Received: 11 August 2019 | Revised: 23 November 2019 | Accepted: 16 December 2019

DOI: 10.1002/ejp.1522

REVIEW ARTICLE

EJP European Journal of Pain

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

Patrick Welsch[1] | **Frank Petzke**[2] | **Petra Klose**[3] | **Winfried Häuser**[1,4]

[1]Health Care Center for Pain Medicine and Mental Health, Saarbrücken, Germany

[2]Pain Medicine, Department of Anesthesiology, University Medical Center Göttingen, Göttingen, Germany

[3]Department Internal and Integrative Medicine, Kliniken Essen-Mitte, Faculty of Medicine, University of Duisburg-Essen, Essen, Germany

[4]Department Psychosomatic Medicine and Psychotherapy, Technische Universität München, Munich, Germany

Correspondence
Winfried Häuser, Health Care Center for Pain Medicine and Mental Health, D-66119 Saarbrücken, Germany.
Email: w.haeuser@web.de

Abstract

Background and Objective: This updated systematic review evaluated the efficacy and safety of opioids compared with placebo for chronic osteoarthritis pain.

Databases and Data Treatment: Clinicaltrials.gov, CENTRAL, MEDLINE and PsycINFO were searched from October 2013 to July 2019. Randomized controlled trials comparing opioids with placebo and at least 4 weeks 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 with 95% confidence intervals. We added two new studies with 397 participants for a total of 22 studies with 8,942 participants. Study duration ranged between 4 and 24 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 and no clinically relevant reduction in disability compared with placebo. There was a clinically relevant harm related to the dropout rate due to adverse events. The frequency of serious adverse events did not differ from placebo. Enriched enrolment randomized withdrawal design: Based on very low– to low-quality evidence, opioids provided no clinically relevant pain relief of 50% or greater and no clinically relevant reduction in disability compared with placebo. Dropout rates due to adverse events and frequency of serious adverse events did not differ from placebo.

Conclusions: Tolerability of opioids is low and efficacy is not clinically relevant in controlled studies from 4 to 24 weeks for osteoarthritis pain.

Significance: Within the context of randomized controlled trials (4–24 weeks), opioids provided no clinically relevant pain relief and no clinically relevant reduction in disability compared with placebo in chronic osteoarthritis pain (hip, knee). Number needed to treat for an additional dropout due to side effects was 5 (95% confidence interval 4–7). Two studies found no signals of abuse and addiction. The frequency of serious adverse events including deaths did not differ from placebo.

1 | INTRODUCTION

Osteoarthritis (OA) is the most common disease of joints in adults around the world. In epidemiologic studies, OA is typically defined by radiographic findings and symptoms (Neogi & Zhang, 2013). About one-third of all adults have radiological signs of osteoarthritis. However, clinically significant osteoarthritis of the knee, hand or hip in terms of chronic pain and/ or disability was found in only 8.9% of the adult population (Hunter, McDougall, & Keefe, 2008). The incidence and prevalence of OA are rising, likely related to the ageing of the population and increasing obesity (Neogi & Zhang, 2013).

The importance of opioids for the long-term management of chronic non-cancer pain syndromes such as OA is under debate due to the opioid crisis (increase in opioid prescriptions and abuse and deaths) in North America (Asbhurn & Fleisher, 2018; Dasgupta, Beletsky, & Ciccarone, 2018). However, from 2007 to 2014, 17% of patients with any joint osteoarthritis were prescribed an opioid for their condition. Yearly rates of prescription were fairly stable over this period in the USA (DeMik et al., 2017). Up to 30% of patients with long-term opioid therapy (LTOT) in Germany were diagnosed with osteoarthritis in 2014 (Häuser, Schubert, Scherbaum, & Tölle, 2018). Therefore, the importance of opioids for the management of OA pain needs to be defined.

To the best of our knowledge, no systematic review of RCTs including all opioids (with and without additional mode of action) has been performed in the last 5 years. A recent Cochrane review analysed tramadol with and without acetaminophen for OA pain (Toupin et al., 2019). Another recent systematic review analysed the harms, but not the efficacy of all opioids for OA pain (Fuggel et al., 2019).

Therefore, we updated our systematic review on efficacy, tolerability and safety of opioids for OA pain in patients of any age in randomized placebo-controlled trials (RCTs) of at least 4 weeks double-blind duration (titration and maintenance) (Schaefert et al., 2015) for the second revision of the German 2015 guidelines on long-term administration of opioids in chronic non-cancer pain (LONTS) (Häuser et al., 2014). In view of the opioid epidemic in North America, we paid special attention to the assessment of physical dependence (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 CRD42019124110).

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 or radiologically confirmed peripheral joint OA and associated pain of at least 3 months duration. Trials exclusively including patients with inflammatory arthritis, such as rheumatoid arthritis, were not included. We excluded studies with mixed study samples (participants with OA and low back pain) where the data from the two groups were not presented separately.

Types of interventions

We considered trials with the following opioids and their administration compared with placebo: (a) Opioids given by oral, buccal and transdermal routes. (b) Opioids administered as abuse deterrent formulations (ADF), e.g. in combination with 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 agonist and norepinephrine reuptake inhibitor. 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 due to the invasive nature of the therapy and its limited clinical relevance in the outpatient setting. We did not assess the effectiveness of opioids delivered by neuraxial implantable pumps, as this has been discussed elsewhere (Noble et al., 2010). (b) In which analgesics other than opioid agonists were combined with opioids (e.g. tramadol with acetaminophen) because it is not possible to disentangle the effects of the opioids from those of the other analgesic. If only used as rescue analgesic, the combination was allowed. (c) In which a defined opioid was compared with the same opioid with ADFs (e.g. oxycodone with and without naloxone) or in which two opioids combined were compared with a single opioid without a placebo group. (d) With opioid receptor agonist/ N-methyl-D-aspartate (NMDA) antagonists (e.g. levorphanol) because these drugs are not available in Germany. e) With methadone and levomethadone because these drugs are nearly primarily used to treat opioid use disorder in Germany. (f) With drugs under development (such

as cepranopadol) which have not been approved by the European Medicines Agency (EMA).

Types of studies

We included fully published double-blind randomized controlled trials (RCTs) that compared opioids as defined above to placebo (pure or pseudo) for therapeutic purposes in CNP. We included both studies with a parallel and an enriched enrolment withdrawal (EERW) design. Studies with a cross-over design were only 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. Study duration had to be at least 4 weeks (titration and maintenance phase for parallel and cross-over design; double-blind withdrawal phase for EERW design). Studies had to include at least 10 patients per treatment arm.

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 (enriched design) We excluded studies with a maintenance or withdrawal period of less than 4 weeks 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 grouped outcome measures according to the length of the double blind (titration and maintenance): short term (4–12 weeks), intermediate (13–26 weeks) and long term (longer than 26 weeks).

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, 2010) 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 Group, 2015).

Primary outcomes.

1. Pain relief of 50% or greater for parallel design and maintenance of pain relief of 50% or greater for EERW design (efficacy; dichotomous variable)
2. Patient global impression to be much or very much improved for parallel design and maintenance of pain relief of patient global impression to be much or very much improved for EERW design (efficacy; dichotomous variable)
3. Disability (efficacy; continuous variable)
4. Dropout 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 for parallel design and maintenance of pain relief of 30% or greater for EERW design (efficacy; dichotomous variable)
2. Pain intensity (efficacy; continuous variable)
3. Sleep problems (efficacy; continuous variable)
4. Dropout rates due to lack of efficacy (efficacy; dichotomous variable)
5. Withdrawal symptoms (safety; continuous or dichotomous variable)
6. Abuse/addiction (safety; dichotomous variable)

2.2 | Searches

2.2.1 | Electronic searches

We searched:

- The Cochrane Central Register of Controlled Trials (CENTRAL) from October 2013 to July 17, 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.
- MEDLINE accessed through PubMed, from October 2013 to July 17, 2019
- PsycINFO, from October 2013 to July 17, 2019

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

2.2.2 | Searching other resources

We searched http://www.clinicaltrials.gov (website of the US National Institutes of Health) for completed trials to June 23, 2019. The search was conducted by WH.

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

2.3 | Measures of treatment effect

The effect measures of choice were risk differences (RD) for dichotomous data and standardized mean difference (SMD) for continuous data (inverse variance method). 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. 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, Schmutzer, Hilbert, Brähler, & Henningsen, 2015). The threshold 'clinically relevant benefit' was set for continuous variables by an effect size of more than 0.2 (Fayers & Hays, 2014).

2.4 | Data collection and analysis

2.4.1 | Selection of studies

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

2.4.2 | Data extraction and management

Using standardized forms, two pairs of authors (FP, WH; 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.

2.4.3 | Assessment of risk of bias in included studies

Two review authors (PW, 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), 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.

See Methods S3 for:

2.4.5 Unit of analysis issues.

2.4.6 Dealing with missing data.

2.4.7 Assessment of heterogeneity.

2.4.8 Grading of evidence.

2.5 | Subgroup analysis

Subgroups were planned a priori to assess the variations in effect size (heterogeneity) for all types of opioids pooled together compared with placebo groups pooled together, different types of opioids (pure opioids vs. opioids with additional modes of action, i.e. tramadol, tapentadol) and treatment duration (short-term, intermediate-term and long-term studies) for the primary outcomes. At least two studies had to be available for subgroup analysis.

2.6 | Sensitivity analysis

We planned to perform sensitivity analysis for all types of opioids pooled together compared with 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.

2.7 | 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) (Moore et al., 2008).

2.8 | Software

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

3 | RESULTS

3.1 | Search

The total number of included studies in the 2015 review was 20 with 8,545 participants analysed (Afilalo et al., 2010; Afilalo & Morlion, 2013; Babul et al., 2004; Breivik, Ljosaa, & Stengaard-Pedersen, 2010; Caldwell et al., 1999, 2002; Delemos et al., 2011; Fishman et al., 2007; Fleischmann et al., 2001; Friedman, Klutzaritz, & Webster, 2011; Gana et al., 2006; Katz, Hale, Morris, & Stauffer, 2010; Langford, McKenna, Ratcliffe, Vojtassak, & Richarz, 2006; Markenson, Croft, Zhang, & Richards, 2005; Matsumoto, Babul, & Ahdieh, 2005; Munera, Drehobl, Sessler, & Landau, 2010; Peloso et al., 2000; Rauck, Rapoport, & Thipphawong, 2013; Thorne et al., 2008; Vojtassak et al., 2011).

The updated searches produced 845 records after duplicates were removed. We included two new studies with 397 participants analysed (Mayorga, Wang, Kelly, & Thipphawong, 2016; Spierings et al., 2013) and thus a total of 22 studies with 8,942 participants into the qualitative and quantitative analysis. We excluded one study with oxycodone as an active comparator because the double-blind phase was 2 weeks (NCT00979953). We excluded one study with tapentadol (Serrie, Lange, & Steup, 2017) because the results have been reported in a paper which was included in the first version of the review (Afilalo & Morlion, 2013). We excluded one RCT with tramadol which reported the pooled analysis of female patients of two RCTs (Kean, Bouchard, & Roderich, 2009) of which one has been included in the first version of the review (Fishman et al., 2007). We excluded one RCT with ADL5859 and ADL5747, a δ - opioid receptor agonists, in which oyxcodone was used as an active comparator because the opioid arms included placebo pills too (NCT00979953) (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

Sixteen studies were conducted in the North America, four studies in Europe and two studies in different continents.

3.2.2 | Types of opioids

Eight studies tested oxycodone and six studies tramadol, two studies each buprenorphine, hydromorphine, morphine and tapentadol and one study each codeine, fentanyl and oxymorphone. In five of eight oxycodone studies, oxycodone was used as an active comparator. All oral opioids were administered by extended release (ER) formulations except one four-arm study which used in one treatment arm immediate release morphine. Eighteen studies used a flexible dosage of opioids, the remaining ones used a fixed dosage. Five studies did not report on rescue medication, three studies prohibited any analgesic rescue medication and 14 studies allowed rescue medication (acetaminophen, NSAIDs, short-acting opioids).

Only nine studies with a flexible dosage reported the average dosages. Average dosages of oxycodone ranged from 45 mg/day to 70 mg/day. One average dose reported for buprenorphine was 11 ug/h, 45 mg/day for morphine, 340 mg/day for tramadol and 350 mg/day for tapentadol.

3.2.3 | Study design

Eighteen studies had a parallel, one study had a cross-over and three studies had an EERW design. Duration of double-blind period (titration and maintenance) was 13–26 weeks in six studies and 4–12 weeks in the remaining 16 studies.

3.2.4 | Criteria of osteoarthritis and pretreatment

Six studies each defined the inclusion criteria for OA by ACR functional capacity I–III or by the ACR radiographic signs. Five studies required radiographic signs II–IV according to the Kellgreen Lawrence scale. Five studies did not specify the radiographic signs required. Three studies did not report on the location of osteoarthritis. The remaining studies included patients with hip and or knee osteoarthritis. Fourteen studies required insufficient pain relief by NSAIDs and/or acetaminophen and/or opioids, five studies by NSAIDS and three did not report if there was a required drug pretreatment. Seventeen studies reported a pretreatment by NSAIDs, 11 each by coxibs and acetaminophen and 14 by opioids. Seven studies each required a pain intensity ≥4 and 5 on a 0–10 scale, two a pain score of ≥2 on a 0–4 scale, and one study each a pain score of ≥7 on a 0–10 scale and ≥150 mm WOMAC pain score. The remaining studies did not report if a defined pain score was required for inclusion.

3.2.5 | Participants

Participants were diagnosed with OA of the hip and/or knee. Seventeen studies excluded patients with current and/ or a history of substance abuse and/ or current major mental disorders. Thirteen studies excluded patients with clinically relevant

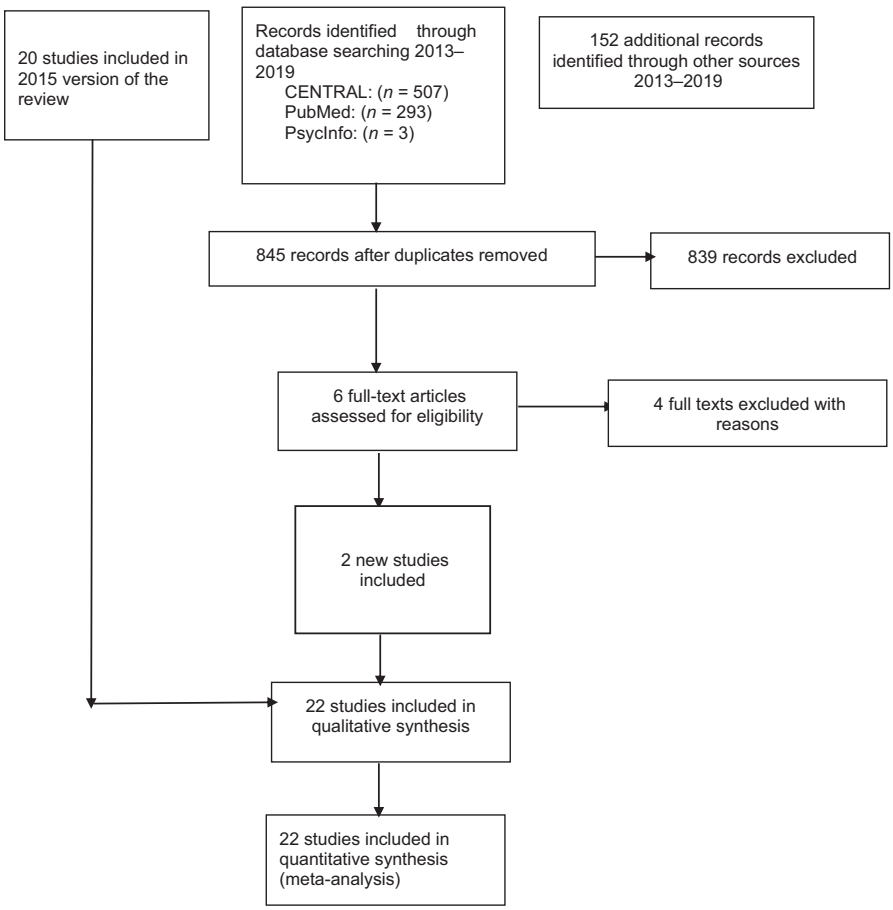

FIGURE 1 PRISMA Flow Diagram

internal diseases (e.g. heart, renal, liver, gastrointestinal and kidney diseases). Nine studies excluded patients with inflammatory arthritis. Thirteen studies did not report if inflammatory arthritis was an exclusion criterion or not. The range of the mean ages of participants in the studies was 58–64 years. The participants were predominantly Caucasian. No studies with African or Asian patients were conducted. The gender ratio was nearly balanced. Two studies included less than 50 participants, 11 included 50–150 and nine studies included more than 150 participants per treatment arm for analysis.

3.2.6 | Funding and conflicts of interest

Three studies did not report on funding. Nineteen studies were sponsored by the manufacturer of the drug. Nine authors did not report their conflicts. Twelve author groups declared their conflicts of interest. One author group reported that they have no conflict of interest.

3.3 | Risk of bias in included studies

According to the predefined categories, 17 studies were moderate-quality studies (unclear risk of bias overall) and 5 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

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: Seventeen studies with 7,695 participants were entered into analysis. The outcome was calculated by an imputation method for 11 studies. One thousand four hundred and eleven of 4,965 (28.4%) with opioids and 696 of 2,730 (25.5%) with placebo reported pain relief of 50% or greater. RD was 0.02 [95% CI 0.00 to 0.05) ($I^2 = 47\%, p = .05$)]. NNTB was 50 (95% CI 25 to indefinite). 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 indirectness, inconsistency and high probability of publication bias) .

Patient global impression to be much or very much improved: Three studies with 2,209 participants were entered

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

Reference (Year) Countries of study centres	Study design	Population type Number of patients randomized	Interventions and control group	Duration of trial
Buprenorphine				
Breivik et al. (2010) Denmark, Finland, Norway, Sweden	Parallel	Osteoarthritis knee or hip pain 199	Stable dose NSAID or Coxib oral plus 7-day buprenorphine flexible 5 or 10 or 20 µg/h transdermal patch Stable dose NSAID or Coxib plus placebo transdermal patch	5–9 days screening 24 weeks double-blind titration and maintenance 4 weeks follow-up
Munera et al. (2010) USA	Parallel	Osteoarthritis knee or hip pain 315	7-day buprenorphine flexible 5 or 10 or 20 µg/h transdermal patch Placebo transdermal patch	1-week run-in period 3 weeks double-blind titration 1 week double-blind titration maintenance
Codeine				
Peloso et al. (2000) Canada	Parallel	Osteoarthritis knee or hip pain 103	Codeine flexible 100–400 mg/d oral Placebo	Duration screening not reported 4 weeks double-blind titration and maintenance
Fentanyl				
Langford et al. (2006) European countries	Parallel	Osteoarthritis knee or hip pain 399	Stable dosage of steroids or NSAIDS oral plus titration to individually optimal dosage of fentanyl 25,50,75 or 100 µg/h transdermal patch Stable dosage of steroids or NSAIDS oral plus placebo transdermal patch	1 week screening 6 weeks double-blind titration and maintenance 3 days tapering off
Hydromorphone				
Rauck et al. (2013) USA	Parallel	Osteoarthritis knee or hip pain 981	Hydromorphone fixed 8 or 16 mg/d oral Placebo	≤ 2 weeks wash out ≤ 16 days double-blind titration 12 weeks double-blind maintenance ≤ 1 week taper
Vojtassak et al. (2011) European countries	Parallel	Osteoarthritis knee or hip pain 278	Hydromorphone 4 to 32 mg/d flexible oral Placebo	≤ 1 week screening 4-week double-blind titration 12-week double-blind maintenance 28 weeks open label
Morphine				

(Continues)

TABLE 1 (Continued)

Reference (Year) Countries of study centres	Study design	Population type Number of patients randomized	Interventions and control group	Duration of trial
Caldwell et al. (2002) USA	Parallel	Osteoarthritis pain, location not reported 295	Extended release morphine 30 mg/d once daily in the morning oral Extended release morphine 30 mg/d once daily in the evening oral Morphine 2x15 mg/d oral Placebo	Duration screening and wash out not reported 4 weeks double-blind maintenance 26 weeks open label
Katz et al. (2010) USA	Enriched-enrolment randomized withdrawal design	Osteoarthritis knee or hip pain 547	Morphine and naltrexone extended release flexible 20 – 160 mg/d oral Placebo	Screening and wash out ≤ 14 days ≤ 45 days open-label titration 12 weeks double-blind withdrawal
Oxycodone				
Caldwell et al. (1999) USA	Enriched-enrolment randomized withdrawal	Osteoarthritis pain, location not reported 107	Oxycodone oral flexible 40 to 100 mg/d oral Placebo	Duration screening and wash out not reported 4 weeks open-label titration 4 weeks double-blind withdrawal
Friedmann et al. (2011) USA	Enriched-enrolment randomized withdrawal	Osteoarthritis knee or hip pain 412	Oxycodone oral flexible 10–80 mg/d oral Placebo	Duration screening and wash out 4–10 days 2 weeks open-label titration 12 weeks double-blind maintenance 6 months open label
Markenson et al. (2005) USA	Parallel	Osteoarthritis pain, location not reported 107	Oxycodone oral flexible up to 120 mg/d oral Placebo	Duration screening and wash out not reported 13 weeks double-blind titration and maintenance
Mayorga et al. (2016) Canada, USA	Parallel	Osteoarthritis knee pain 98 (Oyxocodone and Placebo)	Oxycodone oral flexible up to 100 mg/d oral as active comparator to Fluranumab Placebo	3 weeks screening including 1 week wash out 4 weeks double-blind titration 12 weeks double-blind maintenance 26 weeks post-treatment
Spierings et al. (2013) European countries, USA	Parallel	Osteoarthritis pain hip and knee 299 (Oxcodone and Placebo)	Oxycodone oral flexible 20 to 80 mg/d as active comparator to Tranezumab	Screening (up to 30 days) Wash-out period (2 to 27 days) 8 weeks double-blind maintenance
Oxymorphone				
Matsumoto et al. (2005) USA	Parallel	Osteoarthritis knee or hip pain 489	Oxymorphone oral fixed 40 mg/d or 80 mg/ Oxycodone oral 40 mg/d as active comparator Placebo	2 – 7 days wash out 4 weeks double-blind fixed

(Continues)

TABLE 1 (Continued)

Reference (Year) Countries of study centres	Study design	Population type Number of patients randomized	Interventions and control group	Duration of trial
Tapentadol				
Afilalo et al. (2010) Australia, Canada, New Zealand, USA	Parallel	Osteoarthritis knee pain 1,030	Tapentadol flexible 200–600 mg/d oral Oxycodone flexible 40 – 100 mg/d oral as active comparator Placebo	< 2 weeks screening 3–7 days wash out 3 weeks double-blind titration 12 weeks double-blind maintenance 10–14 days follow-up
Afilalo and Morlion (2013) 13 European countries	Parallel	Osteoarthritis knee pain 987	Tapentadol flexible 200–600 mg/d oral Oxycodone flexible 40–100 mg/d oral as active comparator Placebo	Duration of screening not reported 3–7 days wash out 3 weeks double-blind titration 12 weeks double-blind maintenance 2 weeks follow-up
Tramadol				
Babul et al. (2004) USA	Parallel	Osteoarthritis knee pain 246	Tramadol flexible 100–400 mg/d oral Placebo	3–7 days wash out 12 weeks double-blind maintenance
Delemos et al. (2011) USA	Parallel	Osteoarthritis knee or hip pain 801	Tramadol fixed 100, 200 or 300 mg/d oral Placebo	2–7 days wash out, 12 weeks double-blind maintenance, 1 week follow-up
Fishman et al. (2007) USA	Parallel	Osteoarthritis knee or hip pain 539	Tramadol fixed 100, 200 or 300 mg/d oral Placebo	6 days titration 12 weeks double-blind maintenance
Fleischmann et al. (2001) USA	Parallel	Osteoarthritis knee or hip pain 129	Tramadol flexible 100–400 mg/d oral Placebo	10 days screening and wash out 12 weeks double-blind titration and maintenance
Gana et al. (2006) USA	Parallel	Osteoarthritis knee or hip pain 1,020	Tramadol fixed 100, 200, 300 or 400 mg/d oral Placebo	2–7 days wash out 12 weeks double-blind maintenance 1 week follow-up
Thorne et al. (2008) Canada	Cross-over	Osteoarthritis knee or hip pain 100	Tramadol flexible 100–400 mg/d oral Placebo	Up to 1 week wash out 4 weeks double-blind each period 6 months open label

TABLE 2 Overview of the randomized controlled trials in chronic osteoarthritis pain included into the systematic review (grouped by type of opioid in alphabetical order)

Reference (Year) Countries of study centres	Type of osteoarthritis	Prior analgesic regimen	Exclusion of patients with clinically relevant internal diseases	Exclusion of patients with clinically relevant psychiatric disease (including substance abuse)
Buprenorphine				
Breivik et al. (2010) Denmark, Finland, Norway, Sweden	Hip and/or knee American College of Rheumatology (ACR) Criteria for osteoarthritis, had experienced pain from the relevant joint for at least one year prior to enrolment, had radiographic evidence of osteoarthritis as defined by Grades II to IV of the Kellgren and Lawrence scale	NSAIDs, Coxibs, low potent opioids	Yes	Yes
Munera et al. (2010) USA	Hip and/or knee Documented history and/or radiologic evidence of chronic OA; no other information provided	NSAIDs	No	No
Codeine				
Peloso et al. (2000) Canada	Knee and hip Primary osteoarthritis grade II defined by standard atlas of radiographs	Acetaminophen, NSAIDS or opioids	No	Yes
Fentanyl				
Langford et al. (2006) European countries	Knee and hip American College of Rheumatology diagnostic criteria OA and requiring joint replacement surgery, with radiographic evidence of disease in the affected join	Weak opioids, with or without paracetamol	Yes	Yes
Hydromorphone				
Rauck et al. (2013) USA	Knee or hip Functional Class I–III OA, radiographic severity Grade II–IV	Non-opioids and opioids (no other information provided)	Yes	Yes
Vojtassak et al. (2011) European countries	Knee or hip American College of Rheumatology criteria	NSAIDs or paracetamol	No	No
Morphine				
Caldwell et al. (2002) USA	Knee or hip Grade II–IV radiographic evidence of OA	NSAIDs and acetaminophen or intermittent opioid	No	Yes
Katz et al. (2010) USA	Knee of hip ACR criteria	Non-opioid analgesics, tramadol or another opioid at a dose equivalent of ≤ 40 mg/d morphine	Yes	Yes
Oxycodone				
Caldwell et al. (1999) USA	Location not specified Six radiological criteria	NSAIDs	Yes	Yes
Friedmann (2011) USA	Knee or hip ACR criteria	NSAIds, COX2-inhibitors, opioids	No	Yes

(Continues)

TABLE 2 (Continued)

Reference (Year) Countries of study centres	Type of osteoarthritis	Prior analgesic regimen	Exclusion of patients with clinically relevant internal diseases	Exclusion of patients with clinically relevant psychiatric disease (including substance abuse)
Markenson et al. (2005) USA	Location not specified	NSAIDs, opioid therapy that was equivalent to 60 mg of oxycodone per day	Yes	Yes
Mayorga et al. (2016) Canada, USA	Knee or hip ACR criteria Radiographic evidence of OA (Kellgren–Lawrence grade ≥ 2)	No information provided	No	No
Spierings et al. (2013) European countries, USA	Hip and knee Kellgren–Lawrence grade>=2	Analgesics other than acetaminophen and non-opioids or opioids up to 90 mg/day in morphine equivalents	Yes	Yes
Oxymorphone				
Matsumoto et al. (2005) USA	Knee or hip Minimum of grade 2 in the index joint using the Kellgren–Lawrence scale	NSAID, COX-2 inhibitor, or an opioid analgesic	No	Yes
Tapentadol				
Afilalo et al. (2010) Australia, Canada, New Zealand, USA	Knee ACR criteria Functional capacity I-III	Non-opioids or opioids at doses equivalent to ≤160 mg oral morphine/d	Yes	Yes
Afilalo and Morlion (2013) 13 European countries	Knee	Non-opioids or opioids at doses equivalent to 160 mg oral morphine/d≤	Yes	Yes
Tramadol				
Babul et al. (2004) USA	Knee ACR criteria Functional Class I–III	Acetaminophen, COX-2 inhibitors, NSAIDs, tramadol or opioid analgesics	Yes	Yes
Delemos et al. (2011) USA	Knee ACR criteria Functional Class I–III	Acetaminophen, COX-2 inhibitors, NSAIDs, tramadol or opioid analgesics	No	Yes
Fishman et al. (2007) USA	Knee or hip ACR criteria	No information provided	Yes	Yes
Fleischmann et al. (2001) USA	Knee Radiographic signs	NSAIDs	Yes (probably)	Yes (probably)
Gana et al. (2006) USA	Knee or hip ACR functional class I-III	NSAIDs, COX-2 inhibitor or an opioid at least 75 of 90 mg morphine equivalent/d	Yes	Yes
Thorne et al. (2008) Canada	Knee or hip Radiographic signs	Acetaminophen	Yes	No

into analysis. Seven hundred and eighteen of 1,436 (50.0%) participants with opioids and 326 of 773 (42.2%) participants with placebo reported to be much or very much improved. RD was 0.07 (95% CI 0.00 to 0.14) (I^2 = 61%, p = .04). NNTB was 16 (95% CI 7 to indefinite). 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 and high probability of publication bias).

Disability: Seventeen studies with 7,147 participants were entered into analysis. SMD was −0.18 (95% CI −0.24 to −0.11) (I^2 = 42%; p < .0001). According to the predefined categories, the effect size was not 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: Nineteen studies with 8,525 participants were entered into analysis. One thousand four hundred and fifty nine of 5,517 (26.4%) participants with opioids and 214 of 3,013 (7.1%) with placebo dropped out due to adverse events, RD was 0.19 (95% CI 0.15 to 0.22) (I^2 = 81%; p < .0001). NNTH was 5 (95% CI 4 to 7). 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: Thirteen studies with 6,470 participants were entered into analysis. In 94 of 4,063 (2.3%) patients with opioids and 47 of 2,407 (2.0%) patients with placebo, a serious adverse event was noted. RD was 0.00 (95% CI −0.00 to 0.01) (I^2 = 11%; p = .49). The quality of evidence was very low (downgraded by three levels due to imprecision [low event rate], indirectness and high probability of publication bias).

Deaths: Nine studies with 5,082 participants reported explicitly this outcome. One of 2,960 (0.03%) of participants died in opioid group and 2 of 2,116 (0.09%) died in placebo group. RD was 0.00 (95% CI −0.00 to 0.00) (I^2 = 0%; p = .90). According to the predefined categories, there was no clinically relevant harm by opioids. The quality of evidence was very low (downgraded by three levels due to indirectness, imprecision [low event rate] and indirectness and high probability of publication bias). See Figures S1 for details.

Secondary outcomes

Pain relief of 30% or greater: Seventeen studies with 7,847 participants were entered into analysis. The outcome was calculated by an imputation method for 11 studies. Two thousand three hundred and thirty seven of 4,969 (47.0%) with opioids and 1,227 of 2,905 (42.2%) with placebo reported pain relief of 30% or greater. RD was 0.06 (95% CI 0.01 to 0.10) (I^2 = 75, p = .02). NNTB was 16 (95% CI 10 to 100). 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 and high probability of publication bias).

Mean pain intensity: Nineteen studies with 8,588 participants were entered into analysis. SMD was −0.19 (95% CI −0.26 to −0.12) (I^2 = 53%; p < .0001). According to the predefined categories, the effect size was not 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).

Sleep problems: Six studies with 3,654 participants were entered into analysis. SMD was −0.11 (95% CI −0.18 to −0.04) (I^2 = 3%; p = .002). According to the predefined categories, the effect size was not 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 lack of efficacy: Nineteen studies with 8,684 participants were entered into analysis. Six hundred and fifteen of 5,485 (11.2%) with opioids and 696 of 3,199 (21.7%) with placebo dropped out due to lack of efficacy. RD was −0.11 [95% CI −0.14 to −0.08) (I^2 = 75%, $p \leq$ .0001). NNTB was 9 (95% CI 7 to 12). 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: No study assessed this outcome.

Abuse and addiction: Two studies with 998 participants reported this outcome. Signals of aberrant drug behaviour were not found in both studies. The quality of evidence was very low (downgraded by three levels due to indirectness, imprecision [low number of participants] and high probability of publication bias). See Figures S1 for details.

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

Primary outcomes

Maintenance of pain relief of 50% or greater: This outcome was not reported by the studies.

Maintenance of patient global impression to be much or very much improved: This outcome was not assessed by the studies.

Disability: The outcome was assessed by one study. The p-value of the difference opioid to placebo was 0.06.

Withdrawal due to adverse events: Three studies with 826 participants were entered into analysis. Sixty-four of 410 (15.6%) participants with opioids and 38 of 416 (9.1%) with placebo dropped out due to adverse events, RD was 0.05

(95% CI −0.00 to 0.11) (I^2 = 35%; p = .06). The quality of evidence was low (downgraded by two levels due to indirectness and high probability of publication bias).

Serious adverse events: Two studies with 756 participants were entered into analysis. In 14 of 376 (3.7%) participants with opioids and 13 of 380 (3.2%) participants with placebo a serious adverse event was noted. RD was 0.00 (95% CI −0.01 to 0.03) (I^2 = 0%; p = .40). The quality of evidence was very low (downgraded by three levels due to imprecision [low event rate], indirectness and high probability of publication bias).

Deaths: This outcome was not reported by the studies. See Figures S1 for details.

Secondary outcomes

Maintenance of pain relief of 30% or greater: This outcome was not reported by the studies.

Mean pain intensity: Twelve studies with 4,118 participants were entered into analysis. SMD was −0.47 (95% CI −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: The outcome was assessed by one study. There were no differences between opioid and placebo in the reduction in sleep problems. 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: Four studies with 863 participants were entered into analysis. Twenty five of 447 (5.6%) participants with opioids and 83 of 416 (20.0%) participants with placebo dropped out due to lack of efficacy. RD was −0.14 (95% CI −0.19 to −0.10) (I^2 = 0%, p < .0001). NNTB was 7 (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 levels due to indirectness and high probability of publication bias).

Withdrawal symptoms: This outcome was not assessed by the studies.

Abuse and addiction: This outcome was not assessed by the studies. See Figures S1 for details

3.5 | Subgroup analyses

3.5.1 | Different 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 = 63%, p = .009;

Disability: I^2 = 0%, p = .60; dropout due to adverse events I^2 = 80%, p < .0001 (see Figures S1 for details).

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 0.01 (95% CI - 0.04 to 0.06) (I^2 = 63%, p = .71) for pure opioids and 0.02 (95% CI 0.001 to 0.04) (I^2 = 2%, p < .0001) for tramadol and tapentadol. Pain relief of 50% or greater for tramadol and tapentadol was clinically not relevant. SMD for disability was −0.18 (95% CI −0.29 to −0.07) (I^2 = 57%; p = .009) for pure opioids and −0.17 (95% CI −0.25 to −0.09) (I^2 = 2%; p < .0001) for tapentadol and tramadol. Reduction in disability by both types of opioids was not relevant. RD for dropout rates due to adverse events was 0.24 (95% CI 0.19 to 0.29) (I^2 = 81%; p < .0001) for pure opioids and 0.12 (95% CI 0.09 to 0.15) (I^2 = 46%; p < .0001) for tapentadol and tramadol. Dropout rates due to adverse events were clinically relevant for both types of opioids.

3.5.3 | Study duration

In studies with a duration >12 weeks, RD of pain relief of 50% or greater was - 0.01 (95% CI −0.05 to 0.03) (I^3 = 46; p = .66) and RD was 0.04 (95% CI 0.01 to 0.07) (I^2 = 46; p = .006) in studies ≤12 weeks duration. Pain relief of 50% or greater in studies ≤12 weeks duration was not clinically relevant. SMD for disability was −0.23 (95% CI −0.30 to 0.03) (I^2 = 69; p = .11) for studies with >12 weeks duration and SMD was −0.23 (95% CI −0.30 to −0.16) (I^2 = 88%; p < .0001) in studies ≤12 weeks duration. Reduction in disability was clinically relevant in studies ≤12 weeks duration. RD for dropout rates due to adverse events was 0.24 (95% CI 0.17 to 0.31) (I^2 = 88%; p < .0001) for studies with >12 weeks duration and RD was 0.17 (95% CI 0.13 to 0.21) (I^2 = 72%; p < .0001) in studies ≤12 weeks duration. Dropout rates due to adverse events was clinically relevant in short- and intermediate-term studies.

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 −0.02 (95% CI - 0.08 to 0.05) (I^2 = 67%, p = .57).

3.7 | Publication bias

Studies with 966 participants with a null effect on dropout due to lack of efficacy would have been required to make the

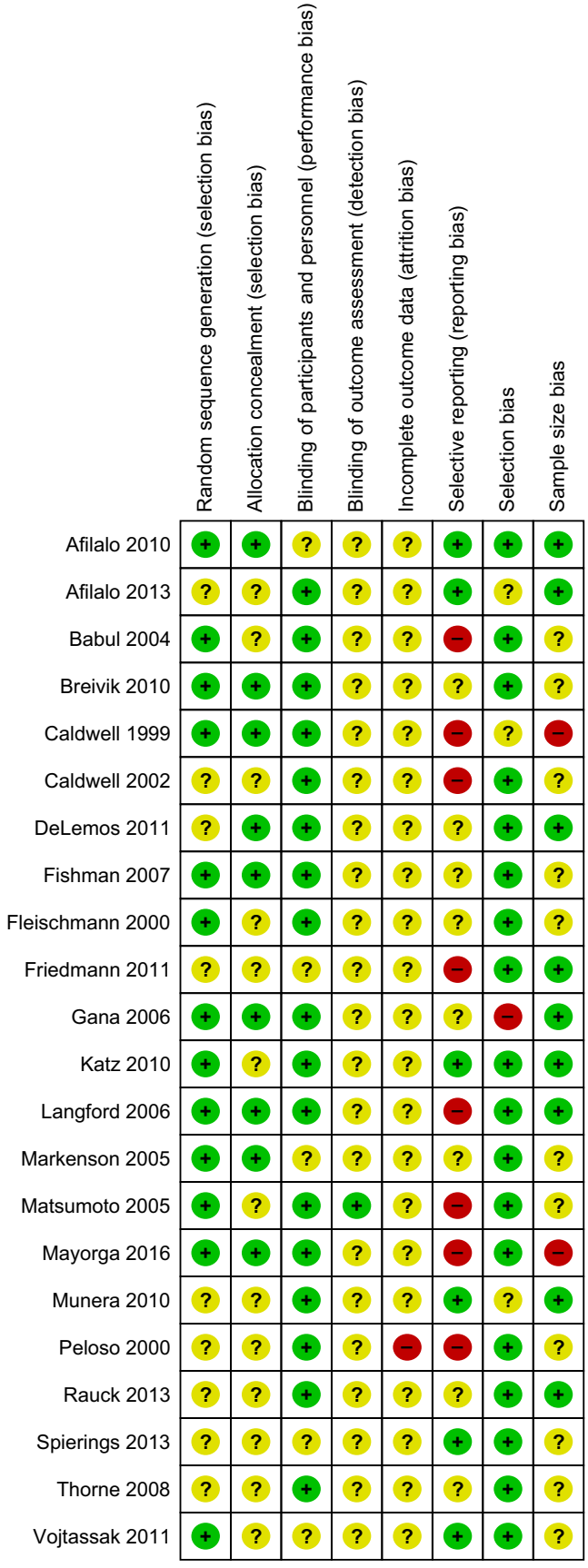

FIGURE 2 Risk of bias graph

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 partially changes the major findings of our previous review in which we stated that *opioids were superior to placebo in terms of efficacy*. Using imputation methods, we confirm the finding of the previous review that opioids did not provide a clinically relevant benefit over placebo in pain relief of 50% or greater. We found a clinically relevant reduction in disability in short-term, but not in intermediate-term studies in the updated review. The clinically relevant reductions in mean pain intensity and the number of patients which reported to be much or very much improved were no longer detectable in the updated review. The finding that opioids provided a clinically relevant benefit with regards to dropping out due to adverse events remained unchanged as well as the clinically relevant worse tolerability of opioids compared with placebo. In both reviews, there were no clinically relevant harms with regard to serious adverse events by opioids compared with placebo. In both reviews, the quality of evidence was low to very low.

4.2 | Overall completeness and applicability of evidence

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

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

1. Most studies were conducted in research centres. No study was conducted in a primary care setting.
2. Most studies excluded patients with clinically relevant somatic diseases and current or previous substance abuse. Somatic and mental comorbidities in patients with chronic pain are prevalent in the general population (Häuser et al., 2015).
3. Nearly all studies included only patients with hip and/ or knee pain, but not with other frequent locations of OA such as shoulder and hands.
4. The majority of the participants were middle-aged Caucasian women. No study was conducted in Asia or Africa.

5. Some studies did not clearly describe important patient characteristics, such as the duration of symptoms and 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 draw conclusions on the long-term (more than 6 months) efficacy and safety of opioids for OA. The European Medicines Agency recommends open-label extension studies to assess long-term efficacy and safety (European Medicines Agency, 2017). The results of a systematic review of open-label extension studies will be published in another paper (Bialas, Maier, Klose, & Häuser, 2019).

4.3 | Potential biases in the review process

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 systematic reviews and studies

Our findings with no convincing proof of efficacy but of reduced tolerability are quite similar with two Cochrane reviews with tapentadol and tramadol. We included two of the tapentadol studies for OA which were included in a Cochrane review which included a study in chronic low back pain and a study with patients with either CLBP or OA pain too. In comparison with placebo, tapentadol was associated with a mean pain reduction of 0.56 points (95% CI 0.92 to 0.20) (NNTB 12 [95% CI 7 to 35]) in the 11-point numerical rating scale at 12 weeks and with a 1.36 increase (95% CI 1.13 to 1.64) in the risk of dropping out to adverse events with NNTB 16 (95% CI 9 to 57). Tapentadol was associated with a 2.7-fold increase (95% CI 2.05 to 3.52) in the risk of discontinuing treatment due to adverse effects with NNTH 10 ((95% CI 7 to 12) for 12 weeks) (Santos, Alarcão, Fareleira, Vaz-Carneiro, & Costa, 2015).

Fuggle et al. analysed 17 RCTs with opioids for OA of which 14 RCTs were included in our review too. They found an increased risk of AEs with opioids compared with placebo (RR 1.70, 95% CI 1.37 to 2.12) (Fuggle et al., 2019).

Only 2 of the 22 studies analysed assessed aberrant drug behaviour and found no signals of abuse and addiction of prescribed opioids. The risk of abuse of hydrocodone and oxycodone in North America was known since 2000 (Cicero, Inciardi, & Muñoz, 2005). We wonder why abuse and addiction was not assessed more systematically in the studies conducted since 2000.

Increased mortality associated with prescriptions of opioids for chronic non-cancer pain is one component of the North American opioid epidemic (Asbhurn & Fleisher, 2018). Prescription of tramadol for osteoarthritis pain in persons aged 50 years or more was associated with all-cause mortality in an UK database of general practitioners between 2000 and 2015 (Zeng et al., 2019). In contrast, this systematic review found no increased mortality in the opioid group in the context of RCTs. Potential reasons for the divergent findings of randomized controlled trials and population-based cohort studies are as follows: a) The time period of the cohort studies is longer than the ones of RCTs. Opioid-associated mortality may increase with the duration of opioid consumptions. b) The strict criteria of RCTs with patients with relevant internal diseases and (history of) substance abuse excluded are not applied in routine clinical care. c) There are methodological limitations of prescription opioid safety research in cohort studies (Ranapurwala, Naumann, Austin, Dasgupta, & Marshall, 2019).

5 | CONCLUSIONS

5.1 | Implications for clinical practice

Our systematic review adds no relevant findings to guide clinicians on neither short- and long-term nor first-, second- or third-line drug therapies for OA pain. With regards to drugs, we know no RCT with head-to-head comparisons and no systematic review with a network meta-analysis comparing all main drug options available for OA pain. A systematic review including RCTs of at least 8 weeks duration with NSAIDs (27 treatment arms) and opioids (14 treatment arms) found that NSAIDs and opioids offered similar pain relief (Smith, Deshpande, Collins, Katz, & Losina, 2016). In a pragmatic randomized trial of 12 months, outcome data showed no significant advantage of escalating 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 escalating non-opioid medication therapy (Step 1 was acetaminophen and NSAIDs. Step 2 included adjuvant oral medications [i.e. nortriptyline, amitriptyline and gabapentin] and topical analgesics [i.e. capsaicin, lidocaine]. Step 3 included drugs requiring prior authorization from the clinic [i.e. pregabalin, duloxetine] and tramadol) in terms of reduction in pain and disability, tolerability and safety (including potential misuse) in patients with chronic low back

pain or hip or knee osteoarthritis pain (Krebs et al., 2018). A network meta-analysis included 76 RCTs with at least 100 participants per treatment arm with NSAIDs, paracetamol or placebo. The authors found no sound evidence of an efficacy of paracetamol and sound evidence that diclofenac 150 mg/day was the most effective NSAID available, in terms of improving both pain and function. However, the authors highlighted the critical safety profile of NSAIDs (da Costa et al., 2017). A network meta-analysis comprising 17 RCTs found that topical NSAIDs and capsaicin in licensed doses may be equally effective for pain relief (Persson, Stocks, Walsh, Doherty, & Zhang, 2018). The most comprehensive systematic review with network meta-analysis analysed RCTs with long-term (≥12 months) outcomes (symptoms, joint structure) from 74 RCTs of analgesics, antioxidants, bone-acting agents such as bisphosphonates and strontium ranelate, NSAIDs, intra-articular injection medications such as hyaluronic acid and corticosteroids, symptomatic slow-acting drugs such as glucosamine and chondroitin sulphate and putative disease-modifying agents such as cindunistat and sprifermin. The authors found uncertainty around the estimates of effect size for change in pain for all comparisons with placebo (Gregori et al., 2018).

Relating to the importance of non-pharmacological versus drug therapies, recent systematic reviews and guidelines paid special attention to the long-term safety of the interventions. A recent systematic review on treatment options for knee OA included 34 RCTs with treatments specifically addressing safety of the treatments and with ≥12 months of follow-up. The authors concluded that lifestyle modifications (moderate exercise and weight loss), glucosamine, intra-articular Hyaluronic Acid and platelet-rich plasma injections have a low risk of harm and beneficial ≥12 month outcomes. Although NSAIDs provide pain relief, they are associated with increased risk of medical complications. Opioids have a lack of evidence for use and a high risk of long-term harm. Total knee replacement is associated with significant medical complications (Charlesworth, Fitzpatrick, Perera, & Orchard, 2019).

Current guidelines gave a limited importance to opioids in the management of OA, too. A systematic review searched the literature until April 2013 and included 16 guidelines. Most guidelines gave strong recommendations for non-pharmacologic modalities such as education/self-management, exercise, weight loss if overweight, walking aids as indicated and thermal modalities. For appropriate patients, joint replacement was recommended. The recommendations of acetaminophen/ paracetamol as first-line therapy in symptomatic OA cannot be supported by current evidence (da Costa et al., 2017). Second-line agents recommended were topical agents (capsaicin and topical NSAIDs) and oral NSAIDs (with appropriate risk stratification and employment of gastroprotective strategies). For refractory symptoms, tramadol was recommended, and consideration could be given to opioids or possibly duloxetine (Nelson, Allen, Golightly, Goode, & Jordan, 2014). Our subgroup analysis of opioids with additional mode of action might support the guideline recommendation to prefer tramadol to pure opioids because tapentadol and tramadol were better tolerated than pure opioids.

To summarize: Opioids provide no clinically relevant pain relief in the short- and intermediate-term for OA pain. They provide a clinically relevant reduction in disability in the short but not in the intermediate term. The short- and intermediate-term tolerability of opioids is low. Therefore, opioids have a limited role in the management of OA pain in selected patients. Potential indications might be a) pain refractory to non-pharmacological and oral or topical NSAIDs in patients with and without joint replacement, b) patients with contraindications for NSAIDs and for joint replacement and c) intermittent use over short period of times in case of an inflammatory flare up.

If a therapy with opioids is considered, the recommended dosages of recent evidence-based guidelines on long-term opioid treatment for non-cancer pain should be followed which range between 90 mg morphine equivalent (MEQ)/d (Busse et al., 2017; Dowell, Haegerich, & Chou, 2016) and 150 mg MEQ/day (Moisset & Martinez, 2016). As with any other therapy, opioids should only continue if they are clinically beneficial (reduction in pain and/ or disability) and have an acceptable individual side-effect profile (O'Brien et al., 2017).

5.2 | Implications for research

Long-term and publically founded studies in natural setting studies with innovative designs (e.g. cluster randomized trials, stepped wedge design) comparing pharmacological and non-pharmacological treatments are necessary to better define the importance of the various treatment options available for OA pain.

ACKNOWLEDGEMENT

We thank Rainer Schaefert for his contributions to the first version of the review.

CONFLICTS OF INTEREST

PW, FP, PK and WH have no financial conflicts of interest to declare. FP and WH are heads of the German guidelines group on long-term opioid therapy for chronic non-cancer pain.

AUTHOR CONTRIBUTIONS

PK and WH performed the search of literature. WH, CS and PW selected the studies. WH, PW, and FP extracted data.

WH entered the data into Revman. FP and PW checked the data entry. WH wrote the manuscript. All authors discussed the results and commented on the manuscript.

REFERENCES

Afilalo, M., Etropolski, M. S., Kuperwasser, B., Kelly, K., Okamoto, A., Van Hove, I., … Haeussler, J. (2010). Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: A randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig*, *30*, 489–505. https://doi.org/10.2165/11533440-000000000-00000

Afilalo, M., & Morlion, B. (2013). Efficacy of tapentadol ER for managing moderate to severe chronic pain. *Pain Physician*, *16*, 27–40.

Ashburn, M. A., & Fleisher, L. A. (2018). Editorial: Increasing evidence for the limited role of opioids to treat chronic noncancer pain. *JAMA*, *320*, 2427–2428. https://doi.org/10.1001/jama.2018.19327

Babul, N. D., Novek, R., Chipman, H., Roth, S. H., Gana, T., & Albert, K. (2004). Efficacy and safety of extended-release, once-daily tramadol in chronic pain: A randomized 12-week clinical trial in osteoarthritis of the knee. *Journal of Pain and Symptom Management*, *28*, 59–71. https://doi.org/10.1016/j.jpainsymman.2003.11.006

Bialas, P., Maier, C., Klose, P., & Häuser, W. (2019). Efficacy and harms of long-term opioid therapy in chronic non-cancer pain: Systematic review and meta-analysis of open-label extension trials with a study duration ≥26 weeks. *European Journal of Pain*. https://doi.org/10.1002/ejp.1496

Breivik, H., Ljosaa, T. M., & Stengaard-Pedersen, K. (2010). A 6-months, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patients naive to potent opioids. *Scandinavian Journal of Pain*, *1*, 122–141.

Busse, J. W., Craigie, S., Juurlink, D. N., Buckley, D. N., Wang, L., Couban, R. J., … Guyatt, G. H. (2017). Guideline for opioid therapy and. chronic noncancer pain. *CMAJ*, *189*, E659–E666.

Caldwell, J. R., Hale, M. E., Boyd, R. E., Hague, J. M., Iwan, T., Shi, M., & Lacouture, P. G. (1999). Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: A double blind, randomized, multicenter, placebo controlled trial. *Journal of Rheumatology*, *26*, 862–869.

Caldwell, J. R., Rapoport, R. J., Davis, J. C., Offenberg, H. L., Marker, H. W., Roth, S. H., … Lynch, P. M. (2002). Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: Results from a randomized, placebo-controlled, doubleblind trial and an open-label extension trial. *Journal of Pain and Symptom Management*, *23*, 278–291. https://doi.org/10.1016/S0885-3924(02)00383-4

Charlesworth, J., Fitzpatrick, J., Perera, N. K. P., & Orchard, J. (2019). Osteoarthritis- a systematic review of long-term safety implications for osteoarthritis of the knee. *BMC Musculoskeletal Disorders*, *20*, 151. https://doi.org/10.1186/s12891-019-2525-0

Cicero, T. J., Inciardi, J. A., & Muñoz, A. (2005). Trends in abuse of Oxycontin and other opioid analgesics in the United States: 2002–2004. *The Journal of Pain*, *6*, 662–672. https://doi.org/10.1016/j.jpain.2005.05.004

Cochrane Pain, Palliative and Supportive Care Group. (2015). PaPaS author and referee guidance. Retrieved from papas.cochrane.org/papas-documents. Accessed June 5, 2015.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Hillsdale: Lawrence Erlbaum Associates.

da Costa, B. R., Reichenbach, S., Keller, N., Nartey, L., Wandel, S., Jüni, P., & Trelle, S. (2017). Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: A network meta-analysis. *Lancet*, *390*, e21–e33. https://doi.org/10.1016/S0140-6736(17)31744-0

Dasgupta, N., Beletsky, L., & Ciccarone, D. (2018). Opioid crisis: No easy fix to its social and economic determinants. *American Journal of Public Health*, *108*, 182–186. https://doi.org/10.2105/AJPH.2017.304187

DeLemos, B. P., Xiang, J., Benson, C., Gana, T. J., Pascual, M. L., Rosanna, R., & Fleming, B. (2011). Tramadol hydrochloride extended-release once-daily in the treatment of osteoarthritis of the knee and/or hip: A double-blind, randomized, dose-ranging trial. *American Journal of Therapeutics*, *18*, 216–226. https://doi.org/10.1097/MJT.0b013e3181cec307

DeMik, D. E., Bedard, N. A., Dowdle, S. B., Burnett, R. A., McHugh, M. A., & Callaghan, J. J. (2017). Are we still prescribing opioids for osteoarthritis*? Journal of Arthroplasty*, *32*, 3578–3582. https://doi.org/10.1016/j.arth.2017.07.030

Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*, *315*(15), 1624–1645. https://doi.org/10.1001/jama.2016.1464

European Medicines Agency. (2010). Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis. Accessed April 20, 2019.

European Medicines Agency. (2017). Guideline on the clinical development of medicinal products intended for the treatment of pain. Retrieved from https://www.ema.europa.eu/en/clinical-development-medicinalproducts-intended-treatment-pain Accessed April 20, 2019.

Fayers, P. M., & Hays, R. D. (2014). Don't middle your MIDs: Regression to the mean shrinks estimates of minimally important differences. *Quality of Life Research*, *23*, 1–4. https://doi.org/10.1007/s11136-013-0443-4

Fishman, R. L., Kistler, C. J., Ellerbusch, M. T., Aparicio, R. T., Swami, S. S., Shirley, M. E., … Bouchard, S. (2007). Efficacy and safety of 12 weeks of osteoarthritic pain therapy with once-daily tramadol (Tramadol Contramid OAD). *Journal of Opioid Management*, *3*, 273–280. https://doi.org/10.5055/jom.2007.0015

Fleischmann, R. M., Caldwell, J. R., Roth, S. H., Tesser, J. R. P., Olson, W., & Kamin, M. (2001). Tramadol for the treatment of joint pain associated with osteoarthritis: A randomized, double-blind, placebo-controlled trial. *Current Therapeutic Research*, *62*, 113–128. https://doi.org/10.1016/S0011-393X(01)80021-7

Friedmann, N., Klutzaritz, V., & Webster, L. (2011). Efficacy and safety of an extended-release oxycodone (Remoxy) formulation in patients with moderate to severe osteoarthritic pain. *Journal of Opioid Management*, *7*, 193–202. https://doi.org/10.5055/jom.2011.0062

Fuggle, N., Curtis, E., Shaw, S., Spooner, L., Bruyère, O., Ntani, G., … Cooper, C. (2019). Safety of opioids in osteoarthritis: Outcomes of a systematic review and meta-analysis. *Drugs and Aging*, *36*, 129–143. https://doi.org/10.1007/s40266-019-00666-9

Gana, T. J., Pascual, M. L. G., Fleming, R. R. B., Schein, J. R., Janagap, C. C., Xiang, J., & Vorsanger, G. J. (2006). Extended-release tramadol in the treatment of osteoarthritis: A multicenter, randomized, double-blind, placebo-controlled clinical trial. *Current Medical Research and Opinion*, *22*, 1391–1401. https://doi.org/10.1185/030079906X115595

Gregori, D., Giacovelli, G., Minto, C., Barbetta, B., Gualtieri, F., Azzolina, D., … Rovati, L. C. (2018). Association of pharmacological treatments with long-term pain control in patients with knee osteoarthritis: A systematic review and meta-analysis. *JAMA*, *320*, 2564–2579. https://doi.org/10.1001/jama.2018.19319

Häuser, W., Bock, F., Engeser, P., Tölle, T., Willweber-Strumpf, A., & Petzke, F. (2014). Long-term opioid use in non-cancer pain. *Dtsch Arztebl Int*, *24*, 732–740. https://doi.org/10.3238/arztebl.2014.0732

Häuser, W., Schmutzer, G., Hilbert, A., Brähler, E., & Henningsen, P. (2015). Prevalence of chronic disabling noncancer pain and associated demographic and medical variables: A cross-sectional survey in the general German population. *Clinical Journal of Pain*, *15*, 886–892.

Häuser, W., Schubert, T., Scherbaum, N., & Tölle, T. (2018). Guideline-recommended vs high-dose long-term opioid therapy for chronic noncancer pain is associated with better health outcomes: data from a representative sample of the German population. *Pain*, *159*, 85–91.

Higgins, J. P. T., Churchill, R., Chandler, J., & Cumpston, M. S. (editors) (2017). Cochrane handbook for systematic reviews of interventions version 5.2.0 (updated February 2017), Cochrane, 2017. Retrieved from https://training.cochrane.org/handbook.

Hunter, D. J., McDougall, J. J., & Keefe, F. J. (2008). The symptoms of osteoarthritis and the genesis of pain. *Rheumatic Diseases Clinics of North America*, *34*, 623–643. https://doi.org/10.1016/j.rdc.2008.05.004

Katz, N., Hale, M., Morris, D., & Stauffer, J. (2010). Morphine sulfate and naltrexone hydrochloride extended release capsules in patients with chronic osteoarthritis pain. *Postgraduate Medicine*, *122*, 112–118. https://doi.org/10.3810/pgm.2010.07.2179

Kean, W. F., Bouchard, S., & Roderich, G. E. (2009). Women with pain due to osteoarthritis: The efficacy and safety of a once-daily formulation of tramadol. *Pain Medicine*, *10*, 1001–1011. https://doi.org/10.1111/j.1526-4637.2009.00677.x

Krebs, E. E., Gravely, A., Nugent, S., Jensen, A. C., DeRonne, B., Goldsmith, E. S., … Noorbaloochi, S. (2018). Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The SPACE randomized clinical trial. *JAMA*, *319*, 872–882. https://doi.org/10.1001/jama.2018.0899

Langford, R., McKenna, F., Ratcliffe, S., Vojtassak, J., & Richarz, U. (2006). Transdermal fentanyl for improvement of pain and functioning in osteoarthritis: A randomized, placebocontrolled trial. *Arthritis and Rheumatism*, *54*, 1829–1837. https://doi.org/10.1002/art.21884

Markenson, J. A., Croft, J., Zhang, P. G., & Richards, P. (2005). Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *Clinical Journal of Pain*, *21*, 524–535. https://doi.org/10.1097/01.ajp.0000146215.86038.38

Matsumoto, A. K., Babul, N., & Ahdieh, H. (2005). Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: Results of a randomized, double-blind, placebo- and active-controlled phase III trial. *Pain Medicine*, *6*, 357–366. https://doi.org/10.1111/j.1526-4637.2005.00057.x

Mayorga, A. J., Wang, S., Kelly, K. M., & Thipphawong, J. (2016). Efficacy and safety of fulranumab as monotherapy in patients with moderate to severe, chronic knee pain of primary osteoarthritis: A randomised, placebo- and active-controlled trial. *International Journal of Clinical Practice*, *70*, 493–505. https://doi.org/10.1111/ijcp.12807

Moher, D., Liberati, A., Teztlaff, J., & Altman, G.; The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine*, *51*, 1–7.

Moisset, X., & Martinez, V. (2016). Opioid use for the management of chronic non-cancer pain: French guidelines. *Revue Neurologique*, *172*, 337–338. https://doi.org/10.1016/j.neurol.2016.05.004

Moore, A. R., Eccleston, C., Derry, S., Wiffen, P., Bell, R. F., Straube, S., & McQuay, H. (2010). "Evidence" in chronic pain-establishing best practice in the reporting of systematic reviews. *Pain*, *150*, 386–389. https://doi.org/10.1016/j.pain.2010.05.011

Moore, R. A., Barden, J., Derry, S., & McQuay, H. J. (2008). *Systematic Reviews in Pain Research: Methodology Refined*. (1st ed.). Washington: IASP Press.

Munera, C., Drehobl, M., Sessler, N. E., & Landau, C. (2010). A randomized, placebo-controlled, double-blinded, parallel-group, 5-week study of buprenorphine transdermal system in adults with osteoarthritis. *Journal of Opioid Management*, *6*, 193–202. https://doi.org/10.5055/jom.2010.0017

NCT00979953 (2015). Efficacy and Safety Study Evaluating ADL5859 and ADL5747 in Participants With Pain Due to Osteoarthritis of the Knee. Retrieved from https://www.clinicaltrials.gov/ct2/show/NCT00979953?term=NCT00979953&rank=1. Accessed June 23, 2019.

Nelson, A. E., Allen, K. D., Golightly, Y. M., Goode, A. P., & Jordan, J. M. (2014). A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. *Seminars in Arthritis and Rheumatism*, *43*, 701–712. https://doi.org/10.1016/j.semarthrit.2013.11.012

Neogi, T., & Zhang, Y. (2013). Epidemiology of osteoarthritis. *Rheumatic Diseases Clinics of North America*, *39*, 1–19. https://doi.org/10.1016/j.rdc.2012.10.004

Noble, M., Treadwell, J. R., Tregear, S. J., Coates, V. H., Wiffen, P. J., Akafomo, C., … Chou, R. (2010). Long-term opioid management for chronic noncancer pain. *Cochrane Database Systematic Review*, *1*, CD006605. https://doi.org/10.1002/14651858.CD006605.pub2

O'Brien, T., Christrup, L. L., Drewes, A. M., Fallon, M. T., Kress, H. G., McQuay, H. J., … Wells, J. C. (2017). European Pain Federation position paper on appropriate opioid use in chronic pain management. *European Journal of Pain*, *21*, 3–19. https://doi.org/10.1002/ejp.970

Peloso, P. M., Bellamy, N., Bensen, W., Thomson, G. T. D., Harsanyi, Z., & Darke, A. C. (2000). Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *Journal of Rheumatology*, *27*, 764–771.

Persson, M. S. M., Stocks, J., Walsh, D. A., Doherty, M., & Zhang, W. (2018). The relative efficacy of topical non-steroidal anti-inflammatory drugs and capsaicin in osteoarthritis: A network meta-analysis of randomised controlled trials. *Osteoarthritis Cartilage*, *26*, 1575–1582. https://doi.org/10.1016/j.joca.2018.08.008

Rauck, R., Rapoport, R., & Thipphawong, J. (2013). Results of a double-blind, placebo-controlled, fixed-dose assessment of once-daily OROS® hydromorphone ER in patients with moderate to severe pain associated with chronic osteoarthritis. *Pain Practice*, *13*, 18–29.

Ranapurwala, S. I., Naumann, R. B., Austin, A. E., Dasgupta, N., & Marshall, S. W. (2019). Methodologic limitations of prescription opioid safety research and recommendations for improving the evidence base. *Pharmacoepidemiology and Drug Safety*, *28*, 4–12.

Review Manager (RevMan) [Computer program]. (2014). *The Nordic Center. Version Version 5.3*. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration.

Santos, J., Alarcão, J., Fareleira, F., Vaz-Carneiro, A., & Costa, J. (2015). Tapentadol for chronic musculoskeletal pain in adults. *Cochrane Database Systematic Review*, *5*, CD009923. https://doi.org/10.1002/14651858.CD009923.pub2

Schaefert, R., Welsch, P., Klose, P., Sommer, C., Petzke, F., & Häuser, W. (2015). Opioids in chronic osteoarthritis pain. A systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks duration. *Schmerz*, *29*, 47–59.

Serrie, A., Lange, B., & Steup, A. (2017). Tapentadol prolonged-release for moderate-to-severe chronic osteoarthritis knee pain: A double-blind, randomized, placebo- and oxycodone controlled release-controlled study. *Current Medical Research and Opinion*, *33*, 1423–1432. https://doi.org/10.1080/03007995.2017.1335189

Smith, S. R., Deshpande, B. R., Collins, J. E., Katz, J. N., & Losina, E. (2016). Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: Systematic analytic review. *Osteoarthritis Cartilage*, *24*, 962–972. https://doi.org/10.1016/j.joca.2016.01.135

Spierings, E. L., Fidelholtz, J., Wolfram, G., Smith, M. D., Brown, M. T., & West, C. R. (2013). A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. *Pain*, *154*, 1603–1612. https://doi.org/10.1016/j.pain.2013.04.035

Thorne, C., Beaulieu, A. D., Callaghan, D. J., O'Mahony, W. F., Bartlett, J. M., Knight, R., … Darke, A. C. (2008). A randomized, double-blind, crossover comparison of the efficacy and safety of oral controlled-release tramadol and placebo in patients with painful osteoarthritis. *Pain Research and Management*, *13*, 93–102. https://doi.org/10.1155/2008/165421

Toupin April, K., Bisaillon, J., Welch, V., Maxwell, L. J., Jüni, P., Rutjes, A. W., … Tugwell, P. (2019). Tramadol for osteoarthritis. *Cochrane Database Systematic Review*, *5*, CD005522.

Vojtaššák, J., Vojtaššák, J., Jacobs, A., Rynn, L., Waechter, S., & Richarz, U. (2011). A phase IIIb, multicentre, randomised, parallel-group, placebo-controlled, double-blind study to investigate the efficacy and safety of OROS hydromorphone in subjects with moderate-to-severe chronic pain induced by osteoarthritis of the hip or the knee. *Pain Research and Treatment*, *2011*, 239501. https://doi.org/10.1155/2011/239501

Zeng, C., Dubreuil, M., LaRochelle, M. R., Lu, N., Wei, J., Choi, H. K., Lei, G., & Zhang, Y. (2019). Association of tramadol with all-cause mortality among patients with osteoarthritis. *JAMA*, *321*, 969–982.

SUPPORTING INFORMATION

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

How to cite this article: Welsch P, Petzke F, Klose P, Häuser W. Opioids for chronic osteoarthritis pain: An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks double-blind duration. *Eur J Pain*. 2019;00:1–19. https://doi.org/10.1002/ejp.1522