Short, Intermediate, and Long-Term Effects of Opioids on Pain Intensity in Patients with Osteoarthritis or Low Back Pain: A Systematic Review and Meta-Analysis

by

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Abstract

Chronic opioid use is associated with the development of hyperalgesia, which may end up attenuating any analgesic benefits over long-term therapy. We wanted to determine whether the analgesic efficacy of opioids compared to control therapy for osteoarthritis and chronic lower back pain differed over short, intermediate, and long-term treatment duration. After publishing our review protocol, we conducted a systematic electronic search in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and Scopus, and extracted relevant papers on September 5, 2019. After dual title/abstract and full text screenings, we were left with 25 eligible randomized controlled trials that enrolled patients with either osteoarthritis and/or chronic lower back pain and compared opioid therapy to placebo/opioid-minimized pain management. Of these, 9 studies employed an "enriched-enrolment randomized-withdrawal design" where opioids were introduced in all participants and then withdrawn in those randomized to the placebo arm. These studies were excluded from the main analysis. Studies were categorized as short (≤4 week), intermediate (4-12 week), or long-term (≥12 week) and our primary outcome was the number of people obtaining a 30% or better reduction in pain, which we analysed using Forest plots of the three duration subgroups.

The analgesic efficacy of opioids compared to control differed significantly between the three subgroups ($Chi^2 = 6.64$, df = 2, P = 0.04). The only significant difference in analgesia was observed in short-term studies, where 53% more patients experienced clinically significant analgesia in the opioid arm compared to the control arm (RR 1.53, 95% CI 1.09 to 2.14). There was no statistically significant difference in analgesic efficacy of opioids compared to control in intermediate-term studies (RR 1.01,

95% CI 0.72 to 1.43), nor in long-term studies (RR 0.86, 95% CI 0.69 to 1.08), which trended towards harm.

This review provides evidence that the analgesic efficacy of opioids in comparison to control in patients with osteoarthritis and chronic lower back pain diminishes over treatment duration. Although we see an analgesic benefit of opioids in the short-term, this benefit is not observed in therapy that lasts over 4 weeks, which supports the hypothesis that opioids may induce hyperalgesia which attenuates their analgesic benefit over time. Medical practitioners should consider prescribing only short courses of opioids for patients with chronic non-cancer pain.

Preface

This thesis is an original work by Liesbeth Froentjes. No part of this thesis has been previously published.

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List of Abbreviations

ALO-02	Oxycodone hydrochloride & naltrexone hydrochloride
BC	British Columbia
bid	Bi-daily
BOCF	Baseline observation carried forward
BPI	Brief Pain Inventory
BTDS	Buprenorphine transdermal system
CENTRAL	Cochrane Central Register of Controlled Trials
CLBP	Chronic lower back pain
CNCP	Chronic non-cancer pain
CNS	Central nervous system
CORE Back Tool	Clinically organized relevant exam back tool
CR	Controlled-release
CV	Cardiovascular
DOR	∂ opioid receptors
EERW	Enriched-enrollment randomized withdrawal
ER	Extended-release
FDA	Food and Drug Administration
GI	Gastrointestinal
GPCR	G-protein coupled receptor
HCl	Hydrochloride
IR	Immediate-release
ITT	Intent-to-treat
KOR	κ opioid receptors
LBP	Lower back pain
LOCF	Last observation carried forward
LS	Life satisfaction
MCID	Minimum clinically important difference
ME	Morphine equivalent
mITT	Modified intent-to-treat
MOR	μ opioid receptors
MS-sNT	Morphine sulphate & naltrexone hydrochloride extended release
NGF	Nerve growth factor
NKTR-181	Oxycodegol
NMDA	N-methyl-D-aspartate
NRS	Numeric Rating Scale
NSAID	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OAPI	Osteoarthritis-related pain intensity
OIH	Opioid-induced hyperalgesia
OUD	Opioid use disorder
PGIC	Patient Global Impression of Change
PNS	Peripheral nervous system
qid	Four-times-daily

RCT	Randomized controlled trial
RR	Risk ratio
SA	Sustained-action
SOCF	Screening observation carried forward
SPACE trial	Strategies for prescribing analgesics comparative effectiveness trial
TD	Transdermal
TDS	Transdermal system
tid	Tri-daily
TRPV1	Transient receptor potential
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Chapter 1

Opioids in the Body

Pain & the Endogenous Opioid System

The experience of pain is complex, as it involves sensory, affective, and cognitive functions.[1] It is modulated in part through our endogenous opioid system, which mainly regulates pain, stress responses, and addiction, but is also involved in managing emotional responses, autonomic functions, respiration, appetite, and body temperature.[2-4] To exert their effects in the body, opioids target three "classic" receptor types: μ, κ, and ∂, of which there are also subtypes.[4] These are highly homogeneous G_i/G_o-coupled receptors (GPCRs): a large family of membrane receptors with a highly conserved structure that respond to many different stimuli.[5] Opioid receptors, like other GPCRs, differ in their extracellular regions and N-terminal tails, which makes sense as these regions are involved in guiding specific ligands to the binding pocket.[6]

Once bound by their specific opioid agonist, the receptors are activated and signal transduction ensues. As a result, nociception is inhibited through either the closing of calcium channels or the opening of potassium channels.[3] The exact mechanism of this process depends on a variety of factors including identity of opioid, location and type of opioid receptor, opioid dose, and patient condition.[2] Generally, if the receptor is located on a presynaptic neuron, then its effects involve inhibiting the release of excitatory neurotransmitters. Once activated by a specific opioid agonist, the presynaptic receptor couples with its G-protein and inhibits adenylyl cyclase, which suppresses the entry of calcium and therefore the release of excitatory neurotransmitters (typically glutamate and neuropeptides) by the neuron.[5] If the opioid receptor is located on a postsynaptic neuron then the mechanism of analgesia involves an activation of potassium channels and an

influx of potassium into the cell, which hyperpolarizes the membrane and inhibits any action potentials from firing.[7] Regardless of the location and mechanism of the receptor, the result is ultimately the inhibition of pain.

Opioid Receptors

Although μ, κ, and ∂ opioid receptors all trigger analgesic responses when bound, they differ in terms of their exact effects. Opioids such as morphine that bind μ opioid receptors (MORs) are generally very potent, and once bound elicit a strong analgesic response.[2] However, the potential for these opioids to cause severe side effects like respiratory depression, constipation, and addiction is relatively high.[5] The effects of opioids are mediated predominantly through MORs, whose activation leads to the widespread biological events mentioned.[8] In fact, studies have found that when mice lack MORs, all morphine responses – including analgesic effects and adverse events – are abolished, [9, 10, 11] Some analgesic effects are also mediated through ∂ and κ opioid receptors (DORs and KORs, respectively): DOR agonists typically provide weaker pain relief but have lower addiction potential and KOR agonists can strongly depress one's emotional affect.[2]

Opioid receptors are located throughout the central and peripheral nervous systems (CNS and PNS, respectively). In the CNS - including brain regions and spinal cord - their activation depresses neural firing in either pre- or postsynaptic neurons. MORs in the CNS are more highly concentrated in brain regions that regulate pain perception, pain-induced emotions, and pleasure and reward.[1] This explains their characteristic analgesic, euphoric, and addictive effects. There is also a high density of MORs in the respiratory centre of the brainstem and in higher brain centres involved in

respiratory control like the thalamus, which accounts for the respiratory depression that they cause.[3] The euphoric effects of opioids are caused by dopamine release in the nucleus accumbens, which is a key reward centre in the brain.[12] Opioid receptors in the PNS are primarily located on the cell bodies of sensory neurons, and their principal mechanism for depressing neuronal firing is through the restriction of calcium entry detailed previously.[13] After exogenous opioid administration, PNS receptors account for up to 80% of the ensuing analgesic response, but don't play a role in the experience of euphoria, addiction, or respiratory depression.[14]

Pharmacology of Opioids

In general, opioids are rapidly absorbed and exert their effects for a relatively short period of time.[5] The more rapidly an opioid is delivered to the brain, the stronger its euphoric effects and the higher its addiction potential.[15] For this reason, snorting and injection are common routes of administration in opioid addicts: the stimulation of the brain is most rapid. Although it was once believed that pain served a protective role against opioid addiction, this is not the case: those prescribed opioids to treat pain are at risk of addiction.[15] In response, there has been much effort put into developing abuse-deterrent opioid formulations to discourage the non-oral administration commonly seen in addiction.[16] These formulations differ in how they provide safe delivery; some combine opioids with opioid antagonists that are only released if injected, others have a slow rate of opioid release (as mentioned previously), and some become viscous and non-injectable/snortable when crushed.[16] However, this does not eliminate abuse potential entirely, as these formulations can still be consumed at high doses orally.

Opioids' Clinical Use

Opioids in Pain Treatment

Clinically, opioids are a standard way to manage both acute and chronic pain. Acute pain is directly related to soft tissue damage, and typically resolves once the tissue has healed. This includes intraoperative, postoperative, and posttraumatic pain, all of which tend to be quite responsive to opioids.[5] Chronic pain, on the other hand, is pain that lasts longer than the amount of time it typically takes tissues to heal (typically 3 months).[8] It is often subdivided into malignant and non-malignant chronic pain, a distinction that is clinically important as they respond differently to opioid therapy. Cancer pain, like acute pain, tends to respond well, while chronic non-cancer pain (CNCP) typically responds better to a multidisciplinary approach.[5, 17] However, the evidence for the use of opioids in CNCP is very mixed, especially as the duration of the prescription increases.[18] Many trials looking at the effectiveness for opioids on CNCP have shown opioids to be more effective for analgesia compared to placebo.[8] Generally, these benefits are much more significant in sedentary compared to active patients.[8] On the other hand, many other trials and systematic reviews have found opioids to offer no advantage to – or even to be inferior to – placebo.[19, 20] Among such trials is the recent SPACE trial, which compared opioid to non-opioid therapy over 12 months in patients with chronic back pain or osteoarthritis of the knee or hip.[20] They found no differences in pain-related function and no clinically relevant differences in analgesia, but a significantly increased risk of adverse events in the opioid group. In general, the evidence in favour of opioids is not consistent, and when supportive it is generally regarding short-

term treatment of fewer than 16 weeks, as long-term trials are lacking.[19, 18]

Osteoarthritis and Chronic Back Pain

Osteoarthritis (OA) and chronic lower back pain (CLBP) are very common sources of CNCP. OA is the most common joint disease in the world, impacting millions of people worldwide.[21] The joint is globally affected: cartilage gradually degrades while subchondral bone and synovium become denser and more brittle. Subchondral bone is highly innervated, it is therefore likely involved in the experience of chronic pain in OA.[21] There are biological, behavioural, and genetic risk factors for OA, which are important to identify as having a more complete picture of the etiology of the disease will help select targets for early prevention and treatment. Of these, age is the strongest risk factor, which may be explained by a reduction in regenerative capacity.[22] OA is more common in women than in men: while only 10% of men over 60 suffer from OA, 18% of women do.[21] Obesity is another risk factor, which makes sense due to an increased load on joints; however, it has a much greater impact on risk of knee OA than risk of hip OA.[23] Furthermore, joint injury can make joints more susceptible to further damage or negatively affect joint mechanics, leading to increased risk of OA development.[21] In terms of OA treatment, it has traditionally consisted primarily of pain management, with joint replacement being an option for later-stage disease.

Low back pain (LBP) is a very common problem, affecting an estimated 80% of people at some point in their lives.[24] It has many etiologies, the most common being nonspecific back pain which entails no identifiable or specific underlying cause and accounts for over 85% of cases of LBP.[25] The majority of these nonspecific cases suffer from acute musculoskeletal pain which typically resolves within 4 weeks, but can lead to

CLBP if the pain lasts longer than 12 weeks.[25] The transition between these acute and chronic states is defined as sub-acute back pain (pain lasting between 4 and 12 weeks).[24] Making this distinction between different durations of back pain is important as the efficacy of therapies differ depending on what point in the trajectory they are administered at.[24] The CORE Back Tool (2016) is a Canadian resource meant to aid physicians and nurse practitioners in the management of LBP. It includes "yellow flags" which help identify the presence of psychosocial risk factors potentially associated with the progression of sub-acute LBP to chronic LBP. These factors include a belief that back pain is harmful/severely disabling, fear/avoidance of activity and movement, low mood and social withdrawal, and a lack of belief that active participation in treatment will help their pain.[26] Other situational and psychological factors associated with the development of LBP include heavy workplace lifting, obesity, physical inactivity, arthritis, age (>30), pregnancy, posture, stress, depression, and smoking.[24] The treatment of CLBP is often very difficult: the maintenance of functionality is the ultimate goal of therapy, even if it proves impossible to eliminate the pain.[24] Psychosocial factors like depression, maladaptive coping mechanisms, and psychological distress are very strong predictors of the LBP outcomes.[27] In many patients, addressing these issues does more for improving the burden of LBP than medical treatments like opioids.[24] In fact, literature is increasingly showing that opioids are not an ideal way to treat CLBP, as non-opioid treatment options including exercise, non-opioid analgesics, cognitive behavioural therapy, and multidisciplinary approaches to treatment tend to have more positive outcomes without the adverse effects associated with opioid therapy.[19, 28-30]

Clinical Adverse Effects

Once opioid receptors are bound to their agonists, they have numerous targets in the body including cardiovascular (CV), respiratory, and gastrointestinal (GI) systems. The higher the opioid dose and the longer the prescription duration, the more prevalent the adverse effects become.[8] In the CV system, high opioid doses are associated with bradycardia which often causes drops in blood pressure.[5] Respiratory depression is another serious adverse effect of opioid use that can lead to death. The generation of respiratory rhythm in the CNS is very sensitive to opioids, as they directly inhibit respiratory neurons in the brainstem and induce respiratory depression. [3, 31] Furthermore, opioids have numerous effects on the functioning of the GI system. Opioid receptors are found in the enteric nervous system throughout the GI tract, and when activated they stimulate contraction of the smooth muscle of the lining, thus inhibiting peristalsis.[5] This ultimately leads to constipation due to increased water absorption and reduced muscular activity necessary for evacuation of stool, a very common adverse effect of chronic opioid therapy. Tolerance is very slow to develop to these effects, which explains why constipation typically continues throughout opioid therapy.[5] Other common GI-related effects are nausea and vomiting. Opioids directly activate the chemoreceptor trigger zone in the brainstem, resulting in nausea.[32] This effect is worsened in active compared to sedentary patients.[5] Other adverse effects often seen in patients on opioid therapy are dry mouth, sedation, dizziness, dermatological rashes and itchiness, and hyperalgesia.[8] Although tolerance eventually develops to all except hyperalgesia, these effects are often the primary reason for intervention group withdrawal in opioid trials.[8]

Opioid Overdose

As mentioned, respiratory depression is a serious adverse effect of opioids caused by an inhibition of neurons in the respiratory control centre of the brainstem. This is the primary mechanism by which opioid overdose - both fatal and non-fatal – occurs.[33] As opioid levels increase, tidal volume and breathing rate decrease, which leads to an excess of carbon dioxide in the blood (hypercapnia).[3] These hypercapnic states contribute to the maintenance of respiration, which can help safeguard against overdose. However, the higher the dosage, the longer-acting the formulation, and the longer the duration of treatment, the higher the risk of overdose is.[8] This is obviously problematic for the use of opioids in CNCP management, as the duration of treatment typically lasts for months. It should be noted that when simultaneously taking other drugs alongside opioids, one needs to be cautious: any inhibitory drugs (prescription or otherwise) that depress respiration could have synergistic effects on the respiratory depression already caused by opioids.[3] Alcohol and benzodiazepines have only mild depressant effects; however, when used in combination with opioids they can precipitate overdose.[3] In fact, there is a negative correlation between blood morphine and ethanol in cases of fatal opioid overdose, which suggests that when these drugs are combined, lower doses of opioids can be fatal.[34]

Certain patient characteristics are also predictive of opioid overdose, including a history of overdose or addiction, respiratory compromise, hepatic dysfunction (impairment opioid metabolism), and suicidal ideation/major depressive disorder, which may predict intentional overdose.[3, 35-37] Those addicted to opioids are especially prone to overdose after periods of prolonged abstinence during which their tolerance decreases.[38] In these cases users may take their “normal” dose, which can cause respiration to be

severely depressed due to decreased tolerance and may potentially result in death. This is evidenced by the fact that opioid levels in fatal overdoses are lower than those seen in living users.[34] To manage these risks, it is important to perform a risk assessment and urine drug screening before prescription.[8] Furthermore, due to their association with increased overdose risk, high dose and long-acting opioid formulations need to be used with caution. Finally, widespread availability of naloxone – the antidote to opioid overdose – for all who are placed on chronic opioid therapy would decrease the risk of overdose and death.[8]

Opioid Tolerance, Physical Dependence, Hyperalgesia, and Addiction

Tolerance & Physical Dependence

Repeated opioid administration over time results in decreased physical and psychological response.[8] When used for pain management, this often results in the need to increase dosage to obtain the same analgesic effect. How quickly and severe this effect occurs depends on the characteristics of the specific opioid, its dose, and its route of administration; however, the exact mechanisms involved in in vivo tolerance development are not entirely understood.[8] In vitro, desensitization occurs via one of three typical pathways: receptor phosphorylation, receptor sequestering, or receptor down-regulation. Phosphorylation of opioid receptors occurs when they are activated by opioid agonists, which increases the receptor's affinity to arrestin.[5] The resulting arrestin-receptor complexes prevent the G-protein binding necessary to initiate the transmission cascade that ultimately results in opioids' effects. Receptors can also be sequestered through endocytosis, which directly relates to tolerance as it results in a fewer number of receptors on the cell's surface and thus a net decrease in opioid-binding.[5] Lastly,

receptors are recycled and down-regulated to reduce their total number.[5] In vivo, tolerance occurs partially through receptor regulation, but it also involves genetics and the reorganization of neural networks associated with learned behaviour.[5] Furthermore, in vivo tolerance does not develop at the same rate for all opioid responses: while dulling of response to stimulant effects like constipation develops quite slowly, it develops relatively quickly to depressant effects like antinociception and respiratory depression.[5] However, among these depressant effects, tolerance to analgesia often develops faster than tolerance to respiratory depression.[38] This is problematic when using opioids to treat chronic pain, as the titration needed to maintain adequate analgesia can increase risk of fatal overdose by respiratory depression.

Physical dependence differs from tolerance; it manifests as mild to severe withdrawal symptoms once opioid administration stops, and usually resolves within 3 to 7 days of treatment cessation.[8] The symptoms typically include diarrhea, chills, and restlessness, among others.[5] The severity and duration of dependence depends on the opioid, but can be avoided if patients are slowly tapered off the opioid medication.[8] While physical dependence is not the same as addiction, the presence of these withdrawal symptoms often causes patients to avoid discontinuation of opioid therapy.[8]

Hyperalgesia

Increased pain sensitivity, or hyperalgesia, can be induced by repeated opioid exposure. This pathway can result in a positive feedback loop of opioid dose tapering and exacerbation of hyperalgesia.[8] This is further facilitated by the development of tolerance to the analgesic effects of opioids. The similarity of the implications of tolerance and

hyperalgesia - namely, increased pain perception - makes it difficult to know whether to increase or decrease opioid dosage when a patient on opioid therapy complains of increased pain.[39] In these cases, it may be beneficial to switch medication to a different opioid or to a non-opioid, something the recent Canadian guideline for opioid use in CNCP recommends in lieu of continually increasing dosage.[40] Despite the similarity of their effects, the mechanisms underlying tolerance and hyperalgesia differ, and their respective management thus requires different approaches. As mentioned, tolerance occurs when the body's analgesic response to opioids decreases after repeated use, thus requiring titrated doses for the same level of antinociception. However, the opioid administration itself does not cause any pain. On the other hand, opioid-induced hyperalgesia (OIH) refers to an increase in pain perception caused by opioids, and manifests as a targeted increase in pain in the specific problem-area or as a more general increase in pain sensitivity.[41] The mechanism underlying its development is very complex, and involves changes in both the peripheral and central nervous systems. Centrally, sensitization in the spinal cord involving increases in glutaminergic system and N-methyl-D-aspartate (NMDA) activity is thought to be the primary mechanism by which hyperalgesia occurs.[41] For example, studies on rodents have shown that NMDA receptors antagonists prevent development of OIH.[42, 43] Furthermore, modulation of input to the spinal cord by brainstem neurons towards pro-nociceptive systems is thought to play a role.[41] Peripherally, OIH is associated with increased mechanical sensitivity and cytokine levels.[44] Peripheral receptors – specifically the transient receptor potential (TRPV1) – are also involved: introduction of TRPV1 antagonists have been shown to reverse the effects of OIH and TRPV1-knockout mice avoid the development of OIH

entirely.[45, 41] Like addiction, some people develop OIH and others do not. Susceptibility depends on many factors, including patient characteristics, types of pain, length of opioid therapy, identity and dose of opioid, and genetic factors.[41]

OIH presents a problem in the use of opioids to treat CNCP. A recent systematic review looked at pain tolerance to painful thermal and electric stimuli in those on opioid therapy compared to controls.[39] They found that tolerance to painful thermal stimuli (both hot and cold) was lower in those on opioid therapy compared to controls. However, there was no difference in regards to tolerance to painful electric stimuli. The authors hypothesized that this could be due to the fact that thermal pain is tonic, while electrical pain is phasic. Tonic pain is more similar to chronic pain, and may therefore involve similar systems to those implicated in OIH.[46] The hyperalgesia associated with opioid therapy could play a role in their relative lack of long-term efficacy, as it may cause inferior analgesia compared to that provided by non-opioid medications. Another recent study compared the life satisfaction (LS) between on-opioid and opioid-naive patients who were scheduled for elective spine surgery.[47] They found that spine surgery significantly improved LS and pain interference in both groups of subjects when compared to baseline. However, they found that pain interference and chronic opioid use were associated: at both baseline and post-surgery, LS and pain interference scores were better in the opioid-naive group compared to the on-opioid group.

OIH presents a problem not only in CNCP, but in acute pain as well.[41] One systematic review looking at pain perception at 24 hours after surgery found that those patients administered opioids intra-operatively reported higher pain scores at all time points compared to controls.[48] This difference was the most pronounced immediately

following surgery, and gradually decreased over the succeeding 24 hours. Furthermore, they found that pain thresholds were lower in opioid patients compared to controls at 24 hours post-surgery. This points to the conclusion that opioids – particularly in high doses – may cause OIH and increase pain perception, even in cases of acute pain.

Addiction

Addiction differs from both tolerance and physical dependence. The latter two phenomena are consequences of repeated and continuous opioid exposure that develop within days irrespective of patient characteristics or specific opioid.[49] Addiction, on the other hand, is a complex mental illness concerning several neural processes involved in reward, conditioning, self-control, and stress responses.[8] It is a psychological dependence that can take months to develop and only occurs in some patients.[5, 49] These three terms are often used interchangeably, which contributes to why estimates of addiction prevalence in patients prescribed opioid therapy range widely from less than 1% to over 26%.[50] In studies that employ careful criteria for addiction diagnosis, rates are less than 8%.[19, 51, 52] However, caution is important when interpreting the results of trials assessing risk of addiction: it can often be underestimated if diagnosis is based only on overall physician judgement and incomplete surveillance.[53]

Motivation for drug use is encouraged by both conditioned cue-response and desire to avoid/alleviate negative affect.[12] As mentioned, opioids cause the release of dopamine in reward centres of the brain like the nucleus accumbens, which produces their euphoric effects. These effects are rate-dependent: the "high" associated with addictive drug use is a result of a rapid increase in dopamine triggered by drugs like

opioids.[12] Eventually, after long-term opioid use, one learns the association between this euphoria and drug administration.[8] It makes sense that the stronger the euphoric effect, the faster this learning occurs. This same associative learning occurs between pain relief and opioids, as well as avoidance of withdrawal symptoms and opioids.[8] Conditioning of the latter association may cause the patient to seek relief in response to mild pain or withdrawal symptoms, resulting in more frequent dosing.[8] Furthermore, associations can be made between environment, context, or affective states and the euphoric effects of opioids.[12] The more frequent and intense one's opioid exposure is, the more these learned associations are reinforced. Eventually, with repeated exposure, these stimuli alone will trigger dopaminergic neuronal firing, resulting in increases in concentration in the nucleus accumbens and expectation of reward.[12] Addiction thus develops over time as one begins to crave the psychological and physical effects associated with the drug, and thus craves the drug itself.[8] Prolonged opioid exposure disrupts prefrontal cortex function and leads to decreased control/self-regulation and compulsive drug intake, which in turn further disrupts prefrontal functioning.[49] This positive feedback loop of addiction is exacerbated by frequent, long-term dosing and fast-acting opioid formulations, and can be extremely difficult to overcome. Furthermore, increases in dopamine triggered by opioids can result in changes in synaptic connections in the associated reward regions. Long-term synaptic potentiation and depression result in long term memory of the drug's rewarding effects and contextual associations.[54] Addicted persons are highly reactive to these associations and stressful stimuli, but show decreased response to natural reward like food. Natural reinforcers are also associated with certain contextual cues such as time of day, which elicit an increase in dopamine that motivates us to obtain reward like

food.[55] However, unlike addictive drugs, dopaminergic cells typically cease firing after the reward is obtained.[55] On the other hand opioids continually increase dopamine release during their usage; usage itself therefore sustains the desire to continue that usage.[12]

Although dopamine does play a central role in addiction, there are other processes involved. For example, in addition to the indirect innervation of dopaminergic neurons previously discussed, opioids may also act directly in the nucleus accumbens to produce a reward response.[54] Another theory posits that addiction is associated with a shift in the involved brain regions from the nucleus accumbens (involved in reward behaviour) to the dorsal striatum (involved in habit formation).[56] As opioid use continues, patients experience inhibition of the prefrontal cortex and decreased self-control.[49] Thus, as addiction progresses, drug use shifts from voluntary to habitual to compulsive. Addiction also causes changes in neural circuits involved in stress reactivity, which leads to increased dysphoria, anxiety, and irritability.[12] These neural changes don't disappear with opioid discontinuation, but persist for years after addiction is overcome: it is therefore considered a chronic mental illness.[8]

Prescription Opioid Use Disorder

Opioid use disorder (OUD) is the compulsive use of opioids that causes distress or impairment, and includes tolerance, physical dependence, and addiction.[57] The development of addiction and subsequent OUD among those prescribed opioids varies significantly. It depends on the exact opioid, as they vary widely in their modes of metabolism and pharmacodynamics and therefore in their risks for overdose and addiction.[8] OUD is also dependent on the patient population, the setting, and the specific

diagnostic criteria.[53] In general, addiction is not a pressing issue in cases of acute pain, as the pain resolves once the tissues are healed.[18] Opioid therapy is therefore relatively short, which can mitigate the risk of addiction. On the other hand, addiction is a serious concern in opioid treatment for chronic pain. As mentioned, careful criteria for addiction diagnosis yield addiction rates of less than 8%. However, given the large prevalence of opioid prescription, this relatively small percentage translates to a large number of people. Furthermore, it is very difficult to assess patient risk of developing OUD. Commonly used instruments like the "Opioid Risk Tool" have not been critically reviewed, and are based on low quality studies.[18] Furthermore, most of these instruments show very poor diagnostic performance. Given the questionable efficacy of opioids in CNCP, the high prevalence of adverse events, and the lack of a reliable way to identify patients for whom long-term opioid treatment is safe, their widespread use in CNCP is problematic at best.

Opioid Epidemic

Origins of the Epidemic

Throughout much of history, civilizations including the Persians, Egyptians, and Mesopotamians have used opioids medically in the form of opium for its analgesic and euphoric effects.[5, 2] Opium is a naturally-occurring opioid extracted from poppies whose active compounds are alkaloid opioids including morphine.[2] Eventually this morphine component was isolated in the early 19th century, and due to its heightened potency and more predictable effects, morphine replaced opium as the analgesic-of-choice and its use became widespread.[5, 58] To this day, morphine is the standard to which all other opioids

are compared.

As the addictive nature of opioids - especially street heroin - was uncovered, a general worldwide aversion to opioids ensued.[59] This lasted up until the mid-1980s, when the under-treatment of pain was addressed by the World Health Organization.[59] The attention this garnered spurred an increase in opioid use to treat cancer pain, which led to improvements in treatment and patient satisfaction. In response to this success, pain organizations, pharmaceutical companies, and physicians criticized the exclusive use of opioids for cancer: why shouldn't CNCP be treated in a similar way? [60] The conflation of the two types of pain ignored the psychosocial aspect of CNCP, and despite warnings, opioid use for CNCP rose.[61]

Over the past three decades, there has been an increase in opioid prescription for antinociception in CNCP across many countries which has contributed to the opioid epidemic we are currently experiencing.[62] In the early 1990s, physicians were assured by the pharmaceutical industry that opioids were a safe choice for pain control, despite recognition that opioids were highly addictive.[28] This was because it was believed that addiction would only affect a small proportion of high-risk individuals, and that these cases would be relatively simple to identify and control. Furthermore, long-acting opioids were heavily promoted as entirely non-addictive due to their delayed action. In particular, Purdue Pharma aggressively promoted the extended-release oxycodone formulation OxyContin to physicians, specifically targeting those they knew to be highest – and typically the least discriminate – prescribers.[63] Another promotional feature of Purdue's campaign was the systematic minimization of OxyContin's addiction potential.[63] Therefore, widespread use and high dosage were not thought to be an issue;

pharmaceutical companies, pain societies, and opinion leaders alike claimed that high-dose, prolonged opioid therapy was an appropriate treatment approach with a large potential for benefit and a small potential for harm.[62] As the following decades revealed the actual harm caused by this massive upswing in overprescribing was sizable, as it turned out to be impossible to reliably identify patients at-risk for addiction.[28] Furthermore, the risk-mitigation employed did not fully protect pain patients on opioid therapy.[28] Another contributor to the crisis was the ease of this approach in treating chronic pain. It is much simpler to prescribe strong analgesics with immediate and noticeable effects than to educate patients about the biopsychosocial model of pain and encourage behavioural changes.[62] Furthermore, patient expectations for "effective treatment" are closely related to symptom – specifically pain – alleviation; thus, opioid therapy tends to be initially accompanied with increased patient satisfaction.[62] This can be seen as a reflection of our current healthcare system's more reactionary and less proactive approach to healthcare.

Burden of the Opioid Epidemic in Canada

Although the majority of literature regarding the opioid epidemic comes from the United States (US), the burden of opioid overdose and addiction in Canada is not to be understated. After the US, Canada is the largest opioid prescriber, with over 20 million prescriptions filled in 2016 alone.[64] These prescriptions flood into communities and are diverted for non-medical use, resulting in increased availability and exposure to opioids and ultimately serious public health consequences. Opioid-related death rates rose from 2016 to 2017, and have remained high since then: there were over 14,700 opioid-related

deaths from January 2016 to September 2019, with 2,900 of them occurring in 2019.[65] However, mortality rate is not the only metric by which the seriousness of the crisis is measured; from 2016 to September 2019 there were over 19,400 opioid-related hospitalizations, and over 3,600 of these occurred in 2019.[65] This corresponds to a 50% increase in opioid-related hospitalizations over the past 10 years.[66] Males and adults over 40 years made up the majority of hospitalized cases, with the age group at highest risk of hospitalization being those over 60 years.[65] Emergency department visits increased significantly across Canada from 2011 to 2017 as well, with the greatest and most alarming increase seen in younger demographics (from 15 to 44).[64] This finding was consistent throughout regions.

Fentanyl

Once in the illegal market, prescription opioids as well as illicit opioid formulations like heroin are often combined with fentanyl: a cheap, synthetic, and very potent opioid. In 2017, over 50% of heroin samples contained fentanyl or an analogue.[64] Additionally, the synthetic opioid carfentanil is of growing concern as it is increasingly being used in a similar manner as fentanyl, but has 100 times the potency.[64] Neither buyers nor users of these drugs are typically aware of the presence of these high-potency drugs, which greatly increases the risk of overdose by opioids obtained through the illegal market. In fact, of the opioid-related deaths that occurred in Canada in 2019, almost 80% of them involved fentanyl/analogues and less than 20% of them involved only pharmaceutical opioids.[65] Although prescription opioids were the preliminary driver of opioid addiction and fatal overdose, the increased prevalence of fentanyl we are seeing on

the illegal market is likely driving the more recent increases in opioid overdose and death.[64, 18].For example, fewer than 10% of all overdose cases in British Columbia (BC) from 2015 to 2016 had an active opioid prescription.[67] Regulation of opioid prescription behaviours therefore may not significantly impact the high incidence of opioid-related overdoses we are seeing, as the harm caused by overprescribing has already been done. However, these overdose cases were more likely to have been prescribed opioids in the preceding 5 years when compared to matched controls.[67] The hope is that limiting opioid overprescription will reduce the prevalence of addiction in the coming generations.

Demographics at Risk

Although the opioid crisis is impacting public health throughout Canada, it does not affect all demographics equally. Alberta and BC are the two most highly impacted regions: when opioid-related deaths in 2016 were stratified by region, Alberta and BC accounted for 56% of them.[68] The territories (excluding Nunavut) have also borne a large burden of the opioid crisis. Gender also plays a significant role, as males were more likely to die of opioid-related causes than females across all regions.[68] However, the magnitude of this gender discrepancy varied; Saskatchewan, New Brunswick, and Newfoundland and Labrador had similar opioid-related mortality experiences between genders, with only between 55 and 57% of cases of fatal opioid overdose being male.[68] In terms of age demographics, those aged 30-39 years were the age group at highest risk of fatal opioid overdose across Canada.[68] Furthermore, First Nations communities - especially First Nations women - are heavily impacted by the opioid crisis. In reports from BC and Alberta, First Nations people were 5 times more likely to overdose and 3

times more likely to fatally overdose than non-First Nations.[69, 70] In particular, middle-aged women (50-54) and younger men (30-34) were at significantly elevated risk.[69, 70] Alberta's report specifically looked at dispensing trends and found that First Nations were twice as likely to be dispensed an opioid and were on average 5 years younger at first prescription than non-First Nations. Finally, housing instability (homelessness) was reported in 30% of opioid overdoses in the report released by BC.[71]

Canada's Opioid Guideline

Busse issued a Canadian guideline for opioid use in CNCP in 2017, and this guideline took into account the growing body of evidence calling this usage into question.[40] Strong recommendations include prioritizing non-opioid treatment options, decreasing daily dosages, and refusing to prescribe to those with active substance use disorders. Furthermore, they recommend formal multidisciplinary programming for those experiencing trouble tapering off of opioid therapy. Although the guideline takes steps to address overprescription of opioids for CNCP, it does not adequately address how to handle patients with OUD. The majority of the multidisciplinary pain clinics recommended by the guideline are located in urban centres, with none in either PEI or the territories.[72] In other words, they are very inaccessible. The opioid guideline estimates the prevalence of OUD among patients with CNCP to be 10%, and tapering or discontinuation in these patients is not a viable option as they often simply turn to the alternate unregulated – and therefore more dangerous – sources.[73] If users go through a period of abstinence when trying to locate these sources, their tolerance will lower and their risk of fatal overdose will increase, especially considering the high prevalence of

fentanyl in these formulations.[73] Accessibility of multidisciplinary pain clinics needs to increase and the protocols for CNCP opioid treatment should address the increased need for tapering and OUD management that are manifestations of the opioid crisis.

Purpose of This Review

Given the association of chronic opioid administration with hyperalgesia, and the potential of this association to minimize analgesic benefits over the long term, we wanted to determine whether the effectiveness of opioids for treating pain in patients with osteoarthritis or back pain decreases over time. The primary goal of this review is to examine how the use of opioids, as compared to placebo or opioid-minimized pain management strategies, affect pain intensity over the short, intermediate, and long-term in adults with osteoarthritis or back pain.

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Chapter 2

Methods

Protocol

This review was registered with PROSPERO (registration number CRD42020147459) and is available from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020147459. The full protocol is also available in Appendix A. We did have to make some alterations to our protocol, which are detailed in Appendix B.

Eligibility Criteria

Eligibility criteria for included studies were as follows:

1. Trials must be randomized.
2. Participants must have osteoarthritis (OA) or chronic lower back pain (CLBP).
3. Interventions must include an opioid medication.
4. The control condition must be treatment with either a placebo or an opioid-minimized pain management strategy (as long as this strategy is also available to the opioid arm).
5. Studies must include a responder analysis – or, a measure of the proportion of patients achieving some pre-defined level of improvement in pain – among their efficacy assessments.

Exclusion criteria were as follows:

1. Studies including exclusively participants with back pain resulting from surgery, cancer, neurogenic claudication, radiculopathy, sciatica, or rheumatic conditions

(for example, rheumatoid arthritis or ankylosing spondylitis).

2. Studies whose opioid interventions include additional non-opioid mechanisms for alleviating pain. Tramadol (which is also a serotonin-norepinephrine reuptake inhibitor) and tapentadol (which is also a norepinephrine reuptake inhibitor) are specifically excluded.[1, 2]
3. Studies that use trade-name formulations that include an opioid in addition to another analgesic compound (e.g. acetaminophen), unless they also administer the non-opioid component to the control group.
4. Studies that allow the use of opioid rescue medication throughout the comparison phase.
5. Studies that require patients to have opioid use disorder.

Search

A systematic electronic search was conducted in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus. Search strategies were developed alongside an experienced librarian and can be found in Appendix C. We did not restrict study eligibility by publication date or language.

Study Selection

Two authors (LF and either CB or DW) independently performed an initial screening based on title and abstract. Included studies were then screened for final selection based on their full text by two authors (LF and either CB or DW). All studies that were deemed eligible by both independent reviewers were included in the systematic

review and meta-analysis. Disagreements between the two reviewers in either of the two screening phases were resolved by discussion and consensus or involvement of a third author (SG).

Data Collection

Two authors (LF and either RC or DW) independently extracted data using the same excel spreadsheet. Extraction discrepancies were adjudicated by a third author (SG). Extracted data included the citation details, the specific condition under study (e.g. knee OA), the study sponsor, the study setting, the proportion of female patients, the mean age of patients, the number of study arms, the specific intervention(s) and comparator, the number of subjects in intervention and control arms, the study duration, the starting daily dosage, the maximum daily dosage, the average daily dosage during the study, the average dosage at all follow-up time points, and all assessments of the number of participants achieving a given response, including the scale used and the time of that assessment. During our screening, it became apparent that the enriched-enrollment randomized-withdrawal (EERW) design was quite prevalent in opioid trials. This design differs from the more classic RCT in that all patients are initially given opioid therapy and titrated to an "stable dosage" over a number of weeks. Only patients that reach this stable dosage, achieve a pre-specified reduction in pain, and do not discontinue are then randomized to either continue with the opioid therapy or switch to placebo. We recognized that the differences in methodology between EERW studies and traditional RCTs could lead to important differences in reported analgesia, and therefore also recorded whether the included studies used EERW or classic (RCT, crossover, etc.)

designs. Given all participants in the EERW studies received opioids during a run-in period, putting the control group at risk of developing hyperalgesia, we did not include these studies in our primary analysis. In the case of missing or unclear data, authors were contacted using the contact information provided in their paper. If this information was not available, we attempted to find contact information using an internet search.

Methods of Analysis

Primary Analysis

Our primary analysis compared clinically meaningful analgesia between opioids and control in short-, intermediate-, and long-term studies. The principal summary measure we used was the risk ratio and our primary outcome was the number of participants achieving a minimum clinically important difference (MCID) in pain. We were combining studies that used different scales and wanted to avoid the loss of clinical meaning that conversion to standard mean differences can introduce. Therefore, we examined only the number of patients showing moderate improvement in pain, defined as ≥30% in pain relative to baseline by consensus guidelines.[3] When this measure was not reported or when multiple responder outcomes were available, we employed an outcomes hierarchy to determine which to use (Appendix A). Included studies were divided into short-term (≤4 weeks), intermediate-term (4-12 weeks), and long-term (≥12 weeks) treatment duration, with CLBP and OA study results grouped together. We then generated Forest plots of the risk ratio for the incidence of clinically meaningful improvements in pain in opioid compared to the control arms for each of the three time periods. The model we used was random effects.

We did not perform an assessment of overall efficacy across all time points, but restricted our estimates to within each individual category of treatment duration. As such, studies that reported results at different time periods were included in the analysis of multiple time periods, but could only contribute once to each individual time period. For studies that provided multiple results for the same time period (e.g. assessments of pain at 2 weeks and 4 weeks) we chose the single result closest to the midpoint of the time period defining that subgroup. Specifically, we chose the time point closest to 2 weeks for the ≤4-week subgroup and the time point closest to 8 weeks for the 4-12 weeks subgroup. As the ≥12-week subgroup had no upper limit, for that subgroup we chose the longest follow-up result available.

When trials used multiple eligible opioid formulations, we included results from all arms separately and divided the patients in the control group - both total number and number of responders - evenly between the arms. For trials with multiple arms of the same opioid at different doses/dosing schedules, we combined the treatment arms (both total number and number of responders). When available, we used a modified intent-to-treat (mITT) population, defined as all randomized patients that received at least one dose of study medication. If this population was not reported, we included all randomized patients in the total. We considered all missing patients in the author-reported responder analysis (aside from those excluded in the mITT population) to be "non-responders".

Secondary Analyses

We wanted to compare clinically meaningful analgesia between opioid and control treatment in low- and high-dose long-term (≥12 weeks) traditional RCTs. In order to perform this analysis, we converted the average opioid dose in each classic, long-term

RCT to corresponding morphine equivalents.[4] This allowed for the comparison of studies that used differing opioid formulations. We preferentially extracted average dosage over the entire study, but accepted average dosage over the maintenance period if the prior was not reported. We then performed a median split analysis in which we defined "high dose" studies as those whose average dosage was in the upper half and "low dose" studies as those in the lower half. In the event of an odd number of studies, we calculated the mean average study dose. If the average study dose in the median study was higher than this mean we categorized it as a "high dose" study, and if it was lower we categorized it as "low dose". We then compared the number of participants achieving a minimum clinically important reduction in pain between these two subgroups using a Forest plot of the risk ratio (random effects model). Analysis of dose was pre-specified, but we altered the manner in which the analysis was done as our intended analysis required that studies report the average dosage at the time of their responder analysis. This data was largely unavailable: most studies only reported average dosage throughout the study.

We also performed a post-hoc comparison of the number of participants achieving a clinically important reduction in pain in opioid compared to control treatment in long-term EERW studies and long-term traditional RCTs. Like the primary and dosage analyses, this comparison was done using a Forest plot of the risk ratio (random effects model).

Risk of Bias

Within Studies

Risk of bias for individual studies was rated by 2 authors (LF and either RC or DW) at the study level using the Cochrane Collaboration Risk of Bias Tool. This tool has authors assess the risk of bias in the following areas as “low”, “unclear”, or “high”: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. A third author (SG or CK) reviewed the assessments and resolved any discrepancies.

Across Studies

Risk of publication bias across studies was analyzed through visual inspection of funnel plots for our primary analysis as well as for the analysis comparing traditional RCTs to those with an EERW design.

Results

Study Selection

The initial database search was performed on September 5, 2019 and yielded 15,493 studies, which was reduced to 9,450 after duplicates were removed. After title and abstract screening, 182 papers made it to full-text screening (Appendix D). Of these, 26 were deemed eligible for inclusion in our systematic review and meta-analysis. The corresponding PRISMA study flow diagram is displayed in Figure 1. Of those excluded, 32 were duplicates that had made it through the previous duplicate deletion and screening, 30 were abstracts of other papers, 28 did not have a responder analysis, 17 did not report the relevant outcome, 12 allowed the use of opioids as rescue medication, 8 had ineligible study designs, 6 were post-hoc analyses with no relevant outcomes, 4 had ineligible interventions, 5 had inadequate comparison groups, 4 enrolled the wrong patient population, and 4 studies did/have not complete(d). We were unable to find the full papers corresponding to 6 studies. For individual reasons for exclusion, see Table 1.

Study Characteristics

Of the 26 included studies, 9 were long-term EERW studies, 8 were long-term traditional RCTs, 2 were intermediate-term traditional RCTs, 6 were short-term traditional RCTs, and 1 was a short-term crossover study. Fourteen studies enrolled participants with OA, 11 enrolled patients with CLBP, and 1 enrolled patients with either OA or CLBP. Interestingly, 7 (77.8%) of the included long-term EERW designs enrolled patients with CLBP while only 3 (37.5%) of the long-term RCTs did. Females accounted for the majority of enrolled patients in all but 4 studies, and the percentage ranged from 23.4% to 73.1%. The average age of patients across included studies was 56.1, and

ranged from 37.0 to 66.5 years. Oxycodone was used by the majority of studies in some formulation: 7 used oxycodone CR, 2 used oxycodone ER, 1 used oxycodone IR, 1 used oxycodone/naloxone CR combination, 2 used oxycodone/naltrexone ER combination, and 1 did not specify which oxycodone formulation they used. Of the remaining studies, 4 used transdermal buprenorphine, 2 used buccal buprenorphine, 1 used a morphine/naloxone combination, 1 used a codeine/paracetamol combination, 1 used transdermal fentanyl, 1 used oxycodegol, 1 used propoxyphene, 1 used cebranopadol, and 1 used general opioid therapy. The majority of studies (24, 92.3%) used placebo as a comparator. Of the two that did not, 1 used non-opioid therapy and 1 used paracetamol. For a summary of the characteristics of each study included in our primary analysis, refer to Table 2. For a summary of the characteristics of each EERW study, refer to Table 3. For detailed descriptions of the study characteristics for each included study, refer to Table 4.

Results

Primary Outcome: Analgesic Efficacy in Short, intermediate, and Long-Term Trials

The analgesic efficacy of opioids compared to control differed significantly between the three subgroups ($Chi^2 = 7.65$, df = 2, P = 0.02). Heterogeneity was relatively high ($I^2 = 73.5\%$). In short-term studies, the incidence of clinically significant analgesia was 53% higher in patients treated with opioids compared to controls (RR 1.53, 95% CI 1.09 to 2.14). Opioids did not differ significantly from control in terms of their analgesic efficacy in intermediate-term studies (RR 1.01, 95% CI 0.72 to 1.43) or long-term studies (RR 0.86, 95% CI 0.69 to 1.08). However, it should be noted that the RR in long-term studies trended towards showing an analgesic benefit of control over opioids.

Heterogeneity was relatively high in all three subgroups with I^2 values of 76% in short-term studies, 81% in intermediate-term studies, and 79% in long-term studies. This was expected, as we were looking at trials that differed in their patient populations, opioids, doses, settings, and durations of treatment. We accounted for the high heterogeneity at least partially with our decision to employ a random effects model. For an overall summary of effect estimates and confidence intervals corresponding to each duration subgroup and individual study, refer to the Forest plot in Figure 2. Studies are ordered from shortest (top) to longest (bottom) duration. Data from this analysis is also presented in the form of a scatterplot (Figure 3) where the RR of the analgesic efficacy of opioids compared to control is plotted against study duration. In the plot, one can see a downward trend in clinically meaningful analgesic efficacy of opioids as study duration increase.

Analgesic Efficacy in EERW Studies and Traditional RCTs

The analgesic efficacy of opioids compared to control was significantly higher in EERW studies compared to traditional RCTs ($Chi^2 = 11.45$, $df = 1$, $P < 0.01$). The heterogeneity in study results was again high, which was expected ($I^2 = 91.3\%$). In long-term EERW studies, the incidence of clinically significant analgesia was 29% higher in patients treated with opioids compared to controls (RR 1.29, 95% CI 1.22 to 1.37). As discussed, this benefit was not seen in the long-term traditional RCT designs (RR 0.87, 95% CI 0.67 to 1.14). Heterogeneity within subgroups varied a lot; in traditional RCTs I^2 = 79% while in EERW trials $I^2 = 0\%$. Effect estimates and confidence intervals corresponding to EERW and traditional RCT subgroups as well as for each individual study included in this analysis can be found in Figure 4.

Analgesic Efficacy in Dosage Split Analysis of Long-Term Traditional RCTs

The average study dose and corresponding morphine equivalent of each study included in the dosage analysis are presented in Table 5. The average daily dose in "low dose" studies was 44.0 mg ME, and the average dose in "high-dose" studies was 76.0 mg ME. The analgesic efficacy of opioids compared to control was significantly higher in low-dose compared to high-dose studies ($Chi^2 = 4.23$, df = 1, P = 0.04). As expected, heterogeneity was relatively high with an I^2 value of 76.4%. While the number of responders did not differ significantly in opioid compared to control treatment in either dosage subgroup, low-dose studies trended towards showing benefit for opioid treatment (RR 1.49 95% CI 0.90 to 2.45) while the high-dose studies trended towards showing harm for opioid treatment (RR 0.79, 95% CI 0.56 to 1.11). Heterogeneity within subgroups varied; in low-dose studies $I^2 = 53\%$ and in high-dose studies $I^2 = 84\%$. For effect estimates and confidence intervals corresponding to high- and low-dose subgroups as well as for individual studies included in this analysis, see the Forest plot in Figure 5.

Risk of Bias Assessments

Within Studies

For risk of bias assessments of individual studies, refer to Table 6. Refer to Figures 6a and b for the risk of bias summary figure and graph for studies included in our primary analysis. Refer to Figures 7a and b for the risk of bias summary figure and graph for EERW studies.

Across Studies

Visual inspection of the funnel plot of our primary analysis (Figure 8) shows a bias in included studies: the lowest-enrolment studies - which are almost all short-term studies - all show a benefit of opioids over control. Although this could point to

publication bias, it could also be a reflection of the predicted decrease in the effectiveness of opioids as treatment duration increases: if opioids are most effective in the short term, then we would expect to see the results of the funnel plot presented. Because we were not interested in the overall effect of opioids across the different time periods (and were actually hypothesizing that analgesic efficacy changes over study duration), combining studies from all three time periods into one funnel plot has limited use. However, the Cochrane handbook recommends a minimum of 10 studies be included in each plot to prevent low power in the asymmetry test.[5] None of our subgroups included this many studies, which is why we made the decision to combine them and interpret the results with caution. The funnel plot corresponding to the post-hoc analysis of long-term EERW studies compared to RCTs is displayed in Figure 9. Visual inspection does not reveal major publication bias. However, almost all EERW studies lie to the side of the plot favouring opioids. This could be a reflection of a bias towards false positive results in the study design itself, which is a criticism of EERW designs.[6, 7]

Discussion

Summary of Evidence

The number of responders in opioid compared to control arms differed significantly between short, intermediate, and long-term studies ($p = 0.02$). The only treatment duration with a significant difference was short-term studies, where we found a 53% greater incidence of clinically meaningful analgesia in opioid therapy compared to control. While the RR point estimate for the intermediate-term studies rested around 1.0, long-term studies trended towards showing harm in the opioids compared to control, albeit insignificantly (RR point estimate = 0.87). Although we saw an analgesic benefit of opioids in the short-term, this benefit was not observed in therapy longer than 4 weeks. In fact, we found that there was a downward trend in clinically meaningful analgesia as treatment duration increased. This lends support to the conclusion that opioid-induced hyperalgesia may attenuate the analgesic benefit of opioids over longer treatment durations. Medical practitioners should therefore be very cautious when prescribing opioid therapy exceeding 4 weeks for OA and CLBP.

The results of our post-hoc analysis of analgesic efficacy in long-term EERW compared to traditional long-term RCT designs also roughly matched our predictions. We found that the number of responders on opioid comapred to control therapy was significantly higher in EERW trials compared to traditional RCTs ($p < 0.01$). In fact, EERW studies showed a 29% higher incidence of responders in opioid arms compared to control arms. This benefit was not seen in long-term RCTs. In fact, as detailed above, long-term RCTs trended towards showing harm in opioids compared to control, albeit insignificantly. This is consistent with the criticism that EERW trials can tend to show

false positive results, which is typically attributed to the possibility of unblinding in the control group as they transition from opioids to placebo, but which could also stem from excluding opioid non-responders from the trial, and perhaps the introduction of hyperalgesia in the control group.[6]

Our final secondary analysis of dosage in traditional long-term (≥12-week) RCTs showed that the number of responders in opioid compared to control treatment was significantly higher in low-dose than in high-dose studies ($p = 0.04$). Although opioids showed no significant benefit in either dosage subgroup, low-dose studies trended towards showing a benefit of opioid therapy compared to control while high-dose studies trended towards showing harm.

Limitations

We decided to eliminate one source of bias that became clear during our screening process. EERW designs have been criticized for their tendency towards false-positive results, potentially caused by the introduction of selection bias. The EERW design requires that all patients initially titrate to a stable and effective opioid dose over a number of weeks. Only those that achieve this stable dosage, do not discontinue, and reach a certain pre-specified level of pain reduction are then randomized to either continue opioid therapy or switch to placebo. The EERW design therefore excludes a significant proportion of patients, many of whom likely responded negatively to treatment. In fact, the average discontinuation rate during the titration phase in the 9 included EERW studies was 39.0% and ranged from 26.2% to 48.7%. This eliminates on average 4/10 patients, a significant proportion of whom do not tolerate or find no benefit from opioids. The study population would therefore consist of those patients that are the

most likely to respond to and tolerate opioids, and would not reflect the average patient faced by the prescribing clinician. However, it is also possible that the EERW design's tendency towards false positives is caused by unblinding that happens after patients randomized to placebo experience a decrease in adverse effects and an increase in withdrawal symptoms.[7] We recognized that the differences between the EERW and traditional RCT study designs could very likely result in differences in reported analgesic efficacy. We therefore compared the reported analgesic efficacy in long-term EERW designs to long-term traditional RCTs, and indeed found that EERW studies showed a significant analgesic benefit of opioids compared to control that was not seen in the more classic RCT design.

Another possible limitation of our study was the a priori decision to restrict eligible studies to those that included a responder analysis, which forced us to exclude studies that would otherwise have been eligible. It is possible that studies in which investigators decided to perform a responder analysis differed as a whole from studies that did not, which could introduce bias into our systematic review. However, if we had decided to combine differing pain scales by using the standard mean difference, we would have lost much of the clinical significance by converting to a measure which has no clinical correlate to which we can relate.

Additionally, the possibility of publication bias is always a potential source of error in systematic reviews. This is especially relevant given that all but three studies were sponsored by pharmaceutical companies. Visual inspection of funnel plots showed a potential publication bias that favoured opioids. However, it was predominantly short-term studies that had the lowest enrollments, and it was these studies that showed a

relative benefit of opioids over control compared to the pooled results of short-, intermediate-, and long-term traditional RCTs. The asymmetry in the funnel plot therefore could have reflected true heterogeneity in study results; it is possible that short-term (≤4-week) opioid therapy is actually beneficial for OA and CLBP, but that this analgesic efficacy diminishes as therapy increases in duration. Lastly, we were unable to locate 7 studies, which could have possibly introduced some bias in our results.

References

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Chapter 3: Conclusion

Overview of Objectives

Literature suggests that opioid-induced hyperalgesia may decrease the analgesic benefit of opioids as treatment duration increases.[1, 2] The main objective of this review was to determine whether the analgesic efficacy of opioid therapy decreases over time when used to treat chronic non-cancer pain (CNCP). To do this, we compared clinically meaningful improvements in pain in opioid versus control therapy over short (≤4 weeks), intermediate (4-12 weeks), and long-term (≥12 weeks) treatment duration for patients with osteoarthritis (OA) or chronic lower back pain (CLBP). Relevant studies were pulled from four databases and double-screened based on titles/abstracts and full text, and eligible studies were included in our review. Our primary analysis was a random-effects Forest plot using the risk ratio of the number of patients achieving a "moderate" improvement in pain in opioid compared to control arms over short, intermediate, and long-term treatment duration.

Summary of Results

The difference in the number of responders on opioid compared to control treatment was significantly different between short, intermediate, and long-term traditional RCTs ($p = 0.02$). Short-term opioid therapy in OA or CLBP provided clinically and statistically significant pain relief compared to control therapy, with 53% more patients experiencing a clinically meaningful analgesic response in opioid compared to control treatment. However, as predicted this benefit did diminish over treatment duration: neither intermediate nor long-term studies showed a benefit of opioid over control. However, what long-term treatment duration did show was a trend towards

harm in opioids versus control therapy (RR = 0.87). Ultimately, these results provide evidence that opioid-induced hyperalgesia may attenuate the analgesic benefit of opioids over long-term therapy used in the treatment of CNCP. Furthermore, the number of responders on opioid compared to control treatment was significantly higher in long-term EERW studies compared to traditional long-term RCTs ($p < 0.01$). We saw a statistically significant benefit of opioids over control in EERW studies that was not seen in traditional RCTs, which actually showed a trend towards harm for opioid therapy. Lastly, we found that the number of responders on opioid compared to control treatment in traditional, long-term RCTs was significantly lower in high-dose studies than in low-dose studies.

Clinical Implications

This systematic review provides evidence that the analgesic efficacy of opioids in comparison to control in CNCP diminishes over treatment duration. Although we do see an analgesic benefit of opioids over control in the short-term, this benefit is not observed in intermediate or long-term treatment. When coupled with the fact that risk of opioid use disorder increases with longer treatment duration and the fact that adverse effects associated with opioid therapy are often severe, this systematic review provides evidence against the use of opioids in CNCP for longer than 4 weeks.[3, 4] It simultaneously raises the question of whether these medications should be offered at all as a treatment for CNCP, in which pain necessarily lasts longer than 4 weeks. However, if physicians do opt to prescribe opioids for longer then 12 weeks, our results do suggest that lower opioid doses may provide better better pain outcomes than do high doses.

This review also provides evidence of a potential bias towards positive results in

long-term EERW opioid trials. Medical practitioners should therefore interpret the results of opioid trials, especially those with EERW designs, with caution.

Future Directions

We found that inclusion of responder analyses in opioid trials was relatively rare, while focus on statistically significant differences in pain scores was ubiquitous. A future direction in terms of opioid trials would therefore be to place a greater emphasis on the importance of clinical significance by making the inclusion of responder analyses more common. Furthermore, although we focused on pain in our review, improvement of function is also extremely important in chronic conditions like OA and CLBP. However, the predominant measurement of treatment success in opioid trials - and our classic medical model - is analgesia; the importance placed upon functional improvement is much weaker. Another future direction would therefore be for opioid trials for CNCP to place a greater value on functional improvement, specifically clinically meaningful functional improvement in the form of responder analyses. Once responder analyses of functional improvement become more commonplace, it would be beneficial to conduct systematic reviews that examine clinically meaningful functional improvement in CNCP patients on opioid compared to control therapy, and whether this relationship changes over treatment duration.

Most included trials - especially long-term - had high discontinuation rates. Only Krebs (2018) was able to retain the vast majority of randomized patients, almost certainly due to their flexible study design.[4] It would be beneficial for future studies to allow a similar amount of flexibility in terms of deviations in study medication and adherence, as results would be more generalizable to clinical practice. Furthermore, only two long-term

studies were longer than 16 weeks. It would be interesting to observe whether the efficacy of opioid compared to control therapy continues to decrease as treatment duration progresses past the typical length of the "long-term" studies we analyzed in this review (12 to 15 weeks).

Conclusions

Opioids offered no additional analgesic benefit over control treatment in therapy that lasted over 4 weeks in patients with OA or CLBP, with therapy longer than 12 weeks actually trending towards harm. This supports the hypothesis that opioid-induced hyperalgesia in CNCP may attenuate the analgesic benefits of opioids in longer-term treatment, and thus contribute to the decreased analgesia seen in patients on longer-term compared to short-term opioid therapy.[1] Due to this decreased efficacy - as well as the adverse effects and potential for addiction associated with opioids - medical practitioners should avoid opioid prescription lasting longer than 4 weeks for OA and CLBP.

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Figure 1: Study flow diagram

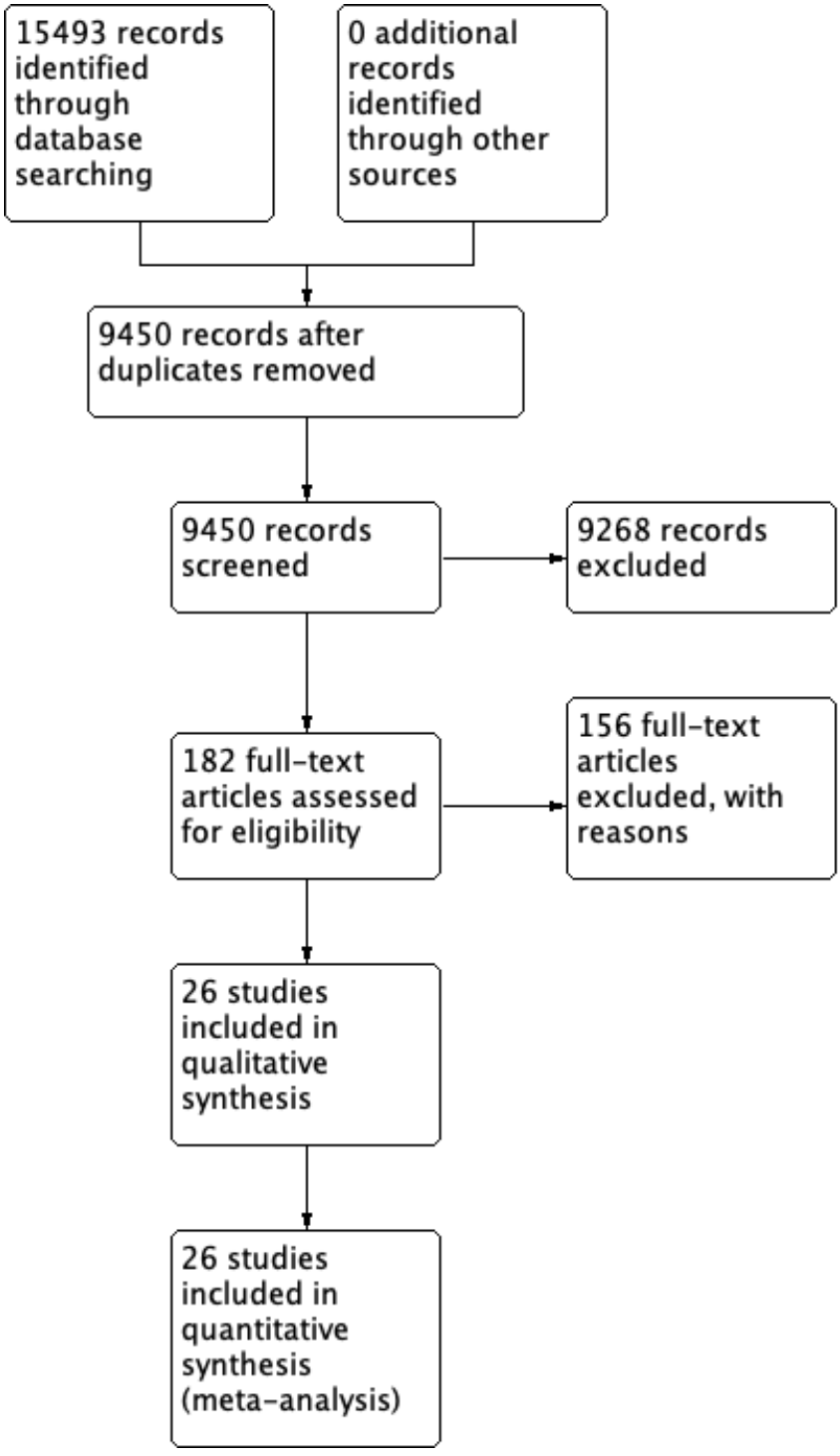


Figure 2: Forest plot of the analgesic efficacy of opioids compared to control therapy for short, intermediate, and long treatment duration. Ordered top-down from shortest to longest duration.

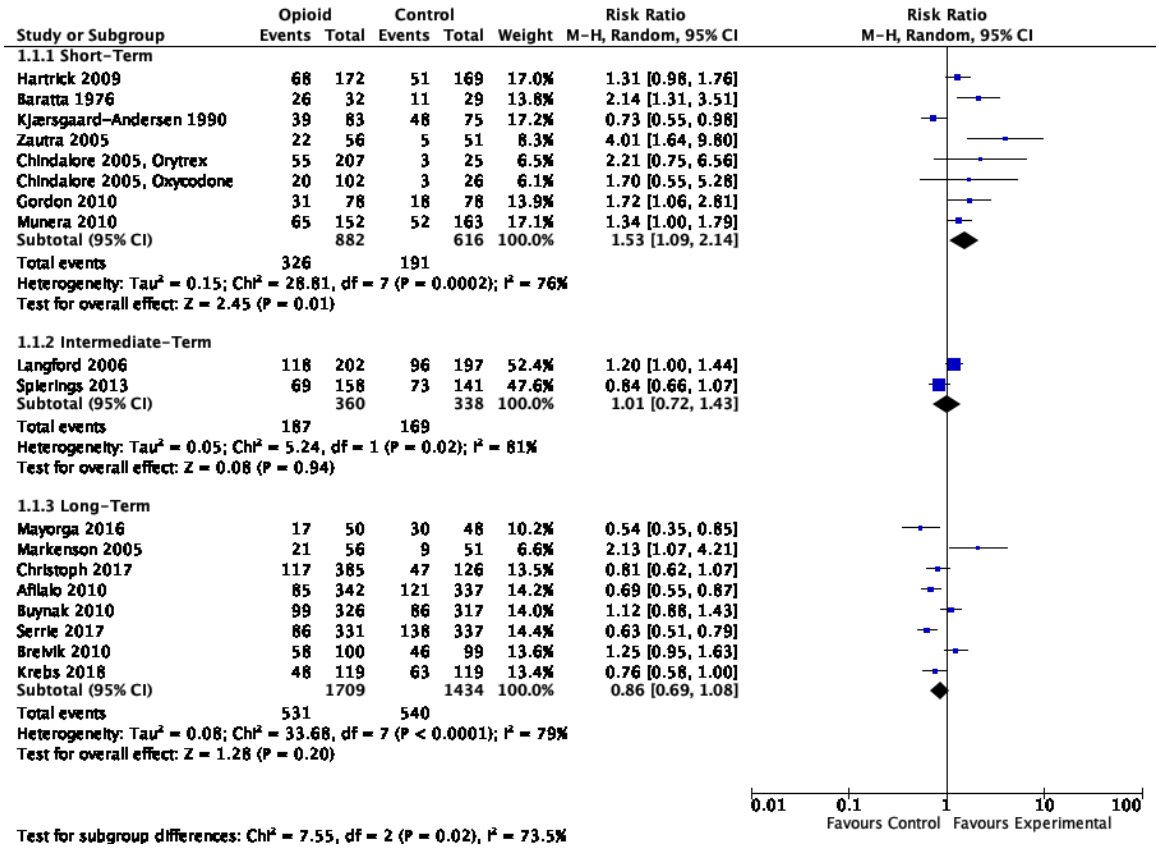
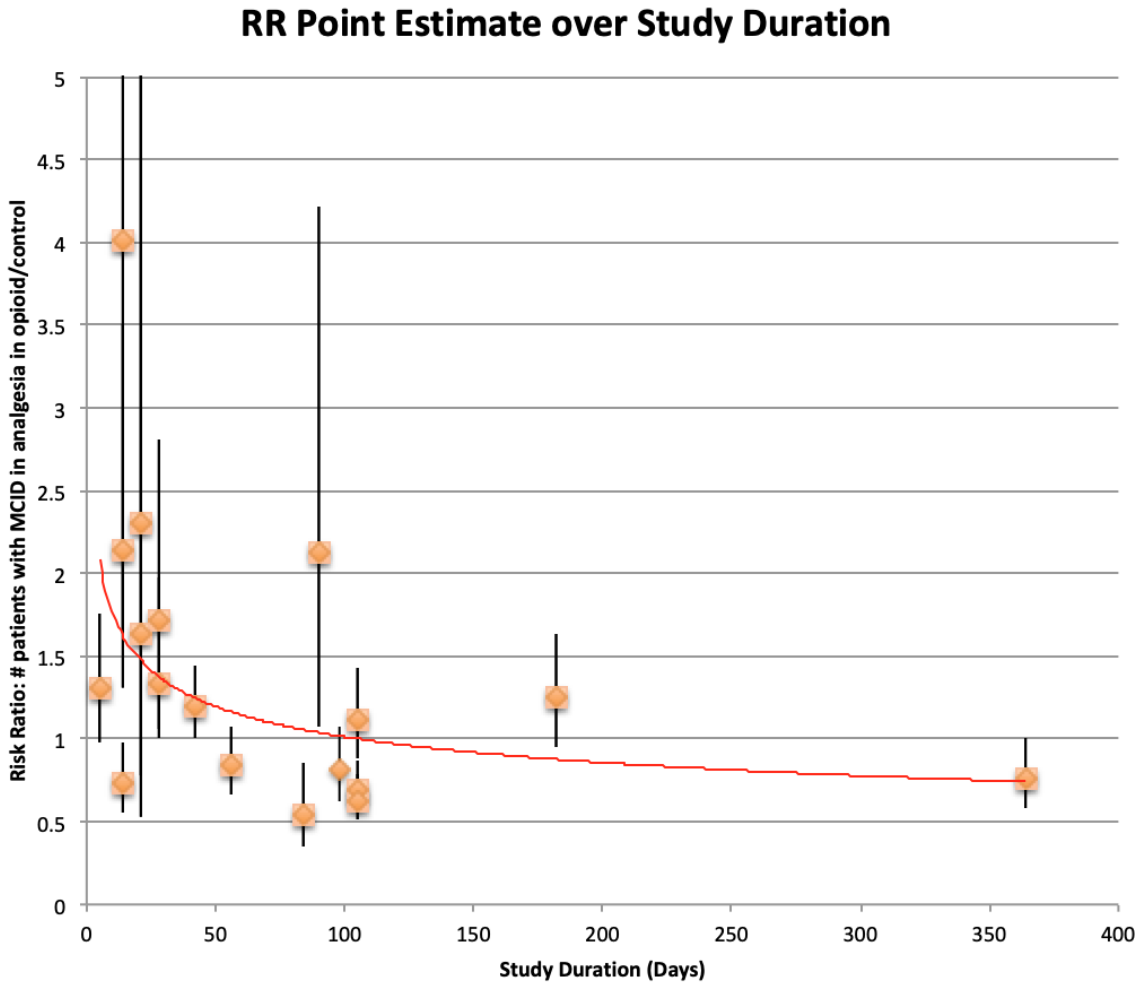


Figure 3: Scatterplot of the RR of the analgesic efficacy of opioids versus control therapy over study duration



RR = risk ratio
MCID = minimum clinically important difference

Figure 4: Forest plot of the analgesic efficacy of opioids compared to control therapy for long-term EERW trials compared to traditional long-term RCTs

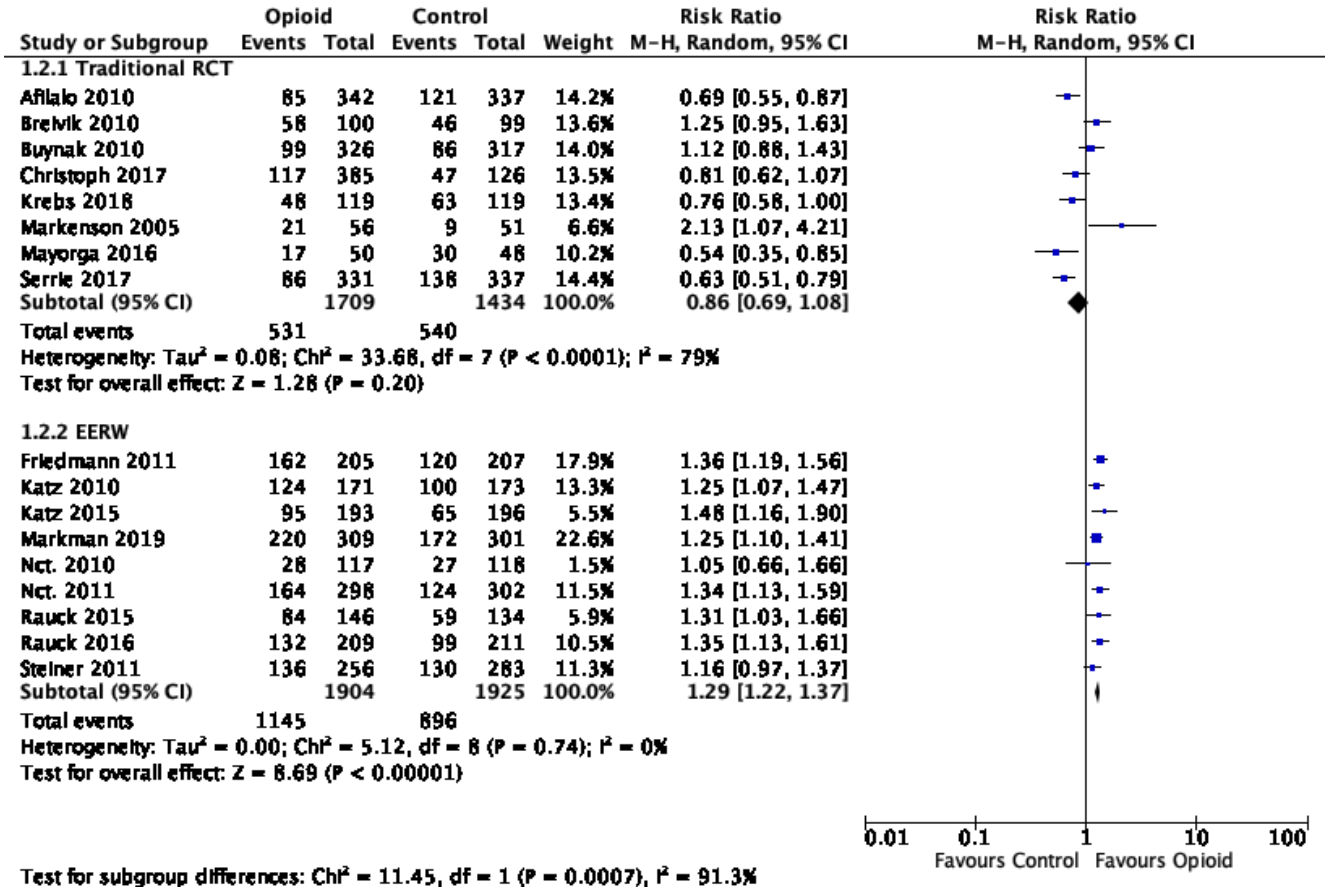


Figure 5: Forest plot of the analgesic efficacy of opioids compared to control therapy for traditional long-term high-dose and low-dose RCTs

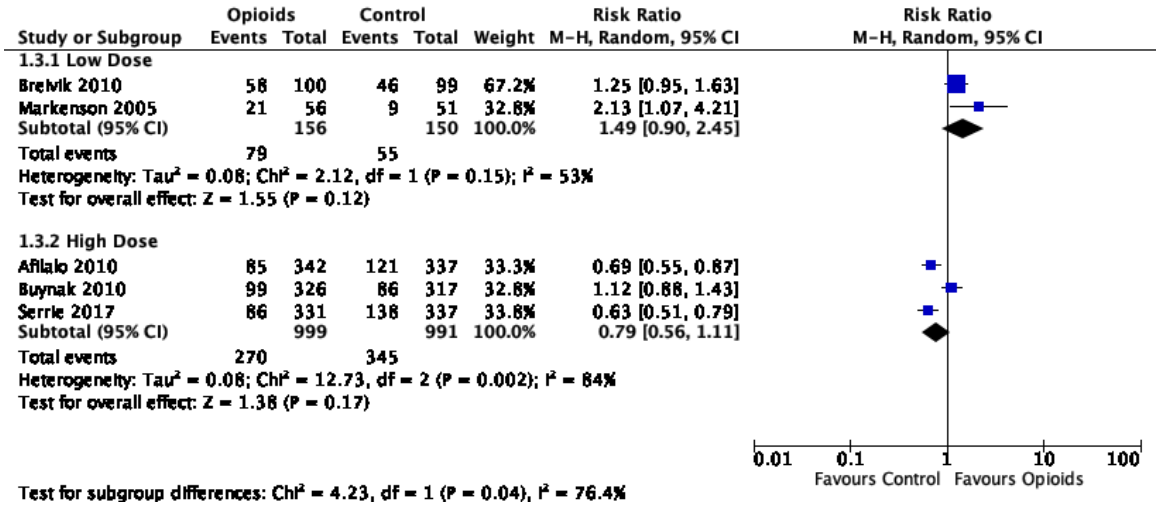


Figure 6a: Risk of bias summary for author judgements of each risk of bias item for each study included in our primary analysis

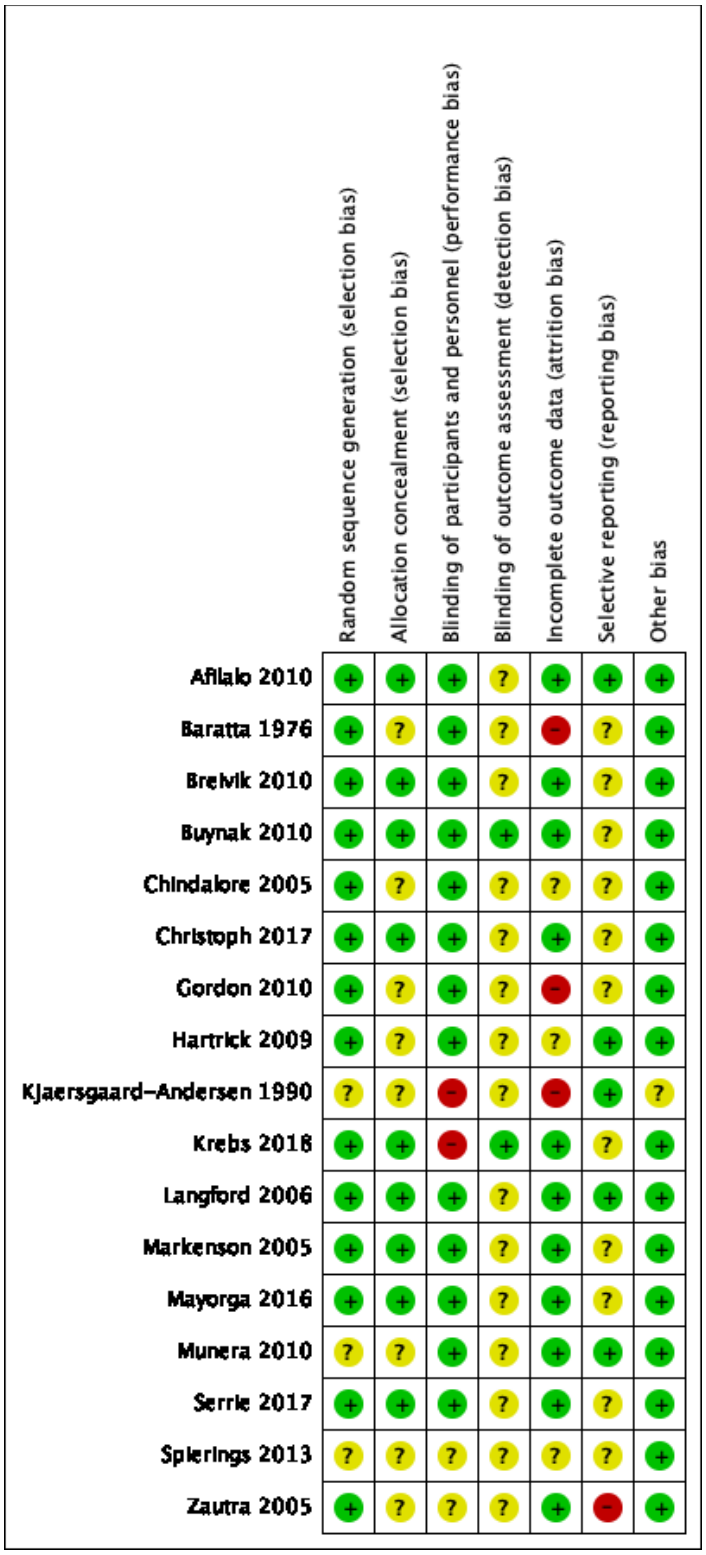


Figure 6b: Risk of bias graph for author judgements of each risk of bias item for each study included in our primary analysis presented as percentages across all included studies

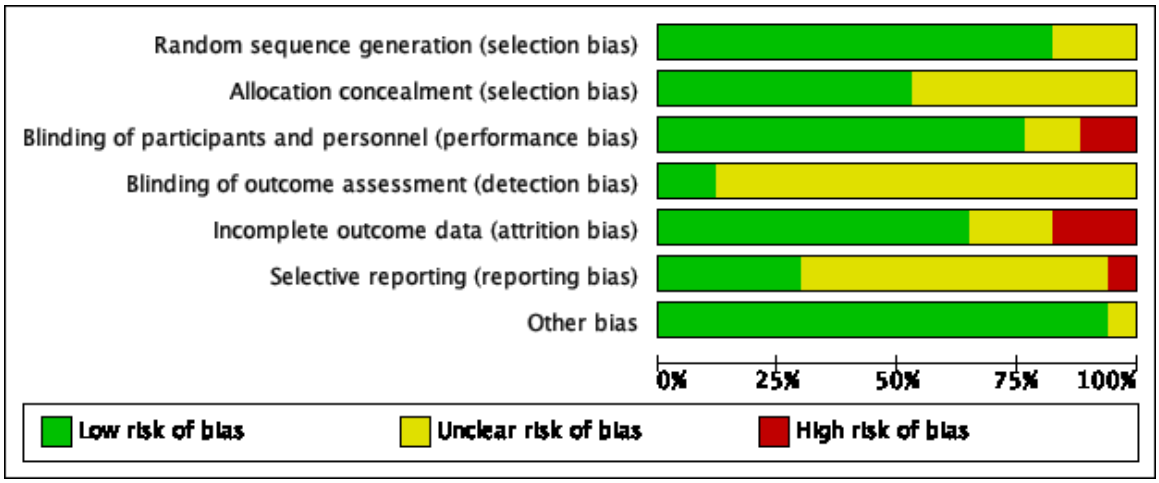


Figure 7a: Risk of bias summary for author judgements of each risk of bias item for each EERW study

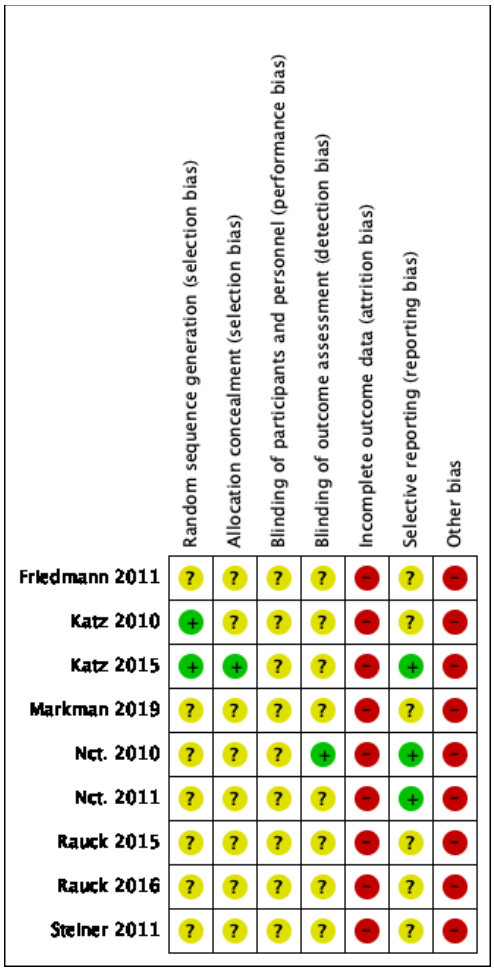


Figure 7b: Risk of bias summary for author judgements of each risk of bias item for each EERW study, presented as percentages across all included studies

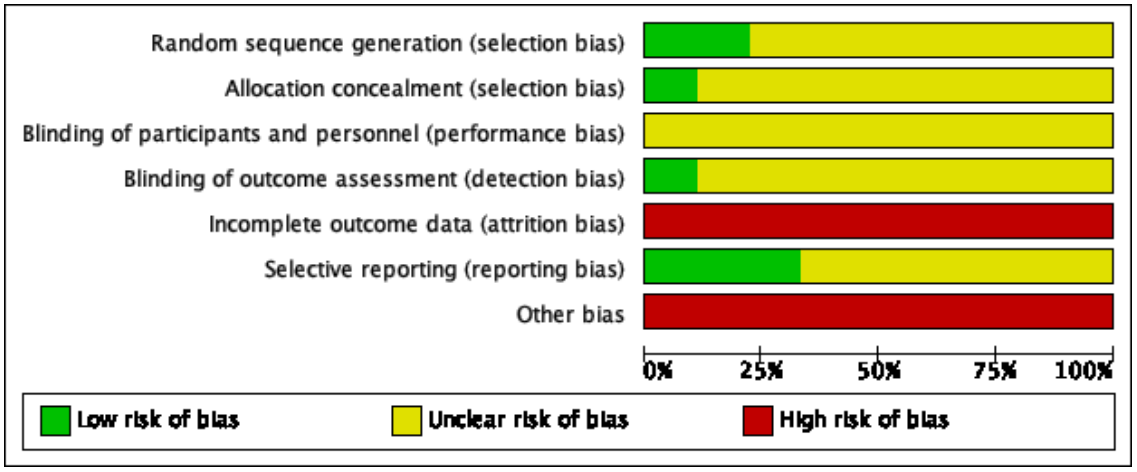


Figure 8: Funnel plot of analysis 1.1 (analgesic efficacy of opioids compared to control therapy for short, intermediate, and long treatment duration)

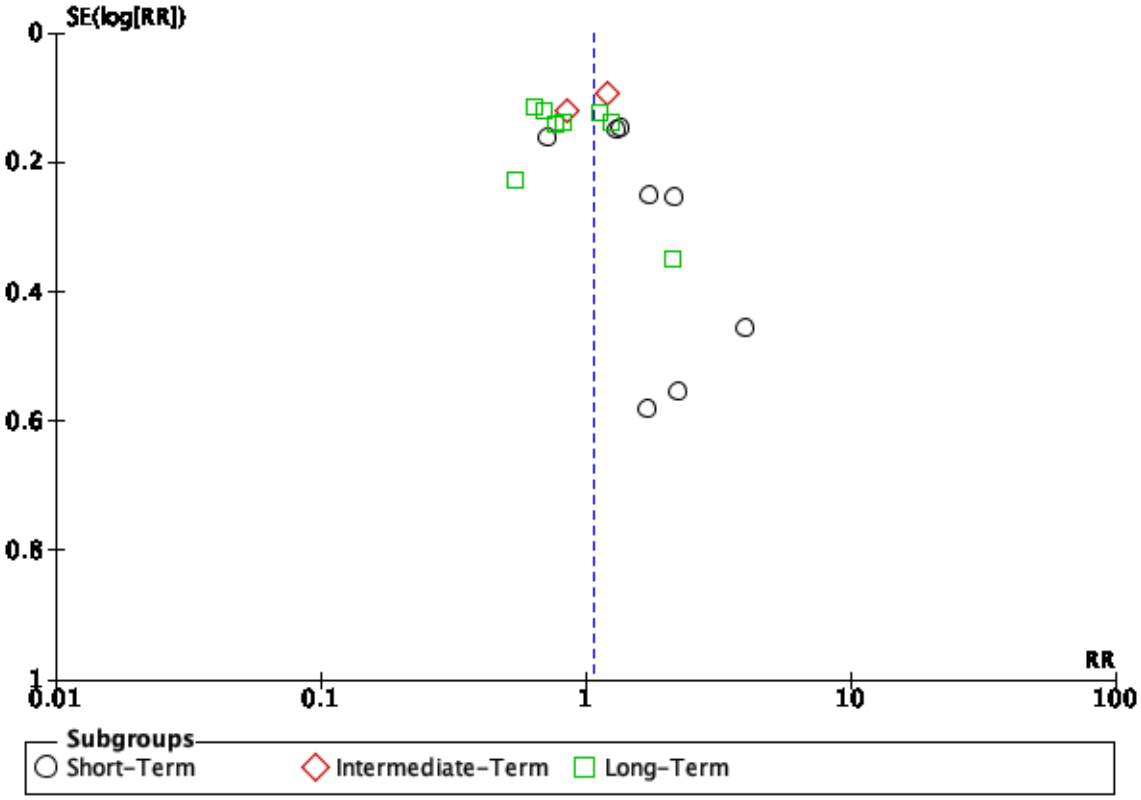


Figure 9: Funnel plot of analysis 1.2 (analgesic efficacy of opioids compared to control therapy for long-term EERW trials and traditional RCT designs)

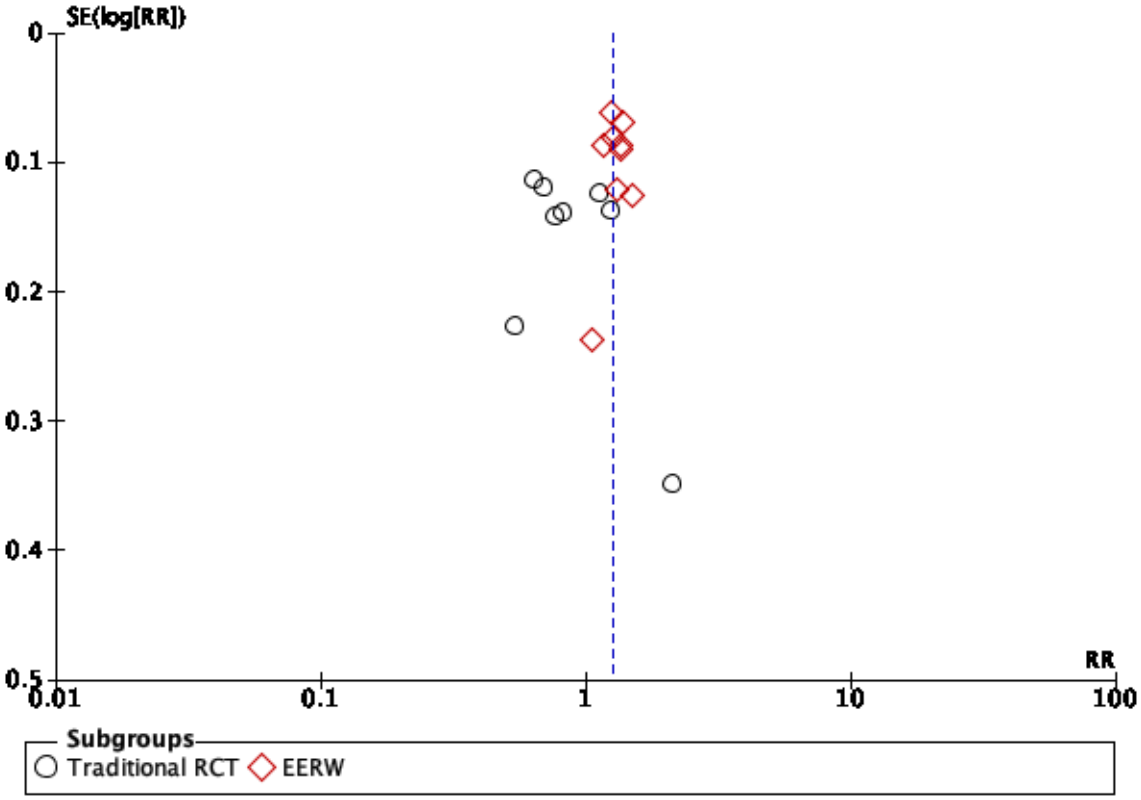


Table 1: Individual exclusion reasons

Study Identifier	Reason for Exclusion
Afilalo 2009	Duplicate
Anonymous 2010	Wrong study design
Aparasu 2014	Wrong study design
Arai 2015	Opioids as rescue medication
Baron 2016	Wrong study design
Bell 2004	Wrong study design
Beyaz 2012	Wrong outcomes
Beyaz 2011	Abstract of another paper
Boissier 1992	Wrong comparator
Breivik 2010	Corrections to previous paper
Bruehl 2014	Wrong outcomes
Bruehl 2013	Wrong patient population
Bruehl 2015	Abstract, unable to find corresponding paper
Buynak 2009	Wrong intervention
Buynak 2009	Duplicate
Buynak 2009	Duplicate
Caldwell 1999	Wrong outcomes
Caldwell 2002	Wrong outcomes
Christoph 2016	Abstract of another paper
Chu 2012	Wrong outcomes
Cloutier 2010	Duplicate
Cloutier 2013	Duplicate
Cloutier n.d.	Duplicate
Codding 2009	Abstract, unable to find corresponding paper
Codding 2008	Abstract, unable to find corresponding paper
Corsinovi 2009	Wrong comparator
DeSouza 2010	Missing: cannot find full text

deSouza 2013	Duplicate
Doak 1992	Missing: cannot find full text
Eerdekens 2016	Duplicate
Etropolski, Lange 2009	Duplicate
Etropolski, Rauschkolb-Loffler 2009	Duplicate
Etropolski n.d.	Wrong intervention
Euctr 2004	Duplicate
Euctr, D.E. 2005	Outcomes were not reported
Euctr, G.B. 2005	Study did not complete
Euctr 2006	Wrong comparator
Euctr, A.T. 2007	Outcomes were not reported
Euctr, C.Z. 2007	Wrong outcomes
Euctr, G.B. 2008	Wrong outcomes
Euctr, H.U. 2008	Wrong intervention
Euctr 2009	Duplicate
Euctr 2011	Outcomes were not reported
Euctr 2013	Duplicate
Euctr 2015	Trial has been temporarily halted
Fidelholtz 2011	Abstract of another paper
Friedman 2015, Academic Emergency Medicine	Abstract of another paper
Friedman 2015, JAMA	No explicit comparison of opioid to placebo
Gimbel 2016	Opioids as rescue medication
Gimbel 2015	Wrong patient population
Gordon, Callaghan 2010	Duplicate
Gordon, Rashiq 2010	Duplicate
Green 2014	Abstract, unable to find corresponding paper
Gross 2008	Wrong outcomes
Hale 1997	Wrong comparison
Hale 2005	Opioids as rescue medication

Hale 2007	Opioids as rescue medication
Hale 2009	Duplicate
Hale 2010	Wrong study design
Hale, Khan 2010	Wrong patient population
Hale, D'Andrea 2012	Abstract, unable to find corresponding paper
Hale, Patrick 2012	Abstract, unable to find corresponding paper
Hale, Laudadio 2015	Opioids as rescue medication
Hale, Zimmerman Jr. 2015	Abstract of another paper
Hale, Zimmerman 2015	Opioids as rescue medication
Hofmann 2016	Secondary analysis, outcome not relevant
Ingpen 1969	Missing: cannot find full text
Isrctn 2008	Duplicate
James 1993	Missing: cannot find full paper
Jamison 2013	Secondary analysis, outcome not relevant
Jensen 2013	Secondary analysis, outcome not relevant
JprnJapicCTI 2013	Duplicate
Katz 2007	Opioids as rescue medication
Kavanagh, Ashworth 2009	Abstract, unable to find corresponding paper
Kavanagh, Lange 2009	Abstract, unable to find corresponding paper
Kawamata 2019	EERW <12 weeks
Kelly, Greene 2009	Duplicate
Kelly, Kuperwasser 2009	Duplicate
Kelly, Etropolski 2010	Duplicate
Kelly, Lange 2010	Duplicate
Kivitz 2006	Wrong outcomes
Kivitz 2012	Abstract, unable to find corresponding paper
Kolcun 2018	Duplicate
Kopecky 2015	Abstract, unable to find corresponding

	paper
Kopecky 2017	Secondary analysis, outcome not relevant
Krebs 2017	Duplicate
Kroner 1991	Abstract of another paper
Kuntz 1996	Wrong outcomes
Leslie 2009	Abstract, unable to find corresponding paper
Likar 1997	Wrong outcomes
Markman 2018	Secondary analysis, outcome not relevant
Matsumoto 2005	Wrong outcomes
Mayorga 2013	Abstract of another paper
Miller 2013	Abstract, unable to find corresponding paper
Nalamachu 2014	Opioids as rescue medication
Nalamachu 2015	Secondary analysis
Nct 2007, nct00420992	Wrong outcomes
Nct 2006, nct00361582	Outcomes were not reported
Nct 2006, nct00411164	No responder analysis
Nct 2016, nct02946073	Outcomes were not reported
Nct 2007, nct00531427	Wrong outcomes
Nct 2016, nct02716857	Outcomes were not reported
Nct 2005, nct00226421	Outcomes were not reported
Nct 2009, nct00979953	Wrong outcomes
Nct 2015, nct02362672	Study has not completed
Nct 2011, nct01344720	Outcomes were not reported
Nct 2011, nct01502644	Wrong outcomes
Nct 2010, nct01240863	Duplicate
Nct 2006, nct00315887	Outcomes were not reported
Nct 2006, nct00315874	Outcomes were not reported
Nct 2008, nct00631319	Outcomes were not reported
Nct 2006, nct00404183	Outcomes were not reported
Nct 2006, nct00315445	Wrong outcomes

Nct 2009, nct01008618	Opioids as rescue medication
Nct 2007, nct00449176	Duplicate
Nct 2007, nct00486811	Duplicate
Nct 2006, nct00315458	Wrong outcomes
Nct 2016, nct02892591	Study has not completed
Nct 2012, nct01675167	Opioids as rescue medication
Nct 2012, nct01633944	Duplicate
Nct 2006, nct00346047	Outcomes were not reported
Nct 2006, nct00345787	Outcomes were not reported
Nct 2015, nct02501564	Outcomes were not reported
Nct 2005, nct00108771	Outcomes were not reported
Nct 2005, nct00236366	Duplicate
Nct 2013, nct01789970	Duplicate
Nct 2010, nct01081912	Wrong patient population
Nct 2012, nct01709214	Duplicate
Nct 2006, nct00313846	Wrong outcomes
Nct 2009, nct00980798	Duplicate
Ogawa 2009	Abstract, unable to find corresponding paper
Quiding 1992	Missing: cannot find full paper
Raffaeli 2006	Wrong outcomes
Rauck 2006	Abstract of another paper
Rauck 2013	Abstract of another paper
Rauck, Hale 2014	Abstract of another paper
Rauck, Nalamachu 2014	Opioids as rescue medication
Rauck 2015	Abstract of another paper
Rauck 2017	Abstract, unable to find corresponding paper
Rauschkolb 2009	Abstract of another paper
Richards 2002	Abstract, unable to find corresponding paper
Roth 2000	Wrong outcomes

Schliessbach 2017	Wrong outcomes
Shapiro 2010	Abstract of another paper
Spierings 2013	Wrong intervention
Stein 1999	Wrong outcomes
Steiner 2009	Abstract of another paper
Taylor 2010	Abstract of another paper
Vojtaššák 2011	Wrong outcomes
Vondrackova 2008	Wrong outcomes
Wallace 1994	Missing: cannot find full text
Webster 2006	Outcomes were not reported
Weil 2017	Wrong outcomes
Wen 2015	Opioids as rescue medication
2004	Wrong study design

Table 2: Study characteristics of studies included in our primary analysis

Study	Design	Condition	Enrolment	Duration (weeks)	Setting	Females (%)	Mean Age	Opioid Intervention	Control
Short-Term Studies									
Baratta 1976	Parallel	Low-back syndrome	105	2	Private family practice	23.4	37.0	Propoxyphene	Placebo
Chindalore 2005	Parallel	OAK, OAH	155	3	Unclear	69.2	54.3	Oxycodone, oxycodone/ naloxone	Placebo
Gordon 2010	Crossover	CLBP	78	8*	Unclear	60.3	50.7	Buprenorphine transdermal	Placebo
Hartrick 2009	Parallel	DJD	674	10 days	Outpatients	49.2	61.4	Oxycodone HCl IR	Placebo
Kjaersgaard-Andersen 1990	Parallel	OAH	158	4	Orthopaedic clinics	45.6	66.5	Codeine/ paracetamol	Paracetamol
Munera 2010	Parallel	OAK, OAH	315	4	Outpatient pain centres	67.3	61.0	Buprenorphine transdermal	Placebo
Zautra 2005	Parallel	OA	107	90 days	Unclear	73.1	63.3	Oxycodone CR	Placebo
Intermediate-Term Studies									
Langford 2006	Parallel	OAK, OAH	416	6	Unclear	66.5	66.0	Fentanyl transdermal	Placebo
Spierings 2013	Parallel	OAK, OAH	614	16	Unclear	62.5	57.4	Oxycodone CR	Placebo
Long-Term Studies									
Afilalo 2010	Parallel	OAK	684	15	Unclear	60.4	58.3	Oxycodone CR	Placebo
Breivik 2010	Parallel	OAK, OAH	199	24	Pain & rheumatology clinics, public advertising	68.3	62.9	Buprenorphine transdermal	Placebo
Buynak 2010	Parallel	CLBP	981	15	Unclear	57.9	49.9	Oxycodone CR	Placebo
Christoph 2017	Parallel	CLBP	641	14	Unclear	64.9	57.5	Cebranopadol	Placebo
Krebs 2018	Parallel	OAK, OAH, CBP	265	52	Primary care clinics	30.0	58.3	Opioids	Non-opioid therapy
Markenson 2005	Parallel	OA	109	90 days	Unclear	72.9	63.0	Oxycodone CR	Placebo
Mayorga 2016	Parallel	OAK	196	16	Unclear	56.1	58.4	Oxycodone CR	Placebo
Serrie 2017	Parallel	OAK	990	15	Unclear	71.6	62.1	Oxycodone CR	Placebo

*8 weeks total: 4 weeks per patient per arm

Table 3: Study characteristics of EERW studies

Study	Design	Condition	Enrolment	Duration (weeks)	Setting	Females (%)	Mean Age	Opioid Intervention	Control
Long-Term EERW Studies									
Friedmann 2011	EERW	OAK, OAH	412†	12*	Unclear	69.9	58.2	Oxycodone ER	Placebo
Katz 2010	EERW	OAK, OAH	344†	12*	Unclear	58.4	54.5	Morphine sulfate/naloxone	Placebo
Katz 2015	EERW	CLBP	389†	12*	Primary care, pain specialists	52.6	49.6	Oxycodone ER	Placebo
Markman 2019	EERW	CLBP	610†	12*	Unclear	58.5	51.4	Oxycodegol	Placebo
Nct. 2010	EERW	CLBP	235†	12*	Unclear	54.5	--	Buprenorphine HCl buccal film	Placebo
Nct. 2011	EERW	CLBP	600†	12*	Unclear	56.3	53.2	Oxycodone/ naloxone CR	Placebo
Rauck 2015	EERW	CLBP	281†	12*	Unclear	55.7	47.4	Oxycodone/ naltrexone HCl ER	Placebo
Rauck 2016	EERW	CLBP	462†	12*	Unclear	56.2	50.1	Buprenorphine buccal film	Placebo
Steiner 2011	EERW	CLBP	541†	12*	Unclear	55.0	49.4	Buprenorphine transdermal	Placebo

†Total randomized after titration phase
*Length of the maintenance period

Table 4: Characteristics of individual studies

Afilalo 2010	
Methods	After an initial washout period, participants were randomized 1:1:1 to tapentadol ER, oxycodone CR, or placebo arms, and entered a 3-week titration period where dosage was increased based on need until their optimal dose was reached. This was followed by a 12-week maintenance phase where patients were encouraged to maintain steady dosage. Paracetamol was available as rescue medication.
Participants	1030 adults aged ≥ 40 years with OA of the knee were recruited to 4 sites in Australia, 15 in Canada, 6 in New Zealand, and 87 the US. Of these patients, 346 were randomized to the tapentadol arm, 345 to the oxycodone arm, and 339 to the placebo arm. 60.4% were female and the average age was 58.3 years.
Interventions	Tapentadol ER 50-250 mg bid, oxycodone HCl CR 10-50 mg bid, placebo bid.
Outcomes	Patient Global Impression of Change (PGIC) at weeks 5, 9, and 12 of maintenance period or at the end of treatment visit. Patients achieving ≥30% and ≥50% improvement in pain intensity from baseline to week 12 of the maintenance period, measured on an 11-point numeric rating scale (NRS) (0 = no pain, 10 = worst pain imaginable). As per our protocol, we used the ≥30% improvement measure.
Baratta 1976	
Methods	Eligible patients were randomized 1:1:1 to carisoprodol, propoxyphene, or placebo arms and were followed for 2 weeks. No additional analgesics were permitted.
Participants	105 patients with "muscle spasm and/or stiffness associated with acute or chronic low-back syndrome" were drawn primarily from private family practices. 11 were excluded from analyses, but authors did not report their assigned groups. Of the remaining 94, 33 were allocated to the carisoprodol arm, 32 to the propoxyphene arm, and 29 to the placebo arm. 23.4% were female, and the average age was 37.0 years.
Interventions	Carisoprodol 350 mg qid, propoxyphene 65 mg qid, placebo.
Outcomes	Investigator assessment of global improvement as "no relief", "mild improvement", or "satisfactory" at week 2. We defined responders as those that investigators assessed as "mild improvement" or "satisfactory", as this was closest to "moderate" improvement.
Breivik 2010	
Methods	After a 5-9 day screening phase where eligibility and patient characteristics were assessed, patients were randomized 1:1 to transdermal buprenorphine or placebo arms and entered a 24-week double-blind phase. Paracetamol was available as rescue medication.
Participants	199 adults aged ≥ 40 years with OA of the knee and/or hip were recruited from pain & rheumatology clinics and public advertising to 19 centres in Sweden, Finland, Norway, and Denmark. 100 were randomized to the buprenorphine arm and 99 to the placebo arm. 68.3% were female and the average age was 62.9 years.
Interventions	Buprenorphine TD 7-day 5-20 µg/h, placebo.
Outcomes	Patient's Global Impression of Change (PGIC) from 1 = ‘very much improved' to 7 = ‘very much worse’ on final visit at week 24. We defined responders as 'minimally improved' and better, as

	this was closest to 'moderate' improvement. Authors only included 185 of 199 randomized patients in their analysis, but we considered those not included as non-responders.
Buynak 2010	
Methods	After a screening and washout period, eligible patients were randomized 1:1:1 to tapentadol, oxycodone, or placebo arms and entered a 15-week double-blind period. Dose titration was permitted for the first 3 weeks, and dose was to be maintained for the final 12 weeks. Acetaminophen was available as rescue medication.
Participants	981 adults aged ≥ 18 years with non-malignant CLBP were recruited from 85 US sites, 15 Canadian sites, and 3 Australian sites. 326 were randomized to placebo, 321 to tapentadol, and 334 to oxycodone. 57.9% were female and the average age was 49.9.
Interventions	Tapentadol ER 100-250 mg bid, oxycodone CR 20-50 mg bid, placebo bid.
Outcomes	Proportion of patients who experienced ≥30% and ≥50% reductions in pain intensity at week 15 relative to baseline, measured on an 11-point NRS (0 = no pain, 10 = worst pain imaginable). As per our protocol, we used the ≥30% improvement measure. Patients global impression of change from 1 = 'very much improved' to 7 = 'very much worse'. Measurement was done twice during the maintenance period and once at the end of study treatment (week 15).
Chindalore 2005	
Methods	After they were assessed for eligibility, patients entered a 3-week double-blind period where they were randomized 2:2:2:1 to the two oxycodone/naloxone arms, the oxycodone arm, and the placebo arm. All oxycodone arms (including the naloxone formulations) received the same daily dose and titration schedule, which started at 10 mg/day and ended at 40 mg/day.
Participants	362 adults aged 18-70 years (inclusive) with OA of the hip or knee were recruited to participate in this study. 52 were assigned to receive placebo, 103 to receive oxycodone qid, 104 to receive oxycodone/naloxone qid, and 103 to receive oxycodone/naloxone bid. 69.2% were female and the average age was 54.3.
Interventions	Oxycodone IR 2.5-10 mg qid, oxycodone IR 2.5-10 mg + naloxone 0.001 mg (Orytrex) qid, oxycodone IR 5-20 mg + naloxone 0.001 mg (Orytrex) bid, placebo bid or qid.
Outcomes	Patient-rated quality of analgesia as poor, fair, good, very good, or excellent at weeks 1, 2, and 3. Authors considered responders to be "very good" or "excellent". Global assessment of study drug as poor, fair, good, very good, or excellent at weeks 1, 2, and 3. Authors considered responders to be "very good" or "excellent"
Christoph 2017	
Methods	After screening and washout periods, eligible patients were randomized 1:1:1:1:1 to placebo, cebranopadol 200 µg, cebranopadol 400 µg, cebranopadol 600 µg, and tapentadol arms. Those in the cebranopadol 200 µg arm maintained this dose throughout the study, while those in the 400 µg and 600 µg arms and those in the tapentadol arm were gradually titrated to these target doses over two weeks. No dose adjustment was allowed after the target was reached. Paracetamol/acetaminophen was available as rescue medication.
Participants	641 adults aged 18-80 years with non-malignant CLBP were recruited from 79 investigational sites in 11 European countries. Of these patients, 131 were randomized to the cebranopadol 200 µg arm, 128 to the cebranopadol 400 µg arm, 130 to the cebranopadol 600 µg arm, 126 to the

	tapentadol arm, and 126 to the placebo arm. 64.9% were female and the average age was 57.5 years.
Interventions	Tapentadol PR 200 mg bid, cebranopadol 200 µg once daily, cebranopadol 400 µg once daily, cebranopadol 600 µg once daily, placebo.
Outcomes	Proportion of patients that achieved ≥30% and ≥50% improvement in 24-hour pain at week 14 compared to baseline, measured on an 11-point NRS scale (0 = no pain, 10 = worst pain imaginable). As per our predefined outcomes hierarchy, we used the ≥30% improvement measure in our analyses. Patient's Global Impression of Change, measured at week 14 or end of treatment visit.
Friedmann 2011	
Methods	This study had an enriched enrolment randomized withdrawal design. After screening and washout periods, all patients with a baseline pain intensity of ≥5 on an 11-point scale (where 0 = "no pain") and a diary compliance of ≥70% continued on to a 2-week open-label titration period. During this phase, patients were given oxycodone and titrated from 5 mg bid to 20 mg bid. Those who tolerated a dosage of 20 mg bid and had a diary compliance of ≥75% entered a 12-week double-blind phase. In this phase, patients were randomized 1:1 to either continue their dosage of oxycodone or switch to placebo. Patients assigned placebo were blindly tapered from oxycodone over 2 weeks: 3 days of 15 mg bid, 4 days of 10 mg bid, and 7 days of 5 mg bid. Patients assigned oxycodone were allowed to alter their dose for 4 weeks, after which it was fixed for the remaining 8 weeks.
Participants	558 adults aged 40-75 years with OA of knee and/or hip were recruited to 61 US sites. 412 entered the double-blind phase where 207 were randomized to placebo and 205 to oxycodone. 69.9% were female, and the average age was 58.2.
Interventions	Oxycodone ER 5-40 mg bid, placebo bid.
Outcomes	Patient-rated quality of analgesia as "poor," "fair," "good," "very good," or "excellent", measured weekly. Reported at week 12. We defined responders to be those patients that reported "fair" or better, as this was closest to "moderate", as defined in our protocol. We considered those with "missing" data to be non-responders. We used this measure in our analyses, as per our predefined outcomes hierarchy. Patient global assessment of study medication as "poor," "fair," "good," "very good," or "excellent", measured weekly. Reported at week 12.
Gordon 2010	
Methods	This was a placebo-controlled crossover study. After an initial washout period (2-7 days), patients were randomized 1:1 to buprenorphine TD or placebo. After 4 weeks, patients crossed over to the alternate treatment for another 4 weeks. Acetaminophen was available as rescue medication.
Participants	78 opioid-experienced adults aged ≥ 18 years with moderate to severe CLBP were recruited to 13 Canadian centres. 39 were randomized to buprenorphine and 39 to placebo. After the initial 4 weeks, 35 patients switched to buprenorphine and 29 switched to placebo. 60.3% were female and the average age was 50.7 years.
Interventions	Buprenorphine TD 7-day 10-40 µg/h, placebo.
Outcomes	Patient- and investigator-rated effectiveness of treatment from 0-3, where 0 = not effective, 1 = slightly effective, 2 = moderately effective, and 3 = highly effective. Measurements were made

	at screening, baseline, week 4 (crossover), and week 8 (end of double-blind phase). Authors considered those that rated the treatment as 2 or 3 to be responders. We considered all discontinuations to be non-responders. We used this measure in our analyses, as per our predefined outcomes hierarchy. Investigator-assessed clinical benefit of therapy from 1-4, where 1 = great deal of benefit, 2 = moderate benefit, 3 = slight benefit, and 4 = no benefit. This measurement was made at the end of the double-blind phase (week 8).
Hartrick 2009	
Methods	After a 28-day screening and run-in period, patients entered a 10-day treatment phase where they were randomly assigned 1:1:1:1 to treatment with tapentadol 50 mg, tapentadol 75 mg, oxycodone, or placebo. Rescue medication was not permitted.
Participants	674 adults aged 18-80 years with degenerative joint disease were randomly assigned to the four treatment arms: 161 to tapentadol 50 mg, 169 to tapentadol 75 mg, 172 to oxycodone, and 172 to placebo. 49.2% were female and the average age was 61.4.
Interventions	Tapentadol IR 50 mg, tapentadol IR 75 mg, oxycodone HCl IR 10 mg, placebo. All were instructed to be taken every 4-6 hours based on need (4-6 times per day).
Outcomes	PGIC from 1 = very much improved to 7 = very much worse, assessed at end of treatment or at discontinuation. Authors defined responders as those who answered "improved" or "very much improved". Proportion of patients with a decrease in pain intensity of ≥30% and ≥50% at day 5 on an 11-point NRS scale (0 = no pain, 10 = worst pain imaginable). We used the ≥30% improvement measure in our analyses, as per our predefined outcomes hierarchy.
Katz 2010	
Methods	This study had an enriched enrolment randomized withdrawal design. After an initial screening/washout period, all eligible patients entered a titration period that lasted up to 45 days where they were titrated up to an appropriate dose of morphine-naloxone. “Responders” to treatment were allowed to enter the double-blind treatment phase. Investigators considered "responders" to be those patients whose "average-pain intensity score on the Brief Pain Inventory (BPI) scale over the last 4 days before the clinic visit was ≤4 and had declined by ≥2 points from baseline". All responders were randomized 1:1 to continue morphine-naloxone treatment or to switch to placebo. Those randomized to placebo were tapered from morphine-naloxone over 2 weeks using a “double-dummy design”. Acetaminophen was available as rescue medication.
Participants	547 outpatients aged ≥ 21 years with OA of the hip and/or knee entered the titration phase. 344 entered the double-blind phase where 173 were randomized to placebo and 171 to morphine-naloxone. 58.4% were female and the average age was 54.5 years.
Interventions	Morphine sulfate with sequestered naltrexone (min. 20 mg) bid, placebo bid.
Outcomes	PGIC on a 7-point scale from “very much improved” to “very much worse” since last visit, measured at weeks 0, 1, 2, 4, 6, 8, 10, and 12. However, the data were uninterpretable as they weren't reporting change from baseline. Data was therefore not reported. Responder analysis of proportion of patients achieving ≥ 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90% improvement in 24-hr average pain intensity from baseline to week 12 of maintenance phase. As per our predefined outcomes hierarchy, we used the ≥30% improvement measure.
Katz 2015	

Methods	This study had an enriched enrolment randomized withdrawal design. After a screening and washout period, patients with a pain intensity score of ≥5 and ≤9 entered a titration phase (up to 6 weeks) where they were titrated to an appropriate dose of oxycodone. Those who were successfully titrated were allowed to move onto a 12-week double-blind maintenance phase. Successful titration required that participants had "(1) remained on a stable (ie, unchanged) dose of Xtampza ER for the last 7 consecutive days, (2) had a 24-hour pain intensity score ≤4 for 6 of the last 7 days, (3) had an average 24-hour pain intensity score ≤4 for the last 7 days, (4) had a reduction of at least 2 points in the average 24-hour pain intensity score for the last 7 days, and (5) had taken ≤2000 mg of acetaminophen daily during the last 7 days". Eligible patients were randomized 1:1 to continue oxycodone or switch to placebo. Those patients randomized to placebo were blindly tapered from oxycodone over 20 days. Acetaminophen was available as rescue medication.
Participants	740 adults aged 18-75 years with moderate to severe CLBP were recruited from primary care and pain specialists. 389 entered the double-blind phase where 196 were randomized to placebo and 193 to oxycodone. 52.6% were female and the average age was 49.6.
Interventions	Oxycodone ER 20-80 mg bid, placebo bid.
Outcomes	PGIC rated on a 7-point scale from "very much improved" to "very much worse" at week 12 of the double-blind phase or at discontinuation. We defined responders as "a little improved" or better, as this was closest to "moderate". Responder analyses of proportion of patients with ≥30% and ≥50% improvements in pain intensity at week 12 compared to baseline. Pain intensity was rated on a NRS from 0-10 (0 = no pain, 10 = worst pain imaginable). As per our predefined outcomes hierarchy, we used the ≥30% improvement measure in our analyses.
Kjaersgaard-Andersen 1990	
Methods	Patients were randomized 1:1 to receive either codeine/paracetamol or paracetamol alone for 4 weeks. There was no washout period before the start of the study. Ibuprofen was available as rescue medication.
Participants	161 adults aged ≥18 years with OA of the hip were recruited from orthopaedic clinics in Denmark. Of these, 158 were randomized: 83 were assigned to codeine/paracetamol and 75 to paracetamol. 45.6% were female and the average age was 66.5.
Interventions	Codeine 60mg/paracetamol 1g tid, paracetamol 1g tid.
Outcomes	Patient-rated overall evaluation of treatment as "poor", "fair", "good", "very good" or "excellent", measured at the end of week 4 (final visit). Investigators considered as "responders" those patients that rated the treatment as "good" or higher. Patient-rated all-week pain for the previous week as "none", "slight", "moderate", "severe", or "unbearable". Measured at baseline and at the ends of weeks 1, 2, 3, and 4. We considered non-responders to be those that rated all-week pain as "moderate", "slight", or "none" and those that discontinued from the study. As per our predefined outcomes hierarchy, we used the 2-week all-week pain measure in our analyses.
Krebs 2018	
Methods	Eligible patients were randomized 1:1 to an opioid arm and a non-opioid arm, and were followed-up for 12 months. Both interventions used three medication steps. The opioid prescribing strategy was as follows: 1) morphine IR, hydrocodone/acetaminophen, oxycodone IR, 2) morphine sustained-action (SA) and oxycodone SA 3) transdermal fentanyl. Although single-opioid therapy was preferred, patients had the option of using an approved SA opioid and

	as-needed IR opioid. The non-opioid prescribing strategy was as follows: 1) acetaminophen and NSAIDs, 2) adjuvant oral medications and topical analgesics, 3) tramadol, pregabalin, duloxetine. Patients initially received step 1 medications, and could alter their treatment plan from there. The non-opioid analgesics were also available to the opioid group. Authors state that "patients were allowed to participate in nonpharmacological pain therapies outside of the study and were encouraged to complete outcome assessments regardless of their participation in the active interventions".
Participants	265 patients with OA of the knee or hip or chronic back pain were recruited from 62 primary care clinics in Minneapolis, Virginia. However, 25 withdrew before randomization, so only 240 were randomized. 120 were assigned to the opioid arm and 120 to the non-opioid arm. 15% were female and the average age was 58.3 years.
Interventions	Opioids (max. 100 morphine-equivalent mg per day), non-opioids.
Outcomes	Proportion of patients reporting ≥30% improvement in pain intensity on the BPI from baseline to the end of month 12.
Langford 2006	
Methods	After a 1 week run-in phase where baseline measures and eligibility were established, patients were randomized 1:1 to receive either fentanyl patch or placebo. All patients were allowed to continue to use any anti-inflammatory drugs used before the study and paracetamol was available as rescue medication.
Participants	416 adults with OA of the knee and/or hip from Canada, the Czech Republic, Hungary, Poland, Slovakia, and the UK were recruited to participate in this study. 197 were randomized to placebo and 202 to a fentanyl TD patch. 66.5% were female and the average age was 66 years.
Interventions	Fentanyl TD 3-day 25-100 µg/h, placebo.
Outcomes	Patient assessment of whether trial patches met their overall expectations ("yes, definitely", "yes, somewhat", or "no"), measured on day 43. We defined "responders" as those that answered "yes, somewhat" and "yes, definitely", as this was closest to "moderate". As per our predefined outcomes hierarchy, we used this measure in our analyses. Investigator global assessment of pain control at final assessment (day 46, 49, 52, or 55, depending on the number of patches the patient had used). Authors reported the proportion of investigators giving a rating of good or very good for pain control. Investigator global assessment of medication at final assessment (day 46, 49, 52, or 55, depending on the number of patches the patient had used). Authors reported the "proportion of investigators giving a rating of good or very good for overall impression".
Markenson 2005	
Methods	After screening, patients who met entry criteria were randomized 1:1 to oxycodone or placebo and entered a 90-day double-blind period. Over the first 15 days, dosage was titrated with the goal of reaching “stable dosing”, which was defined as an "average pain intensity score of ≤4 throughout a 48-hour period on the same dose of study drug". Changes in dosage were allowed throughout the remainder of the study, and patients were allowed to continue to use NSAIDs or acetaminophen.
Participants	109 adults with OA were recruited to 9 US centres. 53 were randomized to the placebo arm and 56 to the oxycodone arm. 72.9% were female and the average age was 63 years.
Interventions	Oxycodone CR 10-60 mg bid, placebo. Dosing was initially done bid but could be increased to a

	maximum of 12 tablets daily (6 tablets every 12 hours).
Outcomes	Proportion of patients that reported ≥30% and ≥50% pain relief at day 90 compared to baseline, measured on an 11-point BPI. As per our predefined outcomes hierarchy, we used the ≥30% improvement measure in our analyses.
Markman 2019	
Methods	This study had an enriched enrolment randomized withdrawal design. After an initial ≤3-week screening period, eligible patients entered a 3-7 week open-label titration period where they were titrated to appropriate doses of oxycodegol (NKTR-181). Dosage was initiated at 100 mg bid, and increases were allowed at weekly intervals up to a maximum of 400 mg bid. After this titration, patients who met the following criteria were allowed to continue onto the 12-week double-blind maintenance phase: "weekly 7-day average pain score ≤4, with daily scores ≤4 on at least 5 of the 7 days, and rescue medication on no more than 2 days... [and] a ≥2-point decrease in the patient's weekly pain score compared with the end of the screening phase". Those that qualified were randomized 1:1 to either continue on oxycodegol or switch to placebo. For the first two weeks of the double-blind phase, hydrocodone/acetaminophen was available as rescue medication "to alleviate withdrawal systems [symptoms] caused by stopping the active drug". For the remainder of the study, acetaminophen was available as rescue medication.
Participants	1190 adults aged 18-75 years with moderate to severe CLBP were recruited to 55 study sites in the US. 610 of these patients entered the double-blind phase where 301 were randomized to placebo and 309 to oxycodegol. 58.5% were female and the average age was 51.4.
Interventions	Oxycodegol 100-400 mg bid, placebo bid.
Outcomes	Proportion of patients achieving ≥30% and ≥50% reduction in average weekly pain intensity from screening to week 12 of the maintenance phase. As per our protocol, we analyzed the ≥30% improvement measure. We used the ≥30% improvement measure, as per our predefined outcomes hierarchy. PGIC measured at week 12. Authors considered responders to be patients who reported ratings of "better" or "a great deal better".
Mayorga 2016	
Methods	After an initial 3-week screening period (which included a washout period), patients were randomized 1:1:1:1 to placebo, fulranumab 3mg, fulranumab 9mg, or oxycodone and entered a 16-week double-blind phase. This phase consisted of 4 weeks of titration and 12 weeks of dose maintenance. To maintain blinding, all patients in the fulmanurab and placebo arms received bid oral placebos, and all patients in the oxycodone and placebo arms received placebo injections every 4 weeks. During the trial, the FDA placed a clinical hold on all anti-NGF trials, and thus this study was only able to enroll 196/300 patients. Acetaminophen was available as rescue medication.
Participants	196 adults aged 40-80 years with OA of the knee were recruited to 7 Canadian and 33 US sites. 48 were randomized to placebo, 48 to fulranumab 3mg, 50 to fulmanurab 9mg, and 50 to oxycodone. 56.1% were female and the average age was 58.4 years.
Interventions	Fulranumab 3mg Q4wk, fulranumab 9mg Q4wk, oxycodone CR 10-50mg bid, placebo.
Outcomes	Proportion of patients showing "≥ 30% or ≥ 50% improvement in average [OA-related pain intensity (OAPI)] to the end of weeks 12 and 16". As per our predefined outcomes hierarchy, we used the ≥30% improvement measure in our analyses. "Responder rate in average OAPI to the end of the [double-blind] phase (16 weeks) or to the

	cutoff date, whichever was earlier". "Responders were patients who completed week 13 visit or had not reached the week 13 visit because of the clinical hold and had a percent improvement in the average OAPI from baseline".
Munera 2010	
Methods	After a 1-week run-in period where patients were required to cease all analgesic medication save ibuprofen, those whose pain intensity reached a 7 or above on a scale from 0-10 (with 10 being worst pain imaginable) were randomized 1:1 to receive either placebo or buprenorphine TD. They entered a 4-week double-blind period which consisted of 3 weeks of titration and 1 week of maintenance. During this double-blind period, no rescue medication was allowed.
Participants	315 adults aged ≥18 years with OA of the hip or knee were recruited from 25 outpatient pain centres in the US. 163 were randomized to placebo and 152 to buprenorphine TD. 67.3% were female and the average age was 61.0.
Interventions	Buprenorphine 7-day TD patch 5-20 µg/h, placebo.
Outcomes	Patient-rated satisfaction with medication from 0-4 ("poor" to "excellent") at day 28 or early termination. Authors defined responders as those that rated the medication as 'good', 'very good', or 'excellent', and non-responders as those that "discontinued study drug due to lack of therapeutic effect or reported a score of poor (0) or fair (1) on the patient satisfaction scale at the last study visit". As per our predefined outcomes hierarchy, we used this measure in our analyses. Proportion of investigators assessing therapeutic response as "positive" taken on day 28.
Nct. 2010	
Methods	This study had an enriched enrolment randomized withdrawal design. Eligible patients entered a ≤4-week open-label dose titration period where they were titrated to effective doses of buprenorphine. Patients that made it through this phase continued on to a 12-week double-blind period where they were randomized 1:1 to either continue buprenorphine or switch to placebo. It is not clear what criteria were used to determine which patients were eligible to move onto the double-blind phase. Rescue medication was available, but it is not clear what that rescue medication was.
Participants	334 adults aged ≥ 18 years with CLBP were recruited to 24 centres in the US. 235 of these patients entered the double-blind period where 117 were randomized to buprenorphine and 118 to placebo. 54.5% were female and the median age was 52.0.
Interventions	Buprenorphine HCl buccal film 60-240 µg bid, placebo bid.
Outcomes	Proportion of participants reporting ≥0% to ≥100% (in increments of 10%) improvement in pain scores from baseline to week 12, measured by an 11-point NRS scale ranging from 0 = no pain to 10 = worst pain. As per our predefined outcomes hierarchy, we used the ≥30% improvement measure in our analyses. PGIC (1 = no change/worsening to 7 = a great deal better) taken at week 12 of the maintenance phase.
Nct. 2011	
Methods	This study had an enriched enrolment randomized withdrawal design. Eligible patients entered an initial open-label titration period where they were titrated to "stable, effective, and tolerable dose[s]" of oxycodone. It is not clear how long this period lasted. After titration, those that did not discontinue and met eligibility criteria were allowed to enter the 12-week double-blind

	maintenance phase. It is not clear what these eligibility criteria were. It is also not clear whether rescue medication was available.
Participants	1095 opioid-experienced adults aged ≥18 years with moderate to severe CLBP were recruited to 132 US sites. 600 patients entered the double-blind maintenance phase where 302 were randomized to placebo and 298 to oxycodone. 56.3% were female and the average age was 53.2.
Interventions	Oxycodone/naloxone CR 10/5-40/20 mg bid, placebo bid.
Outcomes	Proportion of subjects that reported a ≥30% and ≥50% reduction in average daily pain from baseline to week 12 of the maintenance period, measured on an 11-point NRS that ranged from 0 = no pain to 10 = worst pain you can imagine. As per our predefined outcomes hierarchy, we used the ≥30% improvement measure in our analyses. PGIC from 1-7 (1 = very much improved, 7 = very much worse), measured at week 12 of the maintenance period. Investigators defined responders as those that responded "much improved" or "very much improved".
Rauck 2015	
Methods	This study had an enriched enrolment randomized withdrawal design. After an initial screening period, all eligible patients entered a 4-6 week titration phase where they were all titrated to effective doses of oxycodone/naltrexone (ALO-02). Those that met the following response criteria were allowed to move onto the double-blind maintenance phase: "(1) daily NRS-Pain scores for low back pain decreased to ≤4 for at least 4 of the last 7 days, (2) tolerated ALO-02, and (3) remained on the same fixed dose of ALO-02 for at least 7 consecutive days, were randomized into the double-blind treatment period". Those that did not meet these criteria were discontinued. Those that did were randomized 1:1 to either continue oxycodone or switch to placebo. Patients randomized to placebo were blindly tapered off of oxycodone for the first 2 weeks of the maintenance phase. Acetaminophen was available as rescue medication throughout the study.
Participants	410 adults aged ≥18 years with moderate-to-severe CLBP were recruited to 47 centers in the US. 281 of these patients entered the double-blind phase where 134 were randomized to placebo and 147 to oxycodone. 55.7% were female and the average age was 47.4 years.
Interventions	Oxycodone/naltrexone HCl ER 10-80 mg bid, placebo bid. Naltrexone is only released if the drug is crushed (abuse-deterrent formulation).
Outcomes	Proportion of patients showing a "≥30% and ≥50% decrease in weekly average NRS-Pain scores from screening to the final 2 weeks of the double-blind treatment period". As per our predefined outcomes hierarchy, we used the ≥30% improvement measure in our analyses. Patient-completed Satisfaction with Treatment Questionnaire from 1 = very dissatisfied to 5 = very satisfied from baseline to week 12 of the maintenance phase or discontinuation. Authors defined responders as those that reported being 'satisfied' or 'very satisfied'.
Rauck 2016	
Methods	This study had an enriched enrolment randomized withdrawal design. After a 2-week screening period, eligible patients entered the ≤8-week titration phase during which all patients were "titrated to a stable dose of [buprenorphine] that provided adequate analgesia... and was well tolerated". Those patients meeting the following criteria were allowed to enter the double-blind phase: (1) "mean of average daily pain intensity score ≤4 for the last 3 days before randomization and at least two points lower than the score at screening" (2) buprenorphine dose of ≥ 150 µg bid (3) optimal dose of buprenorphine received for ≥2 weeks and (4) no more than one daily dose of rescue medication during the last week". Those that did not meet these criteria

	were discontinued. Those that did were randomized 1:1 to either continue buprenorphine or switch to placebo. Hydrocodone/acetaminophen was available as rescue medication only during the first 2 weeks of the maintenance phase. After this, only acetaminophen was allowed.
Participants	749 opioid-naive adults aged ≥18 years with moderate to severe CLBP were recruited to 60 US sites. 462 patients entered the double-blind phase where 229 were randomized to buprenorphine and 232 to placebo. 56.2% were female and the average age was 50.1.
Interventions	Buccal buprenorphine 75-450 µg bid, placebo.
Outcomes	Proportion of patients that reported a ≥30% and ≥50% reduction in pain intensity score from screening to week 12 of the maintenance period, measured on an 11-point NRS (0 = no pain, 10 = worst pain imaginable). As per our predefined outcomes hierarchy, we used the ≥30% improvement measure in our analyses.
Serrie 2017	
Methods	This study began with screening and washout periods where patients were assessed for eligibility and were required to discontinue analgesic medications. Eligible patients then entered a 15-week double-blind period where they were randomized 1:1:1 to tapentadol, oxycodone, or placebo. This period consisted of a 3-week titration phase followed by a 12-week dose maintenance phase. Paracetamol was "available as rescue medication until the last 3 days of the titration period". After this, it could be used "for no more than 3 consecutive days... for reasons other than study-related chronic pain".
Participants	990 adults aged ≥40 years with OA of the knee were recruited to 12 European study sites. 320 were randomized to the tapentadol arm, 333 to the oxycodone arm, and 337 to the placebo arm. 71.6% were female and the average age was 62.1.
Interventions	Tapentadol PR 50-250 mg bid, oxycodone CR 10-50 mg bid, placebo. After the first 3 days, the minimum dose for the remainder of the study was 100 mg bid tapentadol or 20 mg bid oxycodone.
Outcomes	PGIC in overall health status from 1-7 (1 = very much improved to 7 = very much worse) from baseline to week 15. Authors considered responders to be those that reported "much improved" or "very much improved". Proportion of patients reporting ≥30% and ≥50% improvement in average pain intensity from baseline to week 15, measured on an 11-point NRS (0 = no pain, 10 = worst pain imaginable). As per our predefined outcomes hierarchy, we used the ≥30% improvement measure in our analyses.
Spierings 2013	
Methods	After a screening period (up to 30 days) and a washout period (2-27 days) of all analgesics save acetaminophen, eligible patients entered the 16-week treatment period. Here they were randomized 1:1:1:1 to tanezumab 5 mg, tanezumab 10 mg, oxycodone, or placebo. Dose titration was allowed throughout the study. Acetaminophen was available as rescue medication.
Participants	614 adults with OA of the knee or hip were included in the study. 142 were randomized to placebo, 161 to tanezumab 5 mg, 152 to tanezumab 10 mg, and 159 to oxycodone. 62.5% were female and the average age was 57.4.
Interventions	Tanezumab 5 mg infusion every 8 weeks, tanezumab 10 mg infusion every 8 weeks, oxycodone CR 10-40 mg bid, placebo. Those in the oxycodone arm were given placebo infusions, and those in the tanezumab arms were given oral placebos. Those in the placebo arm received both

	placebos.
Outcomes	Percentage of patients with ≥30%, ≥50%, ≥70%, and ≥90% improvement in WOMAC Pain score versus placebo from baseline to week 8. As per our predefined outcomes hierarchy, we used the ≥30% improvement measure in our analyses.
Notes	"The original primary efficacy endpoint was to be evaluated at week 16, but was changed to week 8 due to the clinical hold to maximize analysis utility. These changes were made prior to the database being locked and any treatment unblinding".
Steiner 2011	
Methods	This study had an enriched enrolment randomized withdrawal design. After a 6-10 day screening phase, eligible patients entered a ≤4-week titration phase during which patients were given buprenorphine and titrated to either 10µg/h or 20 µg/h, depending on their analgesic response and tolerance to treatment. Rescue analgesic was not permitted. Those that met the following inclusion criteria were allowed to proceed to the 12-week double-blind phase: a "two-point or more reduction from screening in 'average pain over the last 24 hours' scores, and an 'average pain over the last 24 hours' score for low back pain of 4 or less" for 3 consecutive days. Those that did not meet these criteria were discontinued. Patients that met these criteria were randomized 1:1 to either continue buprenorphine or switch to placebo. Oxycodone was available as rescue medication for the first six days. Acetaminophen or ibuprofen were available as rescue medication for weeks 2-12. Downward dosage adjustment was permitted once during the maintenance phase, and upward adjustment was always permitted.
Participants	1027 opioid-naive adults aged ≥18 years with moderate to severe CLBP entered the open-label titration period. 541 continued on to the double-blind maintenance phase, where 284 were randomized to the placebo arm and 257 to the buprenorphine arm. 55% were female and the average age was 49.4.
Interventions	Buprenorphine TD 7-day 5-20 µg/h, placebo.
Outcomes	Proportion of patients reporting a ≥30% and ≥50% improvement in average 24-hour pain scores from screening to week 12 of maintenance phase, measured on an 11-point scale (0 = no pain, 10 = worst pain imaginable). As per our predefined outcomes hierarchy, we used the ≥30% improvement measure in our analyses. PGIC at week 12 or discontinuation. Authors define responders as those that reported "much improved" or "very much improved". It is not clear what the other values in the scale were.
Zautra 2005	
Methods	Eligible patients entered a 90-day double-blind comparison period where they were randomized 1:1 to either oxycodone or placebo. Rescue medication was not permitted, but patients were allowed to continue stable regimens of acetaminophens and NSAIDs.
Participants	107 adults with OA were recruited to 9 US centres. 56 were randomized to the oxycodone arm and 51 to the placebo arm. 73.1% were female and the average age was 63.3.
Interventions	Oxycodone CR 10 mg bid-12/day, placebo.
Outcomes	Proportion of patients who reported improvements of ≥2 points on an 11-point NRS (0 = no pain, 10 = worst pain imaginable) on day 14 compared to baseline.

Table 5: average doses and corresponding morphine equivalents for long-term traditional RCTs

Study	Intervention	Average Daily Dose	Conversion	Average Daily Oral ME
Afilalo 2010	Oxycodone CR	48.2 mg	1.5	72.3 mg
Breivik 2010	Buprenorphine TD	11.0 µg/h	2.5	27.5 mg
Buynak 2010	Oxycodone CR	53.0 mg	1.5	79.5 mg
Markenson 2005	Oxycodone CR	44.0 mg	1.5	66.0 mg
Serrie 2017	Oxycodone CR	50.7 mg	1.5	76.1 mg

ME = morpine equivalent
CR = controlled-release
TD = transdermal

Table 6: risk of bias assessments for included studies

Afilalo 2010		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was done using a computer-generated list.
Allocation concealment (selection bias)	Low risk	"Randomization was implemented through an interactive voice response system… to dispense blinded study medication".
Blinding of participants and personnel (performance bias)	Low risk	Neither patients nor investigators were made aware of group assignment until the end of the study.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors do not explicitly mention blinding of outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	Of the study arms we focused on, 224 (64.9%) from the oxycodone group and 134 (39.5%) from the placebo group discontinued the study. However, authors considered these participants as non-responders in their responder analysis. Two patients in each arm did not receive any study drug, and were thus excluded from the analysis. One patient in the oxycodone arm was enrolled twice.
Selective reporting (reporting bias)	Low risk	Investigators reported all outcomes they mention studying.
Other bias	Low risk	Study was funded by Johnson & Johnson Pharmaceutical Research & Development.
Baratta 1976		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was done using a table of random numbers.
Allocation concealment (selection bias)	Unclear risk	Authors do not explicitly mention allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	Medications were identical in appearance to ensure study was double-blind.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors do not explicitly mention blinding of outcome assessor.
Incomplete outcome data (attrition bias)	High risk	Although 105 patients were randomized, 11 (10.5%) patients were excluded from the analysis. 3 of these patients

		discontinued from the study, and 8 requested alternative medication. Although this was a relatively low discontinuation rate, these patients were simply excluded from investigators' analyses. Furthermore, authors did not report which study arms these patients were randomized to, and we therefore could not include them in our analyses either.
Selective reporting (reporting bias)	Unclear risk	Authors do not report outcomes for all timepoints.
Other bias	Low risk	
Breivik 2010		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was done "using a validated computer system".
Allocation concealment (selection bias)	Low risk	Group allocation was automated and the "randomization scheme was... locked after approval [by the Biostatistics and Statistical Programming Department]".
Blinding of participants and personnel (performance bias)	Low risk	The buprenorphine and placebo patches were “identical in appearance, packed in a labelled foil pouch, containing coded treatment group identification”.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors state that all study centre personnel were blinded to the participants' condition, but made no explicit mention of outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	54 (61.4%) patients in the buprenorphine arm and 34 (38.6%) in the placebo arm discontinued from the study. Authors defined the full analysis population as all participants who received at least one dose of study drug and had at least one post-dose observation, which included 185 of 199 patients (93.0%). Authors also defined an ITT population (all enrolled subjects) and a per-protocol population (subjects in the full analysis population who complied with the protocol). “The primary efficacy variable was analysed in both the ITT and [per-protocol] populations. All other efficacy variables were analysed in the full ITT analysis population only”. We included all randomized patients in our analysis.
Selective reporting (reporting bias)	Unclear risk	Authors did not report data for their exploratory endpoints, for their Quality of Sleep measure, or for some of their subgroup comparisons (8 secondary measures in total). All non-reported results were insignificant except for one.
Other bias	Low risk	Study was funded by Norpharma A/S.

Buynak 2010		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomized to treatment arms “based on a computer-generated randomization list, balanced by randomly permuted blocks, and stratified by study site”.
Allocation concealment (selection bias)	Low risk	“Randomization was implemented through an interactive voice response system… that assigned patients to blinded study medication”.
Blinding of participants and personnel (performance bias)	Low risk	“Placebo tablets and capsules (one for each active treatment) were used to maintain the blind in this double-blind, double-dummy design”.
Blinding of outcome assessment (detection bias)	Low risk	Authors do not explicitly mention outcome assessment in the paper. However, on the clinical trials registry they do state that outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	167 (52.4%) in the placebo arm, 152 (47.8%) in the tapentadol arm, and 195 (59.5%) in the oxycodone arm discontinued from the study. Despite this high drop-out rate, authors considered all patients who discontinued as non-responders in their responder analysis. The authors used an ITT population which included "all patients who were randomized and who took at least one dose of study medication". Two patients who were randomized twice were also excluded. The ITT population therefore consisted of 317 in the placebo group, 315 in the tapentadol group, and 326 in the oxycodone group. LOCF was used to impute missing values in the efficacy analyses. To ensure robustness of results of the primary analysis, authors performed a sensitivity analysis using the more-conservative baseline observation carried forward and worst observation carried forward imputation methods.
Selective reporting (reporting bias)	Unclear risk	Authors did not report Clinical Opiate Withdrawal Scale scores, just the p-values corresponding to the comparisons between the treatment arms. They also do not report results for all timepoints mentioned.
Other bias	Low risk	Funding provided by Johnson & Johnson Pharmaceutical Services, L.L.C. and Grünenthal GmbH.
Chindalore 2005		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomized and stratified by sex to treatment arms.
Allocation concealment (selection bias)	Unclear risk	Authors do not explicitly mention allocation concealment.

Blinding of participants and personnel (performance bias)	Low risk	“All study medications were identical in appearance, and patients, site personnel, and study monitors were blinded to treatment assignments”.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors do not explicitly mention blinding of outcome assessment.
Incomplete outcome data (attrition bias)	Unclear risk	32 (30.8%) in the Orytrex qid, 45 (43.7%) in the Orytrex bid, 33 (32.0%) in the Oxycodone, and 11 (21.2%) in the placebo arm discontinued the study. One patient in each of the oxycodone and placebo arms discontinued before receiving treatment, and were excluded from the analysis. Authors imputed missing values for their primary analysis using LOCF imputation. However, it is unclear how or if missing values were imputed for secondary outcomes like the patient assessments of analgesia and global impression of study medication. Authors also don’t state which population they use in their secondary analyses.
Selective reporting (reporting bias)	Unclear risk	Authors report results for all outcomes, but do not report for all time points that outcomes were measured at. They did not report global assessment scores, quality of analgesia ratings, or pain control assessment scores for weeks 1 or 2.
Other bias	Low risk	Study was funded by Pain Therapeutics, Inc.
Christoph 2017		
Random sequence generation (selection bias)	Low risk	Randomization was done using "computer-generated randomization lists”.
Allocation concealment (selection bias)	Low risk	Randomization lists were “provided by an external supplier and was implemented using an interactive response technology system".
Blinding of participants and personnel (performance bias)	Low risk	“Double-dummy methods were used to guarantee the blinding of patients and all personnel involved in the trial”.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors do not explicitly mention blinding of outcome assessor.
Incomplete outcome data (attrition bias)	Low risk	Of all randomized patients, 26 (20.6%) in the placebo arm, 63 (48.1%) in the cebranopadol 200 µg arm, 67 (52.3%) in the cebranopadol 400 µg arm, 76 (58.5%) in the cebranopadol 600 µg arm, and 49 (38.9%) in the tapentadol arm discontinued. Authors used the "full analysis set" in their efficacy analyses, defined as all patients who took at least one dose of study medication and had at least one post-baseline pain assessment. We included all patients who took at least one dose of study medication in our analysis, regardless of whether they had a post-baseline assessment or not.

Selective reporting (reporting bias)	Unclear risk	Authors did not report results from the anxiety and depression sub-scales of the Hospital Anxiety and Depression Scale. They also did not report full results from the PGIC, only the percentage of patients that reported their overall condition as “much improved” or “very much improved”. Furthermore, they did not report results from the Columbia-Suicide Severity Rating Scale or the changes from baseline in vital signs. None of these were primary analyses.
Other bias	Low risk	Study was funded by Grünenthal GmbH.
Friedmann 2011		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were randomized to study arms, but authors do not detail how this was done.
Allocation concealment (selection bias)	Unclear risk	Authors do not explicitly mention allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	“Placebo patients were treated identically to patients randomly assigned to Remoxy in that they were permitted to request dose changes for analgesic effect for 4 weeks even though their dose was actually fixed”. However, given that this study employed an enriched-enrolment design, unblinding in the placebo group after randomization due to alleviation of adverse effects and occurrence of withdrawal symptoms was a strong possibility.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors do not explicitly mention blinding of outcome assessment.
Incomplete outcome data (attrition bias)	High risk	146 (26.2%) patients discontinued from the study during the open-label titration period. These patients were excluded from analysis. During the double-blind phase, 75 (36.2%) in the placebo arm and 70 (34.1%) in the oxycodone arm discontinued from the study. All analyses used the ITT population, which was defined as all randomized patients who received at least one dose of medication and had a post-randomization pain intensity score of ≥1 on an 11-point scale (where 0 = "no pain"). We included all randomized patients in our analyses. Missing values were imputed using LOCF for “average [pain intensity] score by week, quality of analgesia, and global assessment of study medication”. All other assessments did not have missing values imputed.
Selective reporting (reporting bias)	Unclear risk	Authors report all efficacy outcomes they mention studying. However, they do not report results for all timepoints measured. They also do not report all safety measures.
Other bias	High risk	All patients - including those randomized to placebo -

		initially received sizable amounts of study opioid. This has the potential to lead to opioid-induced hyperalgesia, which would negatively impact pain ratings in the placebo group once they switch from the study opioid. This trial was funded by Pain Therapeutics, Inc
Gordon 2010		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomized to treatment sequence, and the "randomization code was generated using PROC PLAN in SAS version 6.12".
Allocation concealment (selection bias)	Unclear risk	Authors make no explicit mention of allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	"Study monitors, investigators, coordinators, pharmacists, patients, and sponsor clinical research personnel remained blinded to treatment allocation throughout the conduct of the study".
Blinding of outcome assessment (detection bias)	Unclear risk	Authors make no explicit mention of blinding of outcome assessor. However, authors do make clear that all study personnel were blinded.
Incomplete outcome data (attrition bias)	High risk	In the first 4 weeks, 4 (10.3%) withdrew from the placebo arm and 10 (25.6%) withdrew from the buprenorphine arm. After crossover, 9 (25.7%) withdrew from the buprenorphine arm and 6 (20.7%) withdrew from the placebo arm in the following 4 weeks. This amounted to a total of 19 (25.7%) withdrawals in the buprenorphine group and 10 (14.7%) in the placebo group. "The primary efficacy analysis included all patients who completed ≥2 consecutive weeks of treatment in each study phase with no major protocol violations". Authors do not state how missing values were handled or which population was used in secondary analyses. However, authors excluded discontinuations from their secondary measure of patient-rated effectiveness: only 48 patients completed all 8 weeks of treatment and the rating measure. We included all randomized patients in our analyses, and considered discontinuations as non-responders.
Selective reporting (reporting bias)	Unclear risk	Authors reported all outcomes they mention studying. However, they do not report them for all timepoints.
Other bias	Low risk	Study was funded by Purdue Pharma.
Hartrick 2009		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was balanced by using permuted blocks of treatment and was stratified by study center".

Allocation concealment (selection bias)	Unclear risk	Authors made no explicit mention of allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	The study was double-blind, and "patients in all groups were provided with study medication in the form of daily blister cards".
Blinding of outcome assessment (detection bias)	Unclear risk	Authors made no explicit mention of blinding of outcome assessor.
Incomplete outcome data (attrition bias)	Unclear risk	Of those randomized, 32 (19.9%) in the tapentadol 50 mg arm, 44 (26.0%) in the tapentadol 75 mg arm, 60 (34.9%) in the oxycodone arm, and 20 (11.6%) in the placebo group discontinued from the study. Of these, 4 in the tapentadol 50 mg arm, 1 in the tapentadol 75 mg arm, and 3 in the placebo arm did not receive any study drug and 7 more did not have a baseline pain assessment: all of these were excluded from analyses. However, for the PGIC measure only those that completed the assessment at discontinuation or study end were included. The LOCF method to impute missing pain measurements in the primary analysis, and a sensitivity analysis was performed using the baseline observation carried forward method. Authors did not mention how or if missing values were imputed for secondary outcomes.
Selective reporting (reporting bias)	Low risk	Authors report all outcomes they mention studying.
Other bias	Low risk	Sponsored by Johnson & Johnson Pharmaceutical Research & Development and Grünenthal GmbH.
Katz 2010		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The outpatient site contacted the Interactive Web Response System to receive a randomization number and treatment assignment" and "randomization was stratified by target joint (hip or knee), the final total daily dose of the titration period (≤ 80 mg, > 80 mg), and site".
Allocation concealment (selection bias)	Unclear risk	Authors do not explicitly mention allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	"Both drug and placebo were packaged so as to be blinded to the investigator, study clinic personnel, and patients". However, given that this study employed an enriched-enrolment design, unblinding in the placebo group after randomization due to alleviation of adverse effects and occurrence of withdrawal symptoms was a strong possibility.
Blinding of outcome	Unclear risk	Authors do not explicitly mention blinding of outcome

assessment (detection bias)		assessment.
Incomplete outcome data (attrition bias)	High risk	203 (37.1%) of patients in the titration phase discontinued before randomization and were excluded from the analysis. Of those randomized, 75 (43.4%) patients in the placebo group and 61 (35.7%) in the morphine-naloxone group discontinued from the study. Authors defined the ITT population as all patients who were rantomized and received at least one dose of double-blind study medication. They used this population in their primary analysis, and imputed missing values using different methods depending on the reason for discontinuation: “screening baseline value was used for patients who discontinued due to AEs and for patients taking [morphine-naloxone] capsules who discontinued due to withdrawal symptoms; randomization baseline was used for patients on placebo who discontinued due to withdrawal symptoms; and last-observation-carried-forward methodology was used in all other instances”. Investigators considered patients who discontinued during the double-blind phase as "nonresponders" in their responder analysis.
Selective reporting (reporting bias)	Unclear risk	Authors did not report PGIC measure because the data were uninterpretable as they did not reflect change from baseline, but change from previous assessment. Authors also did not report all responder analyses.
Other bias	High risk	All patients - including those randomized to placebo - initially received sizable amounts of study opioid. This has the potential to lead to opioid-induced hyperalgesia, which would negatively impact pain ratings in the placebo group once they switch from the study opioid. Funding provided by King Pharmaceuticals, Inc.
Katz 2015		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	“Patients were randomized using a block randomization scheme… stratified by previous opioid use (ie, experienced or naïve)”. Patients were randomized to the study arms using codes prepared by an external-to-study biostatician.
Allocation concealment (selection bias)	Low risk	“Patients were assigned a unique randomization number by an interactive web response system”.
Blinding of participants and personnel (performance bias)	Unclear risk	Authors state that the maintenance phase was double-blind, but don’t detail how they ensured this was the case. Furthermore, given that this study employed an enriched-enrolment design, unblinding in the placebo group after randomization due to alleviation of adverse effects and occurrence of withdrawal symptoms was a strong possibility.

Blinding of outcome assessment (detection bias)	Unclear risk	Authors do not explicitly mention blinding of outcome assessment.
Incomplete outcome data (attrition bias)	High risk	351 (47.4%) of the patients in the titration phase discontinued from the study before randomization. These patients were excluded from efficacy analyses. Of those that entered the double-blind phase, 96 (49.0%) in the placebo group and 71 (36.8%) in the oxycodone group discontinued from the study. All of these patients were included in the ITT population. It was not clear how they accounted for discontinuations in their responder analysis.
Selective reporting (reporting bias)	Low risk	Authors report all outcomes they mention studying.
Other bias	High risk	All patients - including those randomized to placebo - initially received sizable amounts of study opioid. This has the potential to lead to opioid-induced hyperalgesia, which would negatively impact pain ratings in the placebo group once they switch from the study opioid. Funded by Collegium Pharmaceuticals.
Kjaersgaard-Andersen 1990		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors state that patients were randomized to treatment arms, but don't detail how this was done.
Allocation concealment (selection bias)	Unclear risk	Authors do not explicitly mention allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	All patients were initially blind to group assignments, as study medication was "identical in weight, appearance, and taste". However, it is mentioned that investigators broke the study's code for the first 100 patients who had completed the study.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors do not explicitly mention blinding of outcome assessment.
Incomplete outcome data (attrition bias)	High risk	15 (20.0%) in the paracetamol group and 40 (48.2%) in the codeine/paracetamol group discontinued from the study. These patients were not considered in the investigators' analysis. 161 patients actually entered the study, but 1 did not start the study medication and 2 received un-approved analgesics during the study, and were thus excluded from efficacy analyses by the authors. Authors don't mention which study arms the patients who received un-approved analgesics were initially randomized to, so we were not able to include them in our analyses. Furthermore, authors don't

		state how they dealt with missing data. For the overall judgement of treatment measure, authors only included patients who had not dropped out of the study.
Selective reporting (reporting bias)	Low risk	Authors report all outcomes they mention studying.
Other bias	Unclear risk	Due to the high number of discontinuations from the study, investigators prematurely stopped enrolling patients (taerget enrollment was 271, but only 161 were actually enrolled).
Krebs 2018		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	“The SAS (SAS Institute), version 9.4, uniform random number generator was used to produce a computerized randomization table” which was used to randomize patients to treatment arms.
Allocation concealment (selection bias)	Low risk	“The clinical pharmacist initiated random group assignment using a programmed study application that automatically assigned the next unused position in the randomization table”.
Blinding of participants and personnel (performance bias)	High risk	Neither patients nor clinicians were blinded to group assignment.
Blinding of outcome assessment (detection bias)	Low risk	Authors state that "outcome assessors were blinded to group assignment".
Incomplete outcome data (attrition bias)	Low risk	23 (19.3%) patients in the opioid arm and 10 (8.4%) in the non-opioid arm discontinued their study medication. However, all randomized patients that received at least one dose of study medication (all but 2 patients, 1 per study arm) were included in efficacy analyses.
Selective reporting (reporting bias)	Unclear risk	Authors did not report the following secondary outcomes: "the global impression of pain change, the Fullerton Advanced Balance scale, 6-m gait speed, chair stand, grip strength tests, cold pain tolerance, free testosterone, and the Indiana University Telephone-Based Assessment of Neuropsychological Status".
Other bias	Low risk	“This trial was funded by the Merit Review Award (I01-HX-000671) from the US Department of Veterans Affairs Health Services Research and Development Service”.
Langford 2006		

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors state that "randomization was performed using a computer-generated list and stratified by target joint (knee or hip)".
Allocation concealment (selection bias)	Low risk	Authors state that "investigators were unaware of the treatment allocation".
Blinding of participants and personnel (performance bias)	Low risk	“[TD fentanyl] and placebo patches were identical. Investigators were provided with a sealed envelope for each participant, containing coded details of the treatment in the double-blind phase so that the code could be broken in case of emergency. All envelopes were collected at the end of the trial”.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors do not explicitly mention blinding of outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	104 (52.8%) in the placebo group and 96 (47.5%) in the fentanyl group discontinued from the study. “Data were analyzed on an intent-to-treat basis. The [primary outcome] was calculated using data from all patients who provided postbaseline scores. For other parameters, the last observation carried forward method was used for patients who left the study early”. Only 187 in the placebo group and 183 in the fentanyl group completed the patient's assessment of treatment. We considered those that did not complete the assessment as non-responders.
Selective reporting (reporting bias)	Low risk	Authors report all outcomes they mention studying.
Other bias	Low risk	Study was funded by Janssen-Cilag.
Markenson 2005		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to treatment arms using a computer-generated randomization code supplied by the sponsor.
Allocation concealment (selection bias)	Low risk	Randomization was done using study drug bottles labeled with randomization numbers.
Blinding of participants and personnel (performance bias)	Low risk	“Patients who met the entry criteria were randomly assigned in double blind fashion”.

Blinding of outcome assessment (detection bias)	Unclear risk	Authors made no explicit mention of blinding of outcome assessors.
Incomplete outcome data (attrition bias)	Low risk	40 (78.4%) patients in the placebo arm and 33 (58.9%) in the oxycodone arm discontinued from the study. However, “all variables were evaluated by intent-to-treat (ITT) analysis (ie, including all randomized patients who received at least 1 dose of study drug) in which the last observation was carried forward”.
Selective reporting (reporting bias)	Unclear risk	Authors reported all outcomes they mention studying. However, they do not report results for all timepoints.
Other bias	Low risk	Funding provided by Purdue Pharma P.L.
Markman 2019		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors state that patients were randomized to treatment arms, but do not detail how this was done.
Allocation concealment (selection bias)	Unclear risk	Authors made no explicit mention of allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	“To preserve double blinding during randomized treatment, study drug was dosed as indistinguishable tablets (2 tablets per dose) in identical blister packaging”. However, given that this study employed an enriched-enrolment design, unblinding in the placebo group after randomization due to alleviation of adverse effects and occurrence of withdrawal symptoms was a strong possibility.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors made no explicit mention of blinding of outcome assessor.
Incomplete outcome data (attrition bias)	High risk	580 (48.7%) patients discontinued during the titration phase. These patients were excluded from efficacy analyses. Of the remaining patients, 59 (19.6%) in the placebo arm and 60 (19.4%) in the NKTR-181 arm discontinued during the maintenance phase. All randomized patients were included in the ITT population. Patients that discontinued during the maintenance phase were considered as nonresponders in the responder analysis. “Missing scores were substituted through multiple imputation using the imputation rules: the screening score for patients who discontinued due to AEs, the baseline score for patients who discontinued due to opioid-withdrawal symptoms, the last mean carried forward for patients who discontinued due to

		lack of efficacy, and Markov Chain Monte Carlo… methods assuming nonmonotone missing for all other cases".
Selective reporting (reporting bias)	Unclear risk	Authors reported all efficacy outcomes they mention studying. However, they did not report baseline characteristics in the dosage subgroups. They also did not report efficacy measures for all timepoints measured.
Other bias	High risk	All patients - including those randomized to placebo - initially received sizable amounts of study opioid. This has the potential to lead to opioid-induced hyperalgesia, which would negatively impact pain ratings in the placebo group once they switch from the study opioid. Study was funded by Nektar Therapeutics.
Mayorga 2016		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Central randomisation was implemented in this study", and was "stratified by baseline body weight (< 85 or ≥ 85 kg) and by baseline opioid use or non-use".
Allocation concealment (selection bias)	Low risk	"Patients were randomised via an interactive voice response system based on a computergenerated randomisation schedule prepared by the sponsor".
Blinding of participants and personnel (performance bias)	Low risk	To maintain blinding, each patient received both an injection (either placebo or fulranumab) every 4 weeks and bid oral study drug (either placebo or oxycodone CR) that appeared identical.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors make no explicit mention of blinding of outcome assessor.
Incomplete outcome data (attrition bias)	Low risk	22 (45.8%) in the placebo arm, 22 (45.8%) in the fulranumab 3mg arm, 22 (44.0%) in the fulranumab 9mg arm, and 38 (76.0%) in the oxycodone arm discontinued from the study. However, 36 of these were discontinued due to the FDA hold (8 in placebo, 6 in fulranumab 3mg, 13 in fulranumab 9mg, and 9 in oxycodone). The ITT population included all patients who received at least one dose of study drug, and authors classified patients that discontinued as non-responders. The "imputation method for the primary analysis on the ITT analysis set was a combination of baseline observation carried forward for patients who withdrew from the [double-blind] treatment phase prior to the clinical hold and last observation carried forward (LOCF) for patients who were ongoing on the cutoff date of

		the clinical hold".
Selective reporting (reporting bias)	Unclear risk	All outcomes authors mention studying are reported. However, they do not report results for all timepoints.
Other bias	Low risk	"All authors are employees of Janssen Research & Development, LLC, a Johnson & Johnson company and hold stocks in the company".
Munera 2010		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors state that patients were randomized to treatment arms, but don't detail how this was done.
Allocation concealment (selection bias)	Unclear risk	Authors do not explicitly mention allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	The study was double-blind, and "placebo TDS-treated patients received identical looking patches". However, the "blind was broken once in this study, when the identity-concealing label of a BTDS patient's treatment supply was accidentally torn. This patient completed the study."
Blinding of outcome assessment (detection bias)	Unclear risk	Authors do not explicitly mention blinding of outcome assessor.
Incomplete outcome data (attrition bias)	Low risk	77 (47.2%) patients in the placebo arm and 83 (54.6%) in the buprenorphine TD arm discontinued from the study. However, efficacy analyses were done on the ITT population, defined as "all randomized patients who received at least one dose of study medication and had at least one post-dose efficacy assessment". This included 311 patients. The 4 patients that were excluded did not have any post-baseline efficacy data. We included all randomized patients in our analyses.
Selective reporting (reporting bias)	Low risk	Investigators reported all outcomes they mention measuring.
Other bias	Low risk	This study was funded by Purdue Pharma L.P.
Nct. 2010		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors state that patients were randomized to treatment arms, but do not state how this was done.

Allocation concealment (selection bias)	Unclear risk	Authors make no explicit mention of allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Authors state that both participants and investigators were blinded, but do not mention how this was done. Furtermore, given that this study employed an enriched-enrolment design, unblinding in the placebo group after randomization due to alleviation of adverse effects and occurrence of withdrawal symptoms was a strong possibility.
Blinding of outcome assessment (detection bias)	Low risk	Authors state that the outcomes assessors were blinded.
Incomplete outcome data (attrition bias)	High risk	99 (29.6%) of the patients that entered the titration phase discontinued from the study. These patients were excluded from the analysis. Of those that entered the maintenance phase, 37 (31.4%) in the placebo arm and 28 (23.9%) in the buprenorphine arm discontinued from the study. Efficacy analyses were done on all patients that received at least one dose of study medication. This ended up including all randomized patients. Investigators make no mention of how they treated those that discontinued.
Selective reporting (reporting bias)	Low risk	Authors report all outcomes they mention collecting.
Other bias	High risk	All patients - including those randomized to placebo - initially received sizable amounts of study opioid. This has the potential to lead to opioid-induced hyperalgesia, which would negatively impact pain ratings in the placebo group once they switch from the study opioid. Study was sponsored by BioDelivery Sciences International.
Nct. 2011		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors state that patients were randomized to treatment arms, but do not state how this was done.
Allocation concealment (selection bias)	Unclear risk	Investigators make no explicit mention of allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Authors state that both participants and investigators were blinded, but don’t mention how this was done. Furtermore, given that this study employed an enriched-enrolment design, unblinding in the placebo group after randomization due to alleviation of adverse effects and occurrence of withdrawal symptoms was a strong possibility.
Blinding of outcome assessment (detection	Unclear risk	Investigators make no explicit mention of blinding of outcome assessor.

bias)		
Incomplete outcome data (attrition bias)	High risk	494 (45.1%) of those that entered the titration phase discontinued from the study, and these patients were excluded from efficacy analyses. Of those that were randomized to treatment arms, 121 (40.1%) in the placebo arm and 80 (26.8%) in the oxycodone arm discontinued. All randomized patients were included in the efficacy analyses, as all of them received at least one dose of study drug in the double-blind phase. It is unclear whether investigators defined those that discontinued as non-responders or not.
Selective reporting (reporting bias)	Low risk	Investigators report all outcomes they mention studying.
Other bias	High risk	All patients - including those randomized to placebo - initially received sizable amounts of study opioid. This has the potential to lead to opioid-induced hyperalgesia, which would negatively impact pain ratings in the placebo group once they switch from the study opioid. Study was sponsored by Purdue Pharma LP. Furthermore, "there is an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed".
Rauck 2015		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were randomized to treatment arms, but authors do not detail how this was done.
Allocation concealment (selection bias)	Unclear risk	Authors made no explicit mention of allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	The study was double-blind, and “patients randomized to the placebo group received a gradual blinded taper of ALO-02 to avoid withdrawal symptoms and maintain blinding”. However, despite this tapering, unblinding in the placebo group after randomization due to alleviation of adverse effects and occurrence of withdrawal symptoms was a strong possibility given that this study employed an EERW design.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors made no explicit mention of blinding of outcome assessor.
Incomplete outcome data (attrition bias)	High risk	129 (31.5%) of the patients that entered the titration phase discontinued before randomization. These patients were excluded from analyses. Of those randomized, 53 (39.6%)

		in the placebo arm and 40 (27.2%) in the oxycodone arm discontinued. The ITT population included all patients who received at least one dose of study drug. This included all patients except for 1 in the oxycodone group. However, it is not clear how investigators treated discontinuations in their responder analysis. Treatment of missing data differed depending on the reason for study discontinuation. "The randomization baseline score was carried forward as the final score for patients randomized to placebo who discontinued from the study with signs of opioid withdrawal. For all other patients with missing data, on-treatment missing data were imputed with a regression-based multiple imputation approach".
Selective reporting (reporting bias)	Unclear risk	Authors did not report results from the Patient Global Assessment measure (it was insignificant), Subjective Opiate Withdrawal Scale, or all results from the Brief Pain Inventory.
Other bias	High risk	All patients - including those randomized to placebo - initially received sizable amounts of study opioid. This has the potential to lead to opioid-induced hyperalgesia, which would negatively impact pain ratings in the placebo group once they switch from the study opioid. Study was sponsored by Pfizer.
Rauck 2016		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors state that patients were randomized to treatment arms, but do not detail how this was done.
Allocation concealment (selection bias)	Unclear risk	Authors made no explicit mention of allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Authors state that this study was double-blind, but do not detail how they ensured this. However, given that this study employed an enriched-enrolment design, unblinding in the placebo group after randomization due to alleviation of adverse effects and occurrence of withdrawal symptoms was a strong possibility.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors made no explicit mention of blinding of outcome assessor.
Incomplete outcome data (attrition bias)	High risk	290 (38.6%) patients that entered the open-label titration period discontinued, and these patients were excluded from efficacy analyses. Of those randomized, 58 (25.0%) in the placebo arm and 54 (23.5%) in the buprenorphine arm discontinued from the study. The ITT population included

		all patients who received at least one dose of study medication in the double-blind period. This included all but 1 patient in the buprenorphine arm. An additional 41 patients from 1 site were removed from the study and excluded from analyses, but the number of patients per arm was not made clear. Furthermore, the reason for the exclusion was not clear. For the primary analysis, “Missing values due to subjects discontinued from the study were imputed as follows: (1) using the screening observation carried forward (SOCF) imputation if due to AEs/tolerability, (2) using the last observation carried forward (LOCF) imputation if due to lack of efficacy, (3) using the baseline observation carried forward (BOCF) imputation if due to opioid withdrawal and (4) using multiple imputation procedures for all other types of missing values”. For the responder analysis, discontinuations in the double-blind phase were considered "nonresponders".
Selective reporting (reporting bias)	Unclear risk	Authors did not report results from the Medical Outcomes Score - Sleep Subscale or data on rescue medication usage for all time points measured.
Other bias	High risk	All patients - including those randomized to placebo - initially received sizable amounts of study opioid. This has the potential to lead to opioid-induced hyperalgesia, which would negatively impact pain ratings in the placebo group once they switch from the study opioid. Study was sponsored by Endo Pharmaceuticals Inc.
Serrie 2017		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was done using "a computer-generated randomization list balanced by randomly permuted blocks and stratified by study site".
Allocation concealment (selection bias)	Low risk	Randomization was done using an interactive voice response system.
Blinding of participants and personnel (performance bias)	Low risk	"Treatment assignments were masked from investigators and patients".
Blinding of outcome assessment (detection bias)	Unclear risk	Authors make no explicit mention of blinding of outcome assessor.
Incomplete outcome data (attrition bias)	Low risk	The ITT population consisted of all patients who received at least one dose of study medication. This included 987 (99.7%) of randomized patients (all save 1 in the tapentadol arm and 2 in the oxycodone arm). Of these patients, 116 (34.4%) in the placebo arm, 133 (41.7%) in the tapentadol

		arm, and 210 (63.4%) in the oxycodone arm discontinued. "The last observation carried forward (LOCF) approach for missing data in the event of discontinuation was used for primary and secondary end-points, except for WOMAC and responder rates. For the latter, subjects who prematurely discontinued were considered non-responders".
Selective reporting (reporting bias)	Unclear risk	Authors did not report results for the time to treatment discontinuation measure nor for the Patient Assessment of Constipation Symptoms measure.
Other bias	Low risk	Study was funded by Johnson & Johnson.
Spierings 2013		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors state that patients were randomized to treatment arms, but do not detail how this was done.
Allocation concealment (selection bias)	Unclear risk	Authors do not explicitly mention allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Authors state that the maintenance period of this study was double-blind, but do not describe how they ensured this was the case. However, authors do state that all patients received infusions (either placebo or tanezumab) every 8 weeks and oral medication bi-daily (either placebo or oxycodone).
Blinding of outcome assessment (detection bias)	Unclear risk	Authors do not explicitly mention blinding of outcome assessor.
Incomplete outcome data (attrition bias)	Unclear risk	Of those randomized, 4 did not receive any study medication, and were thus excluded from the analysis. Of the remaining, 113 (80.1%) in the placebo arm, 131 (81.4%) in the tanezumab 5 mg arm, 121 (80.7%) in the tanezumab 10 mg arm, and 136 (86.1%) in the oxycodone arm discontinued. Discontinuation rates were this high due to an FDA-mandated hold on all studies involving anti-NGF therapies which accounted for the majority of discontinuations. Because of the hold, investigators also used a modified ITT population in addition to the ITT population (all randomized patients who received at least one dose of study medication) in their efficacy analyses. This included "all patients in the ITT population who had a WOMAC Pain score for week 8 that was collected prior to 23 June 2010". Authors used the LOCF method to impute missing data.
Selective reporting (reporting bias)	Unclear risk	Authors report all outcomes they mention measuring. However, in their responder analysis they report proportions instead of the actual numbers.

Other bias	Low risk	Study was funded by Pfizer. Furthermore, the “clinical hold required changing the landmark analysis from week 16 to week 8, [but] it is unlikely that this change affected the efficacy outcomes for either tanezumab or oxycodone CR”.
Steiner 2011		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors state that patients were randomized to treatment arms, but do not detail how this was done.
Allocation concealment (selection bias)	Unclear risk	Authors do not explicitly mention allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Authors state that the maintenance period of this study was double-blind, as “all patients were provided with immediate release oxycodone for supplementary analgesia during the first six days following randomization” to mediate withdrawal effects in the placebo arm. However, despite these attempts to mediate withdrawal, unblinding in the placebo group after randomization due to alleviation of adverse effects and occurrence of withdrawal symptoms was a strong possibility given this trial’s EERW design.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors do not explicitly mention blinding of outcome assessor.
Incomplete outcome data (attrition bias)	High risk	483 (47.0%) of the patients that entered the titration period discontinued from the study. These patients were excluded from analyses. Of those randomized, 86 (33.6%) in the buprenorphine arm and 84 (29.7%) in the placebo arm discontinued. "All efficacy analyses were performed on the full analysis population, which consisted of all patients who were randomized and received at least one dose of double-blind study drug". This included all but 2 patients (1 in each arm). In the primary analysis, missing data were imputed using different methods depending on the reason for discontinuation: “the screening mean pain was carried forward for discontinuations caused by AEs (BOCF), and the last nonmissing observation (LOCF) was carried forward for discontinuations caused by other reasons”. For the responder analysis, those in the full analysis population that discontinued before week 12 were considered as "nonresponders".
Selective reporting (reporting bias)	Unclear risk	Investigators reported all outcomes they mentioned studying. However, they do not report results for all time points mentioned. Furthermore, quite a few post-hoc evaluations were done. This included evaluation of the PGIC and the ≥50% improvement in pain measures.

Other bias	High risk	All patients - including those randomized to placebo - initially received sizable amounts of study opioid. This has the potential to lead to opioid-induced hyperalgesia, which would negatively impact pain ratings in the placebo group once they switch from the study opioid. Study was sponsored by Purdue Pharma.
Zautra 2005		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomized to treatment arms. “The bottles of medication were labeled with a randomization number and dispensed by the investigators”.
Allocation concealment (selection bias)	Unclear risk	Authors make no explicit mention of allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Authors state that the study was double-blind, but do not detail how they ensured this.
Blinding of outcome assessment (detection bias)	Unclear risk	Authors make no explicit mention of blinding of outcome assessor.
Incomplete outcome data (attrition bias)	Low risk	Over the course of the 90-day study, 38 patients (74.5%) in the placebo arm and 33 (58.9%) in the oxycodone arm withdrew from the study. However, analyses were done on the ITT population, which authors defined as "patients who received at least 1 dose of study medication". Authors also excluded patients without post-baseline pain assessments from their analyses (3 total, 2 in the placebo arm and 1 in the oxycodone arm). However, we included these latter patients in our analyses.
Selective reporting (reporting bias)	High risk	Visits and measurements were made on days 15, 30, 45, 60, 90. However, authors only report 15-day results.
Other bias	Low risk	Supported by Purdue Pharma LP.

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Appendix A: PROSPERO Protocol

Review title: Short, intermediate and long-term effects of opioids on pain intensity in patients with osteoarthritis or back pain

Anticipated or actual start date: 05/09/2019

Anticipated completion date: 30/04/2020

Stage of review at time of this submission: at the time of protocol submission, preliminary searches had completed and piloting of the study selection process had started.

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Funding sources/sponsors: not funded.

Conflicts of interest: none.

Review questions
1. How does the use of opioids, as compared to placebo or opioid-minimized pain management strategies, affect pain intensity over the short, intermediate, and long-term in adults with osteoarthritis or back pain?
2. How does up-titration of opioid doses differ over short, intermediate, and long-term treatment? (i.e. Does tolerance lead to opioid doses increasing over time?)

Searches
A systematic electronic search will be conducted in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus. The search will have no restrictions on publication date or language. Two authors (LF and CB) will independently perform the initial screening (based on title and abstract) as well as the screening for final selection (based on full text). Any disagreement between the two reviewers will be resolved via discussion and consensus and/or involvement of a third author (SG).

URL to search strategy: https://www.crd.york.ac.uk/PROSPEROFILES/147459_STRATEGY_20190903.pdf

Condition or domain being studied

Patients with osteoarthritis and back pain can experience chronic discomfort for which opioids are commonly prescribed. However, there is evidence to suggest that opioids might lower pain tolerance [1], which may negate their analgesic value in the long-term[2]. This review primarily seeks to determine whether the effectiveness of opioids for treating pain in patients with osteoarthritis or back pain decreases over time. If patients develop tolerance to prescription opioids, this may be reflected in an increase in daily opioid doses over time. As this may occur whether starting doses are relatively small or large, this review also seeks to determine whether doses continue to escalate by examining the % change in dose over time when compared to the study's starting dose. Comparing to the starting dose also allows us to control for differences in opioid potency, route of administration, indication, and population studied.

1. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth. 2014;112(6):991-1004. doi: 10.1093/bja/aeu137.

2. Krebs EE et al. 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. 2018;319(9):872-882. doi:10.1001/jama.2018.0899

Participants/population

Participants must have osteoarthritis or mechanical lower back pain. Studies including participants with back pain resulting from surgery, cancer, neurogenic claudication, radiculopathy, sciatica, or rheumatic conditions (for example, rheumatoid arthritis or ankylosing spondylitis) will be excluded. We will also exclude studies requiring participants to have opioid use disorder.

Intervention(s), exposure(s)

Interventions must include an opioid medication with only one known mechanism of action, including but not limited to the following generic opioids: buprenorphine, butorphanol, codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, loperamide, meperidine, methadone, morphine, nalbuphine, oxycodone, pentazocine, propoxyphene, and sufentanil. Tramadol (which is also a serotonin-norepinephrine reuptake inhibitor)[1] and tapentadol (which is also a norepinephrine reuptake inhibitor)[2] possess additional proposed mechanisms for pain relief, and are specifically excluded. Studies that use trade-name formulations that include an opioid in addition to another compound (e.g. acetaminophen) will be excluded unless they also administer the non-opioid component to the control group.

1. Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet. 2004;43(13):879-923. doi: 10.2165/00003088-200443130-00004

2. Rinonapoli G, Coaccioli S, Panella L. Tapentadol in the treatment of osteoarthritis: pharmacological rationale and clinical evidence. J Pain Res. 2019;12:1529-1536. doi: 10.2147/JPR.S190161

Comparator(s)/control
The control condition must be treatment with placebo or opioid-minimized pain management strategies. Studies that introduce pain management strategies that differ only in early, versus minimized, use of opioids will be eligible. However, the same non-opioid pain management options must be available to both groups so that each group differs only in the utilization of opioids.

Types of study to be included
We will consider only randomized trials, and limit eligible results to the period during which intervention and control conditions were maintained (i.e. we will not consider extended open-label follow-up periods).

Main outcome
Our main outcome is the number of participants achieving a minimum clinically important difference (MCID) in pain in studies with follow-up ≤4 weeks, 4-12 weeks, and ≥12 weeks. We will be combining studies that use different scales, and we wish to avoid the loss of clinical meaning that conversion to standard mean differences can introduce. Therefore we will examine only the number of participants achieving a MCID on the available pain scale. When more than one level of response is reported (e.g. reporting both ≥30% reduction in pain and ≥50% reduction in pain) we will choose the response closest to a ≥30% improvement.
We will use the following hierarchy when selecting responder outcome:
1. % participants with minimum response on a pain scale closest to ≥30%. If tied, choose lower response (minimum ≥20%).
2. Change in VAS/NRS closest to ≥2 (10- or 11-point scale) or ≥20 (100-point). If tied, choose lower change in score.
3. Absolute VAS/NRS score closest to ≤4 (10- or 11-point) or ≤40 (100 point). If tied, choose higher score.
4. Patient global assessment of change closest to “moderate”, but NOT lower
5. Clinician global assessment of change closest to “moderate”, but NOT lower
6. Scales blending pain and function

Measures of effect
The outcomes will be grouped by short term (≤4 weeks), intermediate term (4-12 weeks), and long term (≥12 weeks) follow-up periods.

Additional outcome(s)
Percent change in opioid dosage from starting dose.

Measures of effect
We will be analyzing data at all time points provided.

Data extraction (selection and coding)
Two authors (LF and CB) will independently extract data and a third author (CK or SG) will verify the extraction. Extracted data will include the citation details, the specific

condition being studied (e.g. knee OA), the specific intervention and comparator, the number of subjects in intervention and control groups, the study duration, the starting daily dosage, the average daily dosage at all follow-up time points, and all assessments of the number of participants achieving a given response, including the scale used and the time of that assessment.

Risk of bias (quality) assessment

Overall quality of the evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Evidence will be defined as high quality, moderate quality, low quality, or very low quality. It can be downgraded by study quality (risk of bias), inconsistency of results, and imprecision. Risk of bias for individual studies will be rated by two authors (LF and CB) at the study level using the Cochrane Collaboration Risk of Bias Tool. A third author (SG or CK) will review the assessments and adjudicate any discrepancies.

Strategy for data synthesis

1. Number of participants achieving a minimum clinically important reduction in pain: studies contributing to this outcome will be grouped into short-term (≤4 weeks), intermediate-term (4-12 weeks), and long-term (≥12 weeks) duration of treatment. We will examine all subgroups to determine whether response diminishes with time. Back pain and osteoarthritis study results will be grouped together and forest plots for the number of participants achieving a meaningful response in the opioid and control groups will be analyzed for each time period.
2. Percent change in opioid dosage from starting dose will be analyzed by:
a) Comparing the percent change from starting dose at follow-up time intervals using the same short-term (≤4 weeks), intermediate-term (4-12 weeks), and long-term (≥12 weeks) definitions.
b) Producing a scatterplot of percent dose change over time.

Analysis of subgroups or subsets

As described above, we are primarily interested in how perceived pain, and percent change from starting opioid dosage, changes over time. To determine this, we will be reporting outcomes in subgroups according to the time they are reported – specifically breaking them down into short-term (≤4 weeks), intermediate-term (4-12 weeks), and long-term (≥12 weeks).
We will not be performing an overall assessment of efficacy over all studies, but will instead be providing an estimate of efficacy for each of the 3 time periods above. As such, we will allow studies that report results at different time periods to contribute to the analysis of more than one time period, but to only contribute once to each individual time period. When a study provides more than one result for the same time period (e.g. assessments of pain at 1 week, 2
weeks, 3 weeks, and 4 weeks) we will choose the single result closest to the midpoint of the time period defining that subgroup. Hence, for the ≤4 weeks subgroup we will choose the value closest to 2 weeks, and for the 4-12 weeks subgroup we will choose the value closest to 8 weeks. As the ≥12-week subgroup has no upper limit, for that subgroup only we will choose the longest follow-up result available.

Type and method of review
Systematic review and meta-analysis.

Health area of the review
Alcohol/substance misuse/abuse, musculoskeletal

Language: English. There is not an English language summary.

Country: Canada.

Dissemination plans: we intend to publish the review on completion.

Current review status: Ongoing.

Any additional information
Amendments clarifying the restrictions placed on the searches were made to section 16 on January 29, 2020.

Appendix B: Alterations to Protocol

1. Our protocol stated that studies including participants with back pain resulting from surgery, cancer, neurogenic claudication, radiculopathy, sciatica, or rheumatic conditions (for example, rheumatoid arthritis or ankylosing spondylitis) would be excluded. However, we had intended this to mean only studies that exclusively enrolled patients with these conditions. Thus, studies were still included if some - but not all - patients had these conditions.
2. Another exclusion criteria on our protocol stated that studies that used trade-name formulations that included an opioid in addition to another compound would be excluded unless they also administered the non-opioid component to the control group. However, in this criterion we had intended "other compounds" to mean analgesic compounds. Therefore, opioid formulations that contained additional non-analgesic compounds (e.g. opioid antagonists naloxone and naltrexone), which weren't also administered to the control group were still included.
3. During the screening process we observed that numerous studies allowed the use of opioids as rescue medication, which entailed that control participants would receive a sizable amount of opioids over the course of the study. We therefore decided to exclude these studies.
4. Our protocol did not detail how we would deal with missing data. We decided that all patients missing from author-reported responder analyses would be considered as non-responders. However, we did preferentially use the mITT population and therefore did exclude patients who did not receive any doses of study medication from our analyses.
5. We stated in our protocol that if a study reported results at multiple time periods, then we would allow that study to contribute to the analysis of more than one time period subgroup (short, intermediate, or long-term duration), but to only contribute once to each individual time period. However, no studies reported results at multiple time points and this rule was therefore not employed.
6. Our secondary analysis was meant to examine how titration of opioid dosage differs over short, intermediate, and long-term treatment. However, the majority of included studies did not allow dose titration throughout the entirety of the study. We still wanted to examine the potential effect of opioid dosage on analgesic efficacy. Therefore, we decided to substitute our intended analysis with a Forest plot using a median split by average morphine equivalent to divide studies into high- and lose-dose. In the event of an odd number of studies, we calculated the mean average study dose. If the average study dose in the median study was greater than this mean we categorized it as a "high dose" study, and if it was lower we categorized it as "low dose".
7. During the screening process, we noticed that a sizable portion of the included studies employed an EERW design. In this design, all included patients are first entered into an open-label titration period where all are titrated to an "effective" dose of opioid analgesic. This period lasts several weeks and only patients that a) do not discontinue and b) meet certain entry criteria that demonstrate benefit, are randomized to either continue with the opioid treatment or switch to placebo. Those randomized to placebo are then gradually discontinued from opioid

treatment in the comparison phase, and must receive sizable amounts of opioid medication to do so. This biases the intervention group towards opioid responders, and puts the placebo group at risk of opioid induced hyperalgesia. We decided to exclude this study design from our primary analysis due to the high degree of bias it introduces. However, recognizing that evidence on differences in outcomes between traditional and enriched designs would be valuable, we included enriched designs in a post-hoc sensitivity analysis comparing responder outcomes in enriched versus traditional trial designs for studies with 12 weeks or greater follow-up.

Appendix C: Search Strategies

Ovid MEDLINE

Search terms for osteoarthritis and back pain

osteoarthr*.mp. OR spondylosis.mp. OR ((back OR knee* OR hip* OR joint*) adj3 (pain* OR ache* OR discomfort* OR sore*)).ti,ab. OR backache*.mp. OR degenerative adj2 arthritis.mp. OR exp Osteoarthritis/ OR Back Pain/ OR Low back pain/

Search for opioids

(Abstral OR Actiq OR Alfentanil OR Anexsia OR Astramorph OR Avinza OR Buprenorphine OR Butorphanol OR Butrans OR carfentan* OR Codeine OR Co-Gesic OR Demerol OR Diamorphine OR Dilaudid OR Dolophine OR Duragesic OR Embeda OR Endocet OR Exalgo OR Fentanyl OR Fentora OR heroin OR Hycet OR Hycodan OR Hydrocodone OR Hydromet OR hydromorphone OR Hysingla OR Ibudone OR Kadian OR Levorphanol OR Liquicet OR Loperamide OR Lorcet OR Lortab OR Maxidone OR meperidine OR methadone OR Morphabond OR morphine OR MS Contin OR Nalbuphine OR narcotic* OR Norco OR Nubain OR Opana ER OR opiate* OR opioid* OR opium OR Onsolis OR Oramorph OR Ora-Morph OR Oxaydo OR Oxecta OR Oxycet OR oxycodone OR OxyContin OR Oxymorphone hydrochloride OR Palladone OR Pentazocine OR Percocet OR Percodan OR Pethidine OR Propoxyphene OR Reprexain OR Rezira OR Roxanol* OR Roxicet OR Roxicodone OR Roxycodone OR Sublimaze OR Sufentanil OR Targiniq ER OR TussiCaps OR Tussionex OR Tuzistra XR OR Vicodin OR Vicoprofen OR Vituz OR Xartemis XR OR Xodol OR Xtampza ER OR Zohydro ER OR Zolvit OR Zutripro OR Zydone).ti,ab. OR exp Analgesics, opioid/

Search terms for randomized controlled trial design

randomized controlled trial.pt. OR clinical trial.pt. OR randomi?ed.ti,ab. OR placebo.ti,ab. OR dt.fs. OR randomly.ti,ab. OR trial.ti,ab. OR groups.ti,ab. (animals NOT (humans AND animals)).sh.

1 not 2

Ovid EMBASE

Search terms for osteoarthritis and back pain

osteoarthr*.mp. OR spondylosis.mp. OR ((back OR knee* OR hip* OR joint*) adj3 (pain* OR ache* OR discomfort* OR sore*)).ti,ab. OR backache*.mp. OR (degenerative adj2 arthritis).mp. OR exp Osteoarthritis/ OR exp Backache/

Search for opioids

(Abstral OR Actiq OR Alfentanil OR Anexsia OR Astramorph OR Avinza OR Buprenorphine OR Butorphanol OR Butrans OR carfentan* OR Codeine OR Co-Gesic OR Demerol OR Diamorphine OR Dilaudid OR Dolophine OR Duragesic OR Embeda OR Endocet OR Exalgo OR Fentanyl OR Fentora OR heroin OR Hycet OR Hycodan OR Hydrocodone OR Hydromet OR hydromorphone OR Hysingla OR Ibudone OR Kadian OR Levorphanol OR Liquicet OR Loperamide OR Lorcet OR Lortab OR Maxidone OR meperidine OR methadone OR Morphabond OR morphine OR MS Contin OR Nalbuphine OR narcotic* OR Norco OR Nubain OR Opana ER OR opiate* OR opioid* OR opium OR Onsolis OR Oramorph OR Ora-Morph OR Oxaydo OR Oxecta OR Oxycet OR oxycodone OR OxyContin OR Oxymorphone hydrochloride OR Palladone OR Pentazocine OR Percocet OR Percodan OR Pethidine OR Propoxyphene OR

Reprexain OR Rezira OR Roxanol* OR Roxicet OR Roxicodone OR Roxycodone OR Sublimaze OR Sufentanil OR Targiniq ER OR TussiCaps OR Tussionex OR Tuzistra XR OR Vicodin OR Vicoprofen OR Vituz OR Xartemis XR OR Xodol OR Xtampza ER OR Zohydro ER OR Zolvit OR Zutripro OR Zydone).ti,ab. OR exp opiate/
Search terms for randomized controlled trial design
exp clinical trial/ OR randomi?ed.ti,ab. OR placebo.ti,ab. OR dt.fs OR randomly.ti,ab. OR trial.ti,ab. OR groups.ti,ab.
(animals NOT (humans AND animals)).sh
1 not 2

Cochrane Library
Search terms for osteoarthritis and back pain
osteoarthr*:ti,ab,kw OR spondylosis:ti,ab,kw OR ((back OR knee* OR hip* OR joint*) NEAR/3 (pain* OR ache* OR discomfort* OR sore*)):ti,ab,kw OR backache*:ti,ab,kw OR degenerative NEAR/2 arthritis:ti,ab,kw OR MeSH descriptor: [Osteoarthritis] explode all trees OR MeSH descriptor: [Back Pain] this term only OR MeSH descriptor: [Low back pain] this term only
Search for opioids
(Abstral OR Actiq OR Alfentanil OR Anexsia OR Astramorph OR Avinza OR Buprenorphine OR Butorphanol OR Butrans OR carfentan* OR Codeine OR "CoGesic" OR Demerol OR Diamorphine OR Dilaudid OR Dolophine OR Duragesic OR Embeda OR Endocet OR Exalgo OR Fentanyl OR Fentora OR Heroin OR Hycet OR Hycodan OR Hydrocodone OR Hydromet OR Hydromorphone OR Hysingla OR Ibudone OR Kadian OR Levorphanol OR Liquicet OR Loperamide OR Lorcet OR Lortab OR Maxidone OR Meperidine OR Methadone OR Morphabond OR Morphine OR "MS Contin" OR Nalbuphine OR Narcotic* OR Norco OR Nubain OR "Opana ER" OR Opiate* OR Opioid* OR Opium OR Onsolis OR Oramorph OR "Ora-Morph" OR Oxaydo OR Oxecta OR Oxycet OR Oxycodone OR OxyContin OR "Oxymorphone Hydrochloride" OR Palladone OR Pentazocine OR Percocet OR Percodan OR Pethidine OR Propoxyphene OR Reprexain OR Rezira OR Roxanol* OR Roxicet OR Roxicodone OR Roxycodone OR Sublimaze OR Sufentanil OR "Targiniq ER" OR TussiCaps OR Tussionex OR "Tuzistra XR" OR Vicodin OR Vicoprofen OR Vituz OR "Xartemis XR" OR Xodol OR "Xtampza ER" OR "Zohydro ER" OR Zolvit OR Zutripro OR Zydone):ti,ab,kw OR MeSH descriptor: [Analgesics, opioid] explode all trees

Scopus
Search terms for osteoarthritis and back pain
TITLE-ABS-KEY(osteoarthr* OR spondylosis OR "back W/3 pain" OR "back W/3 ache*" OR "back W/3 discomfort" OR "back W/3 sore" OR "knee* W/3 pain" OR "knee* W/3 ache*" OR "knee* W/3 discomfort" OR "knee* W/3 sore" OR "hip* W/3 pain" OR "hip* W/3 ache*" OR "hip* W/3 discomfort" OR "hip* W/3 sore" OR "joint* W/3 pain" OR "joint* W/3 ache*" OR "joint* W/3 discomfort" OR "joint* W/3 sore" OR backache* OR "degenerative W/2 arthritis")
Search for opioids
TITLE-ABS-KEY(Abstral OR Actiq OR Alfentanil OR Anexsia OR Astramorph OR Avinza OR Buprenorphine OR Butorphanol OR Butrans OR carfentan* OR Codeine OR

"Co-Gesic" OR Demerol OR Diamorphine OR Dilaudid OR Dolophine OR Duragesic OR Embeda OR Endocet OR Exalgo OR Fentanyl OR Fentora OR Heroin OR Hycet OR Hycodan OR Hydrocodone OR Hydromet OR Hydromorphone OR Hysingla OR Ibudone OR Kadian OR Levorphanol OR Liquicet OR Loperamide OR Lorcet OR Lortab OR Maxidone OR Meperidine OR Methadone OR Morphabond OR Morphine OR "MS Contin" OR Nalbuphine OR Narcotic* OR Norco OR Nubain OR "Opana ER" OR Opiate* OR Opioid* OR Opium OR Onsolis OR Oramorph OR "Ora-Morph" OR Oxaydo OR Oxecta OR Oxycet OR Oxycodone OR OxyContin OR "Oxymorphone Hydrochloride" OR Palladone OR Pentazocine OR Percocet OR Percodan OR Pethidine OR Propoxyphene OR Reprexain OR Rezira OR Roxanol* OR Roxicet OR Roxicodone OR Roxycodone OR Sublimaze OR Sufentanil OR "Targiniq ER" OR TussiCaps OR Tussionex OR "Tuzistra XR" OR Vicodin OR Vicoprofen OR Vituz OR "Xartemis XR" OR Xodol OR "Xtampza ER" OR "Zohydro ER" OR Zolvit OR Zutripro OR Zydone)

Search terms for randomized controlled trial design

(INDEXTERMS ("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials" OR "random allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "multicenter study" OR "double blind procedure" OR "single blind procedure" OR "crossover procedure" OR "clinical trial" OR "controlled study" OR "randomization" OR "placebo") OR TITLE-ABS-KEY(trial* or random* or "cross-over" or crossover or placebo* or "factorial desig*" or rct* or blind* or "control group*" or groups or controls or "controlled study" or "experimental study" or "quasi-experimental" or "before and after"))

Appendix D: studies in full-text review

Studies included in our primary or sensitivity analyses

1. 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. Clinical drug investigation, 30(8), 489-505. doi:http://dx.doi.org/10.2165/11533440-000000000-00000
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Excluded studies

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