Analgesic effects of non-surgical and non-interventional treatments for low back pain: a systematic review and meta-analysis of placebo-controlled randomised trials

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ABSTRACT

Objectives To investigate the efficacy of non-surgical and non-interventional treatments for adults with low back pain compared with placebo.

Eligibility criteria Randomised controlled trials evaluating non-surgical and non-interventional treatments compared with placebo or sham in adults (≥18 years) reporting non-specific low back pain.

Information sources MEDLINE, CINAHL, EMBASE, PsychInfo and Cochrane Central Register of Controlled Trials were searched from inception to 14 April 2023.

Risk of bias Risk of bias of included studies was assessed using the 0 to 10 PEDro Scale.

Synthesis of results Random effects meta-analysis was used to estimate pooled effects and corresponding 95% confidence intervals on outcome pain intensity (0 to 100 scale) at first assessment post-treatment for each treatment type and by duration of low back pain—(sub) acute (<12 weeks) and chronic (≥12 weeks). Certainty of the evidence was assessed using the Grading of Recommendations Assessment (GRADE) approach.

Results A total of 301 trials (377 comparisons) provided data on 56 different treatments or treatment combinations. One treatment for acute low back pain (non-steroidal anti-inflammatory drugs (NSAIDs)), and five treatments for chronic low back pain (exercise, spinal manipulative therapy, taping, antidepressants, transient receptor potential vanilloid 1 (TRPV1) agonists) were efficacious; effect sizes were small and of moderate certainty. Three treatments for acute low back pain (exercise, glucocorticoid injections, paracetamol), and two treatments for chronic low back pain (antibiotics, anaesthetics) were not efficacious and are unlikely to be suitable treatment options; moderate certainty evidence. Evidence is inconclusive for remaining treatments due to small samples, imprecision, or low and very low certainty evidence.

Conclusions The current evidence shows that one in 10 non-surgical and non-interventional treatments for low back pain are efficacious, providing only small analgesic effects beyond placebo. The efficacy for the majority of treatments is uncertain due to the limited number of randomised participants and poor study quality. Further high-quality, placebo-controlled trials are warranted to address the remaining uncertainty in treatment efficacy along with greater consideration for placebo-control design of non-surgical and non-interventional treatments.

Trial registration number OSF Registries; https://osf.io/2dk9z.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Placebo-controlled randomised trials are the best method for evaluating efficacy of treatments. There is a limited but growing evidence base of placebo-controlled randomised trials investigating the analgesic effects of non-surgical and non-interventional treatments for non-specific low back pain.

WHAT THIS STUDY ADDS

⇒ This is the most comprehensive systematic review of placebo-controlled randomised trials investigating non-surgical and non-interventional treatments for non-specific low back pain, including 301 trials on 56 different treatments or treatment combinations.

⇒ Most non-surgical and non-interventional treatments for low back pain were not efficacious. Around 10% of non-surgical and non-interventional treatments provided small analgesic effects beyond placebo.

⇒ For acute low back pain, there is moderate certainty evidence that NSAIDs are efficacious. For chronic low back pain, there is moderate certainty evidence that exercise, spinal manipulative therapy, taping, antidepressants, and TRPV1 agonists are efficacious.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study supports the efficacy of several non-surgical and non-interventional treatments for reducing pain intensity compared with placebo in low back pain. Further high-quality, placebo-controlled trials to reduce uncertainty in remaining efficacy estimates are warranted as well as greater consideration for the design of placebos of many non-surgical and non-interventional treatments.

Introduction

Low back pain is a common[1] and burdensome problem[2] characterised by debilitating pain, impaired function, societal withdrawal and financial impacts.[3] The majority (80–90%) of low back pain is categorised as non-specific based on the fact that a nociceptive cause cannot be reliably identified clinically.[4] The global burden of low back pain is projected to increase in the coming decades, highlighting the need for efficacious and safe treatments for patients, clinicians, and policymakers.[5]

Non-surgical and non-interventional treatments are recommended as first-line care for low back pain.[6 7] These include a large and heterogenous collection of treatment options with many new treatments continuing to be developed and implemented in clinical practice. With an increasing number of treatment options, it is difficult for key stakeholders to remain updated with what treatments are available, much less understand their analgesic efficacy. It is essential to understand which treatment options are most promising to provide sound recommendations for healthcare providers, funders and patients.

Our group published a systematic review in 2008, that included 76 trials of 34 treatments, which provides the most recent evidence of the analgesic effects of all non-surgical and non-interventional treatments in placebo-controlled randomised trials in a single review.[8] Since then the evidence base has grown substantially with many new treatments investigated using a placebo-controlled design. While systematic reviews for some of these treatments have been published, they only provide evidence on a single treatment. Variability in scope and quality of recent systematic reviews also makes use of the evidence difficult for clinicians, patients, and policymakers. Synthesising the evidence of non-surgical and non-interventional treatments for low back pain in a single review will provide much needed clarity on the effectiveness of available interventions compared with placebo.

The objective of this study is to provide an up-to-date evidence synthesis of the efficacy of non-surgical and non-interventional treatments compared with placebo or sham in adults with low back pain. We expect this review to form an essential part of a body of research that identifies which treatments can be recommended for care, which should be discouraged, and which are promising but require further research.

Methods

The review protocol was prospectively registered on Open Science Framework[9] and reported following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[10] Online supplemental file 1 reports the minor deviations from the protocol and original review.[8]

Eligibility criteria

Study type

We included published randomised placebo-controlled trials of non-surgical and non-interventional treatments for people with non-specific low back pain. Investigating treatments in randomised, placebo or sham controlled trials is an important first step to determine the effectiveness of treatments. Doing so helps identify which treatments have effects beyond the contextual and non-specific effects of receiving care (placebo effects),[11] while also minimising the risk of bias (eg, allocation, attention, detection, performance and attrition biases).[12] Evidence generated from placebo-controlled trials can support promotion of effective treatments and de-implementation of those that are no more effective than placebo. This information cannot be determined from other designs that use no-treatment or other-treatment comparison.

We translated non-English studies with Google Translate except for one study whose full text file was incompatible (eg, JPEG). We excluded trials investigating primary prevention of low back pain (that included pain-free participants) and crossover trials unless data were provided for the first phase before the crossover period. We also excluded unpublished records of trials for pragmatic reasons due to resource restraints in a review of this size.

Participants

Participants were adults with non-specific low back pain. Non-specific low back pain was defined as pain between the lower rib cage and gluteal folds, with or without non-radicular spine-related leg pain,[13] for which no evidence of specific spinal pathology could be reliably detected.[4 14] Lumbar osteoarthritis, spondylolisthesis, disc protrusion, herniation, or prolapse, and facet syndrome were considered as non-specific low back pain and included.[15] Studies that included spine-related leg pain[13] were included unless the sample met our criteria for radiculopathy (positive neurological exam for sensory or motor deficits, for example, dermatomal hypoesthesia or anaesthesia, myotomal weakness, or reduced or absent reflexes). We excluded studies that primarily recruited patients with low back pain due to specific spinal pathologies (eg, cauda equina syndrome, infection, neoplasm, vertebral fracture including spondylolysis, inflammatory disease including axial spondyloarthropathies), lumbar radicular syndromes, spinal stenosis, pregnancy, or recent spinal surgery (≤12 months). Trials reporting mixed populations (eg, non-specific low back pain, upper back pain, and neck pain) were included if ≥75% of the sample had non-specific low back pain.

Interventions

We included non-surgical and non-interventional treatments that aimed to improve pain in people with low back pain. This included conservative (non-invasive) pharmacological (eg, non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants) and non-pharmacological (eg, exercise, massage) treatments that could be provided in primary care. A detailed description of eligible treatment types is provided in online supplemental file 2. We included studies comparing combination medicines (eg, muscle relaxants+NSAIDs) to a placebo and studies that reported standardised co-interventions (ie, the same adjunct therapy provided to both the experimental and placebo groups). Surgical, interventional, and minimally invasive procedures, including laminectomy, posterior fusion, intradiscal electrothermal therapy, chemonucleolysis, radiofrequency denervation, prolotherapy, spinal cord

stimulation, and intraspinal, interspinous and supraspinous injections, were excluded.[16]

Comparison

We included studies if the control intervention was described as a placebo or sham by the study's authors. We excluded studies compared with waitlist, no treatment, and usual care, and studies where it was not possible to isolate the effectiveness of the target intervention—for example, studies comparing a multicomponent non-pharmacological intervention (eg, heat + acupuncture) to the same multicomponent placebo group (eg, sham heat + sham acupuncture).

Outcome

We included studies reporting a continuous measure of pain intensity. Pain intensity is considered a core outcome[17] and primary treatment target[18] for low back pain research, and is considered essential for recovery by people with low back pain.[19] Data on pain intensity was extracted at the first assessment after the end of treatment because this was the time when the treatment was hypothesised to exert the greatest effect. We excluded studies reporting proxy measures (eg, symptom bothersomeness, pain-related disability). We did not extract data on harms (adverse events), disability or other patient reported outcomes because this was beyond the scope of this review.

Data sources and searches

The search strategy was developed in collaboration with a health research librarian. We combined terms for randomised controlled trials and low back pain (as described by the Cochrane Back Review Group[20]), and additional terms including placebo, sham, attention-control, and minimal intervention (online supplemental file 3). We updated the search from the previous review[8] from January 2005 to April 2023 using MEDLINE, CINAHL, EMBASE, APA PsycInfo and Cochrane Central Register of Controlled Trials (Central). Authors of conference abstracts or ongoing trials identified in the search were contacted to determine if these studies had since been published. In addition, the reference lists of relevant systematic reviews were screened for potentially relevant trials. We did not search clinical trials registries or grey literature.

Study selection

All records identified by the search strategy were de-duplicated and imported to Covidence for screening. The review team independently screened all titles and abstracts. We retrieved full length records of potentially eligible titles and screened these in duplicate to determine inclusion. Disagreements between reviewers were resolved through discussion or, when necessary, through consultation with a third reviewer. All studies previously included in the original review[8] were screened against our inclusion criteria.

Data extraction

Two independent reviewers extracted data from eligible studies using a standardised, piloted, data extraction form in Microsoft Excel. We extracted data on the study characteristics, participants, interventions, comparisons, co-interventions and pain outcome from each trial (online supplemental file 4). Outcome data (ie, mean and SD of pain scores) closest to the end of treatment were extracted in duplicate. When end of treatment scores were not reported, we extracted data according to the hierarchy of pre-treatment to post-treatment within group change scores for each eligible treatment arm first, then between group differences and corresponding 95% confidence intervals (95% CI) at follow-up. If pain outcome data were only provided graphically, we estimated the data using the WebPlotDigitizer (version 4.6) software. Where necessary we estimated the SD using a relevant statistic provided in the study (eg, CI, SE, IQR).[21] When no measure of variance was reported, we imputed the SD from the largest trial in the same analysis that used the same measurement tool, or used the SD from another study included in the review using the same measurement tool with similar population characteristics.[21] We resolved disagreements regarding data extraction through discussion, or with arbitration by a third reviewer if necessary. Study authors were contacted when data were not reported.

Risk of bias and certainty of the evidence

When they were available, we extracted ratings for trials from the PEDro database (pedro.org.au); otherwise, two trained independent raters scored the trials using the 0 to 10 PEDro scale (online supplemental file 5).[22 23] Disagreements were resolved by discussion or, where necessary, with a third reviewer. The PEDro scale has acceptable clinimetric properties and convergent validity with earlier versions of the Cochrane Risk of Bias Scale.[23] We considered the PEDro scale items for random allocation, concealed allocation, and adequate follow-up (>85%) as critical domains due to potential to bias treatment effect estimates in placebo-controlled randomised trials.[24] Studies with a PEDro score ≤6/10, or one of the critical items marked as no/unclear, were classified as high risk of bias. Studies with a PEDro score ≥7 and no critical items marked no/unclear were classified as low risk of bias.[23] Methodological quality was not an inclusion criterion.

Two independent reviewers assessed the certainty of the evidence for each analysis using the GRADE system classified as high, moderate, low, or very low certainty.[25 26] Disagreements were resolved by consensus. We downgraded the certainty of the evidence from 'high' certainty by one level if serious flaws were present in each the five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (online supplemental file 6).

Data synthesis and analysis

All analyses were grouped by intervention class (pharmacological or non-pharmacological intervention) due to different challenges designing and implementing appropriate placebo controls.[27] Analyses were further stratified by treatment type based on descriptions provided in online supplemental file 2, and the duration of low back pain in the included trials—(sub)acute (<12 weeks) and chronic (≥12 weeks).[20] When a study included a mix of participants with acute and chronic low back pain, we classified the study as acute when either ≥75% of the population had acute low back pain or if the mean or median symptom duration of the sample was ≤30 days. We classified the study as chronic low back pain when either ≥75% of the population had chronic low back pain or the mean or median symptom duration of the sample was ≥12 months. Studies not meeting the above criteria were not included in our primary analysis, and are reported separately. We conducted meta-analyses where there was more than one study that reported pain intensity. For studies with multiple eligible comparisons, we either treated each comparison as an individual trial if considered in different meta-analyses, or divided the control group sample size by the number of trial arms in the same meta-analysis.[21] To facilitate the interpretation, we converted pain scores to a common 0–100 point scale, with 0 denoting no pain and 100 the worst possible pain.[28 29] To ensure the direction of effect was consistent between studies reporting between group

differences and changes scores, we multiplied the point estimates by −1 when necessary.[21] For each comparison, we classified findings as either efficacious, not efficacious, or inconclusive[30] (online supplemental file 7). We interpreted the size of the mean between group difference based on the definitions from the American College of Physicians and the American Pain Society.[31] A difference of 5 to 10 points was considered small, >10 to 20 points moderate, and >20 points large.

Random effects meta-analytic models were fit using the inverse variance method in Review Manager (RevMan; version 5.4.1). We expressed effects for pain intensity using the mean between group difference and accompanying 95% CI. Meta-analyses were summarised using forest plots and I^2 statistics were calculated to assess the percentage of the total variance due to heterogeneity between trials. We created heat maps to visualise simultaneously the certainty of evidence and the magnitude of the effect. Due to the large number of included studies, we did not perform narrative synthesis on studies with unusable pain intensity data. We conducted sensitivity analyses to assess the potential impact of risk of bias in individual studies on the results of the meta-analysis. This involved examining how results vary with the exclusion of studies judged to be at high risk of bias.

Results

The flow of studies through the review is summarised in figure 1. Overall, 6258 records were identified, 1547 duplicates were removed, and 4651 titles and abstracts screened. A total of 301 trials (377 treatment arms of interest) were included—218 new trials plus 83 from the previous review. Twenty-one trials were not included in the quantitative synthesis because they included participants of mixed low back pain duration (eg, acute and chronic low back pain) (online supplemental file 15).

Study characteristics

The 377 treatment arms of interest investigated 56 different treatments or treatment combinations. Most common were NSAIDs (n=27), opioids (n=26), laser and light (n=25), acupuncture (n=24) and mobilisation (n=19). Fifty-two trials sampled participants with acute low back pain, 228 trials with chronic low back pain, and 21 trials sampled participants with both acute and chronic low back pain (mixed duration). Trials were conducted on six continents (Africa, North America, South America, Asia, Australia, and Europe), in 44 countries. Pain intensity was most often assessed using the Visual Analogue Scale or the Numeric Rating Scale. Study characteristics are reported in online supplemental files 8–10.

Study quality

The median (IQR) score on the 0 to 10 PEDro scale for the included trials was 8 (6–9). Of the 301 trials, 187 (62%) were considered at high risk of bias (online supplemental file 11). The most common risks of bias related to not blinding the therapist (209 trials, 69%), not performing analysis by intention-to-treat (149 trials, 50%), and not concealing allocation (138 trials, 46%).

Certainty of the evidence

Of the 69 treatment comparisons, the certainty of the evidence was moderate for 11 (16%), low for 25 (36%), and very low for 33

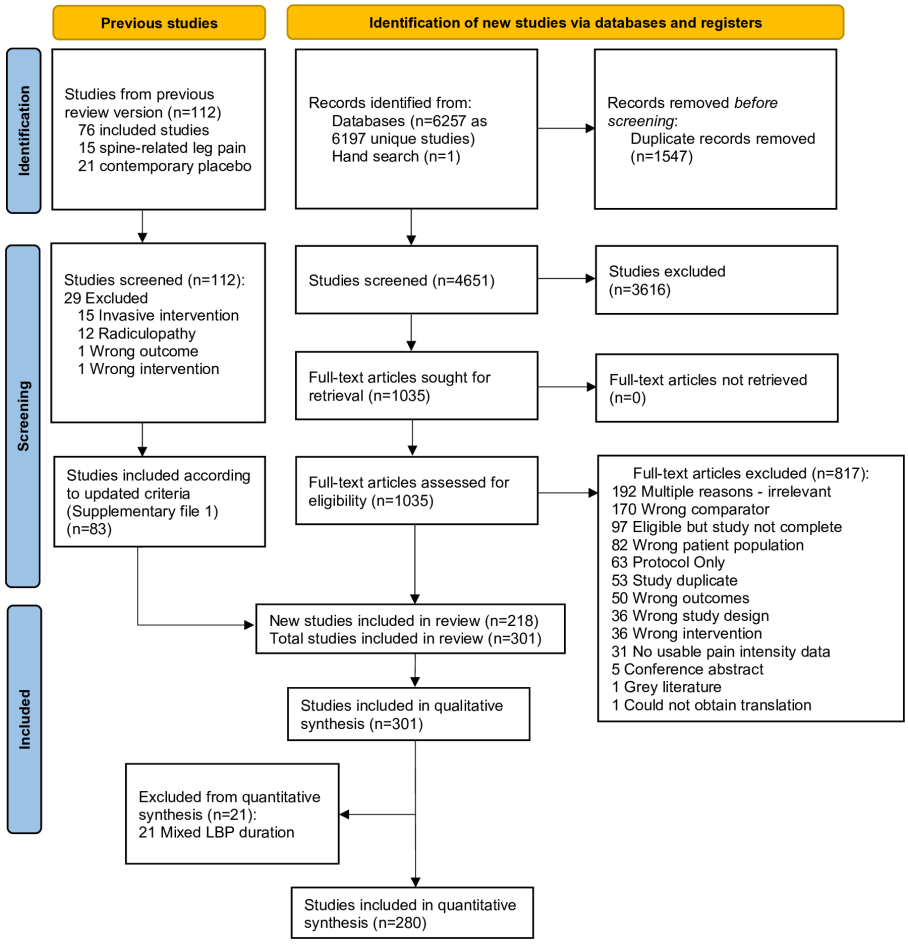

Figure 1 Flow of record selection process. LBP, low back pain.

Table 1 Summary of findings for efficacious interventions

For patients with low back pain, what is the effect of the intervention listed below, compared with placebo on the outcome of pain intensity at the timepoint closest to the end of treatment?				
Intervention	Mean difference 0 to 100 (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Acute low back pain				
Pharmacological intervention				
NSAIDs	−3.8 (−5.8 to −1.8)	1763 (10)	⨁⨁⨁⨀ Moderate*	Probably provide slight reductions in pain
Chronic low back pain				
Non-pharmacological intervention				
Exercise	−7.9 (−13.6 to −2.2)	676 (7)	⨁⨁⨁⨀ Moderate*	Probably provides small reductions in pain
Spinal manipulative therapy	−6.4 (−10.3 to −2.5)	445 (9)	⨁⨁⨁⨀ Moderate*	Probably provides small reductions in pain
Taping	−6.3 (−12.1 to −0.4)	967 (15)	⨁⨁⨁⨀ Moderate†	Probably provides small reductions in pain
Pharmacological interventions				
Antidepressants	−4.9 (−6.8 to −2.9)	1695 (10)	⨁⨁⨁⨀ Moderate*	Probably provide slight reductions in pain
TRPV1 agonists	−8.2 (−13.0 to −3.5)	433 (2)	⨁⨁⨁⨀ Moderate*	Probably provide small reductions in pain

*Downgraded by one level for serious risk of bias.
†Downgraded by one level for serious inconsistency due to heterogeneity or single trial comparison.
GRADE, Grading of Recommendations Assessment; NSAIDs, non-steroidal anti-inflammatory drugs; TRPV1, transient receptor potential vanilloid 1.

(48%). There were no treatment comparisons where the certainty of the evidence was high. The main reasons for downgrading certainty of the evidence were inconsistency (n=52, 75%), risk of bias (n=47, 68%), and imprecision (n=47, 68%).

Analgesic efficacy

Tables 1–3 summarise the analgesic efficacy for all non-surgical and non-interventional treatments for acute and chronic low back pain. Efficacy estimates are presented as a mean difference on a 0–100 point pain scale. Figures 2 and 3 display the effect size and 95% CI (from most to least effective) for treatment comparisons including two or more studies or study arms. Online supplemental figures 1 and 2 display effect size and certainty (GRADE rating) of the evidence together. Detailed analysis for all treatments including the GRADE evidence profile is presented in online supplemental files 12–15.

Evidence for efficacious interventions

Acute low back pain

No non-pharmacological treatments and one pharmacological treatment (NSAIDs; moderate certainty evidence) was found to be efficacious for acute low back pain (table 1).

Chronic low back pain

Three non-pharmacological treatments (exercise, spinal manipulative therapy, taping; moderate certainty evidence) and two pharmacological treatments (antidepressants, transient receptor potential vanilloid

Table 2 Summary of findings for not efficacious interventions

For patients with low back pain, what is the effect of the intervention listed below, compared with placebo on the outcome of pain intensity at the timepoint closest to the end of treatment?				
Intervention	Mean difference 0 to 100 (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Acute low back pain				
Non-pharmacological intervention				
Exercise	−4.1 (−12.0 to 3.7)	412 (2)	⨁⨁⨁⨀ Moderate*	Probably provides little to no difference in pain
Pharmacological intervention				
Glucocorticoid injections	0.4 (−11.8 to 12.6)	111 (2)	⨁⨁⨁⨀ Moderate†	Probably provide little to no difference in pain
Paracetamol	−2.5 (−8.2 to 3.3)	1843 (2)	⨁⨁⨁⨀ Moderate*	Probably provides little to no difference in pain
Chronic low back pain				
Pharmacological interventions				
Anaesthetics	−7.8 (−16.4 to 0.7)	281 (2)	⨁⨁⨁⨀ Moderate†	Probably provide small reductions in pain
Antibiotics/antimicrobials	−7.0 (−14.6 to 0.6)	351 (3)	⨁⨁⨁⨀ Moderate†	Probably provide small reductions in pain

*Downgraded by one level for serious inconsistency due to heterogeneity or single trial comparison.
†Downgraded by one level for imprecision due to <400 participants in the analysis.
GRADE, Grading of Recommendations Assessment.

Table 3 Summary of findings for interventions for which evidence is inconclusive

For patients with low back pain, what is the effect of the intervention listed below, compared with placebo on the outcome of pain intensity at the timepoint closest to the end of treatment?

Intervention	Mean difference 0 to 100 (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Acute low back pain				
Non-pharmacological intervention				
Acupuncture	−10.5 (−13.9 to −7.1)	226 (4)	⨁⨁◯◯ Low*†	May provide moderate reductions in pain
Behaviour/education	−4.4 (−10.3 to 1.4)	376 (3)	⨁◯◯◯ Very low*†‡	May provide little to no difference in pain (evidence is very uncertain)
Extracorporeal shockwave	14.6 (2.0 to 27.2)	53 (1)	⨁◯◯◯ Very low*†‡	May provide moderate increases in pain (evidence is very uncertain)
Heat	−17.6 (−23.7 to −11.4)	255 (2)	⨁◯◯◯ Very low*†§	May provide moderate reductions in pain (evidence is very uncertain)
Laser and light	−4.7 (−19.2 to 9.7)	85 (2)	⨁◯◯◯ Very low*†‡	May provide little to no difference in pain (evidence is very uncertain)
Massage	−22.0 (−34.4 to −9.6)	40 (1)	⨁◯◯◯ Very low*†‡	May provide large reductions in pain (evidence is very uncertain)
Mobilisation	2.9 (−9.3 to 15.0)	117 (3)	⨁◯◯◯ Very low*†‡	May provide little to no difference in pain (evidence is very uncertain)
Osteopathic	−7.7 (−20.6 to 5.2)	202 (2)	⨁◯◯◯ Very low*†‡	May provide small reductions in pain (evidence is very uncertain)
Spinal manipulative therapy	−12.4 (−23.2 to −1.6)	383 (4)	⨁⨁◯◯ Low†‡	May provide moderate reductions in pain
TENS	−14.9 (−42.2 to 12.4)	121 (2)	⨁◯◯◯ Very low*†‡	May provide moderate reductions in pain (evidence is very uncertain)
Pharmacological intervention				
Cannabinoid	4.0 (−6.0 to 14.0)	100 (1)	⨁⨁◯◯ Low†‡	May provide little to no difference in pain
Colchicine	15.0 (−10.6 to 40.6)	15 (1)	⨁◯◯◯ Very low*†‡	May moderately increase pain (evidence is very uncertain)
Immunoglobulin	−34.4 (−56.4 to −12.5)	41 (1)	⨁◯◯◯ Very low*†‡	May provide moderate reductions in pain (evidence is very uncertain)
Muscle relaxants	−13.4 (−18.7 to −8.0)	999 (9)	⨁⨁◯◯ Low*‡	May provide moderate reductions in pain
Muscle relaxants + NSAIDs	−6.0 (−18.8 to 6.8)	105 (1)	⨁◯◯◯ Very low*†‡§	May provide small reductions in pain (evidence is very uncertain)
Nucleoside	−4.0 (−11.5 to 3.5)	161 (1)	⨁◯◯◯ Very low*†‡§	May provide little to no difference in pain (evidence is very uncertain)
Opioids	−24.5 (−30.0 to −19.1)	200 (1)	⨁◯◯◯ Very low†‡¶	May provide large reductions in pain (evidence is very uncertain)
Ozone injections	−13.0 (−20.0 to −6.0)	41 (1)	⨁◯◯◯ Very low*†‡	May provide moderate reductions in pain (evidence is very uncertain)
Pyrazolone derivatives	−12.3 (−18.5 to −6.1)	168 (1)	⨁◯◯◯ Very low†‡§	May provide moderate reductions in pain (evidence is very uncertain)
Topical rubefacients	−14.5 (−22.7 to −6.2)	845 (2)	⨁⨁◯◯ Low‡§	May provide moderate reductions in pain
Chronic low back pain				
Non-pharmacological intervention				
Acupressure	−19.9 (−25.4 to −14.4)	168 (4)	⨁⨁◯◯ Low*†	May provide moderate reductions in pain
Acupuncture	−11.7 (−18.0 to −5.4)	2006 (19)	⨁⨁◯◯ Low‡§	May provide moderate reductions in pain
Behavioural/education	−8.2 (−14.3 to −2.1)	550 (7)	⨁⨁◯◯ Low*‡	May provide small reductions in pain
Biofeedback	−1.1 (−10.5 to 8.4)	178 (5)	⨁◯◯◯ Very low*†‡	May provide little to no difference in pain (evidence is very uncertain)
Diathermy	0.4 (−2.1 to 2.9)	284 (4)	⨁◯◯◯ Very low*†‡	May provide little to no difference in pain (evidence is very uncertain)
Dry cupping	−8.7 (−37.7 to 20.3)	127 (2)	⨁⨁◯◯ Low†‡	May provide small reductions in pain
Electroacupuncture	−8.6 (−28.1 to 10.9)	255 (5)	⨁◯◯◯ Very low*†‡	May provide small reductions in pain (evidence is very uncertain)
Electromagnetic	−8.1 (−19.6 to 3.4)	257 (7)	⨁◯◯◯ Very low*†‡	May provide small reductions in pain (evidence is very uncertain)
Extracorporeal shockwave	−9.8 (−21.1 to 1.5)	179 (5)	⨁◯◯◯ Very low*†‡	May provide small reductions in pain (evidence is very uncertain)
Foot orthotics	−34.7 (−44.3 to −25.1)	51 (1)	⨁◯◯◯ Very low*†‡	May provide large reductions in pain (evidence is very uncertain)
Infrared	−19.6 (−32.2 to −7.1)	92 (2)	⨁◯◯◯ Very low*†‡§	May provide moderate reductions in pain (evidence is very uncertain)

Continued

Table 3 Continued

For patients with low back pain, what is the effect of the intervention listed below, compared with placebo on the outcome of pain intensity at the timepoint closest to the end of treatment?				
Intervention	Mean difference 0 to 100 (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Interferential	−15.7 (−22.9 to −8.6)	691 (7)	⨁⊖⊖⊖ Very low*‡§	May provide moderate reductions in pain (evidence is very uncertain)
Laser and light	−7.2 (−11.8 to −2.7)	1182 (18)	⨁⨁⊖⊖ Low*‡	May provide small reductions in pain
Massage	−22.4 (−33.2 to −11.6)	182 (4)	⨁⊖⊖⊖ Very low*†‡	May provide large reductions in pain (evidence is very uncertain)
Mobilisation	−14.6 (−24.3 to −4.9)	869 (13)	⨁⨁⊖⊖ Low*‡	May provide moderate reductions in pain
Osteopathic	−2.2 (−9.2 to 4.8)	790 (3)	⨁⨁⊖⊖ Low*‡	May provide little to no difference in pain
Radiotherapy	−1.3 (−16.6 to 14.0)	32 (1)	⨁⨁⊖⊖ Low†‡	May provide little to no difference in pain
Reflexology	−8.0 (−19.2 to 3.2)	15 (1)	⨁⊖⊖⊖ Very low*†‡	May provide small reductions in pain (evidence is very uncertain)
TENS	−16.5 (−22.5 to −10.5)	581 (11)	⨁⨁⊖⊖ Low*‡	May provide moderate reductions in pain
Traction	−13.6 (−42.0 to 14.8)	250 (3)	⨁⨁⊖⊖ Low†‡	May provide moderate reductions in pain
Transcranial stimulation	−9.3 (−14.2 to -4.5)	260 (7)	⨁⨁⊖⊖ Low*†	May provide small reductions in pain
Ultrasound	−12.0 (−27.5 to 3.6)	92 (2)	⨁⊖⊖⊖ Very low*†‡	May provide moderate reductions in pain (evidence is very uncertain)
Pharmacological interventions				
GABAA receptor modulator	1.6 (−3.7 to 6.9)	148 (1)	⨁⊖⊖⊖ Very low†‡§	May provide little to no difference in pain (evidence is very uncertain)
Antibody injection	−4.8 (−6.6 to −3.0)	3401 (5)	⨁⨁⊖⊖ Low*§	May provide slight reductions in pain
Anticonvulsants	−10.4 (−18.8 to −2.0)	204 (2)	⨁⊖⊖⊖ Very low*†‡¶	May provide moderate reductions in pain (evidence is very uncertain)
Antidepressants + paracetamol	5.7 (−4.3 to 15.7)	63 (1)	⨁⊖⊖⊖ Very low*†‡	May increase pain (evidence is very uncertain)
Bee venom	−9.3 (−18.7 to 0.1)	54 (1)	⨁⨁⊖⊖ Low†‡	May provide small reductions in pain
Bisphosphonates	−11.4 (−22.9 to 0.2)	61 (2)	⨁⨁⊖⊖ Low†§	May provide moderate reductions in pain
Bushen Huoxue formula	−11.6 (−16.3 to −6.9)	66 (1)	⨁⨁⊖⊖ Low†‡	May provide moderate reductions in pain
Complementary medicines	−10 (−17.7 to −2.3)	1145 (11)	⨁⊖⊖⊖ Very low*‡§	May provide moderate reductions in pain (evidence is very uncertain)
Endogenous steroids	−5.5 (−13.3 to 2.3)	83 (1)	⨁⊖⊖⊖ Very low*†‡	May provide small reductions in pain (evidence is very uncertain)
Hypnotic medicines	−19.9 (−31.5 to −8.3)	52 (1)	⨁⊖⊖⊖ Very low†‡§	May provide moderate reductions in pain (evidence is very uncertain)
Muscle relaxants	−6.3 (−10.4 to −2.2)	268 (2)	⨁⨁⊖⊖ Low*†	May provide small reductions in pain
Muscle relaxants + NSAIDs	−10.0 (−56.0 to 36.0)	18 (1)	⨁⨁⊖⊖ Low†‡	May provide moderate reductions in pain
NSAIDs	−4.9 (−6.6 to −3.1)	2612 (8)	⨁⨁⊖⊖ Low*§	May provide slight reductions in pain
Opioids	−7.9 (−9.8 to −6.0)	7269 (19)	⨁⊖⊖⊖ Very low*‡§	May provide small reductions in pain (evidence is very uncertain)
Opioids + analgesics	−7.5 (−12.5 to −2.5)	821 (4)	⨁⨁⊖⊖ Low*§	May provide small reductions in pain
Probiotics	1.0 (−8.0 to 10.0)	88 (1)	⨁⨁⊖⊖ Low†‡	May provide little to no difference in pain

*Downgraded by one level for serious risk of bias.

†Downgraded by one level for imprecision due to ‹400 participants in the analysis.

‡Downgraded by one level for serious inconsistency due to heterogeneity or single trial comparison.

§Downgraded by one level for publication bias due to evidence of funnel plot asymmetry or ›50% of participants were from industry funded trials with potential conflicts of interest.

¶Downgraded by one level for indirectness due to ›50% of trials included participants with spine-related leg pain.

GABAA, γ-aminobutyric acid type A; GRADE, Grading of Recommendations Assessment; NSAIDs, non-steroidal anti-inflammatory drugs; TENS, transcutaneous electrical nerve stimulation .

1 (TRPV1) agonists; moderate certainty evidence) were found to be efficacious for chronic low back pain (table 1).

Evidence for not efficacious interventions

Acute low back pain

One non-pharmacological treatment (exercise; moderate certainty evidence) and two pharmacological treatments (glucocorticoid injections, paracetamol; moderate certainty evidence) were not efficacious for acute low back pain (table 2).

Chronic low back pain

No non-pharmacological treatments and two pharmacological treatments (anaesthetics, antibiotics; moderate certainty evidence) were not efficacious for chronic low back pain (table 2).

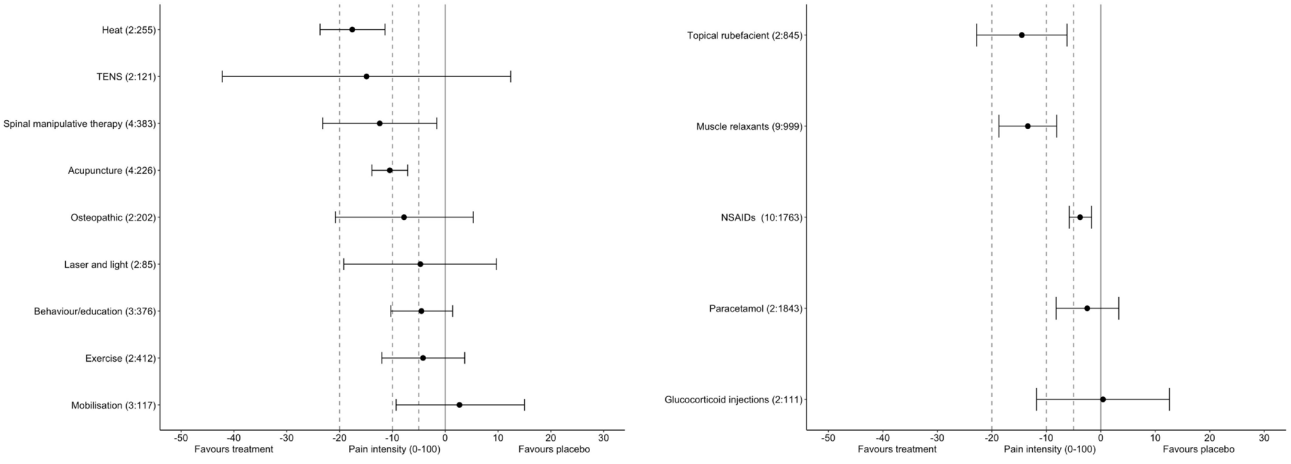

Figure 2 Analgesic efficacy of non-pharmacological (left panel) and pharmacological (right panel) treatments including two or more trials or trial arms for acute low back pain. Circles represent pooled estimates of random effects and error bars represent 95% CIs. Negative values favour treatment. In parentheses: number of trials; total number of participants. The dotted lines define the magnitude of effects: large (›20 points); moderate (›10–20 points); small (5–10 points), and solid line defines the null. NSAIDs, non-steroidal anti-inflammatory drugs; TENS, transcutaneous electrical nerve stimulation.

Interventions for which evidence is inconclusive

Acute low back pain

Ten non-pharmacological treatments (acupuncture, behaviour/education, extracorporeal shockwave, heat, laser and light, massage, mobilisation, osteopathic, spinal manipulative therapy, transcutaneous electrical nerve stimulation (TENS); low to very low certainty evidence) and 10 pharmacological treatments (cannabinoid, colchicine, immunoglobulin, muscle relaxants, muscle relaxants + NSAIDs, nucleoside, opioids, ozone injections, pyrazolone derivatives, topical rubefacients; low to very low certainty evidence) had inconclusive evidence about their efficacy for acute low back pain (table 3).

Chronic low back pain

Twenty-two non-pharmacological treatments (acupressure, acupuncture, behaviour/education, biofeedback, diathermy, dry cupping, electroacupuncture, electromagnetic, extracorporeal shockwave, foot orthotics, infrared, interferential, laser and light, massage, mobilisation, osteopathy, radiotherapy, reflexology, TENS, traction, transcranial stimulation, ultrasound; low to very low certainty evidence) and 16 pharmacological treatments (allosteric modulator of the γ-aminobutyric acid type A (GABAA) receptor, antibody injections, anticonvulsants, antidepressants + paracetamol, bee venom, bisphosphonates, Bushen Huoxue formula, complementary medicines, endogenous steroids, hypnotic medicines, muscle relaxants, muscle relaxants + NSAIDs, NSAIDs, opioids, opioids + analgesics, probiotics; low to very low certainty evidence) had inconclusive evidence about their efficacy for chronic low back pain (table 3).

Sensitivity analyses

Online supplemental file 16 presents detailed results for sensitivity analyses exploring the effect of risk of bias. The results did not substantially vary through statistically different non-overlapping CIs by removing studies at high risk of bias.

Discussion

This review provides the most comprehensive summary of evidence for non-surgical and non-interventional treatments for low back pain. We included 301 placebo-controlled trials with data on an additional 21 treatments or treatment combinations compared with the earlier review version.[8] For this review we separated analyses by intervention class (non-pharmacological and pharmacological) and duration of low back pain (acute and

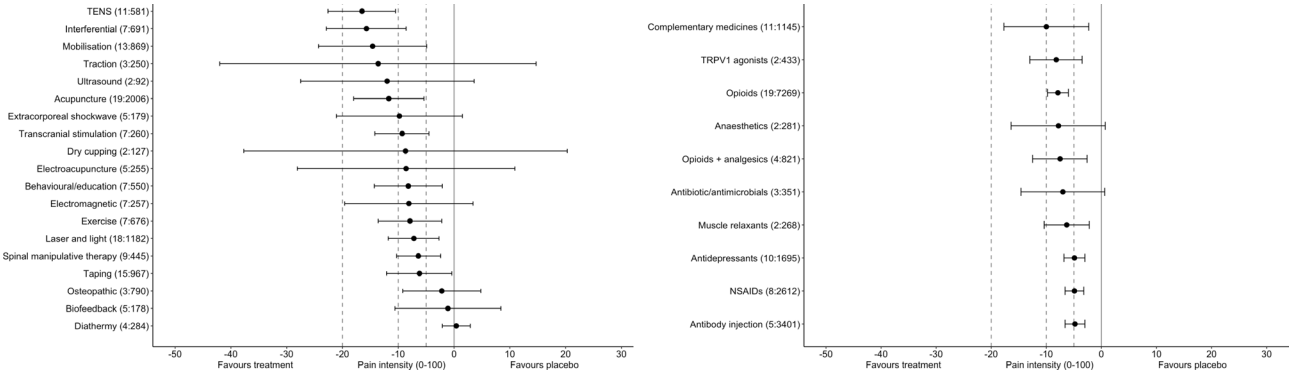

Figure 3 Analgesic efficacy of non-pharmacological (left panel) and pharmacological (right panel) treatments including two or more trials or trial arms for chronic low back pain. Circles represent pooled estimates of random effects and error bars represent 95% CIs. Negative values favour treatment. In parentheses: number of trials; total number of participants. The dotted lines define the magnitude of effects: large (›20 points); moderate (›10–20 points); small (5–10 points), and solid line defines the null. NSAIDs, non-steroidal anti-inflammatory drugs; TENS, transcutaneous electrical nerve stimulation; TRPV1, transient receptor potential vanilloid 1.

chronic) to provide specific evidence to support clinical decisions and policy recommendations. We also assessed the certainty of the evidence using GRADE to assess the confidence in the proximity of the estimated effect to the true population mean effect.

Only one treatment for acute low back pain and five treatments for chronic low back pain had at least moderate certainty evidence for providing statistically significant reductions in pain intensity compared with placebo. Effect estimates for efficacious treatments for acute pain (NSAIDs) and chronic pain (exercise, spinal manipulative therapy, taping, antidepressants, TRPV1 agonists) were small. We identified three treatments for acute low back pain (exercise, glucocorticoids, paracetamol) and two treatments for chronic low back pain (anaesthetics, antibiotics/antimicrobials) for which there is at least moderate quality evidence of no effect. Evidence is inconclusive for other treatments due to few participants, imprecision, or being of low or very low certainty. Further large, high-quality trials may help reduce the uncertainty in the evidence for these treatments.

This systematic review was prospectively registered[32] and reported following recommended guidance.[10] We included all non-surgical and non-interventional treatments evaluated in placebo-controlled randomised trials and published in any language. We assessed the methodological quality of trials using the PEDro scale[23] and evaluated the certainty of the evidence using GRADE.[25 26] Finally, to support clinical and policy interpretation of findings, we provided a visual summary of results organising the findings by the magnitude and certainty of effects as well as classified the findings for each comparison as either efficacious, not efficacious, or inconclusive based on both statistical significance and the certainty of the evidence.

Our review has limitations. The eligibility criteria relied on the comparator being described as a placebo or sham in the identified trials to be included in the review; the definition for what constitutes the placebo or sham group varies between trials. We decided to group similar treatments (eg, selective and non-selective NSAIDs) regardless of route of administration to reduce the number of comparisons reported and support the interpretation for clinical and policy decision making. This is commonly done in the field.[33 34] We included trials in which participants in both groups received the same standardised co-intervention. It is unlikely the inclusion of trials with standardised co-interventions influenced the interpretation of findings. Finally, we did not include unpublished records or trials for pragmatic reasons. The impact of including these studies is uncertain and not routinely considered in low back pain research.[35]

Placebo comparators are an important tool in evidence-based medicine because they separate the specific from non-specific effects of treatments and reduce the risk of common biases. In low back pain research, meta-analyses have demonstrated that placebo interventions have a small analgesic effect (8/100 points) compared with no intervention in the short term.[36] Despite their importance, placebo controlled trials are uncommon in low back pain research, with most trials compared against another treatment or against usual care.[24] For example, there are a lack of placebo-controlled trials of common psychological treatments (eg, cognitive behavioural therapy) for low back pain.[37] Without evidence from placebo-controlled trials, the specific effects of common treatments are unknown. The absence of placebo controlled trials may result from difficulty in design for non-pharmacological interventions,[27 38] confusion with common terminology,[12 39] and challenges in interpretation by consumers.[40]

Interpretation of these findings should consider the challenges in designing and implementing credible and matched placebo controls for all treatment options considered in this review. For example, the participatory and often complex nature of non-pharmacological treatments (eg, exercise and psychological therapies) makes it difficult to design and implement suitable placebo controls.[27] In comparison, methods for placebo controls for medications and unimodal treatments such as acupuncture and electro-physical agents are well-established and straightforward. This may result in higher certainty and more precise estimates of efficacy for treatments such as medications and acupuncture, than for exercise and psychological and behavioural interventions. For this reason, clinicians and policymakers should consider evidence from trials with other types of control interventions in decision making.

Our findings are broadly comparable to those of recent high-quality systematic reviews of single treatment classes (eg, exercise therapy,[34] acupuncture,[41] and antidepressants[42]), overview of pharmacological treatments investigated in Cochrane systematic reviews,[43] and clinical practice guideline recommendations.[6] Discrepancies in findings with other reviews are likely due to differences in: (1) inclusion criteria (eg, PICO elements—population, intervention, comparison, outcome) including use of recent terminology to classify spine-related leg pain[13]; (2) data sources (eg, inclusion of trial registry data[44]); (3) choice of tool and method to assess risk of bias and certainty of evidence; and (4) combination of the above (eg, muscle relaxants[45]). Identified discrepancies related to minor differences in the size of the effect or certainty of the evidence that would not substantially change clinical decisions. The increasing publication of overlapping and low-quality systematic reviews across low back pain research makes direct comparisons across all investigated treatments difficult.[46]

Our review did not find reliable evidence of large effects for any of the included treatments, which is consistent with clinical guidelines and our previous review. While we would like to provide more certain recommendations for where to invest and disinvest in treatments, it is not possible at this time. Certainty in our findings is limited by many of the available trials including few participants and reporting inconsistent results. Further complicating the interpretation of findings is the heterogenous type and quality of some of the placebos used in the included trials. These findings from our review provide important insights for the broader, ongoing conversation about 'where to next' for placebo-controlled trials of low back pain treatments.

Our review identified several unanswered questions for future research. There is a clear need for large, high-quality, placebo-controlled trials to reduce uncertainty in efficacy estimates for many non-surgical and non-interventional treatments. For example, many of the included treatments had only a single trial with less than 100 participants per group. Additional high-quality trials will support the investigation of potential heterogeneity of treatment effects including relevant subgroups. There are also common treatments for which no placebo-controlled trials have been conducted despite being commonly recommended in clinical practice guidelines.[6 47] Finally, there is a need for better consideration around the design of placebos for complex interventions such as behavioural, psychological and exercise treatments with opportunities to draw on recently published guidance.[48]

Conclusion

Best available evidence shows that one in 10 common non-surgical and non-interventional treatments for low back pain are efficacious, providing small analgesic effects beyond

placebo. Further high-quality, placebo-controlled trials are warranted to address the remaining uncertainty in treatment efficacy along with greater consideration for designing placebos of non-surgical and non-interventional treatments.

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Patient and public involvement No patients or members of the public were directly involved in setting the research question or in developing plans for the design of this study because of a lack of funding. We asked patients and members of the public to read the draft manuscript and advise on the writing and interpretation of results. We plan to disseminate the results of this review to relevant patient organisations.

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Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

The dataset used and analysed during this study, and the accompanying code is available from the corresponding author upon reasonable request.

Author note All authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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