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

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## Scientific summary

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## Background

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

## Objectives

Our objective was to assess the efficacy and safety of antidepressants for chronic pain (except headache) in adults.

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

## Search methods

We searched CENTRAL, MEDLINE, EMBASE, CINAHL, LILACS, AMED and PsycINFO databases for randomised controlled trials (RCTs) of antidepressants for chronic pain conditions up until 4 January 2022.

## Selection criteria

We included RCTs that examined antidepressants for chronic pain against any comparator. If the comparator was placebo, another medication, another antidepressant or the same antidepressant at different doses, then the study was required to be double-blind. RCTs with active comparators that were unable to be double-blinded (e.g. psychotherapy) were included but rated as at high risk of bias. We excluded RCTs where the follow-up was < 2 weeks and those with < 10 participants in each trial arm. We included any antidepressant at any dose, for any indication but used primarily for treatment of people with chronic pain and compared to placebo or active intervention.

## Participants

We included adults (aged 18 years or older) reporting primary or secondary pain in any part of their body (except headache) as their primary complaint, that matched the International Association for the Study of Pain definition of chronic pain (i.e. at least 3 months' duration). We included all trials regardless of the severity of participants' chronic pain, although we extracted whether severity was part of the inclusion criteria of the individual studies. We excluded studies where the participants' primary pain condition was headache or migraine.

## Data collection and analysis

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

## Main results

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

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

### *Primary efficacy outcomes*

For pain relief, duloxetine standard dose showed a small to moderate effect for substantial pain relief [odds ratio 0.91, 95% confidence interval (CI) 0.56 to 0.84] and continuous pain intensity [standardised mean difference (SMD) −0.31, 95% CI −0.39 to −0.24]. For pain intensity, milnacipran standard dose also showed a small effect (SMD −0.22, 95% CI −0.39 to 0.06) with moderate-certainty evidence. For mood, mirtazapine had a moderate effect (SMD −0.5, 95% CI −0.78 to −0.22), while duloxetine showed a small effect (−0.16, 95% CI −0.22 to −0.1); however, it is important to note that most trials excluded participants with mental health conditions, and so average anxiety and depression scores tended to be in the 'normal' or 'subclinical' ranges at baseline already.

### *Secondary efficacy outcomes*

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

### *Safety*

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

## Authors' conclusions

Our review and NMAs show that despite studies investigating 25 different antidepressants, there is reliable evidence for only duloxetine in the treatment of chronic pain. Duloxetine was moderately

efficacious across all outcomes at standard dose. There is also promising evidence for milnacipran, although further high-quality research is needed to be confident in these conclusions. Data for all other antidepressants were of low certainty. As RCTs excluded people with low mood, we were unable to establish the effects of antidepressants for people with chronic pain and depression. There is currently no reliable evidence for the long-term efficacy and safety of any antidepressant.

## Study registration

This study is registered as PROSPERO CRD42020171855.

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