



Efficacy, safety, and tolerability of antidepressants for pain in adults: overview of systematic reviews

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ABSTRACT

OBJECTIVE

To provide a comprehensive overview of the efficacy, safety, and tolerability of antidepressants for pain according to condition.

DESIGN

Overview of systematic reviews.

DATA SOURCES

PubMed, Embase, PsycINFO, and the Cochrane Central Register of Controlled Trials from inception to 20 June 2022.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Systematic reviews comparing any antidepressant with placebo for any pain condition in adults.

DATA EXTRACTION AND SYNTHESIS

Two reviewers independently extracted data. The main outcome measure was pain; for headache disorders it was frequency of headaches. Continuous pain outcomes were converted into a scale of 0 (no pain) to 100 (worst pain) and were presented as mean differences (95% confidence intervals). Dichotomous outcomes were presented as risk ratios (95% confidence intervals). Data were extracted from the time point closest to the end of treatment. When end of treatment was too variable across trials in a review, data were extracted from the outcome or time point with the largest number of trials and participants. Secondary outcomes were safety and tolerability (withdrawals because of adverse events). Findings were classified from each comparison as efficacious, not efficacious, or inconclusive. Certainty of evidence was assessed with the grading of recommendations assessment, development, and evaluation framework.

RESULTS

26 reviews (156 unique trials and >25 000 participants) were included. These reviews reported

on the efficacy of eight antidepressant classes covering 22 pain conditions (42 distinct comparisons). No review provided high certainty evidence on the efficacy of antidepressants for pain for any condition. 11 comparisons (nine conditions) were found where antidepressants were efficacious, four with moderate certainty evidence: serotonin-norepinephrine reuptake inhibitors (SNRIs) for back pain (mean difference -5.3 , 95% confidence interval -7.3 to -3.3), postoperative pain (-7.3 , -12.9 to -1.7), neuropathic pain (-6.8 , -8.7 to -4.8), and fibromyalgia (risk ratio 1.4, 95% confidence interval 1.3 to 1.6). For the other 31 comparisons, antidepressants were either not efficacious (five comparisons) or the evidence was inconclusive (26 comparisons).

CONCLUSIONS

Evidence of efficacy of antidepressants was found in 11 of the 42 comparisons included in this overview of systematic reviews—seven of the 11 comparisons investigated the efficacy of SNRIs. For the other 31 comparisons, antidepressants were either ineffective or evidence on efficacy was inconclusive. The findings suggest that a more nuanced approach is needed when prescribing antidepressants for pain conditions.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42022311073.

Introduction

Chronic pain is common and debilitating, affecting about one in five people globally.¹⁻⁴ Musculoskeletal conditions such as back pain are typically the most common conditions leading to chronic pain, followed by headache, orofacial pain, and visceral pain (eg, abdominal, pelvic, or genital).

Chronic pain can be difficult to treat, and management is often suboptimal—for example, the efficacy of the most common non-opioid drug treatment, paracetamol (acetaminophen), is unknown for most pain conditions.⁵ Non-steroidal anti-inflammatory drugs may provide small benefits for pain reduction in some conditions, but they need to be used with caution and for short periods because of the risk of serious adverse events with longer term use.⁶ About a third of people with chronic non-cancer related pain are prescribed opioid analgesics.⁷ The benefits of such drugs for chronic pain are, however, limited, and the potential harms outweigh the small benefits.⁸ Antidepressants are frequently used for the treatment of chronic pain. In a Canadian study, about 9% of all antidepressant prescriptions were for pain conditions.⁹ In Portugal, 12% of people with back pain reported the use of an antidepressant to manage their condition.¹⁰ Among

WHAT IS ALREADY KNOWN ON THIS TOPIC

Antidepressants are commonly used to treat a variety of pain conditions. The National Institute for Health and Care Excellence guideline for chronic primary pain has explicitly recommended against the use of pain medicines, with the exception of antidepressants.

WHAT THIS STUDY ADDS

Some antidepressants were efficacious for some pain conditions; however, efficacy appears to depend on the condition and class of antidepressant. Although three quarters of antidepressants prescribed to treat a pain condition are tricyclic antidepressants, evidence suggests that their efficacy is inconclusive for most pain conditions. The findings suggest that a more nuanced approach is needed when prescribing antidepressants for pain.

older people, recent data from Canada, the United States, the United Kingdom, and Taiwan suggest that chronic pain was the most common condition leading to an antidepressant prescription—even more so than for depression.¹¹ In the Netherlands, prescription of the tricyclic antidepressants amitriptyline for people with osteoarthritis has increased by 17% over the past decade.¹² In that study, long term use (≥ 3 months) was also observed in 40% of those prescribed an antidepressant.

The 2021 National Institute for Health and Care Excellence guideline for chronic primary pain explicitly recommends against the use of pain medicines, with the exception of antidepressants.^{13 14} Chronic primary pain is a recent diagnostic classification that encompasses a large number of conditions, such as fibromyalgia, complex regional pain syndrome, orofacial pain, visceral pain (eg, irritable bowel syndrome, bladder pain), and musculoskeletal pain (eg, back pain).¹⁵ Other types of pain, such as postsurgical, neuropathic, and cancer related are not classified under chronic primary pain, but the efficacy of antidepressants for these conditions has been investigated.¹⁶⁻¹⁹ To provide patients and clinicians with an updated and comprehensive resource on the efficacy, safety, and tolerability of antidepressants to treat pain, we conducted an overview of relevant systematic reviews. Given the heterogeneity in the types of pain conditions for which the efficacy of antidepressants has been documented by existing systematic reviews, we chose to conduct an overview of systematic reviews to appraise efficacy estimates for each condition individually.

Methods

Data sources and searches

This review was prospectively registered on PROSPERO and followed guidance from the preferred reporting items for overviews of reviews (PRIOR) statement,²⁰ which defines an overview of systematic reviews as a review that uses explicit and systematic methods to search for and identify multiple systematic reviews on a similar topic for the purpose of extracting and analysing results across important outcomes. Thus, the unit of searching, inclusion, and data analysis is the systematic review itself.

We searched PubMed, Embase, PsycINFO, and the Cochrane Database of Systematic Reviews from inception to 16 February 2022, with searches updated on 20 June 2022. Supplementary file 1 provides details of the search strategy. We did not consider the grey literature. Two authors (GF and CAS or JZ) independently screened eligible studies by title and abstract and read the full text of potentially eligible studies. Disagreements were resolved by consensus. Supplementary file 2 provides a list of ineligible reviews after full text reading.

Eligibility criteria

We included systematic reviews with or without meta-analysis, published in peer reviewed journals, that

investigated the efficacy of any antidepressant drug compared with placebo used for any pain condition in adults. We defined systematic reviews as peer reviewed studies with a clearly reported research question that used systematic methods to search the literature and synthesise data. Provided that an appropriate English translation could be obtained, we placed no restriction on antidepressant class, dose, or regimen, or on language of the review. Network meta-analyses were eligible if they provided direct effects for the antidepressant versus placebo comparison (to exclude indirect comparisons). Reviews that included populations of children or adolescents, or both, or that did not report pain or safety outcomes were excluded. When more than one review existed on the same topic, we selected the most comprehensive review—that is, the review with the most trials relevant to our comparison of interest (antidepressants versus placebo). When a Cochrane review and a non-Cochrane review included the same trials, we chose the Cochrane review because such reviews are typically of higher quality.^{21 22} The final decision on which reviews to include was based on consensus between two authors (GF and CAS or JZ). In line with the recommendations from Cochrane, we did not conduct trial level searches or a new systematic review within the overview.²³

Data extraction

Two reviewers independently extracted data (GF, JZ). Data were extracted on characteristics of the review (eg, prospective registration, Cochrane or non-Cochrane review), information on antidepressant type and treatment regimen (eg, dose and duration of treatment), number of trials with industry ties, and outcomes for the current overview.

Outcomes

Our primary outcome was pain measured with any instrument and reported as between group differences along with corresponding 95% confidence intervals. We reported mean differences and 95% confidence intervals on a common 0-100 scale. Dichotomous outcomes were converted, if necessary, to risk ratios and corresponding 95% confidence intervals. When data were summarised as standardised mean differences, we examined the information available in the review to determine whether it was possible to convert the data to mean differences on a 0-100 scale. When multiple pain outcomes were available, we chose the one elected by the review as its primary outcome. When multiple time points existed for the same pain outcome within a review, we extracted data from the time point closest to the end of treatment in $>50\%$ of trials. For reviews of headache disorders, we extracted data from the headache frequency outcome in line with guidance on drug trials in chronic migraine,²⁴ tension-type headache,²⁵ and a core outcome set for migraine.²⁶

Safety outcomes were considered as secondary outcomes. We extracted data for any adverse event and tolerability (ie, withdrawals due to adverse events)

but not for individual trial adverse events as we anticipated too much variability in how these would be reported by each review. We also did not extract data on serious adverse events as we anticipated that most trials included in the eligible reviews would not be adequately powered to detect between group differences for these outcomes. For safety and tolerability outcomes, we defined appreciable benefits and harms when risk ratio estimates included 0.75 and 1.25 values, respectively.²⁷

Methodological quality of systematic reviews

Two reviewers (GF, JZ) independently appraised the methodological quality of included systematic reviews with the AMSTAR-2 tool.²⁸ This tool has 16 items, seven of which are considered critical. Using published guidance,²⁸ we classified the quality of the included systematic reviews as high, moderate, low, or critically low. Supplementary file 3 shows the AMSTAR-2 ratings for the eligible reviews.

Risk of bias

We relied on the risk of bias assessment of reviews that assessed risk of bias using the original or revised version of the Cochrane risk of bias tool.^{29,30} For reviews that used a different risk of bias tool, such as the Jadad scale,¹⁷ or where risk of bias was not assessed,³¹ two independent reviewers (GF, JZ) assessed bias of each included trial that contained data for our outcomes of interest using the Cochrane risk of bias tool (see supplementary file 3). We used criteria described previously to assess selection (random sequence generation and allocation concealment), performance (blinding of participants and staff), detection (blinding of outcome assessors), attrition (incomplete outcome data), reporting (selective reporting), and other biases.³² For the other bias item, we assessed whether the review trials had ties with industry. We considered trials with industry ties to be at high risk of bias.³³ A trial was considered to have industry ties if it was sponsored by industry or received funding from industry but did not include a disclosure that the funder had no role in any aspect of the study (ie, design and conduct; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication). For each trial in the included reviews, we classified ties with industry as either present, absent, or unclear. Supplementary file 4 shows all trials included in the eligible reviews that had industry ties.

Certainty of evidence

Two reviewers (GF, JZ) independently assessed the certainty of evidence for the primary outcome (pain) according to the grading of recommendations assessment, development, and evaluation (GRADE) criteria.³⁴ If reviews used GRADE, we checked the ratings and reported our assessment when the ratings differed from the originals. If GRADE was not used in the review, we graded the certainty of evidence

ourselves using prespecified criteria. Briefly, the certainty of evidence was initially set to high and downgraded by one level for each of the following domains: limitation of study design, inconsistency of results, imprecision, and publication bias. We did not upgrade the certainty of evidence for any reason, such as large effect size. Supplementary file 5 presents a detailed explanation of the criteria used, the reviews' ratings, and our ratings.

Data synthesis

We reported data separately by pain condition and by antidepressant class. For each comparison, we calculated the median (minimum-maximum) dose and treatment duration (in weeks). When a trial provided a range of doses, we used the value of the final (highest) dose before tapering for the calculation. We reanalysed data from included reviews in the following instances: If a review reported pooled estimates combining data from different antidepressant classes,³⁵ we reanalysed data and grouped trials by antidepressant class; if our team considered one or more trials included in a review as not appropriate for that comparison (eg, not placebo controlled), we excluded the trial from the analysis and re-ran the analysis³⁵; if the primary outcome of the review was not pain but the included trials measured a pain outcome, we extracted data for the pain outcome from the trials included in the review³⁶; and if a review reported data descriptively, we computed the pooled treatment effect when possible and provided a GRADE rating for that outcome.

A random effects model with a restricted maximum likelihood heterogeneity variance estimator was used to estimate the efficacy of antidepressants on pain (primary outcome) for all comparisons where meta-analysis was possible—that is, when at least two studies were pooled. The random effects model makes less stringent assumptions about the consistency of effects across studies, which is a more appropriate approach when studies within a meta-analysis might differ from each other in ways that could impact on the treatment effect.³⁷ Restricted maximum likelihood is recommended to estimate the heterogeneity variance over other methods, including the widely used DerSimonian and Laird estimator.³⁸ Reanalyses were performed in Stata version 17 using the *metan* package. We presented safety outcomes as reported by the reviews. Supplementary file 6 provides a detailed explanation of which reviews were reanalysed, details on our rationale to reanalyse data, and methods used in each reanalysis. To visually demonstrate the amount of overlap in trials included in more than one review in line, we created a citation matrix and calculated the amount of overlap using the corrected covered area as recommended by Cochrane (see supplementary file 7).³⁹ Values of corrected covered area are interpreted as slight (0-5%), moderate (6-10%), high (11-15%), and very high (>15%).

From each comparison we classified findings as either efficacious, not efficacious, or inconclusive. An antidepressant was considered to be efficacious

for a condition when the difference between intervention and placebo groups was statistically significantly in favour of the antidepressant and the certainty of evidence was at least low. We classified an antidepressant as not efficacious for a condition when the difference between intervention and placebo groups was not statistically significantly in favour of antidepressants and the certainty of evidence was at least low. When the certainty of evidence was very low or a comparison had only one small trial (defined arbitrarily as having a sample size <100 per arm^{40,41}), or both, we considered the evidence of efficacy to be inconclusive regardless of statistical significance, magnitude, or direction of effect.⁴²

Because this review presents data for a series of distinct pain conditions, we purposefully decided a priori not to make judgments about the clinical importance of observed effects for each condition. This was decided because commonly used thresholds (eg, the 10 point reduction on a 0-100 scale commonly used in musculoskeletal pain research⁴³) are arbitrary and may not reflect patients' views on whether an effect is meaningful to them.⁴⁴ No threshold would universally apply to all conditions studied, potentially generating misleading interpretations about the importance of the observed effect.

Sensitivity analysis

To assess the robustness of our findings, we performed a sensitivity analysis. In this analysis we described the effect sizes and included trials of systematic reviews that were excluded owing to overlap with an eligible review and that were published either in the five years preceding the publication of the eligible review or after the eligible review. Five years was chosen as this is the recommended timeframe in which to update a Cochrane systematic review.²³ Supplementary file 8 presents the data for the sensitivity analyses.

Protocol deviations

We stated in our protocol that we would extract data on disability and serious adverse events as secondary outcomes. During data extraction it became evident that most reviews did not have any data on disability and therefore we decided not to extract such data. We also did not extract data on serious adverse events as most trials in each review were not adequately powered to detect such events.

In the protocol we stated that in reviews reporting multiple data time points we would choose the time point at 3-12 months (or closest to six months when multiple time points existed within that time frame) as the primary endpoint. The team subsequently agreed that defining the intermediate term (3-12 months) as the primary time point was not appropriate for this review for several reasons, including: Most reviews only presented one measure of efficacy at the end of the treatment phase, and treatment phases typically had a duration of 6-12 weeks. For reviews that did present data for multiple time points (eg, at three months, six months, and one year), extracting data from the six

month time point (as defined in our protocol) would have been detrimental as data from these reviews would be less comparable to data in others, and fewer trials would be included. As a solution we decided to only extract data from the time point closest to the end of treatment in most trials (>50%) included in each review.

Patient and public involvement

Owing to lack of funding, patients and members of the public were not involved in the design, conduct, or reporting of this study.

Results

Characteristics of included reviews

Overall, 1732 records were identified, of which 948 were duplicates and therefore excluded. The remaining 784 records were screened by title and abstract, and the full texts of 184 potentially eligible reviews were

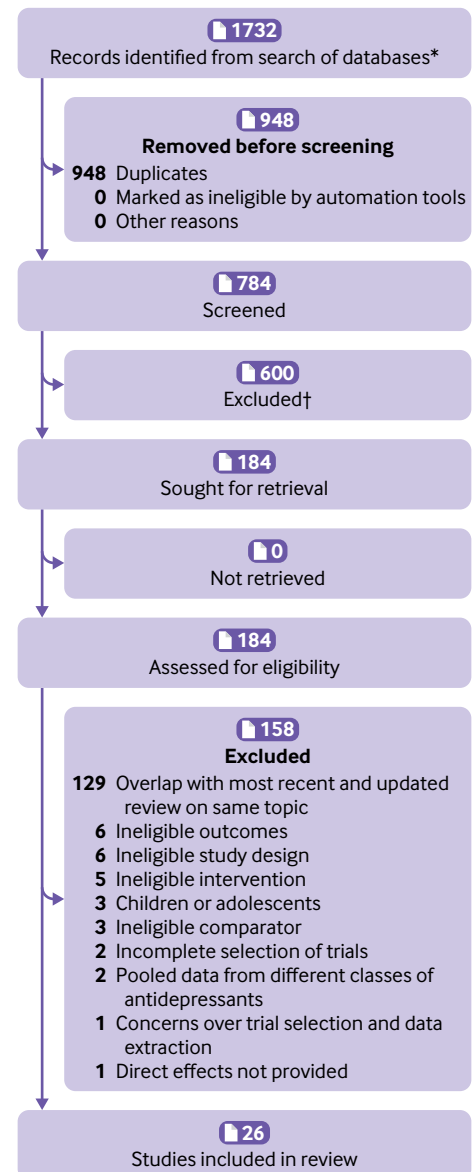


Fig 1 | Flow of studies through review

Table 1 | Characteristics of included reviews (n=26)

Reference	Condition	Antidepressant class	Prospective registration	Type of review	No of trials (No of participants) with data for pain	No (%) of trials with industry ties*
Wang 2022 ¹⁶	Postoperative pain	SNRI, SSRI	Yes	Non-Cochrane	17 (1242)	0
Roberts 2022 ⁵²	Aromatase inhibitor therapy induced pain in breast cancer	SNRI	Yes	Cochrane	1 (255)	0
Ferreira 2021 ³²	Back pain, sciatica, knee osteoarthritis	SNRI, SSRI, TCA, NDRI, SARI, tetracyclic/atypical	Yes	Non-Cochrane	30 (4445)	14 (47)
Farag 2021 ⁵³	Burning mouth syndrome	SARI	No	Non-Cochrane	1 (37)	1 (100)
Ford 2021 ³⁶	Functional dyspepsia	SSRI, TCA, tetracyclic/atypical	No	Non-Cochrane	5 (618)	0
Do 2021 ⁵⁴	Atypical chronic orofacial pain	SNRI, TCA	Yes	Non-Cochrane	2 (60)	1 (100)
Imamura 2020 ⁵⁵	Bladder pain syndrome	TCA	Yes	Cochrane	2 (279)	0
Ford 2019 ⁵⁶	Irritable bowel syndrome	SSRI, TCA	Yes	Non-Cochrane	7 (351)	1 (14)
Caruso 2019 ³⁵	Neuropathic pain	SNRI	Yes	Non-Cochrane	12 (3010)	9 (75)
Perez-Lopez 2019 ⁵⁷	Vulvodynia	TCA	No	Non-Cochrane	1 (58)	0
Christophorou 2019 ⁵⁸	Acute oral mucositis	TCA	No	Non-Cochrane	1 (140)	0
Franco 2019 ⁵⁹	Chronic prostatitis	SSRI	Yes	Cochrane	1 (42)	1 (100)
Welsch 2018 ⁴⁵	Fibromyalgia	SNRI	Yes	Cochrane	15 (6918)	14 (93)
Welsch 2018 ⁴⁶	Fibromyalgia	Tetracyclic/atypical	Yes	Cochrane	3 (591)	2 (66)
Jackson 2017 ⁵¹	Chronic tension-type headache	TCA, tetracyclic/atypical	No	Non-Cochrane	4 (197)	0
Gebhardt 2016 ³¹	Depression and comorbid chronic pain	SNRI, SSRI	No	Non-Cochrane	14 (4380)	15 (79)
Alviar 2016 ⁶⁰	Phantom limb pain	TCA	Yes	Cochrane	1 (39)	0
Walitt 2015 ⁴⁷	Fibromyalgia	SSRI	Yes	Cochrane	6 (343)	5 (83)
Moore 2015 ⁴⁹	Fibromyalgia	TCA	Yes	Cochrane	4 (275)	1 (25)
Banzi 2015 ⁶¹	Chronic migraine	SSRI	Yes	Cochrane	2 (82)	1 (20)
Banzi 2015 ⁵⁰	Chronic tension-type headache	SNRI, SSRI	Yes	Cochrane	2 (127)	1 (50)
Finnerup 2015 ¹⁷	Neuropathic pain	TCA	No	Non-Cochrane	14 (948)	0
Atluri 2015 ⁶²	Non-cardiac chest pain	SSRI	No	Non-Cochrane	4 (184)	2 (50)
Cheong 2014 ⁶³	Chronic pelvic pain	SSRI	Yes	Cochrane	1 (23)	0
Richards 2011 ⁶⁴	Rheumatoid arthritis	TCA	Yes	Cochrane	7 (482)	1 (17)
Tort 2012 ⁴⁸	Fibromyalgia	MAOI	Yes	Cochrane	2 (121)	1 (50)

SNRI=serotonin-norepinephrine reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors; TCA=tricyclic antidepressants NDRI=noradrenaline-dopamine reuptake inhibitors; SARI=serotonin antagonist and reuptake inhibitors; MAOI=monoamine oxidase inhibitors.

*Pain data (primary outcome).

read. After the exclusion of a further 158 reviews (see supplementary file 2 for reasons), 26 studies were included (fig 1).

The 26 reviews, published between 2012 and 2022, included 156 unique trials and >25 000 participants and covered 22 distinct pain conditions representing 42 distinct antidepressant versus placebo comparisons. Each condition was covered by one review, except for fibromyalgia (five reviews),⁴⁵⁻⁴⁹ neuropathic pain (two reviews),^{17 35} and chronic tension-type headache (two reviews).^{50 51} For these three conditions, each review provided data for a different antidepressant class. Table 1 describes the included reviews. In only three of the 156 trials did data overlap in more than one review (see supplementary file 7), yielding a corrected covered area of 0.07%. We explored the effect of removing the overlapping trials from the treatment effect estimates in the reviews in which they were included (see supplementary file 9).

Treatment regimens

The 26 reviews provided efficacy estimates for eight classes of antidepressants. Efficacy estimates for tricyclic antidepressants (TCAs) were provided in 12 reviews,^{17 32 36 49 51 54-58 60 64} followed by selective serotonin reuptake inhibitors (SSRIs) in 11 reviews,^{16 31 32 36 47 50 56 59 61-63} serotonin-norepinephrine reuptake inhibitors (SNRIs) in eight reviews,^{16 31 32 35 45 50 52 54} tetracyclic/atypical

antidepressants in four reviews,^{32 36 46 51} serotonin antagonist and reuptake inhibitors (SARIs) in two reviews,^{32 53} and noradrenaline-dopamine reuptake inhibitors (NDRIs)³² and monoamine oxidase inhibitors (MAOIs)⁴⁸ in one trial each.

Ties with industry

Table 1 describes the number of trials, number of participants, and percentage of included trials in each review with ties to industry. Of the 156 unique trials that were included in at least one included review, we were able to locate 154 (98%) and investigate their ties with industry. Industry ties were present in 69 (45%) reviews, absent in 45 (29%), and unclear in 40 (26%). Of the trials with industry ties, 47 (68%) investigated SNRIs, 13 (18%) investigated SSRIs, 4 (6%) investigated TCAs, 2 (3%) investigated atypical antidepressants and SARIs each, and one (1%) investigated NDRIs and MAOIs.

Conditions for which antidepressants are efficacious

Nine reviews provided evidence that some antidepressants were efficacious compared with placebo for nine conditions in 11 distinct comparisons.^{16 17 31 32 35 45 51 52 56} Most reviews providing evidence that antidepressants were efficacious for pain were of SNRIs—six reviews covering seven conditions.^{16 31 32 35 45 52}

Table 2 | Conditions for which antidepressants show evidence of efficacy

Condition by drug class	Treatment regimen: median (minimum-maximum) dose and duration	Outcome	Effect estimate (95% CI)*	No of trials (No of participants)	Certainty of evidence
SNRI					
Back pain ³²	Duloxetine 60 (20-120) mg for 13 (13-13) weeks (4 trials)	Pain intensity	MD -5.3 (-7.3 to -3.3)	4 (1415)	Moderate
Postoperative pain ¹⁶	Duloxetine 60 (30-60) mg pre-surgery and/or post-surgery for 3 days (1 day to 26 weeks) (15 trials); venlafaxine 37.5 mg for 10 days (1 trial)	Pain intensity (24 hours post-surgery)	MD -7.3 (-12.9 to -1.7)	16 (1128)	Moderate
Fibromyalgia ⁴⁵	Duloxetine 120 (30-120) mg for 12 (12-27) weeks (7 trials); milnacipran 150 (100-200) mg for 12 (6-27) weeks (8 trials)	Pain reduction $\geq 50\%$	RR 1.4 (1.3 to 1.6)	15 (6918)	Moderate†
Neuropathic pain ³⁵	Duloxetine 120 (60-120) mg for 12 (6-12) weeks (8 trials); milnacipran 200 mg for 12 weeks (1 trial); venlafaxine 172.5 (150-225) for 7 (6-8) weeks (2 trials); desvenlafaxine (400 mg for 13 weeks) (1 trial)	Pain intensity	MD -6.8 (-8.7 to -4.8)	12 (3010)	Moderate†
Aromatase inhibitor therapy induced pain in breast cancer ⁵²	Duloxetine 60 mg for 12 weeks (1 trial)	Pain intensity	MD -6.3 (-9.7 to -2.9)	1 (255)	Low†
Depression and comorbid chronic pain ³¹	Duloxetine 60 (60-60) mg for 9 (8-10 weeks) (9 trials); venlafaxine 177 mg for 12 weeks (1 trial); desvenlafaxine 50 mg for 10 weeks (1 trial)	Pain intensity	MD -6.4 (-7.7 to -5.1)	11 (3520)	Low†
Knee osteoarthritis ³²	Duloxetine 60 (60-120) mg for 13 (8-14) weeks (7 trials); milnacipran 200 mg for 8 weeks (1 trial)	Pain intensity	MD -9.6 (-12.3 to -6.9)	8 (1941)	Low†
SSRI					
Depression and comorbid chronic pain ³¹	Paroxetine 20 (20-20) mg for 8 weeks (2 trials); fluoxetine 20 mg for 7 weeks (1 trial); escitalopram 10 mg for 12 weeks (1 trial)	Pain intensity	MD -5.9 (-10.1 to -1.7)	4 (947)	Low†
TCA					
Irritable bowel syndrome ⁵⁶	Amitriptyline 10 mg for 8 weeks (1 trial); nortriptyline 10 mg for 8 weeks (1 trial); doxepin 75 mg for 6 weeks (1 trial); desipramine 150 mg for 8 weeks (1 trial)	Abdominal pain not improving	RR 0.6 (0.4 to 0.8)	4 (184)	Low†
Neuropathic pain ¹⁷	Amitriptyline 75 (65-150) for 5 (4-8) weeks (9 trials); desipramine 201 (160-250) for 6 (6-8) weeks; (3 trials); imipramine 150 mg for 4 weeks (1 trial); maprotiline 75 mg for 4 weeks (1 trial); nortriptyline 100 mg for 9 weeks (1 trial)	Pain reduction $\geq 30\%$	RR 3.4 (2.1 to 5.5)	14 (948)	Low
Chronic tension-type headache ⁵¹	Amitriptyline 100 (50-150) mg for 12 (8-26) weeks	Headache frequency (days)	MD -4.8 (-6.6 to -3)	4 (197)	Low†

CI=confidence interval; MD=mean difference; RR=risk ratio; SNRI=serotonin-norepinephrine reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors; TCA=tricyclic antidepressants.

*Pain intensity outcomes are on a 0-100 scale unless stated otherwise.

†Grading of recommendations assessment, development, and evaluation determined by current authors (see supplementary file 5 for details of the assessment).

No review reported high certainty evidence about the effects of antidepressants for pain. Moderate certainty of evidence suggested that SNRIs were efficacious for chronic back pain,³² postoperative pain (most trials were in orthopaedic surgery),¹⁶ fibromyalgia,⁴⁵ and neuropathic pain.³⁵

Low certainty evidence supported the efficacy of SNRIs, SSRIs, and TCAs for some other conditions. SNRIs were efficacious for aromatase inhibitor therapy induced pain in breast cancer,⁵² depression and comorbid chronic pain,³¹ and knee osteoarthritis.³² SSRIs were efficacious for depression and comorbid chronic pain.³¹ TCAs were efficacious for irritable bowel syndrome,⁵⁶ neuropathic pain,¹⁷ and chronic tension-type headache.⁵¹ Table 2 shows typical treatment regimens, effect estimates, number of trials, and number of participants.

Conditions for which antidepressants are not efficacious

Four reviews provided evidence that some antidepressants were not efficacious compared with placebo for four conditions in five distinct comparisons.^{32 36 47 62} No review reported high certainty evidence. Most reviews providing evidence that antidepressants were not

efficacious for pain were of SSRIs, with four reviews covering three conditions.^{32 36 47 62}

One review provided moderate certainty evidence that TCAs were not efficacious for functional dyspepsia.³⁶ The certainty of evidence for all other reviews was low. SSRIs were not efficacious for back pain,³² fibromyalgia,⁴⁷ functional dyspepsia,³⁶ and non-cardiac chest pain.⁶² Table 3 shows typical treatment regimens, effect estimates, number of trials, and number of participants.

Conditions for which evidence is inconclusive

Eighteen reviews provided inconclusive evidence about the efficacy of antidepressants for 17 conditions in 26 distinct comparisons.^{16 32 36 46 48-50 53-61 63 64} Most reviews presenting inconclusive evidence were of TCAs, with eight reviews covering nine conditions (nine comparisons).^{32 49 54 55 57 58 60 64} For 17 comparisons, only one trial formed the body of evidence for the comparisons. For comparisons with more than one trial available, evidence for SNRIs was inconclusive for sciatica.³² Evidence for SSRIs was inconclusive for irritable bowel syndrome.⁵⁶ Evidence for TCAs was inconclusive for back pain,³² bladder pain syndrome,⁵⁵ fibromyalgia,⁴⁹ rheumatoid arthritis,⁶⁴ and sciatica.³²

Table 3 | Conditions for which antidepressants are not efficacious, by class and certainty of evidence

Condition by drug class	Treatment regimen: median (minimum-maximum) dose and duration	Outcome	Effect estimate (95% CI)*	No of trials (No of participants)	Certainty of evidence
SSRI					
Back pain ³²	Paroxetine 25 (20-30) mg for 8 weeks (2 trials); fluoxetine 16-514 ng/mL for 12 weeks (1 trial)	Pain intensity	MD 1.5 (-5.4 to 8.5)	3 (170)	Low
Fibromyalgia ⁴⁷	Fluoxetine 62.5 (20-80) mg for 12 (6-12) weeks (3 trials); citalopram 40 mg for 12 (8-16) weeks (2 trials); paroxetine 20 mg for 8 weeks (1 trial)	Pain reduction $\geq 30\%$	RR 1.4 (1 to 2)	6 (343)	Low
Functional dyspepsia ³⁶	Venlafaxine 150 mg for 8 weeks (1 trial); sertraline 50 mg for 8 weeks (1 trial)	Pain intensity	MD 1.3 (-5.9 to 8.5)	2 (291)	Low†
Non-cardiac chest pain ⁶²	Paroxetine 45 (40-50) mg for 10 (8-12) (2 trials); sertraline 200 for 9 (8-10) weeks mg (2 trials)	Pain intensity	MD -3.8 (-9.8 to 2.3)	4 (184)	Low†
TCA					
Functional dyspepsia ³⁶	Amitriptyline 37.5 (25-50) mg for 10 (8-12) weeks (2 trials); imipramine 50 mg for 12 weeks (1 trial)	Pain intensity	MD -2.3 (-7.3 to 2.8)	3 (293)	Moderate†

CI=confidence interval; MD=mean difference; RR=risk ratio; SSRI=selective serotonin reuptake inhibitors, TCA=tricyclic antidepressants.

*Pain intensity outcomes are on a 0-100 scale unless stated otherwise.

†Grading of recommendations assessment, development, and evaluation determined by current authors (see supplementary file 5 for details of the assessment).

Evidence for atypical and MAOI antidepressants was inconclusive for fibromyalgia.^{46,48} Table 4 shows typical treatment regimens, effect estimates, number of trials, and number of participants.

Sensitivity analysis

The sensitivity analysis identified 57 reviews covering 13 conditions that were excluded owing to overlap with another eligible review. Many excluded reviews did not conduct meta-analysis. Of the ones that did, effect sizes reported by the excluded reviews were broadly similar to the ones reported in the included reviews (see supplementary file 8).

Safety and tolerability

Supplementary files 10 and 11 present data on safety and tolerability. Most safety and tolerability data were imprecise. SNRIs appeared to increase the risk of any adverse event in patients with chemotherapy induced pain and with back pain, sciatica, and osteoarthritis (data combined from all three conditions), but not with postoperative pain or tension-type headache. Use of TCAs increased the risk of any adverse events for functional dyspepsia,³⁶ irritable bowel syndrome,⁵⁶ acute oral mucositis,⁵⁸ and some adverse events in vulvodynia⁵⁷ and tension-type headache.⁵¹ NDRIs increased the risk of any adverse event in people with back pain in one trial only.³² Estimates for SSRIs,^{16, 32, 50, 56, 61} tetracyclic/atypical antidepressants,^{32, 36, 46, 51} and MAOIs⁴⁸ were all imprecise and not informative.

People tolerated SNRIs less than placebo in reviews of back pain, sciatica, and osteoarthritis (data combined),³² functional dyspepsia,³⁶ neuropathic pain,³⁵ and fibromyalgia.⁴⁵ For SSRIs, TCAs, and tetracyclic/atypical antidepressants, only the review on functional dyspepsia,³⁶ neuropathic pain,¹⁷ and tension-type headache⁵¹ showed lower tolerability compared with placebo, respectively.

Discussion

This overview of systematic reviews summarised evidence on the efficacy, safety, and tolerability of antidepressants for 26 pain conditions. No review

presented high certainty evidence on the efficacy of antidepressants. Moderate certainty evidence supported the efficacy of SNRIs, mostly duloxetine at median doses of 60-120 mg for back pain, postoperative pain, fibromyalgia, and neuropathic pain. We found low certainty evidence that SNRIs were efficacious for aromatase inhibitor therapy induced pain in breast cancer, depression and comorbid chronic pain, and knee osteoarthritis; SSRIs, mostly paroxetine at a median dose of 20 mg, for people with depression and comorbid chronic pain; and that TCAs were efficacious for irritable bowel syndrome, neuropathic pain, and chronic tension-type headache. We found moderate certainty evidence that TCAs were not efficacious for functional dyspepsia, and low certainty evidence that SSRIs were not efficacious for back pain, fibromyalgia, functional dyspepsia, and non-cardiac chest pain. For the other 26 comparisons, evidence for the efficacy of antidepressants was inconclusive.

Strengths and limitations of this review

We performed a comprehensive literature search, conducted every step of the review in duplicate, investigated industry ties for all trials included in the 26 reviews that contributed with an effect estimate for pain, registered our overview prospectively, and reported the few protocol deviations in line with guidelines for research transparency. For 26 comparisons, evidence on the efficacy of antidepressants was inconclusive. Of these, 17 comparisons from 12 reviews were formed by a single small trial (<100 participants in each trial arm).^{16, 32, 36, 50, 53, 54, 57-60, 61, 63} This finding highlights the limited body of evidence supporting the use of several types of antidepressants for various pain conditions. The assessment of publication bias is challenging given that most comparisons had a limited number of trials. For example, only five out of the 42 comparisons in our review had 10 or more trials, which is the minimum number of studies recommended when assessing publication bias with a funnel plot. The GRADE working group recognises the challenge of assessing publication bias.⁶⁵

Table 4 | Conditions for which antidepressants show inconclusive evidence for pain

Condition by drug class	Treatment regimen: median (minimum-maximum) dose and duration	Outcome	Effect estimate (95% CI)*	No of trials (No of participants)	Certainty of evidence
SNRI					
Atypical chronic orofacial pain ⁵⁴	Venlafaxine 37.5-75 mg for 4 weeks (1 trial)	Pain intensity	MD -13 (-26.1 to 0.1)	1 (36)	Low†
Chronic migraine ⁶¹	Venlafaxine 75-150 mg for 10 weeks	Headache frequency (days)	MD -1.4 (-2.8 to -0.1)	1 (49)	Low†
Sciatica ³²	Duloxetine 120 mg for 4 weeks (1 trial); milnacipran 100 mg for 8 (6-10) weeks (2 trials)	Pain intensity	MD -17.8 (-45.5 to 9.9)	3 (96)	Very low
Chronic tension-type headache ⁵⁰	Venlafaxine 150 mg for 12 weeks (1 trial)	Headache frequency (days)	MD -2.3 (-7.3 to 2.7)	1 (59)	Low
SSRI					
Chronic pelvic pain ⁶³	Sertraline 100 mg for 6 weeks (1 trial)	Pain intensity	MD 0 (-6 to 6)	1 (23)	Low†
Chronic prostatitis ⁵⁹	Fluvoxamine 50-300 mg for 8 weeks (1 trial)	Pain intensity	MD -45 (-77.6, -12.4)	1 (42)	Low†
Irritable bowel syndrome ⁵⁶	Fluoxetine 20 mg for 9 (6-12) weeks (2 trials); paroxetine 40 mg for 12 weeks (1 trial)	Abdominal pain not improving	RR 0.6 (0.3 to 1.3)	3 (167)	Very low†
Chronic migraine ⁶¹	S-fluoxetine 40 mg for 12 weeks (1 trial)	Headache frequency (days)	MD -1.4 (-2.7, -0.1)	1 (33)	Low†
Postoperative pain ¹⁶	Escitalopram 10 mg for 7 days (including day of surgery) (1 trial)	Pain 24 hours post-surgery	MD 0 (-7.1 to 7.1)	1 (114)	Low
Chronic tension-type headache ⁵⁰	Citalopram 20 mg for 24 weeks (1 trial)	Headache frequency (days)	MD -0.2 (-3.9 to 3.5)	1 (68)	Low
TCA					
Acute oral mucositis ⁵⁸	Doxepin mouth rinse, single dose of 10 mg/mL×2.5 mL, diluted to 5 mL with 2.5 mL of sterile or distilled water (1 trial)	Pain intensity	MD -44 (-67 to -21)	1 (140)	Low†
Atypical chronic orofacial pain ⁵⁴	Amitriptyline 10 mg for 8 weeks (1 trial)	Pain intensity	MD -15.7 (-32.4 to 1.1)	1 (42)	Low†
Back pain ³²	Amitriptyline 15 (5-25) mg for 17 (8-26) weeks (2 trials); desipramine 60 mg for 12 weeks (2 trials); nortriptyline 100 mg for 8 weeks (1 trial); imipramine 75 mg for 4 weeks (1 trial); doxepin 300 mg for 6 weeks	Pain intensity	MD -10.3 (-18.8 to -1.9)	7 (591)	Very low
Bladder pain syndrome ⁵⁵	Amitriptyline 62.5 (25-100) mg for 14 (12-16) weeks	Pain intensity	MD -12.7 (-33.1 to 7.6)	2 (279)	Very low†
Fibromyalgia ⁴⁹	Amitriptyline 37.5 (25-50) mg for 8.5 (8-24) weeks	50% pain reduction	RR 2.1 (1.2 to 3.6)	4 (275)	Very low
Phantom limb pain ^{60‡}	Amitriptyline 10-125 mg for 6 weeks (1 trial)	Pain intensity	MD 0 (-17.6 to 17.6)	1 (39)	Low†
Rheumatoid arthritis ⁶⁴	Amitriptyline 50 (25-75) mg for 6 (1 day to 12 weeks) weeks (3 trials); dothiepin 75-150 mg for 7-10 weeks (2 trials); imipramine 75 mg for 6 weeks (1 trial); trimipramine 75 mg for 12 weeks (1 trial)	Pain intensity	NE. No benefit of TCA in the descriptive analysis	7 (482)	Very low
Sciatica ^{32§}	Amitriptyline 50 mg for 26 weeks (1 trial); nortriptyline 100 mg for 9 weeks (1 trial)	Pain intensity	MD -16 (-31.5 to -0.4)	2 (114)	Very low
Vulvodynia ⁵⁷	Desipramine 25-150 mg for 12 weeks (1 trial)	Pain intensity	MD 8.2 (-11.8, 28.2)	1 (112)	Low†
NDRI					
Back pain ³²	Bupropion 300 mg for 7 weeks (1 trial)	Pain intensity	MD -1 (-12.2 to 10.2)	1 (44)	Low
SARI					
Back pain ³²	Trazodone 600 mg for 6 weeks (1 trial)	Pain intensity	MD -5.4 (-22.9 to 12.1)	1 (40)	Low
Burning mouth syndrome ⁵³	Trazodone 200 mg for 8 weeks (1 trial)	Pain intensity	MD -1.6 (-6.8 to 3.6)	1 (37)	Low†
Tetracyclic/atypical					
Back pain ³²	Maprotiline 150 mg for 8 weeks (1 trial)	Pain intensity	MD -4.5 (-20.4 to 11.4)	1 (34)	Low
Fibromyalgia ⁴⁶	Mirtazapine 30 (30-45) mg for 13 (7-13) weeks (3 trials)	Pain reduction ≥50%	RR 1.3 (0.9 to 1.9)	3 (591)	Very low
Functional dyspepsia ³⁶	Mirtazapine 15 mg for 8 weeks (1 trial)	Pain intensity	MD 1.7 (-21.2 to 24.6)	1 (34)	Low†
MAOI					
Fibromyalgia ⁴⁸	Pirlindole 150 mg for 4 weeks (1 trial); moclobemide 600 mg for 12 weeks (12 weeks)	Pain intensity	MD -14.5 (-27.1 to -2)	2 (121)	Very low†

CI=confidence interval; MAOI=monoamine oxidase inhibitors; MD=mean difference; NDRI=noradrenaline-dopamine reuptake inhibitors; NE=not estimable; RR=risk ratio; SARI=serotonin antagonist and reuptake inhibitors; SNRI=serotonin-norepinephrine reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors; TCA=tricyclic antidepressants.

*Pain intensity outcomes are on a 0-100 scale unless stated otherwise.

†Grading of recommendations assessment, development, and evaluation determined by current authors (see supplementary file 5 for details of the assessment).

‡Phantom pain is a form of neuropathic pain, although the trial included in this review was not included in the meta-analysis estimates of either of the neuropathic pain reviews (Finnerup et al 2015¹⁷; Caruso et al 2019³⁵).

§Sciatica may be classified as a form of neuropathic pain; however, the sciatica review included substantially more trials (n=6) than previous reviews (eg, Finnerup et al 2015¹⁷ only included one trial).

Only nine of the 26 included reviews were considered to have high methodological quality as assessed by the AMSTAR-2 tool. We took several steps to minimise the impact of the low methodological quality of most reviews on treatment effect estimates. For example, when a Cochrane and a non-Cochrane review included the same trials on the same topic, we included the Cochrane review, which typically has higher methodological standards. We reviewed GRADE ratings for all comparisons or graded the certainty of evidence ourselves when a review did not assess the certainty of evidence. We also reanalysed the data of several reviews and conducted a sensitivity analysis contrasting trials and effect sizes from the 26 included reviews with 57 other excluded reviews.

We identified a systematic review and network meta-analysis investigating the efficacy of various drugs for migraine, including several antidepressant classes.⁶⁶ For various reasons we excluded that review after closer examination of its included trials. Many of those trials, for example, did not report data on headache frequency, which is the recommended outcome for clinical trials of headache.^{25 26} Other trials had important issues with the unit of analysis⁶⁷ or were not randomised.⁶⁸

For some conditions included in this overview, pain might not be the main reason why patients seek care—such is the case for functional dyspepsia, where around four in 10 patients experience some degree of epigastric pain.³⁶ For others, symptoms might include early satiety or postprandial fullness, or both. Findings of this review may therefore not be applicable to clinicians who are considering prescribing an antidepressant with the goal of reducing symptoms of postprandial fullness or another symptom in people with another pain condition. For some patients with pain conditions included in this review, pain might not be the only important outcome to be measured. For example, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group recommends that outcomes other than pain, such as tenderness, fatigue, patient functional ability, and sleep disturbance be measured in all clinical trials.⁶⁹ Our findings therefore may not apply to clinicians who are considering prescribing antidepressants to patients with fibromyalgia whose primary symptom is fatigue or sleep disturbance. In the review on pain and comorbid depression that we included,³¹ nine of the 14 included trials (64%) did not require participants to have pain in addition to depression as part of the inclusion criteria. Findings from this review therefore may not be applicable to patients who seek care primarily because of pain but also have depression.

Meaning of the study

The use of antidepressants has doubled in OECD countries from 2000 to 2015,⁷⁰ and the off-label (unapproved) use of these drugs for pain is thought to be a contributing factor to that increase. In a Canadian study, 29% of antidepressant prescriptions were off-label, and about 26% of these were for

treatment indications covered by our review (eg, pain, fibromyalgia, headache, digestive and urinary system disorders).⁹ Antidepressants are only approved for a few pain conditions. For example, in the UK⁷¹ and Australia,⁷² diabetic neuropathic pain is the only pain condition for which the SNRI duloxetine is approved. In the US, the Food and Drug Administration has approved duloxetine for fibromyalgia and chronic musculoskeletal pain.⁷³ Amitriptyline is approved in the UK for neuropathic pain and prophylactic treatment of headache (tension-type and migraine),⁷⁴ whereas in Australia it is not approved for any pain condition.⁷⁵ For many conditions covered in our review, the use of antidepressants is therefore off-label.

TCAs are the most commonly prescribed off-label antidepressant for pain, with a study showing that 74% of antidepressant prescriptions for a pain condition concerned a TCA.⁹ In our review, we provided efficacy estimates of TCAs for 14 conditions. Of these, we found evidence of efficacy for only three conditions—all with low certainty evidence. For the other 11 conditions, TCAs were either ineffective (one condition, moderate certainty evidence) or the evidence was inconclusive (10 conditions, four with only one small trial). The off-label use of drugs, including antidepressants, has been associated with a higher incidence of adverse drug events.⁷⁶ Given that most safety and tolerability estimates reported in our review were not informative owing to small sample sizes and imprecision (eg, around 63-66% of safety and tolerability estimates had total sample sizes <300), the safety profile of antidepressants for several conditions, many of which are used off-label, is unknown.

Implications for clinicians and future research

Caution is needed in interpreting our findings because 45% of the trials forming the body of evidence for this review had ties to industry. This is particularly relevant for the evidence on the efficacy of SNRIs, where 68% of trials were identified as having industry ties. The influence of industry on outcomes of clinical trials has been recognised as a source of bias in trials.^{77 78} Only one review, however, investigated the influence of industry sponsorship on patient outcomes.³² It is important that future reviews carry out sensitivity analysis based on industry funding when possible. For some pain conditions, where most or all available trials are funded by industry (eg, SNRIs for neuropathic pain and fibromyalgia), future trials free of industry ties are needed. For the three conditions with evidence of efficacy from TCA use (neuropathic pain, chronic tension-type headache, and irritable bowel syndrome), 15 out of 22 trials (68%) were published >20 years ago compared with four out of 67 (6%) trials on SNRIs. This is important as a recent study has identified that older trials of drugs for neuropathic pain (including antidepressants) are likely to have overestimated treatment effects.⁷⁹ We would encourage clinicians, researchers, and policy makers to be aware of these caveats when reading our review and considering the use of SNRIs and TCAs to treat pain.

For conditions where we found that antidepressants are efficacious, it is unclear whether the effects are clinically relevant. For example, in conditions where SNRIs were deemed efficacious with moderate certainty evidence, the reduction of pain compared with placebo was smaller than 10 points on a 0-100 scale (back pain, postoperative pain, and neuropathic pain).^{16 32 35} For fibromyalgia, where outcomes were measured as the proportion of participants with at least a 50% reduction in pain, 31% of people receiving an SNRI improved (compared with around 21% in the placebo group), which translates to an absolute risk reduction of 9% (95% confidence interval 7% to 9%).⁴⁵ We purposefully chose not to make judgments about the clinical importance of observed effects for each condition because commonly used thresholds, such as the 10 point reduction on a 0-100 scale commonly used in musculoskeletal pain research,⁴³ are arbitrary, context specific (specific condition, treatment, comparison, and outcome), and potentially misleading if interpreted inappropriately.⁸⁰ Given the challenges of making judgment calls about the clinical relevance of treatment effects, we encourage clinicians first to conduct a holistic assessment of the evidence, which includes an appraisal of the effect size, certainty of available evidence, and trade-offs between benefits and harms of each antidepressant, and then to involve patients in these discussions.

Our review identified a series of conditions for which the evidence base is scarce and high quality trials are needed. For example, no drug treatment has been shown to provide clear benefits for sciatica.⁸¹ Efficacy estimates for SNRIs and TCAs presented in our reviews may, however, contain clinically important effects, which would warrant further investigation by future trials.

Conclusions

We found evidence of efficacy of antidepressants in 11 (26%) of the 42 comparisons included in this overview of systematic reviews—seven (64%) investigated the efficacy of SNRIs. In four (37%) of the comparisons where antidepressants were efficacious, evidence was of moderate certainty: SNRIs for back pain, postoperative pain, fibromyalgia, and neuropathic pain. For the other 31 (74%) comparisons, antidepressants were either ineffective or evidence on their efficacy was inconclusive. Our findings suggest that a more nuanced approach is needed when prescribing antidepressants for pain.

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Supplementary information: Supplementary files 1-11