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The effect of opioid therapy on sleep quality in patients with chronic non-malignant pain: A systematic review and exploratory meta-analysis

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N.T. and H.S. are investigators on a UK-based multicentric trial, Improving the Wellbeing of People with Opioid Treated Chronic Pain (I-WOTCH), which involves developing a support programme that aims to improve the everyday functioning for people living with chronic pain and reduce their opioid use. N.T. and H.S. recently completed a feasibility study of a hybrid cognitive behaviour therapy for pain-related insomnia in primary care, funded by the NIHR under its Research for Patient Benefit (RfPB) programme (Grant Reference Number PB-PG-0213-30121). H.S. is a director of Health Psychology Services Ltd, which in part provides psychological treatments for those with chronic pain.

Summary

Current guidelines recommend opioid therapy to chronic non-malignant pain (CNP) patients when the benefits for pain *and* function outweigh risks. This systematic review examined the effects of opioid therapy on sleep – a valued functional outcome– in CNP. Electronic and hand searches of relevant studies up through July 2017 identified 18 eligible studies providing data from 3,746 CNP patients for analysis. Twelve of these studies were randomised controlled trials (RCTs) of up to 12-month in duration. Low-medium dosed oxycodone and transdermal fentanyl were the most tested therapies (n=4 each). Only two studies used objective sleep measure in addition to self-report ratings, questionnaires or sleep diary. Whilst calmer sleep with less body/leg movements and fewer awakenings could be achieved following opioid therapy, these might occur with increased sleep-disordered breathing and a much-shortened rapid eye movement (REM) sleep latency. Both the narrative synthesis and exploratory meta-analysis suggest that opioid therapy in CNP is associated with improved self-reported sleep quality. However, the effect is inconsistent, small (Standardised Mean Difference = 0.36), and may be accompanied by excessive daytime sleepiness. As a Cochrane-recommended assessment revealed "unclear" or "high" overall risk of bias for all studies, future opioid trials of stronger methodology and better reporting are needed to confirm and elucidate the effect.

Glossary

AEs	Adverse events
AHI	Apnoea-hypopnoea index
CAI	Central sleep apnoea index
CNP	Chronic non-malignant pain
EORTC-QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
ESS	Epworth Sleepiness Scale
MME	Morphine milligram equivalent
MOS Sleep Scale	Medical Outcomes Study Sleep Scale
MPI	Multidimensional Pain Inventory
NSAIDs	Non-steroid anti-inflammatory drugs
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RCT(s)	Randomised controlled trial(s)
REM	Rapid eye movement (sleep)
SDB	Sleep-disordered breathing
SMD	Standardised mean difference(s)
SPAASMS	SPAASMS score card (one item for each: S- Score for pain, P- Physical activity levels, A- Additional pain medication, A- Additional Physician/ER Visits, S- Sleep, M- Mood, S- Side effects)
SWS	Slow wave sleep
VSH	Verran and Snyder Halpern Scale

1. Introduction

Opioids are potent analgesics with evidence of efficacy for short-term use (i.e., maximum 12 weeks) [1]. The effectiveness and safety of opioids therapy for chronic non-malignant pain (CNP), however, has become controversial following liberalised prescriptions [2-5] that coincided with an increase in fatalities and adverse outcomes [6, 7].

Decisions regarding the introduction or discontinuation of opioid therapy are complex [8], requiring clinicians to balance the potential risks and benefits based on patients' presentation of symptoms, comorbidities, and psychosocial circumstances [9]. Current guidelines recommend non-opioid therapy as the preferred treatment of CNP, with opioids reserved to situations "when benefits for pain *and* function are expected to outweigh risks" [1, 10]. Whilst the effectiveness of opioid therapy is usually measured in terms of pain outcomes, less is known about its effect on day-to-day functions. A particular function of concern to patients with CNP is the ability to get a good night's sleep [11-13].

Opioid medications can induce different patterns of sleep-disordered breathing (SDB), including central or obstructive apnoea, hypopnea, respiratory ataxia and non-apnoeic hypoxemia, with dose-dependent effects [14-16]. The prevalence of central sleep apnoea (defined as a >10-second absence of airflow with the lack of breathing efforts) is estimated at 24% among patients taking chronic opioid medications [17]. Awareness of such respiratory depression effect has led to the recommendation to assess SDB when prescribing opioids for CNP [1, 10]. However, no review has detailed the effect of opioid therapy on sleep quality.

The pain-sleep relationship is typically described as bi-directional [18, 19]. A growing body of experimental and observational research has found evidence in support of pain being a trigger or risk factor of poor sleep and poor sleep, in return, an aggravator of pain [20, 21]. Further, a recent systematic

review has shown that a decline in sleep quality or quantity is prospectively associated with not only an elevation of inflammatory markers, but also an increase in risk of developing a pain condition and of reporting poorer physical functioning status in the long term [22]. In this context, it is a common clinical assumption that - on the positive side of the equation – pain relief achieved with opioid therapy should bring about an overall improvement in sleep quality [23]. However, several lab-based studies have linked the use of opioids such as morphine, methadone and tramadol to a dose-related suppression of slow wave sleep (SWS) and rapid eye movement sleep (REM), as well as an increase in shallower stages of Non REM sleep (particularly stage N2 sleep) [24-27]. Additionally, new evidence based on the analysis of health information of >8400 community dwellers suggests that insomnia is 42% more likely among people prescribed opioids than non-opioid users [28]. These findings raised the possibility that opioid therapy may actually worsen rather than improve sleep quality.

The current systematic review aimed to provide a timely examination of this issue by evaluating objectively measured and self-reported sleep outcomes in randomised controlled trials (RCTs) and other clinical trials where opioids were introduced *de novo* or on a switch from a lower dosed opioid analgesic in CNP. Instead of focusing on SDB for which there is already mounting evidence [14, 16, 29], the primary outcomes of interest were objectively measured sleep architecture and self-reported sleep quality following the introduction of opioid therapy – although SDB findings were also reported to inform the balance of benefits and risks. In addition, attention was given to negative sleep-related adverse events (AEs) reported by patients following opioid initiation, to provide a novel and broader risk-benefit evaluation of opioid therapies for CNP.

2. Methods
2.1 Data source and search strategy
The data source for this systematic review was original studies that specifically evaluated the effect of introducing opioid therapy on sleep or that included measures of sleep as a secondary outcome in the assessment of the new opioid therapy in adult patients with CNP. The relevant medical literature

was identified through both electronic searches performed using PubMed MEDLINE and hand searches of reference lists of included studies, relevant reviews and grey literature on the topic. The PubMed search was carried out by a member of the review team (MTS) for the period from the inception of the database to 7th of July 2017, using search terms selected following several rounds of pilot searches to ensure comprehensive coverage (see Supplementary Materials 1). The structure of the search terms aimed to identify articles concerned with the use of opioid therapy; for CNP; examining the effect of such therapy on sleep; in adult humans. The protocol of this systematic review is registered with PROSPERO – International Prospective Register of Systematic Reviews (registration number: CRD42018089139).

2.2 Selection criteria

All articles identified through the search were subject to a title and abstract screen followed by a full-text screen, both of which were aided with a study selection checklist, co-developed by MTS and NT according to our *a priori* list of inclusion and exclusion criteria.

Specifically, the criteria specified that the participants of the included studies had to be (1) adults aged 18 years or above, (2) with CNP, (3) for at least 3 months at inclusion, and that these participants (4) were provided with opioid analgesics for pain, (5) with sleep measured as either a primary or secondary outcome. (6) The research design of the included studies was restricted to treatment studies - controlled or uncontrolled - only; (7) case studies or case-series with a sample size of ≤5 were excluded for concerns of high risks of bias. Further, studies were excluded if (8) the participant's mean duration of CNP was not specified in the report to confirm the presence of chronic pain or provided by the authors via email correspondence; (9) the patients had comorbid sleep apnoea, a coexisting significant physical or psychiatric illness and/or substance abuse or dependence; (10) the trial included the use of a concurrent pharmacotherapy or psychological intervention for pain, sleep

or mood, except for rescue medication for breakthrough pain; (11) the full-text version of the study was published in a language other than English, German or Italian.

2.3 Search results

Figure 1 depicts the process of the study selection. The initial electronic search returned a total of 2010 records, of which 255 passed the titles and abstract screen. An additional 21 articles were identified on the basis of citations and reference lists. Of the 104 articles read, 18 met all inclusion and exclusion criteria on the selection checklist and were included in the analysis below.

(Insert Figure 1 about here)

2.4 Data extraction

Methodological characteristics and key findings of the included studies were extracted by MTS and TB using a *pro forma*, and then verified by HS, CB and NT. Differences in opinions were resolved via discussion. In the methodological characteristics table (Table 1), we summarised the studies' design; type of opioids used; participants' pain-related characteristics, age and gender at baseline; size of the sample receiving and finishing treatment; and the measure(s) used to assess sleep. In the key findings table (Table 2), we described the opioid analgesic used in greater detail and calculated the morphine milligram equivalent (MME) - according to the Agency Medical Directors' Group 2015 Interagency Guideline on Prescribing Opioid for Pain [30], except for buprenorphine (sublingual and transdermal), for which the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists conversion table was used [31]. We also tabulated the number, timing and reasons of attrition; the number, timing and nature of any sleep-related AEs reported. Finally, we reported the relevant outcomes of each study on sleep and pain. When the relevant information was missing, the corresponding author of the article was contacted by email, with another follow-up email sent after 4 weeks if no response. Requests were sent out for additional information from 18 studies. Six authors responded, four provided the requested information.

2.5 Data synthesis

A narrative approach was chosen for the current review, given the heterogeneity in design and outcome measures used in the studies reviewed. Results of the analysis were described in the text based on the methods and principles recommended by the Cochrane Collaboration [32]. A preliminary synthesis was first developed by describing key features of each study equally. The synthesis was then streamlined to report methodological characteristics and key findings of studies according to their research design (e.g., RCT or not), type of opioid therapy tested, sample of interest, whether sleep was a primary outcome measure, and the nature of the sleep measure (e.g., objective vs. self-reported; validated vs. non-validated).

The reporting was centred on the hypothesis that the introduction of opioid therapy would have an effect on sleep. Evidence in support of a positive and a negative effect was presented with a tally of the number of studies generating such evidence. Considering that the aim of the current review was to examine the effect of opioids on sleep architecture and self-reported sleep quality, we presented the findings on objective sleep measures first, and then the self-reported findings based on questionnaires, ratings, and self-reports of AEs.

As an attempt to quantitatively synthesise the data collated, an exploratory meta-analysis was conducted with a restricted set of data from RCTs comparing the effect of opioid therapy with placebo or no-opioid therapy (e.g., Non-steroid Anti-inflammatory Drugs, NSAIDs, only). Given the variety of sleep outcome measures used, only RCTs that had a quantitative indicator of sleep quality expressed in the form of a composite sleep score, a visual analogue or numerical rating, or the number of sleep hour met the minimal requirement of comparability [33-37]. RCTs that examined more than one opioid treatment arm had more than one comparison in the forest plot, and hence the total number of participants involved was reported based on the number of people in the opioid rather than the

control group. Standardised mean differences (SMD) between the "Opioids" and the "Control"

groups were estimated using a random effect model. Statistical heterogeneity among studies was

assessed with I^2 statistics along with visual inspection of the forest plots. Funnel plots were also

presented to allow visual examination of potential publication biases.

2.6 Risk of bias assessment

Six main categories of bias were considered: random sequence generation (selection bias), allocation

concealment (selection bias), blinding of participants and personnel (performance bias), blinding of

outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting

(reporting bias). In addition, potential conflicts of interests in the conduct of the studies were

considered (other bias). The Cochrane recommended appraisal process for RCTs [32] was also used

for the seven non-RCT studies in order to compare risk of bias across all study designs.

TB, NT and HS carried out the assessment independently. A judgement of "high risk", "low risk" or

"unclear risk", with supporting evidence, was given to each category of bias by each assessor for each

included study. Results of these independent assessments were then pooled and discussed with the

full review team. Differences in opinion were resolved via discussion. The final assessment was

summarised in text and visually presented in the form of a risk of bias graph and summary. The

overall risk of bias of each study was then categorised into "high", "unclear", "low", according to the

Cochrane definition [32]. The results were then inserted into the last column of Table 2.

3. Results

3.1 Overview

The 18 included articles were published between 1997 and 2016, involving a total of 3746 CNP

patients (starting sample size range: n=12 to n=749; mean age at baseline: 43-66 years; enrolled

female%: 38%-79%). The majority of the studies were conducted in the US (n=11; 61%), followed

by two studies from Canada (10%); one study each from Australia, China, Norway, and Sweden; and

one multicentric international study (Canada, Czech, Hungary, Poland, Slovakia, UK) (see Table 1).

(Insert Table 1 about here)

3.2 Characteristics of the included studies

Twelve (67%) were RCTs [33-44](Table 1). Among these RCTs, eight compared the opioid therapy of interest directly with a placebo or control group using a parallel-group design [34, 36, 38-43]. Four involved a titration run-in phase before randomisation, to evaluate the effect of different opioid regimens in the "safety sample" using an enriched enrolment withdrawal or crossover design [35-37, 44]. One RCT adopted a repeated-dose design with five phases, including an experimental phase in which participants were randomly assigned to set-dose oxycodone vs. titrated-dose oxycodone plus morphine sulphate vs. naproxen [33]). The remaining six studies (41.6%) were non-RCTs [45-50]: five were non-randomised single-treatment studies [45-47, 49, 50], and one a feasibility study [48].

The opioid analgesics being evaluated varied in type, dose, and administration route between studies. The most common opioids were morphine sulphate [34, 43, 45, 49], oxycodone [33, 38, 41, 43], and transdermal fentanyl [40, 46, 48, 50]. The other opioids were: tramadol [35, 36, 39], transdermal buprenorphine [39, 48], hydromorphone [37, 38], methadone [34, 47], buccal buprenorphine [44], transmucosal fentanyl citrate [46], and codeine [42]. The mean opioid doses varied from low (<50 MME/day) [33, 35-37, 39, 42, 49] to medium (50-100 MME) [34, 43, 45, 49, 50], high (101-199 MME) [40], and very high (>200 MME) [46, 47]. Four studies did not report the mean values of the doses administered [38, 41, 44, 48]. In terms of the maximum dose allowed, two of the four (50%) studies that used fentanyl fell into the very high dose category [40, 46]. The other very high dose study used methadone [47]. Unsurprisingly, tramadol and codeine studies were in the low doses [35, 36, 39, 42]. The morphine studies were all in the medium range [34, 43, 45, 49].

Eleven (61%) of the studies allowed rescue medications for breakthrough pain, in addition to the opioids being tested [34-37, 39, 40, 42-44, 48, 50]. Specifically, four allowed rescue medications in the form of paracetamol or ibuprofen. The dosage allowed ranged from a maximum of 1000 mg paracetamol a day [37, 44], to 2000 mg paracetamol [39] and 2400 mg ibuprofen [43] a day. One study permitted the use of hydrocodone/paracetamol (5mg/325mg) up to two tablets a day during the first two weeks of titration [44]. Two studies allowed the use of paracetamol, aspirin or low-dose NSAIDs but did not specify the maximum dosage allowed [36, 48]. One study of transdermal fentanyl allowed oral transmucosal fentanyl rescue doses (400 mcg/dose, no daily maximum) [46], whilst another transdermal fentanyl study allowed the use of short-acting oral opioids (name, dose, and daily limit unspecified) as rescue medications [50].

Homogenous diagnostic subgroups were the target samples of the majority of the studies (n=14; 70%). Of these, six included patients with chronic low back pain [33, 36, 37, 43, 44, 50], six with chronic osteoarthritis knee or hip pain [35, 38-40, 42, 49], one with chronic neck pain [41], and one with chronic postherpetic neuralgia [34]. However, inclusion criteria varied in terms of the required level of pain severity, intensity, duration, and prior treatment history (Table 1). Only two studies (16.7%) used the presence of sleep disturbances as an inclusion criterion [37, 49] and one of these specifically screened out patients with sleep apnoea [37]. These two studies were the only ones investigating the effect of opioid therapy on sleep physiology using objective measures of sleep (overnight polysomnography; PSG) [37, 49]. The remaining studies primarily focused on the efficacy of opioids in providing pain relief, with sleep as one of the secondary outcome measures. These studies used self-reports (e.g., questionnaires, ratings, diary) to measure sleep, with eleven relying on non-validated single-item ratings to assess sleep quality [33-36, 39-42, 45, 46, 48].

3.3 Risk of bias in included studies

Summaries of the risk of bias assessment are presented in Figures 2 and 3. Briefly, by category of bias, the majority of the studies were judged to be of either "unclear" or "high" risk of selection bias due to inadequate random sequence generation (n=10 studies; 56%) or allocation concealment (n=12 studies; 67%); performance bias due to insufficient blinding of participants and personnel (n=15 studies; 83%); detection bias due to insufficient blinding of outcome assessment (n=14 studies; 78%); attrition bias due to incomplete outcome data (n=14; 78%); reporting bias due to potential selective reporting (n=18; 100%); and other bias due to potential conflicts of interest (n=11 studies; 61%). Detailed assessment results are provided in supplementary materials.

(Insert Figures 2 and 3 about here)

3.4 The effect of opioid therapy on objectively measured sleep physiology and architecture

Objective sleep measures from the only two PSG studies suggested that the use of opioid therapy is associated with a mix of possible positive and negative changes in sleep physiology and architecture. In their randomised cross-over trial comparing the efficacy of extended-release hydromorphone morning versus evening dose following a no treatment baseline and an immediate-release hydromorphone open-label run in, Webster et al. [37] observed a significant within-group increase in the apnoea-hypopnoea index (AHI) index in the 15 chronic low back pain patients tested; from 12.1 at baseline without opioids to 17.1 when on extended-release hydromorphone (evening dose). This increase raised the level of apnoea from "mild" to "moderate", highlighting that the introduction of opioid therapy of a mean dose of 40 MME was associated with a greater number of apnoea and hypopnoea events during sleep and hence impaired respiratory function. Such change in AHI was accompanied by a statistically but not clinically significant increase in the central sleep apnoea (CAI) index (from 0.9 at baseline to 1.8 when using extended-release opioid treatment in the evening) and reduction in average blood oxygen level as measured with pulse oximetry (from 92.8% at baseline without opioids to 92% when on extended release hydromorphone or 91.7% when on immediate

release hydromorphone) [37]. However, positive changes were also reported in the same study in the form of a significant reduction in leg and body movements during sleep, in wake time after sleep onset, and in sleep efficiency [37]. These changes were statistically but not clinically significant when comparing the use of no opioid at baseline with the use of hydromorphone regardless of the timing of dose and release method, except for sleep efficiency for which a statistically significant difference was only observed between baseline and the use of extended release hydromorphone (evening dose).

In a separate non-randomised single-treatment placebo-lead in study of 34 patients with chronic osteoarthritic knee or hip pain by Rosenthal et al. [49], there was equivocal evidence of possible improvements in sleep efficiency and total sleep time after introducing low (30 MME) to medium (60 MME) doses of morphine. Intriguingly, such improvement was only statistically significant when compared with measurements obtained while the patients were on their original non-opioid analgesics, but not with measurements obtained during the washout period when the patients were not using any pain medication at all. Moreover, the use of opioid therapy reduced REM sleep latency, from 113.9 min when the patients were using their original pain medications, to 84.1 min after the patients had gone through a 5-day washout period, and to 68.5 min at day 13 or 14 of the morphine sulphate treatment.

In summary, the available objective PSG findings based on low to medium opioid doses indicate that there are both risks and benefits associated with the use of opioid therapy. Whilst CNP patients could experience calmer sleep with less body and leg movements as well as fewer night time awakenings, these may occur at the risk of an increase severity in SDB and a much shortened REM latency. Intriguingly, neither of these PSG studies found the introduction of opioid therapy in CNP patients being associated with a reduction in SWS and REM and an increase N2 sleep as commonly seen in studies with healthy, pain-free volunteers [26].

3.5 The effect of opioid therapy on self-reported sleep

A number of validated and non-validated self-reported measures were used to assess subjective aspects of sleep. The validated measures included the Medical Outcomes Study Sleep Scale (MOS Sleep Scale) [51, 52], the Pittsburgh Sleep Quality Index (PSQI) [53] , the Epworth Sleepiness Scale (ESS) [54], and the Verran and Snyder Halpern Scale (VSH) [55]. Non-validated measures mainly took the form of single-item or multi-item ratings of sleep quality and quantity using different word anchors, numerical or analogue scales, and operational definitions of the concepts. Given the variety of measures used, below we report the findings by type of measure in an attempt to integrate results across studies.

Three studies used the MOS Sleep Scale, or a modified version of it, to assess overall sleep quality [37, 38, 44]. Findings of two of these studies evaluating the efficacy of hydromorphone converged to suggest an improvement in sleep disturbance, snoring, awakening due to shortness of breath or headache, when comparing the opioid therapy with a baseline without opioids [37, 38]. However, a study evaluating the efficacy of buccal buprenorphine found no differences in the pre-post treatment change in MOS sleep score between the buprenorphine and placebo groups [44].

Further disparities in results were observed between studies measuring sleep-related parameters using the PSQI, ESS, and VSH. Rauck et al. [43] reported a significant improvement in PSQI score suggesting better overall sleep quality after 8 weeks of morphine sulphate or oxycodone treatment compared to baseline, with the former treatment group showing greater improvement on PSQI than the latter. However, score data were not provided in the paper for further examination. Rosenthal et al. [49], on the other hand, noted a significant increase in ESS score suggesting greater daytime sleepiness after 14 days of morphine sulphate treatment. Simpson et al. [50] found no significant improvement in overall sleep quality as measured with the VSH following a 1-month long treatment

with transdermal fentanyl, although one of the eight subscales (VSH1) indicated a reduction in the number of awakenings during the night compared to baseline.

Three of the studies included questionnaires that contained a single item about sleep, respectively the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ-30 [56]), the SPAASMS score card, which contains one item for each of the following: S- Score for pain, P- Physical activity levels, A- Additional pain medication, A- Additional Physician/ER Visits, S- Sleep, M- Mood, S- Side effects [48], and the Multidimensional Pain Inventory (MPI [57]). Using the EQRTC-QLQ-30 item, Fredheim et al.[47] documented significant improvements in the sleep difficulties and fatigue ratings after up to 9-month of treatment with oral methadone. Using the SPAASMS item, Mitra et al. [48] reported no change in sleep quality rating at 12-month of treatment with either transdermal buprenorphine or fentanyl. Using the MPI item, Raja et al. [34] noted a small reduction in sleep disturbance rating following opioid therapy but not placebo treatment.

Eleven studies involved the use of non-validated single-item rating scales to measure sleep quality [33, 35, 36, 39-42, 45, 46, 48, 49]. All but two studies [33, 48] reported higher sleep quality ratings, reduced sleep disturbance frequency, longer sleep hours, or increased incidence of patients reporting sleep improvement or better sleep quality following opioid treatment and/or compared with placebo. Contradictory findings were noted between the two studies that asked participants to report their sleep duration at different phases of treatment. The mean number of hours of sleep reported increased from 6.1hr at baseline to 6.6hr following 14 days of treatment with morphine sulphate [49], but no differences were found following different oxycodone treatment regimens with or without morphine sulphate [33]. Similar inconsistency was observed within a study that used 2 single-item rating scales to measure sleep quality [40]. Whilst the proportion of patients reporting "mild or moderate problem sleeping" did not separate the transdermal fentanyl group from the placebo group, the percentage of

people reporting "severe insomnia" was nearly 3 times higher in the transdermal fentanyl than the placebo groups.

Only one study collected self-reported sleep data using a daily sleep diary [37], offering the opportunity to examine individual perceived sleep parameters such as sleep onset latency, total sleep time, number and length of awakening after sleep onset, sleep efficiency, and even subjective evaluations of how "enjoyable" sleep was the previous night. However, this study only required participants to keep a daily diary during the treatment periods, but not at pre-treatment baseline. Comparisons could thus only be made between different types of opioid release-method (immediate vs. extended) and timings of dose (morning vs. evening), which had no significant effects on any of the sleep diary parameters.

There was no clear pattern from the findings suggesting that sleep outcomes were associated with the dose and type of opioid tested. By dose, all but one trial [33] with low-dose opioids had positive sleep outcomes [35-37, 39, 42, 49]. Just over half of the trials that used medium-dose opioids were successful [34, 43, 45], whilst the remaining were not [49, 50]. Of the three trials that used high- to very high-dose opioids, one had positive self-reported sleep outcomes [46] but mixed results were reported in the other two [40, 47]. By type, trials that tested hydromorphone [37, 38], codeine [42], tramadol [35, 36, 39], oxycodone [33, 38, 41, 43] and morphine [34, 43, 45, 49] tended to have positive sleep outcomes, whilst inconsistent results were returned for trials that tested fentanyl [40, 46, 48, 50], methadone [34, 47], and buprenorphine [39, 44, 48].

3.7 Reported sleep-related AEs and attrition associated with opioid therapy

Presented also in Table 2 were the sleep-related AEs associated with the introduction of opioid therapy. "Somnolence", "sedation", "drowsiness" and "sleepiness" were the most frequently reported. Other sleep-related AEs reported included "insomnia" [36, 40], "nightmares" [33, 48] and "fatigue" [36, 37, 39, 44]. "Severe sedation and unresponsiveness" was reported as a serious AE in one study that used morphine sulphate [49].

The median attrition rate across the studies was 41.85%, with AEs being the first cause. Other most prominent causes of attrition were lack of efficacy, protocol violation, consent withdrawal and lost to follow-up. Whilst most studies did not specify the nature of the AEs cited as reasons for attrition, "somnolence" and "sedation" were listed as major causes of patient attrition in three studies that used transdermal fentanyl [46, 50] and methadone [47].

In the only study that specifically screened for sleep apnoea, two of the 22 participants enrolled were excluded during the titration phase due to "severe sleep apnoea" and a further patient (of the 15 who started treatment) had to be excluded during the treatment phase due to an AHI index >30, an indicator of severe sleep apnoea [37]. This level of attrition due to impaired respiratory function highlights the importance to screen for symptoms/vulnerabilities of sleep apnoea before administering any opioid therapy, and continued monitoring during ongoing treatment.

In summary, the balance of the evidence from self-reported sleep measures appears to suggest an improvement in overall sleep quality under low to medium dose opioid therapy. However, such an improvement is not consistently detected across studies and may be accompanied by an increase in excessive daytime sleepiness.

3.6 Exploratory meta-analysis
Data available from 5 RCTs, involving a total of 444 person-count in the opioid therapy group, were used to perform an exploratory meta-analysis [33-37]. As evident in Figure 4, the overall effect of opioid therapy on sleep quality was found to be significantly better than control or non-opioid therapy (Z=3.73, p=0.0002). The size of the effect was 0.36 (*95% CI* 0.17, 0.54), which is a small effect size. Heterogeneity between the studies was not detected as an issue (I^2=35%), despite the range of study designs and sleep quality measures used. Visual inspection of the forest plot suggested that the

Webster study [37] contributed most to the effect. Since this study was also the only study in this analysis that set out to examine the effect of opioid therapy on sleep, a sensitivity analysis was carried out by without the Webster study [37]. This reduced the level of heterogeneity to 0%. The effect of opioid therapy on sleep quality attenuated to 0.27 (*95% CI* 0.13, 0.40) but remained statistically significant (Z=3.73, *p*=0.0002). Examination of the asymmetry of the funnel plot (Figure 5) revealed possible biases with studies of greater precision producing smaller or no effect.

(Insert Figures 4 & 5 about here)

4. Discussion

Our synthesis of 18 opioid treatment studies aimed to clarify the effect of opioid therapy on sleep architecture and sleep quality in patients with CNP. The size of the corpus was smaller than expected, considering the high prevalence of opioid therapy [58, 59]. Most of the studies reviewed had sleep as a secondary outcome. Only two studies had sleep as the primary treatment outcome, measuring not only self-reported changes in sleep experience but also more subtle alterations in sleep architecture and physiology. However, both of these studies had small sample sizes and were exposed to more than one source of risk of bias. With several initiatives that call for more comprehensive assessment in pain trials to cover – beyond pain – related outcome domains important to patients [13, 58, 60, 61], there is a trend for newer opioid trials to report treatment associated changes in sleep and fatigue [62]. It is hopeful that a larger and stronger body of research will be available for analysis in future revisions of this systematic review.

For now, based on the studies identified for the current review, the balance of the evidence suggests that the use of opioid therapy in CNP with short to medium term outcomes (max=12 months) is associated with a report of improved overall sleep quality. That said, it must be emphasised that there were inconsistencies in the direction and strength of the sleep improvement findings within and across studies. Meaningfulness of the sleep improvement was not always discussed, even in studies using

validated instruments such as the PSQI and MOS-Sleep Scale that have established score interpretation and cut-offs [37, 38, 43, 44]. Whilst statistical significance of such improvement was found in the exploratory meta-analysis, the magnitude of change was small (SMD = 0.36), such that there is 60% chance that a person randomly picked from the opioid therapy group would have a better overall sleep quality rating than the control group. If we assume that the control group have 10% clinically significant outcome, we need to treat 12.8 more people in order to have one more clinically significant improvement in overall sleep quality in the opioid group. The exploratory meta-analysis was conducted with a selected subset of data, restricted by the heterogeneity in trial design, the type and dose of opioids used, and outcome measures used across studies. It only served as a broad estimation of the possible improvement in self-reported sleep quality following opioid therapy. A high level of caution is required for the interpretation of the results, given the potential publication bias towards positive findings with studies of greater precision producing smaller or no effect.

We cannot tell from the available evidence whether the reported improvement in sleep quality differed by the type or dose of opioid used, although we note that trials testing low-dose opioids tended to have positive self-reported sleep outcomes [35-37, 39, 42, 49] whereas no improvement in sleep quality was found in all of the three studies that used transdermal or buccal buprenorphine [39, 44, 48] and in three of the four studies that used transdermal fentanyl [40, 48, 50]. The majority of the studies used low- to medium-dose opioids. Outcomes in the very high- [47] and high- [40, 46] dose opioid trials did not appear superior to those of trials that used opioids in the mediume- to low-dose range, as the proportion of studies reporting a positive impact on sleep quality was identical (67%) across both ends of the dose spectrum.

The limited PSG data suggest that opioid therapy may have mixed effects on objectively measured sleep parameters [37, 49]. Neither of the PSG studies replicated the sleep disruptive effects (e.g., reduced SWS and REM and increased N1 and N2 sleep) commonly observed following the acute

administration of opioids to healthy pain-free volunteers [16, 63]. Such inconsistent findings may be attributed to the differences in sample characteristics and their interactions with the opioids tested, although future research is required to verify this speculation. Whilst positive changes were observed in the reduction of leg and body movements, minutes of night time awakenings and hence an increase in sleep efficiency, no significant improvements were seen in other important parameters associated with better sleep quality, e.g., (shorter) sleep onset latency, (reduced) number of arousals, (increased) N3 or SWS. It must also be emphasised that, in both trials that had PSG data, more than half of the reported parameters were still within the clinical range at the end of the treatment period (e.g., sleep efficiency < 85%; sleep onset latency >30min; wake after sleep onset >30min [37]). Only one of the two trials reported an increase in total sleep time [49]. In this trial [49], REM latency was also shortened by an average of 16 minutes from baseline to after the opioid therapy. The clinical significance of this finding is unclear as it may only be an artefact of a REM rebound due to pain relief. It is also unclear whether the shortened REM latency was experienced positively or negatively by the patients. REM sleep plays an important role in emotion regulation and affective memory consolidation. A shorter REM latency and an increased REM intensity have been associated with a range of psychiatric symptoms and disorders (e.g., depression, mania, suicidality [64-68]). These findings together present a paradox, as the patterns of changes in objectively measured sleep parameters neither correspond with the self-reported improvement in sleep quality nor do they present a picture of normal sleep following opioid therapy.

Although not the focus of the present review, the only selected study that screened out patients with sleep apnoea showed that opioid therapy increased the mean number of apnoea events (measured by the AHI score) from the 'mild' to the 'moderate' level in patients supposed to be 'safe' to initiate treatment [37]. Notably, of the 14-strong 'safety sample', three further patients had to be excluded during the treatment phase of the study: two in the titration phase because of "severe sleep apnoea" and one due to "unacceptably high AHI score during the final sleep study" [37]. These findings

underline the risk of opioids-induced SDB as established in previous reviews [14, 16, 69]. The respiratory depression effect was particularly strong for extended-release opioid administered in the evening, compared to a morning administration and to the immediate-release formulation [37]. That said, it must be noted that acute use of low-medium dose of morphine does not always worsen SDB, even in high-risk patient samples of pre-existing OSA or on methadone maintenance treatment [27, 70].

On the issue of safety, there was little information on the AEs' definition, threshold for report and impact on the patient's functioning. The most frequently cited sleep-related AEs and reasons for attrition across the reviewed studies were "somnolence", "sedation", "drowsiness" and "sleepiness", suggesting the opioids acted as a double-edge sword for patients when arousal-altering effects were non-specific in timing. Two recent studies have shed new light on the nebulous mechanisms underpinning the arousal-altering function of opioids. Montandon et al. [71] have shown in a paediatric population that preoperative morphine induced a sedative state marked by reduced frontal high-frequency EEG power in the beta range and reduced frontal-occipital beta activity coherence. This may be linked to the loss of sustained attention associated with the use of opioids. In a separate study, reductions in beta power and coherence were found to be strongly, positively correlated with depression in respiratory rate induced by morphine, suggesting that the severity of respiratory depression is associated with reductions in cortical arousal [72].

The discussion above must be considered in light of the limitations of the studies reviewed, with 25% being very small (n<50) and 33% non-RCTs. Amongst the RCTs, a specific concern is concerned with the randomised-withdrawal enriched-enrolment design, where only drug-responders are retained in the trial, which could inflate therapeutic effects. As there was no control in the analyses for the effect of rescue medications, one could argue the trials that authorised such rescues were actually examining the combined effect of opioids and non-opioids analgesics, rather than the effect of opioids on their own. The overall risk of bias assessment revealed that all studies were at 'high' risk of bias,

except 3 that were considered of 'unclear' risk. The risk of bias assessment was conservative, avoiding assumptions in the absence of information, leading to markings of 'unclear' risk for studies that provided insufficient details. Hence, the judgement of 'unclear risk' does not preclude the possibility of a high risk of bias in studies with thin reporting. Clearly, there is much room for future opioid trials to improve on their conduct, reporting, and on the inclusion of more and better sleep outcomes.

In terms of future research directions, aside from striving for better-quality trials with longer follow-up periods, two interesting observations gave us some food for thought:

First, there is poor concordance in the direction of change between the self-reported and objective findings of sleep. Patients can report an improvement in their sleep quality when the severity of SDB has increased and without significant changes in important parameters reflecting deeper and more restorative sleep. Patients' reported improvement of sleep quality can also be accompanied by a reported increase in daytime sleepiness, which is not what we would normally expect with night time sleep improvement. This phenomenon is perplexing, and it is more than just the subjective-objective discrepancy between people's perception of sleep and technologies' estimation of sleep [73-77]. Here, the mismatch in perception is across sleep parameters. We hypothesise that it may be linked to how people reconcile an array of varying, ambiguous bodily information in order to make a categorical judgment whether sleep has improved or not after opioid therapy. If we conceptualise the phenomenon this way, the sleep quality judgment can be understood as a decision-making process whereby people will have to combine all information that they are aware of to make a single response. This hypothesis is supported by our recent work demonstrating that sleep quality is indeed a judgement that can be influenced by different information, including memories from the pre-sleep period, feelings upon-awakening and next day events [78]. People put more weight on total sleep time, feeling refreshed upon waking and mood during the day than on other factors when they make their

judgement of sleep quality [78]. We suspect similar information processing is required when patients are being asked to decide whether the new opioid therapy has improved their sleep quality. The decision could be challenging, and much more variable over time, if the opioid therapy has resulted in mixed improvements (e.g., fewer awakenings in the night, just about the same hours of sleep, but greater drowsiness during the day). Also, they may not be aware of higher number of apnoea events, since they may be too brief to be detected, processed, and/or registered in memory. It raises the question whether in future trials where PSG assessments are carried out, patients should be explained their sleep studies' results before expressing a judgement on the drug's effect on sleep.

Second, many patients believe pain is the main cause of their sleep problems, and as a result, they think getting rid of the pain is a prerequisite to restoring a normal night's sleep [79]. Accordingly, the pain-reliving and hypnotic properties of opioids do make them an attractive option for chronic pain patients with concomitant sleep disturbances [80]. Does the use of opioid therapy bring about better sleep through pain reduction? This question will require future trials with more frequent assessments of both pain and sleep throughout the treatment process, to allow for a proper mediation analysis. Although, we note from our data that 5 of the 18 (27.8%) reviewed studies found no significant improvement in overall sleep quality or day-to-day reports of sleep experience even when opioids demonstrated benefits on pain [33, 40, 44, 48, 50]. Therefore, it appears that pain reduction is not a sufficient condition for sleep to improve. Even if an indirect effect from reduced pain to improved sleep exists, the strength and longevity (both across development of tolerance or following washout) of this effect needs to be determined. If the indirect therapeutic benefit of opioids on sleep is small, short-lived, and/or not guaranteed, such information should be made available in prescription guidelines and shared with patients when making a treatment decision. Such a suggestion would be in line with the recommendation that deciding whether or not to initiate/stop opioid therapy should be based on an informed, collaborative risk/benefit analysis between patients and physicians [1, 8, 10, 81, 82]. Alternative interventions to promote sleep should also be offered; there is good evidence for the efficacy of

cognitive-behavioural interventions for insomnia in this population [83]. New generations of hybrid interventions that target simultaneously pain and sleep issues, both in secondary and primary care, are being developed [84-87]. Given the bidirectional link between sleep and pain, the effects of these interventions on sleep and indirectly on pain and down the line on opioid-sparing should be studied.

In closing, the current systematic review has identified a set of papers with relevant outcomes regarding the effect of opioid therapy on sleep quality and sleep architecture in CNP patients. It extends our understanding from the drug's respiratory depression effect in healthy individuals to the potential risks and utility of opioid therapy for CNP patients with sleep disturbances. Whilst the narrative synthesis and the exploratory meta-analysis of a subset of data both suggest that the use of opioid therapy is associated with an overall report of sleep quality improvement, such an improvement is not consistently replicated across studies or substantiated by improvements in sleep parameters linked to deeper and better-sleep quality. Moreover, the improvement may be accompanied by undesirable side effects and increased daytime sleepiness that contradict with the very idea of improved sleep quality. We are also painfully aware of the methodological limitations of the studies reviewed; their exposure to different sources of biases has heightened the risk of result inflation. To many patients with CNP, improved sleep is a top priority when evaluating the performance of a new drug and non-drug intervention. If we were to advance our current understanding of the opioid-sleep relationship, future trials need to be designed with this interdisciplinary question in mind such that validated measures of sleep can be incorporated as an outcome measure alongside pain. Like pain, sleep is a multidimensional experience. It would be important for future opioid trials to take a more nuanced approach when assessing the effect of opioids on sleep. Different kinds of sleep measures reflect different dimensions of sleep, and there are scientific and clinical reasons to go for a combination of both self-reported and objective measure of sleep. This research approach should be applied to future studies examining the effect of new opioid therapy on CNP, as well as future trials looking into opioids tapering amongst patients on high doses

but are no longer deriving therapeutic benefits [88, 89]. This would be a timely item on the research

agenda riding on the emerging priority to reduce opioid use against the national/international

epidemic of misuse/overdose [7, 8, 58, 59, 90].

Practice Points:

1. Use a combination of validated self-reported measures (questionnaire, sleep diary, spouse report) and objective tools (actigraphy, PSG) for sleep assessment.

2. Inform patients and discuss the effect of opioids on sleep and daytime sedation when considering opioid therapy.

3. If a sleep study was performed before and after opioid therapy, explain the results to patients in full so they are aware of changes to their sleep physiology associated with the drug.

4. Offer alternative sleep interventions for CNP patients who seek opioid therapy as a sleep aid.

5. Routinely assess SDB before, during, and after opioid therapy, even for patients with low risk of sleep apnoea.

Research Agenda:

1. Future opioid trials should include sleep as an outcome, using well-validated sleep quality or architecture measures.

2. Future sleep intervention trials for CNP should include pain and analgesic (including opioid) use as outcomes.

3. Developing a consensus as to which sleep measure(s) should be recommended as core outcome measure(s) in RCTs.

4. To identify the PSG signature of opioids both in terms of macro- and micro-sleep architectural changes.

5. To examine the effect of long-term opioid use (>12 months), opioid switching and opioid tapering on sleep.

6. To investigate the potential opioid-sparing effect of sleep intervention for CNP.

7. To identify the biological, psychological, and contextual factors that influence people's drug preference and categorical judgment of sleep quality following opioid therapy.

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Figure 1. Flow diagram of the study selection process

```
┌─────────────────────────────┐
│ Records identified through  │
│    database searching       │
│       (n = 2010)            │
└─────────────────────────────┘
              │
              ▼
┌─────────────────────────────┐        ┌─────────────────────────────┐
│ Titles/Abstracts screened   │───────▶│     Records excluded        │
│        (n = 255)            │        │        (n = 172)            │
└─────────────────────────────┘        └─────────────────────────────┘
              │
┌──────────────────────────┐            ┌─────────────────────────────┐
│ Records identified from  │            │ Full-text articles excluded │
│ citations and reference  │──────▶     │ by (primary) reason for     │
│    lists (n= 21)         │            │        exclusion            │
└──────────────────────────┘            │        (n = 86)             │
              │                         │  • Not an original study (n=1)│
              ▼                         │  • Not CNP (n=1)            │
┌─────────────────────────────┐        │  • CNP duration criteria not │
│ Full-text articles assessed │        │    specified/established (n=29)│
│      for eligibility        │───────▶│  • Absence of a sleep outcome│
│        (n = 104)            │        │    measure (n=11)           │
└─────────────────────────────┘        │  • Not a RCT or uncontrolled │
              │                         │    treatent studies (n=4)   │
              ▼                         │  • Patients were diagnosed with│
┌─────────────────────────────┐        │    sleep apnea, a significant│
│   Studies included in       │        │    physical or psychiatric illness, or│
│  qualitative synthesis      │        │    substance misuse/dependence│
│        (n = 18)             │        │    (n=4)                    │
└─────────────────────────────┘        │  • The study included/allowed a│
                                        │    concurrent pharmacotherapy│
                                        │    for pain, sleep or mood (n=32)│
                                        │  • The study included/allowed a│
                                        │    concurrent psychological │
                                        │    intervention (n=1)       │
                                        │  • The study was published in a│
                                        │    language other than English,│
                                        │    German or Italian (n=1)  │
                                        │  • Full-text not available (n=2)│
                                        └─────────────────────────────┘
```
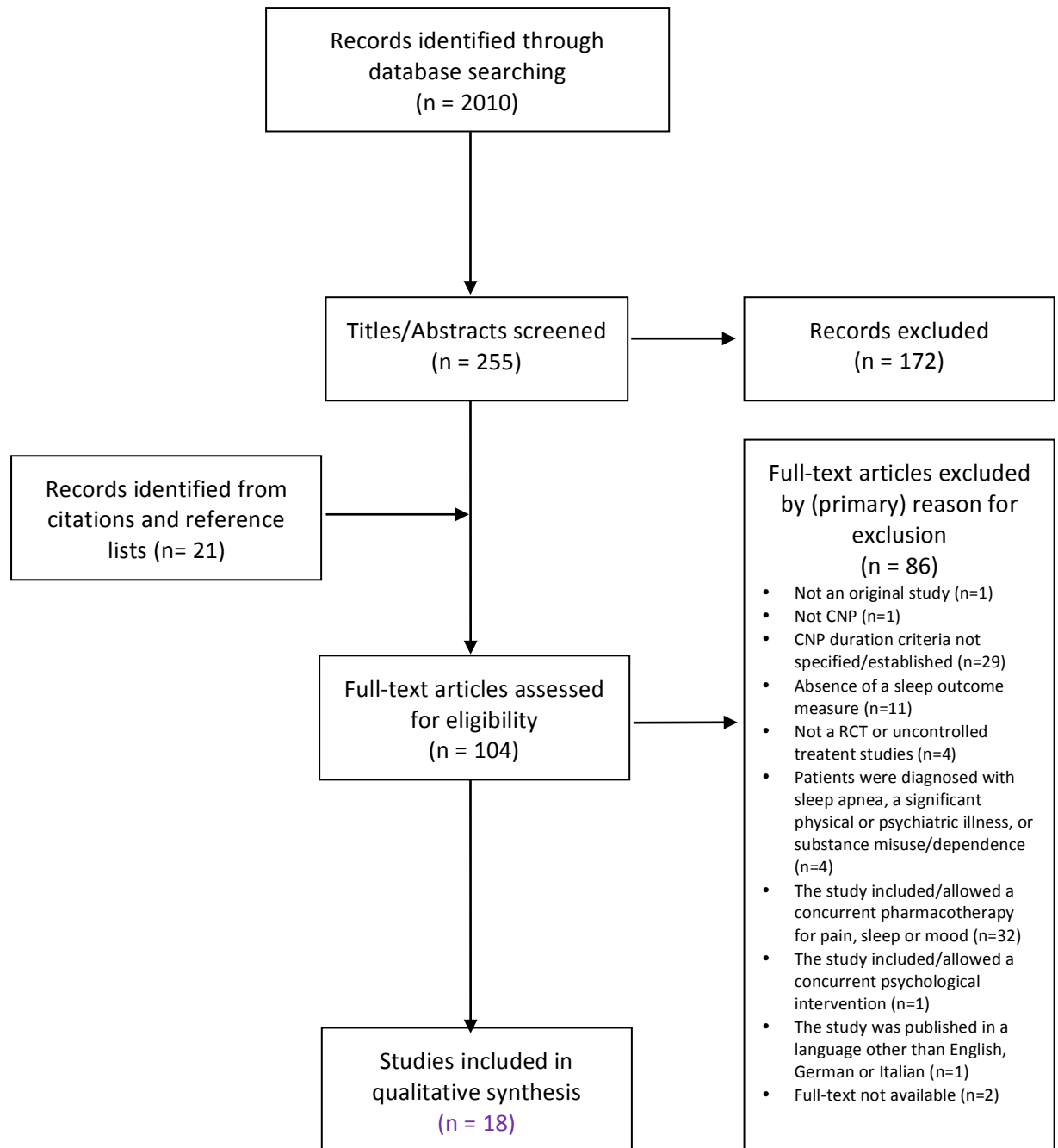
Figure 2. Risk of bias of all included studies. Review authors' judgements about each risk of bias item presented as percentages across all included studies. Other bias refers to potential conflicts of interest.
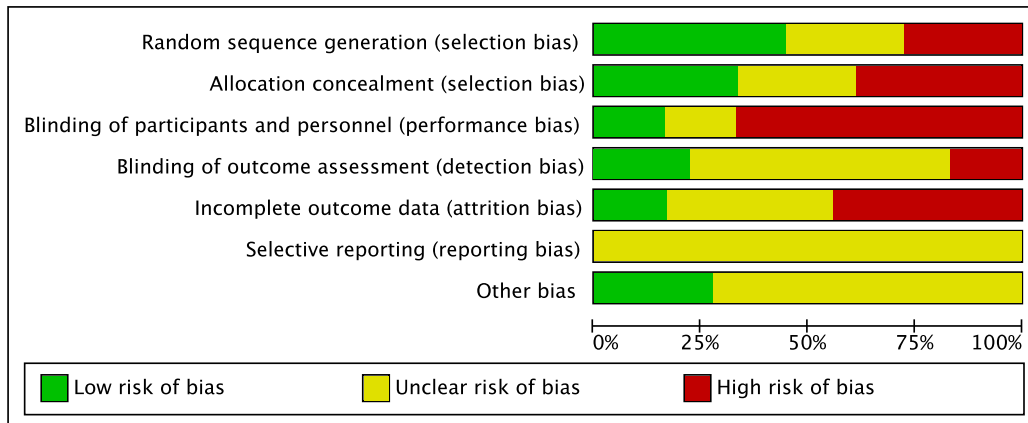
Figure 3. Risk of bias summary. Review authors' judgements about each risk of bias item for each included study [with their respective reference number] are presented. Other bias refers to potential conflicts of interest.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Adams 2006 [45]	−	−	−	?	+	?	?
Collado 2008 [46]	−	−	−	−	?	?	+
Fredheim 2006 [47]	−	−	−	−	−	?	+
Gajria 2008 [38]	+	−	−	?	?	?	?
Jamison 1998 [33]	?	−	−	?	?	?	+
Karlsson 2009 [39]	+	+	−	−	+	?	?
Langford 2006 [40]	+	+	+	+	−	?	?
Ma 2007 [41]	?	?	?	?	?	?	+
Mitra 2013 [48]	+	?	−	+	−	?	+
Peloso 2000 [42]	?	?	?	?	?	?	+
Raja 2002 [34]	+	+	+	+	−	?	+
Rauck 2006 [43]	+	+	−	?	−	?	?
Rauck 2016 [44]	?	?	−	?	−	?	?
Rosenthal 2007 [49]	−	−	−	+	?	?	?
Simpson 1997 [50]	−	−	−	?	?	?	?
Thorne 2008 [35]	?	?	?	?	+	?	?
Vorsanger 2008 [36]	+	+	+	?	−	?	?
Webster 2015 [37]	+	+	−	?	−	?	?

Figure 4. A forest plot comparing the effect of opioid therapy with placebo or non-opioid therapy on sleep quality. Means were multiplied by -1 in those studies where a lower score on the sleep quality indicator was better, to correct for differences in the direction of the sleep quality scales used. Set = Set-dose oxycodone. Tit = Titrated-dose oxycodone + morphine sulphate. 200 = Tramadol 200mg. 300 = Tramadol 300mg. IR H = Immediate release hydromorphone. QAM = Extended release hydromorphone morning dose. QEM = Extended release hydromorphone evening dose. Reference number of each study is presented in square bracket.
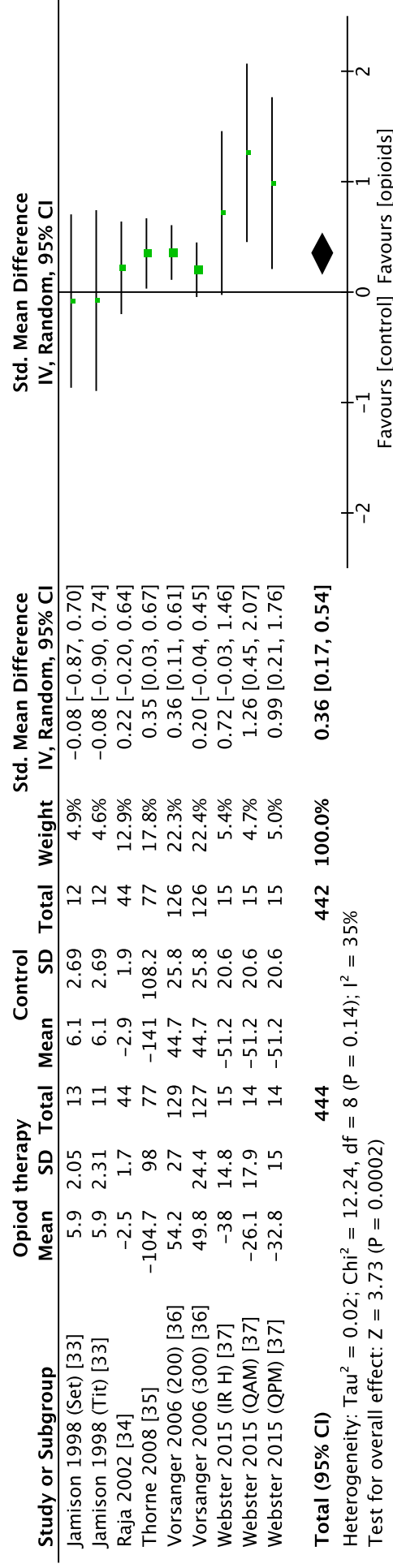

Study or Subgroup	Opiod therapy			Control			Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Jamison 1998 (Set) [33]	5.9	2.05	13	6.1	2.69	12	4.9%	-0.08 [-0.87, 0.70]	
Jamison 1998 (Tit) [33]	5.9	2.31	11	6.1	2.69	12	4.6%	-0.08 [-0.90, 0.74]	
Raja 2002 [34]	-2.5	1.7	44	-2.9	1.9	44	12.9%	0.22 [-0.20, 0.64]	
Thorne 2008 [35]	-104.7	98	77	-141	108.2	77	17.8%	0.35 [0.03, 0.67]	
Vorsanger 2006 (200) [36]	54.2	27	129	44.7	25.8	126	22.3%	0.36 [0.11, 0.61]	
Vorsanger 2006 (300) [36]	49.8	24.4	127	44.7	25.8	126	22.4%	0.20 [-0.04, 0.45]	
Webster 2015 (IR H) [37]	-38	14.8	15	-51.2	20.6	15	5.4%	0.72 [-0.03, 1.46]	
Webster 2015 (QAM) [37]	-26.1	17.9	14	-51.2	20.6	15	4.7%	1.26 [0.45, 2.07]	
Webster 2015 (QPM) [37]	-32.8	15	14	-51.2	20.6	15	5.0%	0.99 [0.21, 1.76]	
Total (95% CI)			444			442	100.0%	0.36 [0.17, 0.54]	

Heterogeneity: Tau² = 0.02; Chi² = 12.24, df = 8 (P = 0.14); I² = 35%
Test for overall effect: Z = 3.73 (P = 0.0002)

Favours [control] Favours [opioids]

Figure 5. A funnel plot of studies presented in Figure 4. Each circle represents an entry in the forest plot. The *x*-axis represents the study results as measured with standardised mean differences (SMD). The *y*-axis represents study precision as measured with standard error (SE) of SMD.
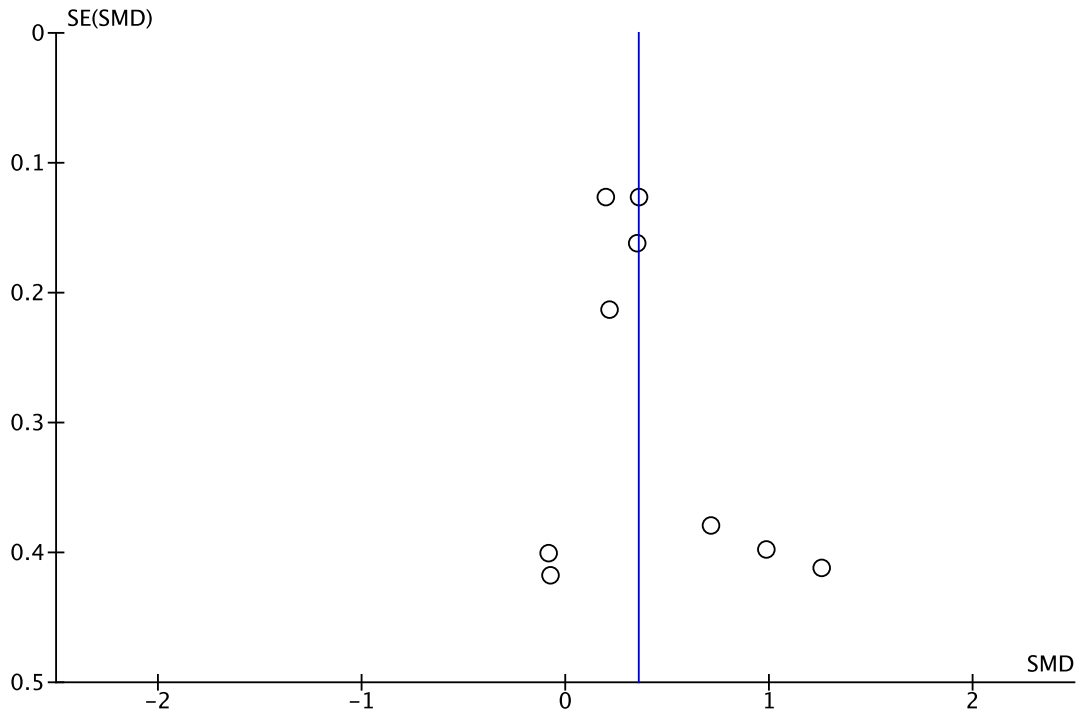
Table 1. Methodological Characteristics of Included Studies

Authors, yr [ref.];country	Study design	Opioids used	Participant group	Age (yr) at baseline	Female (%) at baseline	Received Rx (n)	Finished Rx (n)	Sleep measure(s)
Adams et al., 2006 [45]; USA	Single-treatment (non-randomised) Open-label Multicentre Phase IV 3 months	Morphine, ER	**Mixed CNP** with suboptimal pain control from non-opioid analgesics, short-acting single-entity opioid analgesics, controlled-release opioid, and/or combination analgesics containing opioids	48+	54	491	209	**Multi-item sleep assessment** 6 VAS (0 "never" or 0 "very poor" to 10 "always" or to 10 "excellent") Composite Sleep Score - based on the means of 5 item: trouble falling asleep; needing sleep medication; awakening by pain at night; awakening by pain in the morning overall sleep quality
Collado & Torres, 2015 [46]; USA	Single-treatment (non-randomised) Open-label 6 months	Fentanyl, transdermal and RM: Fentanyl, buccal transmucosal IR	**Mixed CNP** opioid naive, with pain not controlled by NSAIDS at adequate doses	57.6	54.4	215	203	**Quality of sleep** Self-report based on sleep duration ("poor" if <6 consecutive hrs of night sleep)
Fredheim et al., 2006 [47]; Norway	Single-treatment (non-randomised) Open-label 9 months	Morphine, ER vs. Methadone	**Mixed CNP** with poor pain control or unacceptable side effects during treatment with morphine	60.2	41.6	12	7	**Sleep difficulties** A single item from EORTC QLC-C30, a HRQoL questionnaire containing 5 functioning scales, eight symptom scales, global health status and financial impact.
Gajria et al., 2008 [38]; USA	Randomised Open-label Parallel-group Multicentre 6 weeks	Hydromorphone, ER vs. Oxycodone, ER	**Chronic OA knee or hip pain** with moderate/severe pain despite stable doses of non-steroidal, non-opioid, anti-inflammatory therapy	63.5	69.4	138	74§	**Medical Outcomes Study Sleep Scale** A 12-item measure of sleep quality & quantity to generate scores for: sleep adequacy; sleep disturbance; snoring; awakening short of breath or with a headache; somnolence sleep index I (6 items) sleep index II (9 items)
Jamison et al., 1998 [33]; USA	Randomised (1 of 5 phases) Open-label Repeated-dose trial with 5 phases: pre-treatment washout, experimental with random assignment, titration for all patients, tapering for all patients, post-treatment washout 16 week treatment, 12 weeks taper, 1month follow-up (total 8 months)	**Titration phase:** Oxycodone, IR and morphine ER **Study treatment:** Oxycodone, IR, *Set-dose* vs. Oxycodone, IR, *Titrated-dose and morphine, ER* vs. Naproxen	**Chronic back pain** with moderate pain despite 'traditional pain treatment' e.g., back surgery, physical therapy, trials of medication	42.6	57.1	36	U/C	**Hours of sleep**
Karlsson & Berggren, 2009 [39]; Sweden	Randomised Open-label Parallel-group Multicentre Non-inferiority trial 12 weeks	Buprenorphine, transdermal vs. Tramadol, ER	**Chronic OA knee or hip pain** with moderate/severe pain, deriving inadequate pain relief from paracetamol 4000mg/day during screening	64.3	56.7	135	100	**Sleep disturbance** "How many nights have you woken due to pain in the past 7 nights?"
Langford et al., 2006 [40]; Canada, Czech Republic, Hungary, Poland, Slovakia, & UK	Randomised Double-blind Placebo-controlled Multicentre 6 weeks	Fentanyl, transdermal vs. Placebo	**Chronic OA knee or hip pain** with moderate/severe pain not adequately controlled with weak opioids, with or without paracetamol	66	66.5	399	199	**Quality of sleep** "Please rate the quality of sleep over the past 7 nights" (very poor, poor, fair, good, or very good." **Percentage reporting mild-moderate problems sleeping**
Ma et al., 2008 [41]; China	Randomised Double-blind Placebo-controlled 2-4 weeks study period, 28 days follow-up	Oxycodone, ER	**Chronic neck pain** with daily multiple episodes of actual flares and not responding to non-opioid medication	55.7	37.9	116	12	**Quality of sleep** "...rated as good, average, or bad..." **Percentage reporting severe insomnia**
Mitra et al., 2013 [48]; Australia	Randomised Open-label Parallel-group Feasibility study 12 months	Buprenorphine, transdermal vs. Fentanyl, transdermal	**Mixed CNP** opioid naive or experienced, with persistent pain for at least 1 yr	49	52	46	16	**Quality of sleep** One of 7 items on the SPASMS score card: Self-reported rating of sleep quality (0=Very good,1= good, 2=fair, or 3=poor)

Authors, yr [ref;]country	Study design	Opioids used	Participant group	Age (yr) at baseline	Female (%) at baseline	Received Rx (n)	Finished Rx (n)	Sleep measure(s)
Peloso et al., 2000 [42]; Canada	Randomised Double-blind Placebo-controlled Parallel-group Multicentre 4 week	Codeine, ER vs. Placebo	**Chronic OA knee or hip pain** requiring the use of acetaminophen, anti-inflammatory agents or opioid analgesics for the previous 3 months or longer	60.9	62	103	66	**Muti-item sleep assessment** A 7-item questionnaire on sleep. Four 100mm VAS described: trouble falling asleep; need medications to fall asleep; awakening by pain at night; awakening by pain in the morning No information on the remaining 3 items was provided.
Raja et al., 2002 [34]; USA	Randomised Double-blind Placebo-controlled Crossover trial 3x 8 weeks	Morphine, ER (alt.: methadone) vs. Nortriptyline (alt.: desipramine) vs. Placebo	**Chronic postherpetic neuralgia** with moderate to severe pain despite use analgesic and/or antidepressants	71	55.3	71	44	**Sleep interference** A single item from the Multidimensional Pain Inventory measuring the extent to which pain interfered with sleep (0-6)
Rauck et al., 2006 [43]; USA	Randomised Open-label Parallel-group Multicentre 8 weeks	Morphine ER vs. Oxycodone ER	**CLBP** with moderate to severe pain that has had suboptimal analgesic response to nonsteroidal anti-inflammatory drugs, acetaminophen and/or immediate-release opioids	50✤	61	392	266	**Pittsburgh Sleep Quality Index #** A 19-item validated multidimensional sleep scale evaluating sleep quality over the past month.
Rauck et al., 2016 [44]; USA	Randomised-withdrawal Double-blind Placebo-controlled Multicentre trial (with enriched-enrolment) 12 weeks	Buprenorphine, transmucosal buccal	**CLBP** opioid naive, with moderate to severe pain requiring continuous, extended around-the-clock analgesia	50.7	56.6	749 (T) 462 (Rx)	350	**Medical Outcomes Study Sleep Scale #** As described above (Gajria, 2008)
Rosenthal et al., 2007 [49]; USA	Single-treatment (non-randomised) Single-blind Placebo-lead-in Single-centre 8 to 14 days	Morphine, ER	**Chronic OA knee or hip pain** with reports of sleep disturbances	53.7	79	34	31	**Polysomnography** Recordings taken for 480 mins, R&K Scoring. Parameters examined: Sleep efficiency; Total sleep time; No. of awakenings; Latency to persistent sleep; Wake time after sleep onset; REM sleep latency; REM sleep; Stage 2 sleep; Stage 3/4 sleep **Hours of sleep** Self-reported average number of hours of sleep they were getting per night **Quality of sleep** Self-reported rating: 100-mm VAS scale; 0 = poor sleep, 100 = best sleep)
Simpson et al., 1997 [50]; USA	Single-treatment (non-randomised) Open-label 1 month	Fentanyl, transdermal	**CLBP** on short-acting oral opioids for at least 6 mths	48.5	60	68	50	**Veran and Snyder-Halpem Sleep Scale #** 8 VAS (anchors/unit of response not specified): No. of awakenings during the night; Amount of movement during sleep Awakening refreshed; Duration of sleep Time to fall asleep; Depth of sleep Abrupt awakenings; Degree of sleep disturbance **Composite Sleep Score** - sum of:
Thorne et al., 2008 [35]; Canada	Randomised Double-blind Crossover trial 2x 4weeks Followed with a 6-month open label extension phase	Tramadol, ER vs. Placebo	**Chronic OA knee or hip pain** requiring the use of acetaminophen, anti-inflammatory agents or combination opioid and non-opioid analgesics for at least 3 mths	61	55	100	75	**Multi-item sleep assessment** A 7-item questionnaire on sleep with 5 x100mm VAS (never to always) & a final item: no. of hrs of sleep **Composite Sleep Score** - sum of: trouble falling asleep; needed sleep medications to sleep; awakened by pain at night; awakened by pain in the morning

Authors, yr [ref]; country	Study design	Opioids used	Participant group	Age (yr) at baseline	Female (%) at baseline	Received Rx (n)	Finished Rx (n)	Sleep measure(s)
Vorsanger et al., 2008 [36]; USA	Randomised-withdrawal Open-label lead-in Double-blind Placebo-controlled Parallel-group Multicentre 12 weeks	Tramadol, ER vs. Placebo	**CLBP** with moderate/severe pain despite daily treatment with a NSAID, acetaminophen, opioid analgesic, COX-2 selective inhibitor, and/or muscle relaxant for at least 60-90 days prior to study	47.8	50	619	241	**Quality of sleep** Self-reported rating: overall quality of sleep on 100-mm VAS scale (e; 0 = very poor, 100 = excellent
Webster et al., 2015 [37]; USA	Randomised Open-label run-in Double-blind Placebo-controlled (within arm) Crossover trial 2x 14 days	**Titration phase:** Hydromorphone, IR **Study treatment phase:** Hydromorphone, ER vs. placebo QAM: 08:00-10:00 intake of active medication vs. QPM: 20:00-22:00 intake of active medication	**CLBP** without sleep apnoea, using long-term opioid therapy or qualified for around-the-clock opioid therapy for an extended amount of time	44.4	60	22	12	**Polysomnography** 1 night of recording for each of 4 sleep studies. AASM Scoring. Parameters examined: AHI; Sleep onset latency; Sleep efficiency Min. of wake time after sleep onset; Min. in stages 1-4 sleep REM sleep; Respiratory events No. of arousals from sleep ; No. of leg movements Body position changes during sleep **Modified Medical Outcomes Study Sleep Scale #** (modifications N/S) 6 domains reported: Sleep disturbance; Snoring; Awakening short of breath or headache; Sleep quantity Daytime somnolence; Sleep problem index **Sleep Diary** Completed daily, including the following: Sleep onset latency; Total sleep time; How enjoyable was your sleep last night? No. of awakening after sleep onset; Wake time after sleep onset Sleep efficiency; How well do you feel this morning?

Notes. Included studies are presented by lead author's alphabetical order.

N/S = Not specified.+ = And; Vs. = Versus; T = Titration; Rx = Treatment; Yr = Year; Mth = Month; Wk = Week; Hr or h = Hour; Min = Minute; No. = Number; U/C = Unclear; cannot work out the total number of patients completing treatment due to reporting; Alt.= Alternative

♣Median age reported. § Taking into account a subsequent site exclusion due to NIDPOE= Notice of Initiation of Disqualification Proceedings and Opportunity to Explain by the US Food and Drug Agency's Division of Scientific Investigation. ‡ Based on calculation subtracting the number of discontinuation from the stated sample of the respective study phase in the flow diagram, but we noted that the numbers in flow diagram did not add up and were inconsistent with the numbers provided in the text. # Validated sleep questionnaire

Opioids: unless specified otherwise, medications are oral; ER = Extended release (including Controlled release, Slow release, Sustained release) ; IR = Immediate release; QAM= morning dosing, QPM: evening dosing.

AASM = American Academy of Sleep Medicine (2007 scoring manual); AHI = Apnoea-hypopnoea Index; CLBP = Chronic low back pain; CNP = Chronic non-malignant pain; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire; HRQoL = Health-related Quality of Life; OA = Osteoarthritis; R&K = Rechtschaffen & Kales; REM = Rapid eye movement; SPAASMS = On this score card, treatment progress was studied across seven domains: score of pain (S), physical activity (P), additional rescue medication (A), additional general practitioner/emergency department (GP/ED) visit (A), sleep quality (S), mood (M), and side effects of pain medication (S). VAS = Visual analogue scale.

Table 2. A Summary of Relevant Findings of Included Studies

Authors, yr [ref;]country	Opioids regimen	Daily dose in MME	Attrition Reason/timing (n)	Adverse events/Serious adverse events Sleep-related AE/SAE: (n)	Sleep outcomes	Pain outcomes	Risk of bias^
Adams et al., 2006 [45]; USA	Morphine sulphate, ER	**Start dose:** 30 MME **Mth 1 mean:** 66 MME **Mth 3 mean:** 74 MME	**Total:** 282/491 patients (57.4%) did not take the drug for the total planned duration. 171 (34.8%) discontinued treatment drug prematurely. Reasons for discontinuation at Baseline, Mth 1-2, and Mth 3:	**Total:** Opioid-related AEs - N/R; 25 SAEs - 2 were considered drug-related requiring hospitalisations for vertigo, nausea and vomiting **Sleep-related AE/SAE:** N/R	<u>Multi-item sleep assessment (Self-report)</u> Composite Sleep Score significantly reduced from 5.73 at baseline to 4.96 at Mth 3. Significant improvements from baseline to Mth 3 were observed for 2 of the 4 individual VAS items reported; awakening in the morning and need for sleep medication.	<u>Mean one-day pain score (0-10 VAS; 0=no pain; 10=worst possible pain you can imagine) (self report)</u> significantly decreased from 7.83 at baseline to 5.84 at Month 3	High
Collado & Torres, 2015 [46]; USA	**Transdermal fentanyl (TTS)** Start dose:12 µg/h Increases by 25 µg/h Max 125 µg/h *and* **RM: Oral transmucosal fentanyl citrate, IR** (OTFC) 400 µg/dose as needed **Max dose:** 300 MME	**Start dose:** 30 MME **Mth 1 mean:** 104 + RM 160 MME **Mth 3 mean:** 118 + RM 120 MME **Mth 6 mean:** 127 + RM 105 MME	**Total:** 12 /215 patients (5.6%) discontinued due to side effects Reasons for discontinuation at Mth 1, Mths 2-5, and Mth 6: **Mth 1** Nausea/vomiting (7,-,-) Somnolence (1, 1, 1) Dermatitis(-,1,-) **Mth 6** Somnolence (85)	**Total:** 270 records in Mth 1: 172 records in Mth 6 **Sleep-related AE/SAE:** **Mth 1** Somnolence (86) **Mth 6** Somnolence (85)	<u>Quality of sleep (poor, if <6 consecutive hrs of night sleep) (self report)</u> % of patients (n=215) with 'poor quality sleep' decreased from 99% at baseline to 2.8% at the end of the study (after 6 mths of treatment)	<u>Mean pain intensity 0-10 VAS score (self report)</u> decreased from 9.9 (SD=0.35) at baseline to 2.1 (SD=2.05) at the end of the study % of patients with inadequate pain control (pain intensity VAS>4) decreased from 100% at baseline, to 2.3% at the end of the study	High
Fredheim et al., 2006 [47]; Norway	**Baseline treatment:** Oral SR morphine Mean 202 mg/day **Baseline:Morphine** Switch over course of 3 days to methadone **Study drug: Oral methadone** Start dose: 3x5 mg/day Increases by 5 mg over 1 wk No max	**Treatment max dose:** N/R **Baseline:** Mean 202 MME **Wk 2 mean:** 513 MME **Mth 3 mean:** 564 MME **Mth 9 mean:** 568 MME	**Total:** 5/12 patients (41.6%) switched back to morphine Reasons for discontinuation at 3-day opioid switching, 1-wk titration, and 4-wk consultation: Insufficient pain control (1,-,-) Insufficient pain control & anxiety (1,-,-) Sedation (-, 1,-) Drowsiness (-, 1,-) Profuse sweating (-,-, 1)	**Total:** N/S **Sleep-related AE/SAE:** **1-wk titration** Sedation (1)	<u>Single-item sleep difficulties scale (self report)</u> Mean values indicated a slight decrease in sleep difficulties (*Outcome data not provided) 4 patients reported a clinically significant decrease of sleep difficulties, and 5 patients reported a decrease of fatigue, at 9-mth compared to baseline	<u>Brief Pain Inventory 0-10 NRS score (self report)</u> The average decrease in mean pain intensity was 4 at baseline and 2.9 at 9-mth (n=6) follow-ups. <u>EORTC QLQ-C30 pain symptom scale (self report)</u> Mean reductions in pain symptom scale were 24, 29 and 38 at 2-wk, 3-mth, and 9-mth compared to baseline. A change of >10 on the 0-100 scale was considered clinically significant	High

Authors, yr [ref]; country	Opioids regimen	Daily dose in MME	Attrition Reason/timing (n)	Adverse events/Serious adverse events (n) Sleep-related AE/SAE (n)	Sleep outcomes	Pain outcomes	Risk of bias^
Gajria et al., 2008 [38]; USA	**Hydromorphone** (OROS; Osmotic CR oral delivery system) Start dose: 8 mg/day Increases by 8mg Max: 64 mg/day **vs. Oxycodone** (twice-daily ER) Start dose: 20 mg/day Increases by 10-40 mg/day Max:160 mg/day	**Treatment mean dose: N/R** **Hydromorphone** Start dose: 32 MME Increases by 32 MME Max: 256 MME **vs. Oxycodone** Start dose: 30 MME Increases by 15-60 MME Max 240 MME	**Total:** 57 /140 patients (40.7%) at randomisation # Reasons for discontinuation after randomisation and during treatment (OROS:ER) Protocol violation (1, :-) Lost to follow-up (1, :-) Lack of efficacy (-, 1.3) Adverse events (-, 25-22) Consent withdrawn (-, 1.2) Administrative reasons (-, 1:0)	**Total:** 4 records of SAE and 169 records of AE for the 138 who received OROS: ER # **Sleep-related AE/SAE:** Somnolence (18 : 12)	**MOS Sleep Scale (self report)** OROS showed significant but small improvements on sleep quantity, snoring, awakening short of breath, stiffness, both sleep problem indices, compared to baseline.	**OA symptoms & disability (WOMAC) (self report)** Both treatments showed large reductions in pain, stiffness, physical function and the global score, compared to baseline.	High
Jamison et al., 1998 [33]; USA	**Titration phase:** (Titrated-dose Oxycodone, IR + morphine sulphate; SuR) Max total: 200MME **Study treatment:** Set-dose oxycodone: Max: 30 MME Titrated-dose oxycodone: IR Max 20 mg/day **vs.** **IR** **vs.** **Naproxen** Max 1000 mg/day	**Titration phase:** Mean: 62 MME Max: 200 MME **Study treatment:** Set-dose oxycodone: Max: 30 MME Titrated-dose oxycodone: Mean: 41 MME; Max: 130 MME **SuR** Max 200 MME total MME. The conversion factor is not reported * Means and max were provided in MME	**Total:** 1/36 patients (0.03%) dropped out at Mth 7 (during the titration phase) * In addition, 3 patients (1in titrated-dose and 2 in set-dose) discontinued after Mth 1 due to intolerance to the drug; Another 3 patients discontinued as they could not tolerate the adverse effects of opioid during the titration phase.	**Total:** N/R **Sleep-related AE/SAE:** Drowsiness (14.6 : 22.1 : 36.9) Nightmares (1.0 : 1.0 : 1.7)	**Hours of sleep (self report)** No differences in hrs of sleep were found between groups during the Experimental Phase. The mean (SD) no. of hrs of sleep by group (No opioid : Set dose : Titrated dose) were 6.1 (2.69) 5.9 (2.05) and 5.9 (2.31). No differences in hrs of sleep were found for changes in opioid dose. The mean no. of hrs of sleep by changes in dose (reduction of 5-75 mg : reduction of 5-110 mg : no change : increase of 5-110 mg : increase of >110 mg) were: 6.2, 5.8, 6.0, 6.3, and 5.8.	**Pain ratings (average, current, highest, lowest; 0-100; 0=none, 100=worst possible pain) (self report)** Mean scores for pain ratings decreased in all groups during the Experimental Phase. Mean (SD) pain rating (0-100) was 65.5 (19.05) for the No Opioid group (n=12), 59.8 (16.65) Set Dose group (n=13) and 54.9 (15.87) for the Titrated Dose group (n=11). The titrated-dose group had less pain than the other two groups. Both opioid groups also were found to have significantly less pain than the naproxen-only group. A curvilinear relation was found between weekly dose change and pain ratings. Patients who either increased or decreased their dose reported less pain than those who did not change their dose. The mean average pain rating by changes in dose (reduction of >75mg : reduction of 5-75mg : no change : increase of 5-110mg : increase of >110mg) were: 54.6, 58.8, 63.6, 55.8, and 55.9.	High
Karlsson & Berggren, 2009 [39]; Sweden	**Transdermal buprenorphine** Patch dosage: 5, 10, or 20 ug/h Max: 20 ug/h **vs.** **Tramadol, ER** Pill dosage: 75, 100, 150, or 200 mg Max :400 mg/day **RM:** Paracetamol (<2000 mg/day)	**Treatment start and mean dose: N/R** **Buprenorphine:** Max dose: 40 MME **vs.** **Tramadol:** Max dose: 40 MME	**Total:** 35/135 patients (25.9%), 14 in the buprenorphine group. 21 in the tramadol group Reasons for discontinuation between randomisation and end of strudy (Buprenorphine:Tramadol): Adverse event (10 : 19) Protocol violations (3 : 0) Withdrawal of consent (0 : 1) Lost to follow-up (0 : 1) Other (1 : 0)	**Total:** 226 AEs reported in 61 patients (88.4%) in the buprenorphine group and 152 AEs reported in 51 patients (78.5%) in the tramadol group. Timing of AEs unspecified. **Sleep-related AE/SAE** (Buprenorphine:Tramadol); Fatigue (10 : 12)	**Sleep disturbance frequency (self report)** Decreased by 2 nights from baseline to study completion in both treatment groups (Buprenorphine=2.5 nights : Tramadol=2.9 nights). Groups did not differ significantly **Quality of sleep categorical rating (self report)** Improved by at least 1 sleep quality category from baseline to study completion in both treatment groups (Buprenorphine=59% : Tramadol=48%). Groups did not differ significantly	**Pain intensity change (BS-11) (self report)** Decreased mean BS-11 pain score from baseline to study (-2.26 : -2.09). Groups did not differ significantly **OA symptoms & disability (WOMAC) (self report)** Both groups showed improvement on all scales. Groups did not differ significantly	High

Authors, yr [ref];country	Opioids regimen	Daily dose in MME	Attrition Reason/timing (n)	Adverse events/Serious adverse events Sleep-related AE/SAE (n)	Sleep outcomes	Pain outcomes	Risk of bias^
Langford et al., 2006 [40]; Canada, Czech Republic, Hungary, Poland, Slovakia, & UK	**Transdermal fentanyl** Start dose: 25 µg/h increases: 1 extra patch every 3 days Median: 1.7 patches= 42.5 µg/h Max: 100 µg/h **vs.** **Placebo** (patch of same aspect, median use = 2.4 patches) **RM:** Paracetamol up to 4 gr/day	Start dose: 60 MME Median dose: 102 MME Max dose: 240 MME	**Total:** 200/399 (50.1%); 96 in the Transdermal fentanyl group and 104 in the placebo group Reasons for discontinuation throughout study (Transdermal fentanyl : Placebo): Adverse event (54 : 20) Insufficient efficacy (15 : 64) Withdrew consent (17 : 13) Lost to follow-up (1 : 0) Other (9 : 7)	**Total:** 169 patients (78%) in the Transdermal fentanyl group and 101 patients (51%) in the placebo group reported ≥1 AE during the treatment phase; 51 fentanyl=36% : Placebo Group: 37%) **Sleep-related AE/SAE:** **During the treatment phase** (Transdermal fentanyl): Placebo) Somnolence (48 : 7) **During the tapering-off phase** (Transdermal fentanyl : Placebo) Insomnia (16 : 8)	<u>Change in Pain VAS from baseline (expressed with area under the curve) (self report)</u> Similar proportions in each group also reported mild or moderate problems with sleeping (Transdermal <u>% reporting severe insomnia (self report)</u> A higher proportion of patients receiving Transdermal fentanyl group reported severe insomnia (Transdermal fentanyl=22% : Placebo Group: 8%)	<u>Change in Pain VAS from baseline (expressed with area under the curve) (self report)</u> Treatment with transdermal fentanyl was associated with significantly better pain relief than that with the placebo patch; the primary end point of the AUCMBavg was 20±1.4 (mean ± SEM) for patients receiving transdermal fentanyl) and 14.6±1.4 for patients receiving placebo (P= 0.007)	High
Ma et al., 2008 [41]; China	**Oxycodone, CR** (Oxy-CR; per 12h) Start dose: 5-10 mg decrease at day 3 No max described	**Treatment mean and max dose: N/R** Start dose: 15-30 MME	**Total:** 104/166 patients (89.7%) throughout the whole study Reasons for discontinuation at Day 7 (Oxy-CR : Placebo) Itching (1 : 0) Nausea (0 : 1)	**Total:** 120 records of AE **Sleep-related AE/SAE:** **Day 7** (Oxy-CR : Placebo) Somnolence (6 : 0) **Day 14** (Oxy-CR : Placebo) Somnolence (1 : 0)	<u>Quality of sleep categorical rating (self report)</u> Oxy-CR group had significantly better outcome for sleep quality rating compared to placebo, from day 7 onwards At the end of study, the no. of people reporting good, average & bad sleep quality were: Oxy-CR: 5 (71.4%), 2 (28.6%), 0 (0%) Placebo: 0 (0%), 3 (60%), 2(40%)	<u>Pain intensity (0-10 VAS; VAS anchors N/S) (self report)</u> Oxy-CR group had significantly lower pain scores, compared to placebo, from day 7 onwards. The decrease plateaued at day 21 with 63% decrease from the baseline	Unclear
Mitra et al., 2013 [43]; Australia	**Transdermal buprenorphine** start dose: 12.5 µg/h **vs.** **Transdermal Fentanyl:** start dose: at 5µg/h Increase in both arms to optimal dose over 4 wks **RM:** Paracetamol or low-dose NSAIDs (dosage N/S)	**Treatment mean and max dose: N/R** Start dose: **Fentanyl:** 12 MME **Buprenorphine:** 25 MME	**Total:** 30/46 patients (65.2%) Side effects or reporting unsatisfactory pain (TDB: 8/22 : TDF: 8/24) *No further details given on attrition	**Total:** N/S **Sleep-related AE/SAE:** "Immediate side effects, namely **nightmares**, nausea and increased **drowsiness**, were shown to be more intense with TDF patch...TDB had a stronger delayed onset of adverse effects...More TDB users complained of local skin reactions, such as itching, redness, swelling, blisters, etc, ..."	<u>Quality of sleep rating (0=Very good,1= good, 2=fair, or 3=poor) from the SPAASMS score card (self report)</u> There were no significant differences between the two groups in SPAASMS scores. (*Outcome data not provided). Improvement in sleep quality for the initial 6 mths by both groups were not statistically significant. After 6 mths, sleep quality stabilised in both groups.	<u>Pain intensity NRS (0-10; 0 =no pain, 10=most pain) (self report)</u> No significant difference between groups and over time.	High

Authors, yr [ref];country	Opioids regimen	Daily dose in MME	Attrition Reason/timing (n)	Adverse events/Serious adverse events Sleep-related AE/SAE (n)	Sleep outcomes	Pain outcomes	Risk of bias^
Peloso et al., 2000 [48]; Canada	**Codeine, CR** (CR-C) start dose:50 mg/12h Weekly increases Mean: 159 mg/12h Max: 200 mg/12h **vs.** **Placebo** (identical looking pills) **vs.** **RM:** Acetaminophen 650 mg max 3x/day	Start dose: 7.5 MME Mean dose: 24 MME Max dose: 30 MME	**Total:** 37/103 patients (35.9%); 20 in the controlled-release codeine group and 17 in the placebo group. Adverse event (15 : 4) Unrelated illness (1 : 0) Inadequate pain control (1 : 5) Patient experienced the following side effects than the placebo group: constipation (49%, 11%), somnolence (39%, 10%), dizziness (33%, 8%), and overall (82%, 58%),"	**Total:** N/S **Sleep-related AE/SAE:** "For all patients randomized to treatment, a significantly larger proportion (p < 0.01) of patients experienced the controlled release codeine Patient withdrawal (1 : 1) Protocol violation (0 : 1) Other reasons (1 : 5)	Multi-item sleep assessment (self report) 3 of the 7 items were reported. These showed superiority of controlled-release codeine over placebo, with less need for medication (improvements of 73.3% and 10.4%, 76.4% and 22.8%, p = 0.02), and less pain on awakening (improvements of 72.5% and 37.7%, p = 0.02), and less trouble falling asleep (improvements of 72.5% and 37.7%, p = 0.02). No information on the remaining 4 sleep items. No Composite Sleep Score was calculated or reported	WOMAC pain VAS (0–500mm) (self report) There was an improvement in pain of 44.8% in the controlled-release codeine group, compared with 12.3% taking placebo(p =0.0004) Weekly pain intensity VAS (0–100mm) (self report) Similar significant improvements were also found for weekly pain intensity VAS score (p = 0.0001)	Unclear
Raja et al., 2002 [42]; USA	**Morphine:** Start dose: 15 mg Twice weekly increase Mean: 91 mg Max: 240 mg (alternative: **Methadone:** start dose: 5 mg, Mean: 15 mg) **vs.** **Nortriptyline** (mean 89 mg) (alternative: desipramine mean 63 mg) **vs.** **Placebo** **vs.** **RM:** Acetaminophen and NSAIDs	**Morphine:** Start dose: 15 MME Mean: 91 MME Max: 240 MME **Methadone:** Start dose: 20 MME Mean: 60 MME Max N/R	**Total:** 32/76 randomised (42.1%), 5 after randomisation, 11 after treatment period 1, 10 after treatment period 2, 6 after treatment period 3. Primary reasons for drop-out (opioid : triciclyc antidepressant) Side effect (7 : 2) Other medical problems (6 : 1) Concerns of family members (5 : 2) Marked pain reduction & wish to use other drugs (2 : 1)	**Total:**387 AEs, 234 in the Opioid group, 97 in the TCA group, 56 in the Placebo group **Sleep-related AE/SAE:** Throughout treatment and maintenance phase (Opioid : TCA : Placebo) Drowsiness (48 : 18 : 14)	Single rating on sleep interference (0–6) (self report) Comparable reductions in sleep disturbance were observed with opioids (Baseline=2.7±2.1, Maintenance =2.5±1.7; p = 0.01) and TCA (Baseline =3.2±2.0, Maintenance =2.5±1.9; p = 0.02), whereas placebo (Baseline = 3.2±1.8, Maintenance = 2.9±1.9) had no effect on sleep ratings.	Pain intensity rating (0–10) (self report) Greater mean decreases in pain ratings followed therapy with both TCA (mean reduction of 1.4; 95% CI=1.8 to 0.9, n=59) and opioids (reduction of 1.9; 95% CI= 2.3 to 1.4, n=64) than with placebo (reduction of 0.2; 95% CI 0.7 to 0.2, n=56, p<0.001), which had no effect on pain. Pain relief rating (0–100%) (self report) The mean percentage pain relief ratings during treatment with opioids (38%; 95% CI 30 to 46, p<0.001) and TCA (32%; 95% CI=24 to 40, p<0.001) were greater than during the placebo phase (11%; 95% CI=6 to 16). The two active drug treatments were not significantly different.	High

15.7% of all randomised controlled release codeine patients (n=51) experienced somnolence

There was a significant week by drug interaction for both WOMAC pain VAS (p = 0.02)and the weekly pain score (p =0.001), suggesting an improvement in pain over the 4 wks of the study with controlled-release codeine and a lack of change over time with placebo.

Authors, yr [ref]; country	Opioids regimen	Daily dose in MME	Attrition Reason/timing (n)	Adverse events/Serious adverse events Sleep-related AE/SAE (n)	Sleep outcomes	Pain outcomes	Risk of bias^
Rauck et al., 2006 [43]; USA	**Morphine sulphate, ER** (A-MQD), once-a-day capsules taken in the morning) Mean dose (intention to treat): mean: 69.9 mg **vs. Oxycodone hydrochloride, ER** (O-ER; twice-a-day controlled-release tablets) mean: 60.7 mg **RMI:** Ibuprofen (<2400 mg/day)	**Treatment start and max dose: N/R** O-ER **A-MQD:** 70 MME **O-ER:** 91 MME	**Total:** 172/392 patients (43.8%); 93/203 (45.8%) in A-MQD and 79/189 (41.8%) in O-ER **During titration:** 126/172 (73.3%) across groups **During evaluation:** 46/172 (26.7%) across groups Reasons for attrition not specified by timing of the study, but by group (A-MQD : O-ER): Adverse event (38 : 27) Withdrawal of consent (18 : 19) Lost to follow-up (12 : 7) Lack of efficacy (10 : 6) Noncompliance (6 : 5) Opioid dose not stabilised (5 : 4) Investigator withdrawal of patient (1 : 5) Protocol violation (1 : 4) Other (2 : 2)	**Total:** 16 SAEs, but timing and nature not specified. The incidence and severity of AEs were comparable between groups **Sleep-related AE/SAE:** Drowsiness	**PSQI (self report)** Both treatments resulted in improved PSQI scores, with improvement noted by the end of titration and continuing during the 8-wk evaluation phase. The relative changes in PSQI scores from study was significantly better in the A-MQD than the O-ER group at wk 4 (30% vs 17% improvement, p = 0.024), wk8 (33% vs. 17%, p = 0.006) and wks 1, 4, & 8 combined (30% vs. 16%, p = 0.013).	**Pain intensity (Brief Pain Inventory) (self report)** Both groups showed a reduction in pain scores from the baseline to evaluation phase. The weekly average of BPI pain scores remained <4 in both groups, with A-MQD's pain score being lower than O-ER's at each time point and the difference reaching statistical significance at wks 2 & 7.	High
Rauck et al., 2016 [44]; USA	**Buprenorphine, buccal (BBUP)** Start dose: 75µg once/day then increase to 75µg twice/day, and then either 150, 300 or 450 µg twice/day **RMI: 2 first wks:** Hydrocodone/Acetam inophen (< 10 mg/650 mg/day) thereafter: Acetaminophen (<1000 mg/day)	**Treatment mean and max dose: N/R Average dose at time of randomisation:** 26 MME	**Total:** 402/752 (53.5%) Reasons for discontinuation during pre-titration, titration, and treatment (BBUP:Placebo): Not dosed (3,-,-) Adverse event (-, 109, 13:7) Lack of efficacy (-, 33, 8:23) Protocol violation (-, 24, 7:10) Opioid withdrawal (-,-, 3:1) Withdrawal by subject (-, 34, 12:8) Lost to follow-up (-, 22, 4:9) Other (-, 68, 7:0)	**Total:** 540/749 patients (72.1%) reported >1 AE and 4 (0.5%) reported >1 SAE during titration. During treatment, 94/229 patients (41%) in the BBUP group and 101/232 (43.5%) in the Placebo group reported >1 AE; 3 (1.3%) in the BBUP and 1 (0.4%) in the Placebo group reported >1 SAE. **Sleep-related AE/SAE: Titration** Somnolence (52) Fatigue (37) **Treatment** (BBUP : Placebo) Somnolence (2 : 1) Fatigue (0 : 2)	**MOS Sleep Scale (self report)** "..no significant differences between groups on the change from baseline..." *Outcome data not provided	**Pain intensity (0–10 NRS) (self report)** Pain control was superior with BBUP than placebo. Mean pain intensity increase at week 12 from baseline was significantly greater in patients treated with placebo (1.59±2.04) than BBUP (0.94±1.85), p=0.001). The BBUP group had a significantly higher proportion of patients who achieved a ≥30% reduction in pain (63% : 47%, p =0.001) than the placebo group, but not for achieving ≥50% reduction in pain (41% : 33%) **Disability (Roland Morris Disability Questionnaire) (self report)** decreased 30% after titration with BBUP, but scores of the BBUP group did not differ from the placebo group after treatment	High

Authors, yr [ref];country	Opioids regimen	Daily dose in MME	Attrition Reason/timing (n)	Adverse events/Serious adverse events Sleep-related AE/SAE (n)	Sleep outcomes	Pain outcomes	Risk of bias^
Rosenthal et al., 2007 [49]; USA	Morphine sulphate, ER (A-MQD, once a day) **After day 6** N= 10 on 30 MME N= 21 on 60 MME	**Start dose: 30 MME** Start dose:30 mg/day Increase at day 6 if needed Max: 60 mg/day	**Total:** 3/34 patients (8.8%) did not complete treatment long enough to be considered evaluable Reasons of attrition: N/S	**Total:** 22 (71%) patients had >1 AE, 1 (3.2%) patient had a SAE. **Sleep-related AE/SAE:** **Treatment:** Sedation (5) Severe sedation & unresponsiveness (1)	**PSG (Objective)** A-MQD increased sleep efficiency [76.5% (previous analgesics) > 81.8% (placebo) > 83.8% (A-MQD)] and total sleep time [367 min (previous analgesics) >391.1 min (placebo) > 402.5 min (A-MQD)] vs. previous analgesics, but not vs. placebo. A-MQD reduced REM latency [113.9 min (previous analgesic) > 84.1 min (placebo) > 68.5 min (A-MQD)] vs. both previous analgesics and placebo **Sleep quality (0=poor, 100=best sleep) (self report)** A-MQD increased overall sleep quality rating (64.3) vs. previous analgesics (33.3) and baseline placebo-run-in (40.9) **Sleep duration (hrs of sleep reported) (self report)** A-MQD increased overall sleep duration (6.6) vs. previous analgesics (5.9) and baseline placebo-run-in (6.1)	**Pain intensity (BPI avg pain score; NRS 0=no pain, 10=worst pain) (self report)** Reduced with A-MQD (4.1), compared with previous analgesics (6.1) and placebo (6.1) **Pain relief impression (rating 0=none, 5=excellent) (self report)** Higher with A-MQD (3.5), compared with previous analgesic (2.4) and placebo (2.0)	High
Simpson et al., 1997 [50]; USA	**Transdermal fentanyl** 5, 50, 75, or 100 µg/h **RM:** Short acting oral opioids (type & dosage N/S)	Treatment start and max dose: N/R **Mean dose:** 78 MME	**Total:** 18/68 patients (26.5%) **Titration** Nausea/vomiting (10) Drowsiness (1) Protocol violation (3) Transport issues (4)	**Total:** 85 records of AE **Sleep-related AE/SAE:** Titration & maintenance: Sleepiness (7)	**VHS (self report)** No significant change in quality of sleep based on the summed analog VSH scale, although there was a significant improvement in the subscale of number of awakenings, from 77.1 ±22.3 min to 66.24 ±28.16 min (p<0.014). No other subscales showed significant improvement.	**Pain intensity (VAS) (self report)** Declined significantly from before (79.8±30.3) to after (44.2±26.68) **Pain disability (Oswestry Disability Questionnaire) (self report)** Decreased significantly from before (38.4±6.29) to after (35.86±8.55) (p <0.016)	High
Thorne et al., 2008 [35]; Canada	**Tramadol, CR** Start dose 150 mg weekly titration Max. 400 mg/day **vs.** **Placebo** **RM:** Acetaminophen, max. 650 mg up to 6 x/day	Start dose: 15 MME Mean: 340 mg Mean dose: 34 MME Max dose: 40 MME	**Total:** 25/100 patients (25%) **By treatment phase** (CR Tramadol : Placebo) Adverse event (12 : 3) Lack of efficacy (1 : 3) Consent withdrawn (1 : 2) Lost to follow-up (1 : 0) Protocol violation (0 : 1) Other (1 : 0)	**Total:** 288 during the CR Tramadol phase and 166 during the Placebo phase **Sleep-related AE/SAE:** By treatment phase (CR Tramadol : Placebo) are: Somnolence (35 : 19) Insomnia (0 : 4)	**Multi-item sleep assessment (self report)** Significant between-treatment and treatment-baseline differences in the Composite Sleep Score (Baseline: 183.4±123.6, CR Tramadol: 104.7±98, Placebo: 141±108.2) (p = 0.0008) Significantly better scores for the CR tramadol group, compared with the placebo group and with baseline, in five of eight items on the questionnaire ('trouble falling asleep', 'needed pain medication to sleep', 'needed sleep medication to sleep', 'awakened by pain in the morning', 'average hours of sleep per night'). No significant improvements were observed for the "awakened by pain at night', 'partner awakened', and 'quality of sleep' items.	**Pain intensity (VAS) (self report)** During the last week of treatment, the mean VAS score was significantly lower in the CR tramadol group (37.4 ±23.9 mm) than in the placebo group (45.1 ±24.3 mm; P=0.0009). **OA symptoms & disability (WOMAC) (self report)** The composite scores for the pain inventory of the WOMAC OA index during the last week of each treatment phase were significantly better following CR tramadol treatment, compared with placebo treatment. The composite scores for the pain inventory were 189.0 ±105.0 mm (34.5% Change From Baseline, P=0.0001) for CR tramadol treatment and 230.0 ±115.4 mm (19.8% CFB, P=0.0001) for placebo treatment (P=0.0007).	Unclear

Authors, yr [ref]; country	Opioids regimen	Daily dose in MME	Attrition Reason/timing (n)	Adverse events/Serious adverse events Sleep-related AE/SAE (n)	Sleep outcomes	Pain outcomes	Risk of bias^
Vorsanger et al., 2008 [36]; USA	Tramadol, ER Start dose= 100 mg 300 mg over 3-wk run-in followed by randomisation to 300 mg or 200 mg **vs. Placebo** **RM:** low-dose Aspirin or Acetaminophen (dosage N/S)	N= 129 treated with 20 MME N= 128 treated with Placebo: Placebo: 30 MME	**Total:** 378/619 patients (61%) Reasons for discontinuation at Titration and Treatment (300 mg : 200 mg : Placebo): **during titration** (300mg : 200mg : Placebo: Not randomised) Adverse event (128, 13:13:18) Lack of efficacy (41, 13:11:21) Noncompliance (21, -:-:-) Subject choice (20, 5:9:3) Investigator choice (2, -:-:-) Other (21, 11:9:19)	**Total:** 499 (80.6%) patients had AEs during titration; 5% of the AEs was considered serious **Sleep-related AE/SAE:** Somnolence (13 : 17 : 16 : 38) Fatigue (9 : 8 : 6 : 13)	**Quality of Sleep (0=very poor, 100=excellent) (self report)** Both tramadol groups showed improved quality of sleep during the 12-wk treatment phase, compared to pre-treatment . Both tramadol groups showed significantly greater improvement than placebo over the 12-wk treatment phase (Tramadol 300mg = 49.8±24.4, Tramadol 200mg = 54.2±27, Placebo = 44.7±25.8). No difference between the tramadol groups.	**Pain intensity (0-100 VAS) (self report)** Both tramadol groups showed significantly greater improvement than placebo over the 12-wk treatment phase (Tramadol 300mg = 30.5, Tramadol 200mg = 34.1±27.1, Placebo = 40.3±25.2). No difference between the tramadol groups. **Pain disability (Roland Disability Index) (self report)** Both tramadol groups showed significantly lower disability than placebo over the 12-wk treatment phase (300mg = 8.2±5.5, 200mg = 8.5±5.9, placebo = 9.8±5.9). No difference between tramadol groups.	High
Webster et al., 2015 [37]; USA	*Titration phase:* Hydromorphone, IR (14 days adjustment; 7 days stabilisation) 2, 4 or 8 mg tablet *Study treatment:* Hydromorphone, ER 8, 12, or 16mg tablets, 1 tablet of medication a day + 1 tablet of placebo. Mean: 10 mg/day. *Morning dose QAM:* 08:00-10:00 **vs.** *Evening dose QPM:* 20:00-22:00 **RM:** Acetaminophen (<1000 mg/day)	**Titration phase:** Treatment max dose: N/R Mean dose: 40 MME	**Total:** 10/22 (45.5%) Reasons for discontinuation at Titration and Treatment: **Titration phase:** Did not titrate (4,-) Severe sleep apnoea (2,-) Patient decision (1,-) Patient non-compliance (-, 1) High AHI (-, 1) **Treatment (QAM : QPM)** Somnolence (0 : 1)	**Total:** 51; treatment-emergent AEs occurred in 68%, 29% and 40% of patients with IR hydromorphone, ER hydromorphone QAM and ER hydromorphone QPM dosing. **Sleep-related AE/SAE:** **Titration** Fatigue (5) Somnolence (2) **Treatment (QAM : QPM)** Somnolence (0 : 1)	**PSG (objective)** QPM had higher no. of apneas, AHI and CAI vs. no treatment. All treatment groups had fewer body changes, less leg movements and shorter wake time after treatment. QPM had less leg movement than QAM and no treatment, and higher sleep efficiency (83.6±10) vs. no treatment (76.4±12.5). **Modified MOS-Sleep Scale (self report)** No differences in MOS scores between QAM and QPM or between these treatments with IR hydromorphone. QAM and worst pain over last 24 hours (3.9±2, 4.7±2.2) vs. 3 Rx groups showed improvement in sleep disturbance, snoring, awakening short of breath, & sleep problem index vs. no treatment. Sleep problem index was 32.8±15 for QPM, 36.1±17.9 for QAM, 38±14.8 for IR hydromorphone, & 51.2±20.6 for no treatment. **Sleep diary (self report)** No effect between Rx for all daily sleep parameters.	**Pain VAS (Short-form McGill Pain Questionnaire) (self report)** Scores significantly improved in all Rx groups vs. no treatment (55.5±23.1), but only QPM (38.3±22.4) improved vs IR Hydromorphone (47.2±23.8). No significant difference between QAM (46±26.2)and QPM **Daily pain intensity (Daily diary– NRS) (self report)** Time of dosing had no statistically significant effect on SELF-REPORTED pain. QPM group had lower average pain QAM (4.5±1.9, 5.4±2.0) and IR Hydromorphone (4.7±1.9, 5.6±2.0)	High

Supplementary Materials 1 – Search Terms

(((opioid* OR opiate*) AND (pain OR chronic pain OR nonmalignant pain OR non cancer pain OR intractable pain OR recurrent pain) AND (sleep* OR insomnia* OR polysomnogr* OR PSG OR actigr* OR wake* OR (apnea OR apnoea) OR drows* OR respirat* OR breathing OR restless leg OR myoclonus OR somnolence OR sleep architecture OR sleep physiology OR (diary OR log) OR dyssomnia* OR sleep initiation OR sleep maintenance))) NOT (infant OR child OR pediatric OR surgery OR palliative OR epidural OR cannabis OR marijuana).

3.3.1 Random sequence generation

Eight studies describing robust methods of randomising participants were judged as low risk [34, 36-40, 43, 48]. Five non-randomised, single-treatment studies were judged as high risk [45-47, 49, 50]. Five studies mentioning randomisation without adequate detail were judged as unclear risk [33, 35, 41, 42, 44].

3.3.2 Allocation concealment

Six studies outlining procedures to conceal the allocation were judged as low risk [34, 36, 37, 39, 40, 43]. Seven studies either non-randomized or that lacked adequate concealment procedures were judged as high risk [33, 38, 45-47, 49, 50]. Five studies gave insufficient detail of allocation concealment and were judged unclear [35, 41, 42, 44, 48].

3.3.3 Blinding of participants and personnel

Three studies that described robust procedures to maintain blinding of participants and personnel were judged as low risk [34, 36, 40]. One study that was single blind [49], nine studies that were open-label designs [2, 33, 38, 39, 43, 46-48, 50], and two studies that had periods of open-label assessment (titration phase [44] and baseline assessment [37]) were judged as high risk. Three studies that gave insufficient detail of blinding procedures were judged as unclear risk [35, 41, 42].

3.3.4 Blinding of outcome assessment

Four studies that described blinding the outcome assessor of sleep-relevant measures were judged as low risk [34, 40, 48, 49]. Three studies that involved no blinding of the outcome assessor were judged as high risk [39, 46, 47]. Ten studies that gave insufficient

detail of blinding the outcome assessor [33, 35-38, 41, 42, 44, 45, 50] and one study that did not clearly define the outcome assessor [43] were judged as unclear risk.

3.3.5 Incomplete outcome data

Four studies that had acceptable and well-documented attrition were judged as low risk [33, 35, 39, 45]. Eight studies that had significant attrition [34, 40, 43, 47, 48], attrition due to outcome-relevant factors [37], and/or attrition with unclear handling of missing data [36, 44, 48] were judged as high risk. Six studies that provided insufficient detail of attrition [36, 38, 41, 42, 46, 49] or unclear handling missing data [50] were judged as unclear risk.

3.3.6 Selective reporting

One study stated that certain results would be the subject of a future paper [36]; all other studies reported the outcomes outlined in their methods sections. All studies were judged as unclear risk because no protocols could be found to assure that all investigated outcomes had been reported.

3.3.7 Other bias

Eleven studies had potential conflicts of interest whereby their authors or funding were affiliated with a pharmaceutical manufacturer of the study drug [35-40, 43-46, 49, 50].