Short and long-term efficacy and safety of oral and transdermal opioids for musculoskeletal pain in older adults: a systematic review of randomized, placebo-controlled trials

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Introduction
The controversy regarding the efficacy of paracetamol in musculoskeletal conditions (Machado et al., 2015; Roberts et al., 2015; Zhang et al., 2010) and the concerns about both the efficacy (Enthoven, Roelofs, Deyo, van Tulder, & Koes, 2016; Roelofs, Deyo, Koes, Scholten, & van Tulder, 2008) and safety of long-term use of NSAIDs (Trelle et al., 2011; Whelton, 1999; Wolfe, Lichtenstein, & Singh, 1999) have placed opioid analgesics as a necessary drug in the musculoskeletal pain management for some patients. Recent meta-analyses have shown evidence of a modest short-term efficacy of opioids treating chronic low back pain (Chaparro et al., 2013) and knee or hip osteoarthritis (Nuesch, Rutjes, Husni, Welch, & Juni, 2009), however, no long-term benefits were found in patients with physical chronic pain (>3 months) (Chou et al., 2015). In older adults, even though some clinical trials have shown evidence of short-term efficacy in hip and knee osteoarthritis (Rosenthal, Silverfield, Wu, Jordan, & Kamin, 2004; Vorsanger, Xiang, Jordan, & Farrell, 2007), back pain (Ringe et al., 2002; Sasaki, Weil, Ross, & Nicholson, 2007) and chronic pain (Sasaki et al., 2007) and less likelihood of abuse or misuse behaviours compared to younger adults (Papaleontiou et al., 2010), the higher rates of adverse events frequently prevents the use of opioids. One in four opioid-treated patients enrolled in clinical trials involving older adults discontinued treatment because of an adverse event (Papaleontiou et al., 2010).

Opioids have long been considered powerful pain relievers, acting by binding opioid receptors in central nervous system and at presynaptic sites (Inturrisi, 2002). Believing that opioid therapy can relieve pain and improve mood and functioning in many patients, experts and organizations have broadly supported their use for non-cancer chronic pain (Ballantyne & Mao, 2003; Chou et al., 2009), despite the lack of evidence. In older adults with persistent pain, the use of opioids is also recommended by the American Geriatrics Society (American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older, 2009), which states that the benefits of opioids clearly outweigh risks and burden, even acknowledging the low quality of evidence for this recommendation. In the United States, a population-based survey found that approximately 2 per cent of the respondents reported opioid use for at least one month. Arthritis and back pain were the most
prevalent chronic conditions among opioid users (Hudson, Edlund, Steffick, Tripathi, & Sullivan, 2008). In the recent decades, clinicians have become exceedingly opioid-centred in the management of chronic musculoskeletal pain, raising concerns about the rise in opioids prescription in Australia and in the United States (Leong, Murnion, & Haber, 2009; Okie, 2010). The use of opioids is associated with several adverse events such as constipation, nausea and vomiting, sedation, impaired judgment, impaired psychomotor function (Makris, Abrams, Gurland, & Reid, 2014) and increased risk of falls (Buckeridge et al., 2010). Moreover, the long-term use of opioids may result in dysfunction of the hypothalamo-hypophiseal-adrenal axis (Lee, Ludwig, & Duerksen, 2002) and hypogonadism (Daniell, 2002).

The literature regarding the efficacy and safety of opioid use in older patients with musculoskeletal pain is unclear, particularly considering that older adults are often excluded from clinical trials (Bartlett et al., 2005; Paeck et al., 2014). There is a small number of primary studies addressing the opioid use in older patients and some of them were conducted in patients with cancer (Abdulla et al., 2013). The aim of this systematic review is to investigate the efficacy and safety of opioids in older adults with musculoskeletal pain. Only placebo-controlled trials will be included as they are considered the highest standard of evidence for medication use (Freedman, 1990).

**Health Care Question (PICO):**
1. In older adults with musculoskeletal pain, does the use of oral/transdermal opioids, compared to placebos, improve pain intensity, disability or quality of life?
2. In older adults with musculoskeletal pain, does the use of oral/transdermal opioids, compared to placebos, increase the risk of adverse events?

**Methods**

**Data sources and searches**

This systematic review will be conducted following the PRISMA statement (Liberati et al., 2009). A systematic electronic search will be performed in the following databases: Cochrane Library, MEDLINE, EMBASE, Web of Science, AMED, CINAHL and LILACS. A combination of relevant
keywords will be used to construct the search strategy: opioids, opiate, narcotics, acetyldihydrocodeine, alfentanil, allylprodine, alphamethylfentanyl, alphaprodine, benzylmorphine, betaprodine, beztiamide, buprenorphine, butorphanol, bremazocine, carfentanil, codeine, contin, dextromoramide, dextropropoxyphene, dezocine, diacetylmorphine, diamorphine, dihydrocodeine, dihydromorphone, dihydromorphine, diphenoxylate, dipipanone, enadoline, ethylketazocine, ethylmorphine, levomethadyl, levomethorphanol, levorphanol, loperamide, meperidine, meptazinol, methadone, methadyl, methylmorphine, morphine, nalbuphine, nicocodeine, nicomorphine, normorphine, noscapine, ohmefentanyl, oripavine, oxycodone, oxycontin, oxymorphone, papaveretum, papaverin, pentazocine, percoct, peronine, pethidine, phenazocine, phencyclidine, pholcodine, piritramide, prodine, promedol, propoxyphene, and remifentanil for opioids; low back pain, sciatica, vertebral compression fracture, vertebral osteoporotic fracture, fragility fracture, spinal stenosis, lumbar stenosis, osteoarthritis, gonarthritis, coxarthrosis, neck pain, cervical spondylosis, cervical stenosis, shoulder pain, shoulder osteoarthritis, capsulitis adhesive, frozen shoulder, rotator cuff tear, rotator cuff tendinitis, rotator cuff syndrome, shoulder tendinitis; shoulder bursitis; fibromyalgia; myofascial pain syndrome and chronic musculoskeletal pain for musculoskeletal conditions; and placebo, randomized, and controlled trial for study design. Hand searching will be also performed on included studies and relevant systematic reviews. The first screening of potential relevant records will be conducted by one author based on titles and abstract, and two authors will independently perform the final selection of included trials based on full text evaluation. Consensus between the two reviewers will be used to resolve any disagreement.

**Study selection**

Only randomized controlled trials comparing the efficacy of opioids versus placebo will be included. To be eligible, trials have to include participants with acute or chronic musculoskeletal pain conditions and have a mean study population age of 60 or older. Studies that included patients with neuropathic pain (except sciatica), failed back surgery syndrome, post-operative or cancer pain will be excluded. Studies including population with mixed musculoskeletal and non-musculoskeletal chronic pain will be also excluded, unless separated data are reported for
musculoskeletal conditions. Trials will be eligible for inclusion when reporting at least one of
the following primary outcome measures: **pain intensity, disability status, and quality of life.**
Secondary outcomes measures will be adverse events, patient adherence, and use of rescue
medication.

**Data extraction and quality assessment**
Using a standardized data extraction form, study characteristics (details of participants,
interventions, and outcomes) will be extracted from the included trials. For the primary
outcome measures, means, standard deviations, and sample sizes will be extracted. Mean
estimates will be extracted in the following hierarchical order: mean differences, change scores,
and final values. For our secondary outcomes, the number of cases and the total sample size
will be extracted.

The quality of evidence for each outcome will be assessed across studies using the Grading of
Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt et al.,
2008). The outcomes of interest will be ranked according to their clinical relevance as of limited
importance, important, or critical for decision making (Guyatt et al., 2011). The quality of
evidence for each outcome will be defined as: high quality, moderate quality, low quality, and
very low quality (Guyatt et al., 2008). The quality of evidence can be downgraded by one or two
levels according to the following criteria: study limitations (lack of allocation concealment, lack
of blinding, incomplete account of patients and outcomes events, selective outcome reporting
bias or other limitations), inconsistency of results (statistically significant heterogeneity [I²
>50%] or ≤75% of trials with findings in the same direction), and imprecision (wide confidence
intervals or total number of participants <300 for each pooled analysis). The indirectness
criterion will not be considered in this review because we will include a specific population with
relevant outcomes and direct comparisons. The publication bias criterion will be considered
when enough trials are included in each meta-analysis. Similarly, the quality of evidence can be
upgrader by one level when there is a large effect; evidence of a dose response gradient; and
when all plausible confounding would reduce a demonstrated effect or would suggest a
spurious effect when results show no effect. Single trials will be considered inconsistent and
provided “moderate quality” evidence. They can be further downgraded to “low” or “very low”
if there is also imprecision and limitation of study design. The quality of evidence will be defined as: high quality, moderate quality, low quality, and very low quality.

**Data synthesis and analysis**

The outcomes will be grouped according to: a) follow-up duration: immediate-term (≤two weeks), short-term (>two weeks but ≤three months), intermediate-term (>three months but ≤12 months), and long-term (>12 months); b) source of pain: spinal conditions, hip and knee osteoarthritis, or other musculoskeletal conditions. When more than one scale to measure pain is reported, we will extract the more severe estimate reported at baseline. Scores for pain and disability will be converted to 0 (no pain or disability) to 100 (worse pain or disability) scales, if presented on different scales across included studies. Pooled analyses will be conducted using random-effects model and results presented as weighted mean differences and 95% confidence intervals. The $I^2$ statistic was used to assess heterogeneity between trials, and values higher than 50% will be used to identify high heterogeneity (Higgins & Thompson, 2002). The random-effects model will be used to pool estimates for each analysis obtained with Comprehensive Meta-Analysis version 2.2.064 (Englewood, NJ, USA, 2011).

**Subgroup analysis:**

When possible, subgroup analyses will be conducted based on duration of pain: acute pain or sub-acute pain (<3 months) vs. chronic pain (>3 months) and morphine equivalent dose per day.

**Timeline**

**Milestones**

Development of the search strategies – by the end of March

Extraction of the relevant papers – by mid-April

Data extraction – by the end of May

Data synthesis and analysis – by the end of June

Manuscript drafting – by the end of July
Manuscript review and submission to peer-reviewed journals – by the end of August

**Timetable**

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**References**


