

BMJ Open Comparative efficacy and safety of oral or transdermal opioids in the treatment of knee or hip osteoarthritis: a systematic review and Bayesian network meta-analysis protocol

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ABSTRACT

Introduction Osteoarthritis is a common degenerative joint disease that eventually leads to disability and poor quality of life. The main symptoms are joint pain and mobility disorders. If the patient has severe pain or other analgesics are contraindicated, opioids may be a viable treatment option. To evaluate and compare the efficacy and safety of opioids in the treatment of knee or hip osteoarthritis, we will integrate direct and indirect evidence using a Bayesian network meta-analysis to establish hierarchies of these drugs.

Methods and analysis We will search the Medical Literature Analysis and Retrieval System Online, Excerpta Medica database, Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, Web of Science and PsycINFO databases as well as published and unpublished research in international registries and regulatory agency websites for osteoarthritis reports published prior to 5 January 2018. There will be no restrictions on the language. Randomised clinical trials that compare oral or transdermal opioids with other various opioids, placebo or no treatment for patients with knee or hip osteoarthritis will be included. The primary outcomes of efficacy will be pain and function. We will use pain and function scales to evaluate the main outcomes. The secondary outcomes of safety will be defined as the proportion of patients who have stopped treatment due to side effects. Pairwise meta-analyses and Bayesian network meta-analyses will be performed for all related outcome measures. We will conduct subgroup analyses and sensitivity analyses to assess the robustness of our findings. The Grading of Recommendations, Assessment, Development and Evaluations framework will be used to assess the quality of the evidence contributing to each network assessment.

Ethics and dissemination This study does not require formal ethical approval because individual patient data will not be included. The findings will be disseminated through peer-reviewed publications or conference presentations.

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Strengths and limitations of this study

- While previous conventional paired meta-analyses focused on direct comparisons between opioid analgesics and placebo for osteoarthritis, this Bayesian network meta-analysis will combine direct evidence with indirect evidence to assess the interrelationships between a wide range of opioid analgesics, placebo and no treatment in multiple treatment comparisons.
- Subgroup and sensitivity analyses will provide implications for clinically relevant questions for later research directions.
- This method synthesises the data comprehensively and provides a clinically useful summary that can guide the development of a clinical prescription system.
- The different routes of administration (oral or transdermal), durations and frequencies may cause considerable heterogeneity.

INTRODUCTION

Description of the condition

Osteoarthritis (OA), also known as degenerative arthritis or senile arthritis, is a degenerative disease.¹ Increased obesity, age, trauma to joint areas, excessive manual labour and decreased muscle strength and joint stability are important risk factors for OA.²⁻⁵ The main clinical manifestations of OA are chronic pain, joint instability, stiffness, joint deformity and reduced imaging of the joint space; these manifestations eventually lead to progressive disability and reduce patient quality of life.^{1 6} Worldwide, OA, particularly OA of the knee and hip joints, is one of the leading causes of disability among the older adults.^{7 8} Research has shown that around one-third of older adults have OA.⁹ This highly prevalent disease and the accompanying disability have terrible effects on individuals and society. The burden of OA is usually measured by direct

and indirect economic costs, including less explicit intangibles such as pain and reduced quality of life.¹⁰

Cartilage destruction, subchondral bone remodelling and synovitis are the major pathological features of OA. Changes in the internal environment of various tissue structures within the joint cavity are the main causes of these pathological features and include anabolic and catabolic imbalance, especially an increase in articular cartilage catabolism leading to a decrease in the regeneration ability of cartilage.^{11 12} Previous studies have shown that many factors may interfere with chondrocyte homeostasis, including abnormal mechanical loading of proinflammatory mediators and oxidative stress.^{13 14} These mediators can cause inflammation which, in addition to promoting serious chondrocyte apoptosis and articular cartilage damage, can stimulate the sensory nerves in the synovium and surrounding tissues. This nerve stimulation leads to the peripheral and central sensitisation of the adjacent tissues which further leads to chronic pain.¹⁵

Description of the intervention

Pain is the most relevant symptom of OA; as the degree of pain increases, patient mobility is decreased, and the degree of disability increases.^{16 17} Because of pain and functional limitations, the quality of life of patients with OA is even worse than that of patients with gastrointestinal or chronic respiratory system disorders.¹⁸

Therefore, alleviating pain, preventing muscle atrophy and reducing joint deformity, stiffness and other complications are the main therapeutic targets of OA.^{19 20} Currently, the treatment modalities for OA include invasive surgery, non-drug therapy and drug therapy.

Invasive surgery includes intra-articular injections and surgery. Intra-articular injections of agents such as hyaluronic acid, corticosteroids, ozone and platelet-rich plasma are used for the treatment of OA, and these treatments have been proven to be effective.^{21–24} Surgery mainly includes total hip and knee replacement which can improve health-related quality of life in the late stage of OA.^{25 26} However, surgery is not the first choice of treatment for OA in clinical practice due to the limited lifespan of an artificial prosthesis. Furthermore, if a prosthesis fails, the patient may face a second revision operation, and the risk of failure in such operations is high due to the loss of bone mass. Therefore, joint surgery is often considered the ultimate treatment for OA. Non-drug therapy is important for reducing pain and improving the physiological function of patients with OA.²⁷ Non-drug therapies include weight reduction, exercise, changes in lifestyle and other physical therapy measures designed to slow the progression of OA.^{28–30}

Drugs for the treatment of OA pain primarily include non-steroidal anti-inflammatory drugs (NSAIDs), opioid drugs, paracetamol, capsaicin and duloxetine.³¹ Currently, the use of NSAIDs for the treatment of OA pain is preferred in the clinic. However, NSAID use may cause serious adverse cardiovascular, gastrointestinal and renal events.^{32–34} Opioids may be a viable alternative for

patients who do not adequately respond to routine treatment and when other analgesics are contraindicated.³⁵

Why it is important to perform this review

Several systematic reviews have investigated the effectiveness of the agents used to treat OA.^{12 31} However, previous studies have considered only direct evidence from head-to-head comparisons and did not aim to synthesise all the available evidence. As a result, determining the best treatment based on previous studies is often difficult. Indirect comparisons are usually required to establish a 'ranking' (occasionally referred to as a 'league table') of interventions. The Bayesian network meta-analysis method allows for the coinstantaneous comparison of multiple opioid drug interventions in a unitary analysis and ranks the interventions accordingly. This approach provides estimates of treatment differences and uses the heterogeneities and inconsistencies found in the tests to evaluate the uncertainties in the resultant estimates. Therefore, this approach is particularly useful in situations involving many different intervention measures.³⁶

Objectives

To systematically review, compare in terms of efficacy and safety, and rank opioid analgesics for hip or knee OA.

METHODS

Study design

This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (see online supplementary file 1).³⁷

Criteria for the included studies

Types of studies

All randomised controlled trials comparing oral or transdermal opioid therapies with other opioids, placebos or no intervention in patients with knee or hip OA will be included. Trials published as abstracts only will be excluded. We will not apply limits based on the language of the publication.

Types of participants

Trials with mixed populations of patients with OA of the knee or hip must either report the results separately or must have included at least 75% of the patients in the relevant comparisons to be eligible for inclusion.

Types of interventions

Comparisons of oral or transdermal opioid drugs with any type of opioid drug, placebo or no intervention will be included. Trials comparing the same type of opioid at different therapeutic doses will be considered as a different node in the Bayesian network analysis. Consequently, the following comparisons are eligible: opioid versus opioid, placebo versus opioid and no intervention versus opioid.

Table 1 Hierarchy of osteoarthritis pain and function measurement scales^{38 39}

Hierarchy	Pain measurement scales	Function measurement scales
1	Global Pain Index	Global disability score
2	Pain on walking	Walking disability
3	WOMAC Osteoarthritis Index pain subscore	WOMAC disability subscore
4	Composite pain scores other than WOMAC	Composite disability scores other than WOMAC
5	Pain on activities other than walking (such as stair climbing)	Disability other than walking
6	Rest pain or pain during the night	WOMAC Global Scale
7	WOMAC global algofunctional score	Lequesne Osteoarthritis Index global score
8	Lequesne Osteoarthritis Index global score	Other algofunctional scale
9	Other algofunctional scale	Participant's global assessment
10	Participant's global assessment	Physician's global assessment
11	Physician's global assessment	

WOMAC, Western Ontario and McMaster Universities.

Types of outcome measures

Primary outcomes

The primary outcomes will include pain and function. If data from more than one pain or function scale are provided in a single trial, we will follow the method described in previous studies^{38 39} and extract data according to the hierarchy. The detailed scale hierarchy is presented in [table 1](#).

Secondary outcomes

To assess the safety of opioids, we will extract the proportion of participant withdrawals due to adverse events.

Data sources and search strategy

Electronic searches

We will search the Medical Literature Analysis and Retrieval System Online and Excerpta Medica database databases via the Ovid platform, the Cochrane Central Register of Controlled Trials database via the Cochrane Library and the Cumulative Index to Nursing and Allied Health Literature database via EBSCO. We will also search the Web of Science and PsycINFO databases. All databases will be searched from implementation to 5 January 2018 using a previously reported search strategy.^{10 12 29 31} For the strategies that will be used in this review, see online supplementary file 2.

Searching other resources

International registries of published and unpublished articles and the websites of regulatory agencies will be searched in our review. These sources include the following: the WHO International Clinical Trials Registry Platform, clinicaltrials.gov, the University hospital Medical Information Network-Clinical Trials Registry, the American College of Rheumatology, the European League Against Rheumatism and the US Food and Drug Administration reports. No language limitations will be applied.

Study selection

Two independent reviewers (YW and HZ) will evaluate all relevant titles and abstracts. The reviewers will use uniform standards to independently extract key study parameters, and any disagreements will be resolved by the third review (JW). There will be no language restrictions. If multiple studies describe the same experiment, the study with the most relatively complete data will be used in the analyses.

Data extraction and management

Two review authors (YW and HZ) will extract the trial information independently via a single purpose-built electronic database. Any differences will be resolved by consensus or discussion with the third author (JW). The following information will be extracted:

- ▶ Patient characteristics (average age, gender, duration of symptoms and the type of joint affected).
- ▶ Details of the intervention, including the route of administration, dosage (different doses of the same drug will be divided into different nodes), and frequency of the drug therapies and the treatment duration.
- ▶ Types of measures used and pain-related or function-related outcomes.
- ▶ Type of adverse effects related to the outcome.
- ▶ Outcome data for each endpoint of interest.
- ▶ Duration of the follow-up.
- ▶ Trial design (including eligibility criteria of patients).
- ▶ Trial size.
- ▶ Publication status.
- ▶ The type and source of financial support.

We will use the results from intention-to-treat analyses whenever possible.⁴⁰ If we cannot calculate the effect size, we will contact the study authors for additional data. Research from non-English language journals will be electronically translated before assessment.

Box 1 Assessment of the risk of bias in the six domains⁴³

1. Was there adequate sequence generation (selection bias)?
2. Was allocation adequately concealed (selection bias)?
3. Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
4. Were incomplete outcome data adequately addressed (attrition bias)?
5. Are reported of the study free of selective reporting (reporting bias)?
6. Was the study apparently free of other problems that could put it at a risk of bias?

Assessment of the risk of bias in the included studies

Two review authors (ML and LY) will independently use the risk of bias assessment tools generated by the Cochrane Collaboration.⁴¹ Disagreements will be resolved by negotiation. We will systematically evaluate bias across six domains⁴² as illustrated in **box 1**. All included trials will be classified into the following categories: low risk, high risk and unclear.⁴¹

DATA SYNTHESIS AND ANALYSIS**Measures of treatment effects****Relative treatment effects**

We will estimate continuous variables using the standardised mean difference (SMD) with 95% credible intervals (CrIs). For categorical outcomes, ORs with 95% CrIs will be calculated for the analyses. In the presence of minimally informative priors, CrIs can be understood similarly to CIs, and at the conventional statistical significance level, a two-sided $p < 0.05$ can be assumed if the 95% CrIs do not include 0.⁴³ If SDs are not provided, we will calculate them from the SEs, CIs or p values using a method described in previous studies.^{39 44} If some necessary data are not available, we will use approximations as previously described.³⁵ To visually explain the pooled effects, we will transform the effect sizes into differences on a 10 cm Visual Analogue Scale (VAS) based on a median pooled SD of 2.5 cm, as found in large-scale OA trials that have used 10 cm VASs to assess pain.⁴⁴ SMDs of -0.20 correspond to approximate differences in pain scores between the experimental and control groups of 0.5 on a 10 cm VAS, -0.50 of 1.25 on a 10 cm VAS and -0.80 of 2 on a 10 cm VAS.^{44 45} Additionally, we will compare the effects with a prespecified minimal clinically important difference based on the median pooled SD of 0.37 which has been used in recent studies of patients with OA and corresponds to 0.9 cm on a 10 cm VAS.^{46–49} We will also transform the SMDs for function to a Western Ontario and McMaster Universities Osteoarthritis Index score based on a median pooled SD of 2.1 units as observed in large-scale OA trials.^{50 51}

Relative treatment ranking

Each intervention and each outcome will be systematically evaluated and ranked. We will determine a treatment

hierarchy using the surface under the cumulative ranking curve and the mean ranks.⁵²

Data analysis

First, we will conduct paired meta-analyses by synthesising the studies that compare interventions head-to-head using a random-effects model.⁵³ Then, we will use a Bayesian network meta-analysis to compare the different classes of oral or transdermal opioid treatments based on the median of the posterior distribution.^{54 55} A Bayesian random-effects model will be used because this model completely retains the within-trial randomised treatment comparisons of each study while combining all available comparisons between treatments and accounting for multiple comparisons within a trial in cases with more than two treatment arms.^{55 56} The between-trial variance of the treatment effects (τ^2) will be estimated from the posterior distribution. Pooled estimates will be performed with Markov chain Monte Carlo methods. Convergence of the Markov chains will be considered to be achieved if the Gelman-Rubin diagnostic plots indicate that the widths of the pooled runs and individual runs stabilise around the same value, and their ratio is approximately one.⁵⁷

The analyses will be performed using Stata V.14.0 software and WinBUGS (MRC Biostatistics Unit 2007, V.1.4.3; Cambridge, UK).

Assessment of statistical heterogeneity

We will use I^2 statistics and p values to assess the statistical heterogeneity of each pairwise comparison.⁵⁸ In the Bayesian meta-analysis, we will calculate the heterogeneity of the treatment effects estimated from the posterior median between-trial variance (τ^2). Global heterogeneity will be assessed using the I^2 statistic.

Assessment of statistical inconsistency

We will evaluate the inconsistencies locally in the network using the loop-specific approach.⁵⁹ The design-by-treatment interaction model will also be used to calculate the consistency throughout the entire network.⁵⁹

Subgroup analyses

To explore the robustness of the results, we will include the characteristics of the trials as covariates in the Bayesian meta-analysis to assess the primary outcomes based on the clinical characteristics, risk of bias and trial size. A random-effects meta-regression model⁶⁰ will be used to determine whether the treatment effects are affected by the following factors: (1) treatment duration (short term ≤ 1 month and long-term > 1 month); (2) trial size (small-scale: allocated participants ≤ 200 , and large-scale: allocated participants > 200); (3) high methodological quality as defined by adequate concealment of the allocation (adequate vs inadequate or unclear); (4) adequate blinding of the patients (adequate vs inadequate or unclear); (5) intention-to-treat analysis (yes vs no or unclear); (6) source of funding (independent of the pharmaceutical industry or unclear vs no); (7) type of OA (hip only vs knee only vs mixed); (8) type of opioid

(oral vs transdermal); and (9) type of trial (published vs unpublished).

Sensitivity analyses

We will perform sensitivity network meta-analyses for the primary outcomes by omitting unpublished trials and trials with inadequate or unclear allocation concealment.

Other analyses

The Grading of Recommendations, Assessment, Development and Evaluations framework, which characterises the quality of evidence based on the study limitations, publication bias, indirectness, imprecision and inconsistency in the primary outcomes, will be used to evaluate the quality of evidence in each network.⁶¹ Additionally, a comparison-adjusted funnel plot will be drawn to detect any major publication bias in the Bayesian network meta-analysis.⁶²

Ethics and dissemination

This systematic review and Bayesian meta-analysis do not require formal ethical approval because individual patient data are not included. The results will provide a general review and evidence for the efficacy and safety of oral or transdermal opioids in the treatment of knee or hip OA. The findings will be disseminated through peer-reviewed publications or conference presentations. The basic protocol amendments will be recorded in the full review.

Patient and public involvement

No patients or the public participated in the study.

DISCUSSION

This systematic review and Bayesian network meta-analysis will provide an assessment of opioid therapies in patients with knee or hip OA. Currently, NSAIDs remain the first-line drugs for OA treatment. Whether opioids can be used as a routine treatment for knee or hip OA is controversial. One review compared the efficacy of NSAIDs and opioids in the treatment of knee OA and found that the efficacy is essentially the same.⁶³ To date, no systematic review on opioids for OA has carried out a network meta-analysis to compare efficacy and safety across different opioid analgesics. Our results will rank the efficacy and safety of opioids in the treatment of OA which has not been included in previous studies. The conclusions of this study may be beneficial for patients with knee or hip OA, clinicians and policy-makers. We will perform subgroup analysis to explore whether our findings are consistent across subgroups and explore the sources of heterogeneity. The proposed systematic review and network meta-analysis may have some potential limitations. The different routes of administration (oral or transdermal), durations and frequencies may cause considerable heterogeneity. Another limitation may be differences in the quality of the included studies which will limit the ability of this work to reach high-confidence conclusions.

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Contributors JW conceived the review and wrote the first draft of the protocol. WG and ZY revised the protocol. YW and HZ are responsible for the development of the search strategy and data extraction. ML and LY will be responsible for assessing bias and data synthesis and analysis. All the authors have approved the publication of the protocol.

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