BMJ Open

Network meta-analysis for comparative effectiveness of treatments for chronic low back pain disorders: systematic review protocol

Daniel L Belavy ,[1] Ashish D Diwan,[2] Jon Ford,[3,4] Clint T Miller,[5] Andrew J Hahne,[4] Niamh Mundell ,[6] Scott Tagliaferri ,[6] Steven Bowe,[7] Hugo Pedder,[8] Tobias Saueressig ,[9] Xiaohui Zhao,[10] Xiaolong Chen,[11] Arun Prasad Balasundaram,[4] Nitin Kumar Arora,[1,12] Patrick J Owen [5]

To cite: Belavy DL, Diwan AD, Ford J, *et al*. Network meta-analysis for comparative effectiveness of treatments for chronic low back pain disorders: systematic review protocol. *BMJ Open* 2021;**11**:e057112. doi:10.1136/bmjopen-2021-057112

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-057112).

Received 07 September 2021
Accepted 11 November 2021

For numbered affiliations see end of article.

Correspondence to
Professor Daniel L Belavy; belavy@gmail.com

ABSTRACT

Introduction Chronic low back pain disorders (CLBDs) present a substantial societal burden; however, optimal treatment remains debated. To date, pairwise and network meta-analyses have evaluated individual treatment modes, yet a comparison of a wide range of common treatments is required to evaluate their relative effectiveness. Using network meta-analysis, we aim to evaluate the effectiveness of treatments (acupuncture, education or advice, electrophysical agents, exercise, manual therapies/manipulation, massage, the McKenzie method, pharmacotherapy, psychological therapies, surgery, epidural injections, percutaneous treatments, traction, physical therapy, multidisciplinary pain management, placebo, 'usual care' and/or no treatment) on pain intensity, disability and/or mental health in patients with CLBDs.

Methods and analysis Six electronic databases and reference lists of 285 prior systematic reviews were searched. Eligible studies will be randomised controlled/clinical trials (including cross-over and cluster designs) that examine individual treatments or treatment combinations in adult patients with CLBDs. Studies must be published in English, German or Chinese as a full-journal publication in a peer-reviewed journal. A narrative approach will be used to synthesise and report qualitative and quantitative data, and, where feasible, network meta-analyses will be performed. Reporting of the review will be informed by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidance, including the network meta-analysis extension (PRISMA-NMA). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for network meta-analysis will be implemented for assessing the quality of the findings.

Ethics and dissemination Ethical approval is not required for this systematic review of the published data. Findings will be disseminated via peer-reviewed publication.

PROSPERO registration number PROSPERO registration number CRD42020182039.

Strengths and limitations of this study

- This study will enable comparison of a wide variety of treatments for chronic low back disorders via network meta-analysis.
- Our study will provide evidence that can be applied in clinical practice and in low back pain management guidelines.
- The quality of evidence will be assessed via the Grading of Recommendations Assessment, Development and Evaluation (GRADE).
- We will address the potential limitation of heterogeneous pathologies being combined into one population by performing subgroup analyses.
- Baseline pain and disability are known to be predictive of outcome and we will account for this in the analysis.

INTRODUCTION

Low back pain is the greatest cause of disability and lost productivity worldwide.[1] In developed regions, such as the USA, Japan, Europe and Australia, the disease generates substantial financial costs.[2] For example, healthcare expenditure is in excess of $A5 billion per year in Australia[3] and US$100 billion per year in the USA.[3] The majority of acute cases of back pain resolve without specific intervention,[4] yet chronic low back pain disorders (CLBDs; i e, >12 weeks duration) generate the greatest proportion of economic burden[5] and affect 20.1%±9.8% of the population worldwide.[6] To reduce the global burden of disease of CLBDs, identifying and implementing the most effective treatment are urgent priority.[7]

To date, pairwise meta-analyses have typically been used to evaluate individual treatment modes for CLBDs.[8] Current recommendations include education, exercise, manual therapy, psychotherapy and multidisciplinary interventions.[8 9] A comparison of a wide range of common treatments and their relative effectiveness for CLBDs is yet

to be performed. This evidence would inform management guidelines and clinical decision making. These data would also increase the likelihood that patients receive the most efficacious treatment and/or avoid therapies with similar effectiveness but greater harms. Collectively, this would reduce financial burden at the societal level, as well as improve patient outcomes at the individual level.

Network meta-analysis (NMA) permits the ranking of a series of interventions as comparably more or less effective.[10 11] NMA can incorporate data on multiple treatments simultaneously from randomised controlled trials (RCTs) that do not have similar comparator groups by synthesising direct and indirect evidence from a 'network' of studies.[11–13] This overcomes a key limitation for pairwise meta-analysis and allows RCTs that do not have a non-treatment or minimal treatment control group to be included in the analysis.[14] NMA has been used to examine the relative effectiveness of exercise training modalities in non-specific chronic low back pain,[15] exercise and education for back pain prevention,[16] treatments for lumbar disc herniation[17] and medication for sciatica.[18] However, this approach has not been considered simultaneously for a wide range of common treatments of CLBDs. In this study, we will examine CLBDs, encompassing radicular syndromes and non-specific low back pain.[19] Our primary aim is to determine the relative effectiveness of a variety of common treatments for CLBDs via NMA.

METHODS

This systematic review will be conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[20] and the PRISMA extension for network meta-analyses (PRISMA-NMA).[21] Covidence (https://www.covidence.org) will be used for article screening and data extraction. This systematic review was prospectively registered on PROSPERO (CRD42020182039, submitted 24 April 2020) prior to initiating data extraction. We will use the PRISMA-P checklist when writing our report.[22]

Eligibility criteria

For inclusion, studies will be required to be full peer-reviewed publications (ie, grey literature including theses and conference abstracts will be excluded) in English, German or Chinese. A meta-epidemiological study by Nussbaumer-Streit *et al*[23] found that when non-English studies were excluded from systematic reviews of clinical interventions, this had little impact on study conclusions. Furthermore, Cochrane guidelines[24] are ambivalent on the inclusion of non-English language articles and the potential for introduction of bias in reviews. Prior work has suggested that inclusion or exclusion of non-English articles does not influence the effect estimates, but may narrow CIs.[25] We pragmatically chose to include articles in languages in which the author team were fluent. All other inclusion criteria followed the Participants, Interventions, Comparators, Outcomes and Study design (PICOS) framework.[21]

Population

Adults (≥18 years) with CLBDs. Chronic is defined as pain lasting 12 weeks or more.[26] Since not all studies are consistent in their reporting of pain duration, we will use the following approach: if a study defines it collectively as 'chronic', then it will be included. Failing this, if the inclusion criteria of the study are minimum of 12 weeks' pain duration or if the median or mean reported duration of pain at baseline in participants is 12 weeks or more, then the study will be included. Recurrent pain (ie, <12 weeks' duration of symptoms and pain-free period of at least 6 months[27]) is excluded. Low back disorder is defined as back pain with or without leg pain where there are no specific spinal pathologies (ie, vertebral fracture, malignancy, spinal infection, axial spondyloarthritis, cauda equina syndrome[19]). Spondylolisthesis, spondylosis, disc herniation, disc degeneration, scoliosis, deformity (eg, hemivertebrae) and radicular syndromes (eg, radicular pain (leg pain or sciatica), radiculopathy, spinal stenosis) are included.[19] 'Failed back surgery syndrome' is included as this is not a specific disease.[28] If a study only examines post-surgical pain (eg, a comparison of management for immediate post-surgical pain as an RCT), we will consider this iatrogenic pain and the study will be excluded.

Interventions and comparators

The treatment types to be included were determined by the current clinical practice guideline from the American College of Physicians[29] and by the review areas of the Cochrane Back and Neck Group.[30] A detailed list is included in online supplemental data A; however, in brief, we examined acupuncture, education or advice, electrotherapy (including heat and ice electrotherapeutic modalities applied non-invasively), epidural injections, exercise training, manual therapies/manipulation, massage, the McKenzie method, pharmacotherapy, psychological therapies, percutaneous procedures, surgery, traction, physical therapy (otherwise not falling into specific treatment combination), placebo, multidisciplinary pain management, usual care (eg, general practitioner management), no treatment (true control). Treatment combinations will be considered pending data availability and defined according to their component parts (see online supplemental data A for details) for primary and secondary treatment components. Pending articles included in the review, further subgroup classifications will be considered.

Outcomes

Pain intensity (eg, VAS, NRS, McGill Pain Questionnaire, or Box scale, other quantitative pain measures), disability (eg, ODI, RMDQ), mental health (eg, SF-36 MH subscale, depression, anxiety). Adverse events, participant drop-outs and funding sources will be extracted from the included articles.

Study design

RCTs, randomised clinical trials, randomised controlled cluster trials or randomised cross-over trials will be included.

Search strategy

Six databases (MEDLINE, SPORTDiscus, CINAHL, PsycINFO, EMBASE, CENTRAL) were searched with no restriction on publication dates. The search was initially performed from inception to 14 November 2019 and then was updated on 24 July 2020. Search terms were to find articles on (1) low back disorders and (2) RCTs (online supplemental data B). Low back disorder terms included those recommended by the Cochrane Back and Neck review group[31] for non-specific back pain and radicular syndromes.[19] The search terms for identifying RCTs were modelled on Cochrane sensitivity-maximising and precision-maximising search terms to be consistent across databases. Prior systematic reviews in English of any kind of treatment for chronic low back disorders in the last 10 years were screened via a search (January 1990 to July 2019) of MEDLINE, SPORTDiscus, CINAHL, PsycINFO, EMBASE and CENTRAL. Collectively, 285 such systematic reviews were identified. The complete reference lists of these reviews were collated and then screened to remove non-RCTs. Subsequently, 1783 additional references were identified, and after uploading to Covidence, 1008 duplicates were removed, leaving 775 new titles/abstracts. Furthermore, the reference lists of 17 relevant Cochrane reviews not published between January 1990 and July 2019 were screened: 269 additional references were added after discarding 394 duplicates. Following removal of duplicates, a total of 19 522 articles remained for screening.

Study selection

For each record, two independent assessors will screen the studies against the predetermined inclusion/exclusion criteria. Disagreements that cannot be resolved among the assessors will be addressed by an adjudicator. If unsure, the adjudicator will discuss with the broader study team. If still unsure, the study authors will be contacted for clarity. The process for determining study inclusion/exclusion is shown in figure 1.

Data extraction

For each record, two independent assessors will extract the data. Disagreements that cannot be resolved among the assessors will be addressed by an adjudicator. Relevant information pertaining to publication metadata (ie, author, title, year, journal), study design (eg, two-arm or multi-arm parallel trial), number of participants, participant characteristics (eg, age and sex), interventions considered and outcome measures (pain, disability, mental health, adverse events and funding sources) will be extracted by two independent assessors. Extracted outcome data (pain, disability, mental health) will be pre-intervention and post-intervention mean and SD. When available, data will be extracted for the following time-points: immediate (<1 day) effect of treatment, short-term (≥1 day but <3 months), intermediate-term (≥3 but<12 months), long-term (≥12 months). Primary and any secondary intervention components will be labelled as per the protocol described in online supplemental data A.

Data presented as medians or alternate measures of spread will be converted to mean and SD using established formulae.[32] When only figures are presented (rather than numerical data within text), data will be extracted using ImageJ (https://imagej.nih.gov/ij/) to measure the length (in pixels) of the axes to calibrate, and then the length in pixels of the data points of interest.[33] When it is not possible to extract the required data, this information will be requested from the authors at a minimum of three times over a 4-week period. Prior to commencing data extraction, this method will be piloted on 30 studies chosen at random. All discrepancies will be referred to an adjudicator.

Due to the volume of potentially included articles, for each study, information on the population (type of low back pain (non-specific or radicular pain), and subpopulation (eg, 'non-specific', 'low back pain not otherwise stated', 'disc degeneration', 'spondylolisthesis', 'spinal stenosis', 'radiculopathy', 'radicular pain')) and intervention/comparator (intervention duration, free text entry of description of interventions, study-arm labels, primary and secondary intervention classifications (if relevant); see online supplemental data A) will be extracted first. Then, studies that examine different treatment classes (eg, exercise vs control, psychological therapies vs exercise, or surgery vs percutaneous therapies; see

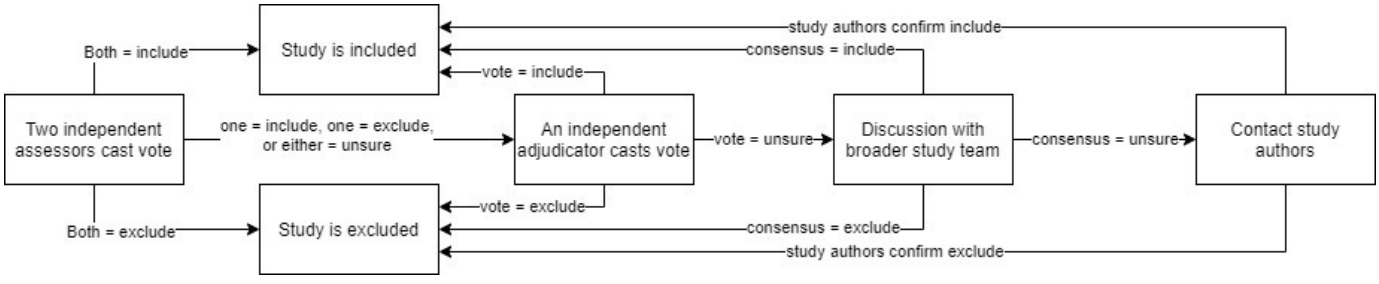

Figure 1 The process for determining study inclusion/exclusion.

online supplemental data A) will be included in subsequent extraction and the remaining studies excluded. This approach will be undertaken because our primary research question concerns different classes of treatments; hence, studies that compare the same class of treatment (eg, exercise vs exercise, or surgery vs surgery) are less informative for this question.

Risk of bias

Two independent assessors will use the Cochrane Collaboration Risk of Bias[34] to examine potential selection bias (random sequence generation and allocation concealment), performance bias (blinding of patients and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting) and other biases. Cluster randomised trials will be assessed as recommended by the Cochrane Collaboration.[35] The revised version of the risk of bias tool[36] will not be used as it was, at initiation of the project, not yet recommended by the Cochrane Collaboration. For each source of bias, studies will be classified as having a low, high or unclear (if reporting was not sufficient to assess a particular domain) risk. All discrepancies will be referred to an adjudicator.

Two independent assessors will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for NMA for assessing the quality of the evidence (online supplemental data C). We will use a range of equivalence of standardised mean difference (SMD), from −0.5 to 0.5, to evaluate imprecision and inconsistency.[37] Publication bias will be assessed via statistical and non-statistical methods.[38] Indirectness will be judged using Schünemann's approach.[39] Risk of bias will be downgraded by one level if >50% of participants were from studies with selection bias and performance bias. This criterion was selected because inadequate randomisation and lack of blinding may lead to an exaggeration of the intervention effect estimates.[40–42] For the categories 'imprecision' and 'inconsistency', we will downgrade by one level if there are some concerns and two levels if there are major concerns. Indirectness will be downgraded by one level if deemed serious and two levels if deemed very serious. We will downgrade one level if publication bias is suspected. The GRADE approach[43 44] will also be used to assess the quality of the evidence of pair-wise comparisons. All discrepancies will be referred to an adjudicator.

Statistical analyses

When studies are reverse scaled (ie, higher values indicated better outcomes rather than lower values), the mean in each group will be multiplied by −1 as recommended in the Cochrane Handbook. As all of the outcomes of interest will be continuous or ordinal, but could be measured on different scales, SMD will be used as the effect estimates.[45] A minimum of 50 participants will be required per class of treatment for it to be included in meta-analysis. We have limited the number of participants to try to limit the impacts of small study effects on the results of any particular class.[45] Furthermore, because we are conducting an analysis of SMDs, small study effects are likely to be exacerbated as both the mean and the SD are likely to be estimated with greater variability in small studies, and for SMD both of these contribute to the treatment effect. To further investigate our choice of SMD as an effect measure, we will conduct sensitivity analyses with internal reference baseline SDs for each scale.[46]

Where a study does not report data in a form where the SD can be extracted or calculated,[32] and authors are not able to fulfil data requests, SDs will be imputed and their impact evaluated in sensitivity analyses. To impute missing SDs, we will perform a regression of log(SD) on log(mean) in studies reporting SD following the approach of Marinho *et al*[47], adjusting for measurement scale and follow-up time. We will then use this regression model to predict SDs that are missing.

Cluster randomised trials will be included in the analysis as per Cochrane guidance. Sensitivity analysis will be conducted in pairwise analyses with a range of different intraclass correlation co-efficients (ICCs) to check the robustness of the results.[48] For crossover trial designs, we will include the estimated relative treatment effect from the study where possible, where the authors have tested for carryover effects and found no evidence of this. Where this is not the case, we will only include the first period of the crossover trial. In time-course Model-Based Network Meta Analyses (MBNMA), only the inclusion of the first time-period will be possible.

Network meta-analysis

Bayesian NMA will be performed at discrete time-points (immediate (<1 day) effect of treatment, short-term (≥1 day but <3 months), intermediate-term (≥3 but<12 months) and long-term (≥12 months)) using the R (r-project.org) package multinma.[49] Time-course MBNMA will be conducted using the R package MBNMAtime.[50 51] This package enables the incorporation of multiple time-points per study in Bayesian NMA to inform estimates of effect size over time. Network connectivity will be explored via network plots. Network plots help to visualise how the evidence in the network is connected and allow identification of which studies compare which treatments. This aids in understanding which treatment effects can be estimated. The time-course relationship will be examined by a time plot, which is a plot of the raw study responses over time. Time plots help to elucidate the underlying time course of the treatment effects and help to identify which statistical time model is appropriate.

Where data allow and where there is a plausible clinical reason for doing so, treatment effects will be assumed to be common or exchangeable within a class. This allows for treatments to be nested within a class, which relaxes assumptions regarding the similarity of interventions while improving network connectivity.[13] We will use the deviance information criterion to compare the different models (common/exchangeable class effect models, time-course models) to assess their parsimony.[52]

For standard NMA models we will rank the relative effects of each treatment/class, and for time-course MBNMA models we will rank the relative effects of each treatment/class for each time-course parameter. We will also rank the full area under the time-course function for each treatment/class at 0–3 months, 0–6 months and 0–12 months. Cumulative rankograms will be plotted; these show the range of rankings of different treatments/classes for each ranked parameter. Sensitivity of model results to the choice of prior distributions will be investigated.

Assessing key assumptions of pairwise and NMA

The authors recommended a strong and rigorous focus on the evaluation of the similarity and homogeneity assumptions.

Assessment of similarity and homogeneity assumptions

A qualitative assessment of the clinical similarity of the different populations and treatments will be performed by important variables such as baseline pain intensity, baseline disability and pain duration. Between-study SD will be estimated and reported from random effects models, and the impacts of subgrouping or meta-regression on this will be examined. Pair-wise meta-analysis of data will be synthesised via SMDs with accompanying 95% CIs using a frequentist random effects model with a restricted maximum likelihood estimator for the between-study variance Tau². These analyses will be carried out with the R package 'metafor'.[53] Visual inspection of the forest plots, statistical estimates of heterogeneity (I^2, Tau) and 95% prediction intervals will be used to assess the validity of homogeneity assumptions. Small study effects and publication bias will be assessed for each pairwise comparison by visual inspection of the contour-enhanced funnel plot. Outlier and influential study analysis will be performed with metafor for pairwise meta-analyses to further detect potential heterogeneity.[54] Meta-regression with potential effect modifiers (pre-intervention pain severity and disability, baseline psychological conditions, presence of co-interventions and type of low back pain)[55–57] will be used to further check for potential heterogeneity among the pairwise comparisons.[58]

In the presence of effect modification in pairwise comparisons (identified using meta-regression), we will also fit network meta-regression with these potential effect modifiers for NMAs conducted at each time-point using the package multinma.[49]

Consistency assumptions

For the Bayesian approach, consistency assumptions will be first checked via an unrelated mean effects (UME) model, which does not assume consistency.[59] The UME model only synthesises direct relative effects between each arm in a study and the study reference treatment. If the consistency assumption holds, then the results from the UME and NMA models will be similar. Changes in between-study SD or residual deviance are also suggestive of inconsistency. If comparison between UME and NMA models is suggestive of inconsistency, node-splitting will be performed.[60] In node-splitting, network contrasts are split into direct and indirect evidence contributions, which can then be compared with examine their similarity.

Additional assumptions required for analysis of time-course data

Given that data will be reported at different follow-up times in different studies, information is unlikely to be available for all treatments at all time-points of interest. For this reason, additional assumptions regarding specific parameters for treatments/classes may be required. For example, in the case of a treatment for which information is only available at shorter follow-up times, explicit assumptions regarding its long-term efficacy will be required. The treatment's long-term efficacy could be assumed to be the same as (or similar to) that of another treatment in the network that might have a similar mechanism of action (eg, within the same class), for which long-term data is available. Alternatively, it could be assigned a specific value or an informative prior as determined by clinical expertise. In such an example, long-term results for this treatment will therefore be sensitive to these assumptions, and results will be interpreted accordingly.[51] Assumptions made in this way will be clearly stated and justified.

Subgroup and sensitivity analyses

Pending data availability, we will perform subgroup analyses to explore whether inconsistency/heterogeneity and group differences in the outcomes are influenced by type of low back disorder (eg, non-specific chronic low back pain, radicular syndrome), type of treatment (eg, surgical, pharmacological) or by exclusion of the multidisciplinary node and the physical therapy (otherwise not falling into specific treatment combination) node from analyses. The treatment node may be a source of significant heterogeneity/inconsistency for the overall NMA due to the variability of this treatment definition compared with other interventions. Subgroup analysis focussing on key participant or study characteristics can produce smaller, more homogenous networks and can be a good strategy to analyse inconsistency/heterogeneity with fewer assumptions and pitfalls then NMA meta-regression.[61] If we are unable to identify the source of inconsistency, we will highlight that this limits the usefulness of the analysis for drawing meaningful conclusions in such a heterogeneous population.

Further, pending data-availability, we will consider the following sensitivity analyses

- Excluding studies with imputed missing SD and imputed medians.
- Study sample size: impact of studies including less than 20 participants in all study-arms.
- Dropout numbers and handling of dropouts within studies: the impact of the proportion of dropouts (if reported) and the kind of analysis individual studies performed (eg, analysing all participants using

imputation of missing data vs analysing complete cases only).

- Comparison of class effect models to a model with fully independent treatment effects that assume no within-class similarity, to assess the statistical validity of class assumptions.
- Secondary treatment components (see online supplemental data A): the impact of treatment combinations where secondary classes of treatment are present in all arms will be considered by fitting models that incorporate combinations as different nodes in the network. This can be used to assess the assumption of additivity of combined treatments. We will also investigate the impact of ordering of primary/secondary treatment components by fitting a model in which the order is ignored (eg, 'Physical therapy +massage' assumed to be equivalent to 'Massage +physical therapy').
- Secondary treatment components (see online supplemental data A): the impact on effect estimates of when secondary treatments are included will be assessed via a sensitivity analysis excluding those interventions with a secondary treatment component.
- As some osteopathic interventions may include visceral techniques not declared in the original methods of the study, the impact of removing this from the manual therapy node will be examined.
- Excluding unclear generic nodes (eg, physical therapy otherwise not falling into specific treatment combination)
- Risk of bias: To examine the influence of specific studies/comparisons on the treatment rankings we will conduct a threshold analysis where possible[51] using the R package nmathresh.
- Choice of SMD as an effect measure by using internal reference baseline SDs for analysis.[46]

DISCUSSION

This NMA will determine the relative effectiveness of a variety of common treatments for CLBDs. Conducting NMA on this topic constitutes a shift towards the highest level of medical evidence.[62] Our NMA has a much broader scope than prior work, such as that concerned solely with pharmacotherapy,[63–66] exercise training,[15 67 68] traditional Chinese medicine[69] or psychotherapy.[70] Moreover, the broad inclusion criteria and number of interventions considered in our NMA will result in a greater number of included interventions than previous broad NMAs that examined non-pharmacotherapy[71] and surgery-based interventions,[72] which included 31 and 12 interventions, respectively. The breadth of our NMA is important given that CLBDs are inherently heterogenous, yet progenitors do not influence decision making regarding treatment sought.[8] For this reason, CLBDs (excluding specific causes) are commonly treated in line with generic clinical guidelines.[73] This underpins the importance of our NMA, as these guidelines do not distinguish whether one treatment is superior to another for this collective of patients with chronic pain. Given the lack of evidence that treatment efficacy differs by underlying pain progenitor, we believe it is reasonable to assume exchangeability of these studies and transitivity within the network in terms of population. Other than recent suggestions that machine learning[74] may one day identify evidence-based subgroups that respond 'better' to specific treatments, we surmise that our NMA will markedly contribute to overcoming current limitations in the management of CLBDs pertaining to treatment decision making.

To our knowledge, there is only one other NMA currently being conducted with a similar scope to our protocol.[75] Our NMA overcomes several cardinal limitations of this protocol: (1) we consider CLBD, rather than solely non-specific low back pain; (2) we consider additional languages for article inclusion, rather than English only; and (3) our treatment classification is more nuanced, rather than simplistic (eg, the other protocol typically considers two types of treatment within a particular class). Of note, we registered our systematic review prior to publication of this other protocol, and it is unclear when their work is due to be published.

Despite the many strengths of our proposed NMA, we would be remiss not to acknowledge potential limitations. First, due to the inclusion of radicular syndromes in the patient population, it might be necessary to analyse this population in different networks/subsets because the presence of this may be an effect modifier[76] and lead to intransitivity. Second, we do not consider multicomponent interventions in our statistical model, which might have an impact on the estimates.[77 78] By ignoring additional treatment components given in both arms of included studies, we assume additivity of different treatment components. While we will investigate the effects of this (see Sensitivity Analyses), fully accounting for it by modelling all combinations of treatments as separate interventions is likely to lead to disconnected networks of evidence, which poses its own problem for evidence synthesis and decision making.[79] Third, while we propose a variety of subgroup analyses to investigate the impact of effect modification, potential effect modifiers may be poorly reported in many studies. However, there is no clear evidence of important effect modification in CLBD to date. As pointed out in the recent Lancet Low Back Pain Series,[8] relative treatment efficacy for different kinds of interventions appears (to date) to be surprisingly similar. Fourth, usual care may vary between included studies (eg, authors' stance on whether or not usual analgesic pharmacotherapy was permitted), yet given few studies in the CLBD field employ methods of strict observation, we surmise that the majority, if not all, of existing studies are inherently at risk of this form of bias.

Finally, as with all meta-analyses, dealing with co-interventions has implicit complexities. Our decision to consider interventions that combine multiple forms of interventions of interest may impede our capacity to differentiate the effects of one individual treatment. However, we contend that this approach allows for the inclusion of more trials that, when compared with a strict

approach that excluded any interventions with co-intervention, reflects more realistically the realities of clinical practice. This, in our view, leads to less potential bias (eg, inclusion of studies that simply failed to report co-interventions) and greater confidence in our effect estimates.

In conclusion, the current project will enable a significant advance in synthesising knowledge on the comparative effectiveness of a wide variety of treatments for chronic low back disorders. This has, to date, not been performed and will inform patient management and clinical practice guidelines.

Author affiliations
[1]Physiotherapy, Hochschule fur Gesundheit, Bochum, Nordrhein-Westfalen, Germany
[2]Department of Orthopaedic Surgery, Spine Service, St. George Hospital, Kogarah, New South Wales, Australia
[3]Advance Healthcare, Melbourne, Victoria, Australia
[4]Low Back Research Team, La Trobe University, Bundoora, Victoria, Australia
[5]Institute for Physical Activity and Nutrition (IPAN), Deakin University, Geelong, Victoria, Australia
[6]Deakin University, Geelong, Victoria, Australia
[7]Biostatistics Unit, Faculty of Health, Deakin University, Geelong, Victoria, Australia
[8]Bristol Medical School, University of Bristol, Bristol, UK
[9]Physio Meets Science GmbH, Leimen, Germany
[10]Xi'an University of Architecture and Technology, Xi'an, China
[11]Department of Orthopaedic Surgery, Spine Service, University of New South Wales, Sydney, New South Wales, Australia
[12]Centre for Physiotherapy and Rehabilitation Sciences, Jamia Millia Islamia, New Delhi, India

Twitter Scott Tagliaferri @ScottTags and Nitin Kumar Arora @nitintarika

Contributors Study conception: DB, ADD, JF, PJO, CTM, AJH, SB; steering committee: DB, AD, JF, PJO, CTM, AJH; statistical planning, implementation, advice: DB, SB, HP, TS, ST, AJH; adjudication in screening: CTM, NM, ST, DB; screening/data extraction: XZ, XC, APB, NKA; drafting manuscript: DB, PJO; approving final version of manuscript: all.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Daniel L Belavy http://orcid.org/0000-0002-9307-832X
Niamh Mundell http://orcid.org/0000-0001-5406-3216
Scott Tagliaferri http://orcid.org/0000-0003-3669-4131
Tobias Saueressig http://orcid.org/0000-0002-3332-3856
Patrick J Owen http://orcid.org/0000-0003-3924-9375

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Supplemental Data A: Definitions of interventions and primary/secondary interventions

Acupuncture (acu)

Per prior Cochrane review [1], the definition of acupuncture used was "*the diagnosis was made using traditional acupuncture theory and the needles were inserted in classical meridian points, extra points or ah-shi points (painful points)*". Dry needling was classified with acupuncture and required needles to be inserted into myofascial trigger points. Acupressure, laser acupuncture and acupuncture via electrical stimulation were excluded from this acupuncture group as they did not involve needling. These interventions were included, respectively, under massage (acupressure) and electrotherapies (laser and electrical acupuncture).

Treatments within Class:

- acu_need: acupuncture following (traditional) acupuncture theory
- acu_dry: dry needling

Education (edu)

Patient education has been defined [2] previously "*a systematic experience, in a one-to one situation, that consists of one or more methods, such as the provision of information and advice and behaviour modification techniques*". Similar to this prior review, we considered education to occur when back pain patients were given information to help them understand their condition, what behaviours are likely to be more beneficial. 'Back school' interventions were considered education. Advice to stay active was considered education. Both group and individual education were included. Using brochure or booklet with education material was included if a clinician explained the information to the patient. Studies on instructions as to how to perform other kinds of interventions (e.g., how to do exercise, or were included, studies on instructions on how to perform exercises were not included.

Treatments within Class:

- edu_school: back school
- edu_pne: pain neuroscience education
- edu_book: via printed materials
- edu_grpind: remaining group and individual education

Electrophysical agents (elc)

Therapeutic heat and cold, laser (including laser acupuncture) and light therapies, classic electrotherapies (e.g., electrical stimulation modalities including TENS; electrical acupuncture also included here), various electromagnetic applications (e.g., pulsed shortwave therapy), ultrasound therapy and a variety of mechanical therapies (e.g., vibration therapy and intermittent pneumatic compression therapy) are included as electrophysical agents given these modalities are considered comparable [3]. The electrophysical agents must be applied externally without breaking or piercing the skin.

Whole body vibration, where a person experiences vibration through their whole body, is excluded.

Treatments within Class:

- elc_electric: electrical stim or input of some form
- elc_hot: heat
- elc_cold: cold

- elc_mech: ultrasound therapy and a variety of mechanical therapies
- elc_etc: magnetic and remaining included

Epidural injections (epi)

As per prior Cochrane review [4], epidural injections involve the delivery of corticosteroid medication to the epidural space via injection. The anatomical approaches considered included, but were not limited to: caudal, interlaminar, and transforaminal approaches.

Treatments within Class:

- epi_caud: caudal approach
- epi_inter: interlaminar approach
- epi_trans: transforaminal approach
- epi_other: other included epidural INT not included in anatomical approaches listed above

Exercise (exe)

Exercise therapy has been [5] defined as "*a series of specific movements with the aim of training or developing the body by a routine practice or as physical training to promote good physical health*". We required that a clinician or study investigator instructed and/or prescribed exercises to patients with the goal of improving the patient's back disorder. Exercise could be performed as a group or individually. Whole body vibration and whole body vibration exercise was excluded.

Treatments within Class:

- exe_res: resistance exericse
- exe_sta: stabilization_motor_control
- exe_eso: pilates, yoga, traditional eastern approaches
- exe_aer: aerobic (e.g cycling, walking)
- exe_str: streching
- exe_oth: other and water based

Manual therapies and manipulation (man)

A prior Cochrane review [6] defined mobilisation as the "*use low-grade velocity, small or large amplitude passive movement techniques within the patient's range of motion and control*" and manipulation as "*a high velocity impulse or thrust applied to a synovial joint over a short amplitude at or near the end of the passive or physiologic range of motion, which is often accompanied by an audible crack*". The term "adjustments" is sometimes used in conjunction with chiropractic or osteopathic manual therapy treatment. Studies that incorporate visceral techniques as part of an osteopathy intervention will be included.

Treatments within Class:

- man_man: manual therapy and mobilisation (without manipulation)
- man_mip: manipulation
- man_chos: chiropractic or osteopathy not otherwise more precisely specified

Massage (mas)

Massage has been [7] defined as "*the manipulation of the soft tissue of whole body areas to bring about generalised improvements in health, such as relaxation or improved sleep, or*

specific physical benefits, such as relief of muscular aches and pains" Trigger point therapy, myofascial release, Shiatsu, reflexology, and acupressure are also classified as massage.

Treatments within Class:

- mas_mas: massage
- mas_tpm: Trigger point therapy, myofascial release
- mas_oth: Shiatsu, reflexology, acupressure and other specifically named treatments determined to be massage

McKenzie (mck)

The McKenzie method [8] has also been termed Mechanical Diagnosis and Therapy and is a system that involves the use of mechanical loading strategies to guide specific treatment based on the patient's responses to these mechanical loading strategies (sub-group membership) [9]. In this treatment approach, treatment is individualized for each patient based on the response of their pain/impairment to mechanical loading strategies (sustained or repeated movements and postures) and classified into dysfunction, posture and derangement syndromes. Given it is the most prevalent classification, studies using directional preference treatment only (for derangement syndrome) will also be included. Directional preference management was defined as individualized treatment based on the response to mechanical loading strategies. Trials evaluating the effect of directional preference management on back pain were included.

Treatments within Class:

- mck_mck: Mckenzie

Pharmacotherapy (pha)

Pharmacotherapy interventions considered in this review included non-steroidal anti-inflammatory drugs (NSAIDs), Opioids, Skeletal muscle relaxants, Benzodiazepines, Antidepressants, Acetaminophen (paracetamol), systemic corticosteroids and anticonvulsants. Analgesic medicines work in various ways to reduce the intensity of pain but may also cause unwanted harmful effects.

Treatments within Class:

- pha_nsai: NSAIDs
- pha_opi: Opioids
- pha_relx: Skeletal muscle relaxants
- pha_benz:Benzodiazepines
- pha_antd: Antidepressants
- pha_para: Acetaminophen (paracetamol)
- pha_cort: systemic corticosteroids and
- pha_conv: anticonvulsants

Psychological therapies (including cognitive-behavioural therapies) (psy)

Per prior Cochrane review [10], psychological interventions were classed as any intervention that is designed following a psychological theory of behaviour and behaviour change. Mindfulness meditation, or other forms of meditation, were not, by themselves, considered psychological therapies.

Treatments within Class:

- psy_cbt: cognitive behavioural therapies

- psy_oth: other psychological therapies

Percutaneous procedures (per)

The following percutaneous procedures were considered:

- Radio frequency denervation: Radiofrequency denervation has been defined [11] as "*a minimally invasive and percutaneous procedure performed under local anaesthesia or light intravenous sedation. Radiofrequency energy is delivered along an insulated needle in contact with the target nerves to denature the nerve*". It was initially developed for the lumbar zygopophyseal joint, and is now applied to denervate other joints in the spine [12].
- Spinal cord stimulation: "*This method was a clinical outgrowth from the well-known gate-control theory for segmental pain suppression. The idea was to apply electric stimulation to the dorsal columns of the spinal cord which are easily accessible and contain large diameter afferent fibers. Thus, stimulating electrodes were applied epidurally to the dorsal aspect of the cord. The gate control theory implied that activation of these coarse fiber systems inhibited transmission of nociceptive information at the segmental level and actually predicted that all types of pain would be equally suppressed*." [13,14]
- Percutaneous multifidus stimulation Percutaneous multifidus stimulation involves "*a stimulating probe is placed into the multifidus muscle via percutaneous procedure, using known anatomical landmarks to target the medial branches of the dorsal rami. Electrical stimulation is applied to target the medial branch of the dorsal ramus after the branch exits the intervertebral foramen prior to innervation of the multifidus and facet joints*."[15]
- Percutaneous rhizolysis, medial bundle branch blocks:
    - Percutaneous rhizolysis (radiofrequency neurotomy), medial bundle branch blocks: "Low-back pain may arise from degenerative changes in the posterior joints of the lumbar spine. These joints are innervated by a branch of the posterior primary ramus, which follows an anatomically constant course. Pain impulses from these joints can be interrupted by coagulating the nerve with a radiofrequency wave, the probe having been placed in the area of the nerve percutaneously." [16]
    - Facet joint medial bundle branch radiofrequency ablation (MBB-RFA) "*involves using energy in the radiofrequency range to perform necrosis of specific nerves (medial branches of the dorsal rami in patients with lumbar facetogenic pain), avoiding the neural transmission of pain. The aim of MBB-RFA is to both provide relief of pain and decrease the possibility of recurrence*". [17,18]

Treatments within Class:

- per_rad: Radio frequency denervation
- per_ssc: Spinal cord stimulation
- per_mfs: Percutaneous multifidus stimulation
- per_rhi: Percutaneous rhizolysis (radiofrequency neurotomy), medial bundle branch blocks
- per_mmb: Facet joint medial bundle branch radiofrequency ablation (MBB-RFA)

Surgery (sur)

The following types of surgery were included:

- Discectomy (any type): open discectomy, sequestrectomy or aggressive discectomy, microdiscectomy, endoscopic open/percutaneous discectomy, automated open/percutaneous discectomy
- Non fusion stabilization [19]: Graf ligament, Dynesys, interspinous stabilisation devices (e.g., Coflex, Wallis ligament, DIAM), total disc arthroplasty (replacement), facet arthroplasty/facet replacement
- Fusion [19]: anterior, posterior, or circumferential spinal fusion (decompression/discectomy/laminectomy/laminotomy) with/without autologous bone graft harvested from the iliac crest or use of allograft femoral rings stuffed with autologous cancellous bone with/without pedicle screw [20]

Surgery may include indirect/direct decompression [21], decompression with/without instrumentation fusion [21,22] PLIF, ALIF, TLIF, minimally invasive spine surgeries (including laparoscopic ALIF, minimally invasive PLIF, XLIF, OLIF, AxiaLIF).

Treatments within Class:

- sur_dis: Discectomy (any type)
- sur_nstab: Non fusion stabilization
- sur_fus: Fusion
- sur_deco: Decompression/laminectomy/laminotomy without an instrument for foraminal/canal stenosis

Traction (tra)

Traction involves application of a distractive axial force to the spine and trunk for therapeutic effect [23]: "*Mechanical or motorized traction (where the traction is exerted by a motorized pulley), manual traction (in which the traction is exerted by the therapist, using his or her body weight to alter the force and direction of the pull), and auto-traction (where the person controls the traction forces by grasping and pulling bars at the head of the traction table)*" [23] were included as traction. Other forms of traction may include the use of gravity to generate the traction force (e.g., on a tilted table, or hung vertically by the lower extremities).

Treatments within Class:

- tra_mech: Mechanical or motorized traction
- tra_man: manual traction
- tra_auto: auto-traction and use of gravity to generate the traction force

Multidisciplinary (multidisciplinary pain management) (mul)

Multidisciplinary pain management incorporates a number of intervention types, such as education (e.g., mechanisms of chronic pain, anatomy), goal setting, exercise, stress management, relaxation and imagery, meditation and aspects of psychological therapies, medication management, family member participation implemented as one package of treatment [24–26]. These may be done as individual sessions or as group sessions. If a study labelled its intervention as multidisciplinary pain management, then this was considered multidisciplinary pain management. Other studies may have combined individual interventions

into a multidisciplinary program but did not specifically label it as multidisciplinary pain management. In this case, if the reviewers agreed that the intervention included a minimum of education, exercise, psychological therapies delivered by a multidisciplinary clinician team (at least 2 clinicians from different fields), this was classified as 'multidisciplinary pain management'. Otherwise, these interventions were classified under 'treatment combinations' (below).

Treatments within Class:

- mul_mdp: Multidisciplinary pain management

Physical therapy (otherwise not falling into specific treatment combination) (pio)
Into this group fall any interventions that are generic 'physiotherapy' or 'physical therapy' treatments, often at the discretion of the clinician, but otherwise not detailed or defined.

Treatments within Class:

- pio_pio: generic physiotherapy or physical therapy treatments

Placebo or sham (pla)
Any intervention defined as a placebo or sham intervention by the study authors, or described as such consistent with previous meta-analysis [27].

Treatments within Class:

- pla_pla: placebo

"Usual care" (e.g., GP Management) (usu)
Intervention deemed 'usual care', including GP management.

Treatments within Class:

- usu_usu: usual care

No treatment (true control) (tru)
No intervention provided, including waitlist control where no treatment is given.

Treatments within Class:

- tru_tru: true control, no intervention
- tru_wait: waiting list control where not treatment is given

Combinations of the above treatments were included and classified according to their primary and secondary treatment components via agreement between the extractors (with adjudication where necessary)

Definition of primary and secondary INT components
The following approach was used to classify primary and secondary intervention components in groups that receive multiple treatments within the same treatment group but did not clearly fall under the multidisciplinary definition above:

1) Pick the primary intervention that contributes to the treatment group: if an intervention comprised >50% of the treatment (per judgement of the extractor), then it was taken as 'primary'. If no intervention component was >50%, then pick the one with the highest proportion.

In cases that were unclear, the following hierarchy of guiding principles was used:

- Any prior publications (e.g., protocol paper, primary outcome publication) arising from the same study were checked.
- A treatment component that is more thoroughly described could be considered the primary component. For example, if exercise was fully described but advice is labelled as "advice" and not described in similar detail, then exercise was considered as the primary.
- Where a treatment component was mentioned in either the article title or the group subheading was labelled as one of the interventions, then that was taken as the primary intervention component. For example, if the group subheading was called "exercise" but it contained exercise and advice components, then exercise was considered the primary component).
- To split true stalemates, the intervention element mentioned first in the treatment description and/or label was taken to be the primary component (e.g., "exercise and advice" = exercise mentioned first and therefore primary component).
- A minimum threshold to be classified as a primary component was 25%.

2) Secondary component of treatments with multiple components: in some cases, a treatment group may have more than two components, but not fall under the multidisciplinary definition. In this case, the following principles were followed: only ONE secondary intervention component was included, regardless of how many there were. To qualify as being classified as a secondary treatment component, it needed to represent at least 20% of the total intervention (per judgement of the extractor), otherwise the intervention will be classified as having only a primary intervention with no secondary component.

3) If a study arm could not be classified according to the above criteria, then it was treated as a non-included INT (see below). We considered including an additional 'multimodal' category beyond the multidisciplinary group defined above. However, we determined this would be uninformative as it would encompass a heterogeneous range of treatments and thus not provide useful guidance for clinical practice.

Where both primary and secondary intervention components are present we will include these in analyses as combinations of intervention and they will be analysed separately. For example, Physical therapy as a primary component and Massage as a secondary component will be analysed as “Physical therapy + massage”. Due to the approach we have described for classifying primary and secondary components, the order of components may be important, such that we assume that “Physical therapy + massage” is not the same as “Massage + physical therapy”.

Where a secondary intervention component is given in all arms of a study, in addition to the analysis above we will also fit a model in which the study treatments are coded as only the primary intervention in order to test whether assuming additivity of treatment efficacy is reasonable, as this may lead to better connected NMAs with more precise estimates.

Handling of studies that examined non-included INTs

Some studies will examine an INT that is not subject of the current review. In this case, the arms in the study were assessed on a case by case basis.

- If the 'primary treatment component' of an arm was a non-included INT (e.g., back belts), then that individual arm was not included in extraction and therefore analysis.
- If the 'primary treatment component' was an included INT but the 'secondary treatment component' a non-included INT, then the individual arm was included.
- Pending these decisions, if at least two arm of an individual study could be included, then the study as a whole was included. Otherwise it was excluded.

For example, in the case of a three arm study [28] on "back belt + exercise" vs "exercise" vs "control", the "back belt + exercise" arm was excluded, but the "exercise" and "control" arms were included. Thus the study could also be included.

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Supplemental Data B: Search Strategy

Date of database search: 13.11.2019

MEDLINE

Search	Query	Hits
#1	back pain[MeSH Terms] OR low back pain[MeSH Terms] OR back pain*[Title/Abstract] OR lumb* pain[Title/Abstract] OR lumbago[Title/Abstract] OR backache*[Title/Abstract] OR back ache*[Title/Abstract] OR spinal stenosis[Title/Abstract] OR canal stenosis[Title/Abstract] OR lumbar stenosis[Title/Abstract] OR lateral stenosis[Title/Abstract] OR foramin stenosis[Title/Abstract] OR neurogenic claudication[Title/Abstract] OR radiculopathy[Title/Abstract] OR radicular pain[Title/Abstract] OR spondylolisthesis[Title/Abstract] OR spondylosis[Title/Abstract] OR sciatica[Title/Abstract] OR intervertebral disc displacement[Title/Abstract] OR referred pain[Title/Abstract] OR spinal nerve roots[Title/Abstract] OR neurologic signs[Title/Abstract] OR radiat* pain[Title/Abstract] OR radiat* symptoms[Title/Abstract] OR parathesia[Title/Abstract] OR numbness[Title/Abstract]	131336
#2	randomized[Title/Abstract] OR placebo[Title/Abstract] OR randomly[Title/Abstract] OR "drug therapy"[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract]	2868072
#3	(animals[MeSH] NOT humans[MeSH]))	4659784
#4	#1 AND #2	25960
#5	#4 NOT #3	24928
#6	#5 AND Filters: Randomized Controlled Trial; Clinical Trial; Humans	7237

SPORTDiscus

Search	Query	Hits
#1	(DE "lumbar pain") OR (DE backache) OR (TI ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR parathesia OR numbness) OR AB ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR parathesia OR numbness))	11187
#2	TI (randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups) OR AB (randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups)	197381
#4	#1 AND #2	2970

CINAHL

Search	Query	Hits
#1	(MH low back pain) OR (MH back pain) OR (TI ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR parathesia OR numbness) OR AB ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR parathesia OR numbness))	45198
#2	TI (randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups) OR AB (randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups)	889333
#3	MH animals NOT MH human	74138
#4	#1 AND #2	11513
#5	#4 NOT #3	11461
#4	#5 AND Filters: Exclude MEDLINE records; Human; Randomized Controlled Trial	1335

PsycINFO

Search	Query	Hits
#1	(MA low back pain) OR (MA back pain) OR (TI ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR parathesia OR numbness) OR AB ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR parathesia OR numbness))	8813
#2	TI (randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups) OR AB (randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups)	1030813
#3	MA animals NOT MA human	196321
#4	#1 AND #2	2829

#5	#4 NOT #3	2809
#6	#5 AND Filters: Human; Journal Article	2377

EMBASE

Search	Query	Hits
#1	'low back pain'/exp OR 'backache'/exp OR 'back pain*':ab,ti OR 'lumb* pain':ab,ti OR lumbago:ab,ti OR backache*:ab,ti OR 'back ache*':ab,ti OR 'spinal stenosis':ab,ti OR 'canal stenosis':ab,ti OR 'lumbar stenosis':ab,ti OR 'lateral stenosis':ab,ti OR 'foramin stenosis':ab,ti OR 'neurogenic claudication':ab,ti OR radiculopathy:ab,ti OR 'radicular pain':ab,ti OR spondylolisthesis:ab,ti OR spondylosis:ab,ti OR sciatica:ab,ti OR 'intervertebral disc displacement':ab,ti OR 'referred pain':ab,ti OR 'spinal nerve roots':ab,ti OR 'neurologic signs':ab,ti OR 'radiat* pain':ab,ti OR 'radiat* symptoms':ab,ti OR parathesia:ab,ti OR numbness:ab,ti	161402
#2	randomized:ab,ti OR placebo:ab,ti OR randomly:ab,ti OR “drug therapy”:ab,ti OR trial:ab,ti OR groups:ab,ti	3957907
#3	'animal'/exp NOT 'human'/exp	5386039
#4	#1 AND #2	33606
#5	#4 NOT #3	32975
#6	#5 AND Filters: Controlled Clinical Trial; Randomized Controlled Trial; Exclude MEDLINE	2627

CENTRAL

Search	Query	Hits
#1	(MeSH descriptor: [back pain] explode all trees) OR (MeSH descriptor: [low back pain] explode all trees) OR (“back pain*” OR “lumb* pain” OR lumbago OR backache* OR “back ache*” OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR parathesia OR numbness):ti,ab,kw	3401
#2	(randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups):ti,ab,kw	1204707
#3	#1 AND #2	2895
#4	(MeSH descriptor: [Animals] explode all trees) NOT (MeSH descriptor: [Humans] explode all trees)	7286
#5	#4 NOT #3	2893
#6	#5 AND Filters: Exclude MEDLINE; Exclude EMBASE; Trials	456

TOTAL from data base searches (with duplicates): 17002

Date of database search: 24/07/2020

MEDLINE

Search	Query	Hits
#1	back pain[MeSH Terms] OR low back pain[MeSH Terms] OR sciatica[MeSH Terms] OR back pain*[Title/Abstract] OR lumb* pain[Title/Abstract] OR lumbago[Title/Abstract] OR backache*[Title/Abstract] OR back ache*[Title/Abstract] OR spinal stenosis[Title/Abstract] OR canal stenosis[Title/Abstract] OR lumbar stenosis[Title/Abstract] OR lateral stenosis[Title/Abstract] OR foramin stenosis[Title/Abstract] OR neurogenic claudication[Title/Abstract] OR radiculopathy[Title/Abstract] OR radicular pain[Title/Abstract] OR spondylolisthesis[Title/Abstract] OR spondylosis[Title/Abstract] OR sciatica[Title/Abstract] OR intervertebral disc displacement[Title/Abstract] OR referred pain[Title/Abstract] OR spinal nerve roots[Title/Abstract] OR neurologic signs[Title/Abstract] OR radiat* pain[Title/Abstract] OR radiat* symptoms[Title/Abstract] OR paresthesia[Title/Abstract] OR paraesthesia[Title/Abstract] OR numbness[Title/Abstract]	141,803
#2	randomized[Title/Abstract] OR placebo[Title/Abstract] OR randomly[Title/Abstract] OR "drug therapy"[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract]	2972235
#3	animals[MeSH] NOT humans[MeSH]	4720975
#4	#1 AND #2	28330
#5	#4 NOT #3	27250
#6	#5 AND Filters: Randomized Controlled Trial; Clinical Trial; Humans	9188

SPORTDiscus

Search	Query	Hits
#1	(DE "lumbar pain") OR (DE backache) OR (DE sciatica) OR (TI ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR paresthesia OR paraesthesia OR numbness) OR AB ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR paresthesia OR paraesthesia OR numbness))	14,427
#2	TI (randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups) OR AB (randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups)	237964
#4	#1 AND #2	4142

CINAHL

Search	Query	Hits
#1	(MH low back pain) OR (MH back pain) OR (MH sciatica) OR (TI ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR paresthesia OR paraesthesia OR numbness) OR AB ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR paresthesia OR paraesthesia OR numbness))	52162
#2	TI (randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups) OR AB (randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups)	997530
#3	MH animals NOT MH human	79989
#4	#1 AND #2	13351
#5	#4 NOT #3	13289
#4	#5 AND Filters: Exclude MEDLINE records; Human; Randomized Controlled Trial	699

PsycINFO

Search	Query	Hits
#1	(MA low back pain) OR (MA back pain) OR (MA sciatica) OR (TI ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR paresthesia OR paraesthesia OR numbness) OR AB ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR paresthesia OR paraesthesia OR numbness))	9726
#2	TI (randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups) OR AB (randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups)	1055873
#3	MA animals NOT MA human	197309
#4	#1 AND #2	3091

#5	#4 NOT #3	3070
#6	#5 AND Filters: Human; Journal Article	2628

EMBASE

Search	Query	Hits
#1	'low back pain'/exp OR 'backache'/exp OR 'sciatica'/exp OR 'back pain*':ab,ti OR 'lumb* pain':ab,ti OR lumbago:ab,ti OR backache*:ab,ti OR 'back ache*':ab,ti OR 'spinal stenosis':ab,ti OR 'canal stenosis':ab,ti OR 'lumbar stenosis':ab,ti OR 'lateral stenosis':ab,ti OR 'foramin stenosis':ab,ti OR 'neurogenic claudication':ab,ti OR radiculopathy:ab,ti OR 'radicular pain':ab,ti OR spondylolisthesis:ab,ti OR spondylosis:ab,ti OR sciatica:ab,ti OR 'intervertebral disc displacement':ab,ti OR 'referred pain':ab,ti OR 'spinal nerve roots':ab,ti OR 'neurologic signs':ab,ti OR 'radiat* pain':ab,ti OR 'radiat* symptoms':ab,ti OR paresthesia:ab,ti OR paraesthesia:ab,ti OR numbness:ab,ti	176118
#2	randomized:ab,ti OR placebo:ab,ti OR randomly:ab,ti OR "drug therapy":ab,ti OR trial:ab,ti OR groups:ab,ti	4102141
#3	'animal'/exp NOT 'human'/exp	5464750
#4	#1 AND #2	37042
#5	#4 NOT #3	36356
#6	#5 AND Filters: Controlled Clinical Trial; Randomized Controlled Trial; Exclude MEDLINE	2718

CENTRAL

Search	Query	Hits
#1	(MeSH descriptor: [back pain] explode all trees) OR (MeSH descriptor: [low back pain] explode all trees) OR (MeSH descriptor: [sciatica] explode all trees) OR ("back pain*" OR "lumb* pain" OR lumbago OR backache* OR "back ache*" OR spinal stenosis OR canal stenosis OR lumbar stenosis OR lateral stenosis OR foramin stenosis OR neurogenic claudication OR radiculopathy OR radicular pain OR spondylolisthesis OR spondylosis OR sciatica OR intervertebral disc displacement OR referred pain OR spinal nerve roots OR neurologic signs OR radiat* pain OR radiat* symptoms OR paresthesia OR paraesthesia OR numbness):ti,ab,kw (Word variations have been searched):ti,ab,kw	23060
#2	(randomized OR placebo OR randomly OR "drug therapy" OR trial OR groups):ti,ab,kw	1228587
#3	(MeSH descriptor: [Animals] explode all trees) NOT (MeSH descriptor: [Humans] explode all trees)	606
#4	#1 AND #2	19342
#5	#4 NOT #3	19340
#6	#5 AND Filters: Exclude MEDLINE; Exclude EMBASE; Trials	1258

TOTAL from data base searches (with duplicates): 20633
TOTAL from prior systematic reviews (with duplicates): 1783

TOTAL from reference lists of 17 relevant Cochrane reviews not included in reviews from last 10 years: 663
Duplicates removed (by Covidence): 3557
TOTAL for screening: 19522

Supplemental Data C: GRADE Criteria

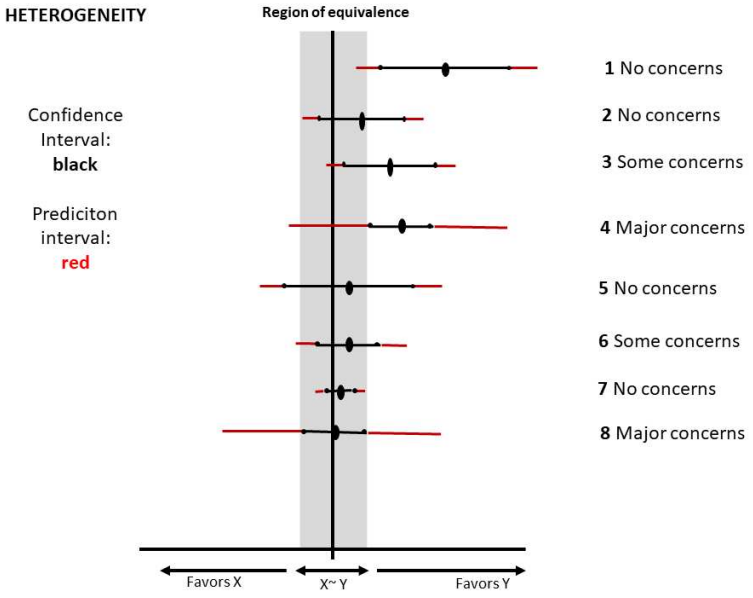
1. Limitations in study design – Cochrane Risk of Bias Tool 1.0

- Selection bias (random sequence generation, allocation concealment, group similarities at baseline);
- Performance bias (blinding of participants and/or healthcare providers);
- Attrition bias (drop outs and intention-to-treat analysis);
- Detection bias (blinding of the outcome assessors and timing of outcome assessment);
- Reporting bias (selective reporting).

We downgraded the quality of the evidence:

- By one level if >50% of participants were from studies with selection bias **and** performance bias.
- Inadequate randomization and lack of blinding may lead to an exaggeration of the intervention effect estimates [1–3].

Unexplained heterogeneity or inconsistency of results



- Pre-defined area/range of equivalence: We define a range of equivalence of SMD -0.5 to 0.5 [4].
- Downgrade two levels if there is a major concern and one level if there are some concerns.
- If there are very few trials, the amount of heterogeneity is poorly estimated and prediction intervals are unreliable, we will downgrade based on reference priors [5].

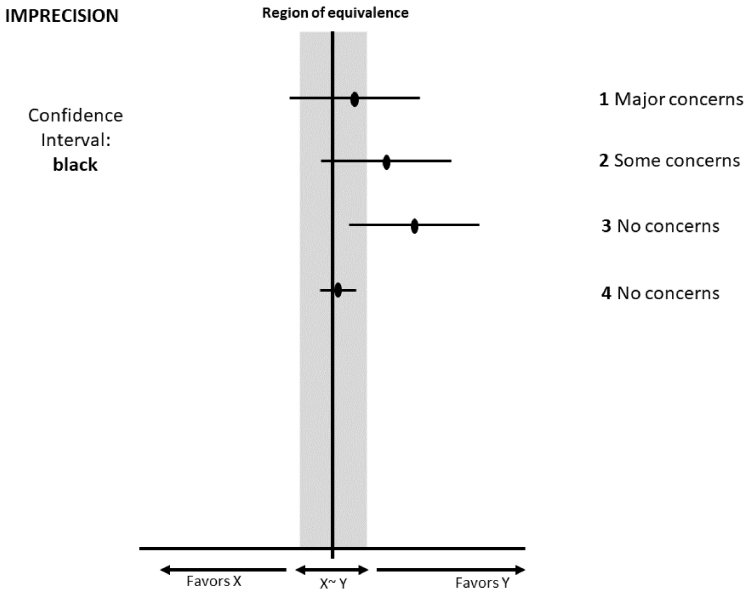
Indirectness

Domain (original question asked)	**Description (evidence found and included, including evidence from other studies) – consider the domains of study design and study limitation, inconsistency, imprecision and publication bias**	**Judgment – is the evidence sufficiently direct?**			
Population:		**Yes**	**Probably yes**	**Probably no**	**No**
Intervention:		**Yes**	**Probably yes**	**Probably no**	**No**
Comparator:		**Yes**	**Probably yes**	**Probably no**	**No**
Direct comparison:		**Yes**	**Probably yes**	**Probably no**	**No**
Outcome:		**Yes**	**Probably yes**	**Probably no**	**No**
Final judgement about indirectness across domains:	**No indirectness ? => No downgrade.** **Serious indirectness ? => Downgrade one level.** **Very serious indirectness ? => Downgrade two levels.**				

Two components for network meta-analysis:

- similarity of studies in the analysis to the target question (PICO)
- similarity of the studies in the analysis to each other (relates to transitivity assumption)

Imprecision



- Downgrade two levels if there is a major concern and one level if there are some concerns.

Publication bias [6]

Reporting bias may be suspected when the following occur:

- Prior documented evidence of reporting bias in trials in the field.
- meta-analysis is based on a small number of new studies, typically positive findings (e.g. new drugs may have positive findings early and later the true effect size becomes apparent).
- Industry-funded trials dominate
- Known unpublished data from grey literature not included.

Reporting bias is considered to not be present in the following situations:

- Analytical methods indicate the findings from small are similar to those in large/published studies
- Findings from unpublished studies agree with published studies.
- Prospective trial registration, protocol publication and/or clinical trial registries are used extensively in the field and do not indicate important discrepancies with published reports.

⇨ Downgrade one level if publication bias is suspected.

Criteria specific to NMA:

- Do **not consider imprecision** when rating the direct and indirect estimates to inform the rating of NMA estimates [7].
- **No need to rate the indirect evidence** when the certainty of the direct evidence is high and the contribution of the direct evidence to the network estimate is at least as great as that of the indirect evidence.

1 Savović J, Turner RM, Mawdsley D, *et al.* Association Between Risk-of-Bias Assessments and Results of Randomized Trials in Cochrane Reviews: The ROBES Meta-Epidemiologic Study. *Am J Epidemiol* 2018;**187**:1113–22. doi:10/gdgm64
2 Armijo-Olivo S, Fuentes J, da Costa BR, *et al.* Blinding in Physical Therapy Trials and Its Association with Treatment Effects: A Meta-epidemiological Study. *Am J Phys Med Rehabil* 2017;**96**:34–44. doi:10/gmhbgv
3 Armijo-Olivo S, Saltaji H, Costa BR da, *et al.* What is the influence of randomisation sequence generation and allocation concealment on treatment effects of physical therapy trials? A meta-epidemiological study. *BMJ Open* 2015;**5**:e008562. doi:10/gb5db8
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5 Rhodes KM, Turner RM, Higgins JPT. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. *J Clin Epidemiol* 2015;**68**:52–60. doi:10/f6thkp
6 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, *et al.* CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLOS Med* 2020;**17**:e1003082. doi:10/ggthw8
7 Brignardello-Petersen R, Bonner A, Alexander PE, *et al.* Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *J Clin Epidemiol* 2018;**93**:36–44. doi:10/gcz4pg