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REVIEW ARTICLE

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Opioids for chronic low back pain: An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks of double-blind duration

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Abstract

Background and Objective: This updated systematic review evaluated the efficacy, tolerability and safety of opioids compared to placebo in non-malignant chronic low back pain.

Databases and Data Treatment: Clinicaltrials.gov, CENTRAL, MEDLINE and PsycINFO were searched from October 2013 to May 2019. Randomized controlled trials comparing opioids with placebo and at least 4 weeks of double-blinded duration were analysed. Primary outcomes were pain relief of 50% or greater, disability, tolerability and safety. Effects were summarized by a random effects model using risk differences or standardized mean differences. We added nine new studies with 2,980 participants for a total of 21 studies with 7,650 participants. Study duration ranged between 4 and 15 weeks. Studies with a parallel and cross-over design: Based on very low to low-quality evidence, opioids provided no clinically relevant pain relief of 50% or greater, but a clinically relevant reduction of disability compared to placebo. Enriched enrolment randomized withdrawal (EERW) design: Based on very low to low-quality evidence, opioids provided a clinically relevant pain relief of 50% or greater, but not a clinically relevant reduction of disability compared to placebo. There was no clinically relevant harm with regard to serious adverse events by opioids compared to placebo in studies with parallel/cross-over and EERW design. There was a relevant harm with regard to drop out rates due to adverse events in studies with parallel/cross-over, but not in studies with EERW design.

Conclusions: Opioids may provide a safe and clinically relevant pain relief for 4–15 weeks in highly selected patients.

Significance: Within the context of randomized controlled trials of 4–15 weeks, opioids provided a clinically relevant pain relief of 30% or greater and a clinically relevant reduction of disability compared to placebo in non-malignant chronic low back pain. Number needed to treat for an additional drop out due to side effects was 11 (95% confidence interval: 6–33). Assessment of abuse and addiction was incomplete. The frequency of serious adverse events including deaths did not differ from placebo.

1 | INTRODUCTION

Low back pain (LBP) is defined as pain in the area of the posterior aspect of the body from the lower margin of the 12th ribs to the lower gluteal folds with or without pain referred into one or both lower limbs. The global point prevalence of low back pain is estimated to be 9.4%. Prevalence and disease burden increase with age (Hartvigsen et al., 2018). Lower back and neck pain was the leading global cause of disability in 2015 in most countries in the Global Burden of Diseases, Injuries, and Risk Factors Study 2015 (GBD, 2016).

LBP aetiology is multifaceted and complex. It has been described as specific versus non-specific, but somatic (e.g. inflammation, degeneration), functional (e.g. disturbed motor coordination) and psychosocial factors (e.g. catastrophizing) contribute to LBP in most patients (Petersen, Laslett, & Juhl, 2017). Several classifications systems exist such as the Quebec Task Force System which includes 11 different categories distinguished principally by clinical manifestations (Quebec Task Force, 1987). Innumerable treatments are offered and most do not have a high level of evidence (Oliveira et al., 2018).

Although recent national guidelines came to divergent recommendations on the importance of opioids in the management of chronic low back pain (CLBP) (Oliveira et al., 2018), opioid analgesics are commonly used for CLBP in Europe and North America (Shaheed, Maher, Williams, Day, & McLachlan, 2016). The long-term use of opioids for chronic non-cancer pain contributed to the opioid crisis in North America with a parallel increase in prescriptions of opioids, their non-medical use and associated increased mortality (Ranapurwala, Naumann, Austin, Dasgupta, & Marshall, 2019). The recent guideline on the clinical development of medicinal products intended for the treatment of pain of the European Medicines Agency (EMA) recommends that trials should study physical dependence and abuse and addiction of prescribed opioids (EMA, 2017). The most up-to-date Cochrane review on opioids for CLBP did not analyse the outcomes physical dependence and abuse (Chaparro et al., 2013). One of the most recent systematic reviews for the American CDC guideline searched the literature until November 2016 and concluded that the evidence for opioids remains limited to short-term trials showing modest effects and that trials were not designed to assess serious harms. Outcomes of physical dependence, abuse and addiction of prescribed opioids were again not analysed (Chou et al., 2017).

For the second revision of the German 2015 guidelines on long-term administration of opioids in chronic non-cancer pain (LONTS) (Häuser et al., 2015), we updated our systematic review on opioids for CLBP (Petzke et al., 2015). In view of the debates on the efficacy and safety of opioids in the management of CLBP, the objectives of this review were to determine the efficacy, tolerability and safety of opioids compared to placebo in non-cancer CLBP patients of any age in randomized placebo-controlled studies of at least 4 weeks of duration (titration and maintenance). We paid special attention to the effects of study duration (short-term [4–12 weeks], intermediate term [13–26 weeks] and long-term [>26 weeks] (Chaparro et al., 2013) and the assessment of physical dependence (reported as withdrawal symptoms), abuse and deaths.

2 | METHODS

The review was performed according to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher, Liberati, Teztlaff, & Altman, 2009) and the recommendations of the Cochrane Collaboration (Higgins, Churchill, Chandler, & Cumpston, 2017).

2.1 | Protocol

Methods of analysis and inclusion criteria were specified in advance (PROSPERO CRD42019124302).

2.1.1 | Criteria for considering studies for this review

Types of participants

We included men and women of all ages and races or ethnicities diagnosed with clinically diagnosed CLBP (nociceptive, neuropathic and mixed pain). A differentiation between specific and non-specific low back pain was attempted based on the review of inclusion and exclusion criteria of the various studies. Trials exclusively including patients with inflammatory arthritis, such as rheumatoid arthritis or axial spondylopathies were not considered. We excluded studies in which participants with osteoarthritis of major joints and low back pain were enrolled and responses of the two groups were not presented separately. We excluded studies which included cancer-related LBP.

Types of interventions

We considered trials with the following opioids and their administration compared to placebo: (a) Opioids given by oral, buccal and transdermal routes. (b) Opioids combined with abuse deterrent formulations (ADF), e.g. naloxone. (c) Tramadol, a centrally acting, synthetic opioid analgesic with two complementary mechanisms of action: binding of parent and M1 metabolite to μ-opioid receptors and inhibition of reuptake of norepinephrine and serotonin. (d). Tapentadol, a drug with two mechanisms of action: μ-receptor agonism and norepinephrine reuptake inhibition. The reason for including both latter drugs into this review was that they are classified as opioids by German medicine agencies.

We excluded trials (a) that examined opioids given by an intravenous route or intrathecal implantable pumps, due

to the invasive nature of the therapy and its limited clinical relevance in the outpatient setting. Furthermore the effectiveness of opioids used in neuraxial implantable pumps has already been discussed elsewhere (Noble et al., 2010), (b) in which drugs other than opioid agonists were combined with opioids (e.g. tramadol with acetaminophen, codein with acetaminophen), except when used as a rescue medication, because it is not possible to disentangle the effects of the opioids from those of the other analgesic, (c) in which a defined opioid was compared to the same opioid with ADFs (e.g. oxycodone with and without naloxone) or in which two opioids combined were compared to a single opioid without a placebo group, (d) in which opioids and placebo were compared as an add-on to other drug therapies or vice versa, (e) in which opioids were compared to non-pharmacological treatments without a placebo group, (f) with opioid receptor agonist/N-methyl-D-aspartate (NMDA) antagonists (e.g. levorphanol) because these drugs are not available in Germany, (g) with methadone and polamidone because in Germany these drugs are nearly exclusively used to treat opiate addiction or cancer pain, (h) with drugs under development (such as cepranopadol) which have not yet been approved by the European Medicines Agency (EMA).

Types of studies

We included fully published double-blind randomized controlled trials (RCTs) that compared opioids to placebo (pure or pseudo) for therapeutic purposes in CNP. We included studies with a parallel and an enriched enrolment withdrawal (EERW) design. Studies with a cross-over design were included if (a) separated data from the two periods were reported, (b) data were presented which excluded statistically significant carry-over effects or (c) statistical adjustments were carried out in the case of a significant carry-over effect. Minimal study duration was at least 4 weeks (including both titration and maintenance phases for parallel and cross-over design; double-blind withdrawal phase for EERW design). At least 10 patients per treatment arm were required.

We excluded studies with a parallel design which conducted an open-label run-in and a consecutive double-blind parallel design with responders from the open-label run-in period. We excluded studies with a combined titration/maintenance or withdrawal period of less than 4 weeks of duration, those with an experimental design (i.e. if the primary purpose was to study pain mechanisms and not pain relief) and studies which were only published as abstracts. We excluded studies in which different dosages of one opioid were compared without a control group.

We grouped outcome measures according to the time of the double-blind phase (including both titration and maintenance): short term (4–11 weeks), intermediate (12–26 weeks) and long term (longer than 26 weeks).

We analysed parallel/cross-over and EERW trials separately because EERW designs might overestimate the tolerability and safety of the drug by including only responders in the double-blind phase (Furlan, 2011).

Types of outcome measures

The selection of outcomes was based on the recommendations of the ACTINPAIN writing group of the International Association for the Study of Pain (IASP) Special Interest Group (SIG) on Systematic Reviews in Pain Relief (Moore et al., 2010), the guideline on the clinical development of medicinal products intended for the treatment of pain of the European Medicines Agency (European Medicines Agency, 2017) as well as those from the Cochrane Pain, Palliative and Supportive Care Systematic Review Group editors for reporting meta-analyses of RCTs in chronic pain (Cochrane Pain, Palliative, & Supportive Care Systematic Review Group, 2015).

Primary outcomes

1. Pain relief of 50% or greater (efficacy; dichotomous variable)
2. Patient global impression to be much or very much improved (efficacy; dichotomous variable)
3. Disability (efficacy; continuous variable)
4. Drop out rates to adverse events (tolerability; dichotomous variable)
5. Frequency of serious adverse events (safety; dichotomous variable)
6. Death (safety; dichotomous variable)

Secondary outcomes

1. Pain relief of 30% or greater (efficacy; dichotomous variable)
2. Pain intensity (efficacy; continuous variable)
3. Sleep problems (efficacy; continuous variable)
4. Drop out rates due to lack of efficacy (efficacy; dichotomous variable)
5. Withdrawal symptoms (safety; dichotomous variable)
6. Abuse/addiction (safety; dichotomous variable)

2.1.2 | Electronic searches

We searched the following:

- The Cochrane Central Register of Controlled Trials (CENTRAL) from October 2013 to 28 May 2019; Most CENTRAL records are taken from bibliographic databases (mainly PubMed and Embase), but records are also derived from other published and unpublished sources, including ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform.
- MEDLINE accessed through PubMed, from October 2013 to 28 May 2019

- PsycINFO, from October 2013 to 28 May 2019

The search strategy for MEDLINE is outlined in Methods S1. The search was conducted by PK.

2.1.3 | Searching other resources

We searched http://www.clinicaltrials.gov (website of the US National Institutes of Health) for completed trials to 12 April 2019. The search was conducted by WH.

All authors searched bibliographies from retrieved relevant articles. Our search included all languages.

2.2 | Measures of treatment effect

The effect measures of choice were risk differences (RD) for dichotomous data and standardized mean difference (SMD) for continuous data (method inverse variance). We used a random-effect model because we assumed that the effects being estimated in the different studies are not identical, but follow some distribution. Uncertainty was expressed using 95% confidence intervals (CIs). Number needed to treat for an additional benefit (NNTBs) was calculated as the reciprocal of the absolute risk reduction (ARR). For unwanted effects, the NNTB becomes the number needed to treat for an additional harm (NNTH) and is calculated in the same manner. For dichotomous data, we calculated risk differences (RDs). The threshold for "clinically relevant benefit" or "clinically relevant harm" was set for categorical variables by an absolute risk reduction or increase ≥10% corresponding a NNTB or NNTH of ≤10 (Moore, Barden, Derry, & McQuay, 2008).

Cohen's categories were used to evaluate the magnitude of the effect size of continuous data, calculated by SMD, with values for Hedges' g as follows:

0.2–0.5 equating to a small effect size, 0.5–0.8 equating to a medium effect size and more than 0.8 equating to a large effect size (Cohen, 1988). We considered values of g less than 0.2 to equate to a "not substantial" effect size (Häuser et al., 2015). The threshold "clinically relevant benefit" was set for continuous variables at an effect size of more than 0.2 (Fayers & Hays, 2014).

2.3 | Data collection and analysis

2.3.1 | Selection of studies

Two review authors (WH and PW) independently scrutinized all the titles and abstracts and selected studies based on inclusion and exclusion criteria.

2.3.2 | Data extraction and management

Using standardized forms, three pairs of authors (CS, WH; FP, WH; and PW, WH) independently extracted data on inclusion and exclusion criteria of studies, participant characteristics, intervention group, clinical setting, interventions, country of study and study sponsorship. If data were not available in a format that was appropriate for data extraction, we did not contact the authors of the trial for further clarification. Any disagreements were resolved through discussion.

2.3.3 | Assessment of risk of bias in included studies

Two review authors (PW and WH) independently assessed the risk of bias of each included trial. Disagreements were resolved by discussion and consensus, otherwise a third review author (FP) acted as arbiter. We assessed the following risks of bias for each study in accordance with methods recommended by The Cochrane Collaboration (Higgins et al., 2017): selection biases (Random sequence generation; allocation concealment; group similarity at baseline), performance bias (Blinding of participants and personnel); detection bias (blinding of outcome assessor), attrition bias (Incomplete outcome data), reporting bias (selective outcome reporting), performance bias and other bias (sample size). For details, see Methods S2.

We defined a high-quality study (low risk of bias) as one that fulfilled six to eight, a moderate-quality study (moderate risk of bias) as one that fulfilled three to five and a low-quality study (high risk of bias) as one that fulfilled zero to two of the eight validity criteria.

2.3.4 | Unit of analysis issues

2.3.5 | Dealing with missing data

2.3.6 | Assessment of heterogeneity

2.3.7 | Grading of evidence

For more details of Sections 2.3.4,2.3.5,2.3.6 and 2.3.7 please refer Methods S3.

2.4 | Subgroup analysis

Subgroups were planned a priori to assess the variations in effect size (heterogeneity) for all types of opioids pooled

together compared to placebo groups pooled together, for different types of CLBP (e.g. specific vs. non-specific), different types of opioids (pure opioids vs. opioids with additional modes of action, i.e. tramadol, tapentadol), treatment duration (short-term, intermediate-term and long-term studies) for pain relief of 50% or greater, disability and drop out rate due to adverse events. At least two studies were required for subgroup analysis.

2.5 | Sensitivity analysis

We planned to perform sensitivity analysis for all types of opioids pooled together compared to placebo groups pooled together for pain relief 50% or more in studies in which we extracted means and/or SDs from figures or calculated SDs from p values or used imputation methods to calculate these outcomes.

2.6 | Publication bias

We assessed publication bias using a method designed to detect the amount of unpublished data with a null effect required to make one major outcome of efficacy irrelevant (usually taken to mean an NNTB of 10 or higher) (Moore et al., 2008).

2.7 | Software

RevMan Analysis (RevMan 5.3.1) software of the Cochrane Collaboration were used for statistical analyses (Review Manager, 2014).

3 | RESULTS

3.1 | Search

The total number of included studies in the 2015 review was 12 (Buynak et al., 2010; Cloutier et al., 2013; Gordon et al., 2010; Hale, Ahdieh, Ma, & Rauck, 2007; Hale, Khan, Kutch, & Li, 2010; Katz et al., 2007; Schnitzer, Gray, Paster, & Kamin, 2000; Steiner et al., 2011; Überall, Mueller-Schwefe, & Terhaag, 2012; Vondrackova et al., 2008; Vorsanger, Xiang, Gana, Pascual, & Fleming, 2008; Webster et al., 2006).

The updated searches (last performed May 2019) produced 1,212 records after duplicates were removed. We included a study which we did not consider in the previous review (Khoromi, Cui, Nackers, & Max, 2007) because it met the criterion of CLBP as defined for this review. We included another new study by revising the submitted draft based on a suggestion of a reviewer.

We included thus eight nine studies (Christoph, Eerdekens, Kok, Volkers, & Freynhagen, 2017; Gimbel et al., 2016; Hale, Zimmerman, Eyal, & Malamut, 2015; Kawamata et al., 2019; Rauck et al., 2015; Rauck et al., 2014; Rauck, Potts, Xiang, Tzanis, & Finn, 2016; Wen, Sitar, Lynch, He, & Ripa, 2015) with 2,980 participants and a total of 21 studies with 7,650 participants into the qualitative and quantitative analyses (see Figure 1).

3.2 | Included studies

The main characteristics of the studies are summarized in Tables 1 and 2, for details see Table S1.

3.2.1 | Settings

In all, 16 studies were conducted in North America, three studies in Europe and one each in several continents and in Japan.

3.2.2 | Types of opioids

Four studies tested buprenorphine, two each with buprenorphine transdermal (maximum 20 ug/h; reported mean dosage 14 ug/h) and with buprenorphine buccal (maximum 1,800 ug/d; no mean dosages reported). Three studies tested hydrocodone (maximum dosage 200 mg/d; no mean dosages reported). One study tested hydromorphone (maximum dosage 64 mg/d; no mean dosages reported). One study tested morphine (maximum dosage 90 mg/d, mean dosage 62 mg/d). Four studies tested oxycodone up to 100 mg/d (mean dosage in one study 53 mg/d). Two studies tested oxycodone/naloxone (maximum dosage 80/20 mg/d; no mean dosages reported). Further two studies tested oxycodone/naltrexone (maximum dosage 160 mg/day; no mean dosage reported). The two studies with oxymorphone did not report on maximum and average dosages. Two studies tested tapentadol (maximum dosage 500 mg/d; mean dose 393 mg/d). Three studies tested tramadol (maximum dosage 400 mg/d; no mean dosages reported).

One study included two opioids (tapentadol with oxycodone as active comparator). One study used tramadol as an active comparator to flupirtine. One study used tapentadol as active comparator to cebranopadol. One study included two dosages of oxycodone/naltrexone and one oxycodone only arm, too, each compared to placebo. One study compared oxycodone, oxycocon/naloxone, and placebo. One study compared two dosages of tramadol compared to placebo. The remaining studies had two study arms (opioid vs. control). All studies but one, which tested against the

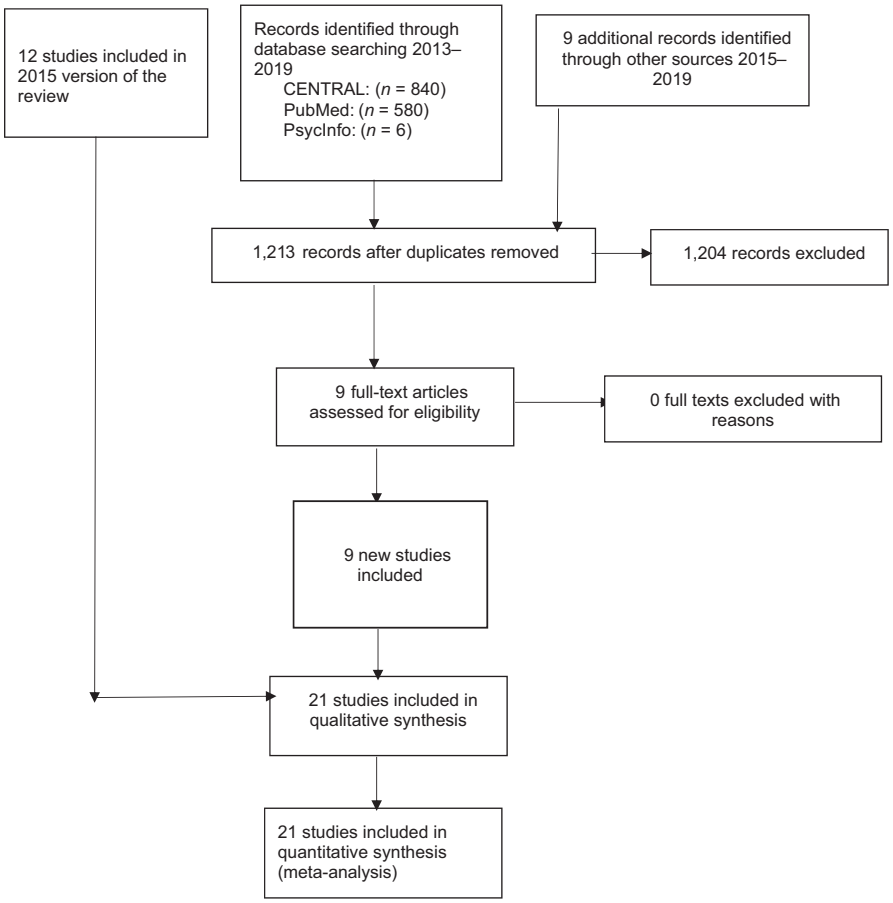

FIGURE 1 PRISMA flow diagram

active placebo benztropine (Khoromi et al., 2007), used a placebo control.

All studies but three used a flexible dosage design.

3.2.3 | Study design

Three studies used a cross-over design, five studies a parallel design and 13 studies an enriched-enrolment randomized withdrawal design. Double-blind phase of all studies ranged between 4 and 12 weeks except three studies with a duration of 15 weeks (Buynak et al., 2010; Vondrackova et al., 2008; Webster et al., 2006).

3.2.4 | Types of CLBP

In all, 11 studies did not specify the type of LBP. Three studies explicitly mentioned that the pain was non-neurological. Two studies included patients with CLBP Quebec class 1–6 and 9, one study Quebec class 1–6, one study with Quebec class 1–4 and two studies Quebec class 1–2. Two studies stated that they included neurological and non-neurological CLPB. One study included patients only with radicular pain. Information provided in the publications on type of LBP did not allow to subgroup according to specific or non-specific low back pain or other categories.

3.2.5 | Participants

The percentage of women in the studies ranged between 33% and 100%. All studies included only adults. If reported, the mean age of the participants ranged between 48 and 65 years. If reported, the percentage of Caucasians ranged between 59% and 99% except one study which included only Asian patients. One study included less than 50 participants, 15 included 50–150 and five included more than 150 participants per treatment arm for analysis.

3.2.6 | Exclusion of clinically relevant somatic disease or mental disorder or substance abuse

In all, 15 studies excluded patients with relevant somatic and psychiatric diseases and 15 with a history of or current substance abuse.

TABLE 1 Overview of the randomized controlled trials in chronic low back pain included into the systematic review (grouped by type of opioid in alphabetical order)

Buprenorphine				
Reference Year Countries of study centres	Study design	Number of patients randomized Exclusion of patients with clinically relevant somatic diseases Exclusion of patients with clinically relevant psychiatric disease (except substance abuse) Exclusion of patients with previous or current substance abuse	Intervention* and control group	Duration of trial
Gimbel, 2016 USA	Enriched enrolment randomized withdrawal	500 No No Yes	Buprenorphine buccal 300–1800 ug/d flexible; Placebo buccal	Screening phase (2 weeks) opioid taper phase (up to 4 weeks) open-label titration phase (up to 8 weeks, including at least 2 weeks at a stable optimal dose double-blind, placebo-controlled, randomized, withdrawal treatment phase (12 weeks) Follow-up phase (2 weeks)
Gordon, 2010 USA, Canada	Cross-over	79 Yes Yes Yes	7-day buprenorphine flexible 5 or 10 or 20 ug/h transdermal patch Placebo transdermal patch	Duration screening not reported 4-week titration and maintenance each 6-month open label
Rauck, 2016 USA	Enriched enrolment randomized withdrawal	420 Yes Yes Yes	Buprenorphine buccal flexible (300 or 600 or 900 ug/d Placebo buccal	2-week wash-out/screening phase; Up to 8-week open label conversion/titration phase 12-week placebo-controlled double-blind treatment 2-week follow up
Steiner, 2011 USA	Enriched enrolment randomized withdrawal	541 Yes No No	7-day buprenorphine flexible 5 or 10 or 20 ug/h transdermal patch Placebo transdermal patch	6–10 days screening Up to 4-week open label titration 12-week double-blind withdrawal
Hydrocodone				
Reference Year Countries of study centres	Study design	Number of patients randomized Exclusion of patients with clinically relevant somatic diseases Exclusion of patients with clinically relevant psychiatric disease (except substance abuse) Exclusion of patients with previous or current substance abuse	Interventions and control group	Duration of trial

(Continues)

TABLE 1 (Continued)

Hydrocodone				
Hale, 2015 USA	Enriched-enrolment randomized withdrawal	371 Yes Yes Yes	Hydrocodone extended release with abuse deterrent technology 30, 45, 60 or 90 mg/d flexible Placebo oral	Duration screening not reported Up to 6-week open label titration 12-week double-blind withdrawal
Rauck, 2014 USA	Enriched-enrolment randomized withdrawal	302 Yes Yes Yes	Hydrocodone extended release flexible (40–200 mg/d) oral flexible Placebo oral	≤2 weeks of wash-out/screening phase; ≤6 weeks of open label conversion/titration phase) 12-week placebo-controlled double-blind treatment
Wen 2015 USA	Enriched-enrolment randomized withdrawal	588 Yes Yes Yes	Hydrocodone extended release flexible (40–200 mg/d) oral flexible Placebo oral	≤2 weeks of wash-out/screening phase; ≤6 weeks of open label conversion/titration phase) 12-week placebo-controlled double-blind treatment 2-week follow-up
Hydromorphone				
Reference Year Countries of study centres	Study design	Number of patients randomized Exclusion of patients with clinically relevant somatic diseases Exclusion of patients with clinically relevant psychiatric disease (except substance abuse) Exclusion of patients with previous or current substance abuse	Interventions and control group	Duration of trial
Hale, 2010 USA	Enriched-enrolment randomized withdrawal	268 Yes Yes Yes	Hydromorphone extended release with abuse deterrent form flexible 12–64 mg/d oral Placebo oral	<2 weeks screening 2- to 4-week open label titration 12-week double-blind withdrawal
Morphine				
Khoromi 2007 USA	Cross-over	55 Yes Yes Yes	Morphine sustained release flexible 15–90 mg/d oral Benztropine flexible (0.25–1 mg/d) (active placebo) oral	Duration screening and wash-out not reported 3-week titration 2-week maintenance 2-week tapering

(Continues)

TABLE 1 (Continued)

Oxycodone				
Reference Year Countries of study centres	Study design	Number of patients randomized Exclusion of patients with clinically relevant somatic diseases Exclusion of patients with clinically relevant psychiatric disease (except substance abuse) Exclusion of patients with previous or current substance abuse	Interventions and control group	Duration of trial (titration and maintenance)
Cloutier 2013 Canada	Cross-over	83 Yes Yes Yes	Oxycodone/Naloxone flexible 20/10 mg or 30/15 mg or 40/20 oral every 12 hr Placebo oral	Two to seven days wash-out 4 weeks for each period 6-month open label
Rauck 2015 USA	Enriched enrolment randomized withdrawal	280 No Yes Yes	Oxycodone/naltrexone extended release flexible (20–160 mg/d) oral Placebo oral	≤2 weeks of wash-out/screening phase; 4- to 6-week open label conversion/titration phase 12-week placebo-controlled double-blind treatment 2-week follow-up
Vondrackova, 2008 Europe	Parallel	463 Yes Yes Yes	Oxycodone extended release fixed 20 or 40 mg/d fixed oral Oxycodone/Naloxone 20/10 oral or 40/20 mg/d fixed oral Placebo oral	≤ 7 days screening 3-week tapering and titration 12-week maintenance 12-month open-label extension
Webster, 2006 USA	Parallel	719 Yes No Yes	Oxycodone extended release flexible 10–80 mg/d oral Oxycodone/naltrexone oral extended release flexible 10–80 mg/d two times/d oral Oxycodone /naltrexone extended release oral flexible 10–80 mg/d once/d Placebo oral	4–10 days wash-out 1- to 6-week titration 12-week maintenance
Kawamata, 2019 Japan	Enriched-enrolment randomized withdrawal	130 No Yes Yes	Oxycodone extended release flexible (maximum 80 mg/d) oral Placebo oral	Duration screening and wash-out not reported Open label titration 2–4 weeks 6-week double-blind withdrawal 1-week tapering 1-week follow-up

(Continues)

TABLE 1 (Continued)

Oxymorphone				
Reference Year Countries of study centres	Study design	Number of patients randomized Exclusion of patients with clinically relevant somatic diseases Exclusion of patients with clinically relevant psychiatric disease (except substance abuse) Exclusion of patients with previous or current substance abuse	Interventions and control group	Duration of trial (titration and maintenance)
Hale, 2007 USA	Enriched-enrolment randomized withdrawal	142 No No No	Oxymorphone extended release flexible (no maximum dosage) oral Placebo oral	Duration screening and wash-out not reported Duration open label titration not reported 12-week double-blind withdrawal
Katz, 2007 USA	Enriched-enrolment randomized withdrawal	205 No No No	Oxymorphone extended release flexible (no maximum dosage) oral Placebo oral	Duration screening and wash-out not reported Open label titration up to 10 days 12-week double-blind withdrawal
Tapentadol				
Reference Year Countries of study centres	Study design	Number of patients Randomized Exclusion of patients with clinically relevant somatic diseases Exclusion of patients with clinically relevant psychiatric disease (except substance abuse) Exclusion of patients with previous or current substance abuse	Interventions and control group	Duration of trial (weeks)
Buynak Australia, Canada, USA 2010	Parallel	981 Yes Yes Yes	Tapentadol extended release flexible 200–500 mg/d oral Oxycodone controlled release flexible 40–100 mg/d oral as active control Placebo oral	Duration of screening not reported 3-week double-blind titration 12-week maintenance Duration of follow-up not reported
Christoph Europe 2017	Parallel	641 Yes Yes Yes	Cepranopadol (3 arms with 391 patients not used for analysis) Tapentadol extended release fixed 400 mg/d oral Placebo oral	Duration of screening not reported 2-week double-blind titration 12-week maintenance Duration of follow-up not reported

(Continues)

TABLE 1 (Continued)

Tramadol				
Reference Year Countries of study centres	Study design	Number of patients randomized Exclusion of patients with clinically relevant somatic diseases Exclusion of patients with clinically relevant psychiatric disease (except substance abuse) Exclusion of patients with previous or current substance abuse	Interventions and control group	Duration of trial (weeks)
Schnitzer USA 2000	Enriched-enrolment randomized withdrawal	254 No No Yes	Tramadol flexible 100–400 mg/d oral Placebo oral	Up to 3-week wash-out 3-week open label titration and maintenance 4-week double-blind withdrawal
Überall 2012 Germany	Parallel	236 (without flupirtine arm) Yes Yes Yes	Tramadol 200 mg/d fixed oral as active comparator Placebo oral	1-week wash-out 4-week maintenance 1-week follow-up
Vorsanger 2008 USA	Parallel	386 No No Yes (within the last 6 months)	Tramadol 200 mg/d fixed oral Tramadol 300 mg/d fixed oral Placebo oral	2–7 days wash-out 3-week open label 12-weeks maintenance

TABLE 2 Inclusion and exclusion criteria of the studies analysed with regard to prior analgesic therapy, duration and aetiology of low back pain

First author Year publication Study drug	Prior analgesic regimen	Duration of low back pain	Exclusion*	Specification for inclusion of low back pain aetiology
Buynak 2010 Tapentadol oxycodone	Opioid (<160 mg/d Morphine equivalent) or non-opioid for 3 months and dissatisfied	>3 months	Malignancy	Non-malignant
Christoph 2017	No details reported.	>3 months	Malignancy	Quebec Task Force classification Non-neuropathic (classes 1 and 2), neuropathic (classes 3–4)
Cloutier 2013 Oxycodone	Non-responder to non-opioids or to opioids	>3 months	None	None
Gimbel 2016 Buprenorphine	Opioid-experienced patients (30–160 mg/d ME)	>6 months	Cancer-related pain	Quebec Task Force classification non-neuropathic (classes 1 and 2), neuropathic (classes 3–6) or symptomatic for 6 months after low-back surgery (class 9)
Gordon 2010 Buprenorphine	Inadequately treated with non-opioids	>6 weeks	None	None
Hale 2007 Oxmorphone	At least 60 mg/d morphine equivalent, stable for the last 2 weeks	>3 months	Neurological aetiology or signs/symptoms, infection, FMS, malignancy, surgery in the last 6 months	None
Hale 2010 Hydromorphone	At least 60 mg/d (but <320 mg/d ME) for 2 months, non-opioids in stable dose	Not specified	Neurological aetiology or signs/symptoms, infection, FMS, malignancy, surgery in the last 6 months	Quebec classification low back pain class 1–6
Hale 2015 Hydrocodone	Opioid naive as well as opioid experienced (>= 10 and < 135 mg Oxycodone equivalent/d) patients	>3 months	No details provided	No details provided
Katz 2007 Oxymorphone	Opioid naive for 2 weeks (<5 mg oxycodone equivalent)	>3 months	Neurological aetiology or signs/symptoms, infection, malignancy, surgery in the last 2 months	None
Kawamata 2019 Oxycodone	Insufficient pain relief despite management for ≥14 days with oral, patch or suppository non-opioid analgesics including analgesic adjuvants or opioid analgesics (doses were pre-specified as follows: oral codeine ≤800 mg/day; oral morphine ≤120 mg/day; and fentanyl patch ≤100 ug/hour	>3 months	No details provided except that malignant and psychogenic LBP was excluded	Degenerative, lumbar spine stenosis, Intervertebral disc herniation, failed back surgery syndrome
Khoromi 2007 Morphine	No details provided	>3 months	Limited non-radicular pain Chronic low back pain	Radicular pain
Rauck 2014 Hydrocodone	"opioid-experienced" not further defined	>3 months	No details provided	No details provided

(Continues)

TABLE 2 (Continued)

First author Year publication Study drug	Prior analgesic regimen	Duration of low back pain	Exclusion*	Specification for inclusion of low back pain aetiology
Rauck 2015 Oxycodone/ Naltrexone	Regular NSAID, as needed or regular opioid with pain ≥4 (NRS) for 4 of 7 days during screening period	>3 months	Pain from structural or progressive lesions; history of lumbosacral radiculopathy, symptomatic spinal stenosis vertebral compression fracture, major trauma of the spine, osteoarthritis of major joints, rheumatoid arthritis, or neuropathic pain syndromes	Quebec Task Force classification non-neuropathic (classes1 or 2)
Rauck 2016 Buprenorphine	"Opioid-naïve" adults, stable non-opioids for ≥4 weeks, ≤10 mg Morphine equivalent/ day allowed	>6 months	None related to spine pain	Quebec Task Force classification Non-neuropathic origin, neuropathic origin or after low back pain surgery (classes not reported)
Schnitzer 2000 Tramadol	On daily NSAID medication for at least 30 days on stable dosage (not further specified)	>3 months	Neurological deficits, malignancy, infection, surgical indication, spondylolisthesis, disk herniation, FMS, spinal stenosis, instability, no surgery for 5 years	None
Steiner 2011 Buprenorphine	Non-responder to non-opioids, and opioid-naïve (less than 5 mg Oxycodone/day	>3 months for several hours/day	Malignancy, radicular symptoms, neural compression, spondylarthropathy, rheumatological conditions, FMS, infection, no surgery the last 6 months	Non-malignant, spinal stenosis, intervertebral disc disease, spondylolisthesis, osteoarthritis of the spine
Vondrackowa 2008 Oxycodone/ Naloxone Oxycodone	Daily opioid with adequate effect for at least 2 weeks (between 10 and 40 mg oxycodone equivalent)	Not specified	Malignancy, more than 1 back surgery	Mixed origin, osteoarthritis of the spine, spondylosis, disc herniation, sciatica, spinal stenosis
Vorsanger 2008 Tramadol	On daily medication (60 of 90 days), opioid or non-opioid or muscle relaxant	>6 months	Malignancy, inflammatory, FMS, history of surgery or chemonucleolysis	None
Webster 2006 Oxycodone/ Naltrexone Oxycodone	No specific information provided, taper for patients < 20 mg oxycodone required	>6 months	Malignancy, autoimmune aetiology, infection, fracture, surgery in the last 4 months, spinal pump, SCS, FMS	None
Wen 2015 Hydrocodone	Opioid-experienced (receiving opioid medication equivalent to 100 mg/day oxycodone or less for 14 days prior to screening) or opioid-naive (defined as a patient receiving < 5 mg a day of oxycodone equivalent during the 14 days prior to screening)	>3 months	Quebec Task Force Classification 3 to 6); inflammatory arthritis; surgical procedures directed towards the source of the CLBP within 6 months of the screening visit, or any major surgery scheduled during the study period	Quebec Task Force classification non-neuropathic (classes 1 or 2)
Überall 2012 Tramadol,	Adequate analgesics according to NVL, yet dissatisfied	>3 months	Malignancy, neurological aetiology, inflammatory, spinal fractures, spinal stenosis or disc problem with neurological impairment, anatomical abnormalities, history of surgery	None

Abbreviations: ME, Morphine equivalent dose in mg; NVL, Nationale Versorgungsleitlinie Kreuzschmerz (German National Patient-Centered Guideline Low Back Pain).

*Surgery refers to spinal surgery.

3.2.7 | Funding and conflicts of interest

In all, 20 studies reported sponsoring by pharmaceutical companies and one study received public funding.

For eight of the 21 studies, author groups did not report their conflicts of interest. Among the 12 studies reporting conflict of interests, one author group reported that they had no conflict of interest.

3.3 | Risk of bias in included studies

According to the predefined categories, one study was a high-quality study (low risk of bias overall), 12 studies were moderate-quality studies (unclear risk of bias overall) and eight were low-quality studies (high risk of bias overall) (see Figure 2 for risk of bias graph and Table S2 for details).

3.4 | Effects of intervention

The methods of outcome assessment for each study are detailed in Table S1.

3.4.1 | Opioids versus placebo in studies with a parallel or cross-over design at the end of treatment

Primary outcomes

Pain relief of 50% or greater. The outcome was calculated by an imputation method for five studies. Seven studies with eight arms and with 55 participants were entered into analysis. In all, 664 out of 1618 (41.0%) with opioids and 227 out of 937 (24.2%) with placebo reported pain relief of 50% or greater. RD was 0.08 (95% CI 0.04 to 0.12) ($I^2 = 0$, $p < .0001$). NNTB was 12 (95% CI 8 to 25). According to the predefined categories, there was no clinically relevant benefit by opioids. The quality of evidence was low (downgraded by two levels due to indirectness [patients with a history of substance abuse and/or major medical diseases excluded] and high probability of publication bias [majority of studies sponsored by manufacturer of the drug]).

Patient global impression to be much or very much improved. Two studies with three study arms and with 1,055 participants were entered into analysis. In all, 313 out of 633 (49.4%) with opioids and 131 out of 422 (31.0%) with placebo reported to be much or very much improved. RD was 0.14 (95% CI 0.02 to 0.26) ($I^2 = 78$, $p = .03$). According to the predefined categories, there was no clinically relevant benefit by opioids. The quality of evidence was very low (downgraded by three levels due to inconsistency, indirectness and imprecision).

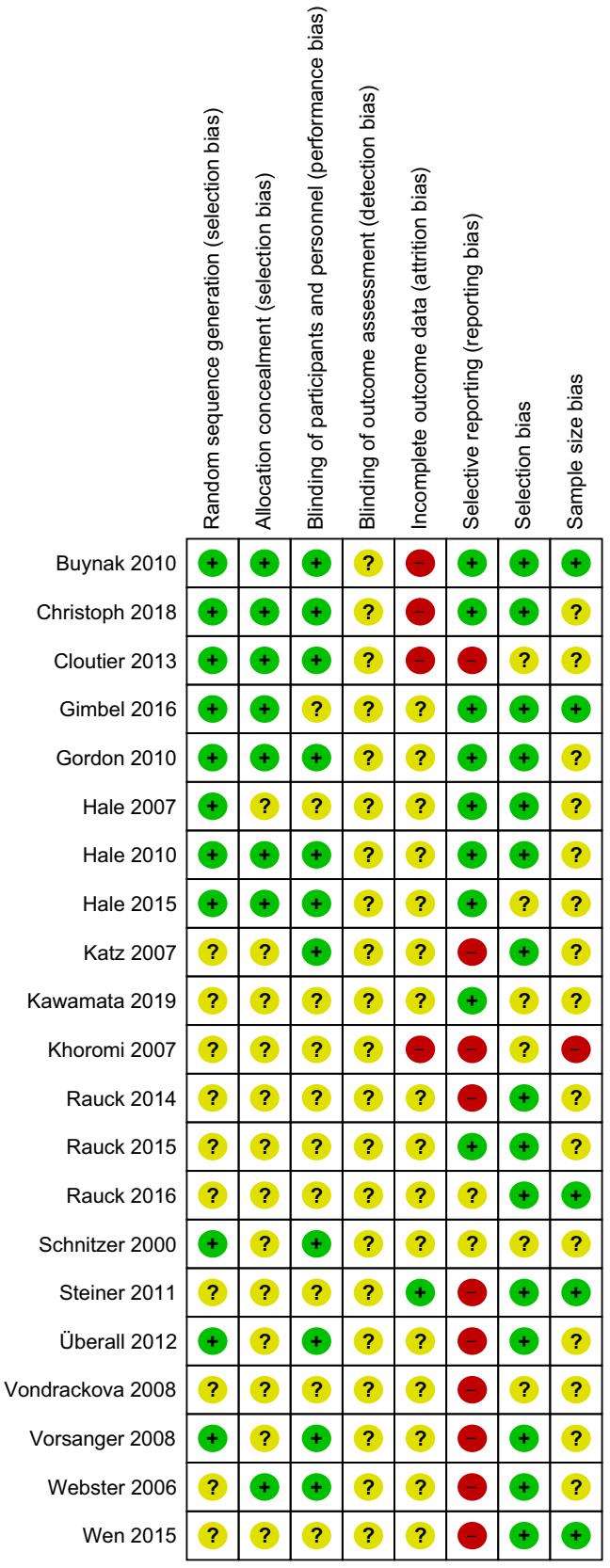

FIGURE 2 Risk of bias summary

Disability. Six studies with 1774 participants were entered into analysis. SMD was − 0.23 (95% CI − 0.33 to − 0.13) ($I^2 = 0\%$; $p < .0001$). According to the predefined categories, the effect size was small and there was a clinically relevant benefit by opioids. The quality of evidence was low (downgraded by two level due to indirectness and high probability of publication bias).

Withdrawal due to adverse events. Eight studies with nine study arms and with 3,436 participants were entered into analysis. In all, 429 of 2,276 (18.8%) participants with opioids and 70 out of 1,160 (6.4%) with placebo dropped out due to adverse events, RD was 0.10 (95% CI 0.04 to 0.17) ($I^2 = 89\%$; $p < .0001$). NNTH was 10 (95% CI 6 to 25). According to the predefined categories, there was a clinically relevant harm by opioids. The quality of evidence was very low (downgraded by three levels due to inconsistency, indirectness and high probability of publication bias).

Serious adverse events. Five studies with six study arms and with 2,462 participants were entered into analysis. In 24 out of 1,650 (1.5%) patients with opioids and 7 out of 812 (0.9%) patients with placebo a serious adverse event was noted. RD was 0.01 (95% CI − 0.00 to 0.02) ($I^2 = 0\%$; $p = .12$). The quality of evidence was very low (downgraded by three level due to imprecision [low event rate], indirectness and high probability of publication bias).

Deaths: Four studies with 1,850 participants reported explicitly this outcome. No deaths were reported in either group ($I^2 = 0$; $p = 1.0$). The quality of evidence was very low (downgraded by three levels due to indirectness, imprecision [low event rate], indirectness and high probability of publication bias).

Secondary outcomes

Pain relief of 30% or greater. The outcome was calculated by an imputation method for four studies. Seven studies with eight study arms and with 2,790 participants were entered into analysis. In all, 947 out of 1852 (51.1%) with opioids and 345 out of 937 (36.8%) with placebo reported pain relief of 30% or greater. RD was 0.11 (95% CI 0.07 to 0.16) ($I^2 = 0$, $p<.0.0001$). NNTB was 9 (95% CI 6 to 14). According to the predefined categories, there was a clinically relevant benefit by opioids. The quality of evidence was low (downgraded by two levels due to indirectness and high probability of publication bias).

Mean pain intensity. Seven studies with eight study arms and with 2,881 participants were entered into analysis. SMD was − 0.29 (95% CI − 0.34 to − 0.21) ($I^2 = 0\%$; $p < .0001$). According to the predefined categories, the effect size was small and there was a clinically relevant benefit by opioids. The quality of evidence was low (downgraded by two level due to indirectness and high probability of publication bias).

Sleep problems. Two studies with 557 participants were entered into analysis. SMD was − 0.34 (95% CI − 0.52 to − 0.17) ($I^2 = 0\%$; $p < .0001$). According to the predefined categories, the effect size was small and there was a clinically relevant benefit by opioids. The quality of evidence was low (downgraded by two level due to indirectness and high probability of publication bias).

Withdrawal due to lack of efficacy. Six studies with seven study arms and with 3,211 participants were entered into analysis. In all, 125 out of 2,114 (5.9%) with opioids and 136 out of 1,097 (12.4%) with placebo dropped out due to lack of efficacy. RD was − 0.07 (95% CI − 0.11 to − 0.03) ($I^2 = 78\%$, $p = .008$). NNTB was 16 (95% CI 9 to 33). According to the predefined categories, there was no clinically relevant benefit by opioids. The quality of evidence was very low (downgraded by three levels due to inconsistency, indirectness and high probability of publication bias).

Withdrawal symptoms. Two studies with three study arms and with 463 participants assessed this outcome. In al, 15 out of 278 (5.4%) participants with opioids and 7 out of 185 (3.8%) participants reported withdrawal symptoms. RD was 0.02 [95% CI − 0.02 to 0.05) ($I^2 = 0\%$, $p = .32$). The quality of evidence was very low (downgraded by two levels due to indirectness, imprecision [low number of participants] and high probability of publication bias).

Abuse and addiction. Only one study assessed this outcome. Vorsanger et al. (2008) used the Addiction Research Center Inventory and found no differences in mean scores between groups (No further details reported).

3.4.2 | Opioids versus placebo in studies with an EERW design at the end of treatment

Primary outcomes

Pain relief of 50% or greater. Nine studies with 3,235 participants were entered into analysis. In all, 707 out of 1623(43.6%) with opioids and 461 out of 1612 (28.6%) with placebo reported pain relief of 50% or greater. RD was 0.16 [95% CI 0.10 to 0.21) ($I^2 = 58$, $p < .0001$). NNTB was 6 (95% CI 5 to 10). According to the predefined categories, there was a clinically relevant benefit by opioids. The quality of evidence was low (downgraded by two level due to indirectness and high probability of publication bias).

Patient global impression to be much or very much improved. Three studies with 1596 participants were

entered into analysis. In all, 303 out of 787 (38.5%) with opioids and 221 out of 809 (27.3%) with placebo reported to be much or very much improved. RD was 0.10 [95% CI 0.06 to 0.15) ($I^2 = 0$, $p < .0001$). NNTB was 10 (95% CI 7 to 17). According to the predefined categories, there was a clinically relevant benefit by opioids. The quality of evidence was low (downgraded by two levels due to indirectness and high probability of publication bias).

Disability. Six studies with 2012 participants were entered into analysis. SMD was − 0.14 (95% CO − 0.24 to − 0.03) ($I^2 = 27\%$; $p = .01$). According to the predefined categories, the effect size was non-substantial and there was no clinically relevant benefit by opioids. The quality of evidence was low (downgraded by two levels due to indirectness and high probability of publication bias).

Withdrawal due to adverse events: In total, 12 studies with 4,011 participants were entered into analysis. In all, 133 out of 2002 (6.6%) participants with opioids and 99 out of 2009 (4.9%) with placebo dropped out due to adverse events, RD was 0.01 (95% CI − 0.01 to 0.03) ($I^2 = 47\%$; $p = .23$). The quality of evidence was low (downgraded by two levels due to indirectness and high probability of publication bias).

Serious adverse events. In all, 12 studies with 4,214 participants were entered into analysis. In all, 35 out of 2,179 (1.6%) participants with opioids and 23 out of 2035 (1.1%) participants with placebo a serious adverse event was noted. RD was 0.00 (95% CI − 0.00 to 0.01) ($I^2 = 0\%$; $p = .40$). The quality of evidence was very low (downgraded by three level due to imprecision [low event rate], indirectness and high probability of publication bias).

Deaths. Five studies with 1930 participants reported explicitly this outcome. No death occurred with opioid treatment in 956 participants and one out of 974 (0.1%) participants died with placebo treatment ($I^2 = 0\%$; $p = .72$). The quality of evidence was very low (downgraded by two levels due to indirectness, imprecision [low event rate]. indirectness and high probability of publication bias).

Secondary outcomes

Pain relief of 30% or greater. Ten studies with 3,365 participants were entered into analysis. In all, 980 out of 1685 (58.2%) with opioids and 677 out of 1,680 (40.3%) with placebo reported pain relief of 30% or greater. RD was 0.17 [95% CI 0.10 to 0.25) ($I^2 = 81$, $p<.0.0001$). NNTB was 6 (95% CI 4 to 10). According to the predefined categories, there was a clinically relevant benefit by opioids. The quality of evidence was very low (downgraded by three levels due to inconsistency, indirectness and high probability of publication bias).

Mean pain intensity. In all, 12 studies with 4,118 participants were entered into analysis. SMD was − 0.47 (95% CO − 0.63 to − 0.31) ($I^2 = 84\%$; $p < .0001$). According to the predefined categories, the effect size was small and there was a clinically relevant benefit by opioids. The quality of evidence was very low (downgraded by three levels due to inconsistency, indirectness and high probability of publication bias).

Sleep problems. Two studies with 718 participants were entered into analysis. SMD was − 0.08 (95% CO − 0.29 to 0.14) ($I^2 = 36\%$; $p = .05$). The quality of evidence was very low (downgraded by three levels due to inconsistency, indirectness and high probability of publication bias).

Withdrawal due to lack of efficacy. In all, 12 studies with 4,011 participants were entered into analysis. In all, 161 out of 2002 (8.0%) with opioids and 452 out of 2009 (22.4%) with placebo dropped out due to lack of efficacy. RD was − 0.16 [95% CI − 0.22 to − 0.10) ($I^2 = 91\%$, $p = .001$). NNTB was 6 (95% CI 5 to 10). According to the predefined categories, there was a clinically relevant benefit by opioids. The quality of evidence was very low (downgraded by three levels due to inconsistency, indirectness and high probability of publication bias).

Withdrawal symptoms. Eight studies with 2,590 participants assessed were entered into analysis. In all, 33 of 1,304 (2.5%) participants with opioids and 55 out of 1,284 (4.3%) participants with placebo reported clinically relevant withdrawal symptoms. RD was − 0.02 [95% CI − 0.04 to 0.01) ($I^2 = 85\%$, $p = .21$). The quality of evidence was very low (downgraded by two levels due to indirectness, inconsistency and high probability of publication bias).

Abuse and addiction. Only a few studies assessed this outcome by different methods which did not allow a quantitative synthesis. Gimbel et al. (2016) reported that there were no adverse events associated with misuse or abuse of the study medication. However, they did not report the methods of assessment. Hale et al. (2015) reported diversion in 12 out of 623 (1.9%) participants and loss of study drugs in 20 out of 623 (3.2%) participants. Kawamata et al. (2019) used two validated questionnaires and found no signals indicative of abuse or addiction. Steiner et al. (2011) did not report on their methods of assessment and stated that no patients were suspected of abuse of buprenorphine. One patient was discontinued from the study for suspected oxycodone abuse. Nine patients either did not return for study visits or did not return study drug and were thus suspected of study drug diversion. Wen et al. (2015) used three questionnaires: The Screener and Opioid Assessment for Patients With Pain Revised, the Addiction Behaviour Checklist and the Current Opioid Misuse Measure questionnaires, but did not report the results.

3.5 | Subgroup analyses

Due to lack of respective data on the type of CLBP, the subgroup analysis on specific versus non-specific CLBP could not be performed.

3.5.1 | All types of opioids

In studies with a parallel and cross-over design, the test for subgroup differences yielded these results: Pain relief of 50% or greater: $I^2 = 0\%$, $p = .81$; Disability: $I^2 = 0\%$, $p = .95$; drop out due to adverse events $I^2 = 38\%$, $p = .17$. In studies with an EERW design, the test for subgroup differences yielded these results: Pain relief of 50% or greater: $I^2 = 0$, $p = .41$; drop out due to adverse events $I^2 = 0\%$, $p = .69$.

3.5.2 | Pure opioids versus opioids with an additional mode of action

In studies with a parallel and cross-over design, RD of pain relief of 50% or greater was 0.07 (95% CI 0.02 to 0.12) ($I^2 = 0\%$, $p = .006$) for pure opioids and 0.09 (95% CI 0.03 to 0.14) ($I^2 = 0\%$, $p = .001$) for tramadol and tapentadol. SMD for disability was − 0.19 (95% CI − 0.34 to − 0.14) ($I^2 = 0\%$; $p = .001$) for pure opioids and − 0.25 (95% CI − 0.39 to − 0.11) ($I^2 = 0$; $p = .0006$) for tapentadol and tramadol. RD for drop out rates due to adverse events was 0.16 (95% CI 0.08 to 0.25) ($I^2 = 85\%$; $p < .0001$) for pure opioids and 0.04 (95% CI − 0.04 to 0.12) ($I^2 = 75\%$; $p = .30$) for tapentadol and tramadol. There were no studies with an EERW for this comparison.

3.5.3 | Study duration

In studies with a duration >12 weeks, RD of pain relief of 50% or greater was 0.08 (95% CI 0.03 to 0.13) ($I^2 = 0\%$, $p = .007$) and 0.07 (95% CI 0.01 to 0.13) ($I^2 = 0\%$, $p = .01$) in studies ≤12 weeks duration, RD for drop out rates due to adverse events was 0.13 (95% CI 0.03 to 0.23) ($I^2 = 93\%$; $p = .01$) for studies with >12 weeks of duration and 0.04 (95% CI − 0.01 to 0.10) ($I^2 = 62\%$; $p = .13$) in studies ≤12 weeks of duration.

3.6 | Sensitivity analyses

Removing the studies with imputed rates of pain relief of 50% or greater in studies with a parallel and cross-over design resulted in a RD 0.07 (95% CI 0.03 to 0.11).

3.7 | Publication bias

Studies with 2,631 participants with a null effect on pain relief of 30% or greater or greater would have been required to make the result clinically irrelevant (NNTB of 10 or higher) in studies with a parallel and cross-over design.

4 | DISCUSSION

4.1 | Summary of main results

The updated review did not change the major findings of our previous review. Based on very low to low-quality evidence, opioids provided no clinically relevant pain relief according to the pre-specified criteria for the primary outcomes of 50% pain relief or greater and global improvement, but a reduction of disability compared to placebo in studies with a parallel and cross-over design. There were no clinically relevant harms with regard to the drop out rate due to adverse and serious adverse events by opioids compared to placebo in these studies. Based on very low to low-quality evidence, opioids provided a clinically relevant pain relief of 50% or greater and general improvement, but not a clinically relevant reduction of disability compared to placebo in studies with an enriched enrolment randomized withdrawal design. There were also no clinically relevant harms with regard to the drop out rate due to adverse and serious adverse events by opioids compared to placebo in these studies.

4.2 | Overall completeness and applicability of evidence

We cannot rule out the possibility that negative study results had not been published or were missed by our search strategy.

The applicability (external validity) of the presented evidence is limited for the following reasons:

1. All studies were sponsored by the manufacturer of the drug tested
2. Most studies were conducted in research centres. No study was conducted in a primary care setting.
3. Most studies excluded patients with clinically relevant somatic and psychiatric diseases as well as current or previous substance abuse. Somatic and mental comorbidities in patients with chronic pain are prevalent in the general population (Häuser et al., 2015 b). However, in some studies, exclusion criteria addressed primarily potential pharmacological interactions and not severity of somatic disease.
4. The majority of the participants were middle-aged Caucasian women. Only one study was conducted in Asia, none in Africa.

5. Some studies did not clearly describe important patient characteristics, such as the duration of symptoms, presence of radiculopathy or use of cointerventions.
6. Results on function were reported as mean differences and not as clinically relevant improvement.
7. Sleep problems, physical dependence, abuse and addiction of prescribed opioids were only analysed in some studies.
8. The studies analysed do not allow to make conclusions on the long-term (more than 6 months) efficacy and safety of opioids for CLBP. EMA recommends open label extension studies to assess long-term efficacy and safety (EMA, 2017). The results of a systematic review of open-label extension studies will be published in another paper (Bialas, Maier, Klose, & Häuser, 2019). There was a weak finding in the subgroup analysis indicating increased drop out rates for studies with duration>12 weeks.

4.3 | Potential biases in the review process

We searched for unpublished studies, but cannot be certain that we identified all other studies that might have been performed but not published. We might have underestimated the methodological quality of some studies which might not have reported some details required for the risk of bias and treatment quality scores used. We relied on the reported data for quality assessment and did not ask authors for further details because we did not want to introduce a "response" bias. We used imputation methods if the rates of a moderate and substantial pain relief were not reported.

4.4 | Agreements with other reviews

Our review suggests a clinically relevant benefit and safety of opioids for CLBP within the context of RCTs of 4–15 weeks of double-blind duration. With regard to efficacy for short-term pain relief, our conclusions are in line with the most recent US reviews: Shaheed et al. (2016) stated that there was moderate-quality evidence that opioid analgesics reduced pain in the short term. Chou et al. (2017) concluded that opioids showed modest effects compared to placebo in the short term. Chou et al. (2017) found small effect sizes for reduction of disability by strong opioids and tramadol. In our analyses, the effects on function were small in studies with a parallel and cross-over design and not substantial in studies with an EERW design.

With regard to tolerability, our results and/or conclusions are different from the US reviews. Shaheed et al. (2016) found that in half of these 13 trials, at least 50% of participants withdrew owing to adverse events or lack of efficacy. The drop out due to adverse events was 19% in our analysis of studies with a cross-over and parallel design and 7% in studies with an EERW design. Drop out rates due to lack of efficacy was 6% in our analysis of studies with a cross-over and parallel design and 8% in studies with an EERW design. We agree with Chou et al. (2017) and Furlan et al. (2011) that studies with an EERW design underestimate the harm of dropping out due to adverse events because a relevant number of patients who do not tolerate opioids are excluded in the open-label period.

With regard to safety, our results and/or conclusions are also partially different from the US reviews. We agree with Chou et al. (2017) that the RCTs were not designed to assess the risk for overdose or opioid use disorder which is part of the US opioid epidemic (Manchikanti et al., 2012). We agree that most studies excluded higher risks patients especially those with a previous or current substance use disorder. In our analyses, symptoms of physical dependence did not differ from placebo in eight trials. Five studies reported no or minimal signals of abuse and addiction. In addition, no deaths were reported in the opioid group by any study. Finally, we do not agree on their statement on "relatively small samples." In all, 14 of the studies in our reviews included 50–150 and five included more than 150 participants per treatment arm for analysis.

5 | CONCLUSIONS

5.1 | Implications for clinical practice

Our systematic review gives no guidance for clinicians on first-, second- or third-line therapies for CLBP. Most guidelines recommend exercise and psychosocial interventions for CLBP (Oliveira et al., 2018), that is to say non-pharmacological treatments. Most also focus on non-specific chronic low back pain (Chenot et al., 2017) and not the heterogeneous population included in the opioid studies in this review. However, these treatments may only be partially effective and are not suitable for all patients with CLBP, or may not be generally available like psychological or interdisciplinary multimodal therapies. Therefore, some patients with CLBP may require and benefit from short-, intermediate-, or even long-term drug treatment as one component of their back pain management. This is, however, only the case if a drug can induce a clinically relevant improvement of pain and/or function with an acceptable tolerability and safety—a scenario which is supported by most guidelines (Oliveira et al., 2018).

Evidence-based alternatives to opioids for CLBP are NSAIDs and possibly duloxetine (Chou et al., 2017). To the best of our knowledge, no network meta-analysis is available to answer the questions if one drug class is superior over another in terms of efficacy, tolerability and

safety. In a pragmatic randomized trial of 12 months, outcome data showed no significant advantage of opioid therapy (Step 1 was morphine, hydrocodone/acetaminophen, and oxycodone immediate release. Step 2 was morphine sustained-action and oxycodone sustained-action. Step 3 was transdermal fentanyl compared) with non-opioid medication therapy (Step 1 was acetaminophen and NSAIDs. Step 2 included adjuvant oral medications (i.e. nortriptyline, amitriptyline, gabapentin) and topical analgesics (i.e. capsaicin, lidocaine). Step 3 included drugs requiring prior authorization from the VA clinic (i.e. pregabalin, [duloxetine] and tramadol) in terms of reduction of pain and disability, tolerability and safety (including potential misuse) in patients with chronic back, knee or hip pain (Krebs et al., 2018).

Recent evidence-based guidelines on long-term opioid treatment for non-cancer pain recommended to restrict the dosage for long-term opioid therapy to 90 mg morphine equivalent (MEQ)/d (Busse et al., 2017; Dowell, Haegerich, & Chou, 2016), 120 mg MEQ/d (Häuser et al., 2015 a) and 150 mg MEQ/d (Moisset & Martinez, 2016). The average dosages reported in the included studies ranged between 60 and 120 MEQ/d. However, the range of dosages reported demonstrate that some patients required higher dosages of opioids for a sufficient pain relief than the recommended thresholds of the guidelines mentioned above.

The opioid epidemic in North America lead to statements of some opinion leaders that the best way to reduce such adverse outcomes is to stop prescribing opioids for common diagnoses like back pain because the available evidence shows they are not effective (Ballantyne, 2016). Our review demonstrates that opioids are moderately effective and safe in the short term and intermediate term within the context of randomized controlled trials. The US Center of Disease Control guidelines for chronic opioid therapy commented only on "chronic pain" and made no distinction between different chronic pain syndromes (Dowell et al., 2016). As mentioned before, chronic low back pain is a descriptive term. The importance of somatic and psychosocial factors and of nociceptive, neuropathic and the so-called nociplastic (central sensitization) pain mechanisms can be very different (Baron et al., 2016). High dosages of opioids might have been prescribed to patients with non-specific (with relevant psychosocial factors and/or nociplastic) CLBP in North America. Opioids have served in this context as a refuge from physical and psychological trauma, economic disadvantage and hopelessness (Dasgupta, Beletsky, & Ciccarone, 2018; Gomes et al., 2011).

European guidelines on opioids for chronic non-cancer pain such as the French (Moisset et al., 2016) and the German (Häuser et al., 2015) guidelines recommended opioids as one drug treatment option for chronic low back pain with defined structural damages and within a multicomponent treatment approach. Opioids should be avoided for patients with somatoform pain disorders, e.g. "psychogenic CLBP."

Even with multimodal interdisciplinary pain management resources available in most European countries, opioids remain a treatment option for the long-term management of some carefully selected and monitored patients with CLBP. As with any other medication, opioid therapy should only continue if it is clinically beneficial, with an acceptable side-effect profile that does not further compromise patient quality of life but improves functionality (O' Brien et al., 2017).

CONFLICTS OF INTEREST

FP, PK, PW and WH have no financial conflicts of interest to declare. FP and WH are members of the German guidelines group on long-term opioid therapy for chronic non-cancer pain. CS has received honoraria for consulting or lectures from Air Liquide, Astellas, Grünenthal and Pfizer.

AUTHOR CONTRIBUTIONS

PK and WH performed the search of literature. WH, CS and PW selected the studies. WH, PW, FP and CS extracted the data. WH entered the data into Revman. CS and PW checked the data entry. WH wrote the manuscript. All authors discussed the results and commented on the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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