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# The short-term effects of opioid and non-opioid pharmacotherapies on sleep in people with chronic low back pain: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Chronic low back pain (LBP) shares a bidirectional relationship with sleep disturbance. Analgesics are often used for chronic LBP management however, the effects on sleep have not been thoroughly reviewed. This systematic review and meta-analysis assessed the effect of opioid and non-opioid medications on sleep in people with chronic LBP. Electronic databases were searched for randomized controlled trials which resulted in 16 eligible articles (14 studies). Sleep measures were secondary outcomes, with one study assessing sleep objectively and all other studies reporting subjective sleep. Twelve studies assessed opioid therapies whilst two studies examined non-opioid therapies. Eight studies (all opioid) were included in meta-analyses of sleep quality and sleep disturbance comparing opioid therapies with placebo-controls. Opioid therapies significantly improved sleep quality (SMD = 0.27, 95% CI: 0.17–0.36) and reduced sleep disturbance (SMD = 0.32, 95% CI: 0.25–0.40) compared to placebo-control. These findings show a clear improvement in subjective sleep associated with opioid therapies however, future studies should examine objective sleep outcomes which remain largely unexplored in chronic LBP. Addressing both pain and sleep together is important for effective management of comorbid conditions of chronic LBP and sleep disturbance due to their bidirectional relationship.



## 1. Introduction

Chronic low back pain (LBP) is one of the most prevalent chronic pain conditions directly affecting over half a billion people worldwide [1–5]. In the US, combined healthcare spending for treating low back and neck pain costed an estimated US$134.5 billion during 2016 making them the most expensive health conditions [6]. In Australia, back problems produce an estimated annual cost of AU$4.8 billion and provide the most common health condition preventing workforce engagement for people aged 45–64 years of age [7]. Chronic LBP is characterized by pain in the lumbosacral region lasting at least 3 months in duration [8]. Not only is chronic LBP characterized by the perception of pain, but it is also associated with negative biological, social and psychological outcomes [8–11].

Chronic LBP has a bidirectional association with sleep disturbance [12–17]. Sleep disturbance is reportedly prevalent in more than half of people with LBP (95% CI: 56.4–60.7%) and its severity is closely associated with perceived pain intensity [17]. Sleep disturbance is a term used to define sleep which is associated with the impairment of initiation, efficiency, duration, and quality of sleep [18]. Sleep problems impose large costs on society with sleep disorders currently estimated to cost US$94.9 billion in the US [19] and sleep disturbance contributed a combined financial and healthcare cost of US$45.2 billion in Australia [20]. Therefore, chronic LBP and

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**Abbreviations**

| | |
|---|---|
| CBTi | cognitive behaviour therapy for insomnia |
| CBTp | cognitive behaviour therapy for pain |
| ER | extended release |
| LBP | low back pain |
| NRS | numerical rating scale |
| NSAID | non-steroidal anti-inflammatory drug |
| OUD | opioid use disorder |
| PSG | polysomnography |
| REM | rapid eye movement |
| RoB | risk of bias |
| SMD | standardized mean difference |
| VAS | visual analogue scale |

sleep disturbance have significant healthcare costs and impair workforce capability.

There are several pharmacological and non-pharmacological treatments shown to be effective in chronic LBP management [21–26]. Healthcare guidelines recommend non-pharmacological interventions such as exercise therapy and psychosocial interventions as first-line treatment options [27]. Despite guidelines discouraging their use, pharmacological interventions remain prevalent in chronic LBP management [23,28,29]. When pain relief is required, healthcare guidelines recommend the use of NSAIDs or antidepressants to ameliorate pain perception [27].

Current healthcare guidelines do not recommend the use of opioid therapies for chronic LBP management as there is inadequate data regarding their efficacy for managing chronic pain conditions [30]. Chronic use of opioids increases the likelihood of addiction and behaviors of misuse and abuse, described as opioid use disorder [31,32]. Healthcare guidelines recommend that weak opioids are suitable for addressing acute episodes of pain following injury or surgery [27,30]. Unfortunately, opioids continue to be prescribed and used in chronic LBP management in addition to other chronic pain conditions.

Determining whether analgesic medications influence sleep is important for optimizing effective management of chronic LBP comorbid with sleep disturbance. A recent systematic review assessing mixed chronic pain populations showed that opioid therapy significantly improved self-reported sleep quality compared with placebo or control treatment options (Effect size = 0.36, 95% CI: 0.17–0.54) [33]. Therefore, the aim of this systematic review and meta-analysis was to assess the effect of opioid and non-opioid therapies on sleep in people with chronic LBP.

## 2. Method

### 2.1. Data source and search strategy

This systematic review and meta-analysis were conducted using the preferred reporting items for systematic reviews and meta-analysis (PRISMA) protocol. The review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42021254084. The following databases: Embase, Medline, Scopus, International Pharmaceutical abstracts, Web of Science and CINAHL were searched using keyword and medical subject headings depending on database search engine parameters. The search strategy focused on three domains: 1) low back pain (LBP) 2) sleep and 3) pharmacological interventions. A full list of the search terms and keywords can be found in the supplementary materials.

### 2.2. Selection criteria

Articles were included if they 1) included a participant population ≥18 years of age with a non-specific condition of chronic LBP; 2) assessed an opioid or non-opioid analgesic intervention; 3) included a comparison (placebo) or control arm; 4) reported a sleep outcome; and 5) used a randomized controlled design.

Articles were excluded if the studies: 1) assessed a population with a specific cause of chronic LBP (such as cancer-induced or neuropathic pain); 2) used a non-pharmacological intervention or hypnotic medication; 3) did not use a randomized controlled design 4) did not include a sleep outcome; 5) Full article could not be accessed in English.

### 2.3. Data extraction and quality assessment

Duplicates were removed and then screened independently by four reviewers (JP, XL, CL, and AL) with JP reviewing all abstracts. Following abstract screening, full text article screening was conducted by the same reviewers. Disagreements were discussed with another author (CG) to reach consensus [34]. The following study characteristics were extracted: study design, age, gender, number of treatment arms, treatment drug and dose range, rescue medication and maximum dose, and any sleep outcome.

Questionnaires that were used to assess sleep outcomes were extracted and categorized into two groups: 1) sleep quality or 2) sleep disturbance. Sleep quality is typically assessed with a single-item sleep quality scale which asks participants to score the quality of their sleep [35]. Sleep disturbance assessments usually include multiple items that assess the difficulty in initiating and maintaining sleep, and awakening when desired [36]. Results were recorded using either a numerical rating scale (NRS) or visual analogue scale (VAS). Quality assessment was performed by one reviewer (JP) using the Cochrane risk-of-bias tool for randomized controlled trials (Rob 2) concerning adherence to intervention, referred to as the “per protocol effect” [37]. Any uncertainties whilst performing the quality assessment were discussed with the senior authors (CG and PF).

### 2.4. Statistical analysis

A random effect model with 95% confidence intervals was used for meta-analyses to account for heterogeneity between study populations and methodology. All results acquired from studies were homogenized to a 100-point scale, 1 = most negative, or undesired, outcome possible; 100 = most positive, or desired, outcome possible. All studies included in the meta-analyses used either a 100 mm VAS or 11-point NRS to report on the sleep outcomes of interest. Standardized mean difference (SMD) values were calculated from these results. Heterogeneity was calculated by measuring the variability in effect sizes ($I^2$ value). The SMD of each study was pooled and analyzed. A z-score was subsequentially calculated from the pooled SMD results to provide the probability-of-benefit of the intervention treatment improving the specified sleep outcome compared to control [38]. Results from studies which implemented fixed-dose intervention arms were averaged prior to determining the study SMD result. A sensitivity analysis was subsequentially performed to determine whether low or high fixed-doses influenced the pooled SMD result. Meta-analyses were performed using Jamovi (2022) [39].

## 3. Results

### 3.1. Search results and study characteristics

After database searching, 1461 abstracts were screened for eligibility. 61 articles were included in the full-text screening, which yielded 16 final articles (reporting 14 research study findings) for qualitative synthesis (Fig. 1).

Eleven studies were conducted in North America [40–50] and three in Europe [51–53] (Table 1). Thirteen of the fourteen studies [40–52] used a double-blind randomized control study design and one study [53] used a single-blind design. Four studies [41–43,50] implemented a crossover in treatment at the midpoint of the treatment period/maintenance period. Three studies [42,43,46] offered participants an optional, open-label extension phase period at the conclusion of the treatment period. Twelve of the studies assessed an opioid intervention [40–51] whilst two studies assessed a non-opioid intervention [52,53]. Ten of the twelve opioid studies [40–48,50] implemented a titration period to determine specified drug dose for each participant. This occurred prior to the randomization of treatment. In the remaining two opioid studies [49,51] fixed-doses of treatment were assessed. One of these studies [49] implemented the titration period before randomization of treatment. In the other study [51] randomization of treatment preceded the titration period.

One of the two non-opioid studies [52] compared two different non-steroidal anti-inflammatory drugs (NSAID). The other non-opioid study [53] assessed the additive effect of an anti-convulsant in participants receiving opioid therapy.

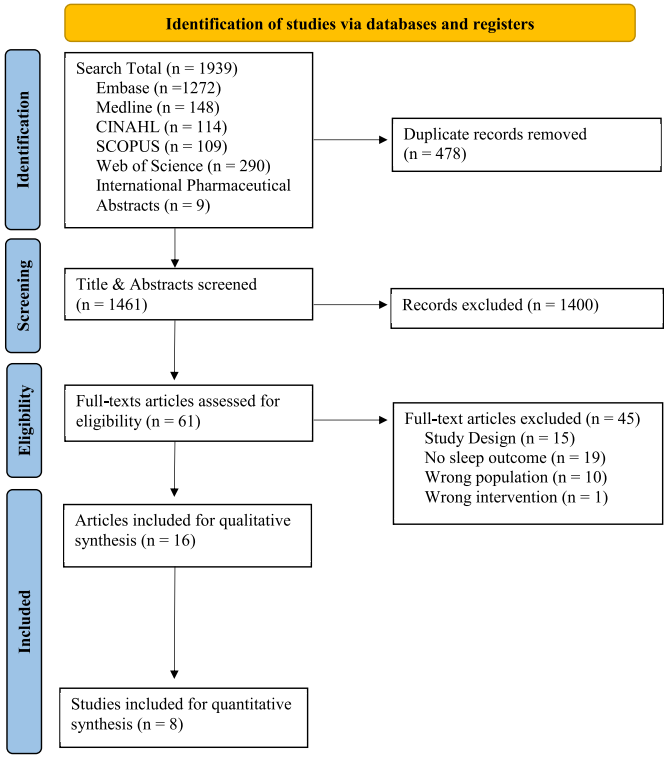


**Fig. 1.** PRISMA flow diagram of database searching, article screening and study inclusion. Contact was attempted with six authors at the time of full text review: three were contacted to request sleep outcomes not reported and the other three were contacted to request data and results specific for the participants with chronic LBP included amongst other chronic pain conditions. None replied.

Overall, thirteen studies offered rescue medication to participants for the management of breakthrough pain [40–46,48–53]. Acetaminophen was the most frequently used rescue medication. Three studies provided it in combination with an opioid [41,43,45].

We were able to meta-analyze eight of the twelve opioid studies [41–45,48,49,51] as they included a placebo-control arm. Meta-analyses of sleep quality and sleep disturbance outcomes were performed using data recorded at the end of the treatment period.

### 3.2. Sleep reporting

All studies measured sleep subjectively through questionnaires. Eleven studies assessed sleep quality [40–43,45,47–52], nine studies assessed sleep disturbance [41–45,47,48,50,53] and seven studies assessed both [41–43,45,47,48,50]. Frequently, questionnaires reported results using either 100 mm VAS or 11-point NRS. One study measured sleep objectively [50] using polysomnography (PSG). They concluded that evening consumption of the opioid ER-hydromorphone improved sleep quality and quantity however, it was also associated with a greater number of sleep-disordered respiratory events than when consumed in the morning.

### 3.3. Sleep quality

Seven studies were included in a meta-analysis of sleep quality [41–43,45,48,49,51]. The pooled SMD was 0.27 at treatment endpoint showing that opioid therapies were associated with a 58% probability (z-score) of improving sleep quality compared to placebo-control (SMD = 0.27, 95% CI: 0.17 to 0.36, $p < 0.001$) (Fig. 2). Rather than assessing a range of intervention doses individually titrated for each participant, Christoph et al., [51] and Vorsanger et al., [49] assessed fixed-doses. A sensitivity analysis was performed to determine whether fixed-dose intervention arms effected the pooled SMD result. Including only the results from the highest fixed-dose intervention arms reduced the pooled SMD (SMD = 0.22, 95% CI: 0.12 to 0.32, $p < 0.001$) (Fig. S1). Meanwhile, including only the results from the lowest fixed-dose intervention arms produced no difference to the pooled SMD (SMD = 0.27, 95% CI: 0.17–0.37, $p < 0.001$) (Fig. S2).

### 3.4. Sleep disturbance

Six studies were included in the meta-analysis of sleep disturbance [41–45,48]. Three of these studies [41–43] reported an overall pain and sleep score derived from summating the results from five items of the pain and sleep questionnaire (PSQ): 1) trouble falling asleep, 2) needing pain medication, 3) needing sleep medication, 4) awakenings during the night, 5) awakening in the morning. The remaining studies asked participants to rate how much their pain interfered with sleep using a single item 11-point NRS (between 0 and 10) [44], or 100 mm VAS [45,48]. The pooled SMD was 0.32 at treatment endpoint showing that opioid therapies were associated with a 59% probability (z-score) of improving sleep disturbance compared to placebo-control (SMD = 0.32, 95% CI: 0.22 to 0.43, $p < 0.001$) (Fig. 3).

### 3.5. Risk of bias

The risk of bias (RoB 2) was performed concerning adherence to intervention, 'per protocol effect', which assesses studies across five dimensions: 1) randomization process; 2) deviations from intended interventions; 3) missing outcome data; 4) measurement of the outcome; 5) selection of the reported result. Overall, it was found that all studies were subject to at least 'some concern' of bias (Fig. 4). Bias was most frequently present in the dimension of

**Table 1**
Characteristics of articles included in the qualitative analysis.

| Author | Country | Randomized design | Population (Baseline/ completion) | Mean Age | Gender | Study arms | Treatment and dose | Treatment duration | Rescue medication during treatment | Outcome measures |
|---|---|---|---|---|---|---|---|---|---|---|
| Buynak et al. (2010) [40] | USA | Double-blind, placebo- and active-controlled, multicentre (USA: 85, Canada: 15, Australia: 3) | 965/451 | 49.9 (13.9) | f = 559 m = 406 | Three | Placebo Tapentadol ER (100 −250 mg) Oxycodone CR (20 −50 mg) | 12 weeks | Acetaminophen 1000 mg/day (no more than 3 consecutive days). Permitted only for pain unrelated to backpain | Sleep questionnaire[i] |
| Christoph et al. (2017) [51] | Germany | Double-blind, placebo- and active-controlled multicentre (79 sites, 11 European countries) | 635/360 | 57.5 (11.7) | f = 412 m = 223 | Five | Placebo Tapentadol (200mg/12) Cebranopadol 200 μg 400 μg 600 μg (once daily) | 12 weeks | Acetaminophen (2000 mg/day) maximum usage of 20 days during the treatment period | CPSI (100 mm VAS) |
| Cloutier et al. (2010) [41] | Canada | Double-blind, cross-over, multicentre (10 sites) | 83/54 | 51.3 (12.5) | f = 44 m = 39 | Two | Placebo/Naloxone CR Oxycodone CR/ Naloxone CR (10 −40 mg /5-20 mg; twice daily) | 8 weeks (crossover at 4 weeks) | Codeine /acetaminophen ablets (30mg/ 300 mg). 2 tablets/6 h. | PSQ (100 mm VAS) |
| Driessens et al. (1994) [52] | Belgium | Double-blind, multicentre (5 sites) | 62/50 | 52.6 (14.3) | f = 33 m = 29 | Two | ibuprofen SR (1600 mg) diclofenac SR (100 mg) | 2 weeks | Acetaminophen (4000 mg/day) | Sleep quality, (9-point NRS) |
| Gordon et al. (2010a) [**42**] | Canada | Double-blind, placebo-controlled crossover. optional open-label extension phase. multicentre (13 sites). | 78/52 | 50.7 (11.9) | f = 47 m = 31 | Two | Placebo BTDS (20 μg/h or 40 μg/h) | 8 weeks (crossover at 4 weeks). 6 month open-label extension phase | Acetaminophen tablets (325 mg). 2 tablets/6 h. | PSQ, Quality of sleep (100 mm VAS) |
| Gordon et al. (2010b) [43] | Canada | Double-blind, placebo-controlled crossover. optional open-label extension phase. | 79/53 | 54.5 (12.7) | f = 25 m = 28[ii] | Two | Placebo BTDS (10 μg/h or 20 μg/h) | 8 weeks (crossover at 4 weeks). 6 month open-label extension phase | Codeine/ acetaminophen tablets (30mg/ 300 mg) 2 tablets/6 h. NSAIDs, aspirin and acetaminophen permitted for other pain | PSQ, Quality of sleep (100 mm VAS) |
| Hale et al. (2005) [44] | USA | Double-blind, Placebo controlled. | 329/139 | 45.5−47.5 (mean age) | f = 155 m = 174 | Three | Placebo Oxymorphone ER (10−110 mg) Oxycodone (20 −220 mg; twice daily) | 18 days | Oral morphine sulphate 30 mg/day | Pain interference with sleep (11-point NRS) |
| Markman et al. (2017) [45] | USA | Double-blind, placebo controlled. | 610/491 | 51.4 (12.6) | f = 357 m = 253 | Two | Placebo NKTR-181 (100 | 12 weeks | hydrocodone/ acetaminophen tablets | MOS-SS |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | multicenter (55 sites) | | | | | −400 mg; twice daily) | | (5mg/300 mg). 2 tablets/day. | |
| Pota et al. (2012) [53] | Italy | Single-blind, Placebo controlled. | 44/44 | 55.5 (8.4) | f = 22 m = 22 | Two | BTDS/placebo (35 μg/h) BTDS/pregabalin (35 μg/300 mg) (once daily) | 3 weeks | N/A | Sleep interfence (11-point NRS) |
| Rauck et al., 2006a [46] | USA | Randomized, open-label, multicentre | 392/266 | 50 | f = 239 m = 153 | Two | Morphine Sulphate ER 30−360 mg/day OxyContin ER 24−349mg/12hr | 8 weeks. 16 weeks optional extension phase of | Ibuprofen (2,400 mg/day). | PSQI |
| Rauck et al., 2006b [75] | USA | Extension phase of Rauck et al., 2006a | 174 | 47.7−49.8 (mean) | f = 105 m = 69 | Two | Morphine Sulphate ER once every 24 h (30−480 mg/day OxyContin ER once every 12 h (20 −320 mg/day) | 16 weeks | Ibuprofen (2,400 mg/day) | PSQI |
| Steiner et al., 2011a [47] | USA | Double-blind, active-controlled, multicentre (75 sites) | 660/433 | 50.0 (12.4) | f = 314 m = 346 | Three | BTDS 5 mg/h 20 mg/h IR-oxycodone (40 mg/day) | 9 weeks | N/A | MOS-SS[iii] |
| Steiner et al., 2011b [48] | USA | Double-blind, placebo-controlled, multicentre (86 sites) | 541/389 | 49.4 (13.0) | f = 298 m = 243 | Two | Placebo BTDS (10 or 20 mg/h) | 9 weeks | Acetaminophen (500 mg/6 h) or ibuprofen (200 mg/6 h) | MOS-SS[iii] |
| Vorsanger et al., 2008 [49] | USA | Double-blind, placebo-controlled | 384 | 47.8 (14.4) | f = 192 m = 192 | Three | Placebo Tramadol ER 200 mg 300 mg (once daily) | 12 weeks | Acetaminophen (2,000 mg/day) | Quality of sleep (100 mm VAS) |
| Webster et al., 2015 [50] | USA | Double-blind, placebo-controlled crossover. | 15/15 | 44.0 (14.0) | f = 9 m = 6 | Four | ER hydromorphone (8 mg, 12 mg or 16 mg twice daily) | 4−6 weeks (crossover at 2−3 weeks) | Acetaminophen (500 mg/6 h) | Comprehensive sleep assessment[iv]; MOS-SS |
| Yarlas et al., 2016 [76] *Trial I (Steiner at al., 2011a)* *Trial II (Steiner at al., 2011b)* | USA | Data from two phase-III, Randomized, double-blind, multicenter trials | *Trial I* = 660/433 *Trial II* = 541/389 | *Trial I* = 50.0 (12.4) *Trial II* = 49.4 (13.0) | *Trial I* = 660/433 *Trial II* = 541/389 | *Trial I* = Three *Trial II* = Two | *Trial I* = BTDS 5 mg/h 20 mg/h IR oxycodone (40 mg/day) *Trial II* = Placebo BTDS 10 or 20 mg/h | *Trial I* = 9 weeks *Trial II* = 9 weeks | *Trial I* = N/A *Trial II* = Acetaminophen (500 mg/6 h) or ibuprofen (200 mg/6 h) | *Trial I* = MOS-SS *Trial II* = MOS-SS |

BTDS − Buprenorphine transdermal patch; NKTR-181 − novel full mu-opioid receptor agonist; ER − Extend release; CR − Controlled release; IR − Immediate release; PSQ − Pain sleep questionnaire; CPSI − Chronic pain sleep inventory; PSQI − Pittsburgh sleep quality index; MOS-SS − Medical outcome survey sleep scale.

i) Items included sleep latency, hours slept, number of awakenings, sleep quality; ii) number of males and females taken from per protocol population; iii) results only provided for the *'sleep disturbance'* subscale domain of the MOS-SS (1 of 4 subscales included in the MOS-SS); iv) Comprehensive sleep assessment included nocturnal apnea-hypopnea index, central and obstructive apnea index (CAI and OAI), number of arousals and lower limb movements.

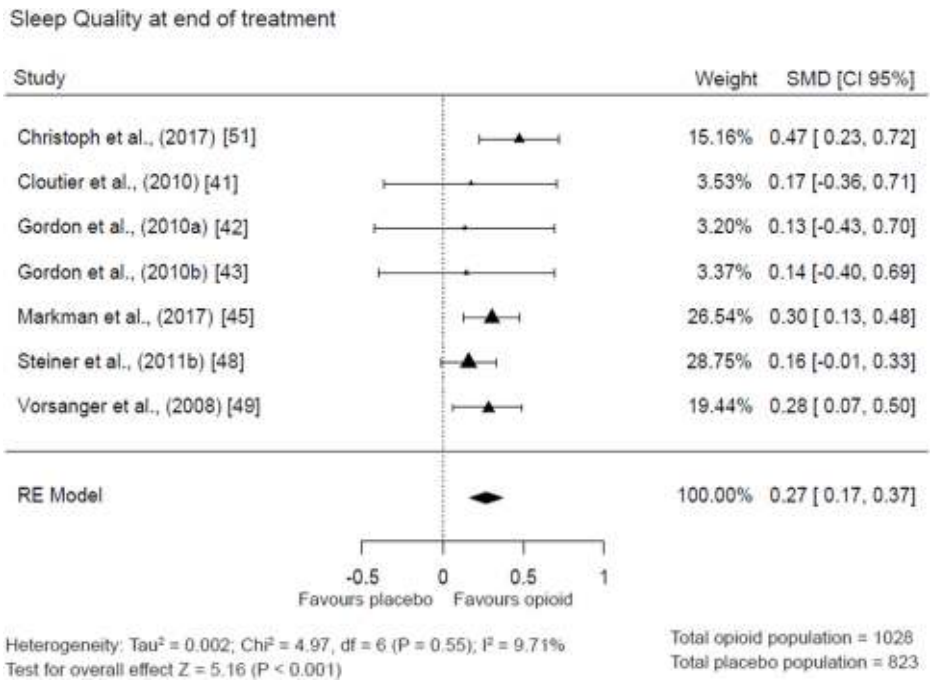


**Fig. 2.** Forest plot comparing sleep quality in studies which included arms for opioid therapies and placebo-control. The SMD values were calculated using a random effects model of mean sleep quality at the end of randomized treatment periods.

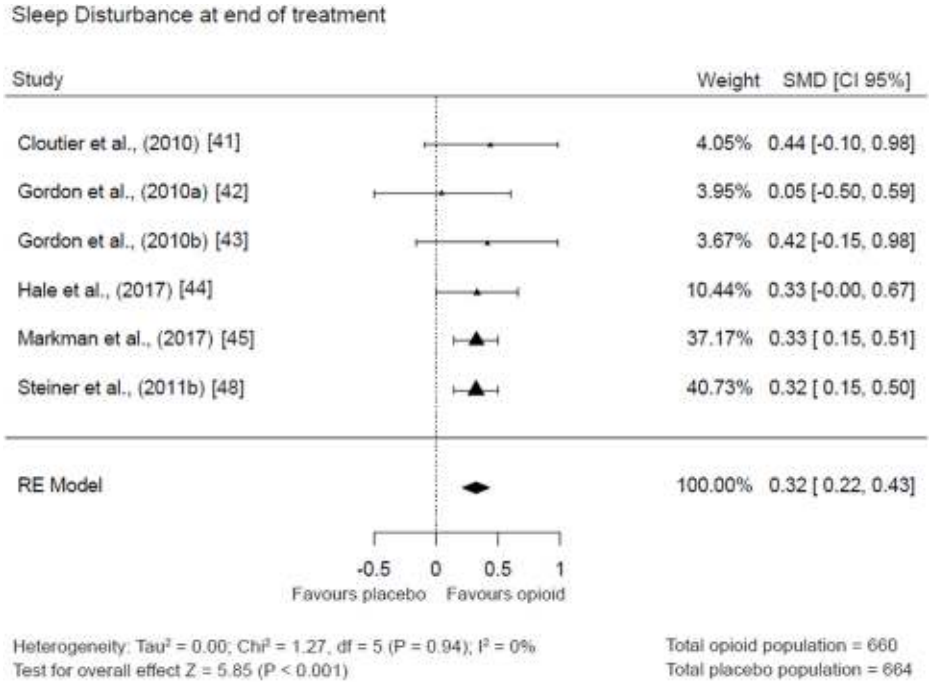


**Fig. 3.** Forest plot comparing sleep disturbance in studies which included arms for opioid therapies and placebo-control. The SMD values were calculated using a random effects model of mean sleep disturbance at the end of randomized treatment periods.

'selection of the reported results'. This was due to a lack of transparency regarding obvious pre-specified analysis plans. 'Deviations from the intended interventions' was another dimension of the RoB 2 where there was at least 'some concern' detected for most studies.

## 4. Discussion

Overall, the meta-analyses showed that opioid therapies improved sleep quality and reduced sleep disturbance in people with chronic LBP. The analysis also showed that the opioid-associated improvements in sleep quality and disturbance occurred irrespective of medication dose and type. This finding is

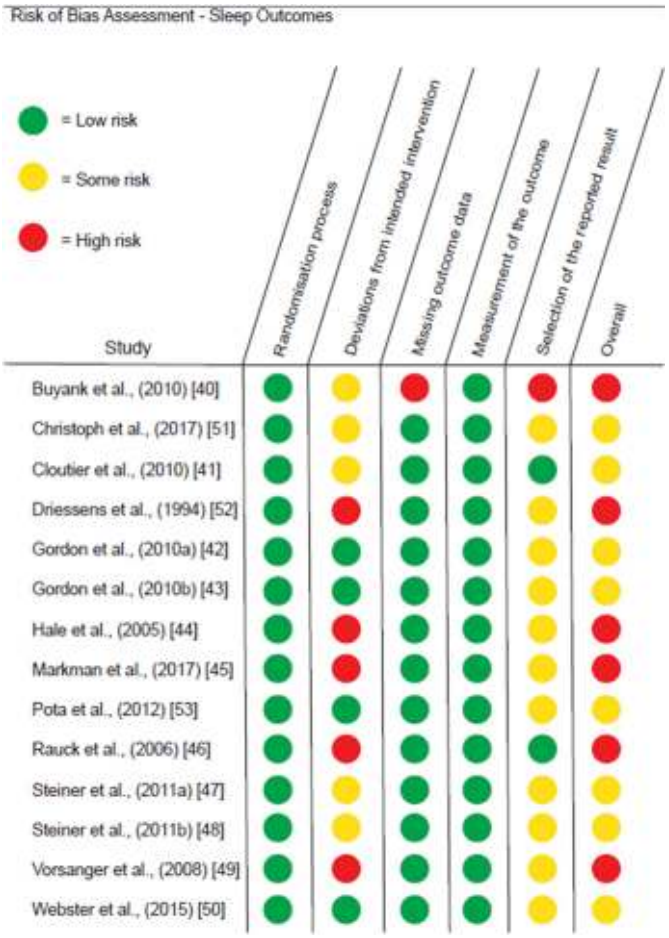


**Fig. 4.** Risk of bias for randomized controlled trials (Rob 2) assessing adherence to intervention, 'per protocol effect'.

consistent with previous research assessing the effects of opioids on sleep in people with mixed chronic non-malignant pain conditions [33]. The sensitivity analysis also showed that the minimal opioid dose used in fixed-dose studies had a positive effect on sleep quality. This suggests that low doses of opioids to treat chronic LBP are also efficacious on sleep.

### 4.1. Opioid therapy influence on sleep

It is important to note that the outcomes assessed by the meta-analyses were recorded at the end of treatment, after 12-weeks or less. Chronic opioid therapies are reportedly associated with subjective increases in sleep disturbance, fatigue and daytime somnolence [54]. A cross-sectional study of people with chronic non-cancer pain receiving chronic opioid therapies found that 87% and 49% of their sample (876 people) had insomnia-related sleeping problems and daytime somnolence respectively [55]. The euphoric and addictive qualities of opioids are risk factors that drive misuse and dependency, commonly referred to as opioid use disorder (OUD) [31] [31,56,57]. Association studies concerning OUD reveal links between opioid use, impaired sleep efficiency, shorter sleep durations, and delayed sleep onset [58]. One study has shown that people with OUD experience a worsening of sleep quality over time [59]. Furthermore, compared with the general population, sleep disturbance is often more severe amongst people with OUD [60]. OUD and sleep disturbance have a bidirectional relationship suggesting that shared biophysiology may facilitate the comorbidity [61].

Research has shown that chronic opioid use impairs objectively measured sleep by increasing the frequency of apneas and hypopneas during sleep and additionally by disrupting sleep architecture [62,63]. A single dose of oral opioid medication can reduce the duration of slow-wave sleep in healthy adults [64], whilst chronic use of the opioid methadone for the management of chronic pain conditions and opioid dependence, reduces the durations of both slow-wave and REM sleep [65]. Moreover, there are differences in the objective findings of single dose studies compared with chronic exposure and further differences depending on whether participants have any underlying health conditions. For example, acute single night exposure to morphine in pain-free patients with obstructive sleep apnea may either increase or decrease sleep apnea severity [66]. It is possible that variations in chemosensitivity and or genetics may govern respiratory and sleep response to opioids [67].

### 4.2. Opioid vs. non-opioid medications

Opioid and non-opioid medications could not be directly compared in this review as there was an insufficient number of studies assessing non-opioid medications. Studies assessing non-opioid medications did not meet inclusion criteria because of their design, population or outcomes assessed. However, an indirect assessment of opioid and non-opioid medications can be derived when considering the results of the meta-analyses alongside the reported use of rescue medication. Simple analgesics were provided as rescue medication in all studies except four [41,43,45,53]. Six studies [41–45,51] which recorded the use of rescue medication unanimously reported that usage was greatest amongst participants receiving placebo-control treatments. Despite the greater use of rescue medication by these participants, improvements to subjective sleep outcomes were greater amongst participants receiving opioid therapies as revealed by the meta-analyses. Unfortunately, we are unable to determine whether non-opioid medications influence sleep in people with chronic LBP. Future research should be conducted to assess this.

### 4.3. Sleep assessments

All studies in this review assessed sleep subjectively as secondary outcomes, which is consistent with the reporting of other recent systematic reviews exploring sleep in mixed chronic pain populations [18,29,68]. In a systematic review assessing sleep in chronic non-malignant pain populations two studies assessed objective sleep outcomes [33]. Both studies assessed opioid therapies and generated inconsistent objective sleep outcomes which were hampered by small sample sizes and risk of bias. One of those two studies were included in this review [50]. Further research should examine objectively measured sleep to provide insights into the effect of opioids on sleep macro-, and micro-architecture.

### 4.4. Non-pharmacological interventions for sleep disturbance

The results of the meta-analyses should be considered alongside the findings of other studies assessing non-pharmacological sleep intervention in chronic pain cohorts. A meta-analysis of mixed chronic pain population showed that cognitive behavior therapy for insomnia (CBTi) is significantly greater than control treatment options, CBT for pain and sleep hygiene, for improving insomnia symptoms (SMD = 0.89, 95% CI: 0.53 to 1.25) [18]. CBTi is often recommended ahead of pharmacotherapies as it can treat the underlying cause of insomnia without exposing patients to significant

risks and side effects however, cost and accessibility remain obstacles to its implementation [69]. Research has proven the efficacy of digitally delivered CBTi which means that cost and accessibility will likely improve with further implementation and clinician support [70]. A review of six randomized controlled trials that examined the efficacy of CBTi in patients with comorbid insomnia and chronic pain concluded that CBTi produced clinically meaningful improvements to sleep but was inconsistent regarding the effects on chronic pain outcomes [71]. Patient function improved more than pain intensity. Further research assessing CBTi in chronic LBP populations is required before definitive conclusions can be made about its effectiveness in this specific population. One future study is examining the efficacy of a hybrid intervention comprising CBTi to address insomnia symptoms and physical therapy to address back pain [72].

### 4.5. Clinical guideline considerations

Current clinical practice guidelines concerning the management of non-specific LBP in primary care indicate that NSAIDs and weak opioids may be used for short time periods where analgesia is required [27]. Considering these recommendations, clinicians may find it appropriate to manage acute relapses of LBP by using low doses of opioids to alleviate heightened pain levels which cause significant sleep disturbance. Chronic use of opioids should continue to be discouraged due to the risks of misuse and development of dependency alongside other side effects. The overprescription and misuse of opioids remains a considerable issue in chronic pain management [73,74]. The findings from this study demonstrate that opioid therapies are effective for improving both pain and sleep in people with chronic LBP. Therefore, clinical practice guidelines should consider the efficacy of short-term opioid use for alleviating the intensity of chronic LBP and sleep disturbance. Considering that prescription and access to opioids are significant contributors driving the opioid epidemic, particularly in the United States, there is a pragmatic challenge in reducing the capacity for opioid misuse to occur. Reporting opioid use to clinicians in addition to prescribing lower doses and lower quantities of opioids may help to reduce opportunities for opioid misuse and abuse to occur.

### 4.6. Limitations

There are limitations to this review. An assessment of non-opioid therapies could not be made due to a lack of existing studies. This meant that including non-opioid studies in a meta-analysis was not possible. This limits the understanding of whether non-opioids affect sleep quality and sleep disturbance in chronic LBP populations. Attempts were made to contact several authors to obtain data which may have further contributed to the meta-analyses however, no response was received from any of the authors contacted. The sleep outcomes of this review and meta-analysis were all secondary outcomes and no included study was powered to find direct effects on sleep. This may limit the generalizability of the findings and future research should examine sleep as a primary outcome in opioid and non-opioid studies of people with chronic LBP.

## 5. Summary

In summary, this review shows that opioid interventions improve sleep quality and reduce sleep disturbance in people with chronic LBP. Caution should be taken regarding these findings and when using opioids as their use exposes one to the risks of misuse and dependency. This review included only two non-opioid studies. Without enough non-opioid studies to meta-analyze, we are unaware of whether non-opioid medications effect sleep in people with chronic LBP.

By considering the prevalence and comorbidity of chronic LBP and sleep disturbance, future chronic LBP research should assess subjective and objective sleep outcomes. Exploring the effect of different types of analgesic medications on sleep is essential for optimizing the management of chronic LBP and sleep disturbance. Furthermore, considering the bidirectional relationship of chronic LBP and sleep disturbance from other directions could provide further insights and alternate pharmacotherapies. One suggestion is to assess the efficacy of hypnotic medications on pain and functional outcomes in chronic LBP populations.

Practice Points

Clinicians providing opioid therapies for patients with chronic low back pain should be aware of the following:

1. Opioid therapies improve sleep quality and reduce sleep disturbance in people with chronic low back pain.
2. Evidence suggests that lower doses of opioid therapies for chronic low back pain are efficacious for improving sleep quality.
3. Opioid therapies should be considered in light of increases in apnea-related respiratory events and disruption of sleep architecture which may result.
4. Opioid usage for people with chronic low back pain and respiratory disorders should be judicious due to the respiratory depressant effects of opioids.
5. Prolonged opioid therapies are not recommended for people with chronic low back pain experiencing sleep disturbance.

Research Agenda

Future research should address the following when exploring the relationship of chronic low back pain and sleep disturbance.

1. Randomized controlled designs that assess the effect of non-opioid drugs on sleep in people with chronic low back pain.
2. Comparing the effects on sleep of opioid and non-opioid medications.
3. The dose-dependent effect on sleep of frequently used analgesic medications.
4. Assessment of any intervention for chronic low back pain should include subjective and objective sleep assessments.
5. The efficacy of hypnotic medications in people with chronic low back pain determined not only by sleep outcomes but also by pain and functional outcomes.
6. The efficacy of combined hypnotic and analgesic use in people with chronic low back pain and sleep disturbance.
7. Cost-effect analysis of chronic low back pain interventions as it is a health condition with significant economic burden.

## Author contributions

Study design: J.M.P., J.J.C., R.R.G., P.H.F., C.J.G.; Data collection: J.M.P., Q.L., C.L., A.J.L., R.R.G., P.H.F., C.J.G.; Data analysis: J.M.P., R.R.G., P.H.F., C.J.G.

## Declaration of competing interest

The authors do not have any conflicts of interest to disclose.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2022.101672.

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