Cochrane Database of Systematic Reviews | Protocol - Intervention

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

Hollie Birkinshaw, Claire Friedrich, Peter Cole, Christopher Eccleston, Marc Serfaty, Gavin Stewart, Simon White, R Andrew Moore, Tamar Pincus Authors' declarations of interest

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Abstract

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the comparative efficacy and safety of antidepressants for adults with chronic pain. We will achieve this by:

- assessing the efficacy of antidepressants by type, class and dose in improving pain, mood, patient global impression of change, physical functioning, sleep quality and quality of life;
- assessing the number of adverse events of antidepressants by type, class and dose;
- ranking antidepressants in the efficacy of treating pain, mood and adverse events.

Background

This is a protocol for a Cochrane Review and network meta-analysis to assess the comparative efficacy and safety of antidepressants for adults with chronic pain.

Description of the condition

Chronic pain is common in adults internationally, and is defined as pain lasting or recurring for more than three months (IASP 2019). Chronic pain can occur with no tissue damage apparent. Therefore, the definition of chronic pain is split into primary chronic pain and secondary chronic pain. Primary chronic pain is diagnosed when the pain cannot be better explained by another condition, and is characterised by disability and emotional distress (e.g. non-specific low back pain; Treede 2015). Secondary chronic pain is pain that can be attributed to a specific, recognisable cause, and is grouped into the following six categories.

- Cancer-related pain: pain caused by cancer or treatment, including pain caused by chemotherapy.

- Postsurgical or post-traumatic pain: pain that develops after tissue trauma.
- Neuropathic pain: pain caused by a lesion or disease of the somatosensory nervous system.
- Secondary headache or orofacial pain: the chronic forms of symptomatic headache or orofacial pain (e.g. dental pain).
- Secondary visceral pain: pain caused by an underlying condition from the internal organs of the head, neck, thoracic, abdominal and pelvic regions.
- Secondary musculoskeletal pain: pain in joints, bones and tendons arising from an underlying disease (e.g. osteoarthritis).

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

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

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

Successful treatment of chronic pain can result in significant improvements in quality of life, including anxiety and depression (Goesling 2013; Moore 2010; Moore 2014). A systematic review identified that for people with fibromyalgia, reductions in pain intensity of 50% or more is associated with self-reports of sleep, fatigue and depression reverting back to normative values (Moore 2014). Therefore, efficacious treatment of the pain condition is essential for improvement of both pain and mood, in addition to potential improvements in sleep, physical function and quality of

life. There are many different treatments aimed at reducing and managing chronic pain, including analgesic medication, physiotherapy, self-management guidance, exercise, psychological therapy, antidepressants, pain management clinics and surgery. The use of these depends upon the pain condition, severity of pain, individual characteristics, availability of services and national policy and guidelines.

Description of the intervention

Antidepressants are medications developed and used primarily for the treatment of clinical depression. Some individual trials have shown a lack of efficacy for antidepressants, however the most recent review and meta-analysis that combined all known research has shown that they are efficacious in the treatment of acute major depression, particularly severe depression (Cipriani 2018).

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

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

For depression, SSRIs are often recommended for the first-line treatment, as TCAs and MAOIs are associated with more toxicities and interactions with other drugs than SSRIs (British National Formulary 2020). Antidepressants can also be used 'off-license' in clinical practice to treat other conditions such as eating disorders, obsessive compulsive disorder and chronic pain. Prescriptions of antidepressants are relatively common in patients with chronic pain internationally; for example, 12.3% of people with chronic low back pain in Portugal report taking antidepressants for pain relief (Gouveia 2017; Kurita 2012). Recent guidance from the National Institute for Health and Care Excellence (NICE) recommends the use of duloxetine, amitriptyline, fluoxetine, paroxetine, citalopram and sertraline in the management of primary chronic pain (NICE 2020). Amitriptyline and duloxetine are also recommended as first-line treatments for neuropathic pain in primary care (NICE 2019). Both of these guidelines recommend these antidepressants regardless of a person's mood, although at lower doses than those used for the treatment of clinical depression. However, other guidelines contradict this, for example antidepressants can be prescribed for people with a chronic physical health condition only if they are also experiencing moderate to severe depression (NICE 2009a), but they are not recommended at all for the treatment of chronic low back pain (without sciatica) (NICE 2017). Therefore, guidance for clinicians is mixed and unclear. Furthermore, as antidepressants can be prescribed for treating mood or pain, the proportions of antidepressants prescribed to people with chronic pain for the primary aim to reduce pain or improve mood is unknown.

There are also risks in the prescription of antidepressants. Adverse events such as dizziness, headache, nausea, ejaculation disorder, weight loss, tremor, sweating and insomnia, have been found by randomised controlled trials to be more common in people taking antidepressants than those taking placebo (Riediger 2017; Sinyor 2020). Use of antidepressants is associated with an increased risk of falls, fractures, all-cause mortality, and stroke in older adults (aged 65 and over), and self-harm and suicide in both younger adults (aged 20 to 64) and older adults (Coupland 2011;

Coupland 2015). Antidepressants also increase the risk of onset of seizures (Hill 2015); and the potential for gastrointestinal bleeding with SSRIs is widely recognised (Jiang 2015). Therefore, long-term use of antidepressants for people with chronic pain is expected to be associated with harms at the population level.

How the intervention might work

Neurotransmitters are chemicals that act as signals or messages throughout the body, transmitting messages between neurons, muscles and other parts of the body. Most antidepressants work by targeting monoamine neurotransmitters and their receptors in the nervous system that are associated with mood and emotion, such as 5-hydroxytryptamine receptors, which are activated by many neurotransmitters including serotonin, dopamine, adrenaline and noradrenaline. Antidepressants prevent the neurotransmitters from being absorbed into neurons, which prolongs their activity in synapses. This then causes repeated signals to be generated, boosting their effect in the brain and resulting in improved mood.

In people with chronic pain, antidepressants may also be used to manage pain as well as mood. Antidepressants can offer an analgesic response in people with pain without depression, specifically for neuropathic pain. In the targeting of neurotransmitters, antidepressants can also affect nerve pain signals. By increasing the amount of serotonin and noradrenaline, this may subsequently block pain signals travelling from the spinal cord to the brain. Therefore, fewer of these signals reach the brain, which reduces perceived pain intensity in certain types of chronic pain.

Furthermore, a part of the brain called the locus coeruleus is also known to have an analgesic effect on pain in the body. Signals from this part of the brain are sent when the body reacts to a stimulus, such as pain, and noradrenaline is released into the dorsal horn in the spine to block receptors. Animal studies have shown that when pain signals are continuously received, this analgesic response lessens over time, and noradrenaline is then not released (Obata 2017). However, when antidepressants such as duloxetine and amitriptyline are given, the analgesic response from the locus coeruleus is recovered.

Why it is important to do this review

There have been no systematic reviews or network meta-analyses investigating all antidepressants for all chronic pain conditions. There is no evidence comparing classes of antidepressants to each other in the management of chronic pain, as identified by the recent NICE guidelines (NICE 2020). Therefore, in the absence of any one randomised controlled trial comparing the efficacy and safety of all antidepressants for chronic pain, a network meta-analysis is required to assess their relative effectiveness.

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

For fibromyalgia, Cochrane Reviews of antidepressants show that there is no unbiased evidence that amitriptyline, desvenlafaxine, venlafaxine or SSRIs are superior to placebo (Walitt 2015; Welsch 2018). There is low-quality evidence that duloxetine and milnacipran have some benefit in improving patients' global impression of change (PGIC) and providing an improvement in pain relief of 30% or more, but no clinical benefit over placebo for improvement in pain

relief of 50% or more, health-related quality of life or fatigue (Welsch 2018). Similarly for mirtazapine, there is evidence for improvement in pain relief of 30% or more, and reduction of mean pain intensity and sleep problems, but this evidence is of low quality, and there is no benefit for improvement in pain relief of 50% or more, PGIC, 20% improvement of health-related quality of life, reduction of fatigue or reduction in negative mood (Welsch 2015).

Only one Cochrane Review has investigated the use of antidepressants for low back pain, and it found no clear evidence to support the use of any antidepressants (Urquhart 2008). A more recent systematic review supports these conclusions (Koes 2018). However, when analysed using imputation methods for missing data, randomised controlled trials have shown duloxetine and etoricoxib to be effective in reducing pain for pain conditions including chronic low back pain (Moore 2010a; Moore 2014). These distributions were bimodal; participants generally responded very well or very poorly, with few in between (Moore 2014). It is not known whether the reason for this is associated with the drugs, the pain condition, an interaction or other reasons.

These previous reviews have shown that there is some contradictory evidence regarding the efficacy of antidepressants in the management of chronic pain conditions. Through this review and network meta-analysis we intend to be able to identify whether certain classes or doses of antidepressants are useful in the management of pain and mood for people with chronic pain, and for certain chronic pain conditions. As antidepressants are also associated with a number of side effects, we will compare the proportion of adverse events occurring with the use of different antidepressants (including different classes of antidepressants, different types of antidepressants, and different dose regimes) within populations living with chronic pain.

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

Objectives

To assess the comparative efficacy and safety of antidepressants for adults with chronic pain. We will achieve this by:

- assessing the efficacy of antidepressants by type, class and dose in improving pain, mood, patient global impression of change, physical functioning, sleep quality and quality of life;
- assessing the number of adverse events of antidepressants by type, class and dose;
- ranking antidepressants in the efficacy of treating pain, mood and adverse events.

Methods

Criteria for considering studies for this review

Types of studies

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

The most common comparators we anticipate finding in the literature are: the same antidepressant at a different dose; a different antidepressant; placebo (both active and inert); other medications for pain management purposes (e.g. pregabalin, gabapentin); analgesics; psychological therapy (e.g. cognitive behavioural therapy, acceptance and commitment therapy); exercise; physiotherapy; multidisciplinary pain programmes; herbal and nutraceuticals (e.g. St John's Wort); and acupuncture. Where the comparator is a placebo, antidepressant, analgesic or other medication for pain management purposes, these trials must be double-blind. We will include trials examining any dosage of antidepressants, with a follow-up duration of at least two weeks and minimum of 10 participants per arm. We will exclude non-randomised studies, case reports, experimental studies, clinical observations and prevention studies.

Types of participants

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

Types of interventions

Decision set

We will include any antidepressant in any dose, for any aim, used primarily in treatment of people with chronic pain and compared to placebo or active intervention. For the purposes of this review, we will expect to find antidepressants grouped into the following classes.

- Tricyclic antidepressants: amitriptyline, imipramine, trimipramine, doxepin, desipramine, protriptyline, nortriptyline, clomipramine, dothiepin, lofepramine, and others.
- Heterocyclic antidepressants: mianserin, trazodone, amoxapine, maprotiline, and others.

- Selective serotonin reuptake inhibitors (SSRIs): zimelidine, fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and others.
- Serotonin-noradrenaline reuptake inhibitors (SNRIs): venlafaxine, milnacipram, duloxetine, and others.
- Monoamine oxidase inhibitors (MAOIs):
    - irreversible: phenelzine, tranylcipromine, izocarboxazid, and others;
    - reversible: brofaramine, moclobemide, tyrima, and others.
- Other antidepressants
    - Noradrenaline reuptake inhibitors (NARIs): reboxetine, atomoxetine, and others.
    - Dopamine and noradrenaline reuptake inhibitors (DNRIs): amineptine, buproprion, and others.
    - Noradrenergic and specific serotonergic antidepressants (NASSAs): mirtazapine, and others.
    - Serotonin antagonist and reuptake inhibitors (SARIs): trazodone, and others.
    - Unclassified: agomelatine, vilazodone, and others.

Supplementary sets

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

Types of outcome measures

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

For pain and mood, where applicable we will also dichotomise outcomes into pain relief or improvement of 50% or greater, in line with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidance, to indicate substantial improvement (Dworkin 2008). We will compare antidepressants to the comparators immediately post-treatment, at short-term follow-up (12 weeks or less) and long-term follow up (over 12 weeks). Where studies include multiple follow-up time points, we will take the most recent time point within each period. If multiple measures are used, then we will extract from the most valid, reliable and widely used measure in the field.

Primary outcomes

- Substantial pain relief: at least 50% reduction in pain intensity from baseline, irrespective of pain measurement method (e.g. visual analogue scale, numerical rating scale).
- Mood (continuous data, e.g. visual analogue scale or validated measures such as the Hospital Anxiety and Depression Scale).

- Number and percentage of participants reporting adverse events (reported adverse events and serious adverse events).

Secondary outcomes

- Moderate pain relief: at least 30% reduction in pain intensity from baseline.
- Patient Global Impression of Change (PGIC): moderate (much or very much improved) and substantial (very much improved).
- Withdrawal (measured by the proportion of participants (number and percentage of total and per arm) withdrawing for any reason).
- Physical functioning (includes measures of physical movement and disability; measured by any validated scale).
- Sleep quality (includes insomnia, restfulness, etc.; measured by any validated scale, e.g. Jenkins Sleep Scale).
- Quality of life (measured by any validated scale).

Search methods for identification of studies

Electronic searches

We will search the following databases, without language restrictions.

- The Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library.
- MEDLINE and MEDLINE In-Process (via OVID).
- Embase (via OVID).
- CINAHL (via EBSCO).
- LILACS (via Birme).
- PsycINFO (via OVID).

We will tailor searches to individual databases. The search strategy for MEDLINE (via OVID) is in Appendix 1. The search strategy will be developed by the Cochrane Pain, Palliative and Supportive Care (PaPaS) Review Group's Information Specialist and will be independently peer reviewed. The PaPaS Information Specialist will perform the searches.

Searching other resources

We will search ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for unpublished and ongoing trials. In addition, we will search grey literature, check reference lists of reviews and retrieved articles for additional studies, and perform citation searches on key articles. We will contact experts in the field for unpublished and ongoing trials. We will contact study authors for additional information where necessary.

Data collection and analysis

Selection of studies

Two review authors (HB and CF) will independently determine eligibility of each study identified by the search. Independent review authors will eliminate studies that clearly do not satisfy inclusion criteria, and will obtain full copies of the remaining studies. HB and CF will read these studies independently to select relevant studies, and in the event of a disagreement, third and fourth authors will adjudicate (TP and CE). We will not anonymise the studies in any way before assessment. We will include a PRISMA flow chart in the full review which will show the status of identified studies (Moher 2009), as recommended in *Cochrane Handbook* (Higgins 2020). We will include studies in the review irrespective of whether measured outcome data are reported in a 'usable' way. We will record reasons for exclusion of any ineligible studies at the full-text stage.

Data extraction and management

Two review authors (HB and CF) will independently extract data using a standard piloted form and check for agreement before entry into Review Manager 5.4 (Review Manager 2020). In the event of disagreement, third and fourth authors (TP and CE) will adjudicate. We will collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will collect characteristics of the included studies in sufficient detail to populate a table of 'Characteristics of included studies' in the full review. We will extract the following information.

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

Assessment of risk of bias in included studies

Two review authors (HB and CF) will independently assess risk of bias for each study, using the criteria outlined in the *Cochrane Handbook* (Higgins 2011), with any disagreements resolved by discussion. We will complete a 'Risk of bias' table for each included study using the Cochrane 'Risk of bias' tool version 1.0 in Review Manager 5.4 (Review Manager 2020).

We will assess the following for each study.

- Random sequence generation (checking for possible selection bias). We will assess the method used to generate the allocation sequence as being at:
    - low risk of bias (any truly random process, e.g. random number table; computer random number generator); or

- unclear risk of bias (method used to generate sequence not clearly stated).
- We will exclude studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).

- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We will assess the methods as being at:
  - low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); or
  - unclear risk of bias (method not clearly stated).
  - We will exclude studies that do not conceal allocation (e.g. open list).
- Blinding of participants and personnel (checking for possible performance bias). Due to the inclusion of trials using any comparator, our review will contain both double-blinded RCTs and those studies in which double-blinding is not possible (i.e. RCTs of psychological therapy or acupuncture). In the RCTs that are double-blinded, we will assess the methods used to blind study participants and personnel from knowledge of which intervention a participant received in the double-blind trials. We will assess methods as being at:
  - low risk of bias (the study states that it was blinded and describes the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); or
  - unclear risk of bias (the study states that it was blinded but does not provide an adequate description of how this was achieved).
  - Studies in which double-blinding was not possible due to the comparator will be considered to have high risk of bias.
- Blinding of outcome assessment (checking for possible detection bias). We will assess the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We will assess the methods as being at:
  - low risk of bias (the study has a clear statement that outcome assessors were unaware of treatment allocation, and ideally describes how this was achieved);
  - unclear risk of bias (the study states that outcome assessors were blind to treatment allocation but it lacks a clear statement on how this was achieved); or
  - high risk of bias (the outcome assessment was not blinded).
- Selective reporting (checking for reporting bias). We will assess whether primary and secondary outcome measures were pre-specified and whether these were consistent with those reported. We will assess the methods as being at:
  - low risk of bias (study protocol is available with pre-specified measures);
  - unclear risk of bias (insufficient information available to permit a judgement of high or low risk of bias); or
  - high risk of bias (not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes have been reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of

interest in the review have been reported incompletely so that they cannot be entered in a meta-analysis; the study report failed to include results for a key outcome that would be expected to have been reported for such a study).

- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We will assess the methods used to deal with incomplete data as being at:
    - low risk of bias (no missing outcome data; reasons for missing outcome data are unlikely to be related to the true outcome; missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups; missing data have been imputed using 'baseline observation carried forward' analysis);
    - unclear risk of bias (insufficient reporting of attrition/exclusions to permit a judgement of low or high risk of bias (e.g. number randomised not stated; no reasons for missing data provided; or the study did not address this outcome)); or
    - high risk of bias (the reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; 'as-treated' analysis was done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation).

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

Measures of treatment effect

We anticipate most studies will report continuous data for our outcomes, which we will extract and convert into standardised mean difference (SMD) with 95% confidence intervals. We will convert all data into SMD as we anticipate that there will be a broad range of outcome measures used across studies. We will interpret SMD as small (0.2), moderate (0.5) and large (0.8), in line with Cohen 1988 and the *Cochrane Handbook* (Higgins 2020). We will also present results for the primary outcomes on a zero-to-100 scale. For dichotomous data, we will use summary odds ratio (OR) with 95% confidence intervals (CIs). To rank the treatments for each outcome by probability of best treatment, we will use the surface under the cumulative ranking curve (SUCRA) and the mean ranks.

Unit of analysis issues

For most RCTs, we do not envisage any unit of analysis complexities as trial participants are likely to be randomised to different study arms, allowing direct analysis. For cross-over RCTs, if the results for the first period (prior to cross-over) are reported, we will extract these in an attempt to avoid cross-over effects. If the results from the first period are not reported then we will extract the final trial results, provided there is a sufficient washout period of at least five times the length of the antidepressant half-life (minimum washout period length will be calculated separately for each antidepressant). For cluster-RCTs we will use meta-analysis to pool effect sizes across the clusters to then take an overall effect size into the network meta-analysis, in line with the guidance in the *Cochrane Handbook* (Higgins 2020).

Dealing with missing data

We will first try to contact the authors of the study for all missing data relevant to our analysis. If we cannot get the data from the authors, then we will follow the guidance from the *Cochrane Handbook* (Higgins 2020). If standard deviations are missing then we will use the Review Manager calculator to calculate these from other data reported in the study. We

will not impute any data, but will assess each study's risk of bias due to missing data, and undertake threshold analysis to assess how sensitive the results are to change. We will then discuss the implications of missing data upon the review and network meta-analysis in the discussion section of the review.

Assessment of heterogeneity

We will assess heterogeneity within the network meta-analyses using the Tau^2 statistic, in line with the guidance in the *Cochrane Handbook* (Higgins 2020). For pairwise analysis, we will assess heterogeneity using the Chi^2 test and the I^2 statistic, calculated for each pairwise comparison on each outcome. As outlined in the *Cochrane Handbook*, we will interpret the I^2 statistic as follows (Higgins 2020).

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

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

Assessment of the transitivity assumption

We will carefully scrutinise transitivity, which is the key underlying assumption of network meta-analysis (NMA). Transitivity requires studies to be similar on average across all the important factors other than the intervention comparison being made (Higgins 2020). To address this, we will only include studies with similar clinical populations (i.e. participants reporting pain lasting at least three months) (Furukawa 2016). Previous research, combined with review authors' clinical experience and knowledge, has identified variables that could potentially influence our primary outcome:

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

We will explore the distribution of these effect modifiers across treatment comparisons to assess the potential for distortion. The inclusion of placebo and concerns about its potential to violate the transitivity assumption have been highlighted in general (Cipriani 2013), and particularly in depression studies (Rutherford 2009). Therefore, we will explicitly compare placebo-controlled studies with those that provide head-to-head evidence as a form of validation of the network.

We will also explore transitivity in relation to clinical and methodological features using threshold analysis. Threshold analysis indicates how much evidence would have to change (due to missing studies, uncertainty around bias or transitivity) to change the results, recommendations and treatment decisions (Phillippo 2019). This ascertains which

comparisons between treatments in the NMA are sensitive and which are robust. Robust comparisons are likely to lead to a higher strength of evidence than more sensitive counterparts, and this will inform our creation of the 'Summary of findings' tables.

Assessment of reporting biases

We will assess reporting bias using the Cochrane 'Risk of bias' tool version 1.0 in Review Manager 5.4 (Review Manager 2020), by checking for study protocols and pre-specified outcomes. We will also use funnel plots for pairwise analyses, as advised in the *Cochrane Handbook* (Higgins 2020).

Data synthesis

We plan to present separate NMAs for each outcome. The NMAs will include all antidepressants and comparators. They will analyse both direct comparisons of interventions within RCTs, and indirect comparisons across trials based on a common comparator (Caldwell 2005; Jansen 2011). Direct comparisons are defined as two or more interventions compared head-to-head in a trial, whilst indirect evidence is a comparison made in the NMA as no trials have been found that compared the interventions head-to-head.

We will analyse the data for all primary and secondary outcomes using Bayesian random-effects NMAs, augmented with pairwise comparisons to explore transitivity assumptions and inform strength of evidence assessments. We will present network diagrams and rankograms for each outcome, in order of their SUCRA values.

Pairwise analysis will consist of random-effects meta-analysis and meta-regression using a restricted maximum likelihood estimator. We will combine study effects using a random-effects NMA model accounting for the correlations induced by multi-group studies using multivariate distributions. We will quantify heterogeneity by comparing the posterior distribution of the estimated heterogeneity variance with its predictive distribution.

Where possible, we will analyse outcomes within three time frames: post-treatment; short-term follow-up (12 weeks or less); and long-term follow-up (over 12 weeks). Where multiple time points are reported within each time frame, we will take the most recent time point.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses for the following factors.

- Class of antidepressant (SSRI, SNRI, TCA, MAOI, etc.).
- Dosage of antidepressant (high, standard, low).
- Type of pain (according to IASP pain categories).
- Aim of the trial (i.e. whether the intervention is aimed at pain or mood).
- Baseline level of depression (none, mild, moderate, severe as defined by the individual measure criteria).

We will use a Bayesian random-effects NMA to account for expected heterogeneity and variation in the data. These methods allow the uncertainty inherent in the between-study variance component to be reflected in effect estimate precision, and can be implemented in metaphor. We will undertake planned a priori analyses to explore dose of antidepressant, class of antidepressant, pain diagnostic groupings (as grouped by the IASP 2019 definitions), the aim of the trial and baseline level of depression as reasons for heterogeneity and will test these as moderators. Where possible, we will perform the subgroup analyses by building separate models, however where this is not possible we will use regressions.

Sensitivity analysis

For the NMA, we will evaluate consistency (i.e. the agreement between direct and indirect evidence) using the design-by-treatment test and by separating direct evidence from indirect evidence as a sensitivity analysis. We will also explore risk of bias within the included trials; we will perform a sensitivity analysis by removing the studies judged to be at high risk of bias overall (i.e. those studies meeting the criteria for high risk of bias for any domain of the Cochrane 'Risk of bias' tool, version 1.0). If data permit, we will also conduct a sensitivity analysis of 'inert' versus 'active placebos' to explore any difference of effect.

Summary of findings and assessment of the certainty of the evidence

Two review authors (HB and CF) will independently rate the certainty of the body of evidence for the outcomes. We will implement the GRADE system, alongside guidelines provided in the *Cochrane Handbook* (Higgins 2020) and the GRADEpro Handbook (Schünemann 2013), to rank the certainty of the evidence using the GRADEprofiler Guideline Development Tool (GRADEpro GDT 2015).

The GRADE approach uses five considerations (study limitations (risk of bias), unexplained heterogeneity and inconsistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each outcome. The GRADE system results in the assignment of one of the following grades to the evidence.

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

The GRADE system considers study design as a marker of quality. RCTs are considered to contain high-quality evidence and can be downgraded for important limitations. Factors that may decrease the certainty level of a body of evidence are as follows.

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

To assess the certainty of the NMA, we will use the Confidence in Network Meta-Analysis (CINeMA) framework (Nikolakopoulou 2020). The CINeMA framework considers the impact of certain issues within network meta-analyses on clinical decision making made from the results. This framework is based on GRADE, and considers the following six domains specific to NMA.

- Within-study bias (impact of risk of bias in the included studies).
- Reporting bias (publication and other reporting biases).

- Indirectness (relevance to the research question, addressing transitivity).
- Imprecision (the precision of the NMA, by combining direct with indirect evidence).
- Heterogeneity (variability in the results of studies).
- Incoherence (agreement between the results of direct and indirect evidence).

To present our findings, we will produce separate 'Summary of findings' tables for our primary outcomes (pain intensity, mood and adverse events). As this is a large and complex meta-analysis in which we anticipate many comparisons, we are unable to specify directly which comparisons will be the most important. Broadly, our main comparisons will be antidepressant versus non-pharmacological intervention, antidepressant versus placebo, and comparisons between different classes of antidepressant.

An example 'Summary of findings' table is given below, with example comparisons listed down the left side (see Table 1).

Table 1. Example 'Summary of findings' table **Open in table viewer**

All antidepressants compared with placebo for chronic pain						
Patient or population: adults with chronic pain						
Settings: any						
Intervention: antidepressants A, B, C, D, E						
Comparison: placebo						
Outcome: pain intensity						
Total studies: XXX **Total participants: XXX**	**Anticipated absolute effect (95% CI)**		**Relative effect (95% CI)**	**SUCRA**	**Certainty of the evidence (GRADE)**	**Interpretation of Findings**
	Without intervention	**With intervention**				
Antidepressant A (x RCT, xxx participants)						
Antidepressant B (x RCT, xxx participants)						
Antidepressant C (x RCT, xxx participants)						
Antidepressant D (x RCT, xxx participants)						
Antidepressant E (x RCT, xxx participants)						

GRADE Working Group grades of evidence

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

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;

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

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

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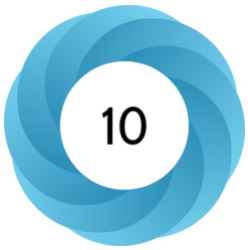

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Authors

Hollie Birkinshaw

Royal Holloway, University of London, London, UK

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Claire Friedrich

Royal Holloway, University of London, London, UK

More by this author on the Cochrane Library

Peter Cole

Oxford Pain Relief Unit, Churchill Hospital, Oxford University Hospitals NHS Trust, Oxford, UK

More by this author on the Cochrane Library

Christopher Eccleston

Centre for Pain Research, University of Bath, Bath, UK

More by this author on the Cochrane Library

Marc Serfaty

University College London, London, UK

More by this author on the Cochrane Library

Gavin Stewart

Newcastle University, Newcastle upon Tyne, UK

More by this author on the Cochrane Library

Simon White

School of Pharmacy and Bioengineering, Keele University, Keele, UK

More by this author on the Cochrane Library

R Andrew Moore

Plymouth, UK

More by this author on the Cochrane Library

Tamar Pincus

Correspondence to: Department of Psychology, Royal Holloway University of London, Egham, UK

t.pincus@rhul.ac.uk

More by this author on the Cochrane Library

Contributions of authors

Draft the protocol	TP, HB, CF, PC, CE, MS, GS, SW, RAM TP is the Principal Investigator for this funded review, responsible for the conception and lead on all aspects of the project
Develop and run the search strategy	TP, HB, CF, PC, CE, MS, GS, SW, RAM PaPaS Information Specialist provided support.

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Declarations of interest

Hollie Birkinshaw: none known.

Claire Friedrich: none known.

Peter Cole is a Consultant in anaesthesia and pain medicine and manages people with chronic pain.

Christopher Eccleston: none known. At the time of writing this protocol, CE was also a PaPaS Co-ordinating Editor, and so we acknowledge the input of Neil O'Connell who acted as Sign Off Editor. CE had no input into the editorial decisions or processes.

Marc Serfaty is a Consultant Psychiatrist and manages people with mental health problems.

Gavin Stewart: none known.

Simon White: none known.

Andrew Moore: none known.

Tamar Pincus had one consultancy advisory meeting with Reckitt Benckiser in February 2020.

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2021 Apr 07	Antidepressants for pain management in adults with chronic pain: a network meta-analysis	Protocol	Hollie Birkinshaw, Claire Friedrich, Peter Cole, Christopher Eccleston, Marc Serfaty, Gavin Stewart, Simon White, R Andrew Moore, Tamar Pincus	**https://doi.org/10.1002/14651858.CD014682**

Appendices

Appendix 1. MEDLINE (OVID) search strategy

1. pain/ or exp abdominal pain/ or exp arthralgia/ or exp back pain/ or breakthrough pain/ or cancer pain/ or exp chest pain/ or chronic pain/ or earache/ or eye pain/ or facial pain/ or flank pain/ or glossalgia/ or exp headache/ or mastodynia/ or metatarsalgia/ or exp musculoskeletal pain/ or exp neck pain/ or neuralgia/ or exp nociceptive pain/ or pain, intractable/ or exp pain, postoperative/ or pain, referred/ or exp pelvic pain/ or renal colic/
2. pain.tw.
3. (headache* or migraine* or fibromyalgia* or neuralgia*).tw.
4. Fibromyalgia/
5. 1 or 2 or 3 or 4
6. exp ANTIDEPRESSIVE AGENTS/
7. exp MONOAMINE OXIDASE INHIBITORS/
8. exp NEUROTRANSMITTER UPTAKE INHIBITORS/
9. ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) and (uptake or reuptake or re uptake)).tw.
10. (noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic or pharmacotherap* or psychotropic).tw.
11. (antidpress* or anti-depress*).tw.
12. (MAOI* or RIMA).tw.
13. monoamine oxidase inhibit*.tw.
14. (Agomelatine or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Brofaromin*).tw.
15. (Bupropion or Amfebutamone or Butriptylin* or Caroxazone or Cianopramin* or Cilobamin* or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine).tw.
16. (Clorgyline or Clovoxamin* or "CX157" or Tyrima or Tririma or Demexiptilin* or Deprenyl or Desipramin* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensin* or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or "DVS-233" or Escitalopram or Etoperidone or Femoxetin* or Fluotracen or Fluoxetine or Fluvoxamin*).tw.
17. (Hyperforin or Hypericum or St John* or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramin* or "Lu AA21004" or Vortioxetine or "Lu AA24530" or Tedatioxetine or "LY2216684" or Edivoxetine or Maprotilin* or Medifoxamin* or Melitracen or Metapramin* or Mianserin or Milnacipran or Minaprin* or Mirtazapin* or Moclobemide).tw.
18. (Nefazodone or Nialamide or Nitroxazepine or Nomifensin* or Norfenfluramin* or Nortriptylin* or Noxiptilin* or Opipramol or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramin* or Tryptophan* or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).tw.
19. or/6-18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. drug therapy.fs.
25. randomly.ab.
26. trial.ab.
27. or/20-26
28. exp animals/ not humans.sh.

29. 27 not 28
30. 5 and 19 and 29
31. limit 30 to "all adult (19 plus years)"