Effects of pharmacotherapy on sleep-related outcomes in adults with chronic low back pain: A systematic review and meta-analysis of randomised controlled trials

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Summary

Background Adults with chronic low back pain (CLBP) suffer impaired sleep. Medications for CLBP can impact sleep which in turn may influence treatment outcomes. This systematic review and meta-analysis examined the effects of pharmacotherapy (any type) on sleep in adults with CLBP.

Methods In this systematic review and meta-analysis, we searched PubMed, CINAHL, SPORTDiscus, PsycINFO, EMBASE, and CENTRAL from inception to 10 July 2022. Randomised controlled trials that investigated the effects of pharmacotherapy on sleep in adults with CLBP were included. Manual citation search of relevant systematic reviews and included studies were also conducted. Mean change from baseline for sleep outcomes (e.g., sleep quality, total sleep time, wake after sleep onset) was the effect of interest. Pairwise inverse-variance random effect meta-analysis was performed to impute pooled estimates (Hedges’ g or risk ratios). The Hartung-Knapp-Sidik-Jonkman method was used where there were ≤5 studies. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used for evaluating the certainty of evidence. This study was registered with PROSPERO (CRD42022309419).

Findings Assessment of 3959 records resulted in nine studies (n = 2927) being included. Pharmacotherapy for CLBP management had a small, yet unlikely clinically significant, effect on improving sleep in adults with CLBP, when compared to placebo (g [95% CI]: −0.23 [−0.37, −0.09], p = .0009; I² = 30.1%; n = 1433; studies: n = 8; GRADE: low). Notably, no eligible studies investigated the effect of sleep medications in this population, despite being within the scope of this review.

Interpretation Pharmacotherapy used to manage CLBP provided improvements in sleep in adults with CLBP. Given that these effects were small and unlikely clinically significant, clinicians could consider alternative treatments (e.g., non-pharmacological interventions) for managing sleep in adults with CLBP. However, low to very low certainty of evidence precluded strong conclusions. To improve certainty of evidence and confidence in the effect estimates, future research needs to use robust method to minimise bias. Additional research evaluating multiple sleep characteristics, using both validated objective and subjective measures, is also warranted to further investigate the influence of distinct sleep parameters.

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Introduction

Low back pain (LBP) remains the leading cause of disability worldwide, with 7.3% of the global population (~540 million people) experiencing activity-limiting LBP at any one time. Disease burden and direct and indirect economic costs attributed to LBP are substantial and are projected to increase in coming decades. Although most LBP recovers within six weeks of pain onset, a quarter of patients still experience LBP after three months and develop chronic LBP (CLBP; ≥12 weeks). Impaired sleep (e.g., difficulties falling asleep, wake after sleep onset, unrefreshing sleep) is common amongst adults with CLBP (>50%). Adults with CLBP who frequently experience some form of impaired sleep have a 13–60% lower probability of recovery from LBP at 10-year follow-up compared to those without impaired sleep. There is evidence to suggest a bidirectional relationship between sleep and pain as impaired sleep exacerbates pain intensity and vice versa. Therefore, identifying strategies to manage sleep impairments in adults with CLBP is critical. Prior evidence in patients with chronic pain (e.g., chronic diabetic peripheral neuropathy, rheumatoid arthritis, heterogenous chronic pain population) indicated that effects of pharmacotherapy on sleep and pain varied by pain conditions, medication types, sleep characteristics (e.g., sleep latency, total sleep time, sleep efficiency), and whether measures are subjectively or objectively collected. Recent evidence in adults with CLBP indicated that opioid therapies improved sleep quality and reduced sleep disturbance, although an estimate as to whether an intervention is better than no treatment (true control) were not quantified. This limited the strength of the findings.

Added value of this study

We conducted a systematic search in PubMed, CINAHL, SPORTDiscus, PsycINFO, EMBASE, and CENTRAL from inception to 10 July 2022. Randomised controlled trials that investigated the effects of pharmacotherapy on sleep in adults with CLBP were included. Our meta-analysis indicated that pharmacotherapy for CLBP management, when compared to placebo, had a small, yet unlikely clinically significant, effect on improving sleep in adults with CLBP. However, low to very low certainty of evidence precluded strong conclusions. Notably, no eligible studies investigated the effect of sleep medications in this population, despite being within the scope of this review.

Implications of all the available evidence

Our results informed clinicians that, given effects of pharmacotherapy on improving sleep were small and unlikely clinically significant, alternative treatments (e.g., non-pharmacological interventions) for managing sleep in adults with CLBP warrant investigation. To improve certainty of evidence and confidence in the effect estimates, future research needs to use robust method to minimise bias.

Additional research evaluating multiple sleep characteristics, using both validated objective and subjective measures, is also warranted to further investigate the influence of distinct sleep parameters.

Research in context

Evidence before this study

Impaired sleep (e.g., difficulties falling asleep, wake after sleep onset, unrefreshing sleep) affects more than 50% of adults with chronic low back pain (CLBP). Evidence suggests a bidirectional relationship between sleep and pain, as impaired sleep exacerbates pain intensity and vice versa. Therefore, identifying strategies to manage sleep impairments in adults with CLBP is critical. Prior evidence in patients with chronic pain (e.g., chronic diabetic peripheral neuropathy, rheumatoid arthritis, heterogenous chronic pain population) indicated that effects of pharmacotherapy on sleep and pain varied by pain conditions, medication types, sleep characteristics (e.g., sleep latency, total sleep time, sleep efficiency), and whether measures are subjectively or objectively collected. Recent evidence in adults with CLBP indicated that opioid therapies improved sleep quality and reduced sleep disturbance, although an estimate as to whether an intervention is better than no treatment (true control) were not quantified. This limited the strength of the findings.

Keywords: Low back pain; Sleep; Pharmacotherapy; Systematic review; Meta-analysis

medications used for pain can have effects on sleep, which vary by medication types, sleep characteristics (e.g., sleep latency, total sleep time, sleep efficiency), and whether measures are subjectively or objectively collected. For example, an antidepressant (duloxetine), when compared to placebo, decreased self-reported sleep continuity (total sleep time and sleep efficiency) in patients with chronic diabetic peripheral neuropathy, while anticonvulsant (pregabalin) increased sleep continuity in the sample. These effects were not different to placebo when sleep was measured objectively via polysomnography. Medications used to manage sleep (e.g., sleep medications such as benzodiazepines, or antidepressants such as trazodone) are also often taken by patients with chronic pain, and effects on sleep and pain vary by types of medications and pain conditions. For example, a review reported that, diazepam (sleep medication) decreased pain in rheumatoid arthritis, but a combination of tenoxicam and bromazepam (both benzodiazepines) was not superior to placebo. Considering medications are often associated with adverse effects (e.g., nausea and vomiting from opioids, somnolence and fatigue from benzodiazepines) and increased risk of misuse or overdose, it is important that clinicians understand implications of all the available evidence on health factors (e.g., sleep in...
patients with CLBP) which may influence treatment outcomes. Additionally, understanding multitargeting properties of a medication can reduce fragmentation of care (where a single symptom is treated with a single medication) and the risks associated with concurrent use of multiple medications. 

Furthermore, prior findings based on heterogeneous or different chronic pain conditions may have limited generalisability to CLBP, given varying chronic pain conditions can respond differently to the same medication and this can influence the sleep and pain relationship.

A recent systematic review of randomised controlled trials (RCT) that examined effects of pharmacotherapies (opioid and non-opioid) on sleep in adults with CLBP indicated that opioid therapies improved sleep quality (standardised mean difference [SMD]: 0.27; 95% CI: 0.17–0.36) and reduced sleep disturbance (SMD [95% CI]: 0.32 [0.25–0.40]); while the effects of non-opioid medications on sleep were not quantified due to data paucity. The scope of this previous review, however, included studies with therapeutic comparators (e.g., studies comparing different medications), as well as randomised withdrawal studies in which all participants received medication before treatment responders were randomised to either an active treatment or a control arm. Therapeutic comparators and withdrawal studies, although often employed for ethical reasons to avoid depriving participants of treatment or by shortening the placebo time, do not provide an unbiased estimate as to whether an intervention is better than no treatment (true control). Additionally, to understand how changes in sleep influence CLBP after an intervention, pain intensity and back-related disability (difficulties in executing daily living activities, e.g., sitting, walking) outcomes (which were not included in the previous review) should also be investigated. To promote specificity and comprehensiveness, the current review aimed to examine the effects of pharmacotherapy (of any type) on sleep in adults with CLBP when compared with non-therapeutic control, and associations between changes in sleep, changes in pain intensity, and changes in back-related disability (difficulties in executing daily living activities, e.g., sitting, walking) in this population.

**Methods**

This review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement and was registered prospectively with PROSPERO (CRD42022309419). For a list of amendments to information registered via PROSPERO, see Table S1.

**Search strategy**

Six electronic databases (PubMed, CINAHL, SPORTDiscus, PsycINFO, EMBASE, and CENTRAL) were searched from inception to 10 July 2022 (Table S2). The search terms and search strategy were adapted from prior work and Cochrane guidelines. To locate additional studies, we searched for relevant systematic reviews via Cochrane Database of Systematic Reviews (search terms: ‘back pain’, ‘sleep’; limits: none) and Google Scholar (search terms: ‘back pain’, ‘sleep’, ‘systematic review’; limits: previous 10 years and first 100 results). The reference lists of relevant systematic reviews and included articles (backward citation tracking), as well as the reference lists of articles citing an included study (forward citation tracking via Scopus) were also manually screened for potentially relevant articles.

**Selection criteria**

Inclusion criteria followed the Population, Intervention, Comparators, Outcomes, Study type (PICOS) framework. Populations were adults (aged ≥18 years) with CLBP (pain between lower rib margins and buttock creases which persisted for ≥12 weeks). Radicular CLBP (with nerve root symptoms) and non-specific CLBP (without specific pathological or neurological cause) were included. Interventions were any pharmacotherapy regardless of reasons for prescription. Comparators were true control (no treatment), waitlist control (delayed treatment), placebo treatment, usual care, or other comparators without active therapeutic components. Primary outcomes were variables related to sleep, sleep characteristics (e.g., sleep quality, total sleep time, wake after sleep onset), and sleep disorders (e.g., insomnia). Secondary outcomes were pain intensity, back-related disability (difficulties executing daily living activities, e.g., sitting, walking), adverse events, and serious adverse events (as categorised by individual studies). Subjectively or objectively measured outcomes using validated or non-validated instruments were included. Study types were parallel (individual or cluster) and crossover-designed RCTs.

Exclusion criteria were as follows: (1) specific CLBP (due to specific disease or spinal pathology e.g., fracture or malignancy); (2) fatigue outcomes (e.g., physical/mental exhaustion, overwhelming/sustained tiredness), given these symptoms were not necessarily related to sleep; (3) quasi RCTs and non-RCTs, given they do not offer an unbiased estimate of the effect size; (5) randomised withdrawal study (i.e., all participants received medication before treatment responders were randomised to either an active treatment or a control arm), given omitting results from non-responders could exaggerate treatment effects; (6) non-English articles, given exclusion of these data does not significantly impact effect size estimates; and (7) grey literature (i.e., non-peer-reviewed articles).

All search results were screened using Covidence (Veritas Health Innovation, Melbourne, Australia) to
automatically remove duplicates. Two independent reviewers (EAC, ARM) evaluated titles/abstracts and subsequently full-text articles against pre-defined eligibility criteria. Data were extracted by two reviewers (EAC, SDT). Disagreements were settled via discussion or adjudication (PJO). For continuous data, we extracted the mean change from baseline (difference between pre- and post-intervention outcome data), pre- and post-intervention mean, and relevant standard deviation (SD). For dichotomous outcome data, we extracted the number of cases. When it was not possible to extract or impute the required data, we requested the information from authors three times over a 4-week period. When outcomes were reported only in figures (rather than as numerical data within text), data were extracted using ImageJ (National Institutes of Health, Maryland, United States of America) following established methods.

**Data analysis**

To estimate the pooled effect for continuous data, standardised mean difference (SMD; Hedges’ g, with 95% CI) between groups was used to allow comparisons between studies (given different outcome measures were used across studies to evaluate similar constructs). The primary measure of effect was mean change from baseline. Where change data could not be imputed from published data, post-intervention mean and SD were used in the meta-analysis. Combining follow-up and change data is valid in meta-analysis as there are no relevant differences between follow-up and change data (i.e., SMD differences are scattered around the null). Hedges’ g tends to be less biased than Cohen’s d, especially in studies with a small sample size (n < 20). To interpret the effect size, the following thresholds were used: g = 0.2 (small effect), g = 0.5 (medium effect), and g = 0.8 (large effect). All sleep outcomes (e.g., sleep quality, total sleep time, insomnia, sleep impairments) were pooled in the meta-analysis to provide an effect estimate for sleep. Where data were available, pooled effects were also estimated for different sleep characteristics.

For dichotomous outcome data, risk ratio (RR) values were used to determine the likelihood of a particular outcome (e.g., adverse events) occurring as odd ratios may exaggerate the effect size when events are common (>10%). RR values > 1 indicated a higher risk of an event occurring in the treatment group. Prior to estimating pooled effects, reverse-scaled means were multiplied by –1 to ensure the direction of effect was the same across studies. Missing values for mean, mean change, or SD were imputed (e.g., using pre-/post-intervention mean, standard error [SE], p-value) using Cochrane formulae. To prevent unit of analysis errors when a study had more than one eligible group (e.g., three-arm RCT), data from homogenous groups (e.g., same medication but different dose) were pooled as per Cochrane recommendations. Where it was not appropriate to pool data (e.g., different medications), the number of participants in the control was divided proportionally prior to inclusion in meta-analysis. This method ensured that a unit of data (e.g., participants, outcomes) was not included more than once in the same pairwise comparison. For crossover RCTs, the number of participants allocated to each treatment block was used in meta-analysis.

To account for heterogeneity when determining the effect of pharmacotherapy, pairwise inverse-variance random effect meta-analysis was performed to impute pooled estimates. Where there were ≤5 studies in a pairwise analysis, the Hartung-Knapp-Sidik-Jonkman method was used to estimate the pooled effect as it produces more adequate error rates where the number of studies is small. The 95% prediction interval was also estimated if there were ≥5 studies in a pairwise analysis in order to determine a range of potential values which could be estimated in future trials.

Heterogeneity was assessed for all pairwise analyses via the $I^2$ statistic and prediction interval. Where a heterogeneity was suspected (e.g., different directions of effects across studies, minimal overlap of 95% CI, $I^2 ≥ 30\%$, wide dispersion of prediction interval in comparison to 95% CI), we explored the causes of heterogeneity through subgroup analyses when there were ≥5 studies in each subgroup with a characteristic that could influence results (e.g., medication classes, CLBP conditions), or through meta-regression analyses when there were ≥10 studies for each covariate. Differences in effect estimates between subgroups were considered relevant if there was a change in the direction of result (from effect to no effect and vice versa) or SMD ≥0.3 (equal to the difference between small and medium or medium and large effect size).

We assessed publication bias via visual inspection of funnel plots and, where there were ≥10 studies in a pairwise analysis, via the Egger’s test. Sensitivity analyses examined the influence of outliers (via Galbraith plots where $I^2 ≥ 40\%$) and influential studies (via leave-one-out meta-analysis). All statistical analyses were conducted in Stata 17.0 (Stata Corp, College Station, Texas, United States of America). An alpha of 0.05 was adopted for all analyses.

Details of individual studies were tabulated and grouped by medication classes and then by year of publication (reverse chronological order). Results from meta-analysis were presented in forest plots structured by the effect size (small to large, favouring treatment) to indicate the order of studies which influenced the magnitude and direction of the pooled estimates.

For clinical interpretation, the minimal clinically important difference (MCID) between groups was assessed for sleep, pain intensity, and back-related disability. To assess the MCID, the pooled effect estimates (Hedges’ g) or the re-expressed value was
evaluated against the recommended threshold\textsuperscript{58}: sleep (MCID \geq SMD 0.5),\textsuperscript{39} visual analogue scale (VAS) for pain intensity (MCID \geq 20/100 points),\textsuperscript{40} and Oswestry Disability Index for back-related disability (MCID \geq 11/100 points).\textsuperscript{11}

Assessments of risk of bias and certainty of evidence
Risk of bias and certainty of evidence were assessed by two reviewers (EAC, SDT) and disagreements were adjudicated (PJO). We used Version 2 of the Cochrane risk of bias tool for randomised trials (RoB-2)\textsuperscript{52} and the certainty of evidence for each outcome was assessed according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.\textsuperscript{19} See Table S3 for criteria used in the GRADE approach.

Role of the funding source
Lead author (EAC) was awarded the Summer Research Scholarship from the Appleton Institute (Central Queensland University, Australia) to support the completion and publishing of this review. The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. EAC, PJO, and GEV had full access to all data used in the study and had final responsibility for the decision to submit for publication.

Results
Search results and study characteristics
There were 3959 records (after removing 1322 duplicates) included in the initial title/abstract screening and 369 in the full-text screening. See Fig. 1 for the PRISMA flow diagram summarising search results. After full-text screening, nine studies (n = 2927) met the eligibility criteria.\textsuperscript{54–62} See Table S4 for a select list of excluded studies with reasons. Of these, eight studies (n = 1946) were included in meta-analysis.\textsuperscript{54–58,60,62} One study was excluded from meta-analysis as the primary outcome (sleep) was insufficiently reported to allow data pooling.\textsuperscript{62} Details of each study are presented in Table 1. We contacted authors of all studies requesting missing data and/or clarification on published results. Responses were received for three studies.\textsuperscript{57,59,62} Eight studies involved data imputation (See Table S5 for details of data handling).\textsuperscript{55–59,60,62}

Mean participant age was 54 (SD = 13) years and 53% were female (n = 1717; range: 27–75%; median 57%; interquartile range: 53–61%). Mean pain intensity at baseline was reported in six studies (n = 2405; re-expressed in VAS-100 [SD]: 70.04 [15.56],\textsuperscript{55–58,60,62} indicating borderline severe pain).\textsuperscript{11} Mean pain duration at baseline was reported in six studies (n = 1,521, M = 6 years; range: 9–14 years).\textsuperscript{54,55,57,58,60,62} No studies specifically investigated participants with comorbid conditions as population of interests.

For a list of medication classes and interventions, see Table 1. For intervention details, see Table S6. All studies allowed the use of specific rescue medications for the management of breakthrough pain (details in Table S7). No eligible studies investigated sleep medications in adults with CLBP, despite being within the scope of this review.

All studies used placebo control. Two studies indicated that placebo followed the same dose titration as the treatment group.\textsuperscript{54,62} The remaining seven studies indicated ‘placebo’ or ‘matching placebo’ with no further details provided.\textsuperscript{55–61}

Outcome measures are summarised in Table 1. Measurement instruments used in all included studies were self-reported measures. To measure sleep outcomes, seven studies (n = 2041) used multiple-item questionnaires: Pain and Sleep Questionnaire (PSQ),\textsuperscript{57,58,62} NRS to evaluate trouble falling asleep and trouble staying asleep;\textsuperscript{61} a sleep questionnaire to evaluate sleep latency, time slept, number of awakenings, and sleep quality;\textsuperscript{62} and Athens Insomnia Scale to evaluate insomnia.\textsuperscript{54,55} Two studies (n = 886) used a single-item from a questionnaire to measure sleep outcomes: PSQ-sleep quality to evaluate sleep quality\textsuperscript{62} and Oswestry Disability Index-sleeping to evaluate sleep disturbance.\textsuperscript{59} Additionally, data for several sleep characteristics were reported: sleep quality (n = 1783; studies: n = 4),\textsuperscript{57,58,60,62} total sleep time (hrs; n = 1142; studies: n = 3),\textsuperscript{58,60,62} insomnia severity (n = 640; studies: n = 2),\textsuperscript{55} trouble falling asleep and trouble staying asleep (wake after sleep onset; n = 420; studies: n = 4),\textsuperscript{56,58,61,62} and the use of medication to aid sleep (n = 240; studies: n = 3).\textsuperscript{58,60,62} Several secondary outcomes were also reported: pain intensity (all studies); back-related disability (n = 1766; studies: n = 7),\textsuperscript{54,55,57,58,60,62} adverse events (all studies), and serious adverse events (all studies). A list of adverse events and serious adverse events reported by \geq 10% of participants is presented in Table S10.

Six studies (n = 2687) were parallel-RCTs (two-arm: n = 3 studies),\textsuperscript{54,55,57} three-arm: n = 1 study,\textsuperscript{60} four-arm: n = 1 study,\textsuperscript{54} five-arm: n = 1 study.\textsuperscript{61} Three studies (n = 240) were crossover two-arm RCTs.\textsuperscript{54,55,62}

All studies received funding from pharmaceutical companies who supplied medications for the trials. Authors of seven studies (n = 2765) declared conflicts of interest, which were mainly associated with current or previous employment, shareholding, consultancy, or financial benefits with funders.\textsuperscript{54,55,57,60,62} Two studies (n = 162) did not confirm the presence or absence of conflicts of interest.\textsuperscript{54,61} Details of source of funding and conflicts of interest are presented in Table S9.
Risk of bias in included studies
Risk of bias assessments for individual studies is shown in Figure S1. In summary, no studies had low risk of bias, two studies had some concerns (22% of studies; 8% of participants, n = 162), and seven studies had high risk of bias (78% of studies; 92% of participants, n = 2765). For summary assessments of each risk of bias domain, see Figure S2 (by number of studies) and Figure S3 (by number of participants).

Effects of interventions and certainty of evidence
The summary of findings from pairwise meta-analysis and certainty of evidence assessments (GRADE) is presented in Table 2.

Primary outcomes: sleep
See Table 2, Fig. 2 (sleep), and Fig. 3 (sleep characteristics) for the results from meta-analysis and GRADE assessments for sleep outcomes. Effect estimates for sleep were based on actual or imputed change-from-baseline data, except for Christoph whereby post-intervention data were used in the meta-analysis per established recommendations (as there were insufficient data to impute post-intervention SD). For sleep characteristics, effect estimates were also based on actual or imputed change-from-baseline data, except for three studies whereby post-intervention data were used.

Sensitivity analysis detected no influential studies for sleep (Figure S4). Visual inspection of the funnel plot did not detect potential publication bias for sleep (Figure S6), although quality of evidence was downgraded by one level for publication bias as all studies were industry funded.

For specific sleep characteristics, sensitivity analysis detected one influential study (opioids) for sleep quality and one (opioid) for use of medication to aid sleep (Figure S5). For sleep quality, when the influential study (with two different opioid experimental arms) was omitted, the pooled effect estimate changed from pharmacotherapy having a small effect on sleep quality...
### Table 1: Study characteristics.

| Medication classes | Antidepressant | IMiD | Opioid |
|--------------------|----------------|------|--------|
| Author (year)      | Skljarevski 2010 | Skljarevski 2009 | Manning 2017 |
| n randomised       | 236 (613/39%)   | 404 (57/43%)   | 180 (56/44%) |
| Control group (n randomised) | Placebo (n = 121) | Placebo (n = 117) | Placebo (n = 91) |
| Treatment duration | 13 weeks        | 13 weeks       | 12 weeks   |
| Type of CLBP       | Non-specific    | Non-specific   | Radicular  |
| Mean age, yr (SD)  | 51 (14)         | 54 (14)        | 55 (13)   |
| Average pain duration | 9 years        | 12 years       | 12 years  |
| Average pain intensity at baseline | NR            | Moderate (6.04/10) | Moderate (6.8/10) |
| Attrition (Exp, Con) | 23% (31, 23)   | 20% (102, 35)  | 22% (25, 15) |
| Country of study   | Brazil, France, Germany, Mexico, and Netherlands | USA | USA |
| Primary outcome measures |
| Sleep measure      | AIS             | AIS            | NRS-10d |
| Insomnia symptom severity | Trouble falling asleep; WASO | Sleep quality | Sleep quality; TST; trouble falling asleep; WASO; medication use to aid sleep |
| Secondary outcome measures |
| Pain intensity     | BPI (average pain) | BPI (average pain) | NRS-10 |
| Back-related disability | RMDQ           | RMDQ           | NR    |

Note: AIS = Athens Insomnia Scale; BPI = Brief Pain Inventory; CLBP = chronic low back pain; Con = control group; Exp = experimental group; IMiD = immunomodulating drug; NP = not reported; NRS = numeric rating scale; ODI = Oswestry Disability Index; PGIC = Patient’s Global Impression of Change; PGI-I = Patient’s Global Impressions of Improvement; PSQ = Pain and Sleep Questionnaire; RCT = randomised controlled trial; RMDQ = Roland-Morris Disability Questionnaire; TST = total sleep time; WASO = wake after sleep onset. *The entire study was omitted from meta-analysis as the primary outcome data (sleep) was insufficiently reported to allow pooling. **This drug was under development (not yet approved by the United States Food and Drug Administration at the time of the current review and may not be available beyond the trial setting. This reflected the inclusion criteria of the study as the actual CLBP duration was not reported. †Data involved imputations (e.g., imputing missing SD or post-intervention effect within group, pooling data, reversing scale) or extraction from images. ‡Post-intervention data for each group was extracted (as change from baseline data was not available and unable to be imputed) and were pooled with change from baseline data in meta-analysis.
### Articles

| Outcome                        | n analysed | Effect estimate | P-value MOID | Implied effect | Risk ratio [95% CI] | Grade | Sensitivity analysis result | Prediction interval | I² (%) |
|--------------------------------|------------|-----------------|--------------|----------------|---------------------|-------|----------------------------|---------------------|--------|
| Sleep                          | 8          | 1.03 (−0.37, −0.09) | <.0009       | 0.915          | Not met (SMO −0.23) | Grade | No change                  | −0.54, 0.08 | 30.1%  |
| Sleep quality                  | 3          | −0.39 (−0.66, −0.12) | <.0001       | 0.999          | Not met (SMO −0.39) | Grade | No change                  | −0.54, 0.08 | 30.1%  |
| Intraocular pressure soreness  | 2          | 0.20 (0.05, 0.35)   | <.0001       | 0.925          | Not met (SMO 0.2)  | Grade | No change                  | −0.54, 0.08 | 30.1%  |
| Total sleep time               | 2          | 0.02 (−0.10, 0.14)  | <.0001       | 0.983          | Not met (SMO 0.2)  | Grade | No change                  | −0.54, 0.08 | 30.1%  |
| Trouble falling asleep         | 4          | 0.11 (−0.15, 0.37)  | <.0001       | 0.925          | Not met (SMO 0.2)  | Grade | No change                  | −0.54, 0.08 | 30.1%  |
| Back-related disability        | 7          | 0.28 (0.01, 0.55)   | <.0001       | 0.953          | Not met (SMO 0.2)  | Grade | No change                  | −0.54, 0.08 | 30.1%  |
| Use of pain medication         | 3          | −0.10 (0.42, 0.21)  | <.0001       | 0.987          | Not met (SMO 0.2)  | Grade | No change                  | −0.54, 0.08 | 30.1%  |
| Pain intensity                 | 8          | −0.25 (−0.35, 0.15) | <.0001       | 0.999          | Not met (SMO −0.3) | Grade | No change                  | −0.54, 0.08 | 30.1%  |
| Back-related disability        | 7          | 0.28 (0.01, 0.55)   | <.0001       | 0.953          | Not met (SMO 0.2)  | Grade | No change                  | −0.54, 0.08 | 30.1%  |

Note: Bold texts indicate significant results. Negative g-values indicate the result favoured the experimental group (i.e., pharmacotherapy resulted in better health outcomes), except for total sleep time where negative g-values indicated the result favoured placebo.

Secondary outcomes: pain intensity, back-related disability, adverse events, and serious adverse events

See Table 2 and Figure S7 for the results from meta-analysis and GRADE assessments for secondary outcomes. Effect estimates for pain intensity and back-related disability were based on actual or imputed change-from-baseline data. Effect estimates for adverse events and serious adverse events were based on the number of events.

Statistical heterogeneity for all secondary outcomes was either absent or low ($I^2 < 40\%$ and 95% CI for individual studies mostly overlapped), indicating low between-study variance across studies. Sensitivity analysis detected no influential study for secondary outcomes (Figure S8). Visual inspection of funnel plots detected potential publication bias for pain intensity and back-disability but not for adverse events or serious adverse events (Figure S9), although quality of evidence was downgraded by one level for publication bias for all secondary outcomes, as all studies were industry funded.

For the study omitted from all meta-analysis due to insufficiently reported primary outcome data, both opioids (tapentadol and oxycodone) significantly reduced pain intensity when compared to placebo ($p < .001$).
Subgroup analysis

A subgroup analysis was conducted to estimate the effect of opioids, given there were \( \geq 5 \) studies investigating this medication class. Results indicated that there was no relevant change (i.e., change in the direction of result or SMD change of \( \geq 0.3 \)) on all outcomes (Table S10).

Discussion

The current systematic review included the first meta-analysis to examine the effects of pharmacotherapy on sleep in adults with CLBP. Low to very low quality evidence indicated that pharmacotherapy used primarily for pain management (pain medications) slightly...
improved sleep by improving sleep quality, and that this effect on sleep was associated with a small reduction in pain intensity and back-related disability. These effects on sleep, pain intensity, and back-related disability, however, did not meet MCID and therefore are unlikely to be clinically meaningful. Very low quality evidence indicated that pain medications had no effect on many sleep characteristics (insomnia symptom severity, total sleep time, trouble falling asleep, trouble staying asleep, or use of medication to aid sleep) in this population. The risk of adverse events was higher in pharmacotherapy groups, while the risk of serious adverse events was no different to placebo. Risk of bias, inconsistency, and imprecision of results reduced our confidence in effect estimates. Notably, there were no eligible studies investigating sleep medications, despite being within the scope of this review. Low to very low certainty of evidence reduced confidence in the effect estimates and precluded strong conclusions.

Our findings were similar to results of other meta-analyses that investigated the effects of pharmacotherapy in patients with chronic pain. For example, in one meta-analysis of eight RCTs, opioids improved sleep quality (SMD [95% CI]: 0.27 [0.17–0.36]) and reduced sleep disturbance (SMD [95% CI]: 0.32 [0.25–0.40]) in adults with CLBP.6 These small effects were comparable to our results albeit differences in the review criteria (i.e., previous review included randomised withdrawal studies and comparators with therapeutic components while our review excluded them) and the data of interest (i.e., previous review used data from per-protocol analysis while our review used data from intention-to-treat analysis). In another review involving patients with chronic non-cancer pain, opioids had a small effect in improving sleep quality VAS-100 [95% CI]; 3.42 points [1.58, 5.26]; n = 6585) as well as reducing pain (VAS-10 [95% CI]: −0.69 points [−0.82, −0.56], n = 16,617) when compared to placebo.45 Similarly, in another meta-analysis (n = 1427), antidepressants provided a small reduction in sleep disturbance (SMD [95% CI]: −0.32 [−0.46, −0.18]) and pain in fibromyalgia syndrome (−0.43 [−0.55, −0.30] respectively) when compared to placebo.44 These results together with our analysis indicated that pharmacotherapy used primarily for pain management could concurrently improve sleep and pain in chronic pain including CLBP, albeit to a small degree. This finding supported the notion that sleep and CLBP are associated,44 although causality cannot be assumed based on the existing study design and we could not estimate how changes in sleep and pain intensity influence each other (insufficient studies <10) to allow meta-regression. Our finding also indicated that small improvement in sleep after pharmacological pain intervention was associated with a small improvement in back-related disability in adults with CLBP. Our finding is consistent with prior evidence which suggested that sleep is moderately correlated with back-related disability in patients with chronic pain (r = 0.42).57

When investigating effects of pharmacotherapy on each different sleep characteristics, the findings from our review indicated that pain medications had a small effect only on subjective sleep quality. Thus, improving subjective sleep quality may be particularly crucial to reduce pain intensity and back-related disability in adults with CLBP. However, it is important to note that we did not find eligible studies which required participants to have comorbid sleep impairments at baseline or studies which investigated sleep medications. Additional studies are needed to investigate potential modifying effects of comorbidity and intervention focus (pain-based vs. sleep-based).

For clinical implications, our analysis demonstrated that pharmacotherapy used to manage CLBP did not achieve clinically meaningful improvements in sleep in adults with CLBP when compared to control. Additionally, in studies which investigated sleep outcomes, pain medications were associated with increased risk of adverse events and lack of clinically relevant improvements in pain intensity and back-related disability in this population. Considering certain medications such as opioids increase risk of drug dependency, abuse, and tolerance,49 adjunct or alternative treatments, including non-pharmacological interventions, to address sleep impairments in this population warrant investigation. For example, non-pharmacological interventions, such as cognitive behavioural therapy for insomnia, are recommended as the first-line treatment option for these forms of impaired sleep.55,69 A meta-analysis estimated that cognitive behavioural therapy for insomnia moderately improved sleep quality (d [95% CI]: 0.67 [0.38, 0.95]; n = 510) and slightly reduced pain in patients with chronic non-cancer pain (including CLBP; 0.18 [0.0, 0.3]; n = 257).69 Other non-pharmacological interventions which may be beneficial in this population include relaxation therapy and mindfulness-based exercise, since in another meta-analysis (n = 1787), mindfulness-based exercise had a small effect in improving sleep quality (SMD [95% CI]: −0.48 [−0.95, −0.01]) while greatly reducing musculoskeletal pain (−0.88 [−1.02, −0.74]) in people with chronic illnesses including lumbar disc herniation and radiculopathy.71 In line with the evidence-based approach, clinical practice guidelines should prioritise high-value care and focus on educating clinicians and patients about realistic benefits and risks associated with pharmacotherapy. Additionally, clinicians treating patients with comorbid disorders should ensure each disorder is assessed and managed without assuming one condition is secondary to another. For example, comorbid insomnia in CLBP population warrants an assessment independent to pain-based interventions for CLBP.

Strengths of the current review included the: (1) focus on RCTs which minimise the risk of bias when
estimating effects, (2) use of Hartung-Knapp-Sidik-Jonkman method to reduce risk of false positives due to heterogeneity, (3) inclusion of subgroup and sensitivity analyses to examine robustness of our results, and (4) inclusion of prediction intervals to indicate potential estimate in future studies.

Limitations included insufficient studies investigating variables which may be effect modifiers. For examples, sleep medications, CLBP conditions, and sleep characteristics (e.g., sleep efficiency, sleep onset latency, symptoms of other sleep disorders) could influence sleep outcomes in CLBP population. Lack of data on these parameters may contribute to an incomplete assessment of the relationship between pharmacotherapy and sleep in adults with CLBP and limit generalisability of the results. Second, studies included in this review only used subjective measures of sleep. Given possible discrepancies between subjectively and objectively measured sleep, the lack of studies using objective sleep measure may further contribute to the incomplete assessment. Third, the use of non-validated single-item questionnaires in two studies to measure incomplete assessment. Third, the use of non-validated objective and subjective measures, is also warranted to further investigate the influence of distinct sleep parameters.

Contributors
Study conceptualisation: EAC, PJO, GEV, DST, SAF, HS, PB, DFE, ARM, DLB; Study design: EAC, PJO, GEV, DST, SAF, HS, PB, DFE, ARM, DLB; Data search: EAC, PJO; Data screener: EAC, ARM; Data extraction: EAC, SDT; Statistical analyses: EAC, PJO; Risk of bias assessment: EAC, SDT; Quality of evidence assessment: EAC, PJO; Adjudicator: PJO, GEV; Write-up: EAC, Editors: PJO, GEV, SDT, SAF, HS, PB, DFE, ARM, DLB. Authors who have accessed and verified the underlying data: EAC, SDT; All authors have approved the final manuscript.

Data sharing statement
The data and the code used to analyse data for this study were presented in Appendix S4.

Declaration of interests
All authors declare that they have no competing interests.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2022.101749.

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