Efficacy and safety of antidepressants for the treatment of back pain and osteoarthritis: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE
To investigate the efficacy and safety of antidepressants for back and osteoarthritis pain compared with placebo.

DESIGN
Systematic review and meta-analysis.

DATA SOURCES
Medline, Embase, Cochrane Central Register of Controlled Trials, CINAHL, International Pharmaceutical Abstracts, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform from inception to 15 November and updated on 12 May 2020.

ELIGIBILITY CRITERIA FOR STUDY SELECTION
Randomised controlled trials comparing the efficacy or safety, or both of any antidepressant drug with placebo (active or inert) in participants with low back or neck pain, sciatica, or hip or knee osteoarthritis.

DATA EXTRACTION AND SYNTHESIS
Two independent reviewers extracted data. Pain and disability were primary outcomes. Pain and disability scores were converted to a scale of 0 (no pain or disability) to 100 (worst pain or disability). A random effects model was used to calculate weighted mean differences and 95% confidence intervals. Safety (any adverse event, serious adverse events, and proportion of participants who withdrew from trials owing to adverse events) was a secondary outcome. Risk of bias was assessed with the Cochrane Collaboration's tool and certainty of evidence with the grading of recommendations assessment, development and evaluation (GRADE) framework.

RESULTS
33 trials (5318 participants) were included. Moderate certainty evidence showed that serotonin-noradrenaline reuptake inhibitors (SNRIs) reduced back pain (mean difference −5.30, 95% confidence interval −7.31 to −3.30) at 3-13 weeks and low certainty evidence that SNRIs reduced osteoarthritis pain (−9.72, −12.75 to −6.69) at 3-13 weeks. Very low certainty evidence showed that SNRIs reduced sciatica at two weeks or less (−18.60, −31.87 to −5.33) but not at 3-13 weeks (−17.50, −42.90 to 7.89). Low to very low certainty evidence showed that tricyclic antidepressants (TCAs) did not reduce sciatica at two weeks or less (−7.55, −18.25 to 3.15) but did at 3-13 weeks (−15.95, −31.52 to −0.39) and 3-12 months (−27.0, −36.11 to −17.89). Moderate certainty evidence showed that SNRIs reduced disability from back pain at 3-13 weeks (−3.55, −5.22 to −1.88) and disability due to osteoarthritis at two weeks or less (−5.10, −7.31 to −2.89), with low certainty evidence at 3-13 weeks (−6.07, −8.13 to −4.02). TCAs and other antidepressants did not reduce pain or disability from back pain.

CONCLUSION
Moderate certainty evidence shows that the effect of SNRIs on pain and disability scores is small and not clinically important for back pain, but a clinically important effect cannot be excluded for osteoarthritis. TCAs and SNRIs might be effective for sciatica, but the certainty of evidence ranged from low to very low.

SYSTEMATIC REVIEW REGISTRATION
PROSPERO CRD42020158521.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Antidepressants are widely used for the treatment of back pain (with and without radicular symptoms) and hip and knee osteoarthritis

Most clinical practice guidelines recommend antidepressants for these conditions

Evidence supporting the use of antidepressants for back pain and hip and knee osteoarthritis is uncertain

WHAT THIS STUDY ADDS

Moderate certainty evidence shows that serotonin-noradrenaline reuptake inhibitors (SNRIs) offer a small, non-clinically relevant benefit for people with back pain and osteoarthritis

SNRIs and tricyclic antidepressants might provide clinically important benefits for sciatica, but the certainty of evidence is low to very low

Only SNRIs increased the risk of adverse events; however, the number of studies evaluating the safety of other antidepressant classes was small, trials were underpowered to detect harm, and the certainty of evidence ranged from low to very low

Introduction

Back pain (low back or neck pain with or without radicular symptoms) and osteoarthritis are leading causes of disability worldwide.[1] The prevalence of low back pain and neck pain is 7.3% and 5.0%, respectively. Osteoarthritis related hip and knee symptoms affect 12% of the global population.[2 3] In 2016, back pain and osteoarthritis pain accounted for $214.5bn (£161.0bn; €177.0bn) in healthcare spending in the US, with the highest expenditure for back pain, among all health conditions.[4]

Prescriptions for antidepressants are increasing worldwide for a range of indications.[5] Among drugs associated with dependence and withdrawal, antidepressants are the most commonly prescribed medicines in the UK, with more people prescribed antidepressants (7.2 million) than prescribed opioid analgesics (5.6 million).[6] The use of antidepressants to treat pain, especially chronic pain, is also common—antidepressants are the fourth most prescribed

medicine for low back pain in the US. More than one quarter of Americans with chronic low back pain are prescribed an antidepressant within three months of a first diagnosis.[7] In Quebec, Canada, the tricyclic antidepressant (TCA) amitriptyline and its active metabolite nortriptyline are commonly prescribed for pain, representing 48.4% and 57.4% of all prescriptions for these antidepressants, respectively.[8] In the UK, 16% of prescriptions for antidepressants in children and adolescents are for pain, and from 2003 to 2014 prescriptions for antidepressants in these age groups almost tripled.[9] The widespread use of antidepressants for pain also occurs in middle income countries. Amitriptyline is widely used in primary care in South Africa, mostly for osteoarthritis. This accounts for just over a quarter of all amitriptyline prescribed.[10]

Antidepressants are endorsed by most (75%) clinical practice guidelines for low back pain[11] and by two recently published osteoarthritis guidelines.[12 13] The American College of Physicians, for example, recommends the serotonin-noradrenaline reuptake inhibitor (SNRI) duloxetine for low back pain.[14] The UK National Institute for Health and Care Excellence recommends amitriptyline or duloxetine as the preferred treatment for people with different forms of neuropathic pain, including back pain with radicular symptoms.[15] Osteoarthritis guidelines, such as those from the Osteoarthritis Research Society International (OARSI) and the American College of Rheumatology recommend duloxetine for pain management.[12 13] In the OARSI guideline, the focus is on people with osteoarthritis who have concomitant depression or widespread pain, or both. Evidence supporting the use of antidepressants is, however, uncertain. Systematic reviews of antidepressants for back pain and osteoarthritis have either not included several published trials,[16 17] considered only one type of antidepressant (eg, duloxetine),[18] or failed to assess the certainty of evidence.[18] None of the existing reviews included unpublished records from trial registries. Reliance on published data alone has been shown to overestimate the efficacy of drug interventions for pain.[19] To close this gap in knowledge, we systematically investigated the efficacy and safety of antidepressants in people with back pain (including sciatica) or hip or knee osteoarthritis.

Methods
Data sources and searches
The review protocol was prospectively registered on PROSPERO (CRD42020158521) and our findings are reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[20] We searched Medline, Embase, Cochrane Central Register of Controlled Trials, CINAHL, International Pharmaceutical Abstracts, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform from inception to 15 November and updated the searches on 12 May 2020 (supplemental file 1). Two authors (GEF,

MOK) independently screened records by titles and abstracts, and two authors (GEF, JZ) read full texts of potentially eligible studies to determine eligibility (see supplemental file 2 for a list of excluded trials with reasons). Any disagreements were resolved by consensus.

Eligibility criteria
We included randomised controlled trials that compared any antidepressant drug with placebo in participants with back pain (neck or low back pain with or without radicular symptoms) or hip or knee osteoarthritis, or both. Symptoms of any duration were included. Trials including drug combinations were eligible if the treatment contrast between groups was antidepressant versus placebo. The placebo comparator could be active (a substance that has no known effect on pain but might mimic the adverse effects of antidepressants) or inert (a substance that is not thought to have a therapeutic or adverse effect). We included reports published in peer reviewed journals as well as unpublished data posted on trial registry platforms (ClinicalTrials.gov and WHO International Clinical Trials Registry Platform). Trials that reported data on either pain, disability, or adverse events were included. No restrictions were placed on language or publication date. We excluded studies that included participants with serious spinal conditions (eg, fractures, cancer) and rheumatic conditions (eg, rheumatoid arthritis), unless these studies also included participants with back pain or hip or knee osteoarthritis, or a combination of these, and their data were reported separately. We considered studies to be eligible when participants received previous back or osteoarthritis surgery but excluded studies that evaluated immediate postoperative pain management (ie, surgery within past month). Abstracts from conferences were also excluded.

Data extraction
Two authors (GEF, JZ) independently extracted data. Whenever possible, for each outcome we extracted post-treatment means, standard deviations, and number of participants in each group. When post-treatment scores were not reported, we extracted data according to the hierarchy of between group differences and corresponding 95% confidence intervals at follow-up and then pre-treatment to post-treatment within group change scores. When a study did not report standard deviations, we used estimation methods recommended by the Cochrane handbook for systematic reviews of interventions.[21] Cochrane's RevMan calculator was used to estimate standard deviations.[22] These methods were used to estimate standard deviations for pre-treatment to post-treatment within group change scores, and to estimate standard deviations for between group differences. Briefly, we used the standard error and number of participants in each group to estimate standard deviations from pre-treatment to post-treatment within group change scores. To estimate standard deviations from between

group differences, we used P values, number of participants, and between group mean differences to obtain standard errors and thus obtain the standard deviation. For crossover trials, we followed guidance from the Cochrane handbook[21] and extracted data from the pre-crossover and post-crossover periods as if the trial were a parallel trial, as this is a conservative approach. When data were not available in the published manuscript, we sought and, when available, extracted data on safety from the trial registry.

Outcomes
The primary outcomes were pain intensity and disability. Adverse events were a secondary outcome. Adverse events included the number of participants who experienced any adverse event (as defined by each study), experienced any serious adverse event (as defined by each study), and withdrew because of adverse effects.

Risk of bias and certainty of evidence
Two reviewers (GEF, MOK) rated risk of bias of trials using the Cochrane Collaboration risk of bias tool.[23] Disagreements were resolved by consensus. We assessed the certainty of evidence using the grading of recommendations assessment, development and evaluation (GRADE) framework.[24] Certainty of evidence refers to the confidence that the true effect lies in a particular range.[25] The certainty of evidence was downgraded by one level if a serious flaw was present in the domains of limitations in study design, inconsistency, imprecision, and small study bias. We did not downgrade for indirectness because patients, interventions, and comparators were similar across comparisons (see supplemental file 3 for a description of the GRADE framework used). The certainty of evidence was then classified as high, moderate, low, or very low. High certainty means we are confident that the true effect lies close to that of the estimate of the effect. Moderate certainty means 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 means our confidence in the effect estimate is limited; the true effect might be substantially different from the estimate of the effect. Very low certainty means we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.[25]

Data synthesis and analysis
We classified follow-up times into two weeks or less, 3-13 weeks, 3-12 months, and more than 12 months. In studies with multiple time points, we extracted data from the time point closest to two weeks and three, six and 12 months. When trials had multiple treatment groups, we divided the number of participants in the placebo group by the number of treatment groups. For dichotomous outcomes, both the number of events and the sample size were divided by the number of treatment groups.[21]

To facilitate the interpretation of our results, we converted pain and disability scores to a common 0-100 scale, with 0 denoting no pain or disability and 100 denoting the worst possible pain or disability. This was done because benchmarks for clinically important differences in pain and disability are expressed in points, usually on a 0-100 scale, and not in proportions of a standard deviation.[26 27] Raw scores were thus expressed as a percentage of the maximum possible score on that scale, as done in previous systematic reviews.[16 28 29] Supplemental files 4 and 5 present details on the pain and disability measures used by studies, and conversion procedures. Mean differences (95% confidence intervals) were calculated for continuous outcome measures, and risk ratios (95% confidence intervals) were calculated for dichotomous outcomes. Statistical heterogeneity in each meta-analysis was determined by means of the I^2 test. A random effects model was used across all comparisons. We grouped antidepressants based on their drug class. A pooled between group mean difference of 10 points (on a 0-100 scale) was considered by us to be the threshold for the smallest worthwhile effect for pain and disability.[30] Pooled mean differences between groups below this threshold were considered clinically unimportant. This threshold has been used in other reviews of drug treatments for back pain,[17 31 32] and it is also the recommended threshold for pain and disability in osteoarthritis.[33 34] We used funnel plots to test for small study effects when at least 10 trials were available within a comparison.[21] The Egger's test was used to investigate small study effects. For comparisons when a funnel plot was available, we downgraded the certainty of evidence when the Egger's test result was significant (two tailed P<0.05). When a funnel plot was not available, we downgraded the certainty of evidence if more than 25% of the participants were from small studies (<100 participants in each arm).[21] For continuous outcomes, we calculated the mean difference between groups and the respective standard error in Comprehensive Meta-analysis V3 and entered these data in RevMan version 5.3 using the Generic inverse variance method to obtain forest plots. For dichotomous outcomes, we used the Mantel-Haenszel method in RevMan version 5.3.

Exploratory meta-regression
We performed meta-regression to explore the moderator effects of risk of bias (high risk of bias if at least one domain was classified as high risk of bias or more than half of the domains were classified as unclear), industry sponsor (yes or no), small study effects (<100 participants in each arm), depression listed as inclusion criteria (yes or no), and dose of antidepressant on pain. For this analysis we grouped all antidepressant classes together.

Patient and public involvement
No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for the design of the study

owing to lack of funding to include them as partners in this review. No patients were asked to advise on interpretation or writing up of results. Results of this review will be disseminated to the relevant patient organisations.

Results
Overall, 2771 records were retrieved. Of these, 1930 records were screened after removal of duplicates and 1795 were excluded based on titles and abstracts. Of 131 potentially relevant trials screened for eligibility, 33 trials enrolling 5318 participants were included (fig 1). Most trials (n=28, 84.9%) used a parallel group design, whereas five (15.2%) used a crossover design with washout periods ranging from one week to two weeks.[35-39] Fourteen trials were sponsored by industry,[38] [40-52] and sponsorship source was unclear in five trials.[39] [53-56] All but one trial reported data from participants with chronic pain.[57] Only five trials restricted inclusion to participants with depression.[45] [53-55] [58] In two other trials, between 40% and 50% of participants had depression.[46] [47] Others either excluded participants with depressive disorder or did not mention depression in the eligibility criteria. The median duration of the drug regimen was eight weeks. Six antidepressant drug classes were evaluated, including SNRIs (15 trials), TCAs (n=14 trials), serotonin reuptake inhibitors (SSRIs, n=3), noradrenaline-dopamine reuptake inhibitors (NDRIs, n=1), serotonin antagonist and reuptake inhibitors (SARIs, n=1), and tetracyclic antidepressants (n=1). Supplemental file 6 provides details of the included trials.

For 26 of 33 trials, at least one domain was classified as high risk of bias (supplemental file 7). Twenty six trials were unclear in describing the methods used to conceal allocation and therefore were at unclear risk of selection bias. One trial was at high risk of performance bias owing to inadequate blinding of participants, and 13 were at unclear risk of performance bias. One trial was at high risk of detection bias owing to inadequate blinding of participants, and another 12 trials were at unclear risk of detection bias. Eighteen trials were at high risk of attrition bias. Five and 14 trials were at high and unclear risk of reporting bias, respectively.

Back pain
Nineteen trials (23 comparisons) determined the efficacy of antidepressants for back pain. Of these, 16 trials reported data for low back pain, one trial reported data for neck pain, and two trials reported data for low back and neck pain. Only one trial evaluated outcomes at 3-12 months. This trial investigated the efficacy of TCAs in participants with back pain. No trials evaluated outcomes at more than 12 months. Only pain outcomes were measured at two weeks or less of follow-up.

Moderate certainty evidence showed that SNRIs reduce pain at two weeks or less (mean difference −3.67, 95% confidence interval −5.91 to −1.42; three trials, 1068 participants) and 3-13 weeks (−5.30, −7.31 to −3.30; four trials, 1415 participants) (fig 2 and

table 1). SNRIs were also shown to reduce disability at 3-13 weeks (−3.55, −5.22 to −1.88; four trials, 1423 participants; supplemental file 8 and table 2). The effect of SNRIs was small and below this review's predetermined threshold of clinical importance. Low to very low certainty evidence showed that TCAs did not reduce pain at two weeks or less (−0.86, −5.40 to 3.68; three trials, 145 participants), 3-13 weeks (−9.96, −21.50 to 1.58; seven trials, 591 participants), and 3-12 months (−7.81, −15.63 to 0.01; one trial, 118 participants) (fig 3). Evidence ranging from low to very low certainty showed no benefit of a range of antidepressant classes, including SSRIs, tetracyclic antidepressants, SARIs, and NDRIs for pain and disability across follow-ups of two weeks or less, 3-13 weeks, and 3-12 months.

A post hoc sensitivity analysis explored the effect of removing one trial from the pooled estimates for back pain.[59] The participants in this trial had neck pain, received a dose of amitriptyline (5 mg/day) lower than the minimum dose recommended for pain relief (10-25 mg/day), and reported unexpectedly large improvements in pain and disability compared with other studies. That trial was also at high risk of attrition bias from lack of intention-to-treat analysis and a large proportion of participants lost to follow-up. The exclusion of this trial fully explained the heterogeneity for disability and heterogeneity was reduced from 92% to 7% for pain. After excluding this trial, TCAs were found to significantly reduce pain (−5.37, −9.93 to −0.80) and disability (−7.24, −11.25 to −3.22), but the effects were still small and below this review's predetermined threshold for clinical importance.

Sciatica
Six trials reported data for sciatica. No trials evaluated outcomes at more than 12 months. Very low certainty evidence showed that SNRIs reduce pain at two weeks or less (−18.60, −31.87 to −5.33; one trial, 50 participants) but not at 3-13 weeks (−17.50, −42.90 to 7.89; three trials, 96 participants). Low to very low certainty evidence showed that TCAs did not reduce pain at two weeks or less (−7.55, −18.25 to 3.15; two trials, 94 participants) but did at 3-13 weeks (−15.95, −31.52 to −0.39; two trials, 114 participants) and 3-12 months (−27.0, −36.11 to −17.89; one trial, 60 participants) follow-ups (fig 4 and table 1). Tricyclic antidepressants did not reduce disability at two weeks or less and at 3-13 weeks but did at 3-12 months (supplemental file 9 and table 2).

Osteoarthritis
Eight trials (eight comparisons) evaluated the efficacy of antidepressants in participants with knee osteoarthritis. All trials were of SNRIs. None of the osteoarthritis trials included participants with hip osteoarthritis or evaluated outcomes at 3-12 months or more than 12 months. Moderate certainty evidence showed that SNRIs reduce pain at two weeks or less (−4.66, −6.28 to −3.04; four trials, 1328 participants) and low certainty evidence that SNRIs reduce pain
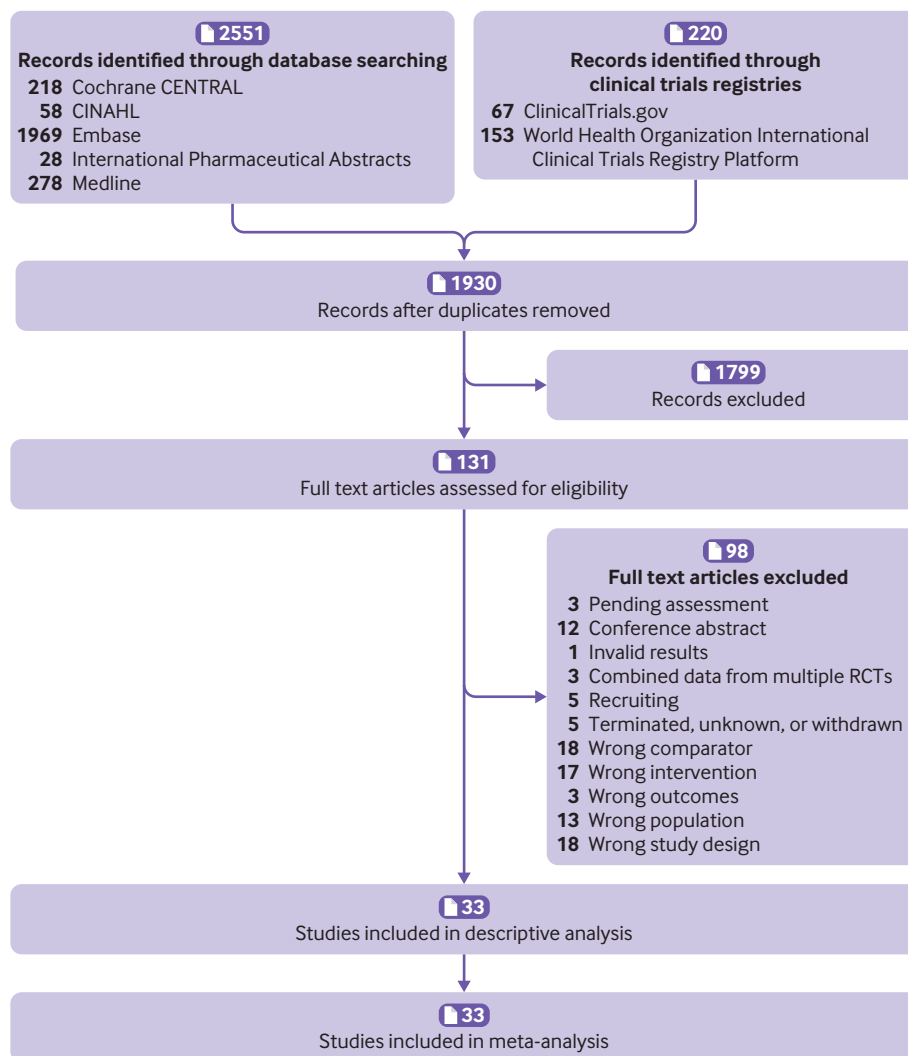
Fig 1 | Study flow diagram. RCTs=randomised controlled trials

at 3-13 weeks (−9.72, −12.75 to −6.69; eight trials, 1941 participants) (fig 5 and table 1). Low certainty evidence showed that SNRIs reduce disability at two weeks or less (−5.10, −7.31 to −2.89; one trial, 353 participants) and 3-13 weeks (−6.07, −8.13 to −4.02; seven trials, 1810 participants) of follow-up (supplemental file 10 and table 2). The effect of SNRIs was small and below this review's predetermined threshold of clinical importance—however, the lower limit of the confidence interval did contain clinically important effects for pain, but not for disability.

Safety
Twenty one trials (25 comparisons) enrolling 4107 participants determined the safety of antidepressants for back pain and osteoarthritis. The type and reporting of adverse events varied noticeably across trials. Nausea was reported as the most prevalent adverse event in eight trials.[43 44 50-52 56 60 61]

Low certainty evidence showed that SNRIs increase the risk of any adverse event (62.5% v 49.7%; relative risk 1.23, 95% confidence interval 1.16 to 1.30; 13 trials, 3447 participants), but not serious adverse

events (1.6% v 1.3%; 1.12, 0.61 to 2.07; 10 trials, 3309 participants) (supplemental files 11 and 12 and table 3). Participants receiving SNRIs were also more likely to drop out of the study because of adverse events (12.4% v 5.3%; 2.16, 1.71 to 2.73) (supplemental file 13 and table 3). Supplemental files 14 to 17 present funnel plots assessing small study effects in comparisons with more than 10 trials. Although other antidepressants, such as TCAs, SSRIs, tetracyclic antidepressants, NDRIs, and SARIs did not seem to increase the risk of adverse events or drop-outs owing to adverse events, the limited number of trials and large uncertainty around the risk estimates limit the ability of this systematic review and meta-analysis to determine the safety of these classes of antidepressants for back pain, sciatica, and osteoarthritis.

Exploratory sensitivity analyses
No interaction was found between risk of bias, study size, industry sponsorship, depression diagnosis, and daily dosage of duloxetine and treatment effects. The meta-regression analysis of dose-response effects of duloxetine in three different doses (20, 60, and 120

Comparisons	Mean difference	SE	Antidepressants total	Placebo total	Mean difference (95% CI), IV, random	Weight (%)	Mean difference (95% CI), IV, random
SNRI (≤2 weeks)							
Skljarevski 2010 (duloxetine 60 mg/day)[44]	-6.7	2.76	111	116		17.2	-6.70 (-12.11 to -1.29)
Skljarevski 2009 (duloxetine 120 mg/day)[43]	-4.7	3.97	108	37		8.3	-4.70 (-12.48 to 3.08)
Konno 2016 (duloxetine 60 mg/day)[40]	-3.3	1.5	230	226		58.1	-3.30 (-6.24 to -0.36)
Skljarevski 2009 (duloxetine 60 mg/day)[43]	-1.6	3.93	108	38		8.5	-1.60 (-9.30 to 6.10)
Skljarevski 2009 (duloxetine 20 mg/day)[43]	-0.9	4.06	56	38		7.9	-0.90 (-8.86 to 7.06)
Subtotal			613	455		100.0	-3.67 (-5.91 to -1.42)
Test for heterogeneity: τ^2=0.00; χ^2=2.08, df=4, P=0.72; I^2=0%							
Test for overall effect: Z=3.21, P=0.001							
SNRI (3-13 weeks)							
Skljarevski 2010 (duloxetine 60 mg/day)[44]	-8.2	2.8	111	116		13.4	-8.20 (-13.69 to -2.71)
Skljarevski 2009 (duloxetine 60 mg/day)[43]	-6.3	3.93	108	38		6.8	-6.30 (-14.00 to 1.40)
Skljarevski 2010 (duloxetine 60 mg/day)[42]	-6.0	2.12	195	199		23.3	-6.00 (-10.16 to -1.84)
Skljarevski 2009 (duloxetine 120 mg/day)[43]	-5.8	3.97	108	37		6.6	-5.80 (-13.58 to 1.98)
Konno 2016 (duloxetine 60 mg/day)[40]	-4.7	1.55	209	200		43.6	-4.70 (-7.74 to -1.66)
Skljarevski 2009 (duloxetine 20 mg/day)[43]	0.8	4.06	56	38		6.4	0.80 (-7.16 to 8.76)
Subtotal			787	628		100.0	-5.30 (-7.31 to -3.30)
Test for heterogeneity: τ^2=0.00; χ^2=3.67, df=5, P=0.60; I^2=0%							
Test for overall effect: Z=5.18, P<0.001							
SSRI (≤ 2 weeks)							
Dickens 2000 (paroxetine 20 mg/day)[45]	-4.3	4.98	44	48		100.0	-4.30 (-14.06 to 5.46)
Subtotal			44	48		100.0	-4.30 (-14.06 to 5.46)
Test for heterogeneity: Not applicable							
Test for overall effect: Z=0.86, P=0.39							
SSRI (3-13 weeks)							
Dickens 2000 (paroxetine 20 mg/day)[45]	0.0	5.02	44	48		49.4	0.00 (-9.84 to 9.84)
Atkinson 1999 (paroxetine 30 mg/day)[72]	2.5	7.26	22	14		23.6	2.50 (-11.73 to 16.73)
Atkinson 2007 (fluoxetine 16-514 ng/mL)[71]	3.5	6.8	31	11		26.9	3.50 (-9.83 to 16.83)
Subtotal			97	73		100.0	1.53 (-5.38 to 8.45)
Test for heterogeneity: τ^2=0.00; χ^2=0.19, df=2, P=0.91; I^2=0%							
Test for overall effect: Z=0.43, P=0.66							

Scale: -50 -25 0 25 50
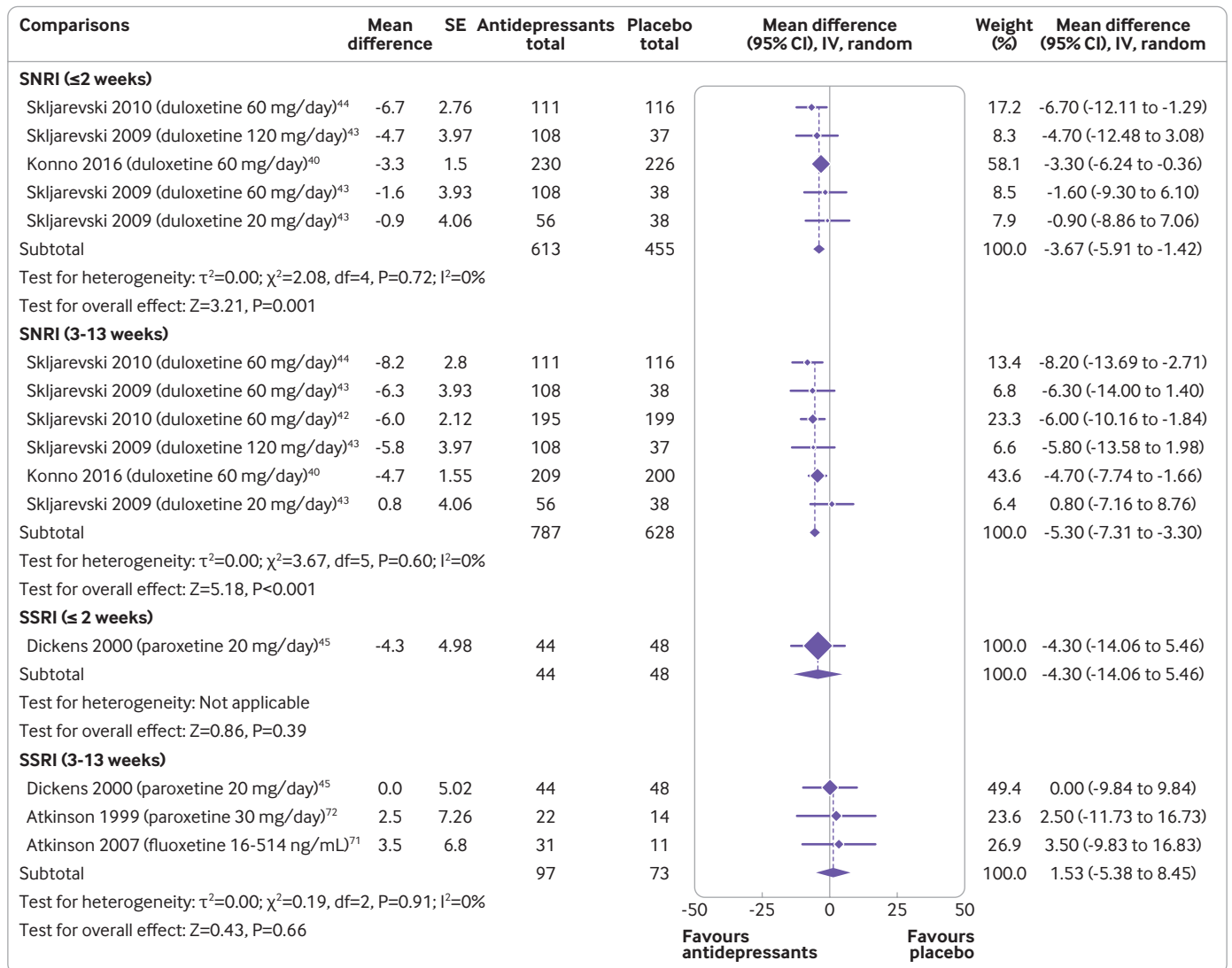Favours antidepressants ← → Favours placebo

Fig 2 | Mean differences (95% confidence intervals) for pain in trials assessing the efficacy of antidepressants for back pain. Pain is expressed on a 0-100 scale. Studies are ordered by effect size. SE=standard error; IV=inverse variance; SNRI=serotonin-noradrenaline reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors; TCA=tricyclic antidepressants; NDRI=noradrenaline-dopamine reuptake inhibitors; SARI=serotonin antagonist and reuptake inhibitors

mg/day) showed no statistically significant difference between dose intensities (P=0.13). For all doses of duloxetine, point estimates of change in pain scores were below the threshold of clinical importance, although for 60 mg/day and 120 mg/day the lower limits of the confidence interval could suggest clinically important effects (supplemental file 18).

Discussion

We found moderate certainty evidence that SNRIs reduce pain and disability in people with back pain up to three months, but these effects are unlikely to be clinically important. For osteoarthritis, we found moderate certainty evidence that SNRIs reduce pain and disability up to three months, and a clinically important effect on pain cannot be excluded. Low certainty evidence showed that TCAs were ineffective for back pain and related disability. Tricyclic antidepressants and SNRIs might reduce pain in people with sciatica. In our review, only SNRIs statistically significantly increased the risk of adverse events. However, the number of studies evaluating the safety of other antidepressant classes was small, trials were underpowered to detect harm, and the certainty of evidence ranged from low to very low.

Strengths and weaknesses of this study

Our review has several strengths. We registered this review prospectively and performed a comprehensive literature search, including searches on clinical trial registries. We also complied with the PRISMA statement.[20] The threshold for clinical importance (≥10 points on a 0-100 scale) used in our review was prespecified and has been widely used in the literature on back pain[17 31 32] and osteoarthritis.[33 34] We have also provided clinically interpretable effect estimates on a 0-100 scale, whereas previous reviews had presented effect sizes in terms of units of standard deviation.[17 18]

Table 1 | Summary of findings and certainty of evidence for pain

	Summary of findings		Certainty of evidence				
	No of participants (No of trials)	Mean difference (95% CI), 0-100	Study design	Inconsistency	Imprecision	Small study effects	Certainty of evidence
Back pain							
SNRI:							
≤2 weeks	1068 (3)	−3.67 (−5.91 to −1.42)	Downgraded*	Not downgraded	Not downgraded	Not downgraded	Moderate
3-13 weeks	1415 (4)	−5.30 (−7.31 to −3.30)	Downgraded*	Not downgraded	Not downgraded	Not downgraded	Moderate
SSRI:							
≤2 weeks	92 (1)	−4.30 (−14.06 to 5.46)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
3-13 weeks	170 (3)	1.53 (−5.38 to 8.45)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
TCAs:							
≤2 weeks	145 (3)	−0.86 (−5.40 to 3.68)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
3-13 weeks	591 (7)	−9.96 (−21.50 to 1.58)	Downgraded*	Downgraded†	Not downgraded	Downgraded§	Very low
3-12 months	118 (1)	−7.81 (−15.63 to 0.01)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
NDRI:							
3-13 weeks	44 (1)	−1.0 (−12.23 to 10.23)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
SARI:							
3-13 weeks	40 (1)	−5.40 (−22.94 to 12.14)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
Tetracyclic antidepressants:							
3-13 weeks	34 (1)	−4.50 (−20.43 to 11.43)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
Sciatica							
SNRI:							
≤2 weeks	50 (1)	−18.60 (−31.87 to −5.33)	Downgraded*	Not downgraded	Downgraded‡	Downgraded§	Very low
3-13 weeks	96 (3)	−17.50 (−42.90 to 7.89)	Downgraded*	Downgraded†	Downgraded‡	Downgraded§	Very low
TCAs:							
≤2 weeks	94 (2)	−7.55 (−18.25 to 3.15)	Downgraded*	Not downgraded	Downgraded‡	Downgraded§	Very low
3-13 weeks	114 (2)	−15.95 (−31.52 to −0.39)	Downgraded*	Downgraded†	Downgraded‡	Downgraded§	Very low
3-12 months	60 (1)	−27.0 (−36.11 to −17.89)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
Osteoarthritis							
SNRI:							
≤2 weeks	1328 (4)	−4.66 (−6.28 to −3.04)	Downgraded*	Not downgraded	Not downgraded	Not downgraded	Moderate
3-13 weeks	1941 (8)	−9.72 (−12.75 to −6.69)	Downgraded*	Downgraded†	Not downgraded	Not downgraded	Low

SNRI=serotonin-noradrenaline reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors; TCA=tricyclic antidepressants; NDRI=noradrenaline-dopamine reuptake inhibitors.
*Downgraded by one level because >25% of participants in this comparison were from studies at high risk of bias.
†Downgraded by one level because heterogeneity (I^2) >50%.
‡Downgraded by one level because the limits of the 95% confidence interval were 20 points different to smallest worthwhile effect.
§Downgraded by one level owing to small study bias.

Table 2 | Summary of findings and certainty of evidence for disability

	Summary of findings		Certainty of evidence				
	No. of participants (No of trials)	Mean difference (95% CI), 0-100	Study design	Inconsistency	Imprecision	Small study effects	Certainty of evidence
Back pain							
SNRI:							
3-13 weeks	1423 (4)	−3.55 (−5.22 to −1.88)	Downgraded*	Not downgraded	Not downgraded	Not downgraded	Moderate
SSRI:							
3-13 weeks	1 (92)	−2.20 (−8.08 to 3.68)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
TCAs:							
3-13 weeks	439 (4)	−12.94 (−26.47 to 0.59)	Downgraded*	Downgraded†	Downgraded‡	Downgraded§	Very low
3-12 months	118 (1)	−4.30 (−10.49 to 1.89)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
SARI:							
3-13 weeks	40 (1)	2.60 (−6.79 to 11.99)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
Sciatica							
SNRI:							
3-13 weeks	8 (1)	−4.40 (−19.92 to 11.12)	Downgraded*	Not downgraded	Downgraded‡	Downgraded§	Very low
TCAs:							
≤2 weeks	60 (1)	−5.00 (−12.23 to 2.23)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
3-13 weeks	116 (2)	−8.42 (18.18 to 1.35)	Downgraded*	Downgraded†	Not downgraded	Downgraded§	Very low
3-12 months	60 (1)	−20.0 (−27.74 to −12.26)	Downgraded*	Not downgraded	Downgraded‡	Downgraded§	Very low
Osteoarthritis							
SNRI:							
≤2 weeks	353 (1)	−5.10 (−7.31 to −2.89)	Downgraded*	Not downgraded	Not downgraded	Not downgraded	Moderate
3-13 weeks	1810 (7)	−6.07 (−8.13 to −4.02)	Downgraded*	Downgraded†	Not downgraded	Not downgraded	Low

SNRI=serotonin-noradrenaline reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors; TCA=tricyclic antidepressants; NDRI=noradrenaline-dopamine reuptake inhibitors.
*Downgraded by one level because >25% of participants in this comparison were from studies at high risk of bias.
†Downgraded by one level because heterogeneity (I^2) >50%.
‡Downgraded by one level because the limits of the 95% confidence interval were 20 points different to smallest worthwhile effect.
§Downgraded by one level owing to small study bias.

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Comparisons	Mean difference	SE	Antidepressants total	Placebo total	Mean difference (95% CI), IV, random	Weight (%)	Mean difference (95% CI), IV, random
TCAs (≤2 weeks)							
Hameroff 1985 (doxepin 300 mg/day)[55]	-4.6	5.49	27	24		17.8	-4.60 (-15.36 to 6.16)
Jenkins 1976 (imipramine 75 mg/day)[47]	-3.0	9.23	23	21		6.3	-3.00 (-21.09 to 15.09)
Schliessbach 2018 (imipramine 75 mg/day)[36]	0.2	2.66	25	25		75.9	0.20 (-5.01 to 5.41)
Subtotal			75	70		100.0	-0.86 (-5.40 to 3.68)
Test for heterogeneity: τ²=0.00; χ²=0.68, df=2, P=0.71; I²=0%							
Test for overall effect: Z=0.37, P=0.71							
TCAs (3-13 weeks)							
Maarrawi 2018 (amitriptyline 5 mg/day)[59]	-27.8	1.66	104	108		16.4	-27.80 (-31.05 to -24.55)
Hameroff 1985 (doxepin 300 mg/day)[55]	-18.1	6.95	27	24		13.5	-18.10 (-31.72 to -4.48)
Atkinson 1998 (nortriptyline 100 mg/day)[73]	-7.9	4.68	28	29		15.0	-7.90 (-17.07 to 1.27)
Gould 2020 (desipramine 15-65 ng/mL)[69]	-6.0	6.64	37	33		13.7	-6.00 (-19.01 to 7.01)
Atkinson 2007 (desipramine 5-242 ng/mL)[71]	-4.0	7.09	30	11		13.4	-4.00 (-17.90 to 9.90)
Jenkins 1976 (imipramine 75 mg/day)[47]	-2.0	8.49	23	21		12.3	-2.00 (-18.64 to 14.64)
Urquhart 2018 (amitriptyline 25 mg/day)[70]	-1.1	3.45	58	58		15.7	-1.10 (-7.86 to 5.66)
Subtotal			307	284		100.0	-9.96 (-21.50 to 1.58)
Test for heterogeneity: τ²=208.82; χ²=72.79, df=6, P<0.001; I²=92%							
Test for overall effect: Z=1.69, P=0.09							
TCAs (3-12 months)							
Urquhart 2018 (amitriptyline 25 mg/day)[70]	-7.81	3.99	61	57		100.0	-7.81 (-15.63 to 0.01)
Subtotal			61	57		100.0	-7.81 (-15.63 to 0.01)
Test for heterogeneity: Not applicable							
Test for overall effect: Z=1.96, P=0.05							
NDRI (3-13 weeks)							
Katz 2005 (bupropion 300 mg/day)[38]	-1.0	5.73	21	23		100.0	-1.00 (-12.23 to 10.23)
Subtotal			21	23		100.0	-1.00 (-12.23 to 10.23)
Test for heterogeneity: Not applicable							
Test for overall effect: Z=0.17, P=0.86							
SARI (3-13 weeks)							
Goodkin 1990 (trazodone 600 mg/day)[46]	-5.4	8.95	21	19		100.0	-5.40 (-22.94 to 12.14)
Subtotal			21	19		100.0	-5.40 (-22.94 to 12.14)
Test for heterogeneity: Not applicable							
Test for overall effect: Z=0.60, P=0.55							
Tetracyclic antidepressants (3-13 weeks)							
Atkinson 1999 (maprotiline 150 mg/day)[72]	-4.5	8.13	20	14		100.0	-4.50 (-20.43 to 11.43)
Subtotal			20	14		100.0	-4.50 (-20.43 to 11.43)
Test for heterogeneity: Not applicable							
Test for overall effect: Z=0.55, P=0.58							

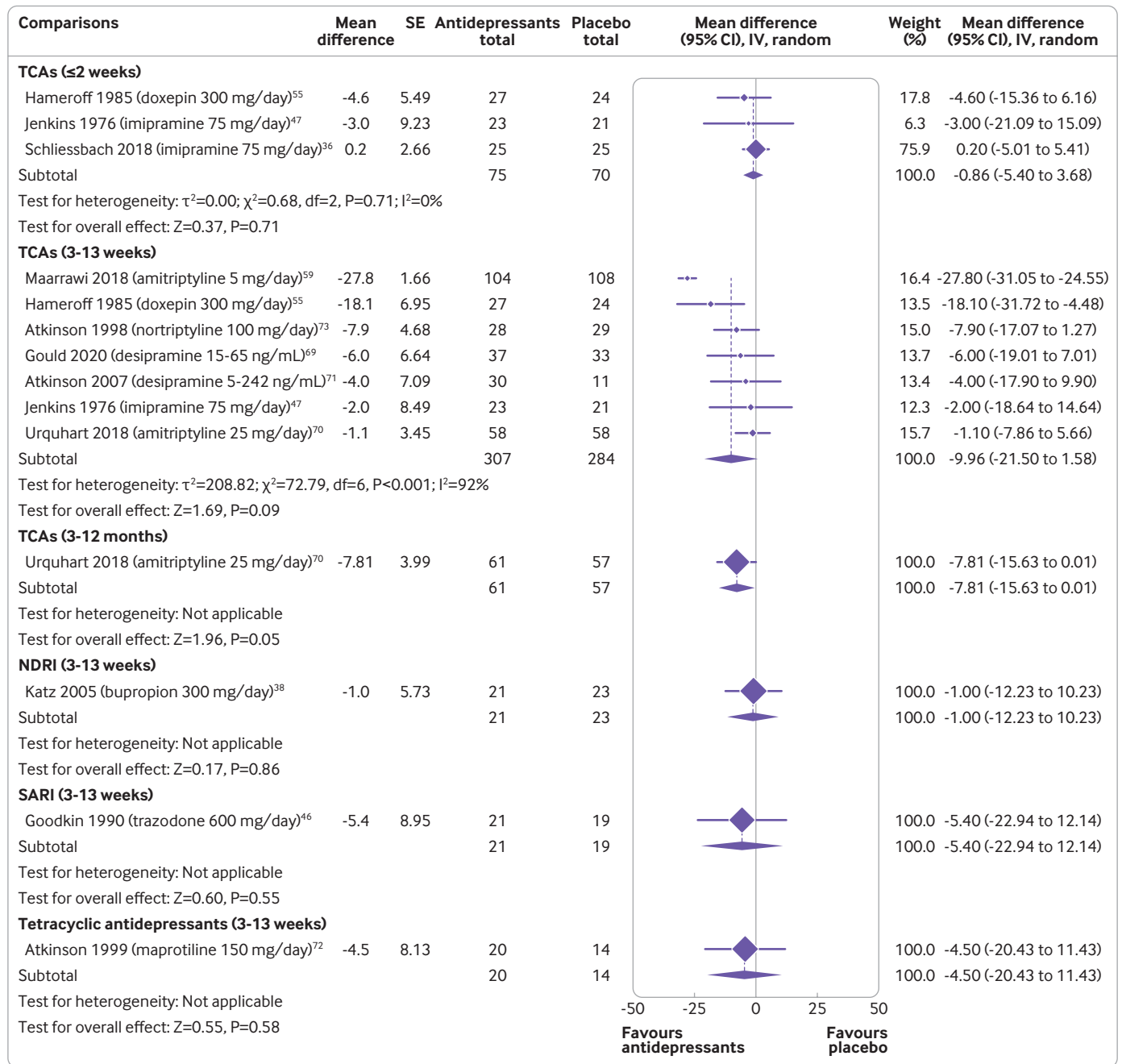Scale: -50 -25 0 25 50. Favours antidepressants ← → Favours placebo

Fig 3 | Mean differences (95% confidence intervals) for pain in trials assessing the efficacy of antidepressants for back pain. Pain is expressed on a 0-100 scale. Studies are ordered by effect size. SE=standard error; IV=inverse variance; TCA=tricyclic antidepressants; NDRI=noradrenaline-dopamine reuptake inhibitors; SARI=serotonin antagonist and reuptake inhibitors

Our review has limitations. Uncertainty in the effects for sciatica and safety outcomes was noticeable. Also, we were not able to explore a dose-response relation for most antidepressants because of the low number of studies and varied doses. Nevertheless, we were able to conduct such an analysis for duloxetine (14 trials) and found that 60 mg/day produced similar effects on pain to 120 mg/day. Finally, although we searched two comprehensive clinical trial registries (ClinicalTrials.gov and WHO International Clinical Trials Registry Platform), we might have missed trials that were conducted before these registries became active (2000 for ClinicalTrials.gov) and therefore were not registered. We identified two trials in these registries that had already been completed but without results available.[62 63] As the authors did not reply to our requests for data, we cannot completely rule out selective reporting or publication bias.

Evidence update
Our review updates the evidence for back pain, sciatica, and osteoarthritis. For example, we included 25 trials (n=2955 participants) for back pain and sciatica, whereas the most recent review included
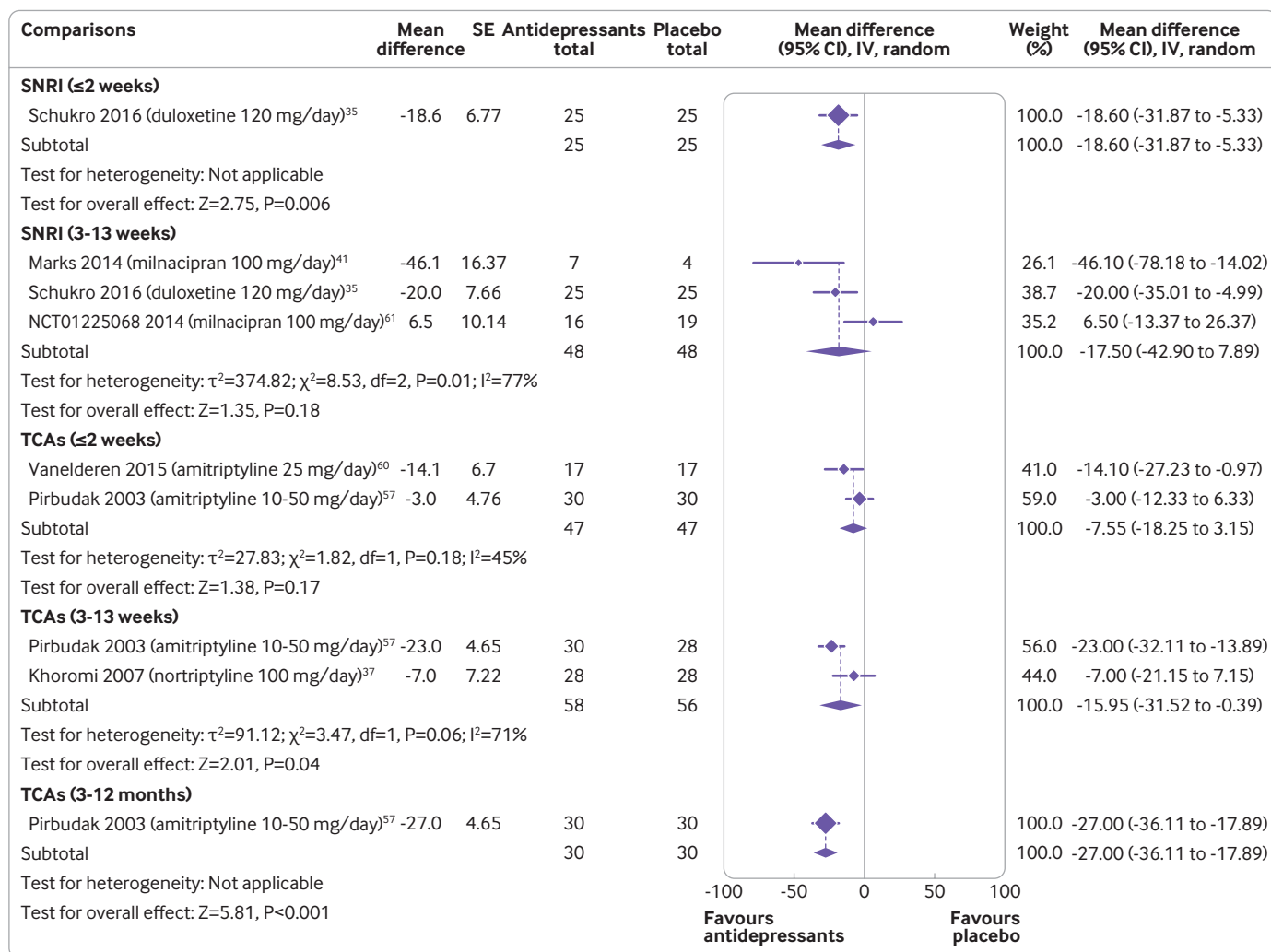
doi: 10.1136/bmj.m4825 | BMJ 2021;372:m4825 | the **bmj**

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Comparisons	Mean difference	SE	Antidepressants total	Placebo total	Mean difference (95% CI), IV, random	Weight (%)	Mean difference (95% CI), IV, random
SNRI (≤2 weeks)							
Schukro 2016 (duloxetine 120 mg/day)[35]	-18.6	6.77	25	25		100.0	-18.60 (-31.87 to -5.33)
Subtotal			25	25		100.0	-18.60 (-31.87 to -5.33)
Test for heterogeneity: Not applicable							
Test for overall effect: Z=2.75, P=0.006							
SNRI (3-13 weeks)							
Marks 2014 (milnacipran 100 mg/day)[41]	-46.1	16.37	7	4		26.1	-46.10 (-78.18 to -14.02)
Schukro 2016 (duloxetine 120 mg/day)[35]	-20.0	7.66	25	25		38.7	-20.00 (-35.01 to -4.99)
NCT01225068 2014 (milnacipran 100 mg/day)[61]	6.5	10.14	16	19		35.2	6.50 (-13.37 to 26.37)
Subtotal			48	48		100.0	-17.50 (-42.90 to 7.89)
Test for heterogeneity: τ^2=374.82; χ^2=8.53, df=2, P=0.01; I^2=77%							
Test for overall effect: Z=1.35, P=0.18							
TCAs (≤2 weeks)							
Vanelderen 2015 (amitriptyline 25 mg/day)[60]	-14.1	6.7	17	17		41.0	-14.10 (-27.23 to -0.97)
Pirbudak 2003 (amitriptyline 10-50 mg/day)[57]	-3.0	4.76	30	30		59.0	-3.00 (-12.33 to 6.33)
Subtotal			47	47		100.0	-7.55 (-18.25 to 3.15)
Test for heterogeneity: τ^2=27.83; χ^2=1.82, df=1, P=0.18; I^2=45%							
Test for overall effect: Z=1.38, P=0.17							
TCAs (3-13 weeks)							
Pirbudak 2003 (amitriptyline 10-50 mg/day)[57]	-23.0	4.65	30	28		56.0	-23.00 (-32.11 to -13.89)
Khoromi 2007 (nortriptyline 100 mg/day)[37]	-7.0	7.22	28	28		44.0	-7.00 (-21.15 to 7.15)
Subtotal			58	56		100.0	-15.95 (-31.52 to -0.39)
Test for heterogeneity: τ^2=91.12; χ^2=3.47, df=1, P=0.06; I^2=71%							
Test for overall effect: Z=2.01, P=0.04							
TCAs (3-12 months)							
Pirbudak 2003 (amitriptyline 10-50 mg/day)[57]	-27.0	4.65	30	30		100.0	-27.00 (-36.11 to -17.89)
Subtotal			30	30		100.0	-27.00 (-36.11 to -17.89)
Test for heterogeneity: Not applicable							
Test for overall effect: Z=5.81, P<0.001							

-100 -50 0 50 100
Favours antidepressants   **Favours placebo**

Fig 4 | Mean differences (95% confidence intervals) for pain in trials assessing the efficacy of antidepressants for sciatica. Pain is expressed on a 0-100 scale. Studies are ordered by effect size. SE=standard error; IV=inverse variance; SNRI=serotonin-noradrenaline reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors; TCA=tricyclic antidepressants; NDRI=noradrenaline-dopamine reuptake inhibitors; SARI=serotonin antagonist and reuptake inhibitors

16 trials.[17] Our findings are in accordance with those from a previous review of drug treatments for chronic low back pain, which found TCAs and SSRIs to be ineffective and SNRIs to be effective, although the effects were small.[17] Our safety analyses showed that SNRIs statistically significantly increased the risk of any adverse event. The increased risk of adverse events with SNRIs had already been described in a review of osteoarthritis[18] and chronic pain[64] but not chronic low back pain.[17]

For this review we pooled data for TCAs and SNRIs for sciatica. Across pain and disability outcomes, TCAs were effective in three of six estimates, whereas SNRIs were effective in one of four estimates. In instances when these drugs were more effective than placebo, the effects exceeded our prespecified threshold for clinical importance. However, these estimates were based on less certain evidence. The low to very low certainty of evidence described in our review contrasts with a recent review of drug treatment for neuropathic pain in adults, which recommends TCAs and SNRIs as

preferred treatment for people with neuropathic pain based on strong evidence.[65]

Our review also updates the evidence for osteoarthritis. We pooled data from eight osteoarthritis trials whereas a previous review only pooled five trials.[18] We also explored the effect of dose on treatment effect estimates for back pain and osteoarthritis. We showed that the effects of duloxetine (an SNRI) were similar regardless of whether the dose used in the trials was 20, 60, or 120 mg/day.

Meaning of the study
Although the observed effect of SNRIs in reducing back pain and related disability was statistically significant, the magnitude of such effects was too small to be considered clinically important. Despite all the studies examining the effects of SNRIs for back pain being sponsored by industry,[40 42-44] the confidence intervals around the effect estimate were narrow enough and did not include clinically important benefits, which further strengthens our confidence in the results.
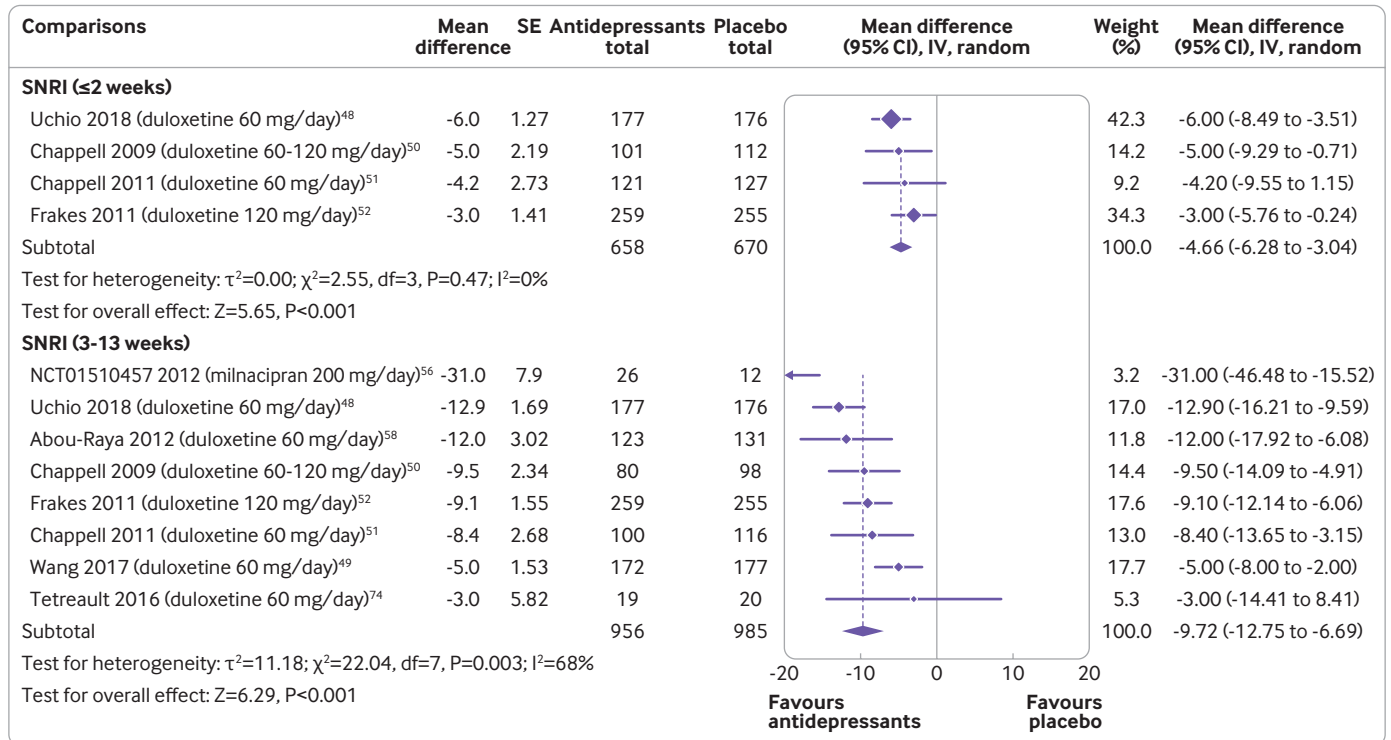
Comparisons	Mean difference	SE	Antidepressants total	Placebo total	Mean difference (95% CI), IV, random	Weight (%)	Mean difference (95% CI), IV, random
SNRI (≤2 weeks)							
Uchio 2018 (duloxetine 60 mg/day)[48]	-6.0	1.27	177	176		42.3	-6.00 (-8.49 to -3.51)
Chappell 2009 (duloxetine 60-120 mg/day)[50]	-5.0	2.19	101	112		14.2	-5.00 (-9.29 to -0.71)
Chappell 2011 (duloxetine 60 mg/day)[51]	-4.2	2.73	121	127		9.2	-4.20 (-9.55 to 1.15)
Frakes 2011 (duloxetine 120 mg/day)[52]	-3.0	1.41	259	255		34.3	-3.00 (-5.76 to -0.24)
Subtotal			658	670		100.0	-4.66 (-6.28 to -3.04)
Test for heterogeneity: τ²=0.00; χ²=2.55, df=3, P=0.47; I²=0%							
Test for overall effect: Z=5.65, P<0.001							
SNRI (3-13 weeks)							
NCT01510457 2012 (milnacipran 200 mg/day)[56]	-31.0	7.9	26	12		3.2	-31.00 (-46.48 to -15.52)
Uchio 2018 (duloxetine 60 mg/day)[48]	-12.9	1.69	177	176		17.0	-12.90 (-16.21 to -9.59)
Abou-Raya 2012 (duloxetine 60 mg/day)[58]	-12.0	3.02	123	131		11.8	-12.00 (-17.92 to -6.08)
Chappell 2009 (duloxetine 60-120 mg/day)[50]	-9.5	2.34	80	98		14.4	-9.50 (-14.09 to -4.91)
Frakes 2011 (duloxetine 120 mg/day)[52]	-9.1	1.55	259	255		17.6	-9.10 (-12.14 to -6.06)
Chappell 2011 (duloxetine 60 mg/day)[51]	-8.4	2.68	100	116		13.0	-8.40 (-13.65 to -3.15)
Wang 2017 (duloxetine 60 mg/day)[49]	-5.0	1.53	172	177		17.7	-5.00 (-8.00 to -2.00)
Tetreault 2016 (duloxetine 60 mg/day)[74]	-3.0	5.82	19	20		5.3	-3.00 (-14.41 to 8.41)
Subtotal			956	985		100.0	-9.72 (-12.75 to -6.69)
Test for heterogeneity: τ²=11.18; χ²=22.04, df=7, P=0.003; I²=68%							
Test for overall effect: Z=6.29, P<0.001							

-20   -10   0   10   20
Favours antidepressants   Favours placebo

Fig 5 | Mean differences (95% confidence intervals) for pain in trials assessing the efficacy of antidepressants for osteoarthritis. Pain is expressed on a 0-100 scale. Studies are ordered by effect size. SE=standard error; IV=inverse variance; SNRI=serotonin-noradrenaline reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors; TCA=tricyclic antidepressants; NDRI=noradrenaline-dopamine reuptake inhibitors; SARI=serotonin antagonist and reuptake inhibitors

Caution is needed in interpreting our findings for sciatica. All sciatica trials were small, had imprecise estimates, and were at high risk of bias, which reduced the certainty of evidence to low and very low. This level of uncertainty indicates that the true estimate of effect of TCAs and SNRIs for sciatica is likely to be substantially different from what we estimated in our review.[25]

For osteoarthritis, although the point estimate was below our prespecified threshold of clinical importance, the lower limit of the confidence interval contains clinically important effects at 3-13 weeks, but not at two weeks or less. Therefore, a clinically important benefit of SNRI in people with osteoarthritis cannot be excluded.[66] Six out of eight trials that

Table 3 | Summary of findings and quality of evidence for safety

	Summary of findings		Certainty of evidence				
	% events antidepressants/ placebo (No of trials)	Relative risk (95% CI)	Study design	Inconsistency	Imprecision	Small study effects	Certainty of evidence
Any adverse event:							
SNRI	62.5/49.7 (13)	1.23 (1.16 to 1.30)	Downgraded*	Not downgraded	Downgraded‡	Not downgraded	Low
SSRI	67.9/66.6 (2)	1.53 (0.19 to 12.61)	Not downgraded	Downgraded†	Downgraded‡	Downgraded§	Very low
TCAs	22.4/13.2 (8)	1.49 (0.95 to 2.34)	Not downgraded	Not downgraded	Downgraded‡	Downgraded§	Low
Tetracyclic antidepressants	90/93.8 (1)	0.96 (0.79 to 1.16)	Downgraded*	Not downgraded	Not downgraded	Downgraded§	Low
NDRI	40/14.3 (1)	2.80 (1.30 to 6.02)	Downgraded*	Not downgraded	Downgraded‡	Not downgraded	Low
Serious adverse events:							
SNRI	1.6/1.3 (10)	1.12 (0.61 to 2.07)	Downgraded*	Not downgraded	Downgraded‡	Not downgraded	
TCAs	2.6/0 (1)	2.62 (0.11 to 62.10)	Downgraded*	Not downgraded	Downgraded‡	Downgraded§	Very low
NDRI	4/2 (1)	1.96 (0.18 to 20.92)	Downgraded*	Not downgraded	Downgraded‡	Downgraded§	Very low
SARI	13.6/15 (1)	0.91 (0.21 to 4.0)	Downgraded*	Not downgraded	Downgraded‡	Downgraded§	Very low
Risk of drop-out owing to adverse events:							
SNRI	12.4/5.3 (12)	2.16 (1.71 to 2.73)	Downgraded*	Not downgraded	Not downgraded	Not downgraded	Moderate
SSRI	17/6.5 (2)	2.36 (0.39 to 14.28)	Downgraded*	Not downgraded	Downgraded‡	Downgraded§	Very low
TCAs	10.8/4.6 (11)	1.48 (0.88 to 2.50)	Downgraded*	Not downgraded	Downgraded‡	Not downgraded	Low
NDRI	6/0 (1)	6.86 (0.36 to 129.48)	Downgraded*	Not downgraded	Downgraded‡	Downgraded§	Very low
SARI	13.6/5 (1)	2.73 (0.31 to 24.14)	Downgraded*	Not downgraded	Downgraded‡	Downgraded§	Very low
Tetracyclic antidepressants	17.6/5.5 (1)	3.18 (0.41 to 24.39)	Downgraded*	Not downgraded	Downgraded‡	Downgraded§	Very low

SNRI=serotonin-noradrenaline reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors; TCA=tricyclic antidepressants; NDRI=noradrenaline-dopamine reuptake inhibitors.
*Downgraded by one level because >25% of participants in this comparison were from studies at high risk of bias.
†Downgraded by one level because the 95% confidence interval include appreciable harm (ie, 95% confidence interval >1.25).

investigated the efficacy of SNRI for osteoarthritis were also sponsored by industry.[48-52 58]

Participants with a diagnosis of depression did not benefit more from antidepressants for pain than those without depression. In both subgroups, improvements were below the threshold for clinically important effects. Furthermore, none of the trials that contributed data for the subgroup with depression were for osteoarthritis. The 2019 OARSI guideline recommends antidepressants (duloxetine) for knee osteoarthritis comorbid with depression or widespread pain disorders, or both.[12] Some of the trials included in our review explored the indirect effect of duloxetine on depression and its role in mediating the effect on pain with path analysis.[40 50 51] However, these trials excluded participants with major depressive disorder, and participants had low average scores (around 5 points[51]) on the Beck depression inventory II, which were within the minimal range and below the proposed thresholds for diagnosing depression.[67]

How this study could promote better decisions

The UK[68] and US[14] guidelines for back pain provide conflicting recommendations on use of SNRIs. Our review shows that although these medicines are effective, the effect is small and unlikely to be considered clinically important by most patients. Our review also showed that about two thirds of patients using SNRIs experience adverse events. We would encourage clinicians to share all this information about SNRIs with patients to allow them to make an informed decision.

The low to very low certainty of evidence does not allow any firm recommendations in favour or against other classes of antidepressants, such as SSRIs, NDRIs, SARIs, and tetracyclic antidepressants for back pain. Nevertheless, our review provides some evidence that neither of these antidepressant classes are effective for back pain and therefore should not be used.

Current guidelines for neuropathic pain recommend antidepressants such as duloxetine (SNRI) and amitriptyline (TCA) as preferred treatment.[15] In our review, despite the potentially clinically important benefits of SNRIs and TCAs for sciatica observed in some comparisons, the low to very low certainty of evidence and the lack of efficacy across several time points for pain and disability mean that evidence is insufficient to confidently guide the use of these drugs for sciatica.

Unanswered questions and future research

Large, definitive trials free of industry ties are urgently needed to evaluate the efficacy of antidepressants. In our review, all but one trial[59] with sample sizes of more than 100 participants in each group were sponsored by industry. New trials will be particularly relevant when testing the efficacy of TCAs and SNRIs in people with sciatica, where clinically important benefits might exist; and in osteoarthritis, where clinically important benefits cannot be excluded but most of the data come from industry sponsored trials.[48-52 58]

The long term effects of antidepressants prescribed for chronic pain conditions is not well known. Trials of chronic pain generally measure safety outcomes for a limited time (3-35 weeks)[64] and therefore do not capture long term effects known to affect those taking antidepressants, such as severe withdrawal symptoms.[6]

Conclusions

Moderate certainty evidence shows that the effect of SNRIs on pain and disability scores is small and not clinically important for back pain, but a clinically important effect cannot be excluded for osteoarthritis. Tricyclic antidepressants and SNRIs might be effective for sciatica, but the certainty of evidence ranged from low to very low. The risk of adverse events but not serious adverse events is slightly increased with SNRIs, although the certainty of the evidence was low. Large, definitive randomised trials that are free of industry ties are urgently needed to resolve uncertainties about the efficacy of antidepressants for sciatica and osteoarthritis highlighted by this review.

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Supplementary information: files 1-18