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Combination drug therapy for low back pain (Protocol)

Mathieson S, Kasch R, Maher CG, Pinto RZ, McLachlan A, Koes BW, Lin CWC

Mathieson S, Kasch R, Maher CG, Pinto RZ, McLachlan A, Koes BW, Lin CWC.
Combination drug therapy for low back pain.
Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD011982.
DOI: 10.1002/14651858.CD011982.

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TABLE OF CONTENTS

[Intervention Protocol]

Combination drug therapy for low back pain

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Editorial group: Cochrane Back and Neck Group.
Publication status and date: New, published in Issue 12, 2015.

Citation: Mathieson S, Kasch R, Maher CG, Pinto RZ, McLachlan A, Koes BW, Lin CWC. Combination drug therapy for low back pain. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.: CD011982. DOI: 10.1002/14651858.CD011982.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The primary objective is to investigate the effects of combination drug therapy in reducing pain and disability in patients with low back pain and/or sciatica presenting to primary care, compared to mono drug therapy, no/minimal treatment or placebo. A secondary objective is to investigate combination drug tolerability, participants' rating of improvement and treatment satisfaction.

BACKGROUND

Description of the condition

Low back pain is a highly prevalent condition, causing considerable disability and burden globally (Hoy 2014). Up to 70% of people will experience low back pain during their lifetime (van Tulder 2002) and although many patients with low back pain improve substantially within the first six weeks, some will still have pain and disability after one year (Menezes Costa 2012). Patients with low back-related leg pain, such as sciatica experience intense radiating leg pain that may be accompanied by neurological signs (Koes 2006). Many patients with sciatica still have symptoms after two years and a quarter of those who recover from that episode of sciatica will have a recurrence within two years (Tubach 2004). Low back pain and sciatica are both associated with high healthcare costs, work absenteeism and economic burden (Hoy 2014; Stafford 2007).

Description of the intervention

Clinical guidelines for patients with low back pain and sciatica provide recommendations on analgesics, which are generally based on single ingredient medicines with few recommendations on combination drug therapy (Chou 2007). Combination drug therapy is commonly used in primary care in patients with chronic low back pain (Gore 2012; Taylor-Stokes 2011) and in those with low back pain with a possible neuropathic pain component (Hall 2013). The use of combination therapy in patients with chronic low back pain increases as pain intensity increases (Taylor-Stokes

2011). Studies have found that the most frequent combinations are opioid analgesics plus non-steroidal anti-inflammatory drugs (NSAIDs) or muscle relaxants (Gore 2012), and opioid analgesics are mostly prescribed in combination with paracetamol rather than as monotherapy (Williams 2010).

How the intervention might work

Combining two or more drugs may give greater pain relief (or equal pain relief with lower doses of each drug in the combination) compared to each drug given alone. This potentially can improve drug safety and tolerability. Obtaining greater or equal pain relief can be achieved with combination drug therapy when drugs have different modes of action or favourable pharmacokinetic properties, whereby the drug combination targets multiple pain mechanisms and produces additive or synergistic treatment effects. For example, opioid analgesics combined with paracetamol is thought to have synergistic effects (Miranda 2002) and combining drugs that target nociceptive and neuropathic pain may be beneficial in conditions such as low back pain where mixed pain mechanisms exist (Attal 2011; Freynhagen 2006).

Why it is important to do this review

There is limited evidence for the use of combination drug therapy in the management of low back pain and sciatica. Two previous systematic reviews on combination therapy in low back pain patients found that some drug combinations, such as pregabalin with celecoxib or opioid analgesics, were effective in reducing pain in patients with chronic low back pain compared to monotherapy (Morlion 2011; Romano 2012). However, these reviews were restrictive in their search strategies by language and date, no protocols were published, and they focused only on low back pain of chronic duration. The first review (Morlion 2011) was industry funded and the authors searched only one database. Furthermore, combination therapy may include a broader range of drugs, not considered in these previous reviews. For example, some studies investigating combination therapy in people with low back pain have used supplements such as vitamin B complex (Vetter 1988) and theramine (Shell 2012) in combination with an NSAID.
Combination drug therapy is used in primary care. Information about these medicine combinations, such as the amount of pain reduction, disability outcomes, and medicine safety over time, is clinically important. The current evidence on combination drug therapy in low back pain and sciatica remains unclear.

OBJECTIVES

The primary objective is to investigate the effects of combination drug therapy in reducing pain and disability in patients with low back pain and/or sciatica presenting to primary care, compared to mono drug therapy, no/minimal treatment or placebo. A secondary objective is to investigate combination drug tolerability, participants' rating of improvement and treatment satisfaction.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled, quasi-randomised controlled and cross-over trials (pre-cross-over data only) where group allocation occurred at random. These study designs minimise bias when evaluating the efficacy of interventions.

Types of participants

The population of interest will include participants of any background and age with non-specific low back pain with or without sciatica. Pain may be (sub)acute (< 12 weeks) or chronic (≥ 12 weeks) in duration (Koes 2006). Trials that include participants with a combination of (sub)acute and chronic symptoms will only be included if the data are reported separately for each duration, or can be obtained. People with low back pain due to pregnancy, post-surgery or specific causes such as neoplasm, metastasis, infection, osteoporosis, rheumatoid arthritis and fracture will be excluded.

Types of interventions

We will include studies that administered two or more different drugs compared to a single drug that formed a part of the combination, a placebo or no/minimal treatment (e.g. advice). Drugs will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system advocated by the World Health Organisation's Collaborating Centre for Drug Statistics Methodology (WHO 2013) or, if no ATC code is available, drug(s) will be categorised by the pain mechanism the drug targets. Drugs may include prescription, over-the-counter, complementary or alternative medicines and supplements, at any dose and duration. The route of administration may be local, systemic (oral or parenteral) or transdermal, as long as the intervention was provided in primary care.

Types of outcome measures

Primary outcomes

- Pain intensity measured by a self-reported outcome measure (e.g. visual analogue scale or numerical rating scale).
- Disability measured by a self-reported outcome measure (e.g. Oswestry Disability Index, Roland-Morris Disability Questionnaire).

Secondary outcomes

- Adverse events. This will be separated into:
  - Serious adverse events, defined as events that were life threatening or resulted in death, hospitalisation, significant incapacity, congenital anomaly or birth defects.
  - Non-serious side effects. This will include health outcomes, e.g. nausea.
- Participants' rating of improvement (e.g. Likert scale).
- Participants'rating of treatment satisfaction (e.g. Likert scale).

Follow-up time points of outcomes will be categorised as immediate ($\leq$ 2 weeks), short (> 2 weeks but $\leq$ 3 months), intermediate (> 3 but < 12 months) or long ($\geq$ 12 months) term. The short follow-up period will be considered the primary outcome time point. If multiple time points fall within the same time period, we will use one time point closest to 2 weeks, 7 weeks, 6 months and 12 months for each follow up period.

Search methods for identification of studies

Electronic searches

We will use the latest search strategies developed by the Cochrane Back and Neck Review Group (Furlan 2009).
We will search the following databases from inception to current:
- Cochrane Central Register of Controlled Trials (CENTRAL, *Cochrane Library*)
- MEDLINE (OvidSP)
- MEDLINE In-Process & Other Non-Indexed Citations (OvidSP)
- EMBASE (OvidSP)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCO)
- PsycINFO (OvidSP)
- Web of Science (Thomson Reuters)
- ClinicalTrials.gov
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)

We will search PubMed using the strategy recommended by Duffy 2014 to identify studies not in MEDLINE and the Cochrane Back and Neck Group's Trials Register through the Cochrane Register of Studies (CRS) for studies not in CENTRAL.

See Appendix 1 for the draft MEDLINE search strategy. It will be translated as closely as possible across the other databases. There will be no language or publication restrictions.
We will conduct additional electronic searches to identify other potentially-relevant studies by searching the International Pharmaceutical Abstracts database (OvidSP), clinical trial registries, including pharmaceutical industry trial registers, and grey literature databases (Open Sigle and Grey Literature Report).

Searching other resources

We will check reference lists of eligible studies and relevant reviews for additional citations, and communicate with content experts to identify any missing studies. If necessary, we will contact authors to retrieve study information to determine eligibility.

Data collection and analysis

Selection of studies

Two review authors from a panel of four (SM, CL, RK, RP) will independently screen identified titles and abstracts to determine eligibility. Potentially-eligible studies will have the full text independently appraised to determine inclusion into the review. Duplicate studies will be removed upon agreement. Disagreements will be resolved by discussion first, then arbitration by an independent third review author (CM). When articles are written in languages that cannot be read by the authors, the authors will seek colleagues to assist with reading the article. Review authors will not assess for inclusion any studies to which they have contributed. The flow of studies will be summarised in a study flow diagram, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati 2009).

Data extraction and management

Two review authors from a panel of five (SM, CL, RP, BK, RK) will independently extract data. Standardised and piloted data extraction forms will be used. The following information will be extracted:
- Bibliometric data (e.g. authors, year of publication, language, funding sources, if prospectively registered)
- Study characteristics (e.g. study design, method of randomisation, sample size)
- Participants (e.g. age, gender, duration of low back pain, type of pain)
- Interventions and controls (e.g. drug class, dose, mode of delivery, treatment period)
- Outcomes and results (e.g. pain score, adverse events, number of drop outs)

We will contact study authors to clarify any uncertainties or obtain additional information. Disagreements will be resolved by discussion first, then arbitration by a third author (CM).

Assessment of risk of bias in included studies

The quality of included studies will be assessed using the 'Risk of bias' assessment tool as recommended by The Cochrane Collaboration (Higgins 2011) and the Cochrane Back and Neck Review Group (Furlan 2009) (Appendix 2). Two review authors from a panel of five (SM, CL, RP, BK, RK) will independently assess risk of bias. We will consider the domains of selection bias, performance bias, detection bias, attrition bias, reporting bias and any other biases identified. Each domain will be scored as either 'low', 'unclear' or 'high' risk of bias and tabulated. If additional information is required, we will contact the study authors. If the authors cannot be contacted, or if the information is no longer available, the criterion will be scored as 'unclear'. A study with low risk of bias will be defined as having low risk of bias in six or more domains without any serious flaws (Furlan 2009). Disagreements will be resolved by discussion first, then arbitration by a third review author (CM).

Measures of treatment effect

Analyses of treatment effects on the primary and secondary outcomes will be conducted separately for participants with (sub)acute (< 12 weeks) and chronic low back pain (≥ 12 weeks) at immediate (≤ 2 weeks), short (> 2 weeks but ≤ 3 months), intermediate (> 3 but < 12 months) and long (≥ 12 months) term follow-up periods per drug combination and its comparator (e.g. NSAID versus combination drug therapy).

For dichotomous variables such as side effects we will report risk ratio (RR) or risk difference (RD) as the effect measure with 95% confidence intervals (CI). For continuous outcomes, such as pain intensity on a visual analogue scale or disability on the Roland-Morris Disability Questionnaire, results will be reported as mean differences (MD) with 95% CI. Where possible, outcomes will be converted to a 0 to 100-point scale to facilitate comparison and interpretability. Analyses will be conducted using Review Manager 5.3 (Review Manager 2014).

Unit of analysis issues

The unit of analysis will be each participant recruited into the included studies. Due to the review's design, each participant will have only been allocated to one intervention. Therefore we anticipate that unit of analysis issues could potentially arise from repeated observations. If this occurs (e.g. in adverse events) we will use only one outcome closest to our defined follow-up time points (i.e. immediate (≤ 2 weeks), short (> 2 weeks but ≤ 3 months), intermediate (> 3 but < 12 months) and long (≥ 12 months) for (sub)acute (< 12 weeks) and chronic low back pain (≥ 12 weeks) participants).

Dealing with missing data

If relevant data are missing, we will first contact the authors for clarification and additional data. Failing that, for outcomes we will estimate the means and standard deviations (SDs) from graphs, if available. If SDs are not reported, we will attempt to estimate them from the CIs or other measures of variance. If SDs are missing for follow-up outcomes, we will use the SD for that outcome at baseline. Finally, if no measure of variation is reported or available from authors, we will estimate the SD based upon other studies with a similar population and risk of bias.

Assessment of heterogeneity

Heterogeneity will be assessed by visual inspection of the forest plot (e.g. P values and overlapping CIs) and by the Chi^2 and I^2 tests, following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will follow the recommended guide for interpretation of I^2 as: 0% to 40%, might not be important; 30% to 60%, may represent moderate heterogeneity; 50% to 90%, may represent substantial heterogeneity; 75% to 100%, considerable heterogeneity (Higgins 2011). If sufficient data are available and studies are clinically and statistically homogeneous (I^2 < 50%) the results will be combined in a meta-analysis using a random-effects model. If heterogeneity is present, we will not pool data but will instead present a narrative synthesis.

Assessment of reporting biases

We aim to perform a comprehensive literature search to reduce the possibility of reporting biases. Reporting bias is considered in Assessment of risk of bias in included studies. If enough studies are retrieved (> 10 studies) we will further examine reporting bias using funnel plots.

Data synthesis

The overall quality of evidence will be assessed for each combination therapy group and outcome. A GRADE approach (Guyatt 2008) will be used to report the overall quality of evidence as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and *Cochrane Back and Neck Review Group method guidelines* (Furlan 2009). The GRADE approach considers the domains of risk of bias, imprecision, indirectness, inconsistency and publication bias (Appendix 3). The quality of evidence may decrease from 'high' in each domain when the criteria are not satisfactorily met.

The five levels of evidence are:

• High quality evidence: there are consistent findings among at least 75% of RCTs with low risk of bias, consistent, direct and precise data and no known or suspected publication biases. Further research is unlikely to change either the estimate or our confidence in the results.

• Moderate quality evidence: one of the domains is not met. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

• Low quality evidence: two of the domains are not met. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

• Very low quality evidence: three of the domains are not met. We are very uncertain about the results.

• No evidence: no RCTs were identified that addressed this outcome.

A 'Summary of findings' (SoF) table will be constructed using RevMan. The main comparison will be analgesic versus analgesic combination drug therapy for the primary outcome of pain, at the short-term follow-up (> 2 weeks but ≤ 3 months) for (sub)acute (< 12 weeks) and chronic low back pain (≥ 12 weeks). The analgesic medicines and their comparisons listed in the SoF table will be dependent on the review's findings.

Subgroup analysis and investigation of heterogeneity

If there are adequate studies, we will conduct subgroup analysis of drug combinations for participants presenting with low back pain with radiating leg pain versus participants with low back pain only.

Sensitivity analysis

If there are adequate studies, we will perform sensitivity analyses to explain any possible sources of heterogeneity between studies and to evaluate the robustness of our analysis. In addition, we will compare treatment effects in both primary outcomes between studies with high and low risk of bias, based on the criteria recommended by the Cochrane Back Review Group (van Tulder 2003) where studies of low risk bias have scored low risk of bias in six or more domains without any serious flaws.

ACKNOWLEDGEMENTS

We thank Shireen Harbin from the Cochrane Back and Neck Review group for her knowledge and assistance in development of the search strategy.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. comparative study.pt.
4. clinical trial.pt.
5. pragmatic clinical trial.pt.
6. cross-over studies/
7. random$.ti,ab,kw.
8. placebo.ab,ti,kw.
9. drug therapy.fs.
10. trial.ti,ab,kw.
11. groups.ab.
12. compar$.ti,ab,kw.
13. (crossover or cross-over).ti,ab,kw.
14. or/1-13
15. (animals not (humans and animals)).sh.
16. 14 not 15
17. dorsalgia.ti,ab,kw.
18. exp Back Pain/
19. exp Low back pain/
20. ((back or lumb$) adj3 (pain or radicul$ or polyradicul$)).ti,ab,kw.
21. (backache or back ache).ti,ab,kw.
22. coccydynia.ti,ab,kw.
23. sciatica.ti,ab,kw.
24. exp sciatic neuropathy/
25. spondylosis.ti,ab,kw.
26. lumbago.ti,ab,kw.
27. back disorder$.ti,ab,kw.
28. or/17-27
29. exp Drug Therapy/
30. exp Delayed-Action Preparations/
31. Drug Therapy, Combination/
32. Herbal Medicine/
33. exp Medicine, Traditional/
34. Plants, Medicinal/
35. Phytotherapy/
36. exp Vitamins/
37. exp Pharmaceutical Preparations/
38. Drug Combinations/
39. Drugs, Chinese Herbal/
40. exp Plant extracts/
41. exp Analgesics/
42. exp Anti-Inflammatory Agents/
43. exp Anti-Inflammatory Agents, Non-Steroidal/
44. exp Narcotics/
45. Analgesia/
46. Analgesia, epidural/
47. Neuroleptanalgesia/
48. Anesthetics/

49. Anesthetics, Local/
50. Anesthetics, Intravenous/
51. Anesthesia, Local/
52. exp Anesthesia, Epidural/
53. Anesthesia, Intravenous/
54. exp Nerve Block/
55. Injections, Epidural/
56. Transdermal patch/
57. exp Anticonvulsants/
58. exp Antidepressive Agents/
59. exp Neuromuscular Agents/
60. exp Neuromuscular Blocking Agents/
61. exp Muscle Relaxants, Central/
62. exp Tranquilizing Agents/
63. exp Benzodiazepines/
64. exp Adrenal Cortex Hormones/
65. exp Glucocorticoids/
66. exp Steroids/
67. exp Cyclooxygenase Inhibitors/
68. Monoamine Oxidase Inhibitors/
69. (drug$ or medicine$ or medication$ or pharmacotherap$).mp.
70. (nsaid$ or anti-inflammator$ or antiinflammator$ or opioid$ or opiate$ or narcotic$ or analgesic$ or antinociceptive$ or anti-nociceptive$ or analgesia or neuromuscular block$ or muscle relaxant$ or anticonvuls$ or anti-convuls$ or antiepileptic$ or anti-epileptic$ or antidepress$ or anti-depress$ or anti-anxiety or antianxiety or anxiolytic$ or neuroleptic$ or tranquil$ or antipsychotic$ or anti-psychotic$ or ((cyclooxygenase or cyclo-oxygenase or cox2 or cox-2) adj2 inhibitor$) or ((mao or monoamine or mono-amine) adj2 inhibitor$) or corticosteroid$ or steroid$ or glucocortic$ or corticoid$ or adrenal cortex hormone$ or anesthesia or anaesthesia or anesthetic$ or anaesthetic$ or (nerve adj2 block$)).mp.
71. (herb$ or plant$ or extract$ or supplement? or vitamin$ or phytotherap$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
72. or/29-71
73. (combin$ or cotreat$ or co-treat$ or coadminist$ or co-administ$ or synerg$ or isobol$ or add-on$ or concomitant$ or concurrent$).mp.
74. 72 and 73
75. 16 and 28 and 74

Appendix 2. 'Risk of bias' criteria

Random sequence generation (selection bias)

Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence

There is a low risk of selection bias if the investigators describe a random component in the sequence generation process such as: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).

There is a high risk of selection bia*s* if the investigators describe a non-random component in the sequence generation process, such as: sequence generated by odd or even date of birth, date (or day) of admission, hospital or clinic record number; or allocation by judgment of the clinician, preference of the participant, results of a laboratory test or a series of tests, or availability of the intervention.

Allocation concealment (selection bias)

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment

There is a low risk of selection bias if the participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially-numbered drug containers of identical appearance; or sequentially-numbered, opaque, sealed envelopes.

There is a high risk of bias if participants or investigators enrolling participants could possibly foresee assignment and thus introduce selection bias, such as allocation based on: an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; or other explicitly unconcealed procedures.

Blinding of participants

Performance bias due to knowledge of the allocated interventions by participants during the study

There is a low risk of performance bias if blinding of participants was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

Blinding of personnel/care providers (performance bias)

Performance bias due to knowledge of the allocated interventions by personnel/care providers during the study

There is a low risk of performance bias if blinding of personnel was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

Blinding of outcome assessor (detection bias)

Detection bias due to knowledge of the allocated interventions by outcome assessors

There is a low risk of detection bias if the blinding of the outcome assessment was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding, or:

- for patient-reported outcomes in which the patient was the outcome assessor (e.g. pain, disability): there is a low risk of bias for outcome assessors if there is a low risk of bias for participant blinding (Boutron 2005);
- for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g. co-interventions, length of hospitalisation, treatment failure), in which the care provider is the outcome assessor: there is a low risk of bias for outcome assessors if there is a low risk of bias for care providers (Boutron 2005);
- for outcome criteria that are assessed from data from medical forms: there is a low risk of bias if the treatment or adverse effects of the treatment could not be noticed in the extracted data (Boutron 2005).

Incomplete outcome data (attrition bias)

Attrition bias due to amount, nature or handling of incomplete outcome data

There is a low risk of attrition bias if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to the true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data were balanced in numbers, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk was not enough to have a clinically-relevant impact on the intervention effect estimate; for continuous outcome data, the plausible effect size (difference in means or standardised difference in means) among missing outcomes was not enough to have a clinically-relevant impact on observed effect size, or missing data were imputed using appropriate methods (although if drop-outs are very large, imputation using even 'acceptable' methods may still suggest a high risk of bias) (van Tulder 2003). The percentage of withdrawals and drop-outs should not exceed 20% for short-term follow-up and 30% for long-term follow-up and should not lead to substantial bias (these percentages are commonly used but arbitrary, not supported by literature) (van Tulder 2003).

Selective reporting (reporting bias)

Reporting bias due to selective outcome reporting

There is low risk of reporting bias if the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way, or if the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

There is a high risk of reporting bias if not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Group similarity at baseline (selection bias)

Bias due to dissimilarity at baseline for the most important prognostic indicators.

There is low risk of bia*s* if groups are similar at baseline for demographic factors, value of main outcome measure(s), and important prognostic factors (examples in the field of back and neck pain are duration and severity of complaints, vocational status, and percentage of patients with neurological symptoms) (van Tulder 2003).

Co-interventions (performance bias)

Bias because co-interventions were different across groups

There is low risk of bias if there were no co-interventions or they were similar between the index and control groups (van Tulder 2003).

Compliance (performance bias)

Bias due to inappropriate compliance with interventions across groups

There is low risk of bias if compliance with the interventions was acceptable, based on the reported intensity/dosage, duration, number and frequency for both the index and control intervention(s). For single-session interventions (e.g. surgery), this item is irrelevant (van Tulder 2003).

Intention-to-treat-analysis

There is low risk of bias if all randomised patients were reported/analysed in the group to which they were allocated by randomisation.

Timing of outcome assessments (detection bias)

Bias because important outcomes were not measured at the same time across groups

There is low risk of bias if all important outcome assessments for all intervention groups were measured at the same time (van Tulder 2003).

Other bias

Bias due to problems not covered elsewhere in the table

There is a low risk of bias if the study appears to be free of other sources of bias not addressed elsewhere (e.g. study funding).

Appendix 3. The GRADE approach to evidence synthesis

The quality of evidence will be categorised as follows:

- High (⊙ ⊙ ⊙ ⊙): further research is very unlikely to change the confidence in the estimate of effect.
- Moderate (⊙ ⊙ ⊙ ◯): further research is likely to have an important impact in the confidence in the estimate of effect.
- Low (⊙ ⊙ ◯◯): further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very Low (⊙ ◯◯◯): any estimate of effect is very uncertain.

The evidence available to answer each sub-question will be graded on the domains in the following manner:

1. Study design

2. Risk of bias

Limitations in the study design and implementation may bias the estimates of the treatment effect. Our confidence in the estimate of the effect and in the following recommendation decreases if studies suffer from major limitations. we will examine all studies on five types of biases:

a) Selection (random sequence generation, allocation concealment, group similarities at baseline)

b) Performance (blinding of participants, blinding of healthcare providers)

c) Attrition (drop-outs and intention-to-treat analysis)

d) Measurement (blinding of the outcome assessors and timing of outcome assessment)

e) Reporting bias (selective reporting)

3. Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. Widely differing estimates of the treatment effect (i.e. heterogeneity or variability in results) across studies suggest true differences in underlying treatment effect. Inconsistency may arise from differences in: populations (e.g. drugs may have larger relative effects in sicker populations), interventions (e.g. larger effects with higher drug doses), or outcomes (e.g. diminishing treatment effect with time). The quality of evidence will be downgraded as follows:

- by one level: when the heterogeneity or variability in results is large (for example: I^2 above 80%)
- by two levels: when the heterogeneity or variability in results is large, and there was inconsistency arising from populations, interventions or outcomes.

4. Indirectness

Indirect population, intervention, comparator, or outcome - the question being addressed in this systematic review is different from the available evidence regarding the population, intervention, comparator, or an outcome in the included randomised trial.

The quality of evidence will be downgraded as follows:

- by one level: when there is indirectness in only one area
- by two levels: when there is indirectness in two or more areas.

5. Imprecision

Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. In this case we judge the quality of the evidence lower than it otherwise would because of resulting uncertainty in the results. Each outcome is considered separately.

For dichotomous outcomes

We will consider imprecision for either of the following two reasons:

(1) There is only one study. When there is more than one study, the total number of events is less than 300 (a threshold rule-of-thumb value) (Mueller 2007).

(2) 95% confidence interval around the pooled or best estimate of effect includes both a) no effect and b) appreciable benefit or appreciable harm. The threshold for 'appreciable benefit' or 'appreciable harm' is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.

The quality of the evidence will be downgraded as follows:

- by one level: when there is imprecision due to (1) or (2)
- by two levels: when there is imprecision due to (1) and (2)

For continuous outcomes

We will consider imprecision for either of the following two reasons:

(1) There is only one study. When there is more than one study, total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β, and an effect size of 0.2 SD, representing a small effect)

(2) 95% confidence interval includes no effect and the upper or lower confidence limit crosses an effect size (standardised mean difference) of 0.5 in either direction.

The quality of the evidence will be downgraded as follows:

- by one level: when there is imprecision due to (1) or (2)
- by two levels: when there is imprecision due to (1) and (2)

6. Publication bias

Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. The quality of evidence will be downgraded

by one level: when the funnel plot suggests publication bias.

7. Magnitude of the effect

8. Dose response gradient

9. Influence of all plausible residual confounding

CONTRIBUTIONS OF AUTHORS

CL conceived the review. CL, CM, AM, BK and RK were involved in the design of the review. CL, AM, RK and SM developed the search strategy. SM drafted the manuscript. All authors commented and approved the manuscript.

DECLARATIONS OF INTEREST

SM, RK, RP have no interests to declare. In-kind research support was received from Pfizer (CM, AM and CL) and in-kind with financial research support received from GalxoSmithKline (CM and AM) to conduct two investigator-initiated non-combination therapy clinical trials in back pain. Neither funder played any role in the study design, data collection, analysis, interpretation and reporting in either study.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Health and Medical Research Council, Australia.

Fellowship (CL,CM), post graduate scholarship (SM).

- University Medicine of Greifswald, Germany.

Research fellowship (health services research) Msd Sharp & Dohme GmbH (RK).

- Association for Orthopaedic Research (AFOR), Germany.

Travel grant (RK).