty of the evidence of antidepressants on quality of life in people with chronic pain

Bayesian network meta-analysis summary of findings table

Patient or population: people with chronic pain

Interventions: duloxetine, esreboxetine. All doses were combined for each antidepressant.

Comparator (reference): placebo

Outcome: quality of life (post-intervention scores) as reported on various scales including the EQ5D and the Fibromyalgia Impact Questionnaire

Direction: higher is better (i.e. a greater improvement in quality of life compared to baseline)

Total studies: 19 **Total participants**: 3103	**Relative effect**	**Anticipated absolute effect (event rate)**			**Certainty of the evidence (CINeMA)**	**Ranking***	**Interpretation of findings****
		With placebo	**With intervention**	**Difference**		**(2.5% to 97.5% credible interval)**	
Esreboxetine RCTs: 1 Participants: 998	-	-	-	**SMD −0.30** (−1.24 to 0.64)	Very low[e]	8 (1 to 21)	Not significantly different from placebo
Duloxetine RCTs: 6 Participants: 867	-	-	-	**SMD 0.02** (−0.56 to 0.58)	Low[a,e]	12 (4 to 20)	Not significantly different from placebo

Network meta-analysis-summary of findings table definitions

* Mean rank and credible intervals are presented

**SMD interpretation based on clinical judgement and in line with Cohen 1988 and the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2022) as small (0.2), moderate (0.5) and large (0.8).

CI: confidence interval; **CINeMA:** Confidence in Network Meta-Analysis; **RCT:** randomised controlled trial; **SMD:** standardised mean difference

The number of participants for each antidepressant reflects the total number of participants taking the antidepressant or placebo from the studies in the network meta-analysis.

CINeMA grades of confidence in the evidence

High: further research is unlikely to change our confidence in the estimate of effect.

Table 19. Quality of life summary of findings *(Continued)*

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

Low: 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: we are very uncertain about the estimate.

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[a]Downgraded due to within-study bias.
[b]Downgraded due to imprecision in the estimate.
[c]Downgraded due to heterogeneity in the estimate.
[d]Downgraded due to incoherence in the network.
[e]Downgraded due to a small number of trials and participants; we cannot draw reliable conclusions.

Table 20. Overview of all interventions in the quality-of-life post-intervention analysis

Treatment	RCTs	Participants
Antidepressants with ≥ 200 participants		
Duloxetine	6	306
Esreboxetine	1	736
Antidepressants with < 200 participants (excluded from summaries)		
Amitriptyline		181
Amitriptyline + fluoxetine	1	19
Amitriptyline + melatonin	1	21
Amitriptyline + splint	1	23
Desipramine		135
Duloxetine + pregabalin	1	39
Fluoxetine		61
Fluoxetine + melatonin	1	50
Imipramine		42
Milnacipran		53
Nortriptyline		36
Non-antidepressant interventions (excluded from summaries)		
ABT-894	1	169
Acupuncture	1	28
Cognitive behavioural therapy		199
Education	1	66
Melatonin	1	48
Pregabalin	1	63
Saffron	1	23
Terbutaline	1	40
Waitlist	1	21

RCT: randomised controlled trial

Participant numbers reflect the total number of participants receiving the antidepressant.

Table 21. Top-ranked antidepressants for quality-of-life analysis

	Standardised mean difference (95% CI)	Mean rank	Credible intervals	
			2.5%	97.5%
Esreboxetine	−0.30 (−1.24 to 0.64)	8.2	1	21
Duloxetine	0.02 (−0.56 to 0.58)	12.1	4	20

CI: confidence interval

Table 22. Patient Global Impression of Change much/very much improved summary of findings

Estimates of effects, credible intervals, and certainty of the evidence of antidepressants on Patient Global Impression of Change in people with chronic pain

Bayesian network meta-analysis summary of findings table

Patient or population: people with chronic pain

Interventions: desvenlafaxine high dose (> 50 mg); duloxetine standard dose (60 mg) and high dose (> 60 mg); esreboxetine standard dose (4-8 mg) and high dose (> 8 mg); milnacipran standard dose (100 mg) and high dose (> 100 mg)

Comparator (reference): Placebo

Outcome: Patient Global Impression of Change (PGIC) – people reporting much or very much improved (i.e. 1 or 2 on the 7-point PGIC scale)

Direction: higher is better (i.e. more people reporting much or very much improved from baseline)

Total studies: 12 **Total participants**: 6995	**Relative effect** **(OR and 95% CI)**	**Anticipated absolute effect (event rate)***			**Certainty of the evidence (CINeMA)**	**Ranking**** **(2.5% to 97.5% credible interval)**	**Interpretation of findings**
		With placebo	**With intervention**	**Difference**			
Duloxetine standard dose RCTs: 3 Participants: 974	2.29 (1.98 to 2.60)	**215 per 1000** 106/493	**382 per 1000** 184/481	**170 more per 1000**	Moderate[a]	2 (1 to 6)	Equivalent to NNTB of 5.9
Duloxetine high dose RCTs: 2 Participants: 567	2.03 (1.62 to 2.44)	**250 per 1000** 70/280	**404 per 1000** 113/287	**154 more per 1000**	Very low[a,e]	4 (1 to 7)	Equivalent to NNTB of 6.5
Milnacipran high dose RCTs: 3 Participants: 2057	1.99 (1.77 to 2.21)	**282 per 1000** 280/992	**439 per 1000** 480/1065	**157 more per 1000**	Low[a]	4 (1 to 7)	Equivalent to NNTB of 6.4
Milnacipran standard dose RCTs: 3 Participants: 2098	1.95 (1.73 to 2.17)	**303 per 1000** 320/1055	**459 per 1000** 462/1043	**156 more per 1000**	Moderate[a]	4 (1 to 7)	Equivalent to NNTB of 6.4
Esreboxetine standard dose	1.79	**291 per 1000**	**423 per 1000**	**133 more per 1000**	Very low[a,e]	5	Equivalent to NNTB of 7.5

Table 22. Patient Global Impression of Change much/very much improved summary of findings *(Continued)*

RCTs: 1 Participants: 811	(1.44 to 2.14)	80/275	226/536			(1 to 7)	
Esreboxetine high dose RCTs: 1 Participants: 550	1.63 (1.24 to 2.02)	**291 per 1000** 80/275	**401 per 1000** 110/275	**110 more per 1000**	Very low[a,e]	6 (2 to 8)	Equivalent to NNTB of 9.1
Desvenlafaxine high dose RCTs: 1 Participants: 528	1.01 (0.58 to 1.44)	**429 per 1000** 54/126	**431 per 1000** 173/402	**2 more per 1000**	Very low[a,b,e]	8 (6 to 9)	Not significantly different from placebo

Network meta-analysis-summary of findings table definitions

* Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

** Mean rank and credible intervals are presented.

CI: confidence interval; **CINeMA:** Confidence in Network Meta-Analysis; **NNTB:** number needed to treat for an additional beneficial outcome; **OR:** odds ratio; **PGIC:** Patient Global Impression of Change; **RCT:** randomised controlled trial; **VAS:** visual analogue scale

The number of participants for each antidepressant reflects the total number of participants taking the antidepressant or placebo from the studies in the network meta-analysis.

CINeMA grades of confidence in the evidence

High: further research is unlikely to change our confidence in the estimate of effect.

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

Low: 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: we are very uncertain about the estimate.

[a]Downgraded due to within-study bias.
[b]Downgraded due to imprecision in the estimate.
[c]Downgraded due to heterogeneity in the estimate.
[d]Downgraded due to incoherence in the network.
[e]Downgraded due to a small number of trials and participants; we cannot draw reliable conclusions.

Table 23. Overview of all interventions in the Patient Global Impression of Change much/very much improved analysis

Treatment	RCTs	Participants
Antidepressants with ≥ 200 participants		
Desvenlafaxine high dose	1	402
Duloxetine high dose	2	287
Duloxetine standard dose	3	481
Esreboxetine high dose	1	275
Esreboxetine standard dose	1	536
Milnacipran high dose	3	1065
Milnacipran standard dose	3	1043
Antidepressants with < 200 participants (excluded from summaries)		
Desvenlafaxine standard dose	1	131
Milnacipran dose unable to be categorised	1	79

RCT: randomised controlled trial

Participant numbers reflect the total number of participants receiving the antidepressant.

Table 24. Top-ranked antidepressants for Patient Global Impression of Change much/very much improved analysis

	Odds ratio (95% CI)	Mean rank	Credible intervals	
			2.5%	97.5%
Duloxetine standard dose	2.29 (1.98 to 2.60)	2.3	1	6
Duloxetine high dose	2.03 (1.62 to 2.44)	3.5	1	7
Milnacipran high dose	1.99 (1.77 to 2.21)	3.6	1	7
Milnacipran standard dose	1.95 (1.73 to 2.17)	3.9	1	7
Esreboxetine standard dose	1.79 (1.44 to 2.14)	4.7	1	7

Table 24. Top-ranked antidepressants for Patient Global Impression of Change much/very much improved analysis *(Continued)*

Esreboxetine high dose	1.63 (1.24 to 2.02)	5.6	2	8
Desvenlafaxine high dose	1.01 (0.58 to 1.44)	8.2	6	9

CI: confidence interval

Table 25. Patient Global Impression of Change continuous summary of findings

Estimates of effects, credible intervals, and certainty of the evidence of antidepressants on Patient Global Impression of Change in people with chronic pain

Bayesian network meta-analysis summary of findings table

Patient or population: people with chronic pain

Interventions: duloxetine low dose (< 60 mg), standard dose (60 mg), and high dose (> 60 mg)

Comparator (reference): placebo

Outcome: Patient Global Impression of Change (PGIC) measured continuously on the PGIC 1-7 scale

Direction: lower is better (1 on the scale represents 'very much improved', 7 represents 'very much worse')

Total studies: 24 **Total participants**: 8415	**Relative effect**	**Anticipated absolute effect (event rate)**			**Certainty of the evidence (CINeMA)**	**Ranking***	**Interpretation of findings**
		With placebo	**With intervention**	**Difference**		**(2.5% to 97.5% credible interval)**	
Duloxetine standard dose RCTs: 14 Participants: 3847	-	-	-	SMD −0.36 (−0.44 to −0.29)	Moderate[d]	3 (1 to 4)	Small to moderate effect
Duloxetine high dose RCTs: 14 Participants: 3520	-	-	-	SMD −0.33 (−0.40 to −0.26)	Moderate[d]	3 (2 to 5)	Small to moderate effect
Duloxetine low dose RCTs: 5 Participants: 1097	-	-	-	SMD −0.23 (−0.35 to −0.11)	Moderate[a,d]	5 (3 to 6)	Small effect

NMA-SoF table definitions

*Mean rank and credible intervals are presented.

**SMD interpretation based on clinical judgement and in line with Cohen 1988 and the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2022) as small (0.2), moderate (0.5) and large (0.8).

CI: confidence interval; **CINeMA:** Confidence in Network Meta-Analysis; **RCT:** randomised controlled trial; **SMD:** standardised mean difference

Table 25. Patient Global Impression of Change continuous summary of findings *(Continued)*

The number of participants for each antidepressant reflects the total number of participants taking the antidepressant or placebo from the studies in the network meta-analysis.

CINeMA grades of confidence in the evidence

High: further research is unlikely to change our confidence in the estimate of effect.

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

Low: 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: we are very uncertain about the estimate.

[a]Downgraded due to within-study bias.
[b]Downgraded due to imprecision in the estimate.
[c]Downgraded due to heterogeneity in the estimate.
[d]Downgraded due to incoherence in the network.
[e]Downgraded due to a small number of trials and participants; we cannot draw reliable conclusions.

Table 26. Overview of all interventions in the Patient Global Impression of Change continuous analysis

Treatment	RCTs	Participants
Antidepressants with ≥ 200 participants		
Duloxetine low dose	5	554
Duloxetine standard dose	14	2183
Duloxetine high dose	14	1838
Antidepressants with < 200 participants (excluded from summaries)		
Desvenlafaxine high dose	1	184
Desvenlafaxine standard dose	1	54
Non-antidepressant interventions (excluded from summaries)		
ABT-394	1	172
Pregabalin	2	552

RCT: randomised controlled trial

Participant numbers reflect the total number of participants receiving the antidepressant.

Table 27. Top-ranked antidepressants for Patient Global Impression of Change continuous analysis

	Standardised mean difference (95% CI)	Mean rank	Credible intervals	
			2.5%	97.5%
Duloxetine standard	−0.36 (−0.44 to −0.29)	2.7	1	4
Duloxetine high	−0.33 (−0.40 to −0.26)	3.4	2	5
Duloxetine low	−0.23 (−0.35 to −0.11)	5.0	3	6

CI: confidence interval

Table 28. Serious adverse events summary of findings

Estimates of effects, credible intervals, and certainty of the evidence for serious adverse events with antidepressants in people with chronic pain

Bayesian network meta-analysis summary of findings table

Patient or population: people with chronic pain

Interventions: desvenlafaxine high dose (> 50 mg); duloxetine low dose (< 60 mg), standard dose (60 mg), and high dose (> 60 mg); esreboxetine standard dose (4-8 mg) and high dose (> 8 mg); milnacipran standard dose (100 mg), high dose (> 100 mg), and dose unable to be categorised; mirtazapine standard dose (30 mg)

Comparator (reference): placebo

Outcome: serious adverse events (events that are life-threatening or resulting in: hospitalisation, persistent or significant disability, or death) as reported per study

Direction: lower is better (i.e. fewer people having serious adverse events)

Total studies: 71 **Total participants**: 19304	**Relative effect** **(OR and 95% CI)**	**Anticipated absolute effect (event rate)***			**Certainty of the evidence (GRADE)**	**Ranking**** **(2.5% to 97.5% credible interval)**	**Interpretation of findings**
		With placebo	**With intervention**	**Difference**			
Desvenlafaxine high dose RCTs: 2 Participants: 912	0.51 (-0.27 to 1.29)	12/221 **54 per 1000**	20/691 **28 per 1000**	**26 fewer per 1000**	Very low[a,b,c]	11 (4 to 24)	Not significantly different from placebo
Milnacipran dose unable to be categorised RCTs: 3 Participants: 272	0.66 (-0.95 to 2.27)	3/69 **43 per 1000**	5/203 **29 per 1000**	**14 fewer per 1000**	Very low[a,b,c]	15 (2 to 36)	Not significantly different from placebo
Duloxetine low dose RCTs: 4 Participants: 935	0.89 (-0.05 to 1.83)	11/462 **24 per 1000**	9/473 **21 per 1000**	**3 fewer per 1000**	Very low[a,b,c]	19 (6 to 32)	Not significantly different from placebo
Duloxetine high dose RCTs: 12 Participants: 3404	0.92 (0.43 to 1.41)	33/1601 **21 per 1000**	40/1803 **19 per 1000**	**2 fewer per 1000**	Very low[a,b,c]	19 (9 to 29)	Not significantly different from placebo

Table 28. Serious adverse events summary of findings *(Continued)*

Milnacipran standard dose RCTs: 7 Participants: 2474	0.94 (0.31 to 1.57)	22/1234 **18 per 1000**	21/1240 **17 per 1000**	**1 fewer per 1000**	Very low[a,b,c]	19 (9 to 31)	Not significantly different from placebo
Mirtazapine standard dose RCTs: 3 Participants: 484	0.99 (-0.83 to 2.81)	3/241 **12 per 1000**	3/243 **12 per 1000**	**0 fewer per 1000**	Very low[b,c]	10 (3 to 38)	Not significantly different from placebo
Milnacipran high dose RCTs: 7 Participants: 2826	1.08 (0.55 to 1.61)	28/1257 **22 per 1000**	35/1569 **24 per 1000**	**2 more per 1000**	Very low[a,b,c]	22 (11 to 32)	Not significantly different from placebo
Duloxetine standard dose RCTs: 15 Participants: 4589	1.16 (0.71 to 1.61)	34/1082 **16 per 1000**	52/2507 **19 per 1000**	**3 more per 1000**	Very low[a,b,c]	23 (13 to 32)	Not significantly different from placebo
Esreboxetine standard dose RCTs: 1 Participants: 833	2.25 (-0.69 to 5.19)	1/277 **4 per 1000**	3/556 **8 per 1000**	**4 more per 1000**	Very low[a,b,c,e]	27 (4 to 41)	Not significantly different from placebo
Esreboxetine high dose RCTs: 1 Participants: 558	2.75 (-0.35 to 5.85)	1/277 **4 per 1000**	2/281 **10 per 1000**	**6 more per 1000**	Very low[a,b,c,e]	28 (4 to 41)	Not significantly different from placebo

Network meta-analysis-summary of findings table definitions

* Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

** Mean rank and credible intervals are presented.

CI: confidence interval; **OR:** odds ratio; **RCT:** randomised controlled trial

The number of participants for each antidepressant reflects the total number of participants taking the antidepressant or placebo from the studies in the network meta-analysis.

Table 28. Serious adverse events summary of findings *(Continued)*

GRADE Working Group grades of evidence

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

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

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

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[a]Downgraded due to within-study bias.
[b]Downgraded due to imprecision in the estimate.
[c]Downgraded due to heterogeneity in the estimate.
[d]Downgraded due to incoherence in the network.
[e]Downgraded due to a small number of trials and participants; we cannot draw reliable conclusions.

Table 29. Overview of all interventions in the serious adverse events analysis

Treatment	RCTs	Participants
Antidepressants with ≥ 200 participants		
Desvenlafaxine high dose	2	691
Duloxetine high dose	12	1803
Duloxetine low dose	4	473
Duloxetine standard dose	15	2507
Esreboxetine high dose	1	281
Esreboxetine standard dose	1	556
Milnacipran high dose	7	1569
Milnacipran standard dose	7	1240
Milnacipran dose unable to be categorised	3	203
Mirtazapine standard dose	3	243
Antidepressants with < 200 participants (excluded from summaries)		
Amitriptyline high dose	1	96
Amitriptyline low dose	1	32
Amitriptyline standard dose	3	114
Amitriptyline dose unable to be categorised	1	25
Bupropion standard dose	1	54
Citalopram standard dose	2	34
Desipramine low dose	1	38
Desipramine + cognitive behavioural therapy	1	37
Desvenlafaxine standard dose	2	199
Esreboxetine dose unable to be categorised	1	134
Imipramine low dose	1	18
Imipramine standard dose	1	51
Milnacipran standard + cognitive behavioural therapy	1	17
Mirtazapine low dose	1	26
Nortriptyline low dose	2	137

Table 29. Overview of all interventions in the serious adverse events analysis *(Continued)*

Nortriptyline unable to be categorised	1	56
Nortriptyline unable to be categorised + cognitive behavioural therapy	1	41
Nortriptyline unable to be categorised + disease management	1	37
Paroxetine low dose	2	62
Paroxetine dose unable to be categorised	2	152
Reboxetine standard dose	1	18
Sertraline high dose	1	30
Trazadone + gabapentin	1	94
Venlafaxine high dose	1	82
Venlafaxine low dose	1	82
Venlafaxine standard dose	1	86
Non-antidepressant interventions (excluded from summaries)		
Carbamazepine	2	99
Cognitive behavioural therapy	3	72
Coping skills training	1	29
Disease management	1	24
Gabapentin	2	56
Nabilone	1	32
Pregabalin	3	643
Terbutaline	1	51

RCT: randomised controlled trial

Participant numbers reflect the total number of participants receiving the antidepressant.

Table 30. Top-ranked antidepressants for serious adverse events analysis

	Odds ratio (95% CI)	Mean rank	Credible intervals	
			2.5%	97.5%
Desvenlafaxine high dose	0.51 (−0.27 to 1.29)	11.4	4	24

Table 30. Top-ranked antidepressants for serious adverse events analysis *(Continued)*

Milnacipran dose unable to be categorised	0.66 (−0.95 to 2.27)	15.5	2	36
Duloxetine low dose	0.89 (−0.05 to 1.83)	18.5	6	32
Duloxetine high dose	0.92 (0.43 to 1.41)	18.8	9	29
Milnacipran standard dose	0.94 (0.31 to 1.57)	19.3	9	31
Mirtazapine standard dose	0.99 (−0.83 to 2.81)	10.0	3	38
Milnacipran high dose	1.08 (0.55 to 1.61)	21.6	11	32
Duloxetine standard dose	1.16 (0.71 to 1.61)	22.8	13	32
Esreboxetine standard dose	2.25 (−0.69 to 5.19)	26.7	4	41
Esreboxetine high dose	2.75 (−0.35 to 5.85)	28.3	4	41

CI: confidence interval

Table 31. Withdrawal summary of findings

Estimates of effects, credible intervals, and certainty of the evidence for withdrawal from studies in people with chronic pain

Bayesian network meta-analysis summary of findings table

Patient or population: people with chronic pain

Interventions: amitriptyline, desipramine, desvenlafaxine, duloxetine, esreboxetine, milnacipran, mirtazapine, nortriptyline, paroxetine, venlafaxine. All doses were combined for each antidepressant.

Comparator (reference): placebo

Outcome: withdrawal from the study (for any reason)

Direction: lower is better (i.e. fewer people withdrawing from studies)

Total studies: 152 **Total participants**: 28120	**Relative effect** **(OR and 95% CI)**	**Anticipated absolute effect (event rate)***			**Certainty of the evidence (GRADE)**	**Ranking**** **(2.5% to 97.5% credible interval)**	**Interpretation of findings**
		With placebo	**With intervention**	**Difference**			
Nortriptyline RCTs: 7 Participants: 612	0.54 (0.09 to 1.17)	**101 per 1000**	**57 per 1000**	**44 fewer per 1000** (111 fewer to 15 more)	Very low[a,b]	13 (5 to 26)	Not significantly different from placebo
Mirtazapine RCTs: 3 Participants: 510	0.99 (0.34 to 1.64)	**120 per 1000**	**119 per 1000**	**1 fewer per 1000** (76 fewer to 63 more)	Very low[b,c]	28 (11 to 52)	Not significantly different from placebo
Amitriptyline RCTs: 34 Participants: 2126	1.12 (0.85 to 1.39)	**138 per 1000**	**152 per 1000**	**14 more per 1000** (18 fewer to 44 more)	Very low[a,b,c]	31 (20 to 43)	Not significantly different from placebo
Duloxetine RCTs: 45 Participants: 10140	1.20 (1.06 to 1.34)	**207 per 1000**	**239 per 1000**	**32 more per 1000** (10 more to 52 more)	Low[a,b]	33 (24 to 43)	Equivalent to NNTH of 31
Desvenlafaxine	1.25	**450 per 1000**	**506 per 1000**	**56 more per 1000**	Very low[a,b,c]	35	Not significantly different from placebo

Table 31. Withdrawal summary of findings *(Continued)*

RCTs: 2 Participants: 1105	(0.82 to 1.68)			(48 fewer to 129 more)		(19 to 53)	
Milnacipran RCTs: 17 Participants: 5088	1.34 (1.12 to 1.56)	**254 per 1000**	**314 per 1000**	**59 more per 1000** (22 more to 93 more)	Very low[a,b]	38 (27 to 49)	Equivalent to NNTH of 17
Venlafaxine RCTs: 6 Participants: 624	140 (0.91 to 1.89)	**158 per 1000**	**208 per 1000**	**50 more per 1000** (12 fewer to 104 more)	Very low[a,b,c]	40 (21 to 59)	Not significantly different from placebo
Esreboxetine RCTs: 2 Participants: 1389	1.42 (1.01 to 1.83)	**251 per 1000**	**322 per 1000**	**71 more per 1000** (2 more to 129 more)	Very low[a,b,c]	41 (23 to 56)	Equivalent to NNTH of 31
Desipramine RCTs: 4 Participants: 368	1.57 (1.02 to 2.12)	**196 per 1000**	**276 per 1000**	**81 more per 1000** (3 more to 145 more)	Very low[a,b,c]	44 (24 to 61)	Equivalent to NNTH of 14
Paroxetine RCTs: 9 Participants: 568	1.68 (1.23 to 2.12)	**173 per 1000**	**260 per 1000**	**87 more per 1000** (32 more to 134 more)	Very low[a,b]	46 (28 to 60)	Equivalent to NNTH of 11

Network meta-analysis-summary of findings table definitions

* Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

** Mean and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

CI: confidence interval; **NNTH:** number needed to treat for an additional harmful outcome; **OR:** odds ratio; **RCT:** randomised controlled trial

The number of participants for each antidepressant reflects the total number of participants taking the antidepressant or placebo from the studies in the network meta-analysis.

GRADE Working Group grades of evidence

Table 31. Withdrawal summary of findings *(Continued)*

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

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

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

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[a]Downgraded due to within-study bias.
[b]Downgraded due to imprecision in the estimate.
[c]Downgraded due to heterogeneity in the estimate.
[d]Downgraded due to incoherence in the network.
[e]Downgraded due to a small number of trials and participants; we cannot draw reliable conclusions.

Table 32. Overview of all interventions in the withdrawal analysis

Treatment	RCTs	Participants
Antidepressants with ≥ 200 participants		
Amitriptyline	34	1326
Desipramine	4	230
Desvenlafaxine	2	885
Duloxetine	45	6082
Esreboxetine	2	978
Imipramine	5	240
Milnacipran	17	3090
Mirtazapine	3	269
Nortriptyline	7	374
Paroxetine	9	389
Venlafaxine	6	409
Antidepressants with < 200 participants (excluded from summaries)		
Amitriptyline + fluoxetine	1	31
Amitriptyline + fluphenazine	1	12
Amitriptyline + naproxen	1	19
Amitriptyline + psychotherapy	1	26
Amitriptyline + splint	1	24
Amitriptyline + support	1	26
Bupropion	1	54
Citalopram	4	76
Clomipramine	2	124
Cognitive behavioural therapy and milnacipran	1	20
Cognitive behavioural therapy and amitriptyline	1	12
Coping skills training + sertraline	1	28
Desipramine + cognitive behavioural therapy	1	37
Desipramine + lidocaine	1	34

Table 32. Overview of all interventions in the withdrawal analysis *(Continued)*

Dothiepin	2	55
Doxepin	1	30
Escitalopram	3	86
Fluoxetine	6	140
Fluphenazine	1	13
Gabapentin + nortriptyline	1	56
Maprotiline	3	98
Melatonin + amitriptyline	1	21
Mianserin	2	109
Moclobemide	1	43
Morphine + nortriptyline	1	55
Nortriptyline + cognitive behavioural therapy	1	41
Nortriptyline + disease management	1	37
Nortriptyline + morphine	1	52
Pirlindole	1	45
Pregabalin + duloxetine	1	41
Pregabalin + imipramine	1	73
Reboxetine	1	18
Sertraline	2	66
Trazodone	3	63
Trazodone + gabapentin	2	94
Trimipramine	1	18
Zimeldine	1	17
Non-antidepressant interventions (excluded from summaries)		
ABT-894	1	172
Acetaminophen (paracetamol)	1	50
Acupuncture	1	24
Aerobic exercise	1	20

Table 32. Overview of all interventions in the withdrawal analysis *(Continued)*

Carbamazepine	2	99
Cognitive behavioural therapy	7	333
Coping skills training	1	29
Cyclobenzaprine	1	42
Disease management	1	24
Education	1	71
Gabapentin	6	269
Lamotrigine	1	53
Lidocaine	1	33
Melatonin	1	21
Morphine	2	107
Naltrexone	1	67
Naproxen	1	19
Neurofeedback	1	20
Panax ginseng	1	19
Physical therapy	1	34
Pregabalin	9	919
Psychotherapy	2	116
Saffron/crocin	2	53
Support	1	24
TENS	1	50
Terbutaline	1	51
Usual treatment	1	70
Waitlist	1	24

RCT: randomised controlled trial; **TENS:** transcutaneous electrical nerve stimulation

Participant numbers reflect the total number of participants receiving the antidepressant.

Table 33. Top-ranked antidepressants for withdrawal analysis

Antidepressant	Odds ratio (95% CI)	Mean rank	Credible intervals	
			2.5%	97.5%
Nortriptyline	0.54 (0.09 to 1.17)	13.3	5	26
Mirtazapine	0.99 (0.34 to 1.64)	27.8	11	52
Amitriptyline	1.12 (0.85 to 1.39)	30.9	20	43
Duloxetine	1.20 (1.06 to 1.34)	33.4	24	43
Desvenlafaxine	1.25 (0.82 to 1.68)	35.3	19	53
Milnacipran	1.34 (1.12 to 1.56)	38.4	27	49
Venlafaxine	1.40 (0.91 to 1.89)	39.9	21	59
Esreboxetine	1.42 (1.01 to 1.83)	40.6	23	56
Desipramine	1.57 (1.02 to 2.12)	43.8	24	61
Paroxetine	1.68 (1.23 to 2.12)	46.3	28	60

CI: confidence interval

Table 34. Top-ranked antidepressant classes for withdrawal analysis.

Class	Antidepressant	Participants	Mean rank	Credible intervals	
				2.5%	97.5%
NaSSA	Mirtazapine	242	3.61	1	10
TCA	Amitriptyline Clomipramine	2593	4.33	2	7

Table 34. Top-ranked antidepressant classes for withdrawal analysis. *(Continued)*

	Desipramine				
	Dothiepin				
	Doxepin				
	Imipramine				
	Nortriptyline				
SNRI	Duloxetine	7804	6.24	4	9
	Esreboxetine				
	Milnacipran				
	Venlafaxine				
TeCA	Maprotiline	207	6.96	2	11
	Mianserin				
SSRI	Citalopram	713	7.7	4	10
	Escitalopram				
	Fluoxetine				
	Paroxetine				
	Sertraline				
	Zimeldine				

NaSSA: noradrenergic and specific serotonergic antidepressant;**SNRI:** serotonin-noradrenalin reuptake inhibitors; **SSRI:** selective serotonin reuptake inhibitors; **TCA:** tricyclic antidepressants; **TeCA:** tetracyclic antidepressants

APPENDICES

Appendix 1. Search strategies

MEDLINE

1. pain/ or exp abdominal pain/ or exp arthralgia/ or exp back pain/ or breakthrough pain/ or cancer pain/ or exp chest pain/ or chronic pain/ or earache/ or eye pain/ or facial pain/ or flank pain/ or glossalgia/ or exp headache/ or mastodynia/ or metatarsalgia/ or exp musculoskeletal pain/ or exp neck pain/ or neuralgia/ or exp nociceptive pain/ or pain, intractable/ or exp pain, postoperative/ or pain, referred/ or exp pelvic pain/ or renal colic/
2. pain.tw.
3. (headache* or migraine* or fibromyalgia* or neuralgia*).tw.
4. Fibromyalgia/
5. 1 or 2 or 3 or 4
6. exp ANTIDEPRESSIVE AGENTS/
7. exp MONOAMINE OXIDASE INHIBITORS/
8. exp NEUROTRANSMITTER UPTAKE INHIBITORS/
9. ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) and (uptake or reuptake or re uptake)).tw.
10. (noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic or pharmacotherap* or psychotropic).tw.
11. (antidpress* or anti-depress*).tw.
12. (MAOI* or RIMA).tw.
13. monoamine oxidase inhibit*.tw.

14. (Agomelatine or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Brofaromin*).tw.
15. (Bupropion or Amfebutamone or Butriptylin* or Caroxazone or Cianopramin* or Cilobamin* or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine).tw.
16. (Clorgyline or Clovoxamin* or "CX157" or Tyrima or Tririma or Demexiptilin* or Deprenyl or Desipramin* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensin* or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or "DVS-233" or Escitalopram or Etoperidone or Femoxetin* or Fluotracen or Fluoxetine or Fluvoxamin*).tw.
17. (Hyperforin or Hypericum or St John* or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramin* or "Lu AA21004" or Vortioxetine or "Lu AA24530" or Tedatioxetine or "LY2216684" or Edivoxetine or Maprotilin* or Medifoxamin* or Melitracen or Metapramin* or Mianserin or Milnacipran or Minaprin* or Mirtazapin* or Moclobemide).tw.
18. (Nefazodone or Nialamide or Nitroxazepine or Nomifensin* or Norfenfluramin* or Nortriptylin* or Noxiptilin* or Opipramol or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramin* or Tryptophan* or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).tw.
19. or/6-18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. drug therapy.fs.
25. randomly.ab.
26. trial.ab.
27. or/20-26
28. exp animals/ not humans.sh.
29. 27 not 28
30. 5 and 19 and 29
31. limit 30 to "all adult (19 plus years)"

Cochrane Central Register of Controlled Trials (CENTRAL)

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

#2 MeSH descriptor: [Monoamine Oxidase Inhibitors] explode all trees

#3 MeSH descriptor: [Neurotransmitter Uptake Inhibitors] explode all trees

#4 (((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) and (uptake or reuptake or re uptake))):ti,ab,kw (Word variations have been searched)

#5 ((noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic or pharmacotherap* or psychotropic)):ti,ab,kw (Word variations have been searched)

#6 (antidpress* or anti-depress*):ti,ab,kw (Word variations have been searched)

#7 (MAOI* or RIMA):ti,ab,kw (Word variations have been searched)

#8 (monoamine oxidase inhibit*):ti,ab,kw (Word variations have been searched)

#9 ((Agomelatine or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Brofaromin*)):ti,ab,kw (Word variations have been searched)

#10 ((Bupropion or Amfebutamone or Butriptylin* or Caroxazone or Cianopramin* or Cilobamin* or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine)):ti,ab,kw (Word variations have been searched)

#11 ((Clorgyline or Clovoxamin* or "CX157" or Tyrima or Tririma or Demexiptilin* or Deprenyl or Desipramin* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensin* or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or "DVS-233" or Escitalopram or Etoperidone or Femoxetin* or Fluotracen or Fluoxetine or Fluvoxamin*)):ti,ab,kw (Word variations have been searched)

#12 ((Hyperforin or Hypericum or St John* or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramin* or "Lu AA21004" or Vortioxetine or "Lu AA24530" or Tedatioxetine or "LY2216684" or Edivoxetine or Maprotilin* or Medifoxamin* or Melitracen or Metapramin* or Mianserin or Milnacipran or Minaprin* or Mirtazapin* or Moclobemide)):ti,ab,kw (Word variations have been searched)

#13 ((Nefazodone or Nialamide or Nitroxazepine or Nomifensin* or Norfenfluramin* or Nortriptylin* or Noxiptilin* or Opipramol or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramin* or Tryptophan* or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone)):ti,ab,kw (Word variations have been searched)

#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 ((headache* or migraine* or fibromyalgia* or neuralgia*)):ti,ab,kw (Word variations have been searched)

#16 (pain):ti,ab,kw (Word variations have been searched)

#17 MeSH descriptor: [Fibromyalgia] this term only

#18 MeSH descriptor: [Abdominal Pain] explode all trees

#19 MeSH descriptor: [Arthralgia] explode all trees

#20 MeSH descriptor: [Back Pain] explode all trees

#21 MeSH descriptor: [Back Pain] this term only

#22 MeSH descriptor: [Cancer Pain] this term only

#23 MeSH descriptor: [Chest Pain] explode all trees

#24 MeSH descriptor: [Chronic Pain] this term only

#25 MeSH descriptor: [Earache] this term only

#26 MeSH descriptor: [Eye Pain] this term only

#27 MeSH descriptor: [Facial Pain] this term only

#28 MeSH descriptor: [Flank Pain] this term only

#29 MeSH descriptor: [Glossalgia] this term only

#30 MeSH descriptor: [Headache] explode all trees

#31 MeSH descriptor: [Mastodynia] this term only

#32 MeSH descriptor: [Metatarsalgia] this term only

#33 MeSH descriptor: [Musculoskeletal Pain] explode all trees

#34 MeSH descriptor: [undefined] explode all trees

#35 MeSH descriptor: [Neuralgia] this term only

#36 MeSH descriptor: [Nociceptive Pain] explode all trees

#37 MeSH descriptor: [Pain, Intractable] this term only

#38 MeSH descriptor: [Pain, Postoperative] explode all trees

#39 MeSH descriptor: [Pain, Referred] this term only

#40 MeSH descriptor: [Pelvic Pain] explode all trees

#41 MeSH descriptor: [Renal Colic] this term only

#42 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41

#43 #14 and #42

Embase

1. *pain/ or exp abdominal pain/ or exp arthralgia/ or exp back pain/ or *breakthrough pain/ or *cancer pain/ or exp chest pain/ or *chronic pain/ or *earache/ or *eye pain/ or *facial pain/ or *flank pain/ or *glossalgia/ or exp headache/ or *mastodynia/ or *metatarsalgia/ or exp musculoskeletal pain/ or exp neck pain/ or *neuralgia/ or exp nociceptive pain/ or *pain, intractable/ or exp pain, postoperative/ or pain, referred/ or exp pelvic pain/ or *renal colic/

2. pain.tw.

3. (headache* or migraine* or fibromyalgia* or neuralgia*).tw.

4. Fibromyalgia/

5. 1 or 2 or 3 or 4

6. exp ANTIDEPRESSIVE AGENTS/

7. exp MONOAMINE OXIDASE INHIBITORS/

8. exp NEUROTRANSMITTER UPTAKE INHIBITORS/

9. ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) and (uptake or reuptake or re uptake)).tw.

10. (noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic or pharmacotherap* or psychotropic).tw.

11. (antidpress* or anti-depress*).tw.

12. (MAOI* or RIMA).tw.

13. monoamine oxidase inhibit*.tw.

14. (Agomelatine or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Brofaromin*).tw.

15. (Bupropion or Amfebutamone or Butriptylin* or Caroxazone or Cianopramin* or Cilobamin* or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine).tw.

16. (Clorgyline or Clovoxamin* or "CX157" or Tyrima or Tririma or Demexiptilin* or Deprenyl or Desipramin* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensin* or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or "DVS-233" or Escitalopram or Etoperidone or Femoxetin* or Fluotracen or Fluoxetine or Fluvoxamin*).tw.

17. (Hyperforin or Hypericum or St John* or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramin* or "Lu AA21004" or Vortioxetine or "Lu AA24530" or Tedatioxetine or "LY2216684" or Edivoxetine or Maprotilin* or Medifoxamin* or Melitracen or Metapramin* or Mianserin or Milnacipran or Minaprin* or Mirtazapin* or Moclobemide).tw.

18. (Nefazodone or Nialamide or Nitroxazepine or Nomifensin* or Norfenfluramin* or Nortriptylin* or Noxiptilin* or Opipramol or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramin* or Tryptophan* or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).tw.

19. or/6-18

20. random$.tw.

21. factorial$.tw.

22. crossover$.tw.

23. cross over$.tw.

24. cross-over$.tw.

25. placebo$.tw.

26. (doubl$ adj blind$).tw.

27. (singl$ adj blind$).tw.

28. assign$.tw.

29. allocat$.tw.

30. volunteer$.tw.

31. Crossover Procedure/

32. double-blind procedure.tw.

33. Randomized Controlled Trial/

34. Single Blind Procedure/

35. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

36. (animal/ or nonhuman/) not human/

37. 35 not 36

38. 5 and 19 and 37

39. limit 38 to (adult <18 to 64 years> or aged <65+ years>)

AMED

1. *pain/ or exp abdominal pain/ or exp arthralgia/ or exp back pain/ or *breakthrough pain/ or *cancer pain/ or exp chest pain/ or *chronic pain/ or *earache/ or *eye pain/ or *facial pain/ or *flank pain/ or *glossalgia/ or exp headache/ or *mastodynia/ or *metatarsalgia/ or exp musculoskeletal pain/ or exp neck pain/ or *neuralgia/ or exp nociceptive pain/ or *pain, intractable/ or exp pain, postoperative/ or pain, referred/ or exp pelvic pain/ or *renal colic/

2. pain.tw.

3. (headache* or migraine* or fibromyalgia* or neuralgia*).tw.

4. Fibromyalgia/

5. 1 or 2 or 3 or 4

6. exp ANTIDEPRESSIVE AGENTS/

7. exp MONOAMINE OXIDASE INHIBITORS/

8. exp NEUROTRANSMITTER UPTAKE INHIBITORS/

9. ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) and (uptake or reuptake or re uptake)).tw.

10. (noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic or pharmacotherap* or psychotropic).tw.

11. (antidpress* or anti-depress*).tw.

12. (MAOI* or RIMA).tw.

13. monoamine oxidase inhibit*.tw.

14. (Agomelatine or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Brofaromin*).tw.

15. (Bupropion or Amfebutamone or Butriptylin* or Caroxazone or Cianopramin* or Cilobamin* or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine).tw.

16. (Clorgyline or Clovoxamin* or "CX157" or Tyrima or Tririma or Demexiptilin* or Deprenyl or Desipramin* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensin* or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or "DVS-233" or Escitalopram or Etoperidone or Femoxetin* or Fluotracen or Fluoxetine or Fluvoxamin*).tw.

17. (Hyperforin or Hypericum or St John* or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramin* or "Lu AA21004" or Vortioxetine or "Lu AA24530" or Tedatioxetine or "LY2216684" or Edivoxetine or Maprotilin* or Medifoxamin* or Melitracen or Metapramin* or Mianserin or Milnacipran or Minaprin* or Mirtazapin* or Moclobemide).tw.

18. (Nefazodone or Nialamide or Nitroxazepine or Nomifensin* or Norfenfluramin* or Nortriptylin* or Noxiptilin* or Opipramol or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramin* or Tryptophan* or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).tw.

19. or/6-18

20. (random* or factorial* or placebo* or assign* or allocat* or crossover).tw.

21. (cross adj over*).tw.

22. (trial* and (control* or comparative)).tw.

23. ((blind* or mask*) and (single or double or triple or treble)).tw.

24. (treatment adj arm*).tw.

25. (control* adj group*).tw.

26. (phase adj (III or three)).tw.

27. (versus or vs).tw.

28. rct.tw.

29. RANDOM ALLOCATION/

30. DOUBLE BLIND METHOD/

31. placebos/

32. randomized controlled trials/

33. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34. 5 and 19 and 33

35. exp adult/

36. 34 and 35

PsycINFO

S29 S20 AND S28

S28 S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27

S27 (singl* OR doubl* OR trebl* OR tripl*) N3 (blind* OR mask*)

S26 clinical N3 trial* OR research N3 design OR evaluat* N3 stud* OR prospectiv* N3 stud*

S25 placebo* OR random* OR "comparative stud*"

S24 DE "Followup Studies"

S23 DE "Placebo"

S22 DE "Treatment Outcomes" OR DE "Psychotherapeutic Outcomes" OR DE "Side Effects (Treatment)" OR DE "Treatment Compliance" OR DE "Treatment Duration" OR DE "Treatment Refusal" OR DE "Treatment Termination" OR DE "Treatment Withholding"

S21 DE "Treatment Effectiveness Evaluation"

S20 S15 AND S19

S19 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S16 OR S17 OR S18

S18 DE "Neurotransmitter Uptake Inhibitors" OR DE "Atomoxetine" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Serotonin Reuptake Inhibitors"

S17 DE "Monoamine Oxidase Inhibitors" OR DE "Iproniazid" OR DE "Isocarboxazid" OR DE "Moclobemide" OR DE "Nialamide" OR DE "Pargyline" OR DE "Phenelzine" OR DE "Pheniprazine" OR DE "Tranylcypromine"

S16 DE "Antidepressant Drugs" OR DE "Bupropion" OR DE "Citalopram" OR DE "Fluoxetine" OR DE "Fluvoxamine" OR DE "Iproniazid" OR DE "Isocarboxazid" OR DE "Lithium Carbonate" OR DE "Methylphenidate" OR DE "Mianserin" OR DE "Moclobemide" OR DE "Molindone" OR DE "Nefazodone" OR DE "Nialamide" OR DE "Nomifensine" OR DE "Paroxetine" OR DE "Phenelzine" OR DE "Pheniprazine" OR DE "Pipradrol" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Sertraline" OR DE "Sulpiride" OR DE "Tranylcypromine" OR DE "Trazodone" OR DE "Tricyclic Antidepressant Drugs" OR DE "Venlafaxine" OR DE "Zimeldine"

S15 S12 OR S13 OR S14

S14 DE "Fibromyalgia"

S13 pain OR (headache* or migraine* or fibromyalgia* or neuralgia*)

S12 DE "Pain" OR DE "Aphagia" OR DE "Back Pain" OR DE "Chronic Pain" OR DE "Headache" OR DE "Myofascial Pain" OR DE "Neuralgia" OR DE "Neuropathic Pain" OR DE "Somatoform Pain Disorder"

S11 PAIN

S10 (Nefazodone or Nialamide or Nitroxazepine or Nomifensin* or Norfenfluramin* or Nortriptylin* or Noxiptilin* or Opipramol or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramin* or Tryptophan* or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone)

S9 (Hyperforin or Hypericum or St John* or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramin* or "Lu AA21004" or Vortioxetine or "Lu AA24530" or Tedatioxetine or "LY2216684" or Edivoxetine or Maprotilin* or Medifoxamin* or Melitracen or Metapramin* or Mianserin or Milnacipran or Minaprin* or Mirtazapin* or Moclobemide)

S8 (Clorgyline or Clovoxamin* or "CX157" or Tyrima or Tririma or Demexiptilin* or Deprenyl or Desipramin* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensin* or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or "DVS-233" or Escitalopram or Etoperidone or Femoxetin* or Fluotracen or Fluoxetine or Fluvoxamin*)

S7 (Bupropion or Amfebutamone or Butriptylin* or Caroxazone or Cianopramin* or Cilobamin* or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine)

S6 (Agomelatine or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Brofaromin*)

S5 monoamine oxidase inhibit*

S4 MAOI* or RIMA

S3 antidpress* or anti-depress*

S2 (noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic or pharmacotherap* or psychotropic)

S1 ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) and (uptake or reuptake or re uptake))

CINAHL

S31 S4 AND S18 AND S30

S30 S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29

S29 TX allocat* random*

S28 (MH "Quantitative Studies")

S27 (MH "Placebos")

S26 TX placebo*

S25 TX random* allocat*

S24 (MH "Random Assignment")

S23 TX randomi* control* trial*

S22 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))

S21 TX clinic* n1 trial*

S20 PT Clinical trial

S19 (MH "Clinical Trials+")

S18 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17

S17 (Nefazodone or Nialamide or Nitroxazepine or Nomifensin* or Norfenfluramin* or Nortriptylin* or Noxiptilin* or Opipramol or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramin* or Tryptophan* or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone)

S16 (Hyperforin or Hypericum or St John* or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramin* or "Lu AA21004" or Vortioxetine or "Lu AA24530" or Tedatioxetine or "LY2216684" or Edivoxetine or Maprotilin* or Medifoxamin* or Melitracen or Metapramin* or Mianserin or Milnacipran or Minaprin* or Mirtazapin* or Moclobemide)

S15 (Clorgyline or Clovoxamin* or "CX157" or Tyrima or Tririma or Demexiptilin* or Deprenyl or Desipramin* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensin* or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or "DVS-233" or Escitalopram or Etoperidone or Femoxetin* or Fluotracen or Fluoxetine or Fluvoxamin*)

S14 (Bupropion or Amfebutamone or Butriptylin* or Caroxazone or Cianopramin* or Cilobamin* or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine)

S13 (Agomelatine or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Brofaromin*)

S12 monoamine oxidase inhibit*

S11 MAOI* or RIMA

S10 antidpress* or anti-depress*

S9 (noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic or pharmacotherap* or psychotropic)

S8 ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) and (uptake or reuptake or re uptake))

S7 (MH "Neurotransmitter Uptake Inhibitors+")

S6 (MH "Monoamine Oxidase Inhibitors+")

S5 (MH "Antidepressive Agents+")

S4 S1 OR S2 OR S3

S3 (MH "Fibromyalgia")

S2 pain OR (headache* or migraine* or fibromyalgia* or neuralgia*)

S1 (MH "Pain+")

LILACS

headache$ or migraine$ or fibromyalgia$ or neuralgia$ or pain [Words] and (Nefazodone or Nialamide or Nitroxazepine or Nomifensin$ or Norfenfluramin$ or Nortriptylin$ or Noxiptilin$ or Opipramol or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin$ or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or

Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin$ or Toloxatone or Tranylcypromin$ or Trazodone or Trimipramin$ or Tryptophan$ or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone) or (Hyperforin or Hypericum or St John$ or Imipramin $ or Iprindole or Iproniazid$ or Ipsapirone or Isocarboxazid$ or Levomilnacipran or Lofepramin$ or "Lu AA21004" or Vortioxetine or "Lu AA24530" or Tedatioxetine or "LY2216684" or Edivoxetine or Maprotilin$ or Medifoxamin$ or Melitracen or Metapramin$ or Mianserin or Milnacipran or Minaprin$ or Mirtazapin$ or Moclobemide) or (Clorgyline or Clovoxamin$ or "CX157" or Tyrima or Tririma or Demexiptilin $ or Deprenyl or Desipramin$ or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensin$ or Dimetacrin$ or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or "DVS-233" or Escitalopram or Etoperidone or Femoxetin$ or Fluotracen or Fluoxetine or Fluvoxamin$) or (Bupropion or Amfebutamone or Butriptylin$ or Caroxazone or Cianopramin$ or Cilobamin$ or Cimoxatone or Citalopram or Chlorimipramin$ or Clomipramin$ or Chlomipramin$ or Clomipramine) or (Agomelatine or Amoxapine or Amineptine or Amitriptylin$ or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Brofaromin$) or ((serotonin or norepinephrine or noradrenaline or neurotransmitter$ or dopamin$) and (uptake or reuptake or re uptake)) or (noradrenerg$ or antiadrenergic or anti adrenergic or SSRI$ or SNRI$ or NARI$ or SARI$ or NDRI$ or TCA$ or tricyclic$ or tetracyclic$ or heterocyclic or pharmacotherap$ or psychotropic) or (antidpress $ or anti-depress$ or MAOI$ or RIMA or monoamine oxidase inhibit$) [Words] and randomised OR randomized OR randomisation OR randomization OR trial OR placebo OR blind OR "phase 3" OR "phase III" [Words]

Appendix 2. Network meta-analysis reporting decisions

Overview

This appendix details the decisions made in the reporting of the network meta-analyses (NMAs) in the results section of the review. For each network we took into account heterogeneity, inconsistency, and network geometry.

Substantial pain relief (50% reduction)

Networks – which model is the best fit?

Our primary analysis was a Bayesian network meta-analysis including treatment. This analysis had high heterogeneity (Tau = 0.26) and inconsistency in both unrelated mean effects and node-splitting models. We also explored networks that separated treatments into different doses, conditions and risk of bias categories and aggregated treatment by class. These networks resulted in models that had similar heterogeneity and variable indications for inconsistency but the model that included antidepressant dose reduced the estimate of heterogeneity by half (Tau = 0.11) and there was no indication of inconsistency. Therefore, the results are based on the treatment-dose model.

Pain intensity

Change scores and post-intervention

Studies in the review reported pain intensity results in two ways: change scores and post-intervention scores. Fifty studies with 14,926 participants reported change scores, 74 studies with 7703 participants reported post-intervention scores. As these two types of scores cannot be combined directly, we selected model-data combinations on the basis of parsimony, minimisation of inconsistency (identified via unrelated mean-effect models (UME) and node-splitting models), residual deviance and heterogeneity (measured as Tau) to minimise the risk of over-fitting.

Networks – which model is the best fit?

For both change-score and post-intervention analyses, we generated networks and models based on treatment and treatment dose.

Change

The treatment analysis had low heterogeneity (Tau = 0.17) and low inconsistency in the UME model, however node-splitting models could not be run due to inappropriate network geometry. Models including dose had lower heterogeneity (Tau = 0.10) and no indications for inconsistency in both UME and node-splitting models.

Post-intervention scores

The treatment analysis had high heterogeneity (Tau = 2.06) compared to change-score analysis and inconsistency in the UME model, that suggest it is not possible to fit a robust model to the data. Models including dose continued to have higher heterogeneity than the change-score analysis (Tau = 0.46), and high residual deviance across multiple studies suggesting that a robust model is unlikely to fit the data. UME models continued to show inconsistency between direct and indirect evidence, although node-splitting models showed no inconsistency within studies.

Mood

Change scores and post-intervention

Studies in the review reported pain intensity results in two ways: change scores and post-intervention scores. Thirty-eight studies with 12,985 participants reported change scores, 46 studies with 3885 participants reported post-intervention scores. As these two types of scores cannot be combined, we reported the most appropriate and robust model for the data.

Networks – which model is the best fit?

For both change-score and post-intervention analyses, the primary analysis was a Bayesian NMA including treatment.

Change

The treatment analysis had low heterogeneity (Tau = 0.09), with no inconsistency in the UME model. We were unable to run node-splitting models due to the network geometry as the majority of the network is formed from two-arm placebo-controlled studies. As the treatment-only analysis had low heterogeneity and no inconsistency, no further analyses were undertaken.

Post-intervention

This analysis had moderate heterogeneity (Tau = 0.69), with high residual deviance across multiple studies. UME models showed inconsistency between direct and indirect evidence, although node-splitting models showed no inconsistency within studies. We were unable to run any further analyses including any covariates due to small sample sizes, network geometry and the risk of over-fitting.

Adverse events

Networks – which model is the best fit?

Our primary analysis was a Bayesian NMA including treatment. This analysis had high heterogeneity (Tau = 0.49), with the UME model indicating high inconsistency and divergent transitions within the network. We were unable to run node-splitting models due to network geometry. Models including dose continued to have high heterogeneity (Tau = 0.59), and the UME model showed high inconsistency, similar to the treatment-only model. There continued to be divergent transitions within the network and low effective sample sizes, however the node-splitting models were able to run and showed no evidence of inconsistency. Due to the network geometry and inappropriateness of running extra models, no further analyses including other covariates were run. The results are based on the treatment-dose model, due to similar levels of heterogeneity and inconsistency, and the ability to run node-splitting models.

Moderate pain relief

Networks – which model is the best fit?

Our primary analysis was a Bayesian NMA including treatment. This analysis had low heterogeneity (Tau = 0.13) and no evidence of inconsistency in both UME and node-splitting models. Therefore, the results are based on a model including treatment only. Divergent transitions suggested unstable models when analysing treatment-dose networks.

Physical function

Change scores and post-intervention

Studies in the review reported physical function results in two ways: change scores and post-intervention scores. Thirty-two studies with 11,760 participants reported change scores, while 30 studies with 3645 participants reported post-intervention scores. As these two types of scores cannot be combined, we reported the most appropriate and robust model for the data.

Networks – which model is the best fit?

For both change score and post-intervention score analyses, the primary analysis was a Bayesian NMA including treatment.

Change scores

Our primary analysis was a Bayesian NMA including treatment. This analysis had low heterogeneity (Tau = 0.05), and there was little evidence of inconsistency in the UME model or node-splitting models. Using a model including dose resulted in lower heterogeneity (Tau = 0.04) and no major indications for inconsistency from both unrelated mean effect and node-splitting models.

Post-intervention scores

Our primary analysis was a Bayesian NMA including treatment. This analysis had moderate heterogeneity, higher than that of the change score analysis (Tau = 0.69) with no inconsistency in both UME and node-splitting models. Models including dose increased the heterogeneity (Tau = 0.82) but continued to show no evidence of inconsistency.

Sleep

Change scores and post-intervention

Studies in the review reported sleep results in two ways: change scores and post-intervention scores. Eighteen studies with 6301 participants reported change scores, while 18 studies with 1921 participants reported post-intervention scores. As these two types of scores cannot be combined, we reported the most appropriate and robust model for the data.

Networks – which model is the best fit?

For both change-score and post-intervention score analyses, the primary analysis was a Bayesian NMA including treatment.

Change scores

Our primary analysis was a Bayesian NMA including treatment. This analysis had low heterogeneity (Tau = 0.06), but due to the star-shaped network geometry we were unable to explore inconsistency using node-splitting models in the treatment-only network. Models including dose also had low heterogeneity (Tau = 0.11) and no indications for inconsistency in UME but node-splitting models indicated inconsistency, although these parameter estimates may be unreliable due to divergent transitions.

Post-intervention scores

The primary analysis was a Bayesian NMA including treatment. This analysis had low heterogeneity (Tau = 0.12) and no inconsistency in both UME and node-splitting models, although there were three divergent transitions. Models including dose had slightly higher heterogeneity (Tau = 0.16), but the network was disconnected requiring four studies to be removed, and there were 12 divergent transitions.

Model used

Comparing the post-intervention and change-score analyses shows that the change-score treatment network is more robust and reliable than the post-intervention network as models without divergent transitions were generated. Therefore, the results are based on a model of change scores including both treatment and dose. Results for the treatment-only model are available in the supplemental files (link provided in Appendix 3).

Quality of life

Change scores and post-intervention

Studies in the review reported pain intensity results in two ways: change scores and post-intervention scores. Twenty-seven studies with 9693 participants reported change scores, 19 studies with 3103 participants reported post-intervention scores. As these two types of scores cannot be combined, we reported the most appropriate and robust model for the data.

Networks – which model is the best fit?

For both change-score and post-intervention analyses, the primary analysis was a Bayesian NMA including treatment.

Change scores

The treatment-only analysis had high heterogeneity (Tau = 0.87), with no evidence of inconsistency in UME and node-splitting models. Models including dose continued to have higher heterogeneity (0.76), with some evidence of inconsistency in the node-splitting models for milnacipran.

Post-intervention scores

The treatment-only analysis had moderate heterogeneity (Tau = 0.55) and no evidence of inconsistency in both UME and node-splitting models, although some residual deviance was present on multiple studies. Models including dose had higher heterogeneity (Tau = 0.67) with similar levels of residual deviance.

Model used

Comparing the post-intervention and change-score analyses shows that the post-intervention score treatment network has lower heterogeneity than the change-score treatment-dose network. Therefore, the results are based on a model of post-intervention scores including treatment. The results of the change-score analyses are available in the supplemental files (link provided in Appendix 3).

Patient Global Impression of Change (PGIC)

PGIC much/very much improved

Networks – which model is the best fit?

Our primary analysis was a Bayesian NMA including treatment. This analysis had low heterogeneity (Tau = 0.12) and no evidence inconsistency in both UME and node-splitting models. However, there were several divergent transitions. Models including dose reduced the heterogeneity (Tau = 0.08) and continued to show no indications for inconsistency. There was only one divergent transition in this model. Therefore, the results are based on a model including treatment and dose. The results of the treatment-only model are included in the appendices.

PGIC continuous

Networks – which model is the best fit?

Our primary analysis was a Bayesian NMA including treatment. This analysis had low heterogeneity (Tau = 0.05) but some evidence of inconsistency in both UME and node-splitting models. Models including dose continued to have low heterogeneity (Tau = 0.05) and evidence of inconsistency. As the models were very similar, we decide to use the treatment-dose model for clinical utility. The results for the treatment-only model are available in the supplemental files (link provided in Appendix 3).

Serious adverse events

Networks – which model is the best fit?

Our primary analysis was a Bayesian NMA including treatment. This analysis had low heterogeneity (Tau = 0.13) and no inconsistency in both UME and node-splitting models. Including dose into the model did not alter the level of heterogeneity (Tau = 0.16), and continued to have no inconsistency in the UME and node-splitting models. Both treatment-only and treatment-dose models had multiple studies with high residual deviance and imprecision. As both models were very similar, we decided to use the treatment-dose model due to clinical utility. The results for treatment only are available in the supplemental files (link provided in Appendix 3).

Withdrawal

Networks – which model is the best fit?

Our primary analysis was a Bayesian NMA including treatment. This analysis had high residual deviance and relatively high heterogeneity (Tau = 0.23). We were unable to examine the model using node-splitting models due to the network geometry, as a large proportion of the model was formed of single study connections only. We decided to use this treatment model for the analysis despite the relatively high heterogeneity, as including dose or condition would increase network complexity and dilute already weakly informative edges.

Appendix 3. Statistical analyses

Where additional analyses and the supplemental files are referred to in the text, these are available on the Open Science Framework (https://osf.io/ka5hr). For additional statistical queries please contact Gavin Stewart (gavin.stewart@newcastle.ac.uk).

HISTORY

Protocol first published: Issue 4, 2021

CONTRIBUTIONS OF AUTHORS

TP, PC, CE, MS, GS, and SW conceived, designed, and gained funding for the review. HB co-ordinated the review. HB and CF were responsible for screening and selection of studies from the search results, data extraction, and risk of bias assessments. HB cleaned the data for analysis. PC, MS, and SW were responsible for decisions requiring clinical knowledge. GS undertook data analysis through network meta analyses, with support from DP. HB and GS assessed the certainty of the evidence using CINeMA. HB drafted the manuscript. All authors contributed to the interpretation of findings, and writing and editing of the manuscript. TP will be responsible for the update of this review.

DECLARATIONS OF INTEREST

Hollie Birkinshaw: none known

Claire Friedrich: none known

Peter Cole is a Consultant in anaesthesia and pain medicine and manages people with chronic pain.

Christopher Eccleston: none known

Andrew Moore: none known

David Phillippo: none known

Marc Serfaty is a Consultant Psychiatrist and manages people with mental health conditions.

Gavin Stewart: none known

Simon White: none known

Tamar Pincus had one consultancy advisory meeting with Reckitt Benckiser Group PLC in February 2020. Reckitt Benckiser Group PLC are a multinational company that produce consumer goods, including pharmacological products such as analgesics. Tamar Pincus was asked to deliver an advisory talk to the company about psychological factors that might compromise randomised controlled trials. The University of Southampton was paid for her time. This talk did not cover the use of antidepressants.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- NIHR Health Technology Assessment programme, UK

  This review is funded by the NIHR Health Technology Assessment programme through a grant awarded to Professor Tamar Pincus (Award ID: NIHR128782).
- National Institute for Health Research (NIHR), UK

  Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are a number of differences between the protocol and the review (Birkinshaw 2021).

- Updating of the background section
  - We removed the International Association for the Study of Pain (IASP) pain categories from the background, as there is currently discourse about the clinical usefulness of primary pain, and we subsequently did not categorise pain types into these. If we were to have used the IASP categories, then a number of distinct pain conditions (e.g. fibromyalgia, low back pain) would have been combined, whereas there is evidence for these types of conditions being kept separate to evaluate the effects.
  - We reference National Institute for Health and Care Excellence (NICE) guidelines to the background which were not published at time of protocol publication.
  - We have updated the literature in the How the intervention might work section for clarity, and to reflect current understanding and theories.
- Methods
  - We reported continuous pain intensity as an outcome, which was not included in the published version of the protocol. This was originally in the protocol, and was removed accidentally during the protocol editing process.
  - We separated adverse events and serious adverse events outcomes as they are defined differently, and we assessed them using separate NMAs. Therefore, we moved serious adverse events to a secondary outcome.
  - We rated studies that imputed missing data using the 'last observation carried forward' method as high risk of bias, unless attrition was very low. This rule was not explained in the protocol.
  - We stated that we would present the primary outcomes on a 0 to 100 scale. As outcomes were reported on a wide variety of scales, this was not possible. Instead, we have reported the 'number needed to treat for an additional beneficial outcome' and 'number needed to treat for an additional harmful outcome' in the summary of findings tables.
  - We planned to use threshold analysis to analyse how much evidence needed to be added for our conclusions to change. We did not undertake threshold analysis in the review as we judged the majority of evidence to be low or very low certainty; and therefore it is already likely that new evidence will affect the conclusions.
  - We have added in the criteria for antidepressant doses, being categorised as 'low', 'standard', or 'high', and clarified how we included dose in the analysis in the 'data synthesis' section (moved from the subgroup analysis section). This was done as networks would not converge when using dose as a continuous measure.
  - We omitted the 'Other bias' domain from the protocol accidentally - we did assess for this in our risk of bias assessments, and so have included this in the methods under the risk of bias section.
  - We reordered parts of the methods section regarding sensitivity analyses for clarification: we moved assessment of consistency to data synthesis and added further information regarding the sensitivity analyses to the sensitivity analysis section. We did this because the assessment of consistency was part of our main analysis methods, not as a standalone sensitivity analysis.