Clinician education unlikely effective for guideline-adherent medication prescription in low back pain: systematic review and meta-analysis of RCTs

Daniel L Belavy,[a] Scott D Tagliaferri,[b] Paul Buntine,[c,d] Tobias Saueressig,[e] Kate Sadler,[b] Christy Ko,[c] Clint T Miller,[f] and Patrick J Owen[b]*

[a]Hochschule für Gesundheit (University of Applied Sciences), Department of Applied Health Sciences, Division of Physiotherapy, Gesundheitscampus 6-8, 44801, Bochum, Germany
[b]Deakin University, Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, 221 Burwood Highway, Burwood, Victoria 3125, Australia
[c]Eastern Health, Box Hill Hospital, Emergency Department, 5 Arnold St, Box Hill, Victoria 3128, Australia
[d]Monash University, Eastern Health Clinical School, Level 2, 5 Arnold Street, Box Hill, Victoria 3128, Australia
[e]Physio Meets Science GmbH, 69181 Leimen; Germany
[f]Deakin University, School of Exercise and Nutrition Sciences, 221 Burwood Highway, Burwood, Victoria 3125, Australia

Summary

Background Effectiveness of implementing interventions to optimise guideline-recommended medical prescription in low back pain is not well established.

Methods A systematic review and random-effects meta-analyses for dichotomous outcomes with a Paule-Mandel estimator. Five databases and reference lists were searched from inception to 4th August 2021. Randomised controlled/clinical trials in adults with low back pain to optimise medication prescription were included. Cochrane Risk of Bias 2 tool and GRADE were implemented. The review was registered prospectively with PROSPERO (CRD42020219767).

Findings Of 3352 unique records identified in the search, seven studies were included and five were eligible for meta-analysis (N=11339 participants). Six of seven studies incorporated clinician education, three studies included audit/feedback components and one study implemented changes in medical records systems. Via meta-analysis, we estimated a non-significant odds-ratio of 0·94 (95% CI (0·77; 1.16), I^2 = 0%; n=5 studies, GRADE: low) in favour of the intervention group. The main finding was robust to sensitivity analyses.

Interpretation There is low quality evidence that existing interventions to optimise medication prescription or usage in back pain had no impact. Peer-to-peer education alone does not appear to lead to behaviour change. Organisational and policy interventions may be more effective.

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Keywords: randomised controlled trial; meta-analysis; systematic review; implementation science; back pain; low back pain; sciatica; radicular pain; chronic pain; controlled before-after studies; interrupted time series analysis; pharmacy; prescription; medication; analgesia; opioid; paracetamol

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Introduction

Low back pain (LBP) affects approximately 540 million individuals worldwide[1] and is the leading cause of disability.[2] Approximately 90% of people will suffer from LBP during their lifetime,[3] which may result in social withdrawal,[4] early retirement and subsequently less lifetime income,[5] mental health issues,[6] and an inability to perform activities of daily living.[7] LBP currently costs the US healthcare system more than $USD100 billion

*Corresponding author. Prof. Daniel L Belavy, Hochschule für Gesundheit (University of Applied Sciences), Department of Applied Health Sciences, Division of Physiotherapy, Gesundheitscampus 6-8, 44801, Bochum, Germany. Tel: +49 234 77727 632
E-mail address: daniel.belavy@hs-gesundheit.de (D.L. Belavy).

Research in context

Evidence before this study

MEDLINE, EMBASE, CINAHL, Web of Science Core Collection and CENTRAL were searched for research published from database inception to August 4, 2021. Google Scholar and reference lists of relevant systematic reviews were searched for research published in the last ten years, as well as reference lists of and future studies that cited the included studies. Randomised controlled/clinical trials in adults with low back pain to optimise medication prescription were included. Of the seven included studies, four were rated as having a low risk of bias and three as having some concerns. Via meta-analysis, we estimated a non-significant odds-ratio of 0·94 (95% CI (0·77; 1.16), I^2 = 0%; n=5 studies, GRADE: low) in favour of the intervention group.

Added value of this study

We find that there is low-quality evidence that interventions did not impact medication prescription or usage in back pain. From our evidence synthesis, peer-to-peer education does not lead to behaviour change, and additional literature suggests that organisational level interventions may be more effective.

Implications of all the available evidence

There is a need for randomised controlled cluster trials of interventions that focus on specific aspects of organisational change (e.g., patient flow, changes to medication prescription requirements and/or changes to electronic medical records systems). Future studies should also report the total number of prescriptions relative to the total number of appointments or patients.

per year,[8] whilst in Australia[9] and Germany,[10] these costs are $AUD9 billion and €50 billion per year, respectively. Hence, there is a need to reduce the burden of disease associated with LBP.

Evidence-based clinical guideline adherence reduces financial costs and may also improve patient outcomes. RCTs (both cluster[11–17] and individual patient[18–21] designs), as well as prospective[22–31] and retrospective[32–39] studies have investigated the impact of guideline adherence on financial costs[11,12,14,16,17,19,22,24–28,30–40] and patient outcomes.[12,13,15,18,20,21,23,24,29,33–35,37,41] Retrospective studies have shown lower costs[32–36,38–40] when guidelines are followed. Prospective non-randomised studies[22,24–28,30,31] are less consistent, yet appear dependent on the modality of intervention examined. RCTs have observed both significant[16,17,19] and non-significant[11,12,14] reduction in financial costs favouring guideline-based approaches. Patient outcomes (e.g., subjective pain intensity and disability) have been shown to improve in retrospective studies,[33–35,37] yet prospective non-randomised studies have yielded inconclusive results.[23,24,29,41] Data from RCTs showed improved[12,13,18] or similar[15,21] effects on patient outcomes when guidelines were followed. Collectively, these data indicate that reductions in financial costs are likely when LBP is managed according to guidelines.

The majority (93%) of evidence-based primary care clinical guidelines recommend the use of non-steroidal anti-inflammatory drugs for non-specific low back pain of any symptom duration.[42] However, the appropriateness of all other medications based on class and duration of symptoms is debated. For example, while 57% of guidelines recommend paracetamol, 36% recommend against it.[42] The majority of guidelines (87%) recommend low potency opioids for short durations if first-line therapies provide no improvement.[42] However, countries such as Australia and Demark are firmly against the use of opioids for non-specific low back pain.[42] Notably, as these guidelines tend to be designed for use in the general practice setting, it is likely that these opioid recommendations overlook the fact that patients presenting in the emergency department setting will often have greater pain intensity and therefore warrant stronger pain relief. Other medications that remain debated by guidelines include antidepressants, muscle relaxants, and herbal medicines.[42] For radicular low back pain, medication recommendations are less established, which stems from the lack of large blinded clinical trials;[43,44] neuropathic agents may[43,44] or may not[45] provide benefits for radicular low back pain.

Currently in primary care (i.e., general practice and back pain presentations to emergency departments), these recommendations are frequently not followed. For adherence to medication prescription/usage guidelines in low back pain in primary care, no systematic reviews have yet been conducted. However, we identified 10 studies[39,46–56] which reported such data. Within the studies[39,46–50] published since 2010 (and so potentially more reflective of current practice) opioids (35%,[46] 40%,[47] 25%,[39] 20%,[49] 19%,[48] 61 %[50]) NSAIDs (62%,[47] 50%,[50] 37%,[49] 35%,[46,48] 20%[39]), and paracetamol (21.5%[52]) were most commonly used in primary care[39,48,49] and the emergency department.[46,47,50] Muscle relaxants were prescribed at varying rates depending on setting and study (0·1% to 53%[39,46,48,50]). Further, while corticosteroid usage was typically under 5%,[39,50] it was still present in back pain management. Use of unnecessary medications for back pain can, depending on dose and duration of use, expose patients to potential harms, such as gastrointestinal disorders (oral NSAIDS), drowsiness or dizziness (opioids, muscle relaxants, neuropathic agents) and dependency (opioids).[57] Overall, the data suggest that there is significant potential for cost savings and harm reduction by implementing changes in clinical practice to align medication prescription in primary care with guidelines.

This study aimed to systematically review approaches to implementing guidelines for optimising

medication usage or prescription in primary care (i.e., general practice and hospital emergency departments). Randomised controlled or clinical trials were considered the highest level of evidence available. Secondary aims were to collate information on prospective interventional non-randomised studies relevant to the review area identified while systematically searching the literature.

Methods

This systematic review was completed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[58] The review was registered prospectively with PROSPERO (CRD42020219767).

Information sources and search strategy

Five online databases (MEDLINE [no limits], EMBASE [excluding MEDLINE], CINAHL [excluding MEDLINE], Web of Science Core Collection [excluding MEDLINE], CENTRAL [excluding MEDLINE, EMBASE and trial registrations]) were electronically searched for research published from database inception to the 22nd June 2020 and revised on 4th August 2021. Trial registries were not searched. The search terms and strategy can be found in Supplemental Digital Content 1. To locate additional relevant records, we also searched Google Scholar and included the reference lists of relevant systematic reviews (identified via the Cochrane Database of Systematic Reviews and Google Scholar) published in the last ten years. The reference lists of included studies were checked for potentially relevant articles. In addition, forward citation tracking of included studies was performed by adding articles that cited the included studies in Web of Science to screening. Furthermore, reference lists of studies excluded solely for not being an RCT (e.g., interrupted time series analyses, controlled before and after studies) were also screened for potentially relevant articles.

Study selection

Results of the search were screened to exclude duplicates. Independent screening of the titles and abstracts of the remaining studies (with reference to predetermined eligibility criteria) was completed by two independent reviewers (KS and CK) who were blinded to each other's assessment. The full-text reports of articles which seemed eligible after this first screening were screened once again using the previously mentioned inclusion and exclusion criteria. Any disagreements were adjudicated by SDT and discussed with the project team as necessary.

Eligibility criteria

Inclusion criteria followed the Participants, Interventions, Comparators, Outcomes and Study design (PICOS) framework.[58] The population (P) considered was adults (≥18 yrs of age) with low back pain. Low back pain was defined as back pain with or without leg pain where there were no specific spinal pathologies (i.e., vertebral fracture, malignancy, spinal infection, axial spondyloarthritis, or cauda equina syndrome[59]). Spondylolisthesis, spondylosis, disc herniation, disc degeneration, scoliosis, deformity (e.g., hemivertebrae) and radicular syndromes (e.g., radicular pain [leg pain or sciatica], radiculopathy, spinal stenosis) were included.[59] "Failed back surgery syndrome" was included, as this is not a specific disease.[60] Our predetermined criteria also included studies in which populations were classified as experiencing otherwise unspecified "back pain". No limitation was placed on interventions (I), and these were classified according to procedures[61] used by the Cochrane Effective Practice and Organisation of Care (EPOC) group into professional, financial, organisational, patient-oriented, structural, or regulatory interventions. Comparators (C) that were considered were, per Cochrane EPOC procedures,[61] no intervention control group, standard practice control group and/or untargeted activity. Medication prescriptions or usage were included outcomes (O). Regarding the study design (S), only full text articles and reports of analytical studies published in English were considered for inclusion. Studies published in a peer-reviewed journal (i.e., grey literature excluded) with a parallel arm (individual- or cluster-designed) randomised controlled or clinical trial design were eligible. Studies that were excluded solely for being non-randomised prospective studies were collated separately. No restrictions were placed on date of publication for inclusion.

Data collection and data items

Data extraction was completed by two independent assessors (KS and CK). Extracted information included relevant publication information (i.e., author, title, year, journal), study design, study funding, conflicts of interest, number of participants, participant characteristics (e.g., age and sex), intervention details (e.g., duration, type, frequency), cluster details for cluster randomised trials (e.g., number of clusters), and outcome measures (e.g., surgical rates). We also extracted participants' pain intensity scores and disability and any adverse events from included trials, where available. Extracted data were the number or percentage of medication use or prescription and the total number of participants or appointment sessions. In all instances where data required for meta-analysis were unavailable, authors were contacted a minimum of three times over a four-week period and asked to provide the information. Similarity between extracted data from the two independent assessors was evaluated through custom spreadsheets set up in Google Sheets. Any discrepancies were

discussed by the assessors, with disagreements adjudicated by SDT.

Risk of bias in individual studies

The Cochrane Collaboration Risk of Bias Tool version 2[62] was used to examine potential bias from the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and in the selection of the reported results for individually and cluster randomised trials. Each domain was assessed for risk of bias and labelled as 'low risk', 'some concerns' or 'high risk'. For each source of bias, studies were then classified as having a low risk, some concerns or high risk as per the overall algorithm. Both independent assessors (KS and CK) assessed risk of bias, and any disagreements regarding risk of bias were adjudicated by SDT.

Synthesis of results

The evidence synthesis for this review was conducted in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines (see Supplemental Digital Content 2).[63]

Statistical analysis

For statistical analysis we created two categories of comparators: (1) multifaceted intervention and (2) no intervention control group, standard practice control group according to the EPOC guidelines.[61] Our primary outcome measure was medication prescription/usage. As effect size we used the odds ratio (OR), as it has favorable statistical properties compared to the risk ratio.[64] For easier interpretation of the OR, we transformed it to a risk difference with corresponding 95% confidence intervals (CI). For this transformation, we used an assumed comparator risk (ACR) based on the mean of the prevalence of medication prescription of two observational studies[65,66] which gives a prevalence of 27·8%. Cluster RCTs were handled by calculating a design effect to correct for clustering of the trials. The design effect is approximately 1+ (M-1) * ICC, where M is the average cluster size and ICC is the intracluster (or intraclass) correlation coefficient.[67] Sample size and the number of events are then divided by the design effect, which results in adjusted sample sizes and numbers of events for the corresponding trial.[67] This is done to adjust for an overestimation of the precision of the estimate. We used either published intracluster (or intraclass) correlation coefficients (ICC) or the most conservative value from the available ICCs to inform a choice for unavailable ICCs of other studies. We also performed sensitivity analysis with a range of different ICCs to check the robustness of the results.[68] A random-effects meta-analysis was used for dichotomous outcomes with a Paule-Mandel estimator for the between study variance T^2, a sample-size-weights (SSW) estimator for the overall effect with weights that depended only on the studies' effective sample sizes, and a 95% CI for the overall effect based on the Hartung-Knapp-Sidik-Jonkman method. We used this method as it outperforms the standard random-effects method and other methods.[69] Measures of heterogeneity used were Cochrane Q and the resulting chi-squared statistic and I^2. Publication bias was assessed via funnel plots, and similarly, we pre-planned to use Egger's test, and trim and fill methods if at least 10 studies were included in the meta-analysis.[70] We performed sensitivity analysis via outlier identification and influence analysis.[71] All calculations and graphics were performed with the software R[72] and the extension packages Meta[73] and dmetar.[74]

Role of the sponsor

Not applicable.

Ethics committee approval

Not applicable.

Results

Study selection

A summary of the systematic review process is presented in Figure 1. Following the removal of 2379 duplicates, 3352 studies were included in title and abstract screening. Following the completion of the title and abstract screening, 117 studies were included in the full-text screening. The examination of full texts resulted in 117 studies being excluded (Supplemental Digital Content 3) and seven[14,75–80] studies being included (Table 1 and Table 2). Of these, five[14,75,77,78,80] studies were eligible for meta-analysis; two[76,79] studies could not be included in quantitative synthesis as we were unable to extract or acquire from the authors data required for inclusion in quantitative synthesis (i.e., the total number of events relative to the total number of patients or appointments). No papers required extraction from an image. Only one non-randomised interventional study[26] was identified.

Study characteristics

Population: The sample sizes included in intervention phases of the studies ranged from 462 to 4625, and the total number of patients included in the review was 11399. Cluster sizes ranged from four to 68, with the number of clusters in each arm of two studies[77,79] being unclear. Attempts to contact authors for further information were unsuccessful. Two studies examined patients with acute LBP,[14,79] five studies examined patients with mixed pain duration, of which the

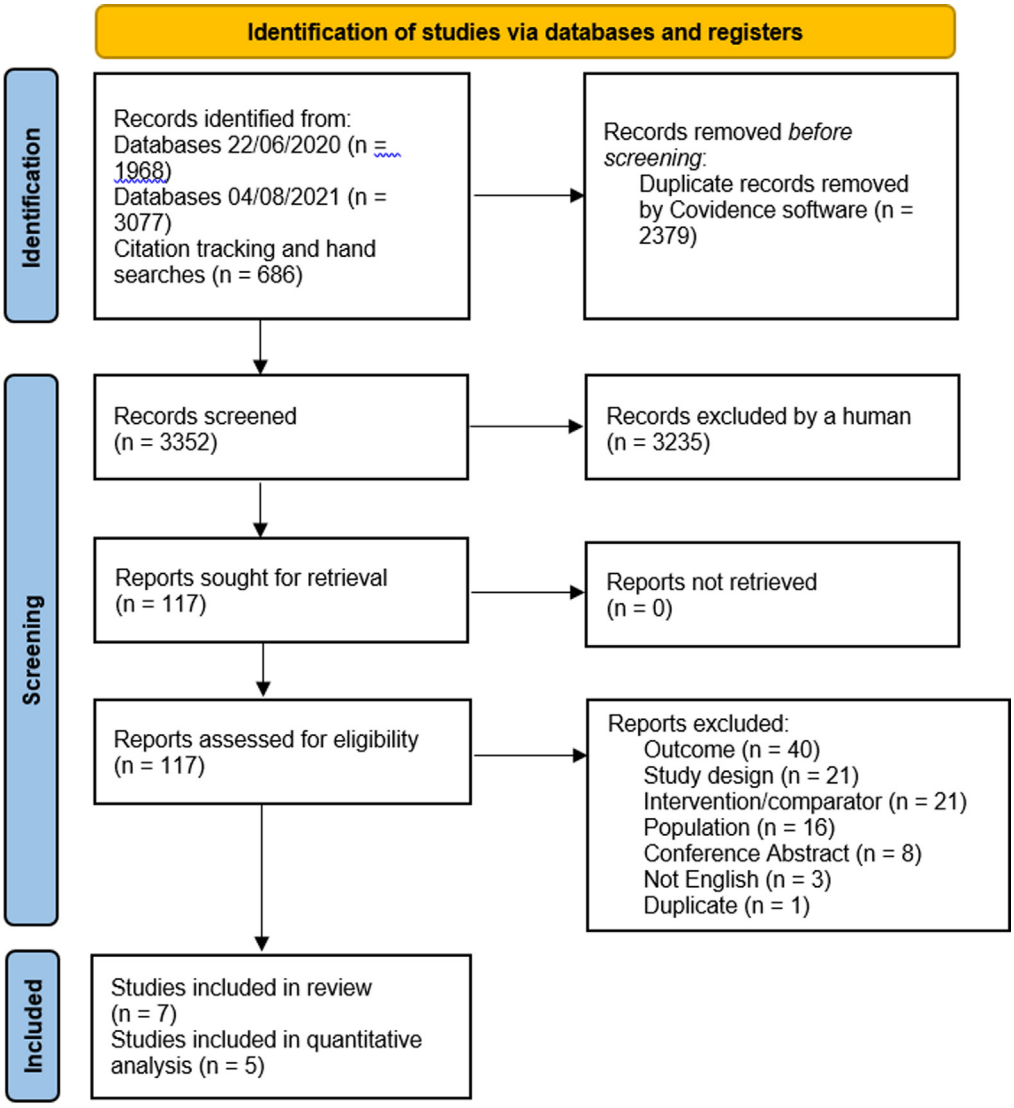

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

majority had less than three months of pain[75–78] and in two[76,80] the duration of pain was unclear. For types of low back pain, three included non-specific pain,[75,78,79] two had mixed non-specific and radicular pain[76,80] and two were unclear (e.g. only reporting the sample as low back pain).[14,77]

Intervention: Six of seven studies[14,75–78,80] incorporated education and/or workshop component interventions for clinicians, with five studies[14,77–80] incorporating some form of passive dissemination of materials to clinicians and three studies[76,77,80] providing forms of audit and feedback to clinicians. One study[76] implemented changes in (electronic) medical records systems to remind clinicians of a guideline-based approach.

Comparator: Five studies[14,75,78–80] implemented a no-intervention control and two studies[76,77] used passive dissemination of materials, one of which[76] provided education and/or workshops to clinicians.

Outcome: Five studies reported medication prescription as a raw number (number of patients receiving a prescription) and/or percentage (percentage of patients receiving a prescription).[14,75,77,78,80] One study reported percent of patients receiving guideline-appropriate medication prescription, and could not be included in meta-analysis as they authors confirmed that all the patients were prescribed medications.[79] One study[76] reported data as number of packages prescribed.

Study design: All included studies were cluster randomised controlled trials. Six studies[75–80] received either

Author	Year	Study Design	N INT	N CON	Type LBP	Duration LBP	N Clusters INT	N Clusters CON	Cluster Type	INT Type	INT Period	INT	CON	Funding	Study Conclusions
Bishop[79] *	2006	Cluster RCT	313	149	Non-specific	Acute	Unclear	Unclear	Family Physicians	Professional (diss|re)	12 weeks	Physician-only arm: passive guideline distribution and reminders via post. Physician + patient arm: same as in physician group plus pamphlet for patients	No intervention	None or public/ non-profit	LBP guideline communication to physicians, with or without the addition of patient education, shows no benefit for medication prescription.
Cherkin[75] †	2018	Cluster RCT	2106 (943 baseline, 1163 study period)	2534 (1061 baseline, 1473 study period)	Non-specific	Mixed	3	3	Primary Care Clinics	Professional (ed)	5 months	Six training sessions on the use of the STarT Back Tool and on diagnosis and management of pain.	No intervention	None or public/ non-profit	There is no statistically significant difference in the prescriptions of analgesics between arms.
Coombs[80]	2021	Cluster RCT	1392	3233	Mixed (Non-specific and radicular)	Unclear	4**	4**	Hospital Emergency Departments	Professional (ed|au.fe)	20 months	Multifaceted: 1. Education seminars 2. Education materials 3. Provision of non-opioid pain management 4. Fast-track referral 5. Audit and feedback	Usual Care	None or public/ non-profit	A multifaceted intervention for guideline implementation reduced the prescription of any opioid medications.
Dey[14]	2004	Cluster RCT	1049	1138	Unclear	Acute	12	11	Health Centres	Professional (ed|diss)	8 months	Outreach visits with interactive discussion between the guideline team and general practitioners on guidelines plus a poster including guideline recommendations	No intervention	Not reported	An educational strategy based on RCGP guidelines failed to change the prescription of opioids and muscle relaxants.

Table 1 (Continued)

Author	Year	Study Design	N INT	N CON	Type LBP	Duration LBP	N Clusters INT	N Clusters CON	Cluster Type	INT Type	INT Period	INT	CON	Funding	Study Conclusions
Engers[78]	2005	Cluster RCT	276	255	Non-specific	Mixed	21	20	General Practitioners	Professional (ed|diss)	9 months	2-hour guideline education workshop, distribution of patient education material to the practitioner, distribution of guidelines and scientific articles.	No intervention	None or public/non-profit	There was no significant difference in the prescription of medications between the arms.
Hoeijenbos[77] ‡	2005	Cluster RCT	242	241	Unclear	Mixed	Unclear	Unclear	Physiotherapy Practices	Professional (ed|diss|au.fe)	1 year	Two group training sessions with education, discussion, feedback interaction and reminders regarding guideline implementation. Dissemination of materials	Passive dissemination of guidelines via mail	None or public/non-profit	The prescription of medications appeared to do down over the time-points but no significant difference existed.
Jensen[76]	2017	Cluster RCT	220	255	Mixed (Non-specific and radicular)	Unclear	26	24	General Practices	Professional (ed|au.fe|org)	1 year	Visit from guideline facilitator, education of risk stratification tools and feedback on guideline adherence. Popups in electronic medical records system.	Informational and educational meetings, newsletters	None or public/non-profit	No statistical results on the differences in pharmaceutical resources utilisation were reported. Raw numbers were reported in the supplementary data.

***Table 1*: Characteristics of studies included in the review.**

* Bishop 2006: 34 clusters in total, but it was unclear how many randomised to each arm. For ICC adjustment in analysis, only the total number of clusters is required.

† Cherkin 2018: Medication outcomes include all participants who visited clinics (not just those who provided patient reported outcomes).

‡ Hoeijenbos 2005: 68 total clusters but unclear how many in each arm. For ICC adjustment in analysis, only the total number of clusters is required.

** Coombs 2021: Step-wedged cluster RCT with four clusters total with control and intervention periods.Specific classification of each intervention is described as 'ed': clinician education/workshops; 'diss': passive dissemination; 'au.fe': audit and feedback to clinicians; 're': reminders to clinicians; 'org': organisational change, administrative changes, electronic medical records system changes and/or government policy change; 'pat.ed': patient education.

Author	Year	Outcome	Baseline INT	Follow-Up INT	Baseline CON	Follow-Up CON	P-Value	n INT for analysis[a]	N INT for analysis	n CON for analysis	N CON for analysis	ICC[b]
Bishop[79] *	2006	% of participants given guideline appropriate medication	-	83%	-	77%	Group 2 - P=0.14 Group 3 - P=0.08	-	-	-	-	-
Cherkin[75] †	2018	Proportion (95%CI) of patients prescribed medication	0.37 (0.28, 0.45)	0.41 (0.32, 0.51)	0.39 (0.30, 0.48)	0.45 (0.35, 0.55)	p=0.757	477	1163	663	1473	-
Coombs [80] ‡	2021	Number and percentage of any opioid or non-opioid medication prescription	-	Strong opioid: 586 (42.5) Opioid: 696 (50.5) Non-opioid: 992 (72.0)	-	Strong opioid: 1588 (52.4) All opioid: 1904 (62.8) Non-opioid: 2095 (69.1)	Strong opioid: 0.075 All opioid: 0.006 Non-opioid: 0.063	Strong opioid: 586 All opioid: 696 Non-opioid: 992	Strong opioid: 1392 All opioid: 1392 Non-opioid: 1392	Strong opioid: 1588 All opioid: 1904 Non-opioid: 2095	Strong opioid: 3233 All opioid: 3233 Non-opioid: 3233	Strong opioid: 0.027 All opioid: 0.017 Non-opioid: 0.003
Dey[14]	2004	Total number and percentage of opioid and muscle relaxant prescription	-	196 (18.7)	-	213 (18.7)	p=0.99	196	1049	213	1138	0.014
Engers[78]	2005	Percentage and number of pain medication prescription per number of consultations	-	60% (198/328)	-	65% (188/288)	Not reported	198	328	188	288	-
Hoeijenbos[77] **	2005	Patient prescribed medications by doctor (% - total number at timepoint) at baseline and 52 weeks	41.5% (242)	11.7% (214)	37.8% (241)	9.9% (213)	Unclear	25	214	21	213	-

Table 2 (Continued)

Author	Year	Outcome	Baseline INT	Follow-Up INT	Baseline CON	Follow-Up CON	P-Value	n INT for analysis[a]	N INT for analysis	n CON for analysis	N CON for analysis	ICC[b]
Jensen[76]	2017	Mean and standard deviation of number of packages prescribed	Analgesics: 0.08 (0.31) NSAIDs: 0.29 (0.51) PPI: 0.03 (0.16) Opioids: 0.18 (0.47) Anti-epileptic: 0.01 (0.13) TCA: 0.02 (0.27)	Analgesics: 0.40 (1.49) NSAIDs: 0.57 (1.44) PPI: 0.36 (1.14) Opioids: 0.64 (2.57) Anti-epileptic: 0.07 (1.01) TCA: 0.12 (0.72)	Analgesics: 0.07 (0.26) NSAIDs: 0.36 (0.64) PPI: 0.05 (0.24) Opioids: 0.26 (0.67) Anti-epileptic: 0.03 (0.21) TCA: 0.02 (0.12)	Analgesic: 0.79 (2.10) NSAIDs: 0.69 (1.37) PPI: 0.35 (1.12) Opioids: 0.85 (2.40) Anti-epileptic: 0.30 (1.98) TCA: 0.21 (1.32)	Not reported	-	-	-	-	-

Table 2: **Outcomes of studies included in the review.**

* Bishop 2006: Author confirmed that 100% of participants were prescribed medications by the physician. The % reported is those that were guideline adherent prescriptions.

† Cherkin 2018: Imaging outcomes include all participants who visited clinics (not just those who provided patient reported outcomes. To get the raw numbers for medication prescription, the proportion of prescription per arm was multiplied by the total number of participants in each arm: INT 0.41×1163=476.83, CON 0.45×1473=662.85.

‡ Coombs 2021: We used the outcome results for 'Received any strong opioid medication' in the main analysis. Sensitivity analysis was conducted using the results for "Received any opioid medication' and 'Received any non-opioid medication' (see Table 3).

** Hoeijenbos 2005: To get the raw numbers for medication prescription, the percentage of prescription per arm was multiplied by the total number of participants in each arm: INT 0.117×214=25.04, CON 0.099×213=21.09. Note: data on percentage medications prescribed by the doctor were contained in the Appendix A Tables 1 and 2 of Hoeijenbos et al.

[a] The n INT/CON number refers to the raw number of imaging use or referral, while the N INT/CON refers to the total number of participants.

[b] ICC = intra-cluster correlation coefficient. ICC was used as per Cochrane guidelines to calculate the effective sample size from cluster randomised trials.The numbers used in analysis reported in the table are those from the primary analysis prior to ICC adjustment.

no funding or were funded by a public/not-for-profit organisation. One study[14] did not report funding sources.

Risk of bias and GRADE assessment

We assessed the risk of bias with the Cochrane Risk of Bias 2 (RoB 2) (Supplemental Digital Content 4). Four studies[14,75,76,80] were rated as having a low risk of bias and three[16,77,79] as having some concerns. For the individual risk of bias domains, all were considered low risk, except for missing outcome data, for which some concerns were present in three of six studies. The certainty of the evidence was rated for meta-analytic outcomes of medication referral or usage as low. Main reasons for downgrading the evidence were study quality and imprecision. Publication bias could not be assessed because the number of studies was fewer than 10.[70]

Quantitative analysis

Five studies[14,75,77,78,80] were included in the meta-analysis. For the primary analysis, we used a conservative ICC value of 0.014 for all studies that had no estimate, and for the other studies, we used the published estimate. For our primary outcome measure (medication prescription/usage), we estimated a non-significant OR: 0·94; [95% CI (0·77; 1.16), I^2 = 0%; 95% CI (0%; 79%); n =5 studies, GRADE: low] in favour of the intervention group (Figure 2). Transformation of the OR into a risk difference with a baseline risk of 27·8% gives a non-significant number fewer than 1000 = 11 with a 95% CI of [49; -30]. That means that of 1000 patients with low back pain, 278 of them typically receive medication. In contrast, with intervention 267 patients (11 patients less) per 1000 would still receive medication. This difference was not statistically significant.

We performed several sensitivity analyses (Table 3). First, we checked whether there were potential outliers or influential studies and what the impact of the removal of these studies would have on the overall summary effect size. We identified no outliers or influential studies. As we used the outcome "strong opioids" for our main analysis for the trial by Coombs et al.,[80] we performed two analyses with "all opioids" and "non-opioid medicine". No substantial differences were found for these analyses. With the fourth sensitivity analysis, we removed one study[78] because it only reported data for the number of consultations and not for the number of participants. We found that the exclusion of this study had no substantial impact on the effect size. Two further sensitivity analysis were done to check if different values of the ICC would change the results which was not the case in a substantial way (Table 3). We conclude that the results of the main analysis are robust regarding the performed sensitivity analyses.

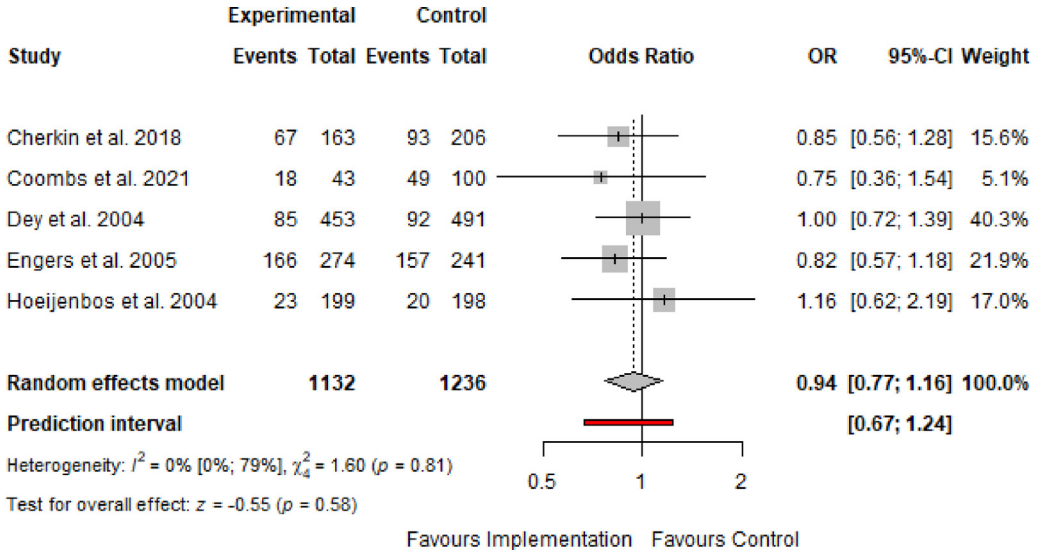

Figure 2. Forest plot for the meta-analysis investigating the effectiveness of implementation interventions vs control group (standard practice control group according to the EPOC guidelines) for the primary outcome measure medication prescription/usage. See also Table 1 for more detail on the included studies. Bishop 2006[79] was unable to be included in meta-analysis as all patients were prescribed medications, and the outcome reported was the guideline adherent percentage. Jensen 2017[76] could not be included as the mean and standard deviation of number of packages prescribed was reported and the data required for meta-analysis could not be acquired from the authors. Per Cochrane guidelines,[67] the data of cluster RCTs are transformed via the ICC prior to meta-analysis (see "Statistical analysis" for more detail). The raw outcome data from each study are located in Table 2.

Discussion

This review examined the effects of interventions on optimising medication prescription in patients with low back pain. All included studies were cluster RCTs and examined clinician-level interventions. Overall, based on the available data, we found low-quality evidence that the interventions had no impact on the outcomes of interest. Furthermore, individually, none of the studies reported an impact of the intervention on medication use or prescription.

Educating clinicians was a common component of the included interventions (five of six studies[14,75–78]), and several also included a passive dissemination component (i.e., providing clinicians with evidence-based clinical guidelines; four studies[14,77–79]). Two[76,77] studies conducted an audit and provided feedback, while another[76] redesigned medical record systems. Given these data, we contend that education and passive dissemination are, in isolation, likely ineffective approaches. One included study[77] that incorporated multiple reinforcement methods had a small positive effect on clinician adherence to guidelines in general, yet this finding was not specific to medication-based outcomes. This finding is consistent with prior systematic review work[81,82] summarising that continuing medical education is, alone, least-effective in changing health care provider behaviour. Currently, viable methods for optimising adherence to evidence-based guidelines for medication prescription remain elusive given the lack of effective interventions identified in our review. However, the use of a multimodal implementation framework may be of benefit in future study designs given improvements in non-medication-based adherence to guidelines.

To modify the behaviour of clinicians, managers, and administrators, it is necessary to understand the determinants underpinning current and desired behaviours,[82] which requires the use of evidence-based principles to ensure efficacy.[83] Interventions should consider multiple aspects that focus on different areas of current behaviour, rather than individual components alone. Frameworks such as the Theoretical Domains Framework[84] should also be considered when designing interventions given that accounting for cognitive, affective, social and environmental influences of behaviour will increase the likelihood of success.[84,85]

To inform future work, we also collated and extracted non-randomised prospective intervention studies (Supplemental Digital Content 5). However, this process only served to elicit one relevant study. This interrupted time-series study implemented clinician education and organisational/structural changes in a single-site design encouraged by the study-leader. Significant reductions in the proportion of patients prescribed medication were observed: 6% during intervention, 17% six months post intervention. This suggests that further exploration into interventions that implement organisational change are warranted. To date, this has been limited to interventions seeking to optimise imaging in LBP, which have tended to demonstrate greater effect sizes. A cluster RCT[16] showed

Outcome	Type ofsensitivity analysis	Excluded influential studies	Meta-analytic result of main analysis(OR [95% CI]I^2 [95%CI]number of studies)	Result of sensitivity analysis(OR [95% CI]I^2 [95%CI]number of studies)	Likely impact on meta-analytic result
Medication prescription/usage	Outlier and Influential Study Analysis	No outliers or influential studies identified.	0.94 [0.77; 1.16] I^2 = 0.0% [0.0%; 79.2%] N = 5	NA	NA
Medication prescription/usage	Coombs et al. was analyzed with data for all opioid medicines.	NA	0.94 [0.77; 1.16] I^2 = 0.0% [0.0%; 79.2%] N = 5	0.94 [0.77; 1.15] I^2 = 0.0% [0.0%; 79.2%]N=5	No substantial impact.
Medication prescription/usage	Coombs et al. was analyzed with data for non-opioid medicines.	NA	0.94 [0.77; 1.16] I^2 = 0.0% [0.0%; 79.2%] N = 5	0.98 [0.80; 1.19] I^2 = 0.0% [0.0%; 79.2%]N=5	No substantial impact.
Medication prescription/usage	Engers et al. was excluded because they had only data for the number of consultations and not for the number of participants.	Engers[78] et al.	0.94 [0.77; 1.16] I^2 = 0.0% [0.0%; 79.2%] N = 5	0.98 [0.77; 1.25] I^2 = 0.0% [0.0%; 84.7%] N = 4	No substantial impact.
Medication prescription/usage	ICC = 0.02 for studies not reporting an ICC	None.	0.94 [0.77; 1.16] I^2 = 0.0% [0.0%; 79.2%] N = 5	0.96 [0.78; 1.18] I^2 = 0.0% [0.0%; 79.2%] N = 5	No substantial impact.
Medication prescription/usage	ICC = 0.001 for studies not reporting an ICC	None.	0.94 [0.77; 1.16] I^2 = 0.0% [0.0%; 79.2%] N = 5	0.91 [0.79; 1.05] I^2 = 0.0% [0.0%; 79.2%] N = 5	No substantial impact.

***Table 3*: Sensitivity Analyses**

NA: Not Applicable

Risk Difference: baseline risk of 27•8% => Transformation of the OR into a risk difference with a baseline risk of 27•8% gives a non-significant number fewer than 1000 = 11 with a 95% CI of [49; -30]. (Main Analysis with strong opioids (Coombs et al.))

that guideline-based reminder messages attached to lumbar spine radiology reports reduced requests by 30-37% (2·17 to 3·07 percentage points). Moreover, prospective[28,31] and retrospective[40] interrupted time series studies have observed that checklist computer systems prior to referral[28] and fewer options for referral reasons to radiology[31,40] reduce imaging referral rates from 23%[28] to 47%.[31] Overall, on the basis of the available data, we argue that organisational changes (such as structural changes to patient flow, updated and enforced requirements for referral or prescription, embedding guideline-aligned approaches or reminders in electronic medical record systems and/or policy; e.g., funding model change) are likely key elements of an effective intervention to approach guideline-adherent medication use or prescription in the management of back pain.

Observations from our review suggest that randomised controlled cluster trials are warranted. This is due to these trials being the most feasible high-quality study design when compared to those where patients are randomised to different interventions. Within the organisational setting, interrupted time series and controlled before and after studies are also feasible, yet the omission of randomisation limits the possibility of drawing high-quality conclusions. Therefore, we recommend future implementation of randomised controlled cluster trials of interventions that focus on specific aspects of organisational change (e.g., patient flow, changes to medication prescription requirements and/or changes to electronic medical records systems). Furthermore, reporting of medication use and prescription in studies was inconsistent and meant that two studies could not be included in our quantitative synthesis. Per Cochrane guidelines,[86] studies should report the total number of prescriptions relative to the total number of appointments or patients, which would allow for meta-analysis. Moreover, cluster randomised controlled trials should[86] report the intra-cluster correlation co-efficient (ICC; a measure of the similarity of patients within clusters[87]) for their study to facilitate integration within meta-analysis. Finally, given potentially different medication recommendations[42] for radicular versus non-specific back pain, future studies should report on the numbers of patients with different types of back pain.

The strengths and limitations of the current review should be considered when interpreting findings. The review's key strength was the use of meta-analysis and further exploration of heterogeneity (i.e., outliers, outcome type, and assumptions relating to ICC values) in the main data estimates via sensitivity analyses. We build on a prior systematic review,[88] by implementing appropriate[86] sample size adjustments for included cluster RCTs. Moreover, we used more efficient[69] (i.e., better coverage probability and less bias estimating the between-study variance Tau) meta-analysis methods. Lastly, we did not include Bishop et al. 2006 in our meta-analysis, as contact with the authors confirmed that all participants were prescribed medications and the number presented represented percentage guideline-adherent prescriptions only.[79] Limitations primarily centred around the limited pool of included RCTs, with few showing a beneficial impact of the intervention on medication-based outcomes. Additionally, interventions were highly heterogeneous in design and implementation. Given these limitations, sub-group analyses on types of intervention were not possible. We excluded two studies from quantitative synthesis as we were unable to acquire the required data from the authors. One[79] reported no significant differences in appropriate medication utilisation, while the other[76] only used medication for cost-analyses. Given the lack of effect in at least one of the studies we do not believe this will alter the main conclusions but cannot conclusively rule it out. Due to the limited number of studies available in the literature, it was not possible to assess for funnel plot asymmetry, which may or may not indicate publication bias. As the included studies were not commercially funded and not small sized studies, GRADE recommendations[89] suggest publication bias is less likely.

In conclusion, this study found low-quality evidence that interventions did not impact medication prescription or usage in back pain. Overall, based on the included studies, approximately 278 patients with low back pain per 1000 patients are likely prescribed medications for their low back pain; of these, the interventions might prevent eleven of these patients (per 1000) being prescribed medication, with the effect being non-significant. Based on the RCT evidence, peer-to-peer education does not appear to lead to behaviour change. In additional literature, it appears that organisation-level interventions may more likely be effective. We recommend trialling such organisational interventions in future RCTs. We also provide recommendations for improving the reporting of cluster RCTs in the future.

Authors' contributions

Conceptualisation: DLB, PJO
Data curation: SDT
Formal analysis: TS
Funding acquisition: DLB
Investigation: ST, KS, CK
Methodology: DLB, PJO, SDT, CTM, PB, TS
Project administration: SDT, PJO, DLB
Resources: DLB, PJO, PB
Software: SDT
Supervision: DLB, PJO, CTM, PB
Validation: NA
Visualisation: TS
Writing – original draft: DLB, SDT, TS
Writing – review & editing: All
Approved final manuscript: All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication

Data sharing statement

Data underlying this study are available within the manuscript.

Declaration of Competing Interest

All authors declare they have no conflicts of interest.

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Supplementary materials

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