Drugs & Aging Supplement – Safety of Anti-Osteoarthritis Medications

**Safety of opioids in osteoarthritis: Outcomes of a systematic review and meta-analysis**

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Running head: Meta-analysis of opioid safety in OA

**Abstract**

Objective: To assess the safety of opioids in the management of osteoarthritis (OA) in a systematic review and meta-analysis of randomized, placebo-controlled trials.

Methods: A comprehensive literature search was undertaken in the databases MEDLINE, Cochrane Central Register of Controlled Trials (Ovid CENTRAL), and Scopus. Randomized, double-blind, placebo-controlled, parallel-group trials that assessed adverse events (AEs) with opioids in patients with OA were eligible for inclusion. Two authors appraised titles, abstracts and full-text papers for suitability and then assessed the studies for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcomes reporting. The primary outcomes of interest were: gastrointestinal (GI) disorders, cardiac disorders, vascular disorders, nervous system disorders, skin and subcutaneous tissue disorders, renal and urinary disorders, respiratory, thoracic and mediastinal disorders, as well as overall severe and serious AEs, and drug-related AEs. Secondary outcomes were withdrawals due to AEs (i.e. the number of participants who stopped the treatment due to AE), and total number of AEs (i.e. the number of patients who experienced any AE at least once).

Results: Database searches identified 2189 records from which, after exclusions, 17 papers were included in the meta-analysis. More disorders of the lower gastrointestinal (GI) tract (constipation, fecaloma) were reported with both immediate-release (IR) and extended-release (ER) formulations of opioids versus placebo: IR opioids (relative risk [RR] = 5.20, 95% confidence interval [CI] 3.42, 7.89); ER opioids (RR = 4.22, 95% CI 3.44, 5.17). The risk of upper GI AEs increased 4-fold with ER opioids compared with placebo (RR = 4.03, 95% CI 0.87, 18.62); and the risk of nausea, vomiting or loss of appetite increased 4 to 5-fold with both formulations: IR opioids (RR = 3.39, 95% CI 2.22, 5.18); ER opioids (RR = 4.03, 95% CI 3.37, 4.83). An increased risk of dermatologic AEs (rash and pruritis) (IR opioids: RR = 3.60, 95% CI 1.74, 7.43; ER opioids: RR = 7.87, 95% CI, 5.20, 11.89) and central nervous system disorders (dizziness, headache, fatigue, somnolence, insomnia) (IR opioids: RR = 2.76, 95% CI 1.90, 4.02; ER opioids: RR = 2.76, 95% CI, 2.19, 3.47) was found with all opioid formulation versus placebo.

Conclusions: Our results confirm that there are considerable safety and tolerability issues surrounding the use of opioids in OA and support the recommendation of international and national guidelines to use opioids in OA after other analgesic options, and for short time periods.

**Key Points** (2-3 key findings and implications)

* Our analysis shows that oral opioids are associated with an increased risk of adverse events of the gastrointestinal, dermatologic, and central nervous systems when compared with placebo, regardless of whether the immediate-release or extended-release formulations are employed.
* We recommend cautious use of opioids in the treatment of osteoarthritis in light of these findings.

**1.0 Introduction**

Osteoarthritis (OA) is the most common form of joint disease and a leading cause of pain and physical disability in older people [1, 2]. OA is a progressive, degenerative disease of the synovial joints causing joint pain and functional impairment with different degrees of disease severity that requires long-term management with various treatment options over the course of the disease [3]. Opioids are potent analgesics that work by targeting mainly spinal and supra-spinal opioid receptors. Cellular studies suggest that there are peripheral opioid receptors in inflamed osteoarthritic synovial tissue which may mediate analgesic effects [4]. Opioid prescription for OA is certainly common [5], but prescribing practices vary widely [6]. Opioids may be considered in OA if the pain is severe, or if other analgesics are contraindicated [7].

However, evidence regarding the safety and efficacy of opioids in OA is contradictory [8, 9]; and thus some guidelines regard the use of opioids in OA as uncertain (the Osteoarthritis Research Society International [OARSI]) [10], while others limit their use to the last pharmacologic option for the severely symptomatic knee OA patient before surgery (the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases [ESCEO]) [11, 12], or for patients with hip or knee OA who have had inadequate response to other therapies and are either unwilling to undergo or are not suitable candidates for surgery (the American College of Rheumatology [ACR]) [13].

A Cochrane review of oral or transdermal opioids in 22 randomized controlled trials (RCTs) up to 2012 concluded that the small mean benefit of non-tramadol opioids is contrasted by a significant increase in the risk of adverse events (AEs) [7, 14]. The estimated effect size for pain was 0.28 (standardized mean difference [SMD], 95% confidence interval [CI] -0.35, -0.20) which corresponds to a difference in pain score of 7 mm on a 100 mm visual analogue scale (VAS) between opioids and placebo; this was considered as of questionable clinical relevance since the 95% CI did not include the minimal clinically important difference (MCID) of 0.37 SMD (9 mm on a VAS) [7]. AEs were more frequent in patients receiving opioids than control: the relative risk (RR) of any AE was 1.49 (95% CI 2.93, 4.82). Patients receiving opioids were nearly 4-times as likely to withdraw due to AEs (RR = 3.76, 95% CI 3.06, 5.38), and 3-times as likely to experience a serious AE (SAE) (RR = 3.35, 95% CI 0.83, 13.56) [14].

A meta-analysis of 19 RCTs and review of opioids found that in spite of analgesic effects, many OA patients stop chronic opioid use due to AEs. Analgesic effects were significantly better than placebo in opioid-treated patients (p = 0.01) [15, 16]. However, opioid treatment was associated with a significantly increased total dropout rate (odds ratio [OR] = 1.3, 95% CI 1.2, 1.4), and discontinuation of treatment was related to AEs (OR = 4.0, 95% CI 3.4, 4.6).

A recent meta-analysis of oral and transdermal opioids for pain in musculoskeletal conditions in older patients (aged >60 years) found that opioid analgesics had only a limited effect on pain and disability. Opioids had a small effect on decreasing pain intensity (SMD = -0.27, 95% CI -0.33, -0.20), while the odds of AEs with opioids were 3-times higher (OR = 2.94, 95% CI 2.33, 3.72) and the odds of treatment discontinuation due to AEs was 4-times higher (OR = 4.04, 95% CI 3.10, 5.25) [17].

Extended-release (ER) or controlled-release (CR) formulations may improve opioid tolerability in OA patients, by preventing the high plasma peaks that are associated with the AEs observed with the immediate-release (IR) formulations [18]. A meta-analysis of 4 RCTs of patients with musculoskeletal pain found that ER tapentadol (100 to 250 mg/day) is associated with a reduction in pain intensity in comparison to placebo and oxycodone. In addition, no increase in SAEs was reported when comparing tapentadol to placebo (RR = 1.02, 95% CI 0.47, 2.16) [19].

There is a paucity of meta-analysis data assessing the relative safety of opioids in OA, for both IR and ER formulations. The objective of our study was to assess the safety of opioids in the management of OA in a systematic review and meta-analysis of randomized, placebo-controlled trials.

**2.0 Methods**

The protocol of this systematic review and meta-analysis was previously registered in the PROSPERO database (Registration number: CRD42017068249). The systematic review was performed in accordance with the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions [20]. The findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. All the review process (study selection and risk of bias assessment) was undertaken using Covidence, the Cochrane platform for systematic reviews and was performed by EC, NF, SS and LS.

**2.1 Eligibility criteria**

Randomized, double-blind, placebo-controlled, parallel-group trials which have assessed the AEs associated with oral opioids: immediate-release (IR) (codeine, oxycodone, tramadol, tapentadol IR) and extended-release (ER) (controlled-release [CR] codeine, CR oxycodone, CR tramadol, hydrocodone ER, morphine sulfate/sequestered naltrexone, OROS hydromorphone, tapentadol ER, morphine sulfate ER, oxymorphone ER), in comparison to placebo or other oral analgesic comparator drug (specifically NSAIDs, COX-2 inhibitors, paracetamol, nefopam hydrochloride, tricyclic antidepressants [amitriptyline, nortriptyline], gabapentin, pregabalin and duloxetine) in patients with OA were identified.

Studies that allowed concomitant anti-osteoarthritis treatments during the trial (other than rescue medication as paracetamol or aspirin) were then excluded, as were animal trials.

**2.2 Data sources and search strategies**

A comprehensive literature search was undertaken in the databases MEDLINE (via Ovid), Cochrane Central Register of Controlled Trials (Ovid CENTRAL) and Scopus. We searched for randomized placebo-controlled trials of opioids in OA, using a combination of study design-, treatment-, and disease-specific key words and/or Medical Subject Heading (MeSH) terms. The databases were searched from inception up to 30 June 2017.

While adverse effects were the outcomes of interest for this study, we decided to avoid the outcome-specific key words in the search strategies, because of the possibility that a study on the efficacy of a drug may have not mentioned terms related to adverse events in its title, abstract or in the keywords sections. The search was limited to English and French publications and to human subjects. Detailed search strategies for MEDLINE/CENTRAL and Scopus databases are reported as **Electronic** **Supplementary Material (ESM1)**.

Two clinical trials registries, ClinicalTrials.gov (clinicaltrials.gov/) and the World Health Organization's International Clinical Trials Registry Platform Search portal (apps.who.int/trialsearch/) were also checked for trial results that would not have been published. Finally, recent meta-analyses were also screened for any additional relevant studies.

**2.3 Study selection**

Two members of the review team independently evaluated each title and abstract to exclude only obvious irrelevant studies, according to the predefined eligibility criteria. At this step, the criteria related to adverse effects was not considered for selection, as studies focusing on the efficacy of a treatment may not report data about adverse effects in the abstract; this means that all trials mentioning only the efficacy information were retrieved at this step. After this first step, the two investigators independently reviewed each of the full-text of the articles not excluded during the initial screening stage to determine whether the studies met all selection criteria. At this stage, studies were excluded due to previously unidentified duplication, conference abstracts alone being available, the absence of a placebo arm against opioid medication in the trial, an indication other than OA, safety not being included as an outcome of the trial, a non-opioid intervention or incorrect study design. All differences of opinion regarding the selection of articles were resolved through discussion and consensus between the two investigators; any persistent disagreement was solved with the intervention of a third person (another member of the review team).

**2.4 Data extraction**

The full-texts of the selected studies were screened by independent reviewers for extraction of relevant data, using a standard data extraction form. Outcome results data were independently extracted by two investigators of the review team. For each study, the following data were extracted: Characteristics of the manuscript, characteristics of the trial, objective and design of the study, characteristics of the patients, characteristics of the disease, characteristics of the treatments, AEs (outcomes) reported during the trial, and the main conclusion of the study. In the case of multiple dosage arms for opioids being included in a trial, the maximum dose was used to categorize the study. If multiple follow-up times were included, the longest follow-up time was used to categorize the study. The raw data (number of events in each group) were extracted for each outcome. The number of patients who experienced at least once any body system related AE (e.g. nervous system, gastrointestinal system), as well as AEs within each body system (e.g. headache, abdominal pain) were extracted. As much as possible, data from the intention-to-treat (ITT) analysis were considered.

**2.5 Outcomes of interest**

The main System Organ Classes (SOCs) that are likely to be affected by the use of opioids in the treatment of OA were explored in this meta-analysis. The primary outcomes of interest were safety and tolerability outcomes, especially those associated with specific bodily systems: gastrointestinal (GI) disorders, cardiac disorders, vascular disorders, nervous system disorders, skin and subcutaneous tissue disorders, renal and urinary disorders, respiratory, thoracic and mediastinal disorders, along with overall severe and serious AEs. Secondary outcomes were: withdrawals due to AEs (i.e. the number of participants who stopped the treatment due to AE), and total number of AE (i.e. the number of patients who experienced at least once, any AE).

**2.6 Assessment of risk of bias in included studies**

Two authors of the review team independently assessed the risk of bias in each study, using the Cochrane Collaboration’s tool for risk of bias assessment [20]. The following characteristics were evaluated:

* Random sequence generation: We assessed whether the allocation sequence was adequately generated.
* Allocation concealment: We assessed the method used to conceal the allocation sequence, evaluating whether the intervention allocation could have been foreseen in advance.
* Blinding of participants and personnel: We assessed the method used to blind study participants and personnel from knowledge of which intervention a participant received and whether the intended blinding was effective.
* Blinding of outcome assessment: We assessed the method used to blind outcome assessors from knowledge of which intervention a participant received and whether the intended blinding was effective.
* Incomplete outcome data: We assessed whether participants exclusions, attrition and incomplete outcome data were adequately addressed in the paper.
* Selective outcomes reporting: We checked whether there was evidence of selective reporting of adverse events.

Each of these items was either categorized as “low risk of bias”, “high risk of bias”, or “unclear risk of bias”. “Low risk of bias” or “High risk of bias” was attributed for an item, when there was sufficient information in the manuscript to judge the risk of bias as “Low” or “High”; otherwise, “Unclear risk of bias” was attributed to the item. Disagreements were solved by discussion between the two reviewers during a consensus meeting and involved, when necessary, another member of the review team for final decision.

**2.7 Data analysis**

Analyses were performed using STATA 14.2 software. The units of analysis were the number of participants experiencing a specific AE. We described harms associated with the treatment as risk ratio (RR) with 95% confidence interval (95% CI). We computed an overall effect size for each primary or secondary outcome (AE). Anticipating substantial variability among trial results (i.e. the inter-study variability), we assumed heterogeneity in the occurrence of the AEs; thus, we planned to use random-effects models for the meta-analyses. We estimated the overall effects and heterogeneity using the DerSimonian and Laird random-effects model [22]. As this method provides biased estimate of the between-study variance with sparse events [23, 24], we also performed the meta-analyses using the Restricted Maximum Likelihood (REML) method [25].

We tested heterogeneity using the Cochran’s Q test. As we are performing a random-effect meta-analysis, we used the Tau-squared (Tau²) estimate as the measure of the between-study variance. The I-squared (I²) statistic was used to quantify heterogeneity, measuring the percentage of total variation across studies due to heterogeneity [26]. In the case of substantial heterogeneity, we pre-specified to undertake subgroup analyses, stratifying the analyses according to: participants’ age in the intervention group, duration of OA complain, location of OA (knee, hand, hip), number of joints involved, drug dose, duration of the treatment, combination of the opioid analgesic with other analgesic, analgesic potency of the opioid (stronger vs weaker); pharmacologic activity of the opioid analgesic (opioid receptors agonist only vs. opioid receptors agonist with other pharmacologic activity); risk of bias in the study (e.g. studies with low risk of bias versus all other studies). The quality of each evidence was assessed using the GRADE approach [27] and a summary of findings table was prepared using the GRADEpro online software [28].

**3.0 Results**

**3.0.1 Study selection**

Database searches initially identified 2189 records. After exclusions, 61 articles were screened in full against the inclusion criteria. A flowchart (**Figure 1**) with the number of studies at each step was established, including the reasons for excluding studies during the full-text reading process. Twenty-seven of these met the eligibility criteria, of which a further 6 were excluded as the trial lacked a placebo arm, and 4 were excluded as the reported outcomes were not relevant to the meta-analysis. Finally, 17 papers were included in the analysis of main study outcomes [29-45].

**3.0.2 Study characteristics**

**Table 1** presents the characteristics of the studies included through the systematic review process. The year of publication of the included studies ranged from 1998–2015 and the follow-up time ranged from 10 days to 16 weeks. Twelve studies included ER or CR formulations of opioids and 5 studies included IR opioids. The numbers of trials including an arm for each specific opioid (or 2 arms if 2 opioids were included) are as follows: tramadol 8, oxycodone 6, tapentadol 2, hydromorphone 2 and hydrocodone 1 trial. The anatomical regions included per trial are as follows: knee 15, hip 10, spine 1, any location 2, low back pain 1, or awaiting joint replacement in 2 trials.

**3.0.3 Risk of bias of individual studies**

**Figures 2 and 3** include a summary of the risk of bias assessed for each study included in the meta-analysis, and the majority of our findings were associated with a “moderate” to “high” certainty of evidence, with the exception of total AEs (“low” certainty of evidence). Forest plots for analyses are reported in the **Electronic Supplementary Material (ESM2)**.

**3.1 Primary outcomes**

We reported only the results from the DerSimonian and Laird random-effects model, because we found no difference in the effects computed by the 2 methods.

Too few studies reported data on severe or serious AEs (SAEs) (2 studies of IR, 2 studies of ER) or drug-related AEs (1 study of IR and no studies of ER) for opioids versus placebo, and thus the relative risk could not be calculated in this meta-analysis. The primary outcomes for SOC-related AEs are reported separately for IR and ER opioid formulations.

* + 1. **Immediate-release opioids**

The relative risk of lower GI AEs (constipation or fecaloma) was significantly increased 5-fold with IR opioids versus placebo (RR = 5.20, 95% CI 3.42, 7.89; I2 = 0%) (**ESM2**). The combined relative risk of nausea, vomiting or loss of appetite was significantly increased with IR opioids vs. placebo (RR = 3.39, 95% CI 2.22, 5.18; I2 = 37.1%). The risk of dry mouth or oral ulceration was increased with IR opioids (RR = 4.43, 95% CI 0.92, 21.24; I2 = 47.5%), though this did not reach statistical significance. The relative risk of upper GI complications with IR opioids could not be calculated as there was insufficient data reported in RCTs versus placebo.

The risk of AEs of the central nervous system (CNS) including dizziness, headache and other “consciousness-related” AEs (including insomnia/drowsiness/sedation/fatigue) was significantly increased with IR opioids compared with placebo (RR = 2.76, 95% CI 1.90, 4.02; I2 = 45.5%).

A significantly increased risk of dermatological AEs (rash and pruritus) was measured with IR opioids versus placebo (RR = 3.60, 95% CI 1.74, 7.43; I2 = 37.8%).

* + 1. **Extended-release opioids**

The relative risk of lower GI AEs (constipation) was significantly increased with ER opioids versus placebo (RR = 4.22, 95% CI 3.44, 5.17; I2 = 24.5%) (**ESM2**). The combined relative risk of nausea, vomiting or loss of appetite was significantly increased with ER opioids vs placebo (RR = 4.03, 95% CI 3.37, 4.83; I2 = 33.4%). The risk of dry mouth or oral ulceration was significantly increased with ER opioids vs. placebo (RR = 3.00, 95% CI 1.85, 4.86; I2 = 8.1%). The relative risk of upper GI AEs (dyspepsia, gastritis, heartburn) was increased with ER opioids versus placebo (RR = 4.03, 95% CI 0.87, 18.62; I2 = 0%) though this did not reach statistical significance.

The risk of AEs of the CNS was significantly increased with ER opioids compared with placebo (RR = 2.76, 95% CI 2.19, 3.47; I2 = 72.9%). The relative risk of specific CNS AEs was as follows: headache (RR = 0.98, 95% CI 0.83, 1.16; I2 = 0%); dizziness (RR = 3.63, 95% CI 2.98, 4.41; I2 = 0%); other (fatigue, somnolence, insomnia, weakness, nervousness) (RR = 3.63, 95% CI 2.90, 4.53; I2 = 14.9%).

A significantly increased risk of dermatological AEs (rash and pruritus) was measured with ER opioids versus placebo (RR = 7.87, 95% CI 5.20, 11.89; I2 = 0%).

* 1. **Secondary outcomes**

For total AEs, a significant increased risk of AEs was found with ER opioids compared with placebo (RR = 1.70, 95% CI 1.37, 2.12; I2 = 79.6%) (**ESM2**). There was insufficient data collected on total AEs with IR opioid formulations versus placebo to allow comparison in this meta-analysis.

Heterogeneity in the reporting of withdrawal rates due to AEs between trials, with some articles reporting ‘discontinuations’, ‘withdrawn from study’ and an insufficient number providing a clear indication of withdrawals due to AEs meant that there was insufficient data to include withdrawal rate in the meta-analysis.

**3.3 GRADE assessment of findings**

We assessed the certainty of evidence for each primary or secondary outcomes for opioids compared with placebo, using the GRADE approach [27]. Our findings were associated largely with “moderate” to “high” certainty of evidence, with the exception of total AEs with ER opioids for which there was low certainty of evidence. Additionally, for many outcomes there were too few or no studies reporting on these outcomes for the GRADE analysis to be performed. **Tables 2** and **3** summarize the findings for IR and ER opioids for all outcomes assessed in this meta-analysis.

**4.0 Discussion**

Overall, our meta-analysis found a significantly increased risk of lower GI, nausea/vomiting/loss of appetite, CNS and rash/pruritus in both IR and ER opioids compared with placebo. In addition, we found a significantly increased risk of dry mouth/oral ulceration, and total AEs with ER formulations of opioids compared with placebo. This level of risk is comparable to the findings of a Cochrane meta-analysis of oral and transdermal (non-tramadol) opioids for OA of the knee or hip ([7] and a recent systematic review and meta-analysis of older people (aged ≥60 years) with musculoskeletal pain [17]). These results may reflect physiological changes in pain processing, pharmacokinetics, and pharmacodynamics in the aging population.

Insufficient data were reported on total AEs and upper GI complications with IR formulations of opioids versus placebo to allow inclusion of a comparison in our meta-analysis. Controlled-, sustained-, and extended-release formulations are designed to avoid the peaks (and troughs) of plasma drug concentrations that are associated with the tolerability issues of IR formulations. A 5-fold increased risk of lower GI AEs (constipation), 3-fold combined increase in nausea, vomiting and loss of appetite, and 3-fold increase in dermatological AEs was measured with IR opioids as compared with placebo.

Our analysis demonstrates that ER opioid formulations are nonetheless associated with a higher rate of AEs compared with placebo: 4-fold increase in lower GI AEs, 4-fold increase in nausea, vomiting and loss of appetite, 3-fold increase in dry mouth or ulceration, and 7-fold increase in dermatological AEs (rash or pruritis). A significantly increased risk of CNS AEs occurred with both IR and ER opioids (RR = 2.76 for each group), largely relating to sedation, drowsiness, fatigue, dizziness and headache.

Tramadol is a centrally-acting weak opioid analgesic with a dual mode of action as an agonist of the μ-opioid receptor and as a noradrenaline reuptake inhibitor, which rarely causes the AEs of respiratory depression and physical dependence commonly associated with conventional opioid drugs [46]. A review of tramadol found a small but statistically significant benefit for tramadol over placebo in OA (number needed to treat to benefit [NNTB] = 6, 95% CI 4, 9); however, the high level of reversible and not life-threatening AEs reported (number needed to treat to harm [NNTH] = 8, 95% CI 7, 12) often caused the participant to withdraw (12.5% of patients on tramadol) which could limit its usefulness in clinical practice [15]. Our analysis included tramadol in both IR and controlled-release (CR) formulations. As an IR formulation, tramadol was associated with GI side effects (constipation, nausea, vomiting), CNS AEs (dizziness, headache, fatigue, insomnia, somnolence) and dermatological AEs (itching and pruritus). The CR formulation of tramadol (200 – 400 mg) was a major contributor to the significantly higher rate of AEs observed with all ER formulations (hydromorphone, oxycodone) included in our study compared with placebo (RR = 1.70, 95% CI 1.37, 2.12). There is some evidence to suggest that the rate of AEs with tramadol can be minimized with slow upward titration of an ER formulation, to improve tolerability and thus avoid premature treatment discontinuations [47].

Tapentadol, has a dual mechanism of action like tramadol, but unlike tramadol it has only weak effects on the reuptake of serotonin and is a significantly more potent opioid with no known active metabolites [48, 49]. Tapentadol ER (75 mg 4-6 hourly and 100-250 mg/day) in two studies included in our meta-analysis was also associated with a higher risk of AEs, including GI disorders (constipation, nausea, vomiting, dry mouth, oral ulceration), CNS disorders (dizziness, somnolence, fatigue) and dermatological AEs (rash and pruritus) compared with placebo. In an analysis of 4 studies of tapentadol ER versus placebo or oxycodone in patients with OA or back pain, tapentadol ER was associated with a 2.7-fold increase in risk of discontinuation due to AEs compared with placebo, but with a 50% reduction in risk of discontinuation due to AEs compared with oxycodone [19].

**4.1 Limitations**

Around half of the studies identified that met the inclusion criteria did not provide AE data suitable for inclusion in the meta-analysis. Many studies lacked detail on AE reporting and there was variation between studies regarding nomenclature and grouping of AEs e.g. “common adverse events”, or “those experienced in >5%”. These different names and grouping of AEs may lead to lack of resolution, and possible double counting. In combining different drugs and doses into one meta-analysis, we have chosen the highest dose when multiple doses were presented in a trial, e.g. “tramadol ER 100mg/200mg/300mg/**400mg**”, which could lead to an exaggeration of AEs. Sensitivity analysis of the two approaches (highest dose, versus multiple dose) revealed only marginal differences in the magnitude of the outcome. Included studies were of short duration, only 2 to 18 weeks. Our analysis was limited to studies in OA patients; thus, safety issues could be missed in relevant subgroups e.g. other musculoskeletal pain, back pain. Our meta-analysis did not examine IR against ER formulations; however, this could be a potential avenue of future research.

**5.0 Conclusions**

In our meta-analysis, oral opioids were associated with an increased risk of GI, CNS and dermatological AEs compared with placebo, for both the IR and ER formulations. The frequent occurrence of side effects limits the use of opioids due to poor tolerability and high rates of treatment withdrawal. To maximize the risk: benefit of opioids, the ESCEO recommends that opioids should only be used as a step 3 treatment for severely symptomatic OA patients, preferably as short-term treatment with a weak opioid [11]. In conclusion, our results confirm that there are considerable safety and tolerability issues surrounding the use of opioids in OA and support the recommendation of international and national guidelines to reserve the use of opioids in OA to the last resort pharmacologic therapy before surgery [10-13].

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***Compliance with ethical standards***

All authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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**Declaration of interests**

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**Table 1** Characteristics of the studies included through the systematic review process

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Location of OA** | **Age of participants by study group (Mean ± SD or Median [P25-P75])** | **Active treatment** | **Dose** | **Trial duration** | **Data provided in the article****(Type of AE)** |
| Afilalo 2010 [29] | knee | Placebo 58.2 (9.15) / active 58.4 (10.09) | tapentadol ER | 100-250 mg od | 12 weeks | TEAEs reported, covering some SOCs (headache, GI disorders overall, pruritis, vomiting, somnolence, fatigue, nervous system disorders, constipation, diarrhea, dry mouth, dizziness, nausea) |
| Afilalo 2010 [29] | knee | Placebo 58.2 (9.15) / active 58.2 (10.29) | CR oxycodone | 20-50 mg od | 12 weeks | TEAEs reported, covering some SOCs (nervous system disorders, diarrhea, headache, nausea, GI disorders overall, constipation, somnolence, fatigue, dizziness, dry mouth, vomiting, pruritis) |
| Burch 2007 [30] | knee | Placebo 62 (9) / active 62 (9) | CR tramadol | 200-300 mg od | 12 weeks | AEs and TEAEs reported, covering some SOCs (overall discontinuation, somnolence, constipation, overall adverse event, nausea, dizziness/vertigo) |
| DeLemos 2011 [31] | hip/knee | Placebo 58.9 (11.6) / active 59.5 (10.2) - tramadol 100 mg od;Placebo 58.9 (11.6) / active 62.0 (9.9) - tramadol 200 mg od;Placebo 58.9 (11.6) / active 59.7 (11.4) - tramadol 300 mg od | CR tramadol | 100 mg od 200 mg od 300 mg od | 12 weeks | AEs and TEAEs covering some SOCs, plus discontinuations reported (at least one AE occurred, nervousness, flushing, diarrhea, fatigue, vomiting, dizziness, headache, anorexia, constipation, nausea, somnolence, dry mouth, upper respiratory tract infection, insomnia, pruritus) |
| Fishman 2007 [32] | knee | Placebo 61 (10) / active 63 (8) - tramadol 100 mg od;Placebo 61 (10) / active 61 (9) - tramadol 200 mg od;Placebo 61 (10) / 60 (9) - tramadol 300 mg od | CR tramadol | 100 mg od 200 mg od 300 mg od | 12 weeks | TEAEs reported, including deaths and discontinuations of treatment (constipation, insomnia, somnolence, small bowel obstruction, gastritis, discontinuation due to AE, dry mouth, vomiting, dizziness/vertigo, nausea, sweating, pruritis, lower abdominal pain, headache, death from myocardial infarction) |
| Fleischmann 2001 [33] | knee | Placebo 62.45 (9.62) / active 62.52 (8.68) | tramadol | 200-400 mg od | 91 days | TEAEs not by SOC and discontinuations reported (pruritus, nausea, constipation, dizziness, headache) |
| Friedmann 2011 [34] | hip and/or knee | Placebo 58.5 (8.44) / active 58.0 (7.86) | oxycodone | 20 mg bid | 12 weeks | TEAEs not by SOC and discontinuations reported (SAE, dizziness, pruritus, dry mouth, somnolence, vomiting, headache, fecaloma, orthostatic hypotension, nausea) |
| Gana 2006 [35] | hip/ knee | Placebo 56.4 (9.8) / active 58.4 (10.9)- tramadol 100 mg od;Placebo 56.4 (9.8) / active 59.1 (9.9) - tramadol 200 mg od;Placebo 56.4 (9.8) / active 58.5 (9.4) - tramadol 300 mg od;Placebo 56.4 (9.8) / active 58.4 (9.7) - tramadol 400 mg od | tramadol | 100 mg od 200 mg od 300 mg od 400 mg od | 12 weeks | TEAEs not by SOC and discontinuations due to AEs reported (postural hypotension, sweating increase, anorexia, flushing, dizziness, insomnia, diarrhea, somnolence, dry mouth, pain, nausea, vomiting, fatigue, headache, pruritus, constipation) |
| Hale 2015 [36] | any site or low back pain | Placebo 52.7 (12.1) / active 53.6 (10.4) | hydrocodone ER | 15-90 mg bid | 12 weeks | TEAEs not by SOC, SAEs and discontinuations due to AEs reported (dry mouth, constipation, upper respiratory tract infection, nausea, pruritus, somnolence, headache, back pain, dizziness, vomiting, pancreatitis, fatigue) |
| Hartrick 2009 [37] | awaiting joint replacement | Placebo 62.0 (20-79) / active 62.0 (41-79) | CR oxycodone | 10 mg, 4-6 hourly | 10 days | TEAEs not by SOC and discontinuations due to AEs reported (fatigue, diarrhea, somnolence, vomiting, nausea, headache, dizziness, pruritus, constipation) |
| Hartrick 2009 [37] | awaiting joint replacement | Placebo 62.0 (20-79) / active 60.0 (31-79) - tapentadol ER 50 mg; Placebo 62.0 (20-79) / active 61.5 (34-78) - tapentadol ER 75 mg | tapentadol ER | 50 mg 4-6 hourly 75 mg 4-6 hourly | 10 days | TEAEs not by SOC and discontinuations due to AEs reported (fatigue, dizziness, headache, nausea, vomiting, pruritus, diarrhea, constipation, somnolence) |
| Malonne 2004 [38] | hip/ knee | Placebo 66.4 (9.2) / active 67.1 (7.1) | CR tramadol | 200 mg od | 2 weeks | TEAEs not by SOC and discontinuations due to AEs reported (diarrhea, somnolence, vomiting, drunken feeling, increased sweating, nausea, asthenia, malaise, constipation, headache, heartburn, epigastric pain, dizziness) |
| Markenson 2005 [39] | any site | Placebo (mean [range]) 64 (41-89) / active (mean [range]) 62 (38-88) | CR oxycodone | 10-60 mg bid | 90 days | TEAEs not by SOC and discontinuations due to AEs reported (dizziness, diarrhea, somnolence, constipation, vomiting, increased sweating, nausea, pruritus, headache) |
| Matsumoto 2005 [40] | hip/ knee | Placebo 61.7 (1.0) / active 62.7 (1.0) - CR oxycodone 20 mg bid; Placebo 61.7 (1.0) / active 61.4 (1.0) - CR oxycodone 40 mg bid | CR oxycodone | 20mg bid 40mg bid | 4 weeks | TEAEs not by SOC and discontinuations due to AEs reported (dizziness, pruritus, constipation, headache, dry mouth, nausea, somnolence, vomiting) |
| Rauck 2013 [41] | knee/ hip | Placebo 60.0 (11.2) / active 59.7 (10.6) - hydromorphone 8 mg od; Placebo 60.0 (11.2) / active 59.5 (10.7) - hydromorphone 16 mg od | OROS hydromorphone | 8 mg od 16 mg od | 12 weeks | TEAEs not by SOC and discontinuations due to AEs reported (headache, nausea, vomiting, constipation, somnolence, pruritus, dizziness) |
| Roth 1998 [42] | hip/knee/spine | Placebo 67.0/ active 65.9 | tramadol | 50-400 mg od | 13 days | TEAEs not by SOC and discontinuations due to AEs reported (dizziness, headache, insomnia, constipation, cold sweats, itching, diaphoresis, vomiting, lightheadedness, dry mouth, nausea, drowsiness, sedation) |
| Spierings 2013 [43] | hip/knee | Placebo 57.2 (28-75) / active 57.6 (33-75) | oxycodone | 10-40 mg bid | 16 weeks | TEAEs not by SOC and discontinuations due to AEs reported (somnolence, nasopharyngitis, peripheral burning sensation, hypoesthesia, dysesthesia, hyperesthesia, paresthesia, vomiting, headache, fatigue, hypertension, pruritus, dizziness, arthralgia, constipation, nausea, peripheral neuropathy, decreased vibratory sense) |
| Vojtassak 2011 [44] | hip/knee | Placebo 66.0 (40-87) / active 65.0 (43-85) | OROS hydromorphone | 4-32mg od | 12 weeks | TEAEs not by SOC, SAEs and discontinuations due to AEs reported (constipation, nausea & vomiting) |
| Vorsanger 2007 [45] | hip/knee | Placebo 68.6 (2.4) / active 69.4 (3.0) - CR tramadol 100 mg od;Placebo 68.6 (2.4) / active 69.2 (2.6) - CR tramadol 200 mg od;Placebo 68.6 (2.4) / active 68.9 (2.7) - CR tramadol 300 mg od;Placebo 68.6 (2.4) / active 69.1 (2.8) - CR tramadol 400 mg od | CR tramadol | 100 mg od 200 mg od 300 mg od 400 mg od | 12 weeks | TEAEs not by SOC and discontinuations due to AEs reported (vomiting, nausea, dry mouth, back pain, postural hypotension, abnormal dreams, dizziness, fatigue, pain in the limb, pruritus, flushing, insomnia, sweating increased, constipation, weight decreased, dyspepsia, weakness, arthralgia, appetite decreased, nasopharyngitis, somnolence, nervousness, headache, pain, anorexia) |

AE, adverse event; ALT, alanine aminotransferase; BP, blood pressure; CV, cardiovascular; GI, gastrointestinal; OA, osteoarthritis; SOC, System Organ Class; SBP; systolic blood pressure; TEAEs, treatment-emergent adverse events

**Table 2 Summary of safety findings for immediate release opioids versus placebo in patients with osteoarthritis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes†** | **№ of participantsFollow-up** | **Certainty of the evidence(GRADE)** | **Relative effect(95% CI)** | **Anticipated absolute effects** |
| **Risk with placebo** | **Risk difference with Immediate release opioids**  |
| Lower gastrointestinal AEs | 1,700 | ⨁⨁⨁⨁HIGH  | **RR 5.20**(3.42 to 7.89)  | 27 per 1000  | **114 more per 1000**(66 more to 187 more)  |
| Nausea, vomiting, loss of appetite  | 2,447  | ⨁⨁⨁⨁HIGH  | **RR 3.39**(2.22 to 5.18)  | 45 per 1000  | **108 more per 1000**(55 more to 189 more)  |
| Dry mouth or oral ulceration  | 860  | ⨁⨁⨁◯MODERATE a | **RR 4.43**(0.92 to 21.24)  | 9 per 1000  | **32 more per 1000**(1 fewer to 187 more)  |
| Central nervous system AEs  | 5,012 | ⨁⨁⨁⨁HIGH  | **RR 2.76**(1.90 to 4.02)  | 36 per 1000  | **64 more per 1000**(33 more to 109 more)  |
| Rash or pruritus  | 1,695 | ⨁⨁⨁⨁HIGH  | **RR 3.60**(1.74 to 7.43)  | 25 per 1000  | **65 more per 1000**(18 more to 160 more)  |
| **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). †The outcomes total AEs, serious AEs, treatment-emergent AEs, upper gastrointestinal, cardiovascular or cerebrovascular, renal and hepatic, and death were reported in either no or too few studies to analyze. AE, adverse event; CI, Confidence interval; RR, Risk ratio  |
| **GRADE Working Group grades of evidence****High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect  |

**Explanations**

a. Large confidence interval

**Table 3 Summary of safety findings for extended release opioids versus placebo in patients with osteoarthritis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes†** | **№ of participantsFollow-up** | **Certainty of the evidence(GRADE)** | **Relative effect(95% CI)** | **Anticipated absolute effects** |
| **Risk with placebo** | **Risk difference with Extended release opioids**  |
| Total AEs  | 1,915  | ⨁⨁◯◯LOW a | **RR 1.70**(1.37 to 2.12)  | 361 per 1000  | **252 more per 1000**(133 more to 404 more)  |
| Upper GI AEs | 1,119  | ⨁⨁⨁◯MODERATE b | **RR 4.03**(0.87 to 18.62)  | 0 per 1000  | **0 fewer per 1000**(0 fewer to 0 fewer)  |
| Lower GI AEs | 6,472  | ⨁⨁⨁⨁HIGH  | **RR 4.22**(3.44 to 5.17)  | 52 per 1000  | **186 more per 1000**(134 more to 254 more)  |
| Nausea, vomiting, loss of appetite  | 10,920  | ⨁⨁⨁⨁HIGH  | **RR 4.03**(3.37 to 4.83)  | 46 per 1000  | **141 more per 1000**(110 more to 178 more)  |
| Dry mouth or oral ulceration  | 2,956  | ⨁⨁⨁⨁HIGH  | **RR 3.00**(1.85 to 4.86)  | 18 per 1000  | **35 more per 1000**(15 more to 68 more)  |
| Central nervous system AEs  | 20,266  | ⨁⨁⨁◯MODERATE c | **RR 2.76**(2.19 to 3.47)  | 51 per 1000  | **90 more per 1000**(61 more to 126 more)  |
| Rash or pruritus  | 4,403  | ⨁⨁⨁⨁HIGH  | **RR 7.87**(5.20 to 11.89)  | 11 per 1000  | **77 more per 1000**(47 more to 122 more)  |
| **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). †The outcomes serious AEs, treatment-emergent AEs, cardiovascular or cerebrovascular, renal and hepatic, and death were reported in either no or too few studies to analyze.AE, adverse event; CI, confidence interval; RR, risk ratio  |
| **GRADE Working Group grades of evidence****High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect  |

**Explanations**

a. I² > 75% (p<0.001)

b. Large confidence interval

c. I² between 50% and 75% (p<0.001)

**Figure 1** Flowchart of the study selection process



**Figure 2** Risk of bias summary: review authors' judgements about each risk of bias item for each included study



**Figure 3** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies)



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