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Efficacy and safety of strong opioids for chronic noncancer pain and chronic low back pain: a systematic review and meta-analyses

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Abstract

In recent years, long-term prescribing and use of strong opioids for chronic noncancer pain (CNCP) has increased in high-income countries. Yet existing uncertainties, controversies, and differing recommendations make the rationale for prolonged opioid use in CNCP unclear. This systematic review and meta-analyses compared the efficacy, safety, and tolerability of strong opioids with placebo or nonopioid therapy in CNCP, with a special focus on chronic low back pain (CLBP). Systematic literature searches were performed in 4 electronic databases (MEDLINE, Web of Science, Cochrane Library, and CINAHL) in July 2019 and updated by regular alerts until December 2020. We Included 16 placebo-controlled randomized controlled trials for CLBP and 6 studies (2 randomized controlled trials and 3 nonrandomized studies) of opioids vs nonopioids for CNCP in the quantitative and qualitative synthesis. Random effects pairwise meta-analyses were performed for efficacy, safety, and tolerability outcomes and subgroup analyses for treatment duration, study design, and opioid experience status. Very low to low certainty findings suggest that 4 to 15 weeks (short or intermediate term) opioid therapy in CLBP (compared with placebo) may cause clinically relevant reductions In pain but also more gastrointestinal arid nervous system adverse events, with likely no effect on disability. By contrast, long-term opioid therapy (≥6 months) in CNCP may not be superior to nonopioids in improving pain or disability or pain-related function but seems to be associated with more adverse events, opioid abuse or dependence, and possibly an increase in all-cause mortality. Our findings also underline the importance and need for well-designed trials assessing long-term efficacy and safety of opioids for CNCP and CLBP.

Keywords: Chronic noncancer pain, Chronic low back pain, Opioids, Efficacy, Safety, Systematic review

Supplementary material to this article is available. For more information see http://hdl.handle.net/21.11116/0000-0008-F4BA-3

1. Background

For decades, opioids have been considered to be among the most potent and important medicines for the management of moderate- to-severe pain.[21] Although in many low-income and middle-income countries access to and use of analgesic opioids still remains low, there has been an upsurge in both availability and use in Organisation for Economic Co-operation and Development (OECD) countries.[7, 51, 68] Among OECD countries, the United States by far has the highest availability and consumption of analgesic opioids with 68% of the global prescribed opioids being used in the country between 2011 and 2013, followed by Germany and Canada.[7] Although opioids are listed by the World Health Organization (WHO) as essential medicines primarily for palliative care, acute pain, cancer pain, and opioid dependence,[102] in the United States and other OECD countries with high opioid consumption a major part of prescribed opioids is used for chronic noncancer pain (CNCP)[23, 40] However, long-term opioid use in CNCP has been subject of much controversy and uncertainty as the evidence base supporting this practice is not well established[4, 23, 52, 57, 65, 90] Furthermore, long-term opioid therapy may cause various adverse effects including constipation, sleep-related breathing disorders, hypogonadism, and fractures,[4, 16] as well as medication tolerance, physical dependence, and opioid use disorder.[3, 5, 71] After tobacco and alcohol, opioid dependence is the third most important substance use disorder contributing to global morbidity and premature mortality.[23] It is estimated that the risk of developing opioid dependence among patients with CNCP in primary care who are prescribed opioid analgesics long term lies between 3% and 26%.[18] Also, it has been reported that opioid misuse and addiction rates in patients with CNCP average between 21% to 29% and 8% to 12%, respectively.[96] These developments might in part also be explained by a global trend towards the increased use of strong opioids for CNCP.[63, 77, 80, 93]
Strong opioids are considered drugs, such as morphine,

hydromorphone, buprenorphine, oxycodone, fentanyl, methadone, etc.,[101] which are mainly used for moderate-to-severe pain according to the WHO pain ladder step III.[13] For example, in Germany, it has been shown that in 2010 almost 80% of prescribed opioid analgesics were for patients with CNCP with an increase in the prescription of WHO-III opioids; fentanyl being the most commonly prescribed strong opioid in ambulatory settings, despite not being the first choice for CNCP.[77] In addition, there was a distinct increase in prescriptions of strong opioids—eg, fentanyl patches—in opioid-naïve patients, which is generally not indicated for first-time opioid users.[33] Strong opioids were primarily used for the treatment of back pain, followed by unspecified pain.[100] Although opioids are commonly being used to treat chronic low back pain (CLBP) ,[1] international guidelines differ in recommendations concerning their use in these patients and emphasize exploring other treatment options, eg, nonopioid analgesics, exercise, and psychosocial therapies.[66, 67]

Given the existing uncertainties on efficacy and safety as well as differences in recommendations on the long-term use of opioids, particularly strong opioids, for the treatment of CNCP, the aim of the current systematic review and meta-analyses (MAs) was to assess the comparative efficacy and safety of long-term use of strong opioids (WHO-III) in comparison with placebo or nonopioid therapy in patients with CNCP. Special attention was paid to nonspecific CLBP as this patient population was of particular interest for the German randomized controlled trials (RCTs)[99] that the current systematic review aimed to inform and because German guidelines on long-term opioid therapy for CNCP provide no clear guidance for the prolonged use of strong opioids in nonspecific CLBP.

2. Methods or design

This systematic review has been conducted to inform a RCT,[99] ie, registered in the German Register for Clinical Studies (trial registration number: DRKS00020358); our systematic review is reported in compliance with the *Preferred* Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard.[61]

2.1. Eligibility criteria

Studies meeting the following eligibility criteria were considered in the systematic review.

2.1.1. Types of participants and setting

Adults aged 18 years or older with chronic (duration ≥3 month) noncancer pain, preferably nonspecific CLBP, in outpatient or ambulatory settings. Trials exclusively including individuals with inflammatory low back pain, neurological back pain conditions (eg, spinal stenosis, cauda equine syndrome, and disc herniation), or low back pain because of other specific causes, including infections and fractures, were excluded. Animal studies and studies of nonambulatory care settings, eg, in-hospital settings (eg, postsurgery, long in-hospital periods, etc.), were excluded.

2.1.2. Types of interventions

We considered studies comparing strong (ie, WHO-III) opioids, eg, morphine, buprenorphine, oxycodone, fentanyl, and methadone, as a monotherapy with a placebo or nonopioid analgesic comparator. We did not put restrictions on opioid dosage or route of administration (eg, oral, transdermal, buccal, etc.; except for intravenous or intrathecal administration because of its invasive nature). Studies reporting less than 4 weeks opioid therapy and studies combining opioids with opioid antagonists (eg, naloxone or naltrexone) or with other analgesics (eg, Non-steroidal anti-inflammatory drugs (NSAIDs) NSAIDs or acetaminophen) were excluded, as it is impossible to separate the analgesic effects of opioids from those of the other analgesics. Studies describing the use of additional analgesics only as rescue medication were not excluded, as in many trials, rescue medication is usually offered for breakthrough pain. Studies were also excluded when (1) comparing opioids with the same or other opioids without also including a placebo or nonopioid comparator, (2) primarily investigating interventions other than opioids, and (3) not including a (placebo) control group.

2.1.3. Types of outcome measures

The following outcomes were considered:

2.1.3.1. Efficacy

(1) Pain intensity (PI) (continuous)
(2) Improvement in PI
  (a) ≥30% PI reduction (dichotomous)
  (b) ≥50% PI reduction (dichotomous)
(3) Disability or improvement in pain-related function
(4) Sleep quality
(5) Trial discontinuations (overall, lack of efficacy, and adverse events (AEs))

2.1.3.2. Safety and tolerability

(1) Opioid withdrawal symptoms (during double-blind treatment and posttreatment)
(2) Opioid dependency
(3) Opioid abuse or misuse
(4) Adverse events (AEs)
  (a) Any AEs
  (b) Serious AEs
  (c) AEs leading to death
  (d) Gastrointestinal and nervous system AEs
    Nausea, vomiting, and constipation
    Dizziness, somnolence, and headache
  (e) Depression and anxiety
  (f) Falls
(5) Suicidal ideation or behavior
(6) Deaths

2.1.3.3. Patient ratings

(1) Patient Global Impression of Change (PGIC) or global change in pain
(2) Patient global rating of study medication
(3) Patient assessed treatment effectiveness

2.1.4. Types of studies

We considered all types of studies which had at least 2 study arms (control being placebo or active treatment). We have included RCTs and nonrandomized studies of interventions (NRSI) (eg, cohort, cross-sectional, and case–control studies, all with at least 2 study arms). Preclinical research studies (eg, in vitro studies, studies on specific blood markers or enzymes, etc.) were not considered.

2.2. Search strategy

Comprehensive systematic literature searches for relevant studies were conducted following the recommendations of

PRESS (Peer Review of Electronic Search Strategies)[59] and with involvement of an information specialist (E.M.). A systematic literature search without date or language restriction was performed in the following electronic databases from inception until July 2019: (1) Medline, Medline Daily Update, Medline In Process & Other Non-Indexed Citations, and Medline Epub Ahead of Print (via Ovid); (2) Science Citation Index Expanded, Conference Proceedings Citation Index - Science, and BioSciences Information Service Citation Index (through Web of Science); (3) Cochrane Library (through Wiley); and (4) Cumulative Index to Nursing and Allied Health Literature (CINAHL). Furthermore, to identify any additional eligible studies, reference lists of relevant studies were reviewed and potentially relevant citations were tracked; the PubMed similar article function was used as well as the Web of Science forward citation tracking function. Searches for ongoing trials or unpublished completed studies were performed in ClinicalTrials.gov and WHO International Clinical Trials Registry Platform. In addition, experts in the field were contacted to enquire about relevant studies not retrieved by electronic searches. Also, regular alerts on new and potentially eligible studies were established to update the searches (last update December 2020). Eligible studies identified through the alerts were also included in the analysis. Additional files 1 shows the final search strategy for Medline (through Ovid), one of the 4 included electronic databases. The search strategies for the other 3 databases were adapted based on this strategy.

2.3. Study selection

Study selection followed the procedures recommended by Cochrane for systematic reviews and was performed independently by 2 reviewers (E.N. and B.N.) in 2 consecutive selection steps. Identified references were first imported into Covidence (www.covidence.org) and automatically deduplicated for title and abstract screening. Two reviewers independently screened titles and abstracts of all identified records using the aforementioned eligibility criteria. After exclusion of noneligible records, full texts of all eligible records were retrieved and independently examined by the 2 reviewers in more detail. Records with missing abstracts but potentially relevant titles were also carried forward to full-text review. Full-text screening and further removal of any remaining duplicates was performed in the EndNote reference manager. Disagreements between the reviewers were resolved by discussion, involving a third reviewer (C.S.) if no consensus could be reached.

2.4. Data extraction

Data extraction was performed by one reviewer (E.N.) and independently verified for accuracy by a second reviewer (C.S.). Disagreements were resolved by discussion. For each study included, the study characteristics (first author, publication year, study design and duration [including data on titration, maintenance, and extension phases], country, number of participants and study arms, follow-up, study fund, and conflict of interest), population characteristics (eg, age, gender, opioid use status, PI score, pain duration, comorbidity, etc), intervention and comparator characteristics (drug name, administration route, administration scheme, treatment duration, and rescue medication use), as well as outcome measures assessed (efficacy, safety or tolerability, and additional measures) were extracted. When required, study authors were contacted to acquire relevant additional or missing information (ie, four study authors were contacted, but only one responded and provided relevant additional information). For each outcome, we extracted baseline and end-of-study means and SD (continuous measures) as well as the number of patients and events (dichotomous measures) for the intervention and comparison arms. For cross-over trials, data were extracted from the last arm. We only considered data that excluded statistically significant carry-over effects or when statistical adjustments were made in the case of a significant carry-over effect. If results were only reported in plot images, a semiautomated tool (WebPlotDigitizer V4.4, https://automeris.io/WebPlotDigitizer) was used to estimate numerical data from the images.

2.5. Risk of bias assessment

For each included RCT, 2 reviewers (E.N. and C.S.) independently assessed the risk of bias (RoB) according to the methodology described in the Cochrane Handbook for Systematic Reviews of Interventions[41] and any disagreements were resolved by consensus. The following RoB domains were addressed using the Cochrane risk-of-bias tool[45]: (1) randomized sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of patients, trial personal, and outcome assessors (performance and detection bias); (4) incomplete outcome data (attrition bias); (5) selective outcome reporting (reporting bias); and (6) other sources of bias. All separate domains were judged as “low,” “high,” or “unclear” RoB, and an overall judgment was made for each included RCT as having low RoB, some concerns, or high RoB.

Risk of bias in NRSI was evaluated using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool.[88] This tool is widely used and recommended for evaluating RoB in (quantitative) studies that did not use randomization to allocate individuals or clusters of individuals to comparison groups.[88] The following 7 domains through which bias might have been introduced were addressed: (1) bias because of confounding, (2) bias in selection of patients into the study, (3) bias in the classification of the intervention, (4) bias because of deviations from the intended interventions, (5) bias because of missing data, (6) bias in measurement of outcomes, and (7) bias in selection of the reported result. Each domain was judged as either “no information,” “low,” “moderate,” “serious,” or “critical” RoB, after which an overall RoB judgement was made across all bias domains for each included study (applying the same judgement options).

2.6. Data synthesis

2.6.1. Statistical analysis

For continuous outcomes, reported mean change (MC) scores (ie, difference between end-of-study means and baseline means) with their corresponding change-from-baseline SD were first pooled as standardized mean differences (SMDs) with corresponding 95% confidence intervals using a random effects model. Standardized mean difference was used for all continuous outcomes as the included RCTs considered the same endpoints but used different scales or instruments with different units, therefore necessitating standardization of results before pooling in meta-analysis. Consequently, SMDs express the intervention effect in standard units rather than the original units of measurement, which makes interpretation difficult. To improve interpretability, for each outcome, the pooled SMD was therefore converted back to a MD on the instrument or scale most frequently used by the included studies for that outcome, applying the valid conversion method by Thorlund et al.[94]

(category 1-i) and the Cochrane Handbook.[83] The pooled effect of an outcome is thus re-expressed in the original units of a familiar instrument, which facilitates interpreting the clinical relevance and impact of the intervention effect. In addition, for each outcome, the minimal important difference (MID), ie, the change in score of a (patient-reported) outcome, ie, meaningful from the perspective of patients or clinicians and would justify a change in patients' management, was used to determine clinically relevant changes for within-group comparisons. Where available, we attempted to base MID thresholds on empirical evidence, published guidelines, or validation studies. In absence of such evidence, input from our clinical expert (E.S.) and consensus of the review team was used. The within-group MID for PI was 2 points on the Numerical Rating Scale (NRS 0-10).[28,69,91] For an improvement in PI, a reduction of ≥30% and ≥50% in PI was considered a "moderate" and "substantial" improvement, respectively.[86] For disability, the MID was 5 points on the Roland–Morris Disability Questionnaire (RMDQ 0-24)[69]; for overall sleep quality, it was 10 mm[106] on the Chronic Pain Sleep Inventory (CPSI, VAS 0-100) and 1 point[24] on the Brief Pain Inventory Sleep Interference (BPISI) subscale (0-10) for pain interference with sleep. For studies that either compared 2 or more alternative opioids or different dosages of the same opioid with a placebo treatment, we separately included each pair-wise comparison, but with shared control groups (ie, placebo) divided out evenly among the comparisons, or combined the opioid intervention groups into a single group for comparison with placebo, using methods described in the Cochrane Hand- book.[42,43] When studies did not report MCs, SD, or change- from-baseline SDs, we calculated missing MC scores from reported baseline and final means and used any suitable reported statistics (eg, CIs, standard errors, and *P*-values) to calculate or estimate missing SDs and change-from-baseline SDs.[43] When no suitable statistics were available, we applied imputation methods as described in the Cochrane Handbook,[43] for missing (change-from-baseline) SDs.

For dichotomous (binary) outcomes, we used risk ratios (RRs) with 95% CIs to summarize trial results and pooled these using a random effects model. Continuity correction using a 0.5 correction factor was applied for studies reporting zero events, ie, no events in one or more arms, according to the Cochrane Handbook.[22] Including zero total event trials in MAs has been recommended as it maintains analytic consistency and incorporates all available data.[15,29] For determining MIDs, we followed guidance of the Agency for Healthcare Research and Quality and the GRADE working group and set the threshold of clinically appreciable benefit or harm at a relative risk reduction or relative risk increase >25%.[6,37] Studies with multiple intervention arms were included in MA according to the methods described in the Cochrane Handbook.[42] Meta-analyses of (MC from baseline to) *end-of-treatment* scores were conducted for all outcomes using Review Manager (RevMan) Version 5.3 and R Version 4.0.2.[73,92] Statistical heterogeneity was investigated and quantified using the chi-squared test and I^2 statistic, where an I^2 >50% was considered as substantial heterogeneity.[22]

We used the individual study participant as unit of analysis and intended to analyze all outcomes on an intention-to-treat (ITT) basis. For dealing with missing data, we followed the guidance of the Cochrane Handbook.[22] As we were particularly interested in trials with a patient population suffering from nonspecific CLBP, results of these trials were analyzed and synthesized separately. Furthermore, we intended to analyze and combine any eligible long-term RCTs and NRSI of general (mixed) CNCP populations in a separate additional evidence synthesis when no long-term (≥6 months follow-up) findings could be retrieved from the CLBP trials. Results were interpreted and reported considering both the magnitude and certainty of an effect, as recommended by the most recent GRADE guideline on communicating findings of systematic reviews of interventions[79] and according to guidance from the Cochrane Handbook.[82,84]

2.6.2. Secondary analyses, sensitivity analyses, and publication bias

Secondary analyses were planned to investigate whether effect estimates were influenced by differences in study design (parallel, cross-over, or enriched enrollment randomized withdrawal [EERW]), participant (opioid experience status), and intervention characteristics (treatment duration). The definition of opioid therapy duration was based on a highly cited Cochrane review on the efficacy of opioids in adults with CLBP[14] and divided in short term (1 to 3 months), intermediate term (more than 3 but less than 6 months), and long term (6 months or longer). At least 2 studies were required for secondary analyses. Sensitivity analyses were planned by excluding RCTs rated as high RoB. As recommended by the Cochrane Handbook[44] and Sterne et al.,[89] for comparisons with at least 10 studies, the possibility of small study effects resulting from publication bias or other biases was examined through visual inspection of funnel plots.

2.7. Grading of Recommendations Assessment, Development and Evaluation (certainty of the evidence)

For all outcomes, 2 reviewers independently (E.N. and C.S.) rated the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[81] In short, this approach assesses (1) study limitations (ie, RoB), (2) inconsistency (ie, differences in effect estimates across studies that assessed the same comparison), (3) indirectness (eg, patients, interventions, or outcomes differing from those of interest), (4) imprecision (eg, wide 95% CIs), (5) dissemination bias, and (6) potential criteria that can increase certainty (eg, large effect estimates). Based on these criteria, the certainty of evidence for each outcome was categorized as either high, moderate, low, or very low. More details on the grading of the evidence can be found in Supplementary file 2 (methods S2, available at http://hdl.handle.net/21.11116/0000-0008-F4BA-3). The results of the GRADE assessment are presented in GRADE evidence profiles as suggested by the GRADE working group[36] (Supplementary file 1).

3. Results

3.1. Literature search

3.1.1. Chronic low back pain

The screening and selection process of the identified records are displayed in **Figure 1A**. The electronic database and supplementary searches identified 10,311 citations, including 3596 duplicates. Of the 6715 records screened, 572 met the eligibility criteria and were considered for full-text screening. Of these, 16 RCTs, corresponding to 23 publications[10,19,20,32,34,35,38,39,48–50,53,55,56,60,64,74,87,95,98,103–105] published between 2006 and 2019 and with a total of 5771 participants, were included in the systematic review and meta-analysis. No eligible NRSIs were identified.

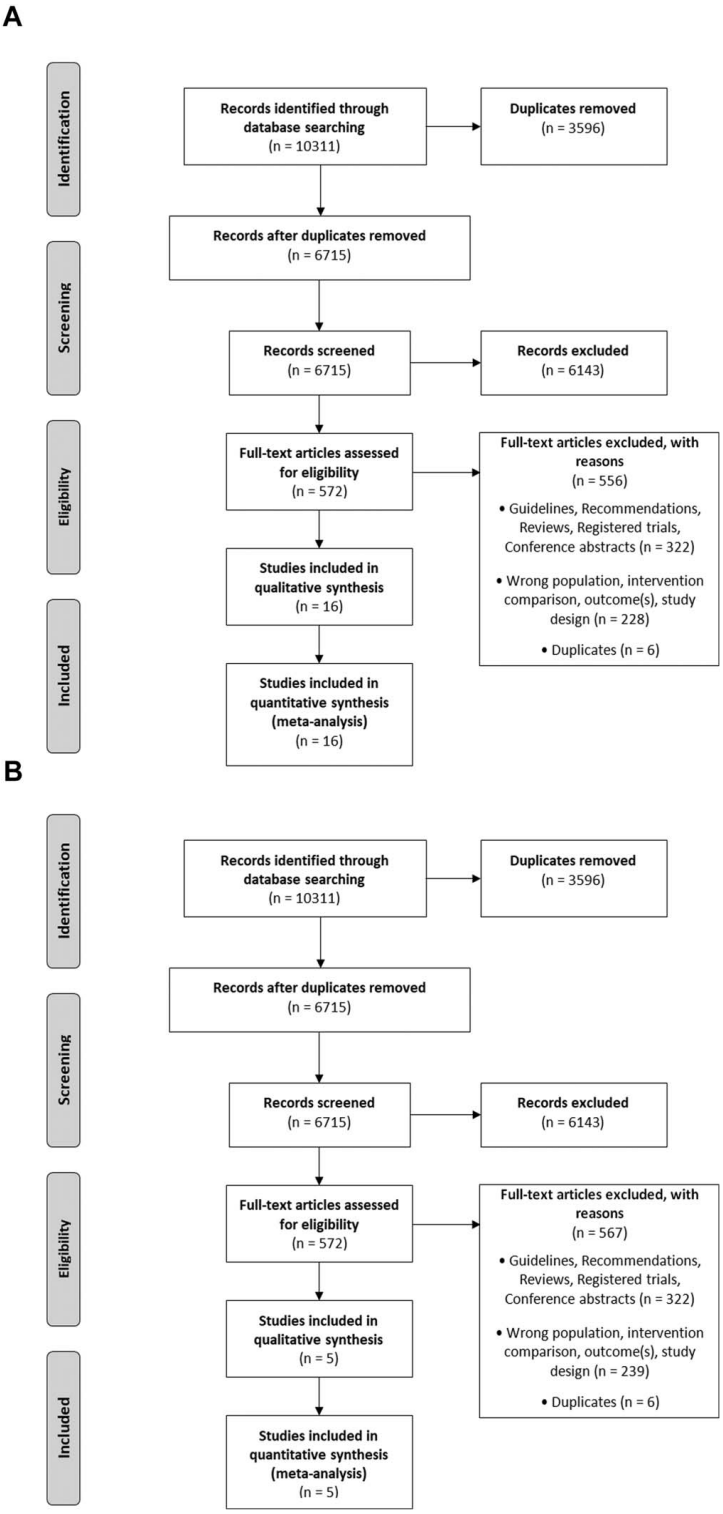

Figure 1. (A) PRISMA flow diagram showing the study screening and selection process for chronic low back pain studies. (B) PRISMA flow diagram showing the study screening and selection process for chronic noncancer pain studies. CNCP, chronic noncancer pain; CLBP, chronic low back pain.

3.1.2. Chronic noncancer pain

Because most CLBP trials only had a treatment duration of 12 weeks, we reviewed our search results for any eligible long term RCTs and NRSI in a (mixed) CNCP population. The resulting screening and selection process of the identified records are presented in **Figure 1B**. Of the 572 records considered for full-text screening, 5 studies (2 RCTs and 3 NRSI),[2,26,27,54,75] published between 2006 and 2018 and with a total of 626,389 participants, were included in the quantitative and qualitative synthesis.

3.2. Risk of bias assessments

Apart from a high RoB because of incomplete outcome data, all other bias domains were judged as unclear or low RoB across the included CLBP trials. The results of the RoB assessment are displayed in Supplementary figure S1 (Supplementary file 1).

For the included CNCP studies, RCTs were judged as having a high RoB because of inadequate allocation concealment, blinding of study participants, personnel, and outcome assessors (Supplementary file 1; Figure S1) and nonrandomized studies were judged as being at high RoB because of serious concerns regarding bias caused by confounding and bias in the selection of participants (Supplementary file 1; Table S1).

3.3. Findings from chronic low back pain trials

3.3.1. Key characteristics of included studies

3.3.1.1. Trial characteristics

The trials were conducted in North America, Europe, Asia or Australia, and most of them were multicentric (**Table 1**). Eight trials used an EERW design, 6 trials a parallel and 2 trials a cross-over design. Of all trials, 12 had 2 arms (placebo controlled), 2 trials had 3 arms (active controlled and placebo controlled), and in 2 trials either 4 or 5 arms were used (active controlled and placebo controlled, with varying opioid administration doses or frequencies). Study duration, ie, double-blind treatment, ranged from 4 to 15 weeks, with most trials having a duration of 12 weeks. Findings from these trials hence mainly concern short-term opioid therapy. 13 studies reported being funded or sponsored by pharmaceutical companies, 2 studies reported being publicly funded, and 1 study did not disclose its funding source. Similarly, declarations of conflict of interest were reported by 13 studies, of which the authors in 2 studies (that also reported public funding) declared that they had no conflict of interest. Three studies did not provide any statements on conflicts of interest. Interestingly, the study that did not report any funding information also did not provide a conflict of interest statement. More details on trial characteristics are shown in **Table 1**.

3.3.1.2. Participant characteristics

All included trials were conducted in adults, with the mean age of participants ranging between 42 and 64 years. The proportion of females in the trials ranged between 33% and 65%. Five trials were conducted in opioid experienced, 5 in opioid naïve, and 6 in both opioid naïve and experienced participants. All trials (n = 16) excluded participants with (chronic) pain comorbidities (which could potentially influence study assessments), and the majority also excluded participants with mental health (MH) or psychiatric disorders (n = 11) and current or past substance abuse (n = 11).

3.3.1.3. Intervention and comparator characteristics

Most trials (n = 10) tested oxycodone or buprenorphine, 5 trials for each. Six trials investigated morphine, oxymorphone, or tapentadol, 2 trials for each. Hydromorphone or cebranopadol (a novel strong opioid currently in clinical development) were tested in only one trial for each. Details on dosing and administration routes and schemes are displayed in **Table 1**. In all trials, strong opioids were compared with a placebo control alone (n = 12) or to another opioid and a placebo control (n = 4). Additional study and participant characteristics are summarized in **Table 1**.

Table 1

Study characteristics of the included chronic low back pain randomized controlled trials.

Study	Country	Study design and conduct	Patients randomized	Arms	Study population	Female (%)	Mean age	Treatment arms	Administration scheme	Treatment duration (wk)
Chu et al.[12]	USA	Single-center, parallel (double-blind) Study session 1: Baseline (BL) pain sensitivity assessment without opioids + establishing BL opioid-dose analgesic response relationship before chronic morphine exposure. Study drug titration Study session 2: Reassessment of pain sensitivity/opioid dose–analgesic response relationship after 1 month of treatment + treatment taper down to 0 capsules/day over 10 days with a dose decrease of 1 capsule/2 day. Follow-up: Online follow-up survey approximately 1 year after study completion.	139	2	Opioid-naïve and opioid-experienced adults (18-70 year) with nonmalignant chronic low back pain (CLBP) of ≥ 6 months and pain level of ≥40 (VAS) Note: Participants were not currently taking opioid pain medication above 30 mg oral morphine equivalent dose (MED) per day, which was defined as low-dose opioid therapy	61 (43.9)	45.0	I Morphine SA (N = 69), oral C Placebo (N = 70), oral	Initially 15 mg b.i.d., then every 2-day dose increase of 15 mg/day (max. 120 mg/d; 8 capsules), for 1 month. Weight-matched capsules with same administration scheme as morphine treatment, for 1 month. Rescue/additional medication (all participants): Low-dose opioids users could continue normal drug routine; however, they were not allowed to take daily pain medication ≥10 hour before pain testing sessions.	4
Katz et al.[48]	USA	Multicenter (N = 46), EERW (double-blind) Total study duration up to 24 wk, including the following: Screening phase (≤4 wk): Patients entered a screening phase that lasted up to 4 wk and consisted of a washout period during which all prohibited analgesic medications (ie, all analgesics with the exception of APAP [up to 2000 mg/d] rescue medication) were discontinued for a min. of 7 days before the start of the titration phase. Open-label titration phase (≤6 wk): initiation or conversion to oxycodone ER starting dose, then titration. Double-blind maintenance phase (12 wk). Follow-up safety phase (2 wk).	389	2	Opioid-naïve and opioid-experienced adults (18-75 year) with moderate-to-severe CLBP and pain intensity score of ≥5 to ≤9 (11-point Pain Intensity-NRS [PI-NRS]) of ≥ 6 months before the screening visit.	206 (52.6)	49.6	I Oxycodone ER (N = 193), oral C Placebo (N = 196), oral	Individual stable dose (≥40 to ≤160 mg oxycodone HCl equivalents *P*/day), b.i.d., Q12h for 12 weeks. Matched inactive capsules with same administration scheme as oxycodone treatment for 12 weeks. Note: Blinded dose taper (≤20 day) from a stable dose of oxycodone ER to a matching placebo. Rescue/additional medication (all participants): Acetaminophen ≤2000 mg/day (500 mg unit doses) permitted as rescue medication.	12

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Study design and conduct	Patients randomized	Arms	Study population	Female (%)	Mean age	Treatment arms	Administration scheme	Treatment duration (wk)
Kawamata et al.[50]	Japan	Multicenter (N = 54), EERW (double-blind) Double-blind study (4 periods): Open-label dose-titration period (14-28 days). Double-blind period (35 days). Tapering period (7 days). Follow-up period (7 days).	130	2	Opioid-naïve and opioid-experienced adults (20-79 year) with non–cancer-related CLBP of ≥3 months, and a BPI score of ≥4 before enrollment despite management for ≥14 days with oral, patch, or suppository nonopioid analgesics or opioids (doses prespecified as oral codeine, ≤800 mg/day; oral morphine, ≤120 mg/day; and fentanyl patch, ≤100 μg/h).	65 (50.0)	63.9	I Oxycodone HCL CR (N = 62), oral C Placebo (N = 68), oral	DB period: Constant individual dose as determined during the dose-titration period (max. 80 mg/day), b.i.d. for 35 days. Matched inactive tablets, b.i.d. for 35 days. Rescue/additional medication (all participants): Yes, but not further specified.	5
Buynak et al.[10]	USA, Canada, and Australia	Multicenter (N = 103), parallel (double-blind) Screening visit; Washout period: 3-day to 7-day washout of all previous analgesics; 15-week treatment period: a 3-week, double-blind titration period followed by a 12-week, double-blind maintenance period; Follow-up period: Visit 4 day after the end of treatment + poststudy telephone call.	981	3	Opioid-naïve and opioid-experienced adults (≥18 years) with nonmalignant LBP of ≥ 3 months; required to have been taking analgesics for low back pain for ≥3 months before screening; dissatisfied with their current treatment; with a BL pain intensity of ≥5 (NRS) after a 3-day to 7-day washout period of all previous analgesics. Note: For patients on opioids, daily doses of opioids had to be equivalent to ≤160 mg of oral morphine.	559 (57.9)	49.9	I Tapentadol ER (N = 321), oral Oxycodone HCL CR (N = 334), oral C Placebo (N = 326), oral	100 -250 mg, b.i.d., for 12 weeks. 20-50 mg, b.i.d., for 12 weeks. Matched inactive tablets/capsules, b.i.d. for 15 weeks. Rescue/additional medication (all participants): Concomitant analgesics were prohibited during the study, except APAP during 1) the 3-week titration period, ≤1000 mg/day rescue medication as needed, and 2) the maintenance period, when deemed necessary for reasons unrelated to low back pain; and then, only ≤1000 mg/day was allowed, for a max. of 3 consecutive days.	15 3 titration + 12 maintenance

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Table 1 (*continued*)

Study	Country	Study design and conduct	Patients randomized	Arms	Study population	Female (%)	Mean age	Treatment arms	Administration scheme	Treatment duration (wk)
Christoph et al.[19]	Europe (11 countries)	Multicenter (N = 79), parallel (double-blind) Enrollment period (≤24 day): patients' eligibility was assessed, previous analgesic medication was washed out (3-21 day), and the analgesic medication-free baseline pain intensity was determined (3 day). Double-blind treatment period (14 wk): comprised a 14-day titration phase and a 12-week maintenance phase. Randomization took place at the baseline visit (start of treatment period). Follow-up period (10-14 days): from the day after the EoT visit until the follow-up phone call, scheduled 10-14 days after last intake of trial medication. The follow-up visit was scheduled within 3 to 5 days after the last intake of trial medication.	641	5	Opioid-naïve and opioid-experienced adults (18-80 years) with moderate-to-severe nonmalignant CLBP of ≥3 months, on stable opioid or nonopioid analgesic medication with regular intake of ≥3 months and dissatisfied with their current analgesic treatment; an average 24h analgesic medication-free, baseline pain score ≥5 (0-10 NRS) was required 3 days before randomization.	412 (64.9)	57.5	I Cebranopadol 200 μg (N = 131), oral Cebranopadol 400 μg (N = 128), oral Cebranopadol 600 μg (N = 130), oral Tapentadol 200 mg ER (N = 126), oral C Placebo (N = 126), oral Rescue/additional medication (all participants): Acetaminophen was allowed as rescue medication for unacceptable CLBP (max. total daily dose of 2 g and max. 20 days of use during maintenance phase).	Fixed 200 μg dose, once daily; starting with 200 μg and increasing to target dose of 400 μg/600 μg using 200 μg steps, once daily, for 14 weeks. Starting with 50 mg and increasing to target dose of 200 mg using 50 mg steps, b.i.d, for 14 weeks. B.i.d., for 14 weeks.	14 2 titration + 12 maintenance
Gimbel et al.[32]	USA	Multi-center (n = 66), EERW (double-blind) Screening phase (2 week); Opioid taper phase (up to 4 week); Open-label Buprenorphine titration phase (up to 8 week, including at least 2 week at a stable optimal dose); Double-blind, withdrawal treatment phase (12 week); Follow-up phase (2 week).	511	2	Opioid-experienced (30-160 mg/day MED) adults (≥18 year) with moderate-to-severe CLBP of >6 month Note: Existing opioid doses were tapered down to ≤30 mg MED/day before entering open-label titration with Buprenorphine.	278 (54.5)	53.6	I Buprenorphine HCL (N = 254), oral C Placebo (N = 257), oral Rescue/additional medication (all participants): To minimize opioid withdrawal risk in patients randomized to placebo, ≤2 doses/day of opioid rescue medication (1-2 tablets of 5/325 mg hydrocodone/acetaminophen per dose) was allowed for the first 2 week in all patients; Thereafter, one dose per day was permitted.	Buccal film, individual optimal dose (max. 900 μg), Q12h, for 12 week. Matched inactive buccal film, Q12h, for 12 week.	12

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Table 1 (*continued*)

Study	Country	Study design and conduct	Patients randomized	Arms	Study population	Female (%)	Mean age	Treatment arms	Administration scheme	Treatment duration (wk)
Gordon et al.[34]	Canada	Multicenter (n = 13), EERW (double-blind) Screening visit: medical history and physical examination; Washout (2-7 days): Washout of previous opioids before randomization to buprenorphine or placebo. Double-blind treatment phase: (8 wk): after randomization treatment with BTDS or placebo; after 4 wk of the assigned treatment, patients crossed over to the alternative treatment for an additional 4 wk.	78	2	Opioid-experienced adults (age >18 years) with LBP of at least moderate intensity (≥2 points on a 5-point OS) for >3 months, and who currently required ≥1 tablet/day of an opioid analgesic.	47 (60.3)	50.7	I Buprenorphine (N = 39), TDS patches C Placebo (N = 39), TDS patches	Initial dose of 10 μg/h, with uptitration using 10 and 20 μg/h (max 40 μg/h) based on efficacy and tolerability; 4 week, then cross-over to placebo. Matched inactive patches; 4 week, then cross-over to buprenorphine.	8
								Rescue/additional medication (all participants): Acetaminophen 325 mg, 1-2 tablets every 4-6 hours as needed for unmanageable pain in both treatment arms. Patients were permitted to continue nonopioid analgesics at doses that had been stable for 2 weeks before enrollment, and antidepressants or anticonvulsants at doses that had been stable for 8 week before enrollment.		
Hale et al[39]	USA	Multicenter (n = 30), EERW (double-blind) Screening and opioid conversion: All opioid-experienced patients were converted to an approx. equivalent analgesic dose of oxymorphone ER. Open-label titration (4 wk): Patients entered an open-label titration period, during which they were stabilized on a dose of oxymorphone ER b.i.d. that provided adequate pain relief and tolerability (on basis of adverse events [AEs]). Double-blind treatment (12 wk): Patients meeting stabilization criteria entered a 12-week, randomized, double-blind, placebo-controlled treatment period.	143	2	Opioid-experienced adults (≥18 year) with moderate-to-severe CLBP for at least several hours each day for ≥ 3 months, who were receiving stable around the clock (ATC) opioid pain medication of 60 mg/day oral morphine for the management of their LBP for the 2 weeks before screening.	64 (44.8)	47.1	I Oxymorphone ER, N = 70), oral C Placebo (N = 73), oral	Starting with a b.i.d. dose that was approximately equivalent to the dosage of opioid analgesic at screening; uptitration by 10-mg steps (b.i.d.) every 3-7 days until adequate pain relief/stabilized fixed dose. Thereafter, stabilized fixed dose, 2 equal doses once Q12h, for 12 weeks. Two equal doses once Q12h, for 12 weeks.	12
								Rescue/additional medication (all participants): 1) Oxymorphone 5-mg every 4-6 hour as needed, during the titration period for breakthrough pain and for the first 4 days of the DB treatment period; thereafter, max. 10 mg/day, and 2) other analgesics, short-acting NSAIDs, or other adjuvant analgesics were not permitted except for the treatment of nonpain symptoms (eg, cardiovascular prophylaxis or fever).		

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Table 1 (*continued*)

Study	Country	Study design and conduct	Patients randomized	Arms	Study population	Female (%)	Mean age	Treatment arms	Administration scheme	Treatment duration (wk)
Hale et al.[38]	USA	Multicenter (n = 66), EERW (double-blind) Screening phase (<2 wk): Medical history and physical examination + discontinuation of all (nonopioid) analgesics (except: aspirin ≤325 mg/day as cardiovascular prophylaxis). Open-label conversion/titration phase (2-4 wk): conversion to hydromorphone ER. Double-blind treatment phase (12 wk).	268	2	Opioid-experienced/tolerant adults (18-75 years) with moderate-to-severe CLBP for ≥3 h/day (20 days per month) for ≥6 months; who were on daily opioid treatment with ≥60 mg oral morphine equivalent (max. ≤320 mg) per day within 2 month before the screening visit, and on stable doses of all prior analgesics ≥2 weeks before the screening visit.	134 (50.4)	48.6	I Hydromorphone ER (N = 134), oral C Placebo (N = 134), oral Rescue/additional medication (all participants): Hydromorphone IR (2, 4, and 8 mg) provided as rescue medication during 1) conversion/titration phase: unrestricted for first 3 day and thereafter max. 2 tablets/day, and 2) DB treatment phase: ≤ 6 tablets/day in wk 1; ≤ 4 tablets/day in wk 2; thereafter, 2 tablets/day.	Individual fixed dose established in dose-conversion/titration phase (12-64 mg/daily); once daily, for 12 wk. Matched inactive tablets; once daily, for 12 wk. Note: Patients were tapered down from their stable hydromorphone dose over the first 2 wk of the 12-week treatment period and then received placebo for the remaining 10 wk.	12
Lin et al.[55]	USA	Single-center, parallel (double-blind) Baseline (premorphine) assessment. Double-blind treatment: Participants were randomly assigned to receive placebo or morphine therapy. Posttreatment assessment: after 4 week, all participants returned for a second scan session.	21	2	Opioid-naive adults (18-70 years) with chronic, moderate-to-severe low back pain (mean pain duration 8.1 years) and low daily opioid use at the time of enrollment (<30 mg of oral morphine equivalents per day).	7 (33.3)	41.9	I Morphine SR (N = 11), oral C Placebo (N = 10), oral Rescue/additional medication (all participants): allowed to continue taking over-the-counter analgesics.	Initially 15 mg b.i.d., then every 2 days a daily dosage increase by 15 mg (max. 120 mg/day = 8 capsules); for 4 wk Matched inactive double-encapsulated capsules; the "dose' was titrated according to the same criteria as the morphine group, up to a max. of 8 capsules/day; for 4 wk	4

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Study	Country	Study design and conduct	Patients randomized	Arms	Study population	Female (%)	Mean age	Treatment arms	Administration scheme	Treatment duration (wk)
Rauck et al.[74]	USA	Multicenter (N = 60), EERW (double-blind) Screening phase (2 wk). Open-label titration phase (≤8 wk): All prior analgesics were discontinued, and patients were titrated to a stable dose of BBUP that provided adequate analgesia/was well tolerated for last 14 days of the open-label period; Double-blind treatment phase (12 wk): Patients entering this phase were titrated to a BBUP dose ≥ 150 μg b.i.d., had received their stable optimal dose of BBUP for ≥2 wk, and required max. 1 dose/day of rescue APAP during the last 7 days. Follow-up phase (2 wk).	462	2	Opioid-naive adults (≥18 years) with CLBP of ≥6 months and a pain intensity score ≥5 to <10 (0-10 NRS), with a stable daily maintenance dose of nonopioid analgesics for ≥4 weeks (≤10 mg/day MED).	259 (56.2)	50.1	I Buprenorphine HCl (N = 229), oral C Placebo (N = 232), oral	Buccal film, individual stable optimal dose reached at the end of the open-label phase (≥150 μg), b.i.d., for 12 weeks. Matched inactive buccal film, b.i.d., for 12 weeks.	12
								Rescue/additional medication (all participants): 5 mg/325 mg hydrocodone/acetaminophen tablets as rescue medication during the first 2 weeks and acetaminophen 500 mg tablets only thereafter.		
Steiner et al.[87]	USA	Multicenter (N = 86), EERW (double-blind) Screening period (6-10 days): Discontinuation of all medications for chronic pain for the duration of the screening period. Open-label run-in period (≤27 day): All patients received BTDS 5 μg for 3 days followed by BTDS 10 μg for 10 ±2 days, after which the analgesic response/tolerability was evaluated. Patients who tolerated but did not achieve required analgesic response to BTDS 10 had their dose titrated to BTDS 20 for an additional 10 ±2 days. Double-blind phase (12 wk): Patients who tolerated/responded to BTDS (10 or 20 μg/h) during the run-in period were randomized to continue BTDS 10 or 20 μg/h or receive matching placebo.	541	2	Opioid-naïve adults (≥18 years) with moderate to severe CLBP of ≥3 months and an "*average pain over the past 14 days*" score of ≥5 (NRS 0-10) while taking nonopioid analgesics for CLBP (if applicable).	298 (55)	49.4	I Buprenorphine (N = 257), TDS patches C Placebo (N = 284), TDS patches	10 or 20 μg/h (1 down and 1 uptitration allowed in BTDS 20 μg group), for 12 weeks. Matched inactive patches with identical administration scheme as BTDS group (1 down and 1 uptitration allowed in placebo 20 μg group), for 12 weeks.	12
								Rescue/additional medication (all participants): Oxycodone IR ≤10 mg/d during first 6 day of the DB phase (as withdrawal symptoms could potentially occur in patients randomized to placebo TDS); acetaminophen 500 mg every 6 hours (max. 2 g/day) or ibuprofen 200 mg every 6 hours (max. 800 mg/day) for the remainder of the DB phase; no additional analgesics were permitted during the run-in period.		

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Study	Country	Study design and conduct	Patients randomized	Arms	Study population	Female (%)	Mean age	Treatment arms	Administration scheme	Treatment duration (wk)
Katz et al.[49]	USA	Multicenter (N = 29), EERW (double-blind) Screening visit: Current pain medications were discontinued the evening before the screening visit. Open-label titration period (4 wk): Patients meeting the eligibility criteria were initially enrolled into an open-label titration period. Patients received oxymorphone ER 5 mg Q12h for 2 days; thereafter, patients were titrated at increments of 5–10 mg Q12h for 3–7 days until dose stabilization was achieved. Double-blind treatment period (12 wk): Patients who were successfully stabilized onto the study medication were randomized into 1 of 2 groups (oxymorphone ER or placebo) for a 12-week treatment period.	205	2	Opioid-naïve adults (≥18 years) with moderate-to-severe CLBP that was present daily for at least several hours per day for ≥ 3 months and an initial pain intensity score of ≥ 50 mm (VAS) Note: Opioid-naïve was defined as taking ≤5 mg/day of oxycodone, or equivalent, for the 14 days before screening.	109 (53.2)	49.7	I Oxymorphone ER (N = 105), oral C Placebo (N = 100), oral	Individual stabilized dose, Q12h, for 12 weeks. Matched inactive tablets, Q12h, for 12 weeks. Rescue/additional medication (all participants): Oxymorphone IR ≤ 5 mg every 4–6 h as needed during the first 4 days; thereafter, max. 2 doses/day for breakthrough pain. Supplemental rescue medication was not permitted during the dose-titration period. Short-acting NSAIDs for nonpain symptoms (eg, fever) or other adjuvant analgesics (except opioids or acetaminophen) that were dose stabilized before screening was permitted.	12
Gordon et al[35]	Canada	Multicenter (n = 6), crossover (double-blind) Washout + phase I (4 wk): All prestudy analgesics/opioids were discontinued the evening before randomization to either 5 μg/h BTDS or placebo TDS. Phase II (4 wk): Patients returned for weekly clinic visits, and after 4 weeks, they were switched over to the alternate treatment for another 4 wk.	79	2	Opioid naïve and opioid-experienced adults (>18 years) with LBP of at least moderate severity (≥2 points on 5-point ordinal scale [OS]) for >6 weeks duration that was inadequately treated with nonopioids.	25 (47.2)	54.5	I Buprenorphine (N = 37), transdermal system (TDS) patches C Placebo (N = 42), TDS patches	Initial dose of 5 μg/h, with up-titration to 10 and 20 μg/h (max. dose) based on efficacy and tolerability, for 4 weeks then cross-over to placebo. Matched inactive patches, for 4 week then cross-over to buprenorphine. Rescue/additional medication (all participants): Acetaminophen 300 mg/codeine 30 mg, 1-2 tablets every 4-6 hours as needed rescue analgesia. Nonopioid analgesics that had been administered at a stable dose for 2 weeks before enrolment were permitted at that stable dose during study.	8

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Table 1 (*continued*)

Study	Country	Study design and conduct	Patients randomized	Arms	Study population	Female (%)	Mean age	Treatment arms	Administration scheme	Treatment duration (wk)
Vondrackova et al.[95]	Hungary, Germany	Multicenter (n = nr), parallel (double-blind) Screening period (≤ 14 day): Prospective assessment and gradual tapering of prior opioids. Run-in/opioid titration period (≤ 14 day): Uptitration with oxycodone IR to achieve adequate analgesia and stable/comparable pain status for all randomized patients. Double-blind phase (12 wk): Assessing safety and efficacy of oxycodone PR/naloxone PR combination therapy compared with placebo (and oxycodone PR).	464	3	Opioid-experienced adults (>18 year) with moderate-to severe CLBP, adequately managed with daily opioid therapy for at least 2 wk before enrollment.	285 (61.6)	56.3	I Oxycodone PR (N = 151), oral Oxycodone PR/naloxone PR (N = 154), oral C Placebo (N = 158) Rescue/additional medication (all participants): During the screening (opioid taper) and double-blind phase, all patients could receive oxycodone IR every 4-6 hours as required as rescue medication at a quarter of the dose of their total daily opioid medication.	10 mg or 20 mg oxycodone PR, Q12h, for 12 wk. 10/5 mg or 20/10 mg of oxycodone PR/naloxone PR, Q12h, for 12 wk. Matched placebo tablets, Q12h, for 12 wk.	12
Webster et al.[98]	USA	Multicenter (n = 45), parallel (double-blind) Wash-out phase (4-10 day): after an initial screening visit. Randomization DB titration phase (1-6 wk): Patients titrated their daily dose to a pain score ≤2, until a tolerable level of side effects were experienced, or to a maximum of 80 mg/day; DB maintenance phase (12 wk): After the titration period, patients remained on their final dose for 12 weeks.	719	4	Opioid-naïve and experienced adults (18-70 years) with persistent LBP of ≥6 months, requiring daily analgesics, with a baseline pain intensity (PI) score ≥5 at the screening visit, a mean daily PI score 5 over the last 3 days of the washout period while off all analgesics except APAP, and confirmatory PI score 5 at baseline visit at the end of washout.	442 (61.5)	48.1	I Oxycodone (N = 206), oral Oxycodone/naltrexone (N = 206), oral Oxycodone/naltrexone (N = 206), oral C Placebo (N = 101) Rescue/additional medication (all participants): No other analgesics were allowed during the treatment period. Note: Patients taking a daily opioid dose equivalent to >20 mg of oxycodone required a taper and a 72-h period of no opioid medication before screening.	10-80 mg oxycodone, q.i.d., for 12 wk. 10-80 mg/d oxycodone/naltrexone, q.i.d., for 12 wk. 10-80 mg/d oxycodone/naltrexone, b.i.d., for 12 wk. Matched placebo pills, b.i.d. or q.i.d., for 12 wk.	15 1-6 titration + 12 maintenance

AEs, adverse events; ATC, around-the-clock; APAP, acetyl-para-aminophenol (acetaminophen); b.i.d. twice a day; BL, baseline; BTDS, buprenorphine transdermal system; BPI, Brief Pain Inventory; BBUP, buccal film buprenorphine; CR, controlled released; C, comparison; CLBP, chronic low back pain; DB, double-blind; EoT, end-of-treatment; ER, extended release; EERW, enriched enrollment randomized withdrawal; HCl, hydrochloride; I, intervention; IR, immediate releases; MED, morphine equivalent dose; NRS, Numerical Rating Scale; nr, not reported; OS, ordinal scale; q.i.d., 4 times a day Q12h, every 12 hour; SA, sustained acting; SAEs, serious AEs; SR, sustained release; TEAEs, treatment-emergent AEs; TDS, transdermal system; VAS, Visual Analog Scale.

3.4. Efficacy outcome

3.4.1. Pain intensity

The effect estimate for the outcome PI, measured with the self-reported Numerical Rating Scale (NRS 0-10; 10 = worst pain), Visual Analog Scale (VAS 0-100; 100 = worst pain), and pain severity subscale of the Brief Pain Inventory (BPI-PS; NRS 0-10; higher is worse pain severity) for opioids compared with placebo treatment (**Fig. 2**), was SMD -0.40 (95% CI: −0.46 to −0.34; $I^2 = 0\%$; $P < 0.001$; n = 15 RCTs; low certainty of evidence). The SMD re-expressed as MD on the NRS 0 to 10 (most frequently used in the included RCTs), resulted in a MD of 0.9 points lower (from 1.03 to 0.76 lower) with opioids, suggesting that treatment with opioids results in little to no difference in PI: MD -0.9 (95% CI: −1.03 to −0.76).

3.4.2. Improvement in pain intensity

3.4.2.1. ≥30% pain intensity reduction

The proportion of patients who responded with ≥30% reduction in PI at treatment end was 1081/2080 (52.0%) with opioids and 607/1606 (37.8%) with placebo treatment (**Fig. 3**): RR 1.40 (95 CI: 1.26-1.56; $I^2 = 50\%$; $P < 0.001$; n = 9 RCTs; low certainty of evidence); 151 more per 1000 (from 98 to 212 more) patients with opioids, suggesting that opioid treatment may result in an increase of patients achieving a pain reduction of at least 30%.

3.4.2.2. ≥50% pain intensity reduction

The proportion of patients who responded with ≥50% reduction in PI at treatment end was 738/2018 (36.6%) with opioids and 394/1538 (25.6%) with placebo (**Fig. 4**): RR 1.49 (95% CI: 1.30-1.70; $I^2 = 33\%$; $P < 0.001$; n = 8 RCTs; low certainty of evidence); 126 more per 1000 (from 77 to 179 more) patients with opioids, suggesting that opioid treatment may result in an increase of patients with a pain reduction of at least 50%.

3.4.3. Disability

For disability, measured with the Roland–Morris Disability Questionnaire (RMDQ 0-24; 24 = most severe disability), Oswestry Disability Index (ODI 0-100; 100 = complete disability), and Pain Disability Index (PDI 0-10; 10 = total disability), the SMD was −0.21 (95% CI: −0.30 to −0.12; $I^2 = 18\%$; $P < 0.001$; n = 9 RCTs; low certainty of evidence) (**Fig. 5**). Re-expressed as MD on the RMDQ (most commonly used instrument in the included RCTs), the MD was 1.09 points lower (from 1.56 to 0.63 lower) with opioids, suggesting that opioid treatment may result in little to no difference in disability: MD − 1.09 (95% CI: −1.56 to −0.63).

3.4.4. Sleep quality

3.4.4.1. Overall

Sleep quality was measured with the CPSI (VAS 0-100; 100 = excellent sleep) and Pain and Sleep Questionnaire (PSQ, VAS 0-100; 100 = excellent sleep) (Supplementary file 1; Figure S2): SMD 0.30 (95% CI: −0.09 to 0.50; $I^2 = 5\%$; $P = 0.005$; n = 2 RCTs; moderate certainty of evidence). Re-expressed as MD on the CPSI (VAS 0-100) resulted in an MD of 8.80 points higher (from 2.64 higher to 14.67 higher), suggesting that opioids likely result in an increase in overall sleep quality: MD 8.80 (95% CI: −2.64 to 14.67).

In addition, 2 studies descriptively reported results. Whereas Rauck et al.[74] found no significant differences in change from baseline Medical Outcomes Score Sleep Subscale between intervention groups, Buynak et al.[10] reported that baseline to end-of-trial (overall) sleep quality ratings only “significantly” improved in the tapentadol group ($P = 0.003$), but not in the oxycodone controlled-release group ($P = 0.091$) when compared with placebo.

3.4.4.2. Pain interference with or pain impact on sleep

This outcome was measured with the Brief Pain Inventory Sleep Interference (BPISI) subscale (0-10; 10 = completely

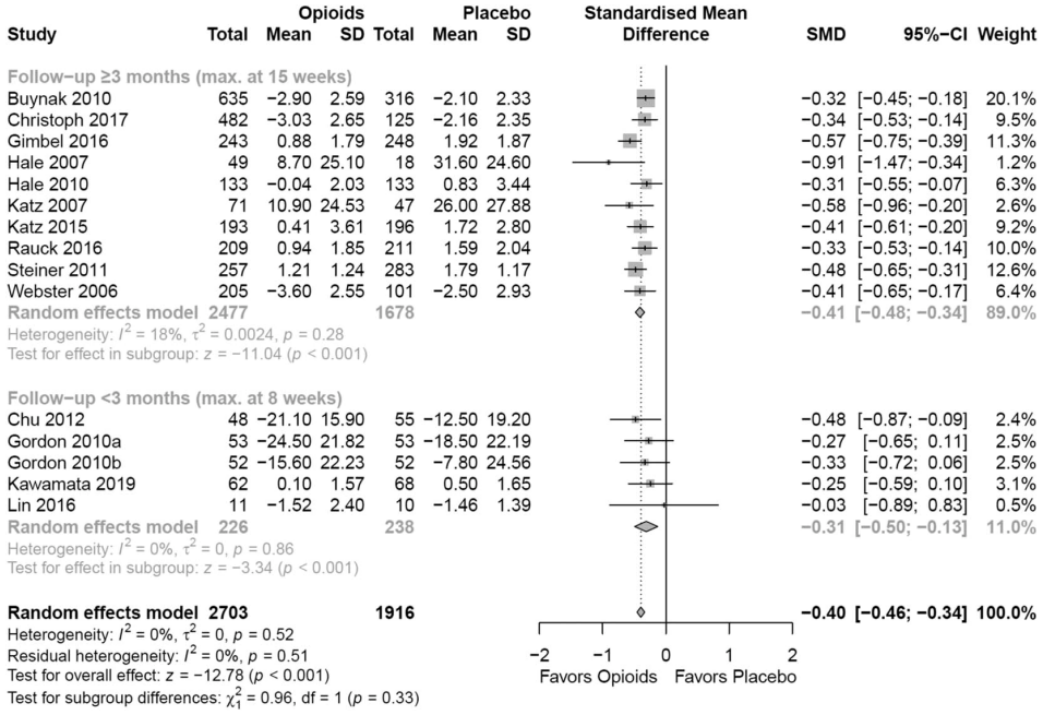

Figure 2. Pain intensity: Mean changes from baseline; treatment duration min. 4 to max. 15 weeks; assessed with Numerical Rating Scale 0–10 and Visual Analog Scale 0 to 100.

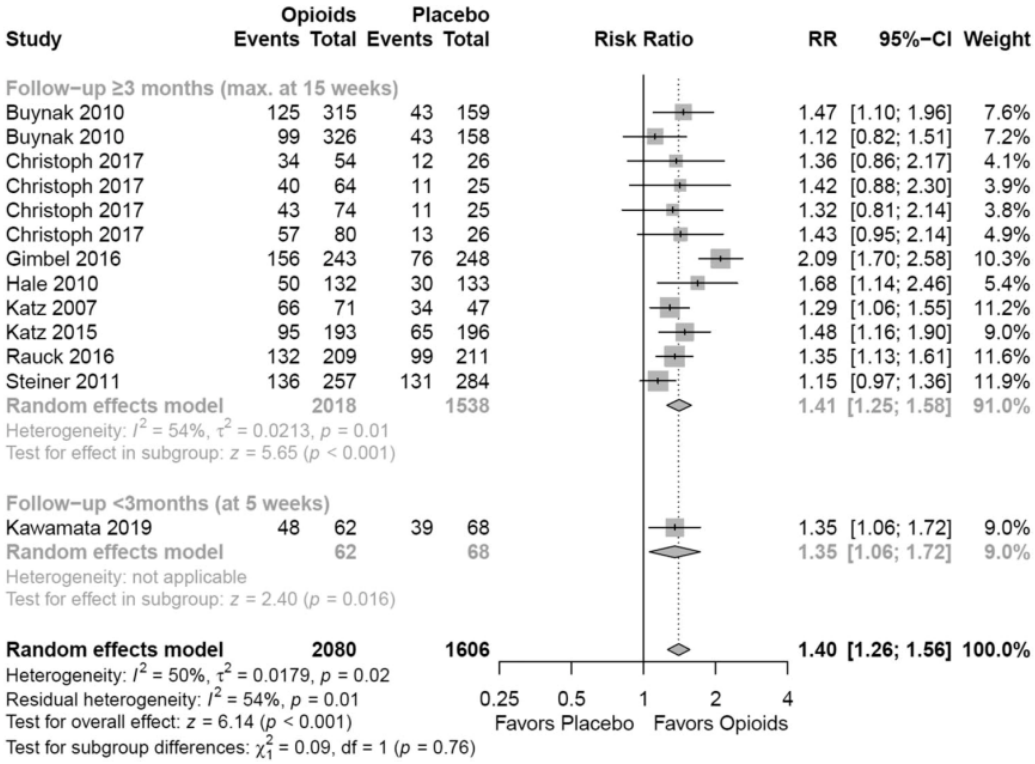

Figure 3. ≥30% pain intensity reduction: Events refer to the number of patients with ≥30% reduction in pain intensity at the end of treatment (treatment duration: min. 5 to max. 15 weeks).

interferes with sleep) and the Pain and Sleep Questionnaire (VAS 0-100 mm; 100 = pain always impacts sleep) (Supplementary file 1; Figure S3): SMD −0.36 (95% CI: −0.73 to 0.02; I^2 = 67%; P = 0.063; n = 3 RCTs; very low certainty of evidence) and SMD re-expressed as MD on the BPISI: −0.58 (95% CI: −1.18 to 0.03). The result suggests that opioids may somewhat reduce pain interference with or pain impact on sleep, but the evidence is very uncertain. An additional RCT, descriptively reported a "significant" improvement in the BPISI score in the opioids group (P = 0.0030) compared with placebo but did not provide numerical data to be included in the meta-analysis.

3.4.5. Trial discontinuations

3.4.5.1. Overall

Data on overall trial discontinuations were available for all 16 trials (5308 patients) and suggested no difference between opioids and placebo treatment, but the evidence is very uncertain (Supplementary file 1; Figure S4, available

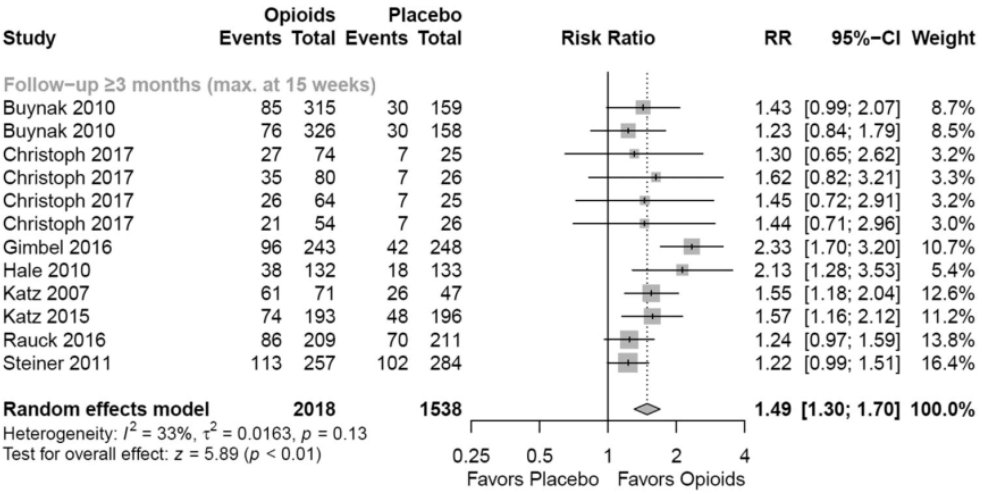

Figure 4. ≥50% pain intensity reduction: Events refer to the number of patients with ≥50% reduction in pain intensity at treatment end; treatment duration: min 12 to max 15 weeks.

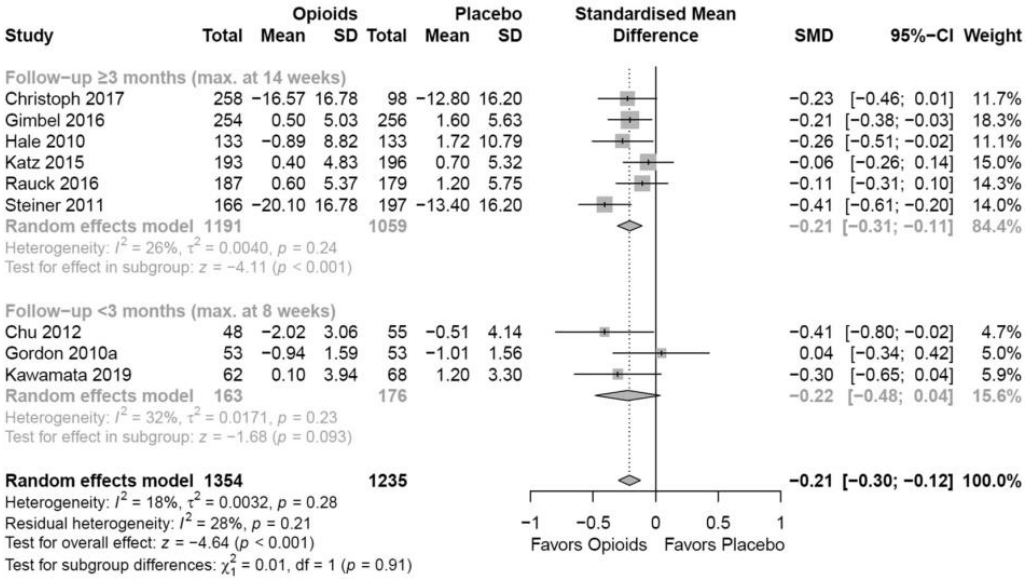

Figure 5. Disability: Mean changes from baseline; treatment duration min. 4 to max. 14 weeks; assessed with RMDQ 0-24, ODI 0-100, and PDI 0-100.

at http://links.lww.com/PAIN/B445): RR 0.97 (95% CI: 0.80-1.16; $I^2 = 82\%$; $P = 0.71$; n = 16 RCTs; very low certainty of evidence).

3.4.5.2. Adverse events

Discontinuations because of AEs, however, occurred more often in the opioids group (554/3048 patients) as compared with the placebo group (132/2260 patients), indicating that treatment with opioids may cause more discontinuations because of AEs, but the evidence is very uncertain (Supplementary file 1; Figure S5): RR 2.24 (95% CI: 1.48-3.38; $I^2 = 70\%$; $P = 0.0001$; n = 16 RCTs; very low certainty of evidence).

3.4.5.3. Lack of efficacy

Discontinuations because of a lack of efficacy, on the other hand, showed the opposite image (175/2906 [opioids] vs 426/2125 [placebo]) (Supplementary file 1; Figure S6): RR 0.33 (95% CI: 0.26-0.41; $I^2 = 39\%$; $P < 0.0001$; n = 14 RCTs; low certainty of evidence).

3.4.6. Safety and tolerability outcomes

3.4.6.1. Opioid withdrawal symptoms

Withdrawal symptoms were assessed with the Subjective Opiate Withdrawal Scale, Clinical Opiate Withdrawal Scale, and

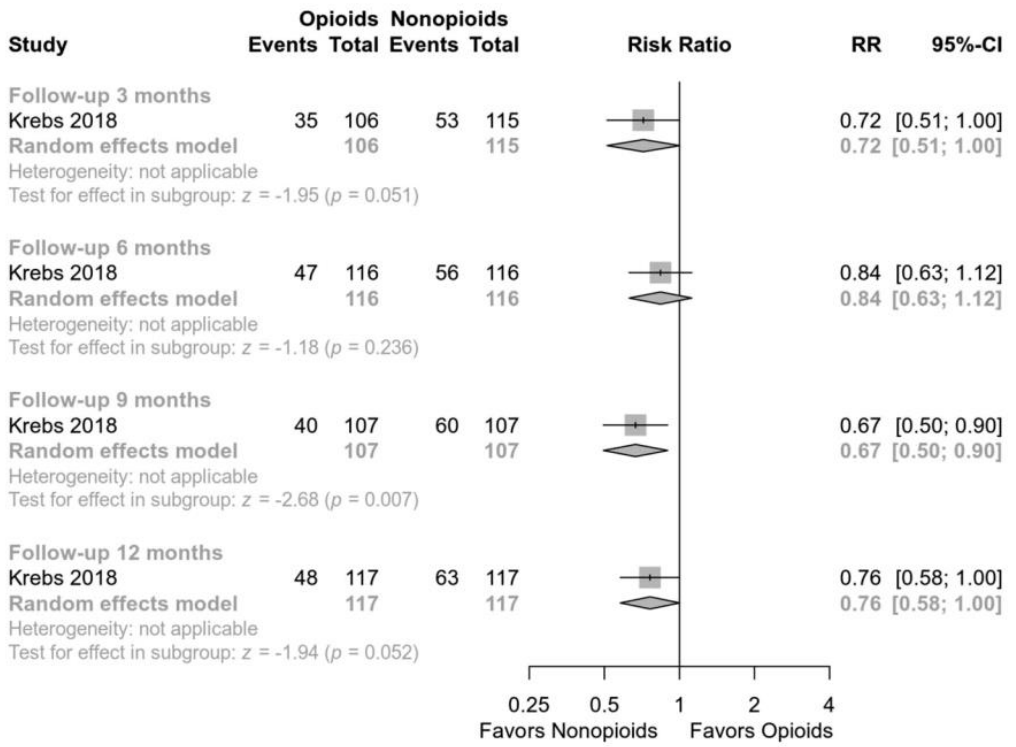

Figure 6. ≥30% reduction in BPI paint severity score: treatment duration of 3, 6, 9, and 12 months. BPI, Brief Pain Inventory.

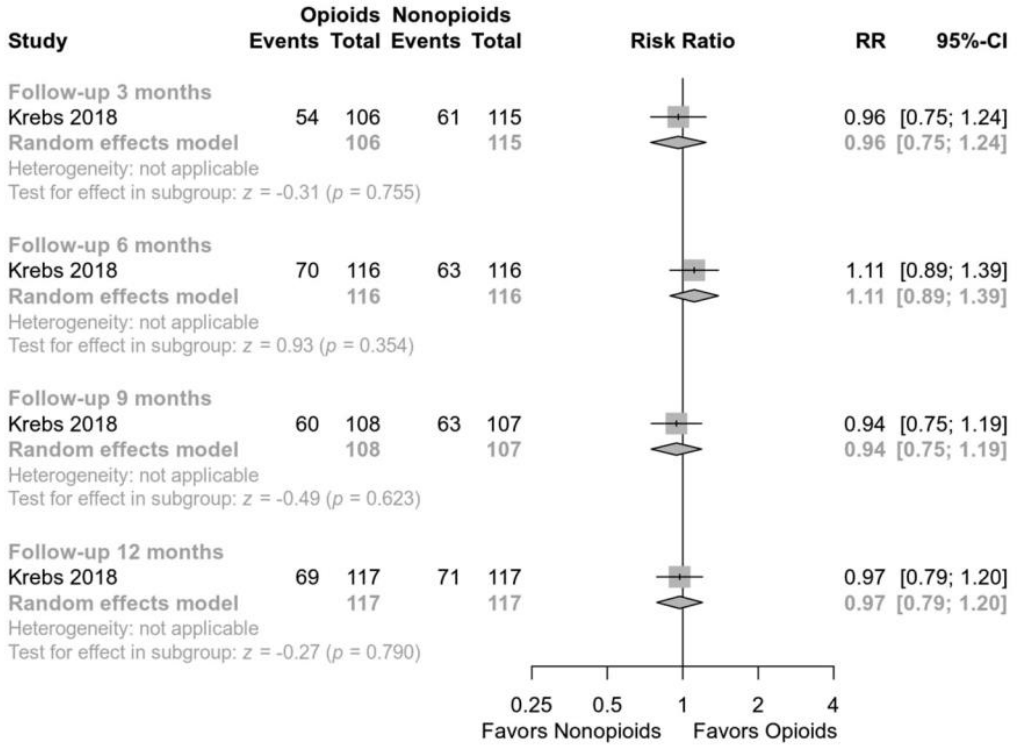

Figure 7. ≥30% reduction in BPI interference score: treatment duration of 3, 6, 9, and 12 months. BPI, brief pain inventory.

Adjective Rating Scale for Withdrawal. They were reported by 64 of 2481 (2.6%) participants in the opioids and 35 of 1794 (2.0%) participants in the placebo group (Supplementary file 1; Figure S7): RR 0.82 (95% CI: 0.38-1.75; $I^2 = 33\%$; $P = 0.60$; n = 12 RCTs; very low certainty of evidence).

3.4.6.2. Opioid dependency

This outcome was only evaluated in one study[50] using the Dependency-2-A (D-2-A) and Dependency-2-B (D-2-B) questionnaires, which reported that no participants had developed drug dependency in either the opioid (n = 62) or placebo (n = 68) treatment group.

3.4.6.3. Opioid misuse or abuse

Three studies assessed opioid misuse or abuse. Gimbel et al.[32] found no cases of misuse or abuse of study medication, and Steiner et al.[87] reported that no participants were suspected of study medication abuse; both trials had a duration of 12 weeks. Although Kawamata et al.[50] also did not report additional concerns about study drug abuse, it should be noted that this trial only had a duration of 5 weeks. None of these trials provided any additional details (eg, on assessment instruments used) for this outcome.

3.4.6.4. Adverse events

3.4.6.4.1. Any adverse events

Overall, more patients in the opioids group (1859/2757 [67%]) as compared with patients in the placebo group (1091/2077 [53%]) reported AEs (Supplementary file 1; Figure S8): RR 1.20 (95% CI: 1.13-1.28; $I^2 = 43\%$; $P < 0.0001$; n = 13 RCTs; low certainty of evidence).

3.4.6.4.2. Serious adverse events

Similarly, more patients on opioids (55/3032) than patients on placebo (23/2248) reported serious AEs (Supplementary file 1; Figure S9): RR 1.49 (95% CI: 0.90, 2.45; $I^2 = 0\%$; $P = 0.12$; n = 15 RCTs; very low certainty of evidence).

3.4.6.4.3. Deaths

None of the 10 trials addressing mortality reported any treatment-related deaths in either intervention arm (low certainty of evidence).

3.4.6.4.4. Gastrointestinal and nervous system AEs

Treatment with opioids was associated with an increased incidence of nausea, vomiting, and constipation (Supplementary file 1; Figures S10-12): RR^{nausea} 1.86 (95% CI: 1.35-2.56; $I^2 = 62\%$; $P = 0.0001$; n = 13 RCTs; very low certainty of evidence); $RR^{vomitting}$ 3.26 (95% CI: 2.08-5.09; $I^2 = 34\%$; $P < 0.0001$; n = 11 RCTs; low certainty of evidence); and $RR^{constipation}$ 2.73 (95% CI: 1.98-3.77; $I^2 = 20\%$; $P < 0.0001$; n = 13 RCTs; low certainty of evidence).

Similarly, the nervous system AEs dizziness and somnolence were reported more frequently in patients treated with opioids than in those treated with placebo (Supplementary file 1; Figures S13-14): RR 2.91 (95% CI: 2.17-3.90; $I^2 = 0\%$; $P < 0.001$; n = 10 RCTs; low certainty of evidence) and RR 3.47 (95% CI: 2.33-5.17; $I^2 = 4\%$; $P < 0.001$; n = 10 RCTs; low certainty of evidence). On the other hand, there was no difference between opioids and placebo treatment for the AE headache (Supplementary file 1; Figure S15): RR 1.01 (95% CI: 0.81-1.27; $I^2 = 0\%$; $P = 0.92$; n = 11 RCTs; very low certainty of evidence).

3.4.6.4.5. Depression and anxiety

One trial[20] measured self-rated mental depression, using the Beck Depression Inventory (BDI 0-63; higher scores indicate more severe depression), but found no statistically significant changes at treatment end in either the opioid ($P = 0.32$) or placebo group ($P =$

0.67). Also, change from baseline BDI scores between both groups did not significantly differ ($P = 0.32$). Similarly, another trial[19] assessed the presence of depression and anxiety but also found no clear effect of either treatment on anxiety or depression after 14 weeks of treatment, ie, changes from baseline in the Hospital Anxiety and Depression Scale anxiety and depression subscale scores showed both improvement and worsening of depression and anxiety across comparison arms at the treatment end. Meta-analysis was not possible as no suitable numerical data were reported or could be obtained for these studies.

In addition, MH was assessed in 3 trials using the Short Form Health Survey 12 and 36 (SF-12v2 and SF-36; 0-100, 100 = the best). Although these trials did not directly address the outcomes depression and anxiety, specific SF-12, SF-36 Mental Component Score, and MH cut-off points, developed and validated for the purpose of depression and anxiety screening in the general population and patients with a chronic back pain or a similar condition (rheumatoid arthritis),[31,58,97] to a certain extent, allowed indirect assessment of depression and anxiety. Both SMD and SMD re-expressed as MD (on SF-36 Mental Component Score) were not different between opioid and placebo treatment (Supplementary file 1; Figure S16): SMD −0.01 (95% CI: −0.37 to 0.36; $I^2 = 85\%$; $P = 0.973$; n = 3 RCTs; very low certainty of evidence); MD -0.1 (95% CI: −3.52 to 3.43; surrogate result, therefore no MID).

3.4.6.5. Suicidal ideation or behavior

This outcome was only reported by 3 trials. Christoph et al.[19] used the Columbia-Suicide Severity Rating Scale and reported no events in either the placebo (n = 126) or opioid group (n = 511). Steiner et al.[87] reported one event of suicidal ideation (ie, homicidal thoughts) in the placebo group (n = 283) compared with none in the opioids group (n = 256), and Hale et al.[38] reported the opposite, ie, one in the intervention group (n = 134) and none in the placebo group (n = 134); both trials did not provide any details on the assessment instrument used. The certainty of evidence was judged to be very low.

3.4.7. Patient ratings

3.4.7.1. Patient global impression of change

More patients with opioids (761/1378) reported a rating of "much improved or very much improved' on the PGIC at the end of treatment compared with patients receiving placebo (366/1050) (Supplementary file 1; Figure S17): RR 1.58 (95% CI: 1.40-1.78; $I^2 = 36\%$; $P < 0.0001$; n = 5 RCTs; low certainty of evidence).

3.4.7.2. Patient global rating of study medication

In 3 RCTs, patients rated their study medication using a 5-point categorical scale (1 = fair, 2 = poor, 3 = good, 4 = very good, and 5 = excellent). At the final visit of the double-blind treatment period, a larger proportion of patients treated with opioids rated their medication as good, very good, or excellent compared with those who received placebo (Supplementary file 1; Figure S18): RR 1.80 (95% CI: 1.19-2.70; $I^2 = 88\%$; $P = 0.005$; n = 3 RCTs; very low certainty of evidence).

3.4.7.3. Patient-assessed treatment effectiveness

In the 2 cross-over RCTs, treatment effectiveness was assessed by patients at treatment end, using a 4-point categorical scale (0 = not effective, 1 = slightly effective, 2 = moderately effective, and 3 = highly effective). More patients with opioids (55/101) compared with placebo (34/101) rated their treatment as moderately or highly effective (Supplementary file 1; Figure S19): RR 1.63 (95% CI: 1.18-2.25; $I^2 = 0\%$; $P = 0.003$; n = 2 RCTs; low certainty of evidence).

3.4.8. Subgroup analyses, sensitivity analyses, and publication bias

In CLBP trials, subgroup analyses mostly did not suggest any differences in relation to treatment duration, study design, and opioid status at trial start (see Table S2-S12 [Supplementary file 1]). However, some significant interactions for study design and opioid status were detected for these trials:

3.4.8.1. Study design

The test of subgroup differences revealed significant differences between trials with an EERW, parallel, or cross-over study design for the outcomes: nausea ($P = 0.02$), overall discontinuations ($P < 0.0001$), and discontinuations because of AEs ($P = 0.009$) (Table S3-S4). Subgroup analyses showed less risk for nausea in EERW (RR = 1.32, 95% CI: 1.01-1.74) compared with parallel (2.15 95% CI: 1.11-4.19) and cross-over (2.66, 95% CI: 1.76-4.01) trials. The same was observed for discontinuations because AEs: EERW (RR = 1.28, 95% CI: 0.85-1.94) vs parallel (RR = 3.82, 95% CI: 1.87-7.80) and cross-over (RR = 3.29, 95% CI: 1.64-6.61) trials. The subgroup analysis also identified opposite effects on overall discontinuations between EERW (RR = 0.67, 95% CI: 0.53-0.86) and parallel (RR = 1.27 95% CI: 0.99-1.63) or cross-over (RR = 1.81, 95% CI: 1.10-2.98) trials.

3.4.8.2. Opioid status

The test of subgroup differences showed significant differences between trials with either opioid-naïve, opioid-experienced, or opioid-naïve and experienced patients for ≥30% PI reduction ($P < 0.0001$), ≥50% PI reduction ($P = 0.002$), pain interference or impact on sleep ($P = 0.02$), opioid withdrawal symptoms ($P = 0.03$), nausea ($P = 0.05$), somnolence ($P = 0.03$), and overall discontinuations ($P = 0.03$) (Table S9-S11). Subgroup analyses demonstrated larger pain improvement in trials with opioid-experienced patients compared with trials with opioid-naïve or opioid-naïve and opioid-experienced patients (Table S9). Results of the other subgroup analyses showed no significant differences. The planned sensitivity analysis could not be performed because of a lack of low RoB trials. Visual examination of funnel plots suggested minor to moderate asymmetry for constipation, somnolence, and headache (Supplementary file 2).

3.5. Findings from chronic noncancer pain studies

3.5.1. Key characteristics of included studies

3.5.1.1. Study characteristics

3.5.1.1.1. Randomized controlled trials

Both trials, of which one was multicentric, were conducted in the United States and had a parallel design. Each trial used 3 and 2 arms (active controlled), respectively. One[54] was pragmatic, and

in the other,[2] physicians had the option of prescribing any medication deemed necessary based on patients' response to study medication (no additional details were reported). Both trials had a follow-up of 12 months after randomization. The first trial reported public funding, and all study authors, except for one, declared having no conflict of interests. The second trial reported being industry funded and did not provide conflict of interest disclosures. More details on trial characteristics are shown in **Table 2**.

3.5.1.1.2. Nonrandomized studies of interventions

Of the 3 included NRSI, 2 were retrospective cohort studies conducted in the United States[26,75] and one was a retrospective cross-sectional study from Germany.[27] The longest follow-up was 18 months (**Table 3**). Both cohort studies reported being non-industry funded, and the study authors declared having no relevant conflict of interests; the cross-sectional study was industry funded and one of the study authors disclosed a relevant conflict of interest.

3.5.1.2. Participant characteristics

3.5.1.2.1. Randomized controlled trials

Both trials were conducted in adults (age range 18-80 years) with CNCP (**Table 2**). One trial included 11,352 patients, 17% of whom had chronic back pain, and the other trial included 240 patients, 65% of whom were suffering from chronic back pain. The proportion of women was 68% and 13%, respectively. Both trials excluded patients who reported (long-term) opioid therapy, current substance abuse, and conditions that could impede outcome assessment. Whereas patients with MH disorders were included in the pragmatic trial, they were excluded in the other trial. **Table 2** provides more details on participant characteristics.

3.5.1.2.2. Nonrandomized studies of interventions

All studies included adults (age range 18-74 years) with CNCP. In both cohort studies, health (claims) data of 568,640 and 45,824 patients, respectively, were used; for the cross-sectional study, interview and questionnaire data of 333 patients were used. More than 58% of study participants were female in all 3 studies. Overall, patients with substance abuse issues or severe comorbidities were excluded. More details on patient characteristics are shown in **Table 3**.

3.5.1.3. Intervention and comparator characteristics

3.5.1.3.1. Randomized controlled trials

The pragmatic trial compared opioid with nonopioid drug therapy, using a specific 3-step prescribing strategy in each arm consisting of multiple drugs options. In this trial, morphine, oxycodone, hydrocodone, and fentanyl were tested against acetaminophen, NSAIDs, adjuvant drugs (eg, nortriptyline), topical analgesics (eg, lidocaine), and medications requiring prior clinical approval (eg, pregabalin). The second trial compared hydrocodone, tramadol, and NSAIDs. More details on prescription strategies, dosing, and administration routes can be found in **Table 2**.

3.5.1.3.2. Nonrandomized studies of interventions

One of the cohort studies compared different durations (ie, acute or chronic) and doses of opioids (ie, low, medium, and high) with no opioid use. In the other cohort study, strong, long-acting opioids were tested against anticonvulsants (eg, gabapentin) or low-dose cyclic antidepressants (eg, amitriptyline). The cross-sectional study compared opioids with nonopioid analgesics (eg, NSAIDS, anticonvulsants, antidepressants, or muscle relaxants). Prescribed opioids in the 3 studies included morphine, oxycodone, fentanyl, methadone, buprenorphine, and tapentadol. More details on opioids used, dosing, and administration schemes can be found in **Table 3**.

3.5.2. Efficacy outcomes

3.5.2.1. Evidence from randomized controlled trials

3.5.2.1.1. Pain intensity

The effect estimate for PI after 12 months of treatment measured with the self-reported Brief Pain Inventory pain severity subscale (BPI-PS; NRS 0-10; higher is worse pain severity) for opioids compared with nonopioids was 0.50 (95% CI: 0.95-0.05; $P = 0.029$; n = 1 RCT; low certainty of evidence).

3.5.2.1.2. Disability or pain-related function

The effect estimate for pain-related function assessed with the BPI interference scale (NRS 0-10; higher is worse function) for opioids compared with nonopioids was 0.20 (95% CI: −0.41 to 0.81; $P = 0.52$; n = 1 RCT; very low certainty of evidence).

3.5.2.1.3. Improvement in pain severity (≥30% reduction in Brief Pain Inventory severity score)

The proportion of patients who responded with ≥30% reduction in pain severity was greater in the nonopioid group than in the opioid group at all follow-up times (**Fig. 6**), eg, $RR^{12\ months}$ 0.76 (95 CI: 0.58-1.00; $P = 0.05$; n = 1 RCT; low certainty of evidence); 129 fewer per 1000 (from 226 to 0 fewer) patients with opioids, suggesting that prolonged treatment with opioids may result in a reduction of the number of patients achieving at least 30% pain severity reduction.

3.5.2.1.4. Improvement in pain-related function (≥30% reduction in Brief Pain Inventory interference score)

After 3, 9, and 12 months of treatment, no relevant difference between opioid and nonopioid treatment regarding functional response (**Fig. 7**) was observed, but the evidence is very uncertain, eg, $RR^{12\ months}$ 0.97 (95 CI: 0.79-1.20; $P = 0.79$; n = 1 RCT; very low certainty of evidence). At 6 months of follow-up, opioids may have been slightly more beneficial, but the evidence again is very uncertain: RR 1.11 (95 CI: 0.89-1.39; $P = 0.35$; n = 1 RCT; very low certainty of evidence).

3.5.2.1.5. Global change in pain ≥ moderately better (responders)

The number of patients who reported a clinically important improvement (ie, a response of "moderately better" or "much better") was greater for nonopioid treatment than for opioid treatment at all follow-up times, suggesting that nonopioids may be more beneficial (Supplementary file 1; Figure S20), eg, $RR^{12\ months}$ 0.75 (95 CI: 0.57-0.98; $P = 0.04$; n = 1 RCT; low certainty of evidence).

3.5.2.2. Evidence from nonrandomized studies of interventions

3.5.2.2.1. Pain severity and disability

Although the proportion of patients with moderately limiting pain and high disability or severely limiting pain and high disability was

slightly lower in the nonopioid group (23/163 and 127/163) compared with the opioid group (20/137 and 111/137), both treatments seemed to be comparable in efficacy (Supplementary file 1; Figure S21), but the evidence is very uncertain: RR 1.03 (95 CI: 0.59-1.80; $P = 0.90$; n = 1 NRSI; very low certainty of evidence) and RR 1.04 (95 CI: 0.93-1.17; $P = 0.51$; n = 1 NRSI; very low certainty of evidence).

3.5.3. Safety and tolerability outcomes

3.5.3.1. Evidence from randomized controlled trials

3.5.3.1.1. Drug abuse
Drug abuse was determined by the number of patients with ≥1 positive score(s) or case(s) on the Abuse Index or with a clinician-assessed ABC score of ≥3 during 12 months of follow-up. More cases of drug abuse were reported in the opioids group (219/4397 patients) as compared with the nonopioid group (226/8708 patients) (Supplementary file 1; Figure S22): RR 1.89 (95% CI: 1.57, 2.27; $I^2 = 0\%$; $P < 0.001$; n = 2 RCTs; low certainty of evidence).

3.5.3.1.2. Falls
One RCT assessed the number of patients with falls after 12 months of follow-up and reported no difference between opioid (55/118) and nonopioid (56/119) treatment (Supplementary file 1; Figure S23): RR 0.99 (95% CI: 0.76-1.30; $P = 0.94$; n = 1 RCT; very low certainty of evidence).

3.5.3.2. Evidence from nonrandomized studies of interventions

3.5.3.2.1. Opioid abuse or dependence
One cohort study[26] compared the number of patients with an opioid abuse or dependence diagnosis for low (1-36 mg morphine equivalents [ME]s) or medium (36-120 mg ME) or high dose (>120 mg ME), chronic opioid use, and no opioid (0 mg) use. It is noteworthy that cases of opioid abuse or dependence were not only reported with chronic, low dose (50/6902 [0.7%]), medium dose (47/3654 [1.3%]), and high dose (23/378 [6.1%]) opioid use but also in the no opioid use group (150/371,371 [0.04%]) (Supplementary file 1; Figure S24): eg, $RR^{\text{medium dose}}$ 31.85 (95% CI: 22.99, 44.12; $P < 0.00,001$; n = 1 NRSI; very low certainty of evidence). The proportion of patients with opioid abuse or dependence diagnoses increased with higher opioid doses used.

3.5.3.2.2. Any adverse events
More patients (111/170 [65%]) in the opioids group as compared with patients in the nonopioids group (73/165 [45%]) reported any AEs (Supplementary file 1; Figure S25): RR 1.48 (95% CI: 1.2, 1.81; $P = 0.0002$; n = 1 NRSI; low certainty of evidence). Reported AEs comprised constipation, fatigue, nausea or vomiting, and other AEs (not further specified).

3.5.3.2.3. Deaths
All-cause mortality for patients on either long-acting opioids or nonopioid drugs (ie, anticonvulsants or cyclic antidepressants) was assessed after the first 30 days of therapy (ie, 31-180 days) and after 180 days of therapy. In both follow-up periods, more deaths were reported in the opioids (70/12,194 and 62/5582) than in the nonopioids (40/11,752 and 34/3765) treatment group (Supplementary file 1; Figure S26): $RR^{>180\ \text{days}}$ 1.23 (95% CI: 0.81-1.86; $P = 0.33$; n = 1 NRSI; very low certainty of evidence); 2 more deaths per 1000 (from 2 fewer to 8 more) with opioids, suggesting that opioids may increase all-cause mortality, but the evidence is very uncertain.

4. Discussion

This systematic review and MA synthesized the best available research evidence from RCTs and NRSI on the treatment of CNCP, especially CLBP, with strong opioids in short-term and long-term use.

4.1. Short-term opioid use (chronic low back pain trials)
Based on very low to low certainty evidence from RCTs of 4–15 weeks treatment duration, our findings suggest that treatment of CLBP with opioids may be more beneficial than placebo to reduce pain. Although there was a small, statistically significant but clinically nonrelevant, difference between treatments in mean PI and disability reduction from baseline to treatment end, data suggest that opioids may provide a clinically relevant pain reduction of 30% or greater and 50% or greater. Regarding sleep quality outcomes, there were no clinically relevant differences between opioid and placebo treatment. The results on overall trial discontinuations suggest that there were no differences between treatments. However, when looking at the specific causes for study discontinuation, discontinuations because of AEs occurred more often in the opioids group, whereas discontinuations because of a lack of efficacy were more often reported in the placebo group. In addition, adverse and serious AEs seemed to occur more frequently in the opioid compared with the placebo group. No treatment-related deaths were reported with either treatment. Similarly, there were no or no major differences in reported cases of opioid withdrawal symptoms, dependency, misuse or abuse, and suicidal ideation or behavior in either group. Also, self-reported depression and anxiety scores did not appear to significantly differ between opioid and placebo treatment in both direct and indirect assessments of these outcomes. By contrast, gastrointestinal and nervous system AEs (except for headache) were reported significantly more frequently in the opioid group compared with the placebo group. Patient ratings of improvement, study medication, and treatment effectiveness suggest that opioids may be more beneficial than placebo treatment. In additional analyses, some important subgroup differences were detected when comparing study designs and opioid experience status, which may explain the large heterogeneity observed for some outcomes (eg, overall trial discontinuations).

However, it needs to be stressed that all findings were based on very low to low certainty evidence. This in particular because most included trials had an EERW design. For instance, nearly 80% of the CLBP trials included in this systematic review for the endpoints ≥30% and ≥50% PI reduction had an EERW design. Enriched enrollment randomized withdrawal trials are conducted in an enrichment phase followed by a double-blind randomized withdrawal phase.[12] The enrichment phase consists of a prerandomization, open-label period where patients receive the study drug at flexible doses titrated to individual effectiveness, with the purpose of identifying study drug responders and

Table 2

Study characteristics of the included randomized controlled CNCP trials.

Study	Design and country	Patients randomized	Arms	Study population	Exclusions	Treatment groups	Mean age (y)	Female (%)	Follow-up
Adams et al.[2]	Prospective, parallel-group RCT* USA	11,352	3	Adults (18-74 yr) with chronic (≥4 months) nonmalignant pain, initiating a new therapy that included a prescription for one of the reference medications Note: 1885 patients (16.6%) with CBP	chronic headache; serious mental disturbances (eg, psychotic or suicidal); current substance abuse problem; patients taking any contra-indicated medications (eg, other opioids)	I Tramadol (N = 4168) I Hydrocodone (N = 3145) C NSAIDs (N = 4039)	Nr. 86.8% of the patients were >36 yr	7742 (68.2)	12 months
Krebs et al.[54]	Pragmatic, multiclinic (N = 62), parallel-group, RCT† USA	240	2	Adults (21-80 yr) with moderate-to-severe chronic (≥6 months) back pain or hip or knee osteoarthritis pain despite analgesic use Moderate or greater severity: Score of ≥ 5 on the 3-item pain intensity, interference with enjoyment of life, and interference with general activity (PEG) scale (range 0-10) Note: 156 patients (65%) with CBP	Patients on long-term opioid therapy or with contraindications to all drug classes in either group (eg, active substance use disorder), and conditions that could interfere with outcome assessment (eg, life expectancy <12 months) Note: "Patients with severe depression or posttraumatic stress disorder symptoms were not excluded because these patients often receive opioids in practice."	I Opioid therapy (N = 120) Step1—morphine IR, oxycodone IR or hydrocodone IR Step2—morphine SA or oxycodone SA. Step3—fentanyl TD Max. daily dosage of 100 morphine equivalent (ME) mg "Single-opioid therapy was preferred, but dual therapy with a scheduled SA opioid and as-needed IR opioid was considered based on patient needs and preferences."	56.8	32 (13)	at 3, 6, 9, 12 month
						C Nonopioid medication therapy (N = 120) Step 1—acetaminophen or NSAIDs Step 2—adjuvant oral medications (ie, nortriptyline, amitriptyline, and gabapentin) and topical analgesics (ie, capsaicin and lidocaine). Step 3—drugs requiring prior clinic authorization (ie, pregabalin and duloxetine) and tramadol "Patients were initially prescribed a step 1 medication, unless all were clinically inappropriate. Subsequent changes included titrating, replacing, or adding medications."	59.7		

Note: "Medications were changed, added, or adjusted within the assigned treatment group according to individual patient response."

* Adams 2006: "Once a subject was enrolled, it became a natural history study, in that physicians could prescribe whatever medication was therapeutically appropriate based on response to the initial medication; thus, some subjects may have been taking NSAIDs, hydrocodone, or tramadol at different times during the study. All data were collected and analyzed by the drug the subject was taking at the time of the interview not the drug to which they were randomized."

† Krebs 2018: "The trial was pragmatic, meaning that patients were enrolled from primary care settings and interventions were delivered with flexibility in medication selection and dosing according to individual patient response."

C, comparison; CBP, chronic back pain; I, intervention; IR, immediate release; Nr, not reported; SA, sustained action; TD, transdermal.

Table 3

Study characteristics of the included nonrandomized CNCP studies.

Study	Design and country	Patients randomized	Arms	Study population	Exclusions	Treatment groups	Mean age (y; SD)	Females (%)	Follow-up
Edlund et al.[26]	Retrospective cohort study USA Using health claims data	568,640	2	Individuals (≥18 yrs) with a new chronic noncancer pain episode (no diagnosis in prior 6 months) and no opioid use or OUD in the prior 6 months. Eligible individuals required to have 12 months of continuous eligibility before and 18 months of continuous eligibility after the index date (day of the first diagnosis) Note: The proportion of patients with CBP was not reported.	Individuals with OUD diagnoses or prescription opioid use in the prior 6 months; individuals with cancer diagnoses at any time in 12 months before or after 18 months after the index date; residents of nursing homes and those receiving hospice benefits.	I Opioid use (N = 197269): - acute (1-90 days) or chronic (91+ days); - Low dose (1-36 mg), medium dose (36-120 mg), and high dose (>120 mg) Opioid prescriptions included morphine, fentanyl, levorphanol, oxycodone, methadone, oxymorphone, hydromorphone, meperidine, hydrocodone, and tramadol. Buprenorphine was excluded "as the oral formulation is not FDA approved for pain treatment." C No opioid use (N = 371371): 0 days; 0 mg	Nr. 69% of patients were >40 yrs	331,533 (58.3)	18 months
Ray et al.[75]	Retrospective cohort study USA Using health claims data	45,824	2	Individuals (30-74 yr) initiating therapy with the study drugs with a diagnosis of chronic pain (back, other musculoskeletal, abdominal, headache, and other neurologic pain) in the past 90 days. Note: 17,071 patients (75%) in the opioids group and 17,333 patients (76%) in the control group had CBP.	Persons aged 75 years; patients with cancer, other life-threatening diseases, or evidence of hospice or other terminal care; persons with recorded evidence of drug abuse; and nursing home residents. Patients were also excluded if the starting daily dose was not recommended for chronic pain or was unusually high.	I Long-acting opioids (N = 22,912): Morphine SR 30 mg, oxycodone CR 20 mg, fentanyl TD 15mcg/hr, and methadone 10 mg. C Anticonvulsants (for CP) or low-dose cyclic antidepressant (N = 22,912): gabapentin 900 mg, pregabalin 200 mg, carbamazepine 600 mg, amitriptyline 100 mg, desipramine 100 mg, doxepin 100 mg, imipramine 100 mg, nortriptyline 50 mg, protriptyline 15 mg, trimipramine 100 mg, amoxapine 100 mg, maprotiline 100 mg, and clomipramine 100 mg.	47.9 (10.5) 47.9 (10.7)	13,738 (60) 13,696 (60)	≥6 months
Elsesser et al.[27]	Retrospective, cross-sectional study* Germany Using interview and questionnaire data from patients	333	2	Individuals (>18 yr) with chronic pain (>6 months). See "treatment groups" for additional study population specifications. Note: 266 patients (77%) had disorders of the musculoskeletal system.	Pain due to cancer, comorbid dementia, psychotic or bipolar disorder, a history of alcohol, or opioid dependence. Patients with opioid analgesics for <3 months also excluded from further analysis. Note: Involvement in other kinds of	I Opioids† (N = 170): buprenorphine, fentanyl, hydromorphone, morphine, oxycodone, oxycodone + naloxone, tapentadol, tilidine, and tramadol. The opioid group comprised patients with continuous opioid intake during at least	65.9 (13.5)	125 (73.5)	≥6 months

(*continued on next page*)

Table 3 (*continued*)

Study	Design and country	Patients randomized	Arms	Study population	Exclusions	Treatment groups	Mean age (y; SD)	Females (%)	Follow-up
					treatment (eg, physical therapy, TENS) did not lead to exclusion in any group.	the previous 3 months‡. 55% was treated with high potency (WHO-III) opioids.			
						C Nonopioid analgesics (N = 163): Patients treated with different kinds of analgesics or coanalgesics, eg, NSAIDS, anticonvulsants, antidepressants, or muscle relaxants, but not with opioids in the previous 3 months.	62.7 (15.3)	124 (76.2)	

* Elsesser 2017: The assignment of the patients into the study groups was "based on retrospective information about the history of analgesia intake (ie, ex post facto)."
† Elsesser 2017: Analgesic intake classified according to WHO pain relief ladder, differentiating between low (WHO-II) and high potency (WHO-III) opioids. In case of the use of more than one opioid at the time of data collection, the one with the highest opioid potency determined classification.
‡ Elsesser 2017: Prescription time of opioids in the opioids group varied between 3 months and 15 years with an average time of intake of about 3 years. Most patients in the opioids group (N = 137; 81%) were under opioid medication for more than 6 months.
C, comparison; CR, controlled release; CBP, chronic back pain; CP, chronic pain; FDA, Food and Drug Administration; I, intervention; Nr, not reported; SR, sustained release; TD, transdermal.

excluding nonresponders or those with severe AEs.[12] The remaining "enriched" responder population is then randomized to continue the study drug or switch to a placebo or active control arm to compare efficacy and adverse effects of the experimental drug during the double-blind randomized withdrawal phase.[12] This trial design has been criticized for its limited external validity (ie, generalizability) and tendency to underestimate AEs, among other issues, and it has been claimed that "*EERW helps find the 'right patient for the drug' within the context of the clinical trial but fails to help clinicians find the right drug for the patient […].*"[12]

4.2. Long-term opioid use (chronic noncancer pain studies)

In addition, based on very low to low certainty evidence from RCTs and NRSI with 12 months to 18 months treatment duration, our results suggest that long-term treatment of CNCP with (strong) opioids may not be superior to nonopioids for improving PI or pain-related function or disability. In addition and contrary to findings on short-term use, the number of patients reporting a global change (ie, improvement) in pain of clinical relevance was greater with nonopioid treatment, suggesting that nonopioids may be more beneficial than opioids on the long term. However, the proportions of patients reporting moderately or severely limiting pain with high disability or falls did not differ between these treatment groups. Furthermore, long-term treatment with opioids was associated with more AEs and cases of abuse or dependence, and all-cause mortality seemed to be higher than with nonopioids.

4.3. Comparison with other systematic reviews

Similar to our systematic review, a recent meta-analysis of RCTs by Petzke et al.[72] found opioids to be more effective than placebo in providing a clinically meaningful pain reduction of 30% or more in CLBP. They also reported a clinically relevant reduction in disability (for parallel or cross-over trials alone) and in mean PI (for all trials) with opioids. Although we also found small reductions in disability and mean PI with opioid treatment, these did not reach thresholds of clinical importance in our MA. The differences with our MA may be partly explained by differences in opioids considered (eg, Petzke et al. also included non–WHO-III opioids), as well as differences in the thresholds for clinical relevance. Their findings on serious AEs and drop-outs because of AEs with opioids—suggesting more harm by opioid treatment—and on drop-outs because of efficacy lack with placebo—suggesting more benefit by opioids—are in line with our findings. Similarly, the MA by Petzke et al. supports our findings on mortality, opioid abuse, and opioid dependence, suggesting no differences between opioid and placebo treatment in the short term (≤15 weeks). Our findings on efficacy also closely match those of a Cochrane review,[14] which found that strong opioids are more effective than placebo for reducing pain (ie, mean PI, ≥30% and ≥50% pain reduction) and for improving disability in CLBP in the short term, but no statements on the clinical relevance of these findings were made. Similar to our findings, they found that patients treated with opioids had higher risk for gastrointestinal and nervous system AEs. Our results on pain and disability improvements are also consistent with 2 other systematic reviews,[1,17] which found that opioids for CLBP provided small or modest short-term improvements in pain reduction and small improvements in disability. Similarly, these reviews also found that AEs were more commonly associated with opioids. In addition, we support the conclusion of one of these reviews that trials were not designed to allow adequate assessments of long-term harms of opioids[17] because of the frequently used but inappropriate EERW study design and short follow-up times. Indeed, a comprehensive meta-analysis of RCTs[9] found that, compared with placebo or nonopioids, opioids were associated with increased vomiting, nausea, constipation, and dizziness but that it was not possible to evaluate long-term associations of opioid treatment in CNCP as none of the trials had a follow-up of longer than 6 months. This is consistent with another U.S. systematic review[18] that did not identify any placebo-controlled trials of at least 6 months duration or studies comparing opioids with placebo or no or nonopioid therapy, which assessed long-term pain and function outcomes in patients with chronic pain. The

review did find evidence for long-term opioid treatment being associated with an increased risk of opioid abuse or dependence in patients with CNCP, matching our findings.

Our systematic review found that long-term treatment of CNCP with strong opioids does not seem to be more effective than treatment with nonopioids in improving pain and pain-related function or disability. Rather, it was associated with more AEs, opioid abuse or dependence, and deaths. By contrast, a recent systematic review of uncontrolled, open-label extension (≥6 months) RCTs[8] found long-term opioid therapy for CNCP to be effective in sustaining pain and disability reduction. Although they reported no major safety and tolerability concerns, it seemed that discontinuations because of AEs or efficacy lack, as well as serious AEs and deaths, increased with trial duration.

4.4. Strengths and limitations

The present systematic review has several strengths and limitations that need to be considered. Strengths of our review lie in the comprehensive and rigorous literature search without language restrictions, quantitative and qualitative synthesis of the existing literature, inclusion of studies with long-term outcomes, detailed RoB assessment with validated tools, and GRADE certainty of evidence assessments of both RCTs and NRSI. In addition, we used minimally important differences from validation studies and input from a clinical expert to determine the clinical relevance of outcomes. We also re-expressed standardized effect estimates in original units of the assessment instruments, facilitating interpretation of the clinical relevance and size of the intervention effect. In regard to assessment of heterogeneity, we have performed extensive subgroup analyses that addressed differences in treatment duration, trial design, and opioid experience status, although we did not perform metaregression. Also, some of the regression analyses may not have been sufficiently powered to detect a difference. Results are further limited by the exclusion of weaker and combination opioids because our research focused on the efficacy and safety of pure, strong (WHO-III) opioids. Findings of CNCP studies are limited by a high RoB, particularly in the areas of allocation concealment and blinding (RCTs) and because of serious concerns about confounding and bias in participant selection (NRSI). For the CLBP trials, results should be interpreted with caution considering the high RoB because of incomplete outcome data. Data obtained from the included retrospective observational studies may have been subjected to recall or interviewer bias, although this is unlikely for 2 of the 3 included NRSI as health claims data were used. The RCTs included in the comparative analyses of the efficacy and safety of opioids vs placebo for the treatment of CLBP did not have sufficiently long follow-ups to draw conclusions about long-term effects of opioids in CLBP. However, the study populations in the included long-term CNCP trials and observational studies, also included many patients with chronic back pain (proportions ranging from 17% to 77% of the total study population), allowing some inferences on the long-term effects of opioids in CLBP. Furthermore, most studies excluded patients with current or past substance abuse, severe comorbidities, and MH disorders, limiting generalizability of the results as patients with MH illness, particularly depressive and anxiety disorders, show high rates of CNCP and are also often prescribed opioids for pain relief in practice.[11,25,70] In addition, most study participants in the included studies were women of middle age, further limiting the generalizability of our findings. It has been shown, however, that older patients are among the groups most likely to use opioids long term (≥1 year),[85] and opioid prescribing seems to be highest (25%) among the elderly (≥65 years).[76] The generalizability of our findings for CLBP may also have been limited by the EERW design used in most of the included CLBP trials; although a MA comparing EERW and non-EERW trials of opioids in CNCP found an underestimation of AEs, no more pronounced efficacy outcomes in EERW trials.[30] In addition, most of the included CLBP trials were industry funded, raising concerns about underestimation of AEs.

4.5. Implications for future research

Our findings confirm and re-emphasize the urgent call from researchers and clinicians worldwide for well-designed studies assessing the long-term efficacy and safety of opioid treatment for CNCP.[18,72] Existing placebo-controlled trials are conducted short term or medium term and often have an EERW design, ie, not suitable for assessing long-term efficacy or safety and tolerability outcomes and limit external validity due to no representative study populations. More non–industry-funded pragmatic RCTs are needed, like the one identified in our systematic review,[54] mimicking clinical practice in real-world settings and including both a sufficiently large number of patients as well as those with mental illness or other comorbidities who are commonly prescribed opioids in the real-world clinical setting. Furthermore, future research should focus on designing and evaluating methodologically sound long-term trials on the comparative efficacy and safety of opioids vs nonpharmacological or multidisciplinary biopsychosocial approaches and assess the long-term benefits of such approaches as they seem to be promising,[46,47,62,78] but more research is needed to bridge research gaps.

5. Conclusion

Based on very low to low certainty evidence from placebo-controlled RCTs of 4 to 15 weeks treatment duration, it seems that strong opioid analgesics may provide a clinically relevant reduction in pain but not disability in CLBP, whereas AEs may be significantly more common with opioids. Very low to low certainty long-term evidence from RCTs of 12 months and NRSI of up to 18 months treatment duration suggests that there may be no benefit of prolonged opioid therapy compared with nonopioids for improving PI or pain-related function or disability in CNCP but shows that opioids may be associated with more AEs, cases of abuse or dependence, and possibly increased all-cause mortality.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplementary material to this article is available. For more information see http://hdl.handle.net/21.11116/0000-0008-F4BA-3

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