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Ketamine and other NMDA receptor antagonists for chronic pain (Protocol)

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[Intervention Protocol]

Ketamine and other NMDA receptor antagonists for chronic pain

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ABSTRACT

Objectives

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

To evaluate the benefits and harms of ketamine and other NDMA receptor antagonists compared to placebo, usual care, or other medicines for adults with chronic non-cancer pain.

BACKGROUND

Description of the condition

Chronic pain is defined as pain that persists for three months or longer (Treede 2019). It is common, affecting approximately 20% of adults in the USA (Dahlhamer 2018), 19% in Europe (Breivik 2006), and 33% in low- and middle-income countries (Jackson 2015), with prevalence estimates varying according to definition and severity. The most common chronic pain conditions are low back pain, neck pain, migraine, and other musculoskeletal disorders, representing four of the 10 leading causes of disability in low- and high-income countries (Rice 2016; Vos 2015). Chronic pain has considerable personal consequences, affecting mood, social participation, and ability to work (Dueñas 2016; Moore 2014). The economic burden of chronic pain has been estimated at USD 560 to USD 635 billion per year in the USA and AUD 139 billion per year in Australia, arising from medical costs and productivity losses (Institute of Medicine 2011; Painaustralia 2019).

In 2019, the World Health Organization (WHO) made significant revisions to the classification of chronic pain in the International Classification of Diseases 11th Revision (ICD-11), formally distinguishing between chronic primary pain and chronic secondary pain (Treede 2019). Chronic primary pain is characterised by persisting pain and associated emotional distress and disability that cannot be accounted for by another condition (e.g. fibromyalgia; Treede 2019). Chronic secondary pain arises, at least initially, as a symptom secondary to an identifiable underlying disease or condition (e.g. neuropathic pain; Scholz 2019).

Description of the intervention

N-methyl-D-aspartate (NMDA) receptor antagonists are a group of medicines classed according to their mechanism of action. These medicines are presumed to exert their effects by inhibiting the action of the NMDA receptor, a widely distributed glutamate-gated ion channel that mediates excitatory neurotransmission (Paoletti 2013; Traynelis 2010). Due to the NMDA receptor's role in neuronal development and synaptic plasticity (Hansen 2017), NMDA receptor antagonists are used clinically for their anaesthetic, analgesic, antidepressive, and neuroprotective properties.

Ketamine, a widely used, non-competitive NMDA receptor antagonist, was first synthesised in 1962 as a derivative of phencyclidine (PCP; Mion 2017). Ketamine is a dissociative anaesthetic which, at high doses, causes general anaesthesia, and at lower doses, analgesia and sedation (Cohen 2018; Peltoniemi 2016). Ketamine is licenced as an anaesthetic across most jurisdictions, and since 2019, also as an antidepressant for treatment-resistant depression in an intranasal formulation in the USA, the UK, Europe, and Australia. Physicians commonly prescribe oral or intravenous ketamine off label to treat chronic pain (van Hecke 2014).

Ketamine is available as a racemic mixture of R(-) and S(+) stereoisomers or as the S(+)-enantiomer alone, which may have greater analgesic efficiency and a shorter recovery time (Bell 2017). Possible routes of administration include intravenous, intramuscular, intranasal, subcutaneous, oral, and topical. The oral bioavailability of ketamine is low, with a reported rate of 24% for racemic preparations (Chong 2009), and 11% for S-ketamine (Peltoniemi 2013). The drug has a rapid plasma half-life of approximately 2.3 (standard deviation(SD) 0.5) hours (Cohen 2018), and undergoes oxidative hepatic metabolism via cytochrome P450 CYP3A and CYP2B6 enzymes to norketamine, its active metabolite (Mion 2013). Extensive first-pass metabolism via CYP3A enzymes makes ketamine vulnerable to interactions with other drugs (Dinis-Oliveira 2017), particularly benzodiazepines and opioids such as morphine (Dickenson 1997; Lilius 2015).

Ketamine is commonly administered for acute pain as an intravenous bolus of 0.3 to 0.5 mg/kg with or without a continuous infusion of 0.1 to 0.2 mg/kg/hr (Schwenk 2018). For chronic pain, ketamine is usually administered as 0.5 to 2 mg/kg single day outpatient or three- to five-day inpatient infusions (Cohen 2018). Ketamine administration is associated with psychotomimetic effects (e.g. delusions and delirium), and other adverse effects such as nausea, vomiting, and hypersalivation, each dose-dependent (Brinck 2018). Ketamine has a risk of addiction, dependence, and withdrawal, and studies have associated the chronic use of the drug with hepatobiliary toxicity (Cotter 2021; Wong 2014) and cystitis (Grégoire 2008; Shahani 2007), although high-quality safety data are lacking (Bell 2018).

The requirement for hospital admission and monitoring during intravenous administration, the potentially undesirable side effect profile, and the risks associated with prescribing oral formulations have limited the clinical use of ketamine for chronic pain. Uncompetitive, low- or moderate-affinity NMDA receptor antagonists may be suitable alternatives to ketamine, due to their increased tolerability, higher oral bioavailability, and lower risk of abuse. Several NMDA receptor antagonists have been investigated for their analgesic effects on chronic pain, including memantine, licenced for the treatment of moderate-to-severe Alzheimer's disease (Pickering 2018); amantadine, licenced for the treatment of Parkinson's disease and type A influenza virus (Mata-Bermudez 2021); dextromethorphan, a commonly used cough suppressant (Weinbroum 2000); and magnesium (Urits 2021).

How the intervention might work

Increased excitability and synaptic efficacy of neurons involved in central nociceptive pathways are key physiological correlates of chronic pain (Woolf 2011). One mechanism thought to contribute to these changes in synaptic plasticity is sustained glutamatergic NMDA receptor activity (Latremoliere 2009; Woolf 1991). Pharmacological blockade of NMDA receptors may slow or reduce these changes, leading to a reduction in pain intensity (Kreutzwiser 2019). NMDA receptor antagonists are administered to reduce pain in conditions where central mechanisms are thought to predominate (Cohen 2014). Ketamine specifically may exert an analgesic effect by alleviating the affective component of pain (Niesters 2012).

Why it is important to do this review

Physicians are increasingly prescribing intravenous ketamine as a 'third-line' therapy for the treatment of people with refractory chronic non-cancer pain (Bell 2018), despite its uncertain efficacy and safety (Orhurhu 2019). Surveys in South Korea and the Netherlands found that 60% to 70% of pain clinics used ketamine to manage chronic pain, with most reporting intravenous administration (Anaya 2018; Mangnus 2022).

In the UK, the 2021 National Institute for Health and Care Excellence (NICE) guideline for the management of chronic primary pain advised against the use of ketamine in people aged 16 years and over (NICE 2021). The American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists guidelines provided a weak-evidence recommendation for ketamine infusions in spinal cord injury-related pain, and a moderate-evidence recommendation for ketamine infusions in complex regional pain syndrome-related pain (Cohen 2018). The Australian and New Zealand College of Anaesthetists Faculty of Pain Medicine published a position statement on the use of ketamine in the management of chronic non-cancer pain, offering guidance on the evidence for the benefits and harms of this approach, and ethical and safety considerations (ANZCA FPM 2021). In 2022, a French Delphi survey established national consensus on ketamine's treatment indications, adverse events, routes of administration and dosing, and combination with non-pharmacological treatments (Voute 2022).

The Cochrane Library contains no reviews that focus on ketamine and other NMDA receptor antagonists for chronic non-cancer pain. Given the increasing use and uncertain efficacy and safety of these interventions, there is a need for an up-to-date Cochrane Review to provide reliable information for people with chronic pain, clinicians, and policymakers, and to guide future research and treatment guidelines.

OBJECTIVES

To evaluate the benefits and harms of ketamine and other NDMA receptor antagonists compared to placebo, usual care, or other medicines for adults with chronic non-cancer pain.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) with parallel or cross-over design, and with individual or cluster randomisation. Randomised trials are the best design to minimise bias when evaluating the effectiveness of an intervention.

We will include data from studies published as full texts, online clinical trial registries, summaries of otherwise unpublished clinical trials, and abstracts; if abstracts contain insufficient data for analysis, we will attempt to locate the full study (e.g. by contacting the study authors). If the data from the full study are unavailable, we will add the abstract to 'Studies awaiting classification'.

We will exclude non-randomised studies, experimental studies using pain induction, case reports, and clinical observations.

Types of participants

We will include studies of adults aged 18 years and older reporting chronic pain of greater than three months' duration, with average baseline (pre-intervention) pain intensity levels of at least 4/10 or its equivalent. We will exclude studies of participants with pain arising from cancer or headache, as the authors of previous Cochrane Reviews have done (O'Connell 2021; Williams 2020). We will include studies in which only a subset of participants meets these criteria, if the relevant data are provided separately.

Types of interventions

We will include trials that evaluate ketamine or another NMDA receptor antagonist, at any dose and by any route of administration (intravenous, subcutaneous, intranasal, intramuscular, oral, sublingual/buccal, or topical), for the treatment of chronic pain, compared to inactive placebo, active placebo (i.e. a placebo that mimics the active drug's side effects), usual care, or another medicine. We will also include trials that compare an NMDA receptor antagonist plus another medicine with placebo plus the other medicine. As there are no consensus-driven criteria to classify NMDA receptor antagonists, this review will only include medicines that have a primary effect on the NMDA receptor and that are used clinically for the treatment of chronic pain. These are ketamine (its enantiomers, and active metabolite norketamine), memantine, dextromethorphan, amantadine, and magnesium.

Participants may receive concomitant treatments such as other medicines, physical therapies, or psychological interventions, provided these treatments are administered equally across treatment arms. We will list all treatment arms of each study in the 'Characteristics of included studies' table.

Types of outcome measures

Our outcomes are based on the IMMPACT core outcome set for clinical trials of treatments for chronic pain (Dworkin 2005).

Primary outcomes

- Participant-reported pain intensity scores, measured using a visual analogue scale (VAS), a numeric rating scale (NRS), a verbal rating scale, a Likert scale, a rating scale within a composite measure of pain, or an ordinal scale.
- Adverse events, defined as the total number of participants experiencing at least one adverse event, and the total number of participants experiencing the following specific adverse events.
  - Dissociative symptoms
  - Psychotomimetic effects (delusions/delirium/paranoia)
  - Hallucinations
  - Sedation
  - Nausea
  - Vomiting
  - Dizziness
  - Diarrhoea
  - Headache
  - Serious adverse events (i.e. adverse events that result in death, are life-threatening, require hospitalisation or prolong an existing hospitalisation, result in disability or permanent damage, result in a congenital anomaly or birth defect, or that require medical intervention to prevent one of the listed outcomes)

We will analyse specific adverse events as separate outcomes, and include other adverse events in an 'other' category.

Secondary outcomes

- Disability, measured with a validated subjective rating scale or questionnaire, or a functional testing protocol

- Depressive symptoms, measured with a validated questionnaire (e.g. Hospital Anxiety and Depression Scale), a rating scale, or a rating scale within a composite measure of depressive symptoms
- Health-related quality of life, measured with a validated quality of life scale (e.g. EuroQol Five-Dimension Health Questionnaire; EQ-5D)
- Tolerability, measured by the number of participants who withdraw from treatment due to adverse effects
- Opioid consumption, measured in morphine milligram equivalents

Time points of measurement

For outcomes assessing benefit (pain intensity, disability, depressive symptoms, health-related quality of life, and opioid consumption), we will classify the follow-up time points as follows.

- Immediate term: 48 hours to one week after randomisation
- Short term: more than one week to three months after randomisation
- Medium term: more than three months to six months after randomisation
- Long term: more than six months after randomisation

Where studies report multiple time points within a single category, we will use the latest date.

For outcomes assessing harms (adverse events, tolerability), we will use data measured at the end of the treatment period.

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) in the Cochrane Library (latest issue)
- MEDLINE (via Ovid: 1946 to date of search)
- Embase (via Ovid; 1974 to date of search)

We will tailor searches to individual databases. Appendix 1 presents the search strategy for MEDLINE.

The search strategy will be developed by the PaPaS Review Group's Information Specialist and will be independently peer-reviewed. The PaPaS Information Specialist will perform the searches.

We will not perform a separate search for adverse effects of the target intervention(s). We will consider adverse effects described in the included studies only.

Searching other resources

We will search the following trials registries for ongoing trials.

- US National Institutes of Health (NIH) Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov)
- WHO International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch)
- Australian New Zealand Clinical Trial Registry (anzctr.org.au)

In addition, we will check the reference lists of included studies and relevant reviews 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 (MF and AC) will independently screen the titles and abstracts of the records identified by the search, eliminating those that are clearly ineligible. We will retrieve the full-text reports of the remaining records, and the same two review authors will independently assess them against our eligibility criteria. If any disagreements arise, a third review author (JM) will adjudicate. We will not anonymise the studies in any way before assessment. We will document the study selection process in sufficient detail to create a PRISMA flowchart (Page 2021). We will include studies in the review irrespective of whether they have reported outcome data in a usable way.

Data extraction and management

Two review authors (MF and AC) will independently extract data using a standard piloted form and ensure their extracted data coincide before entering them into Review Manager Web (RevMan Web 2022). In the event of disagreement, a third review author will adjudicate (JM). 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.

- Methods: study design, total duration of study, number of study centres and location, country of origin, study setting, date of study
- Participants: number randomised, number lost to follow-up/withdrawn, number analysed, mean age, age range, sex, severity of condition, diagnostic criteria, inclusion/exclusion criteria, characteristics that stratify health opportunities (PROGRESS: place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, social capital; O'Neill 2014)
- Interventions: type of intervention(s), including duration, dosage, route of administration, and details of run-in/wash-out periods; type of comparator; rescue analgesia; concomitant medications; excluded medications
- Outcomes: outcomes specified and collected, time points reported
- Characteristics of trial design as outlined below (Assessment of risk of bias in included studies)
- Trial funding, notable conflicts of interest of study authors
- Information needed to assess GRADE (e.g. baseline risk in the control group for key outcomes)

Assessment of risk of bias in included studies

Two review authors (MF and AC) will independently assess risk of bias for each study using the Cochrane risk of bias tool (RoB 2), outlined in Chapter 8 of the *Cochrane Handbook for Systematic*

Reviews of Interventions (Higgins 2022a). We will resolve any disagreements by recourse to a third review author (JM).

RoB 2 assesses the risk of bias in individual studies across the following domains.

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

We will assess the risk of bias for the effect of assignment to the interventions at baseline, regardless of whether participants receive the interventions they were assigned (the 'intention to treat' effect), for the following outcomes:

- Pain intensity (continuous measures)
- Pain intensity (dichotomous measures)
- Adverse events (total number of participants experiencing at least one adverse event)

For pain intensity outcomes, we will assess risk of bias in the immediate term, short term, medium term, and long term. For adverse events, we will assess risk of bias at the end of the treatment period.

Where outcome data are missing from included studies, as part of the RoB 2 domain 'bias due to missing outcome data', we will consider whether the imputation method is last observation carried forward (LOCF) when we answer signalling question 3.2, 'Is there evidence that the result was not biased by missing outcome data?'.

The primary analysis will include all studies, regardless of their risk of bias. We will conduct sensitivity analyses to demonstrate the influence of high risk of bias studies on the primary outcomes by repeating the analyses without those studies.

We will present our RoB 2 judgements for each outcome with the corresponding forest plot using Review Manager Web (RevMan Web 2022). Where we have used unpublished data or correspondence with a study author to inform a judgement, we will note this in the footnote of the forest plot.

For each domain, we will assign an overall judgement of risk of bias as follows (Sterne 2019).

- Low risk of bias: the trial is judged to be at low risk of bias for all domains.
- Some concerns: the trial is judged to raise some concerns for at least one domain, but not to be at high risk of bias for any domain.
- High risk of bias: the trial is judged to be at high risk of bias for at least one domain, or the trial is judged to have some concerns for multiple domains, in a way that substantially lowers confidence in the results.

We will summarise risk of bias judgements for each domain, where the overall risk of bias for the result is the least favourable assessment across the domains of bias.

We will use the RoB Excel tool and word templates (available at riskofbias.info) to record and manage RoB 2 assessments and processes, and we will make available the full data related to this process on the Open Science Framework.

Risk of bias assessments will inform GRADE and the summary of findings tables.

RoB 2: assessment of risk of bias in cross-over and cluster-randomised trials

As we plan to use data from only the first phase of cross-over studies (see Unit of analysis issues), we will assess them as though they were of parallel design. For cluster-RCTs, we will add RoB 2 domain 1b, 'Bias arising from the timing of identification and recruitment of participants' with its corresponding signalling questions, to assess identification/recruitment bias (Higgins 2022b).

Measures of treatment effect

We will analyse continuous data as mean difference (MD) and 95% confidence interval (CI) where studies use the same measurement scale. We will convert aggregate outcome data for pain intensity to a common VAS of 0 mm (no pain) to 100 mm (worst pain) to improve clinical interpretability of results (Dworkin 2008). Where studies use different scales to measure the same conceptual outcome, we will use the standardised mean difference (SMD) and 95% CI. We will enter all data presented as a scale with a consistent direction of effect. We will consider a between-group difference of 10 mm on the 0 mm to 100 mm VAS as the minimal clinically important difference (MCID) for pain intensity, as recommended by the OMERACT 12 group (Busse 2015).

Where data are available, we will present outcomes in a dichotomised format (responder analysis), considering a 30% or greater reduction in pain intensity to represent a moderately important benefit, and a 50% or greater reduction in pain intensity to represent a substantially important benefit (Dworkin 2008). For dichotomised outcome measures, we will calculate the risk ratio (RR) and risk difference (RD) with 95% CI, the number needed to treat for an additional beneficial outcome (NNTB), and the number needed to treat for an additional harmful outcome (NNTH).

Where an RCT does not present data in a format that we can enter directly into a meta-analysis, we will convert them to the required format using the information in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022c).

Unit of analysis issues

The unit of analysis for all included trials will be the participant. Where included RCTs have multiple eligible arms, we will split the control group between arms to avoid double-counting. For cross-over studies, we will only include data from the first phase of the study when they are available, due to the strong potential for carryover effects from the interventions of interest. Given the nature of the intervention, we do not expect to identify cluster-RCTs; however, if we include any, we will seek direct estimates of the effect from an analysis that accounts for the cluster design. When the analysis in a cluster trial does not account for the cluster design, we will use an approximate analysis approach, presented in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b).

Dealing with missing data

Where key study characteristics or numerical outcome data are missing from published reports, we will contact investigators or study sponsors to obtain these data. Where this is not possible and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by sensitivity analyses. We will describe any assumptions and imputations used to handle missing data and explore the effect of imputation by sensitivity analyses. We will preferentially calculate effect sizes derived from intention-to-treat analyses. Where studies have used more than one method of imputation, we will preferentially calculate effect sizes from baseline observation carried forward (BOCF) or probabilistic imputation methods over LOCF.

Where possible, we will use methods recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* to compute missing SDs from standard errors (SEs), CIs or P values (Higgins 2022c). If we cannot calculate SDs, we will impute them from other similar studies in the meta-analysis.

Assessment of heterogeneity

We will deal with clinical heterogeneity by only combining studies that examine similar interventions. We will not combine studies that evaluate an intervention of interest versus placebo with studies that evaluate an intervention of interest versus usual care or another medicine. To estimate statistical heterogeneity, we will calculate the Chi^2 statistic, the between study variance (Tau^2), and the proportion of this variance not due to sampling error (I^2). Where there are at least 10 studies in a meta-analysis, we will calculate 95% prediction intervals to indicate the potential effect of the intervention in a new population similar to that included in the meta-analysis (Deeks 2021; Riley 2011). We will use these measures, together with visual inspection of the forest plots, to form judgements about heterogeneity. If we identify substantial heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

We will consider the potential influence of small-study biases on review findings. For meta-analyses of continuous outcomes, we will use funnel plots to visually explore small-study biases where there are at least 10 included studies. When possible, we will test for the possible influence of publication bias on dichotomous outcomes by estimating the number of participants in studies with a null effect required to change the NNTB to an unacceptably high level (NNTB of 10) as recommended by Moore 2008.

Through searching clinical trial registries, we will identify the number of unpublished trials and report the number of participants this represents. When outcome data are available in trial registries but not in a published report, we will include these data as part of a sensitivity analysis to assess the influence of including unpublished data on our results.

Data synthesis

We will pool the results of included studies using a random-effects model to account for the anticipated clinical heterogeneity between studies. We will conduct separate analyses by medicine type and route of administration in the immediate, short, medium, and long term for outcomes assessing benefits, and at end of treatment for outcomes assessing harms. For the primary analysis, we will pool data from studies regardless of the specific diagnosis. Where there are inadequate data to enable statistical pooling, we will conduct narrative synthesis of the evidence based on the same key comparisons.

We will analyse data using Review Manager Web (RevMan Web 2022), and where this software does not support additional functions, we will use the R package metafor (Viechtbauer 2010).

Subgroup analysis and investigation of heterogeneity

We plan to conduct the following subgroup analysis for the investigation of important heterogeneity in pain intensity and adverse event outcomes.

- Clinical condition (peripheral neuropathic pain/central neuropathic pain/complex regional pain syndrome/fibromyalgia).
- Duration of medicine administration (up to one day/from more than one day to seven days/from more than one week to one month/more than one month).
- Data permitting, for each drug we will consider whether medication dose impacted treatment outcomes, via meta-regression in analyses of 10 or more studies, or via low/medium/high subgroups in analyses of fewer than 10 studies.

We will use the test for subgroup differences to explore whether there are differences on mean effects between subgroups (Deeks 2021). We will compare the magnitude of the effects between subgroups by assessing the overlap of CIs of the summary estimate, with non-overlap indicating statistical significance.

Sensitivity analysis

Where sufficient data are available, we will conduct the following sensitivity analyses to investigate the robustness of the treatment effect on pain intensity and adverse effect outcomes.

- Risk of bias: we will explore the impact of risk of bias by repeating the analyses and excluding studies judged at high risk of bias.
- Missing data: we will explore the effect of data imputation by repeating the analyses and excluding studies where measures of variance or outcome data have been imputed.
- Unpublished data: we will explore the impact of including data from unpublished trial registry reports by repeating the analyses and including outcome data from trial registries.
- Type of comparator: we will explore the impact of combining active and inactive placebos by repeating the analyses and only including studies that use inactive placebo as a comparator.

Summary of findings and assessment of the certainty of the evidence

Two review authors (MF and AC) will independently rate the certainty of the body of evidence for the outcomes. We will resolve any disagreements by discussion or by involving a third review author (JM). We will justify, document, and incorporate judgements into reporting of results for each outcome. We will use the GRADE system to rank the certainty of the evidence using GRADEpro software (GRADEpro GDT) and the guidelines provided in the *CochraneHandbook for Systematic Reviews of Interventions* (Schünemann 2022).

The GRADE system considers study design as a marker of certainty. Evidence from RCTs is considered of high certainty initially, but 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

We will decrease the GRADE rating by one, two, or three levels based on the level of concern it raises. We will interpret the GRADE ratings as follows.

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

We plan to include summary of findings tables to present the main findings for each intervention versus each control comparison in a transparent and simple tabular format. We will include key information concerning the certainty of the evidence, the magnitude of effect of the interventions examined, and the sum of available data for the following outcomes.

- Pain intensity (continuous measures; short- and medium-term)
- Pain intensity (dichotomous measures; short- and medium-term)
- Adverse events (total; end of treatment period)

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Editorial and peer-reviewer contributions

Cochrane Pain, Palliative and Supportive care supported the authors in the development of this systematic review.

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Prof Christopher Eccleston, Centre of Pain Research, University of Bath, Bath, UK
- Contact Editor: Sebastian Straube, Professor and Division Director, Division of Preventive Medicine, Department of Medicine, University of Alberta, Edmonton, Canada
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Jessica Thomas, Cochrane Pain, Palliative and Supportive care, Pain Research Unit, Oxford, UK
- Copy Editor (copy-editing and production): Julia Turner
- Peer-reviewers (provided comments and recommended an editorial decision): Marieke Niesters, Department of Anesthesiology, Leiden University Medical Center, Leiden, Netherlands (clinical peer reviewer); Elina Brinck, MD, PhD, Helsinki University and Helsinki University Hospital, Helsinki, Finland (clinical peer reviewer); and one additional peer reviewer, who provided clinical and consumer peer review but chose not to be publicly acknowledged.

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APPENDICES

Appendix 1. MEDLINE Search Strategy

Check link to Appendix 1 in Electronic searches.

1. Receptors, N-Methyl-D-Aspartate/

2. NMDA receptor*.tw.

3. n-methyl-d-aspartate receptor*.tw.

4. n methylaspartate receptor*.tw.

5. (Dextromethorphan or Amantadine or Ketamine or memantine or magnesium).tw.

6. Ketamine/ or exp Amantadine/ or Dextromethorphan/ or magnesium/

7. 1 or 2 or 3 or 4 or 5 or 6

8. exp PAIN/

9. ((chronic adj2 pain*) or (complex adj3 pain*)).tw.

10. (chronic adj2 (discomfort or ache* or neuralgi* or dysmenorrhea)).tw.

11. exp fibromyalgia/

12. fibromyalgia*.tw.

13. ((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or post-stroke or complex or regional or spinal cord) adj4 pain*).tw.

14. (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whiplash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).tw.

15. 8 or 9 or 10 or 11 or 12 or 13 or 14

16. exp headache/ or cancer pain/

17. 15 not 16

18. 7 and 17

19. randomized controlled trial.pt.

20. controlled clinical trial.pt.

21. randomized.ab.

22. placebo.ab.

23. drug therapy.fs.

24. randomly.ab.

25. trial.ab.

26. 19 or 20 or 21 or 22 or 23 or 24 or 25

27. exp animals/ not humans.sh.

28. 26 not 27

29. 18 and 28

CONTRIBUTIONS OF AUTHORS

Conception of the review: MCF, AGC, NOC, EJV, CAS, MAW, SMG, JHM
Drafting of the protocol: MCF, AGC, NOC, EJV, CAS, MAW, SMG, JHM
Development of search strategy and search for studies: MCF (PaPaS Information Specialist provided support)
Obtention of copies of studies: MCF
Selection of studies: MCF, AGC
Data extraction: MCF, AGC
Risk of bias evaluation of GRADE assessment: MCF, AGC
Data entry into RevMan Web: MCF
Analysis: MCF
Interpretation of analysis: MCF, AGC, NOC, EJV, CAS, MAW, SMG, JHM
Drafting of final review: MCF, AGC, NOC, EJV, CAS, MAW, SMG, JHM
Review update: MCF, AGC, NOC, EJV, CAS, MAW, SMG, JHM

DECLARATIONS OF INTEREST

As NOC is an author as well as a PaPaS Co-ordinating Editor, we acknowledge the input of Sebastian Straube and Christopher Eccleston, who acted as Sign Off Editors for this review. NOC had no input into the editorial decisions or processes for this review.

2020 Conflicts of Interest Policy

MCF is involved in a randomised controlled trial testing memantine for complex regional pain syndrome, funded by the National Health and Medical Research Council and Medical Research Future Fund (Australia) and sponsored by Neuroscience Research Australia. The trial is currently recruiting participants and is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621000175875). MCF will not be involved in the screening or assessment of this trial registry record.

AGC is involved in a randomised controlled trial testing memantine for complex regional pain syndrome, funded by the National Health and Medical Research Council and Medical Research Future Fund (Australia) and sponsored by Neuroscience Research Australia. The trial is currently recruiting participants and is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621000175875). AGC will not be involved in the screening or assessment of this trial registry record.

NOC is involved in a randomised controlled trial testing memantine for complex regional pain syndrome, funded by the National Health and Medical Research Council and Medical Research Future Fund (Australia) and sponsored by Neuroscience Research Australia. The trial is currently recruiting participants and is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621000175875). NOC will not be involved in the screening or assessment of this trial registry record.

EJV is involved in a randomised controlled trial testing memantine for complex regional pain syndrome, funded by the National Health and Medical Research Council and Medical Research Future Fund (Australia) and sponsored by Neuroscience Research Australia. The trial is currently recruiting participants and is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621000175875). EJV will not be involved in the screening or assessment of this trial registry record. EJV is a specialist pain medicine physician and anaesthetist and manages people with chronic pain conditions.

CAS: none known.

MAW: none known.

SMG is involved in a randomised controlled trial testing memantine for complex regional pain syndrome, funded by the National Health and Medical Research Council and Medical Research Future Fund (Australia) and sponsored by Neuroscience Research Australia. The trial is currently recruiting participants and is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621000175875). SGM was an investigator for a trial likely to be included in the review and will not be involved in the screening or assessment of these trials.

JHM is involved in a randomised controlled trial testing memantine for complex regional pain syndrome, funded by the National Health and Medical Research Council and Medical Research Future Fund (Australia) and sponsored by Neuroscience Research Australia. The trial is currently recruiting participants and is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621000175875). JHM will not be involved in the screening or assessment of this trial registry record.

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