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Pharmacological treatments for low back pain in adults: an overview of Cochrane Reviews (Review)

Cashin AG, Wand BM, O'Connell NE, Lee H, Rizzo RRN, Bagg MK, O'Hagan E, Maher CG, Furlan AD, van Tulder MW, McAuley JH

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[Overview of Reviews]

Pharmacological treatments for low back pain in adults: an overview of Cochrane Reviews

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ABSTRACT

Background

Pharmacological interventions are the most used treatment for low back pain (LBP). Use of evidence from systematic reviews of the effects of pharmacological interventions for LBP published in the Cochrane Library, is limited by lack of a comprehensive overview.

Objectives

To summarise the evidence from Cochrane Reviews of the efficacy, effectiveness, and safety of systemic pharmacological interventions for adults with non-specific LBP.

Methods

The Cochrane Database of Systematic Reviews was searched from inception to 3 June 2021, to identify reviews of randomised controlled trials (RCTs) that investigated systemic pharmacological interventions for adults with non-specific LBP. Two authors independently assessed eligibility, extracted data, and assessed the quality of the reviews and certainty of the evidence using the AMSTAR 2 and GRADE tools. The review focused on placebo comparisons and the main outcomes were pain intensity, function, and safety.

Main results

Seven Cochrane Reviews that included 103 studies (22,238 participants) were included. There is high confidence in the findings of five reviews, moderate confidence in one, and low confidence in the findings of another. The reviews reported data on six medicines or medicine classes: paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, benzodiazepines, opioids, and antidepressants. Three reviews included participants with acute or sub-acute LBP and five reviews included participants with chronic LBP.

Acute LBP

Paracetamol

There was high-certainty evidence for no evidence of difference between paracetamol and placebo for reducing pain intensity (MD 0.49 on a 0 to 100 scale (higher scores indicate worse pain), 95% CI -1.99 to 2.97), reducing disability (MD 0.05 on a 0 to 24 scale (higher scores indicate worse disability), 95% CI -0.50 to 0.60), and increasing the risk of adverse events (RR 1.07, 95% CI 0.86 to 1.33).

NSAIDs

There was moderate-certainty evidence for a small between-group difference favouring NSAIDs compared to placebo at reducing pain intensity (MD -7.29 on a 0 to 100 scale (higher scores indicate worse pain), 95% CI -10.98 to -3.61), high-certainty evidence for a small between-group difference for reducing disability (MD -2.02 on a 0-24 scale (higher scores indicate worse disability), 95% CI -2.89 to -1.15), and very low-certainty evidence for no evidence of an increased risk of adverse events (RR 0.86, 95% CI 0. 63 to 1.18).

Muscle relaxants and benzodiazepines

There was moderate-certainty evidence for a small between-group difference favouring muscle relaxants compared to placebo for a higher chance of pain relief (RR 0.58, 95% CI 0.45 to 0.76), and higher chance of improving physical function (RR 0.55, 95% CI 0.40 to 0.77), and increased risk of adverse events (RR 1.50, 95% CI 1. 14 to 1.98).

Opioids

None of the included Cochrane Reviews aimed to identify evidence for acute LBP.

Antidepressants

No evidence was identified by the included reviews for acute LBP.

Chronic LBP

Paracetamol

No evidence was identified by the included reviews for chronic LBP.

NSAIDs

There was low-certainty evidence for a small between-group difference favouring NSAIDs compared to placebo for reducing pain intensity (MD -6.97 on a 0 to 100 scale (higher scores indicate worse pain), 95% CI -10.74 to -3.19), reducing disability (MD -0.85 on a 0-24 scale (higher scores indicate worse disability), 95% CI -1.30 to -0.40), and no evidence of an increased risk of adverse events (RR 1.04, 95% CI -0.92 to 1.17), all at intermediate-term follow-up (> 3 months and ≤ 12 months postintervention).

Muscle relaxants and benzodiazepines

There was low-certainty evidence for a small between-group difference favouring benzodiazepines compared to placebo for a higher chance of pain relief (RR 0.71, 95% CI 0.54 to 0.93), and low-certainty evidence for no evidence of difference between muscle relaxants and placebo in the risk of adverse events (RR 1.02, 95% CI 0.67 to 1.57).

Opioids

There was high-certainty evidence for a small between-group difference favouring tapentadol compared to placebo at reducing pain intensity (MD -8.00 on a 0 to 100 scale (higher scores indicate worse pain), 95% CI -1.22 to -0.38), moderate-certainty evidence for a small between-group difference favouring strong opioids for reducing pain intensity (SMD -0.43, 95% CI -0.52 to -0.33), low-certainty evidence for a medium between-group difference favouring tramadol for reducing pain intensity (SMD -0.55, 95% CI -0.66 to -0.44) and very low-certainty evidence for a small between-group difference favouring buprenorphine for reducing pain intensity (SMD -0.41, 95% CI -0.57 to -0.26).

There was moderate-certainty evidence for a small between-group difference favouring strong opioids compared to placebo for reducing disability (SMD -0.26, 95% CI -0.37 to -0.15), moderate-certainty evidence for a small between-group difference favouring tramadol for reducing disability (SMD -0.18, 95% CI -0.29 to -0.07), and low-certainty evidence for a small between-group difference favouring buprenorphine for reducing disability (SMD -0.14, 95% CI -0.53 to -0.25).

There was low-certainty evidence for a small between-group difference for an increased risk of adverse events for opioids (all types) compared to placebo; nausea (RD 0.10, 95% CI 0.07 to 0.14), headaches (RD 0.03, 95% CI 0.01 to 0.05), constipation (RD 0.07, 95% CI 0.04 to 0.11), and dizziness (RD 0.08, 95% CI 0.05 to 0.11).

Antidepressants

There was low-certainty evidence for no evidence of difference for antidepressants (all types) compared to placebo for reducing pain intensity (SMD -0.04, 95% CI -0.25 to 0.17) and reducing disability (SMD -0.06, 95% CI -0.40 to 0.29).

Authors' conclusions

We found no high- or moderate-certainty evidence that any investigated pharmacological intervention provided a large or medium effect on pain intensity for acute or chronic LBP compared to placebo. For acute LBP, we found moderate-certainty evidence that NSAIDs and muscle relaxants may provide a small effect on pain, and high-certainty evidence for no evidence of difference between paracetamol and placebo. For safety, we found very low- and high-certainty evidence for no evidence of difference with NSAIDs and paracetamol compared to placebo for the risk of adverse events, and moderate-certainty evidence that muscle relaxants may increase the risk of adverse events. For chronic LBP, we found low-certainty evidence that NSAIDs and very low- to high-certainty evidence that opioids may provide a small effect on pain. For safety, we found low-certainty evidence for no evidence of difference between NSAIDs and placebo for the risk of adverse events, and low-certainty evidence that opioids may increase the risk of adverse events.

PLAIN LANGUAGE SUMMARY

Pharmacological treatments for low back pain in adults: an overview of Cochrane Reviews

Key messages

For acute low back pain

• NSAIDs and muscle relaxants may provide small benefits on pain, however muscle relaxants may be associated with unwanted effects. Paracetamol had no effect on pain or unwanted effects.

For chronic low back pain

• Opioids may reduce pain but may be associated with unwanted effects. NSAIDs may reduce pain without unwanted effects and antidepressants may make little or no difference on pain.

• Physicians should discuss the possibility for a small effect on pain and increased risk for unwanted effects when considering different medicines for treating low back pain. Funders and researchers should prioritise identification of medicines that provide clinically meaningful benefits to people with low back pain.

What is low back pain and how is it treated?

Low back pain (LBP) is a common and debilitating health condition. In most cases, the cause or causes of low back pain cannot be reliably identified and is described as 'non-specific' LBP. Physicians commonly prescribe medicines to treat LBP. There are many types of medicines and medicine classes available, for example, opioid analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and paracetamol. With so many options available, there is a need to determine which medicines are best and safest.

What did we want to find out?

We wanted to summarise the evidence from Cochrane Reviews on the most effective and safest medicines for adults with non-specific LBP.

What did we do?

We searched for all Cochrane systematic reviews that assessed the benefits and harms of medicines for adults with non-specific LBP to produce an overview of Cochrane evidence.

What did we find?

We found seven reviews (that included 103 studies on a total of 22,238 people). Five reviews were assessed as having high quality. The included reviews reported data on six distinct medicines or medicine classes: paracetamol, NSAIDs (for example, ibruprofen), muscle relaxants (for example, cyclobenzaprine), benzodiazepines (for example, diazepam), opioids (for example, tapentadol), and antidepressants (for example, paroxetine). Five reviews included participants reporting LBP lasting longer than six weeks. The confidence in the evidence ranged from very low to high.

For people with acute LBP, we found that NSAIDs and muscle relaxants may reduce pain in the short-term (≤ three months postintervention). However, muscle relaxants may be associated with unwanted effects. Paracetamol had no effect on pain or unwanted effects and no reviews looked at opioids or antidepressants. For chronic LBP, we found that opioids may reduce pain in the short-term but may be associated with unwanted effects such as nausea, headache, constipation, and dizziness. NSAIDs may reduce pain in the intermediate term (> 3 months and ≤ 12 months postintervention) without unwanted effects. Antidepressants had no effect on chronic LBP and no review looked at paracetamol for chronic LBP.

What are the limitations of the evidence?

We have reduced confidence in the evidence because one review was of moderate quality and one review was of low quality and six reviews were published more than five years ago. There is a need to update these Cochrane Reviews following recommended guidance.

For acute LBP, we are at least moderately confident about the effects of paracetamol, NSAIDs and muscle relaxants on short-term pain and function. For other time points and other medicines (e.g. opioids, antidepressants), we have no evidence to inform treatment decisions.

For chronic LBP, we are at least moderately confident about the effects of paracetamol and opioids on short-term pain and function but less confident about the effects of other medicines (e.g. NSAIDs, antidepressants, muscle relaxants, and benzodiazepines). Factors that decreased confidence in findings included flaws in how the studies were designed (patients were not assigned to treatments randomly, allocation to treatment assignment was not concealed, patients were not compliant to their prescribed treatment), not having enough studies or participants to be certain about the results, and variations between treatment delivery.

The definition and reporting of unwanted effects for each medicine within each review was limited, making it difficult to assess safety for each pharmacological intervention. There remains clear gaps in the evidence base for the safety of medicines for LBP.

How up to date is this evidence?

This evidence is up to date to June 2021

BACKGROUND

Description of the condition

Low back pain (LBP) is a common health condition that has a major impact on function and quality of life (Koes 2006). It is estimated that 7% of people across the globe have LBP at any time (Abajobir 2017). Furthermore, an estimated 38% might experience significant LBP during their lifetime (Hoy 2012). LBP is comparatively more common in people aged 40 to 69 years (Hoy 2012), and in those experiencing socioeconomic disadvantage (Schofield 2012). Amongst all diseases and injuries included in the Global Burden of Disease Study, LBP has been the leading cause of reduced function since 1990 (Abajobir 2017). In 2016, 57.65 million years lived with disability were attributed to LBP (Abajobir 2017). LBP is also an increasing cause of overall disease burden. In 1990, it was the eleventh largest cause of disease burden for women and the seventeenth for men, but by 2017 it had become the seventh-largest cause for women and tenth for men (Kyu 2018).

Although the prognosis of acute LBP is typically favourable (Menezes Costa 2012), 30% to 40% of people report symptoms beyond three months (Henschke 2008), at which time they are considered to have chronic LBP. In approximately 85% of cases in primary care, the cause or causes underlying the development and persistence of LBP are unknown (Koes 2007; Maher 2017), or cannot be reliably identified (Hancock 2007). The label 'non-specific' LBP means it is not currently possible to attribute the clinical presentation to any specific disease process (e.g. infection, inflammatory condition, cancer) or structural pathology (e.g. fracture, nerve root compression) (Koes 2007; Maher 2017). Research is ongoing to reliably determine the cause(s) of LBP in those cases currently labelled 'non-specific', though the impact that specific labels would have on management and outcomes is unclear.

There are significant economic consequences associated with non-specific LBP. In 2013, LBP incurred the third-highest costs (USD 87.6 billion) of any health condition in the USA (Dieleman 2016). By 2016, this had increased to the highest costs (USD 134.5 billion, Dieleman 2020). In the UK, the total direct healthcare costs for an individual with chronic LBP are double that for someone without chronic LBP, matched by age, sex, and geographic region (Hong 2013). Data from Australia suggest that non-specific chronic LBP is the most common health-related reason for early retirement, resulting in income poverty for this group (Schofield 2008; Schofield 2012).

Description of the interventions

Pharmacological interventions are the treatment option most used for LBP (Carey 2009; Gore 2012; Hart 2015; Ivanova 2011). There are multiple classes of these interventions, including opioid analgesics, nonsteroidal anti-inflammatory drugs (NSAIDS), muscle relaxants, benzodiazepines, antidepressant medicines, anticonvulsant medicines, and systemic corticosteroids. Opioid analgesics and NSAIDs are the most used classes of pharmacological interventions in the countries for which data on usage are available (Australia, Italy, Portugal, UK, USA) (Gore 2012; Gouveia 2017; Hart 2015; Michaleff 2012; Piccoliori 2013). The relative usage of the less common classes of medicine varies across these countries (Gore 2012; Gouveia 2017; Hart 2015; Michaleff 2012; Piccoliori 2013).

Pharmacological interventions are used to improve pain and physical function and may achieve this through numerous pathways such as reducing muscular spasm, modulating sensory nerve function, or altering the availability of signalling chemicals in the brain. This Overview of Cochrane Reviews focuses on systemic pharmacological interventions used to improve pain and physical function in people with LBP.

How the intervention might work

Pharmacological interventions for LBP are designed to act on various neurobiological targets within the body. The mechanisms by which different pharmacological interventions might improve pain and function are not fully understood and differ across medicine classes. Below, we present commonly proposed mechanism(s) for each class of medicine.

NSAID and paracetamol (acetaminophen)

NSAIDs and paracetamol act on cyclo-oxygenase (COX) enzymes to interfere with natural inflammatory processes (Brune 2015). Specifically, they reduce the production of prostaglandins — signal chemicals that modulate inflammation, nociception, and other autonomic processes (Jóźwiak-Bebenista 2014). Longer-term use of these medicines may be associated with increased risk of cardiovascular events, such as stroke (Roberts 2016). Furthermore, when taken together, they can cause gastrointestinal bleeding (Anderson 2022; McCrae 2018). Certain NSAIDs, depending on degree of COX-2 selectivity, are associated with increased risk of gastrointestinal side effects, such as stomach ulcers (Van der Linden 2009).

Muscle relaxants

Muscle relaxants are a broad class of chemically varied medicines grouped together by their shared function (Cashin 2021; Trevor 2018). The two main categories are antispasmodic medicines, commonly prescribed for the treatment of muscle spasm associated with muscle injury, and antispastic medicines, commonly prescribed to reduce heightened muscle tone, known as spasticity (Cashin 2021). Muscle relaxants are thought to act on the central nervous system, or in some cases, the skeletal muscle cell (Trevor 2018; Witenko 2014). Each muscle relaxant medicine has different clinical uses, mechanism(s) of action, and associated side effects, although feelings of dizziness, drowsiness, and nausea are common to all muscle relaxants (See 2008). Certain muscle relaxants, such as carisoprodol, are associated with an increased risk of misuse and dependency (Cashin 2021).

Benzodiazepines

Benzodiazepines act on the central nervous system, increasing the effects of the neurotransmitter gamma-aminobutyric acid (GABA). Although benzodiazepines share functional muscle relaxing properties similar to muscle relaxants (Trevor 2018), they are not classified by the US Food and Drug Administration as muscle relaxants and are considered separately by some clinical guidelines (Qaseem 2017). Benzodiazepines produce strong sedative effects and are associated with problems with addiction, overdose, and withdrawal (Bachhuber 2016; Hood 2014).

Opioid analgesics

Opioid analgesic medicines act on the naturally occurring (endogenous) opioid receptors in the nervous system, to reduce

the contribution of nociceptive (danger-signalling) information to the pain experience (Rivat 2016). Opioid medicines are often classified as either weak (e.g. codeine, tramadol) or strong (e.g. oxycodone, tapentadol) according to their relative potency. Opioid medicines may cause adverse effects that commonly include constipation, nausea, and sedation, depending on the location and type of receptor (Kalso 2004). Longer-term use can contribute to opioid tolerance (requiring progressively higher doses), possible dependence, and death (Deyo 2015).

Antidepressants

Antidepressants are another class of medicines of varied chemical structure, subclassified by their function, which act on neurotransmitters in the brain. This is thought to produce analgesic effects independent of their effects on depression (Cohen 2001; Micó 2006), although the precise mechanisms are unclear (Harmer 2017). Categories of antidepressants prescribed to treat pain in order of perceived effectiveness include serotonin-norepinephrine re-uptake inhibitors (SNRIs, e.g. duloxetine), tricyclic antidepressants (TCAs, e.g. amitriptyline), and selective serotonin reuptake inhibitors (SSRIs, e.g. sertraline) (Ferraro 2021). People with LBP may also be prescribed these medicines to improve sleep and reduce depression or anxiety. Side effects differ between the categories, although drowsiness, dry mouth, and dizziness are common (Chou 2010).

Anticonvulsants

Anticonvulsant medicines act across several sites in the central nervous system. The analgesic action of anticonvulsant medicines is thought to occur through limiting neuronal excitation and enhancing inhibition, although the precise mechanisms are unclear (Maizels 2005). Anticonvulsant medicines have a long history of off-label use in pain conditions. Common dose-related side effects include drowsiness and dizziness (Derry 2019).

Systemic corticosteroids

Corticosteroids are a class of medicines that are structurally similar to the naturally occurring human adrenal hormone cortisol, considered an important regulator of homeostasis (Chou 2016; Van der Laan 2008). These medicines mimic the physiological actions of cortisol to produce a wide range of effects, including both anti-inflammatory and immunosuppressive effects. Corticosteroid medicines differ by their relative potency, duration, and mechanism(s) of action. Short-term use of corticosteroids is associated with increased rates of sepsis, venous thromboembolism, hyperglycaemia, and fracture (Waljee 2017).

Why it is important to do this overview

Pharmacological interventions are the interventions most used by people with LBP to manage their pain. People with LBP, clinicians, researchers, and health policymakers need accessible, high-quality information on the effect size and certainty of the evidence for efficacy, effectiveness, and safety of pharmacological interventions (Chou 2018a; Chou 2018b; Lim 2019). Cochrane Reviews have investigated the effects of pharmacological interventions and are available to decision-makers through the Cochrane Library. There are multiple reviews, of varying recency, scope, and methodology. This may inhibit decision-makers' access to this evidence.

There is a need to synthesise this evidence into a single accessible review. Overviews, or systematic reviews of systematic reviews, allow multiple systematic reviews on similar or related topics, to be brought together systematically for appraisal and synthesis of results (Hunt 2018). Systematic reviews incorporating network meta-analysis (NMA) are another method for synthesis. However, NMAs only answer singular clinical questions on a subset of trials and require trial- or participant-level data, which is often not available at sufficient detail in systematic reviews (Bagg 2018a; Mills 2012; Salanti 2012). Moreover, overviews are appropriate for appraisal of systematic review conduct. An overview should improve access to high-quality information and describe the recency and scope of the information, which may extend across multiple clinical and policy questions. This may support people with LBP, clinicians, and policymakers to use this evidence in their health decision-making (Hunt 2018). Information on recency, scope, and methodology across the reviews may also support researchers, funders, and policy decision makers to identify important evidence gaps for conducting updates of reviews or planning prospective reviews.

OBJECTIVES

To summarise the evidence from Cochrane Reviews of the efficacy, effectiveness, and safety of systemic pharmacological interventions for adults with non-specific LBP.

METHODS

Criteria for considering reviews for inclusion

Types of reviews

We included all Cochrane Reviews of randomised controlled trials (RCTs) on pharmacological interventions for people with non-specific LBP, published in the Cochrane Library. We excluded reviews that included randomised and non-randomised designs, unless data for the randomised designs was available separately. We also excluded Cochrane Reviews that had been withdrawn or superseded. We identified Cochrane Review protocols and listed them as ongoing reviews that might be relevant for future updates.

Types of participants

Participants were adults, 18 years or older, with non-specific LBP (e.g. non-radicular LBP, with or without non-specific degenerative changes), of any duration. LBP is defined as a primary area of pain between the twelfth rib and gluteal fold, with or without associated leg pain (Koes 2006). We excluded systematic reviews that included participants with spinal stenosis (back and leg pain associated with narrowing of the spinal canal), LBP caused by known structural or pathological processes (e.g. nerve root compression, osteoporosis, fractures, infection, neoplasm, metastasis) or specific medical conditions (e.g. pregnancy, inflammatory disease) (Koes 2007; Maher 2017), unless the review reported results for non-specific LBP separately. We excluded reviews that included participants younger than 18 years, unless they reported separate results for participants 18 years or older.

Types of interventions and comparisons

We included systemic pharmacological interventions, used with the intent to improve pain and function, for people with LBP. We considered systemic pharmacological interventions broadly as any medicine that affects the body as a whole, rather than individual parts or organs. We made no restriction on route

of administration or dose. We also included combinations of pharmacological interventions.

Comparisons of interest were as follows.

- Pharmacological intervention versus placebo or sham intervention (efficacy comparisons)
- Different forms of the same pharmacological intervention (e.g. selective NSAID versus a non-selective NSAID) (effectiveness comparisons)
- Pharmacological intervention versus a different type of pharmacological intervention (effectiveness comparisons)
- Pharmacological intervention versus a non-pharmacological intervention (effectiveness comparisons).

Types of outcome measures

Our outcomes reflect the core outcome set for non-specific LBP (Chiarotto 2015), and recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin 2005). We made no restriction on time of measurement. We grouped outcomes into a short-term period (≤ 3 months postintervention), an intermediate-term period (> 3 months and ≤ 12 months postintervention), and a long-term period (> 12 months postintervention). In cases where a review reported outcome data for multiple time points within a period, or measured the outcome at different time periods, we included the outcome measure closest to the midpoint of the period.

Major outcomes

- Pain, defined as pain intensity, assessed on a continuous self-report scale (e.g. a visual analogue scale (VAS), numerical rating scale (NRS), the brief pain inventory (BPI) (Cleeland 1989), or other validated measure), or in dichotomous format (e.g. as the proportion of participants in each group who attained a predetermined threshold of improvement).
- Physical function, defined as back-pain related function, assessed through continuous self-report scales (e.g. Roland-Morris Disability Questionnaire (RMDQ) (Roland 1983), Oswestry Disability Index (ODI) (Fairbank 1980)), functional testing protocols or other validated quantitative measures.
- Safety, defined as adverse events including amongst others: incidence and severity of adverse events, trial withdrawal due to adverse events, and incidence of serious adverse events, as described by the systematic review.

Minor outcomes

- Participant ratings of improvement, defined as global perceived effect, assessed with a validated tool (e.g. Patient Global Impression of Change Scale (Guy 1976)).
- Health-related quality of life, assessed with a validated tool (e.g. the 36-Item Short Form Health Survey (SF-36) (Ware 2000)).
- Workplace participation, defined as days to return-to-work, days of absenteeism, or days of reduced work activities.

Search methods for identification of reviews

Electronic searches

We conducted a sensitive search of the *Cochrane Database of Systematic Reviews* (The Cochrane Library, current issue) using a combination of Medical Subject Headings (MeSH) and keywords (Appendix 1), without restriction up to Issue 5 of 12, 2021. The search strategy is presented in Appendix 1. We managed retrieved citations using EndNote 2017 and Covidence.

Data collection and analysis

Selection of reviews

We assessed the eligibility of identified Cochrane Reviews in two stages. Two overview authors (AGC and RRNR) independently screened the results of the electronic search by title and abstract against the inclusion criteria. We obtained the full texts of reviews meeting these criteria and two authors (AGC and RRNR) independently screened them again to confirm inclusion. We planned to use a third overview author to resolve discrepancies when the two first authors could not reach consensus, however, no discrepancies occurred. We provide a PRISMA flow diagram documenting the screening and review selection process (see Figure 1).

Data extraction and management

We designed a data extraction form, which was piloted by four overview authors (AGC, BMW, NEOC, RRNR). Two overview authors (AGC and RRNR) independently extracted data using the finalised data extraction form. We planned to involve an independent third overview author to resolve disagreements; however, this was not required. The data extraction form included the following details.

Review characteristics

- Objectives of the review
- Dates of publication, most recent search, and planned update
- Resources searched
- Number of included trials
- Characteristics of included participants (e.g. duration of pain, pain severity, sex, age, race, comorbidities, prior treatment history (to the extent possible))
- Description of interventions and comparisons
- Outcomes and time points assessed
- Details of meta-analyses, if applicable

Statistical summaries

- Point estimates, 95% CIs, and accompanying measures of heterogeneity for the pooled estimates of intervention effects, for all relevant comparisons at all available time points (e.g. risk ratios (RRs), risk difference (RD), odds ratios (ORs), number needed to treat for an additional beneficial effect (NNTB) or additional harmful effect (NNTH), mean differences (MDs), standardised mean difference (SMD))
- Results of responder analyses, including prespecified criteria for response and power calculation
- Results from exploration of heterogeneity, including subgroup analyses/meta-regression and whether these were prespecified
- Results from sensitivity analyses, including details of the approach taken, and whether these were prespecified
- Judgements of risk of bias in the evidence, including details of the approach used (e.g. Cochrane ROB tool)
- Judgements of certainty in the evidence, including details of the approach used (e.g. GRADE)

If we could not extract the required information from the reports, we planned to contact the authors of included reviews. We did not plan on contacting authors of individual studies included in the reviews.

Assessment of methodological quality of included reviews

Quality of included reviews

Two overview authors (AGC and RRNR) independently assessed the methodological quality of included systematic reviews using the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews (Shea 2017)). The 16 items in the AMSTAR 2 instrument provide a broad assessment of systematic review quality that, taken together, inform a judgement of confidence in the review findings (see Appendix 2). We resolved discrepancies through consensus or recourse to a third overview author (NEOC). We also used AMSTAR 2 assessments to identify consistency of review methods and conduct, as well as to identify areas for improvement.

We considered the following seven items recommended by Shea 2017 as critical when forming an overall judgement on the quality of the included systematic review:

- item 2: protocol registered before commencement of the review;
- item 4: adequacy of the literature search;
- item 7: justification for excluding individual studies;
- item 9: risk of bias from individual studies being included in the review;
- item 11: appropriateness of meta-analytical methods;
- item 13: consideration of risk of bias when interpreting the results of the review;
- item 15: assessment of presence and likely impact of publication bias).

Our ratings were as follows:

- High overall confidence in the results of the review if there were either no non-critical weaknesses or only one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest;
- Moderate if there was more than one non-critical weakness: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review;
- Low if there was one critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest;
- Critically low if there was more than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

Risk of bias of primary studies included in reviews

We reported the risk of bias assessments for the primary studies in each included systematic review. We did not repeat or update these assessments. We reported the risk of bias tool used, including details regarding dimensions assessed (e.g. allocation concealment, participant blinding), and results of the assessments.

Certainty of evidence in included reviews

We reported, where available, the GRADE judgement of certainty for each core comparison for our primary outcomes (Balshem 2011). The GRADE approach uses five considerations (risk of bias, inconsistency, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each outcome. First, two overview authors (AGC and RRNR) independently extracted the GRADE assessments for each systematic review for each independent outcome. Second, for reviews which did not report GRADE assessments, two overview authors (AGC and RRNR) independently conducted GRADE assessments of certainty in the evidence using a checklist for the primary outcomes and placebo comparisons (Meader 2014). We resolved discrepancies through consensus. We planned to involve an independent third overview author to resolve disagreements, however, this option was not required.

When required, we used the following to assign GRADE judgements.

- Serious study limitations: we downgraded once if less than 50% of studies were at low risk of bias across all risk of bias criteria.
- Inconsistency: we downgraded once if point estimates varied widely across studies, confidence intervals showed minimal or no overlap, statistical tests for heterogeneity were statistically significant, or the I^2 statistic was greater than 50%.
- Indirectness: we downgraded once if greater than 50% of participants were outside the target group.
- Imprecision: we downgraded once if there were fewer than 400 participants for continuous outcomes and fewer than 300 events for dichotomous data.
- Publication bias: we downgraded once where there was direct evidence of publication bias or if estimates of effect based on small scale, industry sponsored studies raised suspicion of publication bias.

GRADE judgements indicate the following degree of certainty in the conclusions of the systematic review.

- High: very certain that the true effect lies close to that of the estimate of the effect.
- Moderate: moderately certain 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 in the effect estimate is limited – the true effect may be substantially different from the estimate of the effect.
- Very low: very little certainty in the effect estimate and the true effect is likely to be substantially different from the estimate of the effect.

Overlap between reviews

Following recommended guidance by Hennessy 2020, we examined the degree of overlap of primary studies in the included reviews. This involved creating a citation matrix of the primary studies (rows) included in each review (columns) to calculate the corrected covered area (CCA). Pieper 2014 suggests interpreting CCA values lower than five to indicate slight overlap and CCA values greater than or equal to 15 to indicate high overlap.

Data synthesis

We presented data from each systematic review for the primary and secondary outcomes for each comparison and follow-up duration, where available. We presented narrative descriptions of results only when statistical outcome data was not available. We stratified the data by the duration of LBP observed in the included studies as follows:

- Acute (0 to 6 weeks);
- Sub-acute (6 to 12 weeks);
- Chronic (> 12 weeks);
- Mixed (multiple symptom durations grouped together, e.g. acute and subacute or subacute and chronic);
- Unclear (symptom duration not reported).

We did not conduct any novel statistical synthesis of data or make any indirect comparisons. We planned to convert effect sizes, where possible, to common scales to facilitate interpretation.

We classified the size of the effect for the mean between-group difference for the outcomes pain and function based on the definitions from the American College of Physicians and the American Pain Society (Chou 2017):

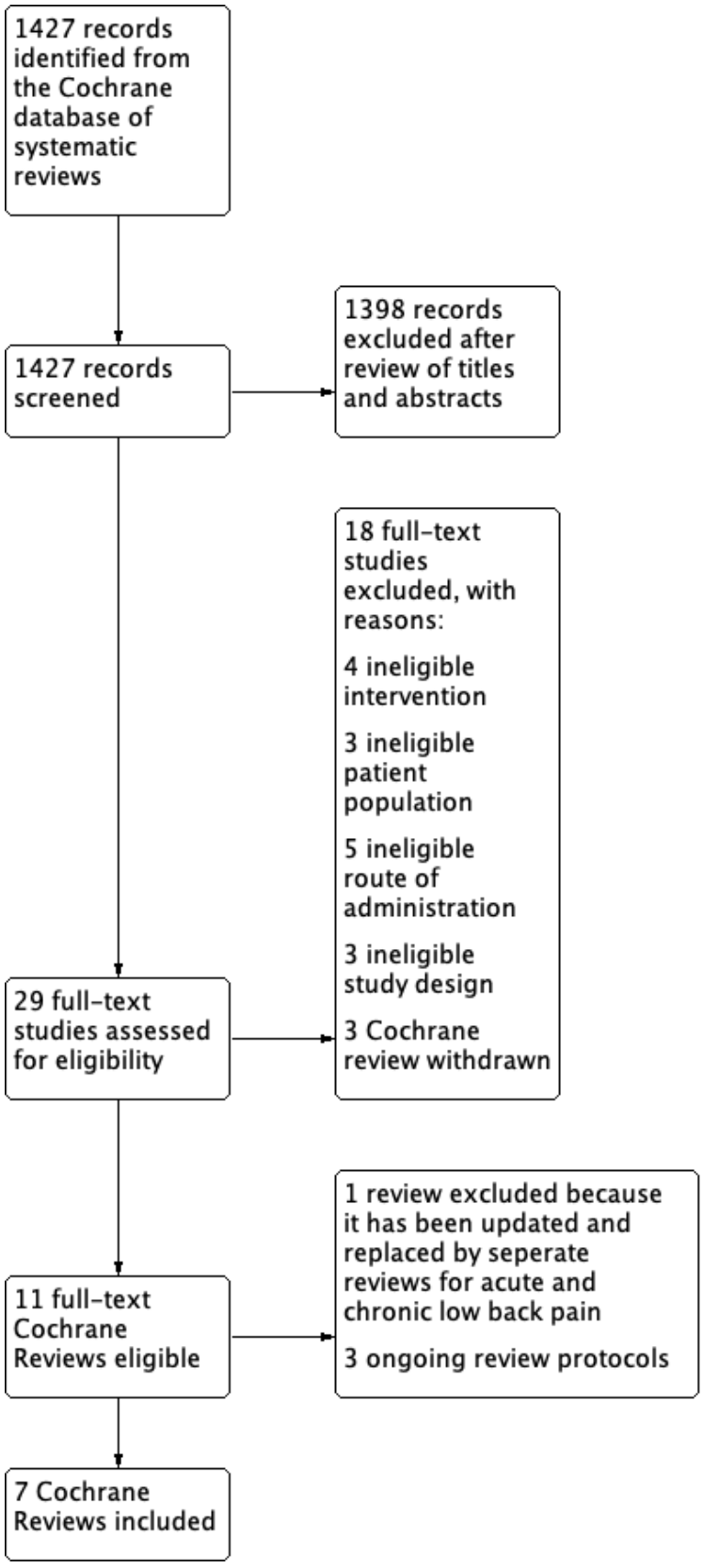
- Large effect: > 20 points on a 0 to 100 scale or > 0.8 SMD;
- Medium effect: > 10 to 20 points on a 0 to 100 scale or > 0.5 to 0.8 SMD;
- Small effect: 5 to 10 points on a 0 to 100 scale or 0.2 to 0.5 SMD;
- No evidence of difference: boundaries of the 95% CI span both sides of the line of no effect;
- Harmful: boundaries of the 95% CI fall completely within harm.

We presented the short-term efficacy of the intervention compared to placebo on pain intensity in a summary of findings table, as described in Chapter 5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We presented the results of the remaining primary and secondary outcomes at each time point in an overview of reviews table. We also included two summary of results tables highlighting the size and certainty of the evidence, by considering both the effect size and GRADE rating for the outcomes of pain and function at the short-term follow-up.

RESULTS

The initial search of the Cochrane Library (Issue 5, 3 June 2021) identified 1427 Cochrane Review records. We excluded 1398 records after review of title and abstracts and excluded a further 18 records after full-text assessment (Figure 1). Seven reviews were deemed eligible for inclusion (Chaparro 2013; Enthoven 2016; Santos 2015; Saragiotto 2016; Urquhart 2008; Van der Gaag 2020; Van Tulder 2003). Reasons for exclusion included: ineligible intervention (four reviews), ineligible patient population (three reviews), ineligible route of administration (five reviews), ineligible study design (three reviews), Cochrane Review withdrawn (three reviews), and one review was excluded because it had been updated and replaced with two separate reviews, both of which were included in this overview (Appendix 3). We identified three review protocols as potentially eligible for future updates once published, details of these protocols can be found in Table 1.

Figure 1. Flow diagram



Description of included reviews

A detailed description of the characteristics of the included Cochrane Reviews is presented in Table 2.

The seven reviews included 22,238 participants across 103 unique RCTs. The number of included RCTs in each review ranged from 2 in Saragiotto 2016 to 32 RCTs in Van der Gaag 2020. Sample sizes ranged from 722 participants in Urquhart 2008 to 5540 participants in Chaparro 2013. The median (interquartile range (IQR)) year of review publication was 2015 (2010 to 2016) with six reviews published before 2017. Six reviews searched trial registry records, but none of the reviews included outcome data extracted directly from trial registry records. When reported by the systematic review, only a small proportion of the included RCTs in each review were prospectively registered (2 out of 13 in Enthoven 2016 and 3 out of 32 in Van der Gaag 2020). However, many RCTs were published before trial registry platforms were established and registration was mandatory (Cashin 2021). None of the reviews reported any direct funding perceived to be a conflict of interest. Five of the seven reviews reported the funding of included RCTs. Of these five reviews, all reported that half or more of the included RCTs were either funded by a pharmaceutical company or declared relationships with a pharmaceutical company. This is reflective of previous systematic reviews, that found that the majority of trials of pharmacological interventions are industry-funded (Barden 2006; Bourgeois 2010). Although trials funded by a drug or device company have been shown to be more likely to have positive conclusions and statistically significant results (Lundh 2017), there can be substantial variation in the degree to which funding or the declared relationships can impact the validity and magnitude of the study findings (Chopra 2003).

Van der Gaag 2020 included only acute to sub-acute LBP (< 12 weeks), Chaparro 2013, Enthoven 2016 and Santos 2015 included only chronic LBP (> 12 weeks, and three reviews did not restrict the duration of LBP included (Saragiotto 2016; Urquhart 2008; Van Tulder 2003). However, Saragiotto 2016 only identified RCTS including people with acute LBP (≤ 6 weeks duration) and Urquhart 2008 only identified RCTS including people with chronic LBP (> 12 weeks duration). Santos 2015 restricted inclusion to RCTs with participants reporting moderate to severe LBP, defined as pain ≥ 4 on a 0 to 10 pain scale. All seven reviews included pain as the primary outcome. Two reviews included patient-reported pain relief as a primary outcome measure with categorisation into "responder" groups reporting more than 30% and/or 50% pain relief (Chaparro 2013; Santos 2015). One review reported pain as a dichotomous effect measure – the risk of experiencing no pain relief using risk ratios – where risk ratios smaller than one indicate that the chance of "not getting pain relief" is less in the intervention group compared to the comparator (Van Tulder 2003). Other commonly reported primary outcome measures included back pain-specific function, global measure of improvement, safety (adverse events), and return to work. No reviews provided clear definitions for how adverse events or serious adverse events were operationalised as outcomes in the review. Only one review reported that serious adverse events were considered as defined by each included RCT (Saragiotto 2016). We found that most reviews were not able to report data across each of the preplanned outcomes due to a lack of adequate data.

No reviews discussed issues related to health equity or considered the social determinants of health when synthesising and interpreting the evidence. This, in part, could be because of incomplete reporting of sociodemographic characteristics from the included RCTs. Chaparro 2013 highlights that "many studies neglected to report other parameters affecting outcomes, such as duration of pain prior to enrolment, employment or compensation status or poor response to previous treatment". Only two reviews considered the representativeness of the evidence reporting concerns generalising the evidence beyond the restricted and limited participant population (Chaparro 2013; Saragiotto 2016).

Interventions

The seven reviews reported on six pharmacological interventions or intervention classes:

- Paracetamol (Saragiotto 2016);
- NSAIDs (Enthoven 2016; Van der Gaag 2020);
- Muscle relaxants (Van Tulder 2003);
- Benzodiazepines (Van Tulder 2003);
- Opioids (Chaparro 2013; Santos 2015);
- Antidepressants (Urquhart 2008).

The most investigated intervention classes were NSAIDs (45 RCTs, 10,163 participants), opioids (19 RCTs, 8653 participants), and muscle relaxants (26 RCTs, 2538 participants). Santos 2015 and Saragiotto 2016 reported on pharmacological interventions administered orally, and five reviews reported multiple routes of administration (Chaparro 2013; Enthoven 2016; Santos 2015; Urquhart 2008; Van der Gaag 2020). Treatment duration ranged from a single injection to 24 weeks.

Comparisons

All reviews included placebo as a prespecified comparator, and two reviews considered placebo as the only comparator (Saragiotto 2016; Urquhart 2008). Five reviews used other pharmacological interventions as a comparator (Chaparro 2013; Enthoven 2016; Santos 2015; Van der Gaag 2020; Van Tulder 2003). Two reviews used non-pharmacological interventions (Enthoven 2016; Van der Gaag 2020).

We found that most reviews were unable to report across all of their preplanned comparisons and outcomes because of a lack of adequate data. In addition to a lack of data, heterogeneity in reported outcomes and comparisons limited the ability for all seven reviews to conduct all pre-planned meta-analyses. Five reviews could not complete subgroup analyses due to heterogeneity (Chaparro 2013; Enthoven 2016; Santos 2015; Saragiotto 2016; Van Tulder 2003), and two reviews could not inspect for small study bias using funnel plots (Chaparro 2013; Enthoven 2016).

Overlap between reviews

We identified three overlapping RCTs which were included in more than one review. The CCA was 0.5% suggesting very minimal overlap between reviews (Pieper 2014).

Certainty of evidence

We found all seven reviews employed formal tools to assess risk of bias (Table 3): two used the Higgins 2011 Cochrane risk of bias tool (Santos 2015; Saragiotto 2016); one used the Van Tulder 1997 criteria for internal validity recommended by the Cochrane Back Review Group (Van Tulder 2003); one review used the Van

Tulder 2003a criteria for methodological quality recommended by the Cochrane Back Review Group (Urquhart 2008); two used the Furlan 2009 criteria for risk of bias recommended by the Cochrane Back Review Group (Chaparro 2013; Enthoven 2016); and one used the Furlan 2015 criteria for risk of bias recommended by the Cochrane Back and Neck Group (Van der Gaag 2020).

All reviews included at least one RCT assessed at unclear or high risk of bias across the investigated domains. The most common contributors to high risk of bias across the studies included in the seven reviews were failure to report intention-to-treat (ITT) analysis (attrition bias) in 30 RCTs (29%) and inadequate allocation concealment (selection bias) in 19 RCTs (18%). Out of 103 RCTs, sixty-seven (65%) were rated as low risk of bias for blinding participants and personnel (performance bias) and sixty-three (61%) were rated as low risk for blinding of outcome assessors (detection bias).

Four reviews used the GRADE approach to rate the overall certainty of the evidence (Chaparro 2013; Enthoven 2016; Saragiotto 2016; Van der Gaag 2020). We conducted additional GRADE assessments for comparisons of 23 pharmacological interventions to placebo for primary outcomes pain, function, and safety across five reviews (Chaparro 2013; Enthoven 2016; Santos 2015; Urquhart 2008; Van Tulder 2003). The most common reasons for downgrading were study limitations and imprecision.

Methodological quality of included reviews

See Table 4

Results of the AMSTAR 2 assessment showed that we have high confidence in the findings of five reviews (Enthoven 2016; Santos 2015; Saragiotto 2016; Van der Gaag 2020; Van Tulder 2003), moderate confidence in the findings of Chaparro 2013, and low confidence in the findings of Urquhart 2008. One review did not assess the potential impact of risk of bias in individual studies on the results of the meta-analysis and did not provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review (Chaparro 2013). One review did not report on the sources of funding for the studies included in the review and did not carry out an adequate investigation of publication bias (small study bias), and discuss its likely impact on the results of the review (Urquhart 2008).

Effect of interventions

See Table 5 for a summary of findings for the short-term efficacy of pharmacological interventions compared to placebo on our primary outcome of pain intensity.

See Table 6, Table 7, Table 8, Table 9, and Table 10 for an overview of reviews for all other comparisons and outcomes for each pharmacological intervention or intervention class.

See Table 11 and Table 12 for a summary of results highlighting the effect size and certainty of the evidence for the primary outcomes (pain and physical function) and placebo comparisons for short-term follow-up.

Data, where available, for each primary and secondary outcome for the remaining effectiveness comparisons for all interventions is reported in Appendix 4, Appendix 5, and Appendix 6.

Very few reviews reported data for intermediate term follow-up (> 3 months and ≤ 12 months postintervention) and no reviews reported data for long-term follow-up (> 12 months postintervention). Outcome data are therefore presented below for short-term (≤ 3 months postintervention) follow-up unless otherwise stated.

Paracetamol (acetaminophen) versus placebo

One Cochrane Review, judged to be of high quality, included evidence on the effects of paracetamol compared to placebo (Saragiotto 2016). It included two studies, of which only one three-arm study investigating time-contingent prescription of paracetamol, as required prescription of paracetamol, and placebo contributed to any meta-analyses. The total sample size was 1785 participants with acute LBP. No studies were identified for participants with subacute or chronic LBP.

Acute LBP

Pain: Saragiotto 2016 reported a pooled analysis of 1516 participants. The review reported no evidence of a difference between paracetamol and placebo (MD of 0.49 on a 0 to 100 pain intensity scale (higher scores indicate worse pain) (95% CI -1.99 to 2.97, I^2 = 0%)), which they rated as high-certainty evidence.

Physical function: Saragiotto 2016 reported a pooled analysis of 1516 participants. The review reported no evidence of a difference between paracetamol and placebo (MD of 0.05 on a 0 to 24 Roland Morris Disability questionnaire (higher scores indicate worse disability) (95% CI -0.50 to 0.60, I^2 = 0%)), which they rated as high-certainty evidence.

Safety: Saragiotto 2016 reported a pooled analysis of 1516 participants. The review reported no evidence of an increased risk of experiencing an adverse event (RR of 1.07 (95% CI 0.86 to 1.33, I^2 = 0%)) or a serious adverse event (RR of 0.90 (95% CI 0.30 to 2.67, I^2 = 0%)) between paracetamol and placebo, which they rated as high-certainty evidence.

Participant ratings of improvement: Saragiotto 2016 reported a pooled analysis of 1511 participants. The review reported no evidence of a difference between paracetamol and placebo (MD of -0.10 on a -5 to 5 global perceived effect scale (higher scores indicate greater improvement) (95% CI -0.33 to 0.13, I^2 = 0%)), which they rated as high-certainty evidence.

Health-related quality of life: Saragiotto 2016 reported a pooled analysis of 1145 participants. The review reported no evidence of a difference between paracetamol and placebo on the 12-item Short Health Survey physical component (higher scores indicate better physical health functioning) (MD of -0.79 (95% CI -1.94 to 0.36, I^2 = 0%)) and on the 12-item Short Health Survey mental component (higher scores indicate better mental health functioning) (MD of -0.6 (95% CI -1.38 to 0.17, I^2 = 0%)), which they rated as high-certainty evidence.

Workplace participation: this was not an outcome of interest in Saragiotto 2016.

NSAIDs versus placebo

Two Cochrane Reviews, judged to be of high quality, included evidence on the effects of NSAIDs compared to placebo (Enthoven

2016; Van der Gaag 2020). Van der Gaag 2020 included 32 studies with a total sample size of 5356 participants with acute LBP. Enthoven 2016 included 13 studies with a total sample size of 1354 participants with chronic LBP. Enthoven 2016 only reported outcome data at ≤ 16 weeks follow-up (median [IQR] follow-up was 84 days [42 to 105 days]), which we classified as intermediate follow-up (> 3 months and ≤ 12 months postintervention).

Acute LBP

Pain: Van der Gaag 2020 reported a pooled analysis of four studies (five comparisons, 815 participants). The review reported a small between-group difference favouring NSAIDs (MD of -7.29 on a 0 to 100 pain intensity scale (higher scores indicate worse pain) (95% CI -10.98 to -3.61; I^2 =35%)), which they rated as moderate-certainty evidence. Van der Gaag 2020 narratively reported the results of one study (240 participants) for the intermediate follow-up (> 3 months and ≤ 12 months postintervention), reporting no evidence of a difference between NSAIDs and placebo on reducing pain intensity.

Physical function: Van der Gaag 2020 reported a pooled analysis of two studies (three comparisons, 471 participants). The review reported a small between-group difference favouring NSAIDs (MD of -2.02 on a 0 to 24 Roland Morris Disability questionnaire (higher scores indicate worse disability) (95% CI -2.89 to -1.15; I^2 = 0%)), which they rated as high-certainty evidence. Van der Gaag 2020 narratively reported the results of one study (240 participants) for the intermediate follow-up (> 3 months and ≤ 12 months postintervention), reporting no evidence of a difference between NSAIDs and placebo on physical function.

Safety: Van der Gaag 2020 reported a pooled analysis of six studies (eight comparisons, 1394 participants). The review reported no evidence of an increased risk of experiencing an adverse event (RR 0.86, 95% CI 0. 63 to 1.18; I^2 = 0%), between NSAIDs and placebo, which they rated as very low-certainty evidence.

Participant rating of improvement: Van der Gaag 2020 reported a pooled analysis of five studies (seven comparisons, 1201 participants). The review reported an increased risk for experiencing global improvement for NSAIDs compared to placebo (RR 1.40, 95% CI 1.12 to 1.75; I^2 = 52%), which they rated as low-certainty evidence.

Health-related quality of life: Van der Gaag 2020 did not report data on health-related quality of life because it was not an outcome of interest in the review.

Workplace participation: Van der Gaag 2020 reported data from one study (one comparison, 266 participants). The review reported no evidence of an increased risk for workplace participation (RR 1.48, 95% CI 0.98 to 2.23) between NSAIDs and placebo, which they rated as very low-certainty evidence.

Chronic LBP

Pain: Enthoven 2016 reported a pooled analysis of six studies (six comparisons, 1354 participants) at intermediate follow-up. The review reported a small between-group difference favouring NSAIDs (MD of -6.97 on a 0 to 100 pain intensity scale (higher scores indicate worse pain) (95% CI -10.74 to -3.19; I^2 = 52%)), which they rated as low-certainty evidence. The same review reported pooled analyses for non-selective NSAIDs compared to placebo (4 studies, 4 comparisons, 847 participants) and selective NSAIDs (2 studies, 2 comparisons, 507 participants) compared to placebo at intermediate follow-up. The review reported a small between-group difference in favour of non-selective NSAIDs (MD of -5.96 on a 0 to 100 pain intensity scale (higher scores indicate worse pain) (95% CI -10.96 to -0.96; I^2 = 55%)) and selective NSAIDs (MD -9.11 on a 0 to 100 pain intensity scale (higher scores indicate worse pain) (95% CI -13.56 to -4.66; I^2 = 0%)), which we rated as low- and moderate-certainty evidence respectively.

Physical function: Enthoven 2016 reported a pooled analysis of four studies (four comparisons, 1161 participants)at intermediate follow-up. The review reported a small between-group difference favouring NSAIDs (MD of -0.85 on a 0 to 24 Roland Morris Disability questionnaire (higher scores indicate worse disability) (95% CI -1.30 to -0.40; I^2 = 46%)), which they rated as low-certainty evidence.

Safety: Enthoven 2016 reported a pooled analysis of six studies (six comparisons, 1354 participants) at intermediate follow-up. The review reported no evidence of an increased risk of an adverse event (RR 1.04, 95% CI -0.92 to 1.17; I^2 = 20%), between NSAIDs and placebo, which they rated as low-certainty evidence. The same review reported pooled analyses for non-selective NSAIDs (4 studies, 4 comparisons, 847 participants) and selective NSAIDs (2 studies, 2 comparisons, 507 participants) compared to placebo at intermediate follow-up. The review found no evidence of an increased risk of an adverse event with non-selective NSAIDs (RR 0.94, 95% CI -0.82 to 1.08; I^2 = 0%), which we rated as low-certainty evidence. However, selective NSAIDs were associated with an increased risk of adverse events (RR 1.25, 95% CI 1.00 to 1.56; I^2 = 17%), which we rated as moderate-certainty evidence.

Participant rating of improvement: Enthoven 2016 was unable to identify data on the outcome participant rating of improvement.

Health-related quality of life: this was not an outcome of interest in Enthoven 2016.

Workplace participation: Enthoven 2016 was unable to identify data on the outcome workplace participation.

Muscle relaxants and benzodiazepines versus placebo

One Cochrane Review, judged to be of high quality, included evidence on the effects of muscle relaxants (antispasmodics and antispastics) and benzodiazepines compared to placebo (Van Tulder 2003). It included 31 studies with a total sample size of 2884 participants with acute and chronic LBP. Twenty four of the included studies were on people with acute LBP.

Acute LBP

Pain: Van Tulder 2003 reported a pooled analysis of three studies (three comparisons, 244 participants). The review reported a higher chance of pain relief for antispasmodic muscle relaxants compared to placebo (RR 0.58, 95% CI 0.45 to 0.76; I^2 = 0%), which we rated as moderate-certainty evidence. The same review narratively reported the results of two high quality studies (220 participants) of antispastic muscle relaxants compared to placebo and one low quality study (50 participants) of benzodiazepines compared to placebo. The review reported that both antispastic muscle relaxants and benzodiazepines were more effective than placebo for pain relief.

Physical function: Van Tulder 2003 reported a pooled analysis of three studies (three comparisons, 251 participants). The review reported a higher chance of improving physical function for antispasmodic muscle relaxants compared to placebo (RR 0.55, 95% CI 0.40 to 0.77; I^2 = 0%), which we rated as moderate-certainty evidence.

Safety: Van Tulder 2003 reported a pooled analysis of eight studies (eight comparisons, 724 participants). The review reported an increased risk of experiencing an adverse event (RR 1.50, 95% CI 1. 14 to 1.98; I^2 = 0%) with antispasmodic muscle relaxants compared to placebo, which we rated as moderate-certainty evidence.

Participant rating of improvement: Van Tulder 2003 reported a pooled analysis of four studies (four comparisons, 323 participants). The review reported no evidence for a difference in participant rating of improvement (RR 0.68, 95% CI 0.41 to 1.13; I^2 = 34%) between antispasmodic muscle relaxants compared to placebo. The same review narratively reported the results from one high quality trial (one comparisons, 200 participants) investigating antispastic muscle relaxants compared to placebo. The review reported that people given antispastic muscle relaxants rated their improvement higher than those given a placebo.

Health-related quality of life: this was not an outcome of interest in Van Tulder 2003.

Workplace participation: Van Tulder 2003 was unable to identify data on the outcome workplace participation.

Chronic LBP

Pain: Van Tulder 2003 narratively reported the results from two high quality trials (219 participants) investigating antispasmodic muscle relaxants compared to placebo. The review reported conflicting results on whether antispasmodic muscle relaxants are more effective than placebo for pain relief. The same review reported a pooled analysis of two studies (two comparisons, 246 participants) investigating benzodiazepines compared to placebo. The review reported a higher chance of pain relief for benzodiazepines compared to placebo (RR 0.71, 95% CI 0.54 to 0.93; I^2 = 0%), which we rated as low-certainty evidence.

Physical function: Van Tulder 2003 was unable to identify data on the outcome physical function.

Safety: Van Tulder 2003 reported a pooled analysis of two studies (two comparisons, 246 participants). The review reported no evidence of difference in the risk of experiencing an adverse event (RR 1.02, 95% CI 0.67 to 1.57) between antispasmodic muscle relaxants and placebo, which we rated as low-certainty evidence.

Participant rating of improvement: Van Tulder 2003 narratively reported the results from two high quality studies (two comparisons, 219 participants). The review reported that antispasmodic muscle relaxants were more effective than placebo on participant ratings of improvement. The same review reported a pooled analysis of two studies (two comparisons, 151 participants) investigating benzodiazepines compared to placebo. The review reported a higher chance for experiencing an improvement with antispasmodic muscle relaxants compared to placebo (RR 0.63, 95% CI 0.42 to 0.97; I^2 = 17%).

Health-related quality of life: this was not an outcome of interest in Van Tulder 2003.

Workplace participation: Van Tulder 2003 was unable to identify data on the outcome workplace participation.

Opioids versus placebo

Two Cochrane Reviews included evidence on the effects of opioids compared to placebo (Chaparro 2013; Santos 2015). Santos 2015 was judged to be of high quality and Chaparro 2013 judged to be of moderate quality. Chaparro 2013 included 15 trials with a total sample size of 5540 participants with chronic LBP. Santos 2015 included 4 trials with a total sample size of 4094 participants with chronic musculoskeletal pain (e.g. chronic LBP, osteoarthritis). Neither review aimed to identify studies including participants with acute LBP.

Chronic LBP

Pain: Santos 2015 reported the results of one study (one comparison, 637 participants) investigating tapentadol compared to placebo. The review reported a small between-group difference favouring tapentadol (MD of -0.80 on a 0 to 10 pain intensity scale (higher scores indicate worse pain) (95% CI -1.22 to -0.38)), which we rated as high-certainty evidence. Chaparro 2013 reported a pooled analyses for tramadol (five studies, five comparisons, 1378 participants) and strong opioids (six studies, six comparisons, 1887 participants) compared to placebo. The review reported a medium between-group difference favouring tramadol (SMD -0.55, 95% CI -0.66 to -0.44; I^2 = 86%) and small between-group difference favouring strong opioids (SMD -0.43, 95% CI -0.52 to -0.33; I^2 = 0%), which they rated at low- and moderate-certainty evidence respectively. Chaparro 2013 also reported a pooled analysis for buprenorphine (two studies, two comparisons, 653 participants) compared to placebo, which we reanalysed following the detection of an error. The review found a small between-group difference favouring buprenorphine (SMD -0.41, 95% CI -0.57 to -0.26; I^2 = 0%), which we rated as very low-certainty evidence.

Both reviews also reported responder analyses for pain intensity. Santos 2015 reported the results of one study (one comparison, 632 participants) investigating tapentadol compared to placebo. The review reported a higher chance for a 50% reduction in pain intensity for tapentadol compared to placebo (RR 1.43, 95% CI 1.07 to 1.9), which we rated as high-certainty evidence. Chaparro 2013 reported a pooled analysis of two studies investigated buprenorphine compared to placebo (two comparisons, 594 participants). The review reported an increased likelihood of a 30% reduction in pain intensity favouring buprenorphine (OR 1.49, 95% CI 1.08 to 2.06; I^2 = 69%), which we rated as low-certainty evidence. The same review also reported the results for one study (one comparison, 498 participants) comparing buprenorphine to placebo. The review reported an increased likelihood of experiencing a 50% reduction in pain favouring buprenorphine (OR 1.39, 95% CI 0.97 to 1.99), which we rated as low-certainty evidence. Finally, Chaparro 2013 reported a pooled analysis of three studies (three comparisons, 819 participants) investigating strong opioids compared to placebo. The review reported an increased likelihood of experiencing a 30% reduction in pain intensity favouring strong opioids (OR 1.91, 95% CI 1.41 to 2.58; I^2 = 38%), which they rated as moderate-certainty evidence. The same review reported a pooled analysis of

two studies (two comparison, 750 participants) comparing strong opioids to placebo. The review reported an increased likelihood in experiencing a 50% reduction in pain intensity favouring strong opioids (OR 1.89, 95% CI 1.34 to 2.66), which they rated as very low-certainty evidence.

Physical function: Chaparro 2013 reported a pooled analyses for tramadol (five studies, five comparisons, 1348 participants), buprenorphine (one studies, one comparison, 101 participants), and strong opioids (four studies, five comparisons, 1375 participants) compared to placebo. The review reported a less than small between-group difference favouring tramadol (SMD -0.18, 95% CI -0.29 to -0.07; I^2 = 0%), which they rated at moderate-certainty evidence, a less than small between-group difference favouring buprenorphine (SMD -0.14, 95% CI -0.53 to -0.25), which they rated as very low-certainty evidence, and a small between-group difference favouring strong opioids (SMD -0.26, 95% CI -0.37 to -0.15; I^2 = 0%), which they rated as moderate-certainty evidence.

Safety: Santos 2015 reported the results of one study (one comparisons, 637 participants) investigating tapentadol compared to placebo. The review reported that tapentadol was associated an increased risk of experiencing an adverse event (RR 1.27, 95% CI 1.14 to 1.41), an increased risk of experiencing a serious adverse event (RR 2.34, 95% CI 0.61 to 8.97) and an increased risk of treatment withdrawal due to an adverse event (RR 3.41, 95% CI 1.96 to 5.94), rated as high-, moderate- and high-certainty evidence respectively. Chaparro 2013 reported safety data for specific adverse events, most commonly nausea, headaches, constipation, dizziness, and somnolence for opioids (all types) compared to placebo. The review reported 10 studies (10 comparisons, 3747 participants) investigating nausea, 10 studies (10 comparisons, n=3747) investigating headaches, nine studies (nine comparisons, 3493 participants) investigating constipation, nine studies (nine comparisons, n =3493) investigating dizziness, and eight studies (eight comparisons, 3257 participants) investigating somnolence. The review reported that, compared to placebo, opioids may be more likely to cause nausea (RD 0.10, 95% CI 0.07 to 0.14; I^2 = 63%), headaches (RD 0.03, 95% CI 0.01 to 0.05; I^2 = 32%), constipation (RD 0.07, 95% CI 0.04 to 0.11; I^2=78%), dizziness (RD 0.08, 95% CI 0.05 to 0.11; I^2 = 68%), and somnolence (RD 0.06, 95% CI 0.03 to 0.09; I^2 = 66%). We rated this as low-certainty evidence.

Participant rating of improvement: Chaparro 2013 was unable to identify data on the outcome participant rating of improvement. Santos 2015 did not report separate data on participants with chronic LBP for this outcome.

Health-related quality of life: Santos 2015 did not report separate data for participants with chronic LBP on this outcome and it was not an outcome of interest in Chaparro 2013.

Workplace participation: Chaparro 2013 was unable to identify data on the outcome workplace participation and it was not an outcome of interest in Santos 2015.

Antidepressants versus placebo

One Cochrane Review, judged to be of low quality, included evidence on the effects of antidepressants (all types) compared to placebo (Urquhart 2008). It included 10 trials with a total sample size of 722 participants with chronic LBP. No trials were identified for participants with acute or subacute LBP. We have low overall confidence in the results from this systematic review because of one critical and one non-critical flaw. Therefore, this review may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

Chronic LBP

Pain: Urquhart 2008 reported a pooled analysis of six studies (nine comparisons, 376 participants) investigating antidepressants (all types). The review reported no evidence of difference between groups on pain intensity (SMD -0.04, 95% CI -0.25 to 0.17; I^2 = 0%), which we rated as low-certainty evidence. The same review reported pooled analyses for SSRI antidepressants (three studies, three comparisons, 199 participants) and TCA (three studies, four comparisons, 148 participants) compared to placebo. The review reported no evidence of a difference between SSRI antidepressants and placebo (SMD 0.11, 95% CI -0.17 to 0.39; I^2 = 0%) and TCA (SMD -0.10, 95% CI -0.51 to 0.31; I^2 = 32%) on pain intensity, which we rated as moderate- and very low-certainty evidence respectively.

Physical function: Urquhart 2008 reported a pooled analysis of two studies (two comparisons, 132 participants) and found no evidence of a difference on physical function (SMD -0.06, 95% CI -0.40 to 0.29; I^2 = 0%), which we rated as low-certainty evidence.

Safety: this was not an outcome of interest in Urquhart 2008.

Participant rating of improvement: Urquhart 2008 was unable to identify data on the outcome participant rating of improvement.

Health-related quality of life: Urquhart 2008 was unable to identify data on the outcome health-related quality of life.

Workplace participation: Urquhart 2008 was unable to identify data on the outcome workplace participation.

DISCUSSION

Summary of main results

Our main objective was to summarise the evidence from Cochrane Reviews of systemic pharmacological interventions for adults with non-specific LBP on pain, physical function, and safety. We synthesised the results of published Cochrane Reviews and identified significant gaps in the evidence for a number of our comparisons of interest, as well as a degree of inconsistency in approaches taken to evaluate the evidence in the included Cochrane Reviews.

We included seven reviews including a total of 22,238 participants across 103 unique RCTs on paracetamol (Saragiotto 2016), NSAIDs (Enthoven 2016; Van der Gaag 2020), muscle relaxants (Van Tulder 2003), benzodiazepines (Van Tulder 2003), opioids (Chaparro 2013; Santos 2015), and antidepressants (Urquhart 2008). Five reviews were in people with sub-acute or chronic LBP. All seven reviews included pain as the primary outcome and included placebo as a primary prespecified comparator. Overall, the quality of the reviews was high. We have high confidence in the results of five of the seven reviews based on the AMSTAR 2 results (Shea 2017). We have moderate confidence in the results from one review and low confidence in the results of another review.

Despite the overall high methodological quality of included reviews, we found the evidence within the included reviews

to be of varying certainty. Four reviews formally rated the certainty of the evidence using the GRADE approach (Chaparro 2013; Enthoven 2016; Saragiotto 2016; Van der Gaag 2020). We conducted additional GRADE assessments for five reviews for missing assessments of placebo comparisons for primary outcomes pain, function, and safety (Chaparro 2013; Enthoven 2016; Santos 2015; Urquhart 2008; Van Tulder 2003). The majority of the evidence was rated as low- or very low-certainty. Evidence from the included reviews indicates that most trials of pharmacological interventions provide potentially biased estimates and suggest only small reductions on pain in the short-term, if any effect at all. Data on function is reported less often than pain and effects are typically smaller and often not observed.

For the outcome of pain intensity in acute LBP, we found moderate-certainty evidence that NSAIDs provide a small improvement, moderate-certainty evidence that muscle relaxants provide a small improvement and high-certainty evidence for no evidence of a difference between paracetamol and placebo. For the outcome of physical function in acute LBP, we found high-certainty evidence that NSAIDs provide a small improvement, moderate-certainty evidence that muscle relaxants provide a small improvement and high-certainty evidence for no difference between paracetamol and placebo. There is little evidence available for the effects of pharmacological interventions in acute LBP beyond the short term.

For the outcome of pain intensity in chronic LBP, we found moderate-certainty evidence that selective NSAIDs and strong opioids provide a small improvement, high-certainty that tapentadol (opioid) provides a small improvement, and moderate-certainty evidence for no evidence of a difference between placebo and SSRIs (antidepressants). For the outcome of physical function in chronic LBP, we found moderate-certainty evidence that both strong opioids and tramadol (opioid) provide a small improvement. Again, there is little evidence available for the effects of pharmacological interventions in chronic LBP beyond short-term follow-up.

We found that most reviews were not able to report data across each of the pre-planned outcomes due to a lack of adequate data. Furthermore, many of the reviews were unable to conduct quantitative syntheses due to clinical heterogeneity in the participants and comparisons in the included trials, as well as inconsistency in the type and timing of outcome measurement.

Without valid definitions and consensus on what constitutes a minimal clinically important effect, we chose to describe the magnitude of the effect and the certainty of the evidence when discussing the findings in this overview. Clinicians should establish what their patients consider to be a clinically important effect when interpreting the effect size and certainty of the evidence of pharmacological interventions during treatment discussions. This should include appropriate consideration from the patient for the proposed benefit, safety, costs, risks, and inconveniences of therapy, rather than benchmarking effect sizes against an arbitrary value (Ferreira 2013).

Overall completeness and applicability of evidence

This overview summarises published Cochrane Reviews of all RCTs examining systemic pharmacological interventions for adults with non-specific LBP. However, six of the seven reviews were published more than five years ago (Chaparro 2013; Enthoven 2016; Santos 2015; Saragiotto 2016; Urquhart 2008; Van Tulder 2003). Two reviews were published more than 10 years ago (Urquhart 2008; Van Tulder 2003). Additional RCTs have probably now been published that might alter the results of the reviews, in particular those relating to muscle relaxants and antidepressants (Cashin 2021; Ferraro 2021). There is a need to update a number of the Cochrane Reviews. There are also several pharmacological intervention classes where Cochrane Reviews are not available (e.g. anticonvulsants, systemic corticosteroids), or with very few RCTs available (e.g. paracetamol).

Although this overview aimed to consider all durations of LBP, most reviews included participants with sub-acute or chronic LBP. In addition to fewer reviews, there were also fewer medicine classes investigated for people with acute LBP - only paracetamol, NSAIDs, and muscle relaxants were investigated in this population.

Outcome measures were inconsistent, and different measures were used at different times between RCTs and between reviews. For example, only two reviews assessed quality of life, although very few data were available (Santos 2015; Saragiotto 2016). There is a need for trialists and review authors to consider the core outcome set for non-specific LBP (Chiarotto 2015), and recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT, Dworkin 2005). Very few RCTs provided data on longer-term follow-up. Currently, it is unclear whether the investigated interventions have any sustained benefits or long-term harms.

The definition and reporting of adverse events within each review was limited, making it difficult to assess safety for each pharmacological intervention. We found that none of the reviews provided a definition for how adverse events were considered, and when reported, the description of adverse events was vague or incomplete. Although reporting of harms in primary studies is often inadequate (Ioannidis 2009), systematic reviews can compound this problem by failing to report harms or by doing so inadequately (Zorzela 2014). Further, commonly used methods to assess benefits in systematic reviews may not be appropriate to be used to assess harms (Qureshi 2021). For example, systematic reviewers might reach incorrect conclusions if they focus on evidence of harms found in published reports of RCTs. This is partly because RCTs are often designed to minimise adverse events (e.g. by excluding patients with medical or psychological comorbidities) and are not commonly powered to detect differences in adverse events, particularly serious (rare) adverse events, which would require larger samples and longer-term follow-up. Reviews of RCTs may therefore be misleading if they do not identify any differences in adverse events (suggesting safety where this might not be case). Valid and reliable syntheses of evidence of harms requires different types of data, and different methods for synthesis compared with evidence of benefit. Together, these limitations highlight clear gaps in the evidence base of safety for pharmacological interventions. Considering these gaps, evidence on adverse events for many common analgesic medicines could be obtained from other populations (e.g. osteoarthritis) until more robust data for LBP becomes available.

None of the included reviews reported comprehensive data on the included participants (e.g. demographic and clinical characteristics, including baseline pain intensity). Without an adequate description of participants, it is difficult to establish for whom the evidence is applicable (i.e. the target population). More

comprehensive reporting of the participants' characteristics in RCTs, and the reviews that summarise them, will help assessment of the applicability and potential generalisability of the evidence. The PROGRESS-Plus acronym could be used as a framework to help guide RCTs and review authors identify and report participant characteristics that stratify health opportunities and outcomes (O'Neill 2014).

Given the number of different pharmacological interventions, heterogeneity, low certainty of the evidence, and gaps in the current literature, it is not surprising that pharmacological intervention prescription practice varies between clinicians. In the absence of a robust evidence base, guidelines and clinical treatment will continue to be based upon other considerations, including clinician experience, cost, adverse effects, regulatory approvals, and established local practices.

Quality of the evidence

We used AMSTAR 2 in our evaluation of quality in the included systematic reviews. Five of the seven reviews were judged to have overall high confidence, one as moderate confidence, and one as low confidence in the results of the review. Only one review did not satisfy a critical domain - the review authors did not carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review (Urquhart 2008). Cochrane Reviews are generally regarded as having high methodological rigour and more complete reporting than non-Cochrane Reviews (Dosenovic 2018; Goldkuhle 2018, Page 2016). Similar to Pollock 2017, we found that not all Cochrane Reviews are high quality, at least not to current standards. However, we acknowledge that standards for conducting and reporting reviews has evolved over time, and at the time of publication, each of these reviews had gone through the Cochrane editorial process and peer review. Further, several of the included Cochrane Reviews were published before methodological and reporting standards had been developed (e.g. GRADE and PRISMA), which could partly explain this finding. Finally, we did not assess the recency of publication when evaluating quality. As six of the included reviews were published more than five years ago, this may decrease our confidence in their findings.

Potential biases in the overview process

We conducted this overview according to the published protocol (Cashin 2020). We used a broad and inclusive search strategy, which was designed under expert guidance by the Cochrane Back and Neck Review Group. This was an overview of Cochrane Reviews and the search to identify published reviews and planned or ongoing reviews (protocols) was conducted within the Cochrane Database of Systematic Reviews across all years up to June 2021. Given the sensitive search strategy, it is reasonable to suggest this overview offers a current summation of Cochrane Reviews investigating the effect of pharmacological interventions in adults with LBP.

Several of the included reviews (Chaparro 2013; Enthoven 2016; Saragiotto 2016; Urquhart 2008; Van der Gaag 2020; Van Tulder 2003), were authored by members of this overview team (MWvT, ADF, CGM). As such, there may have been a risk of potential bias with review and appraisal of this work. We minimised this risk by allocating data extraction and quality assessment to members of the overview team who were not authors on the original reviews (AGC, RNNR).

We included only Cochrane Reviews; there are other more recent systematic reviews on pharmacological interventions for LBP published outside the Cochrane Library, but we are unable to comment on the biases this might introduce. Results and outcomes reported in non-Cochrane reviews may have showed different results from those presented here, though it is worth noting that non-Cochrane reviews are generally of lower quality than Cochrane Reviews (Goldkuhle 2018; Page 2016; Pollock 2017).

Finally, since this is an overview, we were reliant on the reporting quality of the included reviews in addition to the RCTs that they synthesised. It is possible, that problems with reporting quality in the original RCTs filtered through to the systematic review and finally to the overview level. For example, all reviews explicitly stated that they included participants with non-specific LBP. However, inadequate, or opaque reporting of the original RCTs may have meant that some RCTs could have included more heterogenous populations including radicular LBP. In addition, we were reliant on the GRADE judgements reported in the included reviews. Given that GRADE assessments include an element of subjectivity, it is possible that the review authors may have used slightly different thresholds for making GRADE judgements, and as a result, the same evidence may have been judged of higher certainty in some reviews than others.

Agreements and disagreements with other studies or reviews

We found no published overviews of pharmacological interventions for managing LBP in adults. One review was identified which investigated recent systematic reviews of RCTs covering pharmacological interventions for chronic LBP (Koes 2018). Despite this review including both Cochrane and non-Cochrane reviews, the conclusions were consistent with ours, namely, "the overall impression of the efficacy of pharmacological treatments for patients with chronic low back pain is rather sobering. The effects on pain reduction and improvement of function are commonly small to moderate and short lasting when compared to placebo. At the same time, the various types of drugs are not without side-effects". The authors also highlighted the low certainty of the evidence due to systemic methodological shortcomings of the included RCTs.

Other published overviews have focused on pain relief for a specific medicine class, such as paracetamol (Abdel Shaheed 2021), or have conducted systematic reviews of reviews and high-quality RCTs to provide evidence to inform clinical guidelines (e.g. Chou 2017), and a Lancet LBP series (Foster 2018). There was considerable overlap between the Cochrane Reviews included in these overviews with our current overview. Despite slight variations in interpretations of the clinical relevance and certainty in the data, the reviews report consistent conclusions with this overview and highlight common issues related to the outcomes measured and inadequate methodological conduct of included RCTs.

AUTHORS' CONCLUSIONS

Implications for practice

This overview summarises the evidence from Cochrane Reviews of RCTs of systemic pharmacological interventions for adults with non-specific low back pain (LBP), and can be used by researchers, clinicians, and policymakers to assist them in decision-making and

knowledge translation. We found evidence that nonsteroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants may provide a small improvement in pain and function, and no evidence of a difference between paracetamol and placebo for acute LBP. We found no evidence for the use of opioids or any other medicines for acute LBP. For chronic LBP, we found evidence that NSAIDs and opioids may provide a small improvement in pain. We acknowledge that some of the evidence from these reviews is more than 10 years old and implications for practice may change when newer randomised controlled trials (RCTs) are included.

While there are some discrepancies between the recommendations from current international clinical practice guidelines for the pharmacological treatment of LBP, a substantial proportion of recommendations were consistent with the evidence from our overview (Oliveira 2018). Most, but not all guidelines recommend NSAIDs and weak opioids for acute LBP, and NSAIDs and antidepressants for chronic LBP (Oliveira 2018). Data from this overview cannot contribute to the recommendation of weak opioids for acute LBP because no reviews aimed to provide relevant data. Further, recommendations for the use of antidepressants for chronic LBP by some guidelines (e.g. the US (Qaseem 2017) and Canada (TOP 2015)) does not reflect our finding that antidepressants probably provide no difference to placebo for pain intensity.

Overall, the available evidence suggests that pharmacological interventions for adults with non-specific LBP appear to be ineffective or only marginally effective, and carry an increased risk of adverse events. There is a clear need to prioritise new effective and cost-effective treatment strategies to improve help for people with LBP.

Implications for research

There is a need to update most of the published Cochrane Reviews and complete the three published Cochrane review protocols on pharmacological interventions for LBP. We recommend that these review updates follow updated guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). Further, updated guidance from Cochrane Musculoskeletal could improve the consistency of methods applied by review authors.

New RCTs investigating pharmacological interventions should follow the core outcome set for non-specific LBP (Chiarotto 2015), and the recommendations by IMMPACT (Dworkin 2005), to improve the synthesis of results and compatibility between trials. Trialists should also adhere to methodological safeguards to reduce bias and report their findings transparently following the Consolidated Standards of Reporting Trials statement (Schulz 2010). It is important that new RCTs clearly and comprehensively describe the characteristics of the included participants, such as demographics and clinical characteristics, to improve understanding of the population included in the RCT. Currently, it is unclear to whom the available evidence is applicable.

There are substantially fewer comparative studies for pharmacological interventions. Additional comparative studies would enable us to draw firmer conclusions about which treatments are most effective. The use of network meta-analysis could also offer information to help guide clinical decision-making regarding which medicine is most effective for acute and chronic LBP (Wewege 2020). More research is also needed to improve understanding of whether combining pharmacological interventions is associated with incremental benefits, and which combinations and sequences are the most effective (Chou 2017). Finally, further research is required to determine which people are most likely to benefit from pharmacological interventions. Currently, most RCTs are underpowered to explore subgroup effects. Research initiatives that focus on identifying which patients respond more favourably to specific classes of pharmacological interventions may help to individualise care for people with LBP and optimise treatment effectiveness.

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ADDITIONAL TABLES

Table 1. Details of ongoing reviews

Reference	Review aim	Dates/notes
Bagg 2018	To determine the analgesic effects, safety, effect on function, and relative rank according to analgesic effect, safety and effect on function of a single course of opioid analgesics, NSAIDs or paracetamol or combinations of these medicines.	Published 09 June 2018
Bezerra 2014	To assess the effectiveness and safety of anticonvulsants for the management of chronic low back pain, with or without radiculopathy.	Published 23 June 2014
Chou 2016a	To determine the benefits and harms of systemic corticosteroids compared with placebo or no systemic corticosteroid for patients with acute, subacute, or chronic radicular or non-radicular low back pain.	Published 05 December 2016

Table 2. Characteristics of included reviews

Review	Date of last search	Total number of participants (RCTs)	Population	Interventions	Comparisons	Outcomes planned
Chaparro 2013	October 2012	5540 (15 RCTs)	Adults (≥ 18 years) with chronic (≥ 12 weeks), non-specific LBP with or without leg pain	Opioids	Placebo, other drugs	Primary: • pain • function • global improvement • proportion of patients reporting 30% and 50% pain relief Secondary: • work-related disability • treatment related adverse events • healthcare usage • non-opioid medication consumption • addiction • overdose-related events
Enthoven 2016	June 2015	4807 (13 RCTs)	Adults (≥ 18 years) with chronic (≥ 12 weeks), non-specific LBP	NSAIDs	Placebo, NSAID, other drugs, other non-drug treatments	Primary: • pain • global measure of improvement • back pain-specific functional status

Table 2. Characteristics of included reviews *(Continued)*

						• return to work • adverse events Secondary: • physiological outcomes • generic functional status • healthcare consumption
Santos 2015	March 2014	4094 (4 RCTs)	Adults (≥ 18 years) with chronic (≥ 12 weeks), moderate-severe (≥4/10 NRS) musculoskeletal pain (including non-specific LBP)	Opioids (tapentadol)	Placebo, other drugs (oxycodone)	Primary: • pain • safety Secondary: • patient global impression of change • quality of life scores • requirements for breakthrough analgesia • functional health status and well-being • sleep evaluation • withdrawal rate • adverse events
Saragiotto 2016	August 2015	1785 (2 RCTs)	People with acute (< 6 weeks), non-specific LBP	Paracetamol	Placebo	Primary: • pain • disability Secondary: • quality of life • function • adverse events • global impression of recovery • sleep quality • patient adherence • use of rescue medication
Urquhart 2008	November 2008	722 (10 RCTs)	Adults (≥ 18 years) with non-specific LBP with or without leg pain	Antidepressants	Placebo	Primary: • pain • overall improvement proportion of patients recovered • back pain-specific functional status • return to work • depression

Table 2. Characteristics of included reviews *(Continued)*

						Secondary: • physiological outcomes generic functional status
Van der Gaag 2020	January 2020	5356 (32 RCTs)	Adults (≥ 18 years) with acute (< 12 weeks) non-specific LBP with or without leg pain	NSAIDs	Placebo, NSAID, paracetamol, other drug, non-drug treatment	Primary: • pain • back pain-specific functional status • global measure of improvement • adverse events • return to work Secondary: none
Van Tulder 2003	October 2002	2884 (30 RCTs)	People with non-specific LBP with or without leg pain	Muscle relaxants (antispasmodics, antispastics), benzodiazepines	Placebo, NSAIDs, other muscle relaxants, placebo + analgesics/NSAIDs	Primary: • pain • global measure of improvement • back specific function return to work physiological outcomes generic functional status Secondary: none

LBP: low back pain;**NSAID**: nonsteroidal anti-inflammatory drugs;**RCT**: randomised controlled trial

Table 3. Risk of bias in the included reviews

Review	Number of studies assessed	GRADE	Methodological quality assessment tool	Risk of bias assessment (from review authors)
Chaparro 2013	15	Yes	2009 Updated Method Guidelines for Systematic Reviews in the Cochrane Back Review Group (Furlan 2009)	Random sequence generation: low risk 10/15 studies Allocation concealment: low risk 6/15 studies Blinding (participants): low risk 14/15 studies Blinding (providers): low risk 8/15 studies Blinding (outcome assessors): low risk 2/15 studies Incomplete outcome data (drop-outs): low risk 0/15 studies Incomplete outcome data (ITT): low risk 12/15 studies Similarity of baseline characteristics: low risk 11/15 studies Co-interventions avoided or similar: low risk 14/15 studies

Table 3. Risk of bias in the included reviews *(Continued)*

				Compliance acceptable: low risk 4/15 studies Timing of outcome assessment similar: low risk 14/15 studies Free from selective reporting: low risk 9/15 studies
Enthoven 2016	13	Yes	2009 Updated Method Guidelines for Systematic Reviews in the Cochrane Back Review Group (Furlan 2009)	Random sequence generation: low risk 6/13 studies Allocation concealment: low risk 4/13 studies Blinding (participants): low risk 10/13 studies Blinding (providers): low risk 8/13 studies Blinding (outcome assessors): low risk 10/13 studies Incomplete outcome data (drop-outs): low risk 6/13 studies Incomplete outcome data (ITT): low risk 3/13 studies Similarity of baseline characteristics: low risk 10/13 studies Co-interventions avoided or similar: low risk 10/13 studies Compliance acceptable: low risk 5/13 studies Timing of outcome assessment similar: low risk 12/13 studies Selective reporting: low risk 2/13 studies
Santos 2015	4	No	Cochrane risk of bias tool 1.0 (Higgins 2011)	Random sequence generation: low risk 4/4 studies Allocation concealment: low risk 3/4 studies Blinding (participants, providers): low risk 3/4 studies Blinding (outcome assessors): low risk 3/4 studies Incomplete outcome data: low risk 0/4 studies Selective reporting: low risk 4/4 studies Duration: low risk 4/4 studies Outcomes: low risk 2/4 studies Size: low risk 4/4 studies
Saragiotto 2016	2	Yes	Cochrane risk of bias tool 1.0 (Higgins 2011)	Random sequence generation: low risk 1/2 studies Allocation concealment: low risk 1/2 studies Blinding (participants, providers): low risk1/2 studies Blinding (outcome assessors): low risk 1/2 studies

Table 3. Risk of bias in the included reviews *(Continued)*

				Incomplete outcome data: low risk 2/2 studies Selective reporting: low risk 1/2 studies
Urquhart 2008	10	No	Updated Method Guidelines for Systematic Reviews in the Cochrane Collaboration Back Review Group (Van Tulder 2003a)	Random sequence generation: low risk 5/10 studies Allocation concealment: low risk 4/10 studies Blinding (participants): low risk 10/10 studies Blinding (providers): low risk 9/10 studies Blinding (outcome assessors): low risk 9/10 studies Incomplete outcome data (drop-outs): low risk 3/10 studies Incomplete outcome data (ITT): low risk 8/10 studies Similarity of baseline characteristics: low risk 7/10 studies Co-interventions avoided or similar: low risk 3/10 studies Compliance acceptable: low risk 3/10 studies Timing of outcome assessment similar: low risk 9/10 studies studies
Van der Gaag 2020	32	Yes	2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group (Furlan 2015)	Random sequence generation: low risk 12/32 Allocation concealment: low risk 10/32 studies Blinding (participants, providers): low risk 12/32 studies Blinding (outcome assessors): low risk 12/32 studies Incomplete outcome data: low risk 10/32 studies Selective reporting: low risk 3/32 studies Other bias: low risk 32/32 studies
Van Tulder 2003	30	No	Method Guidelines for Systematic Reviews in the Cochrane Collaboration Back Review Group for Spinal Disorderd (Van Tulder 1997)	Random sequence generation: low risk 6/30 studies Allocation concealment: low risk 2/30 studies Blinding (participants): low risk 28/30 studies Blinding (providers): low risk 28/30 studies Blinding (outcome assessors): low risk 28/30 studies Incomplete outcome data (drop-outs): low risk 20/30 studies Incomplete outcome data (ITT): low risk 12/30 studies

Table 3. Risk of bias in the included reviews *(Continued)*

	Similarity of baseline characteristics: low risk 17/30 studies Co-interventions avoided or similar: low risk 12/30 studies Compliance acceptable: low risk 5/30 studies Timing of outcome assessment similar: low risk 27/30 studies

Table 4. AMSTAR 2 quality assessment

AMSTAR 2 item	Cochrane review						
	Chaparro 2013	Enthoven 2016	Santos 2015	Saragiotto 2016	Urquhart 2008	Van der Gaag 2020	Van Tulder 2003
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Yes	Yes	Yes	No	Yes	Yes

Table 4. AMSTAR 2 quality assessment *(Continued)*

11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Yes	Yes	Yes	Yes	Yes	Yes
13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Yes	Yes	Yes	Yes	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?*	Yes	Yes	Yes	Yes	No	Yes	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rating of overall confidence	**Moderate**	**High**	**High**	**High**	**Low**	**High**	**High**

*Critical domain

Table 5. Summary of findings table: pharmacological intervention versus placebo for adults with low back pain (LBP)

Patients or population: adults with LBP

Intervention: pharmacological

Comparison: placebo

Outcome	Low back pain (duration)	Intervention	Relative effect (95% CI)	I^2 (%)	Number of participants (RCTs)	Certainty of the evidence (GRADE)	Comments

Table 5. Summary of findings table: pharmacological intervention versus placebo for adults with low back pain (LBP) *(Continued)*

Pain 0 to 100 scale, where 0 is no pain **Short-term follow-up** (≤ 3 months postintervention)	Acute	Paracetamol	MD 0.49 (-1.99 to 2.97)	0%	1516 (1 RCT)	**High**
Pain 0 to 100 scale, where 0 is no pain **Short-term follow-up** (≤ 3 months postintervention)	Acute	NSAID	MD -7.29 (-10.98 to -3.61)	35%	815 (4 RCTs)	**Moderate**[1]
Pain Pain improved (scales varied)[5] **Short-term follow-up** (≤ 3 months postintervention)	Acute	Muscle relaxants (non-benzodiazepine antispasmodic)	RR 0.58 (0.45 to 0.76)	0%	244 (3 RCTs)	**Moderate**[1]
Pain Pain improved (scales varied)[6] **Short-term follow-up** (≤ 3 months postintervention)	Chronic	Benzodiazepine	RR 0.71 (0.54 to 0.93)	0%	146 (2 RCTs)	**Low**[1,2]
Pain SMD (scales varied)[7] **Short-term follow-up** (≤ 3 months postintervention)	Chronic	Antidepressant	SMD -0.04 (-0.25 to 0.17)	0%	376 (6 RCTs)	**Low**[1,2]
Pain SMD (scales varied)[7]	Chronic	Antidepressant (SSRI)	SMD 0.11 (-0.17 to 0.39)	0%	199 (3 RCTs)	**Moderate**[2]

Table 5. Summary of findings table: pharmacological intervention versus placebo for adults with low back pain (LBP) *(Continued)*

Short-term follow-up (≤ 3 months postintervention)						
Pain SMD (scales varied)[8] **Short-term follow-up** (≤ 3 months postintervention)	Chronic	Antidepressant (TCA)	SMD -0.1 (-0.51 to 0.31)	32%	148 (3 RCTs)	**Very low**[1,2,3]
Pain SMD (scales varied)[9] **Short-term follow-up** (≤ 3 months postintervention)	Chronic	Opioid (tramadol)	SMD -0.55 (-0.66 to -0.44)	86%	1378 (5 RCTs)	**Low**[1,3]
Pain SMD (scales varied)[9] **Short-term follow-up** (≤ 3 months postintervention)	Chronic	Opioid (buprenorphine)	SMD -0.41 (-0.57 to -0.26)	99%	653 (2 RCTs)	**Very low**[1,4]
Pain 30% reduction **Short-term follow-up** (≤ 3 months postintervention)	Chronic	Opioid (buprenorphine)	OR 1.49 (1.08 to 2.06)	67%	594 (2 RCTs)	**Low**[1,3]
Pain 50% reduction	Chronic	Opioid (buprenorphine)	OR 1.39 (0.97 to 1.99)	NA	498 (1 RCT)	**Low**[1,2]

Table 5. Summary of findings table: pharmacological intervention versus placebo for adults with low back pain (LBP) *(Continued)*

Short-term follow-up (≤ 3 months postintervention)							
Pain SMD (scales varied)[9] **Short-term follow-up** (≤ 3 months postintervention)	Chronic	Opioid (strong)	SMD -0.43 (-0.52 to -0.33)	0%	1887 (6 RCTs)	**Moderate**[1]	
Pain 30% reduction **Short-term follow-up** (≤ 3 months postintervention)	Chronic	Opioid (strong)	OR 1.91 (1.41 to 2.58)	38%	819 (3 RCTs)	**Moderate**[1]	
Pain 50% reduction **Short-term follow-up** (≤ 3 months postintervention)	Chronic	Opioid (strong)	OR 1.89 (1.34 to 2.66)	81%	750 (2 RCTs)	**Very low**[1,2,3]	
Pain 0 to 100 scale, where 0 is no pain **Short-term follow-up** (≤ 3 months postintervention)	Chronic	Opioid (enriched)	MD -21.34 (-22.77 to 19.91)	90%	382 (3 RCTs)	**Low**[1,3]	
Pain 0 to 100 scale, where 0 is no pain **Short-term follow-up** (≤ 3 months postintervention)	Chronic	Opioid (tapentadol)	MD -8.00 (-12.2 to -3.8)	NA	637 (1 RCT)	**High**	MD converted from 0 to 10 scale to a 0 to 100 scale by multiplying by 10.

Table 5. Summary of findings table: pharmacological intervention versus placebo for adults with low back pain (LBP) *(Continued)*

Pain 50% reduction **Short-term follow-up** (≤ 3 months postintervention)	Chronic	Opioid (tapentadol)	RR 1.43 (1.07 to 1.91)	NA	632 (1 RCT)	**High**	
Pain 0 to 100 scale, where 0 is no pain **Intermediate-term follow-up** (> 3 months and ≤ 12 months postintervention)	Chronic	NSAIDs	MD -6.97 (-10.74 to -3.14)	52%	1354 (6 RCTs)	**Low**[1,4]	Outcome assessed at ≤16 weeks
Pain 0 to 100 scale, where 0 is no pain **Intermediate-term follow-up** (> 3 months and ≤ 12 months postintervention)	Chronic	NSAIDs (non-selective)	MD -5.96 (-10.96 to -0.96)	5%	847 (4 RCTs)	**Low**[1,3]	Outcome assessed at ≤16 weeks
Pain 0 to 100 scale, where 0 is no pain **Intermediate-term follow-up** (> 3 months and ≤ 12 months postintervention)	Chronic	NSAIDs (selective)	MD -9.11 (-13.54 to -4.66)	0%	507 (2 RCTs)	**Moderate**[1]	Outcome assessed at ≤16 weeks

CI: confidence interval; **MD**: mean difference; **OR**: odds ratio; **RR**: risk ratio; **SMD**: standardised mean difference; **NA**: not applicable

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 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.

[1]Downgraded for study limitations

[2]Downgraded for imprecision
[3]Downgraded for inconsistency
[4]Downgraded for other factors
[5]Scales were 0 to 10 scale, where 0 is no pain; 0 to 100 scale, where 0 is no pain; 4-point scale, where 0 is no pain
[6]Scales were 5-point scale, where 1 is no pain; other scale not specified
[7]Scales were 0 to 10 scale, where 0 is no pain; 0 to 20 scale, where 0 is no pain; 0 to 100 scale, where 0 is no pain
[8]Scales were 0 to 10 scale, where 0 is no pain; 0 to 20 scale, where 0 is no pain
[9]Scales were 0 to 10 scale, where 0 is no pain; 0 to 100 scale, where 0 is no pain

Table 6. Overview of reviews table: paracetamol versus placebo for adults with low back pain (LBP)

Paracetamol for low back pain in adults ≤3 months postintervention (short-term)

Outcome	Low back pain (duration)	Relative effect (95% CI)	I^2	Number of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
Physical function	Acute	MD 0.05 (-0.50 to 0.60)	0%	1506 (1 RCT)	**High**	MD on a 0 to 24 scale
Safety (adverse events)	Acute	RR 1.07 (0.86 to 1.33)	0%	1624 (1 RCT)	**High**	
Safety (serious adverse events)	Acute	RR 0.9 (0.30 to 2.67)	0%	1643 (1 RCT)	**High**	
Health-related quality of life (physical)	Acute	MD -0.79 (-1.94 to 0.36)	0%	1145 (1 RCT)	**High**	MD on a 0 to 100 scale
Health-related quality of life (mental)	Acute	MD -0.60 (-1.38, 0.17)	0%	1145 (1 RCT)	**High**	MD on a 0 to 100 scale
Participant rating of improvement	Acute	MD -0.1 (-0.33 to 0.13)	0%	1511 (1 RCT)	**High**	MD on a -5 to +5 scale

CI: confidence interval; **MD**: mean difference; **RR**: risk ratio

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 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.

Table 7. Overview of reviews table: NSAIDs versus placebo for adults with low back pain (LBP)

NSAIDs for low back pain in adults ≤3 months postintervention (short-term)

Outcome	Low back pain duration	Intervention and comparison	Relative effect (95% CI)	I^2	Number of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
Pain	Acute	NSAID (selective) versus NSAID (non-selective)	MD -2.6 (-9.23 to 4.03)	57%	437 (2 RCTs)	**Low**[1,2]	MD on a 0 to 100 scale
Pain	Acute	NSAID versus paracetamol	SMD -0.12 (-0.35 to 0.12)	0%	289 (2 RCTs)	**Low**[1,3]	
Physical function	Acute	NSAID versus placebo	MD -2.02 (-2.89 to -1.15)	0%	471 (2 RCTs)	**High**	MD on a 0 to 24 scale
Physical function	Acute	NSAID (selective) versus NSAID (non-selective)	MD -7 (-13.15 to -0.85)	NA	104 (1 RCT)	**Moderate**[1]	MD on a 0 to 50 scale
Physical function	Chronic	NSAID versus placebo	MD -0.85 (-1.30 to -0.40)	46%	1161 (4 RCTs)	**Low**[1,4]	MD on a 0 to 24 scale
Safety (adverse events)	Acute	NSAID versus placebo	RR 0.86 (0.63 to 1.18)	0%	1394 (6 RCTs)	**Very low**[1,2,3,5]	
Safety (adverse events)	Acute	NSAID (selective) versus NSAID (non-selective)	RR 0.97 (0.63 to 1.50)	22%	444 (2 RCTs)	**Very low**[1,3]	
Safety (adverse events)	Chronic	NSAID versus placebo	RR 1.04 (0.92 to 1.17)	20%	1354 (6 RCTs)	**Low**[1,4]	
Safety (adverse events)	Chronic	NSAID (non-selective) versus placebo	RR 0.94 (0.82 to 1.08)	0%	847 (4 RCTs)	**Low**[1,4]	
Safety (adverse events)	Chronic	NSAID (selective) versus placebo	RR 1.25 (1.00 to 1.56)	18%	507 (2 RCTs)	**Moderate**[1]	
Safety (adverse events)	Chronic	NSAID versus paracetamol	RR 1.5 (0.15 to 14.68)	NA	28 (1 RCT)	**Not reported**	

Table 7. Overview of reviews table: NSAIDs versus placebo for adults with low back pain (LBP) *(Continued)*

Safety (adverse events)	Chronic	NSAID versus tramadol	RR 0.83 (0.75 to 0.91)	NA	1583 (1 RCT)	**Not reported**
Safety (adverse events)	chronic	NSAID versus pregabalin	RR 0.8 (0.23 to 2.74)	NA	72 (1 RCT)	**Not reported**
Participant rating of improvement	Acute	NSAID versus placebo	RR 1.4 (1.12 to 1.75)	52%	1201 (5 RCTs)	**Low**[2,5]
Participant rating of improvement	Acute	NSAID versus other drug	RR 1.01 (0.81 to 1.25)	0%	162 (2 RCTs)	**Moderate**[3]
Participant rating of improvement	Chronic	NSAID versus paracetamol	RR 1.39 (0.82 to 2.37)	NA	28 (1 RCT)	**Not reported**
Participant rating of improvement	Chronic	NSAID versus tramadol	RR 1.26 (1.16 to 1.38)	NA	1583 (1 RCT)	**Not reported**
Workplace participation	Acute	NSAID versus placebo	RR 1.48 (0.98 to 2.23)	NA	266 (1 RCT)	**Very low**[1,3]

CI: confidence interval; **MD**: mean difference; **RR**: risk ratio; **SMD**: standardised mean difference; **NA**: not applicable

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 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.

[1]Downgraded for study limitations
[2]Downgraded for inconsistency
[3]Downgraded for imprecision
[4]Downgraded for other factors
[5]Downgraded for indirectness

Table 8. Overview of reviews table: muscle relaxants and benzodiazepines versus placebo for adults with low back pain (LBP)

Muscle relaxants and benzodiazepines for low back pain in adults ≤3 months postintervention (short-term)

Table 8. Overview of reviews table: muscle relaxants and benzodiazepines versus placebo for adults with low back pain (LBP) *(Continued)*

Outcome	Low back pain duration	Intervention and comparison	Relative effect (95% CI)	I^2	Number of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
Pain	Acute	Non-benzodiazepine antispasmodic + analgesic/NSAID versus placebo + analgesic/NSAID	RR 0.64 (0.37 to 1.09)	84%	469 (2 RCTs)	**Not reported**	
Physical function	Acute	Non-benzodiazepine antispasmodic versus placebo	RR 0.55 (0.40 to 0.70)	0%	251 (3 RCTs)	**Moderate**[1]	
Safety (adverse events)	Acute	Non-benzodiazepine antispasmodic versus placebo	RR 1.5 (1.14 to 1.98)	0%	724 (8 RCTs)	**Moderate**[1]	
Safety (adverse events)	Chronic	Non-benzodiazepine antispasmodic versus placebo	RR 1.02 (0.67 to 1.57)	0%	246 (2 RCTs)	**Low**[1,2]	
Safety (adverse events)	Acute	Non-benzodiazepine antispasmodic + analgesic/NSAID versus placebo + analgesic/NSAID	RR 1.3 (0.62 to 2.75)	84%	506 (3 RCTs)	**Not reported**	
Participant rating of improvement	Acute	Non-benzodiazepine antispasmodic versus placebo	RR 0.68 (0.41 to 1.13)	34%	323 (4 RCTs)	**Not reported**	
Participant rating of improvement	Acute	Non-benzodiazepine antispasmodic + analgesic/NSAID versus placebo + analgesic/NSAID	RR 0.37 (0.08 to 1.77)	80%	148 (2 RCTs)	**Not reported**	
Participant rating of improvement	Chronic	Benzodiazepine versus placebo	RR 0.63 (0.42 to 0.97)	17%	151 (2 RCTs)	**Not reported**	

CI: confidence interval; **RR**: risk ratio

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 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.

[1]Downgraded for study limitations
[2]Downgraded for imprecision

Table 9. Overview of reviews table: opioids versus placebo for adults with low back pain (LBP)

Opioids for low back pain in adults ≤3 months postintervention (short-term)

Outcome	Low back pain duration	Intervention and comparison	Relative effect (95% CI)	I^2	Number of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
Pain	Chronic	Tramadol versus celecoxib	RR 0.82 (0.76 to 0.90)	NA	1583 (1 RCT)	**Not reported**	
Pain (30% reduction)	Chronic	Tramadol versus celecoxib	OR 0.63 (0.52 to 0.77)	NA	1583 (1 RCT)	**Very low**[1,2,3]	
Pain	Chronic	Opioids versus antidepressants	SMD 0.21 (-0.03 to 0.45)	0%	272 (2 RCTs)	**Very low**[1,2]	
Pain	Chronic	Tapentadol versus oxycodone	MD 0 (-0.4 to 0.4)	NA	not reported (1 RCT)	**Not reported**	MD on a 0 to 10 scale
Pain (50% reduction)	Chronic	Tapentadol versus oxycodone	RR 1.16 (0.89 to 1.51)	NA	641 (1 RCT)	**Not reported**	
Physical function	Chronic	Tramadol versus placebo	SMD -0.18 (-0.29 to -0.07)	0%	1348 (5 RCTs)	**Moderate**[1]	
Physical function	Chronic	Buprenorphine versus placebo	SMD -0.14 (-0.53 to 0.25)	NA	101 (1 RCT)	**Very low**[1,2]	
Physical function	Chronic	Opioids (strong) versus placebo	SMD -0.26 (-0.37 to -0.15)	0%	1375 (4 RCTs)	**Moderate**[1]	
Physical function	Chronic	Opioids versus antidepressants	SMD -0.11 (-0.63 to 0.42)	NA	56 (1 RCT)	**Very low**[1,2]	
Safety (adverse events)	Chronic	Tapentadol versus placebo	RR 1.27 (1.14 to 1.41)	NA	637 (1 RCT)	**High**	
Safety (serious adverse events)	Chronic	Tapentadol versus placebo	RR 2.34 (0.61 to 8.97)	NA	637 (1 RCT)	**Moderate**[2]	
Safety (nausea)	Chronic	Opioids (all types) versus placebo	RD 0.10 (0.07 to 0.14)	63%	3747 (10 RCTs)	**Low**[1,4]	
Safety (headaches)	Chronic	Opioids (all types) versus placebo	RD 0.03 (0.01 to 0.05)	32%	3747 (10 RCTs)	**Low**[1,4]	

Table 9. Overview of reviews table: opioids versus placebo for adults with low back pain (LBP) *(Continued)*

Safety (constipation)	Chronic	Opioids (all types) versus placebo	RD 0.07 (0.04 to 0.11)	78%	3493 (9 RCTs)	**Low**[1,4]
Safety (dizziness)	Chronic	Opioids (all types) versus placebo	RD 0.08 (0.05 to 0.11)	68%	3494 (9 RCTs)	**Low**[1,4]
Safety (somnolence)	Chronic	Opioids (all types) versus placebo	RD 0.06 (0.03 to 0.09)	66%	3257 (8 RCTs)	**Low**[1,4]
Safety (adverse events)	Chronic	Tapentadol versus oxycodone	RR 0.89 (0.82 to 0.96)	NA	646 (1 RCT)	**Not reported**
Safety (serious adverse events)	Chronic	Tapentadol versus oxycodone	RR 0.66 (0.26 to 1.67)	NA	646 (1 RCT)	**Not reported**
Safety (withdrawal due to adverse events)	Chronic	Tapentadol versus placebo	RR 3.41 (1.96 to 5.94)	NA	637 (1 RCT)	**High**
Safety (withdrawal due to adverse events)	Chronic	Tapentadol versus oxycodone	RR 0.49 (0.37 to 0.66)	NA	646 (1 RCT)	**Not reported**

CI: confidence interval; **MD**: mean difference; **OR**: odds ratio; **RR**: risk ratio; **SMD**: standardised mean difference; **NA**: not applicable

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 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.

[1]Downgraded for study limitations
[2]Downgraded for imprecision
[3]Downgraded for indirectness
[4]Downgraded for inconsistency

Table 10. Overview of reviews table: antidepressants versus placebo for adults with low back pain (LBP)

Antidepressants for low back pain in adults ≤3 months postintervention (short-term)

Table 10. Overview of reviews table: antidepressants versus placebo for adults with low back pain (LBP) *(Continued)*

Outcome	Low back pain duration	Intervention and comparison	Relative effect (95% CI)	I^2	Number of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
Physical function	Chronic	Antidepressant versus placebo	SMD -0.06 (-0.40 to 0.29)	0	132 (2 RCTs)	**Low**[1,2]	

CI: confidence interval; **SMD**: standardised mean difference

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 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.

[1]Downgraded for study limitations
[2]Downgraded for imprecision

Table 11. Summary of results table: pain

	Large effect	Medium effect	Small effect	No evidence of difference	Harmful
High certainty evidence			Opioid (tapentadol)[2]	Paracetamol[1]	
Moderate certainty evidence			NSAIDs[1], muscle relaxants[1] Opioids (strong)[2], NSAIDs (selective)[2]	Antidepressants (SSRIs)[2]	
Low certainty evidence		Opioid (tramadol)[2]	NSAIDs[2], NSAIDs (non-selective)[2], opioid (buprenorphine)[2]	Antidepressants[2]	
Very low certainty evidence				Antidepressants (TCAs)[2]	

The size of the effect for the mean between group difference are based on the definitions from the American College of Physicians and the American Pain Society (Chou 2017):
Large effect: > 20 points on a 0 to 100 scale or > 0.8 SMD
Medium effect: > 10 to 20 points on a 0 to 100 scale or > 0.5 to 0.8 SMD
Small effect: 5 to 10 points on a 0 to 100 scale or 0.2 to 0.5 SMD
No evidence of difference: boundaries of the 95% confidence interval span both sides of the line of no effect
Harmful: boundaries of the 95% confidence interval fall completely within harm.

[1]Acute low back pain
[2]Chronic low back pain

Table 12. Summary of results: physical function

	Large effect	Medium effect	Small effect	No evidence of difference	Harmful
High certainty evidence			NSAIDs[1]	Paracetamol[1]	
Moderate certainty evidence			Muscle relaxants[1] Opioid (tramadol)[2], Opioid (strong)[2]		
Low certainty evidence			NSAIDs[2]	Antidepressant[2]	
Very low certainty evidence				Opioid (buprenorphine)[2]	

The size of the effect for the mean between group difference are based on the definitions from the American College of Physicians and the American Pain Society (Chou 2017):
Large effect: > 20 points on a 0 to 100 scale or > 0.8 SMD
Medium effect: > 10 to 20 points on a 0 to 100 scale or > 0.5 to 0.8 SMD
Small effect: 5 to 10 points on a 0 to 100 scale or 0.2 to 0.5 SMD

Table 12. Summary of results: physical function *(Continued)*

No evidence of difference: boundaries of the 95% confidence interval span both sides of the line of no effect
Harmful: boundaries of the 95% confidence interval fall completely within harm.

[1]Acute low back pain
[2]Chronic low back pain

APPENDICES

Appendix 1. Search strategy: The Cochrane Library

#1 MeSH descriptor back pain explode all trees
#2 MeSH descriptor pain explode all trees
#3 (back or spine or spinal) adj2 pain
#4 lumbar* or lumbo*
#5 backache* or back ache*
#6 (#1 OR #2 OR #3 OR #4 OR #5)
(Limited to Cochrane Reviews and Cochrane protocols)

Appendix 2. AMSTAR-2 assessment criteria

AMSTAR-2 is a 16-item critical appraisal tool to assist in identifying high quality systematic reviews. There is no summary score but an overall rating based on weaknesses across 7 critical domains*.

1. Did the research questions and inclusion criteria for the review include the components of PICO?

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?*

3. Did the review authors explain their selection of the study designs for inclusion in the review?

4. Did the review authors use a comprehensive literature search strategy?*

5. Did the review authors perform study selection in duplicate?

6. Did the review authors perform data extraction in duplicate?

7. Did the review authors provide a list of excluded studies and justify the exclusions?*

8. Did the review authors describe the included studies in adequate detail?

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?*

10. Did the review authors report on the sources of funding for the studies included in the review?

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?*

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?*

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?*

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Ratings in overall confidence in the results of the review are as follows.

High - zero or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

Moderate - more than one non-critical weakness*: the systematic review has more than one weakness, but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.

Low - one critical flaw with or without non-critical weaknesses: the systematic review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

Critically low - more than one critical flaw with or without non-critical weaknesses: the systematic review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

Appendix 3. Reasons for excluded reviews

Name of review	Reason for exclusion
Dagenais 2007	Ineligible intervention
Derry 2014a	Ineligible patient population
Derry 2016	Ineligible route of administration
Derry 2014b	Ineligible route of administration
Derry 2015	Ineligible route of administration
Furlan 2014	Ineligible study design
Haroutounian 2012	Ineligible patient population
Noble 2010	Ineligible study design
Oltean 2014	Ineligible intervention
Quigley 2013	Cochrane Review withdrawn
Roelofs 2008	Cochrane Review updated
Samuel 2012	Ineligibleintervention
Seidel 2013	Ineligible patient population
Soares 2014	Ineligible study design
Staal 2008	Ineligible route of administration
Waseem 2011	Ineligible route of administration
Wiffen 2010	Cochrane Review withdrawn
Wiffen 2011	Cochrane Review withdrawn
Zaina 2016	Ineligible intervention

Appendix 4. Effectiveness comparison (Different forms of the same pharmacological intervention (e.g. selective NSAID versus a non-selective NSAID))

Outcome data is for short-term (≤ 3 months postintervention) unless otherwise stated.

NSAIDs

Acute LBP

Pain: Van der Gaag 2020 performed a pooled analysis of two studies (two comparisons, 437 participants) investigating selective versus non-selective NSAIDs and reported an MD of -2.6 (95% CI -9.23 to 4.03; I^2 = 56%; low-certainty evidence) on a 0 to 100 pain intensity scale [higher scores indicate worse pain] favouring selective NSAIDs. The same review narratively reported the results of thirteen studies (thirteen comparisons, 1823 participants) investigating different types of non-selective NSAIDs and found no clear or clinically meaningful differences on pain intensity.

Physical function: Van der Gaag 2020 narratively reported the results of five studies (five comparisons, 1006 participants) investigating different types of non-selective NSAIDs and found no clear or clinically meaningful differences on function. The same review narratively reported the results from two studies (two separate comparisons, 444 participants) investigating selective versus non-selective NSAIDs and reported conflicting results for improvements in function.

Safety: Van der Gaag 2020 performed a pooled analysis of two studies (two comparisons, 444 participants) investigating selective versus non-selective NSAIDs and reported a RR of 0.97 (95% CI 0.63 to 1.50; I^2 = 22%; very low-certainty evidence) on risk of adverse events. The same review narratively reported the results of fourteen studies (fourteen comparisons, 2337 participants) investigating different types of non-selective NSAIDs and found no clear difference between treatments in the proportion of participants experiencing adverse events.

Participant rating of improvement: Van der Gaag 2020 narratively reported the results of seven studies (seven comparisons, 987 participants) investigating different types of non-selective NSAIDs and one study (one comparison, 333 participants) investigating selective versus non-selective NSAIDs and found no clear or clinically meaningful differences on participant ratings of improvement.

Health-related quality of life: we did not find any reviews providing useable data or evidence for the effects of pharmacological interventions on this outcome for this comparison.

Workplace participation: Van der Gaag 2020 narratively reported the results of one study (one comparison, 30 participants) investigating different types of non-selective NSAIDs and found no differences for return to work.

Chronic LBP

Pain: Enthoven 2016 narratively reported the results of two studies (two separate comparisons, 90 participants) investigating different types of non-selective NSAIDs and one study (one comparison, 440 participants) investigating selective versus non-selective NSAIDs and found no evidence of differences on pain intensity.

Physical function: we did not find any reviews providing useable data or evidence for the effects of pharmacological interventions on this outcome for this comparison.

Safety: Enthoven 2016 narratively reported the results of two studies (two separate comparisons, 90 participants) investigating different types of non-selective NSAIDs and one study (one comparison, 440 participants) investigating selective versus non-selective NSAIDs and found no evidence of differences in experienced adverse events.

Opioids

Chronic LBP

Pain: Santos 2015 reported data on one study (one comparison, 641 participants) investigating tapentadol versus oxycodone and reported a RR of 1.16 (95% CI 0.89 to 1.51) on 50% reduction in pain intensity and an MD of 0 (95% CI -0.40 to 0.40) on a 0 to 10 pain intensity scale.

Safety: Santos 2015 reported the results of one study (one comparison, 646 participants) investigating tapentadol versus oxycodone and reported a RR of 0.89 (95% CI 0.82 to 0.96) for the risk of experiencing and adverse event, reported a RR of 0.66 (95% CI 0.26 to 1.67) for the risk of experiencing a serious adverse event, and reported a RR of 0.49 (95% CI 0.37 to 0.66) for risk of withdrawal due to an adverse event.

Appendix 5. Effectiveness comparison (Pharmacological intervention versus a different type of pharmacological intervention (e.g. NSAID versus opioid))

Outcome data is for short-term (≤ 3 months postintervention) unless otherwise stated.

NSAIDS

Acute LBP

Pain: Van der Gaag 2020 performed a pooled analysis of two studies (two comparisons) investigating NSAIDs versus paracetamol and reported a SMD of -0.12 (95% CI -0.35 to 0.12, I^2 = 0%; 289 participants; low-certainty evidence). The same review narratively reported the results of four studies (four comparisons, 391 participants) investigating NSAIDs versus other drugs and reported no clinically meaningful differences between the groups.

Physical function: Van der Gaag 2020 narratively reported the results of one study (one comparison, 219 participants) investigating NSAIDs versus paracetamol and reported no clear differences between the groups.

Safety: Van der Gaag 2020narratively reported the results of two studies (two comparisons, 289 participants) and found low-certainty evidence that NSAIDs led to a greater proportion of participants experiencing an adverse event compared to paracetamol. The same review narratively reported the results of four studies (four comparisons, 391 participants) and found that those who took NSAIDs were more likely to report adverse events than those who took other drugs.

Participant rating of improvement: Van der Gaag 2020 performed a pooled analysis of two studies (two comparisons) investigating NSAIDs versus other drugs and reported a RR 1.01 (95% CI 0.81 to 1.25; I^2 = 0%; 162 participants; moderate-certainty evidence).

Workplace participation: Van der Gaag 2020 narratively reported the results of one study (three comparisons, 45 participants) investigating NSAIDs versus paracetamol and reported no clear differences between groups.

Chronic LBP

Safety: Enthoven 2016 reported data on one study (one comparison) investigating NSAIDs versus paracetamol, one study (one comparison) investigating NSAIDs versus tramadol, and one study (one comparison) investigating pregabalin and reported a RR of 1.50 (95% CI 0.15 to 14.68; 28 participants), a RR of 0.86 (95% CI 0.75 to 0.91; 1 study, 1583 participants), and a RR of 0.80 (95% CI 0.23 to 2.74; 72 participants) for the risk of reporting adverse events respectively.

Participant rating of improvement: Enthoven 2016 reported data on one study (one comparison, 28 participants) investigating NSAIDs versus paracetamol and one study (one comparison, 1583 participants) investigating NSAIDs versus tramadol and reported a RR of 1.39 (95% CI 0.82 to 2.37) and a RR of 1.26 (95% CI 1.16 to 1.38) respectively.

Workplace participation: we did not find any reviews providing useable data or evidence for the effects of pharmacological interventions on this outcome for this comparison.

Opioids

Chronic LBP

Physical function: one review reported the results of one study (one comparison) investigating opioids versus antidepressants and reported a SMD of -0.11 (95% CI -0.63 to 0.42; 56 participants; very low-certainty evidence) (Chaparro 2013).

Antidepressants

Chronic LBP

Pain: Urquhart 2008 performed a pooled analysis of two studies (two comparisons) investigating opioids versus antidepressants and reported a SMD of 0.21 (95% CI -0.03 to 0.45; I^2 = 0%; 272 participants; very low-certainty evidence). The same review reported the results of one study (one comparison) investigating tramadol versus celecoxib (a NSAID) and reported a RR of 0.82 (95% CI 0.76 to 0.90; 1583 participants) for reducing pain intensity and an OR of 0.63 (95% CI 0.52 to 0.77; 1583 participants; very low-certainty evidence) for a 30% reduction in pain intensity.

Appendix 6. Effectiveness comparison (Pharmacological intervention versus a non-pharmacological intervention (e.g. NSAID versus spinal manipulative therapy))

Outcome data is for short-term (≤ 3 months postintervention) unless otherwise stated.

NSAIDs

Acute LBP

Pain: Van der Gaag 2020 narratively reported the results of four studies (six comparisons, 353 participants) and found very low-certainty evidence that three studies showed no clinically meaningful difference between NSAIDs and spinal manipulation at short-term follow-up, and no clear difference in the intermediate term follow-up.

Physical function: Van der Gaag 2020 narratively reported the results of two studies (two comparisons, 193 participants) and found conflicting results; one study found a clinically meaningful difference between NSAIDs and spinal manipulation in favour of spinal manipulation and the other did not (very low-certainty evidence). The same review reported no clear difference in the intermediate term follow-up.

Safety: Van der Gaag 2020 narratively reported the results of two studies (two comparisons, 189 participants) and found very low-certainty evidence of no clear difference between NSAIDs and spinal manipulation on risk of adverse events.

Participant rating of improvement: Van der Gaag 2020 narratively reported the results of two studies (three comparisons, 180 participants) and found conflicting results; one study found a clinically meaningful difference between NSAIDs and spinal manipulation in favour of spinal manipulation and the other did not, very low-certainty evidence. The same review reported no clear difference in the intermediate term follow-up.

Workplace participation: Van der Gaag 2020 narratively reported the results of one study (one comparison, n = not reported) and found low-certainty evidence of no clear difference between NSAIDs and spinal manipulation on workplace participation.

Chronic LBP

Pain: Enthoven 2016 narratively reported the results from one study (one comparison, 201 participants) and reported that there was no difference in pain reduction between NSAIDs and home-based exercise.

Physical function: Enthoven 2016 narratively reported the results from one study (one comparison, 201 participants) and reported that functional status was better with home-based exercise compared to NSAIDs.

HISTORY

Protocol first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

AGC, BMW, NEO, JHM conceived the idea for an overview of pharmacological treatments for low back pain. AGC and RNNR conducted the search, screening, data extraction, AMSTAR 2 and GRADE assessments. AGC wrote the first draft included drafting the tables and results of this overview. All authors provided review and feedback to the draft versions and approved the final version published.

DECLARATIONS OF INTEREST

MKB has received support from his institution (UNSW) for conference travel that is unrelated to the present work, from the Chiropractor's Association of Australia to speak about pain rehabilitation and from the Memorial University of Newfoundland to speak about engagement with research evidence, including evidence about medicines. MKB's salary was provided by scholarships. MKB is first author on the Cochrane Review 'Paracetamol, NSAIDs or opioid analgesics for chronic low back pain: a network meta-analysis' and was not involved in any decisions about this review in the overview.

CGM has received competitive grants from government agencies and industry to support his research. As an invited speaker at conferences, he has had his expenses covered and also received small gifts such as a box of chocolates or a bottle of wine. He has received honoraria for marking theses, reviewing grants, and preparing talks. CGM is on the Editorial Board of the Cochrane Back and Neck Review Group. Mitigation of conflict of interest: CGM was not involved in editorial decisions on this review.

ADF: Google LLC, D/B/A YouTube (Independent Contractor - Other). The institutions where ADF works have received various grants from external organisations, including government and public institutions in Ontario, Canada, and the UK.

MWvT is on the Editorial Board of the Cochrane Back and Neck Review Group. MWvT was Co-ordinating Editor until September 2017. MWvT was not involved in editorial decisions on this review. MWvT has no additional competing interest; all research funding comes from non-profit, governmental funding agencies, and all funding (including travel and stay expenses) were paid to the VU University.

HL has consulted for Cancer Council Australia and has received funding from the Australian Health and Medical Research Council (grant no. APP1126767), Center for Effective Global Action (CEGA), and Berkeley Initiative for Transparency in the Social Sciences (BITSS).

BMW has received payment for lectures on the non-pharmacological management of chronic low back pain. He has received honoraria for marking theses related to low back pain.

AGC, NEO, RNRR, EO and JHM have no known declarations.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

One additional review author joined the review team: Rodrigo RN Rizzo (RRNR).

We did not use the planned definition of a 10-point reduction in pain intensity and disability as the minimally important difference. Instead, we used the definitions from the American College of Physicians and the American Pain Society, to improve interpretation of the size of the effect, without making judgements on what would be considered minimally important by an individual (Chou 2017).

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [therapeutic use]; *Acute Pain [drug therapy]; Analgesics, Opioid [adverse effects]; Anti-Inflammatory Agents, Non-Steroidal [adverse effects]; *Buprenorphine [therapeutic use]; *Low Back Pain [drug therapy]; Systematic Reviews as Topic; *Tramadol [therapeutic use]

MeSH check words

Adult; Humans