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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 with mobility pain and disorders as the main symptoms, eventually leading to disability and poor quality of life. 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 the direct and indirect evidence using a Bayesian network meta-analysis to establish hierarchies of these drugs.

Methods and analysis: We will search the Medicine, Embase, CINAHL, Cochrane Library, Web of Science, and PsycINFO databases as well as published and unpublished research in international registries and websites of regulatory agencies for osteoarthritis reports published prior to January 5, 2018. There will be no restrictions on the language. Randomized 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 GRADE 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 as individual patient data will not be included. The findings will be disseminated through peer-reviewed publications or conference presentations.

Trial registration number: PROSPERO CRD42018085503.

Strengths and limitations of this study

▪While conventional paired meta-analyses focus on direct comparisons of single interventions, this Bayesian network meta-analysis will combine

direct evidence with indirect evidence to assess the interrelationships between all treatments in multiple treatment comparisons.

▪ There is controversy over the efficacy and safety of the use of opioids in the treatment of knee or hip osteoarthritis. We will rank the efficacy and safety of the available opioid drugs.

▪ Subgroup and sensitivity analyses will provide implications for clinically relevant questions for later research directions.

▪ This method synthesizes the data comprehensively and provides a clinically useful summary that can guide the development of a clinical prescription system.

Introduction

Description of the condition

Osteoarthritis (OA) is a degenerative disease that is also known as degenerative arthritis or senile arthritis.[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, and these manifestations eventually lead to progressive disability and reduce the patient's quality of life.[1,6] OA, particularly OA of the knee and hip joints, is one of the leading causes of disability in the world among the elderly, and it is estimated that the global age-standardized incidence rates are 3.8% in the knee and 0.85% in the hip.[7-8] The impact of this disease is widespread and serious, and there are currently no effective interventions to prevent the development of OA.[1]

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.[9-10] Previous studies have shown that many factors may interfere with chondrocyte homeostasis, including abnormal mechanical loading of proinflammatory mediators and oxidative stress.[11-12] These mediators can cause inflammation, which, in addition to promoting serious chondrocyte apoptosis and articular cartilage damage, can also stimulate the sensory nerves in the synovium and surrounding tissues. This nerve stimulation leads to the peripheral and central sensitization of the adjacent tissues, which further leads to chronic pain.[13]

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.[14-15] A previous study showed that because of pain and functional limitations, the quality of life of patients with OA is even worse than those of patients with gastrointestinal or chronic respiratory system disorders.[16]

Therefore, alleviating pain, preventing muscle atrophy, and reducing joint deformity, stiffness and other complications are the main therapeutic targets of OA.[17-18] 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 (HA), corticosteroids, ozone, and platelet-rich plasma (PRP) are used for the

treatment of OA, and these treatments have been proven to be effective.[19-22] Surgery mainly includes total hip and knee replacement, which can improve the health-related quality of life in the late stage of OA.[23-24] However, surgery is not the first choice of treatment for OA in clinical practice due to the limited lifetime 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 as the ultimate treatment for OA. Non-drug therapy is important for reducing pain and improving the physiological function of OA patients.[25] Non-drug therapies include weight reduction, exercise, changes in lifestyle and other physical therapy measures designed to slow the progression of OA.[26-28]

Drugs for the treatment of OA pain primarily include non-steroidal anti-inflammatory drugs (NSAIDs) and opioid drugs.[29] Currently, the use of NSAID drugs for the treatment of OA pain is preferred in the clinic. However, NSAID use may cause serious adverse cardiovascular and gastrointestinal events.[30-31] Opioids may be a viable alternative for patients who do not adequately respond to routine treatment and when other analgesics are contraindicated.[32]

Why it is important to perform this review

Several systematic reviews have investigated the effectiveness of the agents used to treat OA.[10,29] However, previous studies only considered direct evidence from head-to-head comparisons and did not aim to synthesize all the available evidence. Moreover, the authors of these previous studies have often refrained from conducting meta-analyses due to differences in the outcome measures reported in individual trials, thus limiting their use to inform clinical practice. As a result, it often difficult

to determine the best treatment based on previous studies. 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 opioids 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. [33]

Objectives

To systematically analyse the efficacy and safety of opioid medications against those of other opioids, placebos or interventions in the treatment of knee or hip OA.

METHODS

Criteria for the included studies

Types of studies

All randomized controlled trials (RCTs) comparing oral or transdermal opioid therapies with other opioids, placebos, or no intervention in patients with knee or hip OA will be included. Trials only published as abstracts 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 vs. opioid, placebo vs. opioid, and no intervention vs. opioid.

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[34-35] 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 participants who experienced adverse events. We will define adverse effects as nausea, constipation, drug addiction or dependence, cessation of drug use, extended length of hospitalization, hospitalization, life-threatening complications, or death.[29]

Data sources and search strategy

Electronic searches

We will search the MEDLINE and EMBASE databases via the Ovid platform, the CENTRAL database via the Cochrane Library, and the CINAHL database via EBSCO. We will also search the Web of Science and PsycINFO databases. All databases will be searched from implementation to January 5, 2018 using a previously reported search strategy.[10,29] For the strategies that will be used in this review, see **Appendix 1**.

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 UMIN-Clinical Trials Registry, the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and U.S. Food and Drug Administration (FDA) 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, and frequency of the drug therapies and the treatment duration;

-Types of measures used and pain- 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; and

-The type and source of financial support.

We will use the results from the intention-to-treat analyses whenever possible.[36] 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.

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.[37] Disagreements will be resolved by negotiation. We will systematically evaluate bias across six domains[38] as illustrated in **Table 2**. All included

trials will be classified into three categories: low risk, high risk, and unclear.[37]

Data synthesis and analysis

Measures of treatment effects

Relative treatment effects

We will estimate the continuous variables using the standardized mean difference (SMD) with 95% credible intervals (CrIs). For the categorical outcomes, odds ratios (ORs) with 95% CrIs will be calculated for the analyses. In the presence of minimally informative priors, CrIs can be understood similarly to confidence interval (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.[39] If standard deviations (SDs) are not provided, we will calculate them from the standard errors, CIs, or p-values using a method described in previous studies.[35,40] 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.[40] 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.[40-41] Additionally, we will compare the effects with a pre-

specified minimal clinically important difference based on the median pooled SD of 0.37 units, which has been utilized in recent studies of patients with OA and corresponds to 0.9 cm on a 10-cm VAS.[42-45] We will also transform the SMDs for function to a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score based on a median pooled SD of 2.1 units as observed in large-scale OA trials. [46-47]

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 (SUCRA) and the mean ranks.[48]

Data analysis

First, we will conduct paired meta-analyses by synthesizing the studies that compare interventions head-to-head using a random-effects model.[49] 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.[50-51] A Bayesian random-effects model will be used because this model completely retains the within-trial randomized 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.[51-52] 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 stabilize around the same value and their ratio is approximately one.[53]

The analyses will be performed with Stata 14.0 software (StataCorp, College Station, TX, USA) and WinBUGS (MRC Biostatistics Unit 2007, Version 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.[54] 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.[55] The design-by-treatment interaction model will also be used to calculate the consistency throughout the entire network.[56]

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 model[57] 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 versus inadequate or unclear); (4) adequate blinding of the patients (adequate versus inadequate or unclear); (5) intention-to-treat analysis (yes versus no or unclear); (6) source of funding (independent of the pharmaceutical industry or unclear versus no); (7) type of OA (hip only versus knee only versus mixed); (8) type of opioid (oral versus transdermal); and (9) type of trial (published versus 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 GRADE framework, which characterizes 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.[58] Additionally, a comparison-adjusted funnel plot will be drawn to detect any major publication bias in the Bayesian network meta-analysis.[59]

Ethics and dissemination

This systematic review and Bayesian meta-analysis does not require formal ethical approval as individual patient data are not included. The

results will provide a general review of 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.

DISCUSSION

This systematic review and Bayesian network meta-analysis will provide an assessment of opioid therapies in patients with knee or hip OA. Whether opioids can be used as a routine treatment for knee or hip OA is controversial. 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. 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.

Collaborators: None

Contributors: JW conceived the review and wrote the first draft of the protocol. WLG and ZSY 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 the data synthesis and analysis. All the authors have approved the publication of the protocol.

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Table 1 Hierarchy of osteoarthritis pain and function measurement scales[34-35]

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.

Table 2 Assessment of the risk of bias in the six domains[39]

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?

Appendix 1. MEDLINE, EMBASE, CINAHL, and CENTRAL search strategy

Ovid MEDLINE

Search terms for design

1.randomized controlled trial.pt.

2.controlled clinical trial.pt.

3.randomized controlled trial.sh.

4.random allocation.sh.

5.double blind method.sh.

6.single blind method.sh.

7.clinical trial.pt.

8.exp clinical trial/

9.(clin$ adj25 trial$).ab,ti.

10.((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ab,ti.

11.placebos.sh.

12.placebo$.ab,ti.

13.random$.ab,ti.

14.research design.sh.

15.comparative study.sh.

16.exp evaluation studies/

17.follow up studies.sh.

18.prospective studies.sh.

19.(control$ or prospectiv$ or volunteer$).ab,ti.

Search terms for Osteoarthritis

20.exp osteoarthritis/

21.osteoarthriti$.ab,sh,ti.

22.osteoarthro$.ab,sh,ti.

23.gonarthriti$.ab,sh,ti.

24.gonarthro$.ab,sh,ti.

25.coxarthriti$.ab,sh,ti.

26.coxarthro$.ab,sh,ti.

27.arthros$.ab,ti.

28.arthrot$.ab,ti.

29.((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ab,ti.

30.((knee$ or hip$ or joint$) adj3 stiff$).ab,ti.

Search terms for Opioids

31.exp Analgesics, Opioid/

32.exp Narcotics/

33.acetyldihydrocodeine.tw.

34.alfentanil.tw.

35.allylprodine.tw.

36.alphamethylfentanyl.tw.

37.alphaprodine.tw.

38.benzylmorphine.tw.

39.betaprodine.tw.

40.bezitriamide.tw.

41.buprenorphine.tw.

42.butorphanol.tw.

43.bremazocine.tw.

44.carfentan$.tw.

45.codeine.tw.

46.contin.tw.

47.dextromoramide.tw.

48.dextropropoxyphene.tw.

49.dezocine.tw.

50.diacetylmorphine.tw.

51.diamorphine.tw.

52.dihydrocodeine.tw.

53.dihydromorphine.tw.

54.dihydromorphone.tw.

55.diphenoxylate.tw.

56.dipipanone.tw.

57.enadoline.tw.

58.ethylketazocine.tw.

59.ethylmorphine.tw.

60.etonitazene.tw.

61.etorphine.tw.

62.fentanyl.tw.

63.heroin.tw.

64.hydrocodone.tw.

65.hydromorphin$.tw.

66.hydromorphone.tw.

67.ketazocine.tw.

68.ketobemidone.tw.

69.lefetamine.tw.

70.levomethadon.tw.

71.levomethadyl.tw.

72.levomethorphan$.tw.

73.levorphanol.tw.

74.loperamide.tw.

75.meperidine.tw.

76.meptazinol.tw.

77.methadone.tw.

78.methadyl.tw.

79.methylmorphine.tw.

80.morphin$.tw.

81.nalbuphine.tw.

82.narcotic$.tw.

83.nicocodeine.tw.

84.nicomorphine.tw.

85.normorphine.tw.

86.noscapin$.tw.

87.ohmefentanyl.tw.

88.opiate$.tw.

89.opioid$.tw.

90.opium.tw.

91.oripavine.tw.

92.oxycodone.tw.

93.oxycontin.tw.

94.oxymorphone.tw.

95.papaveretum.tw.

96.papaverin.tw.

97.pentazocine.tw.

98.percocet.tw.

99.peronine.tw.

100. pethidine.tw.

101.phenazocine.tw.

102.phencyclidine.tw.

103.pholcodine.tw.

104.piritramid$.tw.

105.prodine.tw.

106.promedol.tw.

107.propoxyphene.tw.

108.remifentanil.tw.

109.sufentanil.tw.

110.tapentadol.tw.

111.thebaine.tw.

112.tilidine.tw.

113.tramadol.sh,tw.

114.ultracet.sh,tw.

Combining terms

115.31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114

116.20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

117.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

118.115 and 116 and 117

119.animal/

120.animal/ and human/

121.119 not 120

122.118 not 121

123.remove duplicates from 122

Ovid EMBASE

Search terms for design

1.randomized controlled trial.sh.

2.randomization.sh.

3.double blind procedure.sh.

4.single blind procedure.sh.

5.exp clinical trials/

6.(clin$ adj25 trial$).ab,ti.

7.((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ab,ti.

8.placebo.sh.

9.placebo$.ab,ti.

10.random$.ab,ti.

11.methodology.sh.

12.comparative study.sh.

13.exp evaluation studies/

14.follow up.sh.

15.prospective study.sh.

16.(control$ or prospectiv$ or volunteer$).ab,ti.

Search terms for Osteoarthritis

17.exp osteoarthritis/

18.osteoarthriti$.ab,sh,ti.

19.osteoarthro$.ab,sh,ti.

20.gonarthriti$.ab,sh,ti.

21.gonarthro$.ab,sh,ti.

22.coxarthriti$.ab,sh,ti.

23.coxarthro$.ab,sh,ti.

24.arthros$.ab,ti.

25.arthrot$.ab,ti.

26.((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ab,ti.

27.((knee$ or hip$ or joint$) adj3 stiff$).ab,ti.

Search terms for Opioids

28.exp Analgesics, Opioid/

29.exp Narcotic Analgesic Agent/

30.acetyldihydrocodeine.tw.

31.alfentanil.tw.

32.allylprodine.tw.

33.alphamethylfentanyl.tw.

34.alphaprodine.tw.

35.benzylmorphine.tw.

36.betaprodine.tw.

37.bezitriamide.tw.

38.buprenorphine.tw.

39.butorphanol.tw.

40.bremazocine.tw.

41.carfentan$.tw.

42.codeine.tw.

43.contin.tw.

44.dextromoramide.tw.

45.dextropropoxyphene.tw.

46.dezocine.tw.

47.diacetylmorphine.tw.

48.diamorphine.tw.

49.dihydrocodeine.tw.

50.dihydromorphine.tw.

51.dihydromorphone.tw.

52.diphenoxylate.tw.

53.dipipanone.tw.

54.enadoline.tw.

55.ethylketazocine.tw.

56.ethylmorphine.tw.

57.etonitazene.tw.

58.etorphine.tw.

59.fentanyl.tw.

60.heroin.tw.

61.hydrocodone.tw.

62.hydromorphin$.tw.

63.hydromorphone.tw.

64.ketazocine.tw.

65.ketobemidone.tw.

66.lefetamine.tw.

67.levomethadon.tw.

68.levomethadyl.tw.

69.levomethorphan$.tw.

70.levorphanol.tw.

71.loperamide.tw.

72.meperidine.tw.

73.meptazinol.tw.

74.methadone.tw.

75.methadyl.tw.

76.methylmorphine.tw.

77.morphin$.tw.

78.nalbuphine.tw.

79.narcotic$.tw.

80.nicocodeine.tw.

81.nicomorphine.tw.

82.normorphine.tw.

83.noscapin$.tw.

84.ohmefentanyl.tw.

85.opiate$.tw.

86.opioid$.tw.

87.opium.tw.

88.oripavine.tw.

89.oxycodone.tw.

90.oxycontin.tw.

91.oxymorphone.tw.

92.papaveretum.tw.

93.papaverin.tw.

94.pentazocine.tw.

95.percocet.tw.

96.peronine.tw.

97.pethidine.tw.

98.phenazocine.tw.

99.phencyclidine.tw.

100. pholcodine.tw.

101.piritramid$.tw.

102.prodine.tw.

103.promedol.tw.

104.propoxyphene.tw.

105.remifentanil.tw.

106.sufentanil.tw.

107.tapentadol.tw.

108.thebaine.tw.

109.tilidine.tw.

110.tramadol.sh,tw.

111.ultracet.sh,tw.

Combining terms

112 .28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111

113.17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

114.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

115.112 and 113 and 114

116.animal/

117.animal/ and human/

118.116 not 117

119.115 not 118

120.remove duplicates from 119

CINAHL through EBSCOhost

Search terms for design

1. (MH “Clinical Trials+”)

2. (MH “Random Assignment”)

3. (MH “Double-Blind Studies”) or (MH“Single-Blind Studies”)

4. TX (clin$ n25 trial$)

5. TX (sing$ n25 blind$)

6. TX (sing$ n25 mask$)

7. TX (doubl$ n25 blind$)

8. TX (doubl$ n25 mask$)

9. TX (trebl$ n25 blind$)

10. TX (trebl$ n25 mask$)

11. TX (tripl$ n25 blind$)

12. TX (tripl$ n25 mask$)

13. (MH "Placebos")

14. TX placebo$

15. TX random$

16. (MH "Study Design+")

17. (MH "Comparative Studies")

18. (MH "Evaluation Research")

19. (MH "Prospective Studies+")

20. TX (control$ or prospectiv$ or volunteer$)

21. S1 or S2 or (…) or S20

Search terms for Osteoarthritis

22. osteoarthriti$

23. (MH "Osteoarthritis")

24. TX osteoarthro$

25. TX gonarthriti$

26. TX gonarthro$

27. TX coxarthriti$

28. TX coxarthro$

29. TX arthros$

30. TX arthrot$

31. TX knee$ n3 pain$

32. TX hip$ n3 pain$

33. TX joint$ n3 pain$

34. TX knee$ n3 ach$

35. TX hip$ n3 ach$

36. TX joint$ n3 ach$

37. TX knee$ n3 discomfort$

38. TX hip$ n3 discomfort$

39. TX joint$ n3 discomfort$

40. TX knee$ n3 stiff$

41. TX hip$ n3 stiff$

42. TX joint$ n3 stiff$

43. S22 or S23 or S24(…)or S42

Search terms for Opioids

44. MH " Analgesics, Opioid"

45. MH "Narcotics"

46. TX acetyldihydrocodeine

47. TX alfentanil

48. TX allylprodine

49. TX alphamethylfentanyl

50. TX alphaprodine

51. TX benzylmorphine

52. TX betaprodine

53. TX bezitriamide

54. TX buprenorphine

55. TX butorphanol

56. TX bremazocine

57. TX carfentan$

58. TX codeine

58. TX contin

60. TX dextromoramide

61. TX dextropropoxyphene

62. TX dezocine

63. TX diacetylmorphine

64. TX diamorphine

65. TX dihydrocodeine

66. TX dihydromorphine

67. TX dihydromorphone

68. TX diphenoxylate

69. TX dipipanone

70. TX enadoline

71. TX ethylketazocine

72. TX ethylmorphine

73. TX etonitazene

74. TX etorphine

75. TX fentanyl

76. TX heroin

77. TX hydrocodone

78. TX hydromorphin$

79. TX hydromorphone

80. TX ketazocine

81. TX ketobemidone

82. TX lefetamine

83. TX levomethadon

84. TX levomethadyl

85. TX levomethorphan$

86. TX levorphanol

87. TX loperamide

88. TX meperidine

89. TX meptazinol

90. TX methadone

91. TX methadyl

92. TX methylmorphine

93. TX morphin$

94. TX nalbuphine

95. TX narcotic$

96. TX nicocodeine

97. TX nicomorphine

98. TX normorphine

99. TX noscapin$

100. TX ohmefentanyl

101. TX opiate$

102. TX opioid$

103. TX opium

104. TX oripavine

105. TX oxycodone

106. TX oxycontin

107. TX oxymorphone

108. TX papaveretum

109. TX papaverin

110. TX pentazocine

111. TX percocet

112. TX peronine

113. TX pethidine

114. TX phenazocine

115. TX phencyclidine

116. TX pholcodine

117. TX piritramid$

118. TX prodine

119. TX promedol

120. TX propoxyphene

121. TX remifentanil

122. TX sufentanil

123. TX tapentadol

124. TX thebaine

125. TX tilidine

126. TX tramadol

127 .TX ultracet

128. S44 or S45 or(…)S127

Combining terms

129. S21 and S43 and S128

CENTRAL

Search terms for Osteoarthritis

#1. MeSH descriptor Osteoarthritis explode all trees

#2. (osteoarthritis* OR osteoarthro* OR gonarthriti* OR gonarthro* OR coxarthriti* OR coxarthro* OR arthros* OR arthrot* OR ((knee* OR hip* OR joint*) near/3 (pain* OR ach* OR discomfort*)) OR ((knee* OR hip* OR joint*) near/3 stiff*)) in Trials

Search terms for Opioids

#3. MeSH descriptor Analgesics, Opioid explode all trees

#4. MeSH descriptor Narcotics explode all trees

#5. (acetyldihydrocodeine OR alfentanil OR allylprodine OR alphamethylfentanyl OR alphaprodine OR benzylmorphine OR betaprodine OR bezitriamide OR buprenorphine OR butorphanol OR bremazocine OR carfentan* OR codeine OR contin ORdextromoramide OR dextropropoxyphene OR dezocine OR diacetylmorphine OR diamorphine OR dihydrocodeine OR dihydromorphine OR dihydromorphone OR diphenoxylate OR dipipanone OR enadoline OR ethylketazocine OR ethylmorphine OR etonitazene OR etorphine OR fentanyl OR heroin OR hydrocodone OR hydromorphin* OR hydromorphone OR ketazocine OR ketobemidone OR lefetamine OR levomethadon OR levomethadyl OR levomethorphan* OR levorphanol OR loperamide OR meperidine OR meptazinol OR methadone OR methadyl OR methylmorphine OR morphin* OR nalbuphine OR narcotic* OR nicocodeine OR nicomorphine OR normorphine OR noscapin* OR ohmefentanyl OR opiate* OR opioid* OR opium OR oripavine OR oxycodone OR oxycontin OR oxymorphone OR papaveretum OR papaverin OR pentazocine OR percocet OR peronine OR pethidine OR phenazocine OR phencyclidine OR pholcodine OR piritramid* OR prodine OR promedol OR propoxyphene OR remifentanil OR sufentanil OR tapentadol OR thebaine OR tilidine OR tramadol OR ultracet) in Trials

Combining terms

#6. (#1 OR #2)

#7. (#3 OR #4 OR #5)

#8. (#6 AND #7) in Clinical Trials

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No(page)	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1	Identify the report as a protocol of a systematic review
Update	NA	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	15	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	NA	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	15	Indicate sources of financial or other support for the review
Sponsor	15	Provide name for the review funder and/or sponsor
Role of sponsor or funder	15	*Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol*
INTRODUCTION		
Rationale	3-5	Describe the rationale for the review in the context of what is already known
Objectives	6	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	6-8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	8-9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	8	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated

Study records:		
Data management	8-10	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	8-10	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	8-10	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	15	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	7-8	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	9	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	10-13	Describe criteria under which study data will be quantitatively synthesised
	10-13	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	10-13	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	10-13	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	13	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	13	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022142.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Jul-2018
Complete List of Authors:	Wang, Jun; The First Affiliated Hospital of Anhui Medical University, Anhui, China, Department of Orthopaedics Wang, Yin ; The Fourth Affiliated Hospital of Anhui Medical University, Anhui, China, Department of Plastic Surgery Zhang, Hui; The First Affiliated Hospital of Anhui Medical University, Anhui, China, Department of Orthopaedics Lu, Ming; The First Affiliated Hospital of Anhui Medical University, Anhui, China, Department of Orthopaedics Gao, Weilu; The First Affiliated Hospital of Anhui Medical University, Anhui, China, Department of Orthopaedics Yin, Li; The First Affiliated Hospital of Anhui Medical University, Anhui, China, Department of Orthopaedics Yin, Zongsheng
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Medical management
Keywords:	opioid, osteoarthritis, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Hip < ORTHOPAEDIC & TRAUMA SURGERY, opioids, osteoarthritis, knee, hip

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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Keywords: opioids, osteoarthritis, knee, hip

Word count: 3086 (excluding title page, references, figures)

ABSTRACT

Introduction: Osteoarthritis is a common degenerative joint disease that eventually leads to disability and poor quality of life. The main symptoms are mobility pain and 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 Medicine, Embase, CINAHL, 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 January 5, 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 GRADE 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.

Trial registration number: PROSPERO CRD42018085503.

Strengths and limitations of this study

▪While conventional paired meta-analyses focus on direct comparisons of single interventions, this Bayesian network meta-analysis will combine

direct evidence with indirect evidence to assess the interrelationships between all treatments 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 elderly.[7-8] In a Dutch study, the prevalence of symptomatic hip OA was 5.9% in adults aged 45-54 years and 17% in adults aged 75 years and older; the prevalence of knee OA in adults aged 55 years and older was 15.6% in men and 30.5% in women.[9] This highly prevalent disease and the accompanying disability have terrible effects on individuals and society. The burden of disease of OA is usually measured by direct and indirect economic costs, including

less explicit intangibles such as pain and reduced quality of life.[10] In general, the impact of this disease is widespread and serious, and there are currently no effective interventions to prevent the development of OA.[1]

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 (HA), corticosteroids, ozone, and platelet-rich plasma (PRP) 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 OA patients.[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, capsaisin 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 **Supplementary file 1**. [37]

Criteria for the included studies

Types of studies

All randomised controlled trials (RCTs) 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 vs. opioid, placebo vs. opioid, and no intervention vs. opioid.

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**.

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	WOMAC disability

	osteoarthritis index pain subscore	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.

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 (MEDLINE) and Excerpta Medica database (EMBASE) databases via the Ovid platform, the Cochrane Central Register of Controlled Trials (CENTRAL) database via the Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database via

EBSCO. We will also search the Web of Science and PsycINFO databases. All databases will be searched from implementation to January 5, 2018 using a previously reported search strategy.[10,2912,31] For the strategies that will be used in this review, see **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 World Health Organization (WHO) International Clinical Trials Registry Platform, clinicaltrials.gov, the University hospital Medical Information Network (UMIN)-Clinical Trials Registry, the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and U.S. Food and Drug Administration (FDA) 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- 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; and

-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.

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 domains[42] as illustrated in **Table 2**. All included

trials will be classified into the following categories: low risk, high risk, and unclear.[41]

Table 2 Assessment of the risk of bias in the six domains[43]

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?

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, odds ratios (ORs) with 95% CrIs will be calculated for the

analyses. In the presence of minimally informative priors, CrIs can be understood similarly to confidence interval (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 standard deviations (SDs) are not provided, we will calculate them from the standard errors, 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 pre-specified minimal clinically important difference based on the median pooled SD of 0.37 units, which has been utilised 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 (WOMAC) 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 (SUCRA) 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 with Stata 14.0 software (StataCorp, College Station, TX, USA) and WinBUGS (MRC Biostatistics Unit 2007,

Version 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.[60]

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 model[61] 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 versus inadequate or unclear); (4) adequate blinding of the patients (adequate versus inadequate or unclear); (5) intention-to-treat analysis (yes versus no or unclear); (6) source of funding (independent of the pharmaceutical industry or unclear versus no); (7) type of OA (hip only versus knee only

versus mixed); (8) type of opioid (oral versus transdermal); and (9) type of trial (published versus 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 (GRADE) 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.[62] Additionally, a comparison-adjusted funnel plot will be drawn to detect any major publication bias in the Bayesian network meta-analysis.[63]

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.[64] 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.

Collaborators: None

Contributors: JW conceived the review and wrote the first draft of the protocol. WLG and ZSY 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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Competing interests: None declared.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No(page)	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1	Identify the report as a protocol of a systematic review
Update	NA	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	17	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	NA	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	17	Indicate sources of financial or other support for the review
Sponsor	NA	Provide name for the review funder and/or sponsor
Role of sponsor or funder	NA	*Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol*
INTRODUCTION		
Rationale	3-5	Describe the rationale for the review in the context of what is already known
Objectives	6	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	6-8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	8-9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	8-9	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated

Study records:		
Data management	8-10	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	8-10	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	8-10	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	15	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	7-8	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	9-10	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	11-13	Describe criteria under which study data will be quantitatively synthesised
	11-13	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	11-13	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	11-13	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	14	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	14	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix 1. MEDLINE, EMBASE, CINAHL, and CENTRAL search strategy

Ovid MEDLINE

Search terms for design

1.randomized controlled trial.pt.

2.controlled clinical trial.pt.

3.randomized controlled trial.sh.

4.random allocation.sh.

5.double blind method.sh.

6.single blind method.sh.

7.clinical trial.pt.

8.exp clinical trial/

9.(clin$ adj25 trial$).ab,ti.

10.((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ab,ti.

11.placebos.sh.

12.placebo$.ab,ti.

13.random$.ab,ti.

14.research design.sh.

15.comparative study.sh.

16.exp evaluation studies/

17.follow up studies.sh.

18.prospective studies.sh.

19.(control$ or prospectiv$ or volunteer$).ab,ti.

Search terms for Osteoarthritis

20.exp osteoarthritis/

21.osteoarthriti$.ab,sh,ti.

22.osteoarthro$.ab,sh,ti.

23.gonarthriti$.ab,sh,ti.

24.gonarthro$.ab,sh,ti.

25.coxarthriti$.ab,sh,ti.

26.coxarthro$.ab,sh,ti.

27.arthros$.ab,ti.

28.arthrot$.ab,ti.

29.((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ab,ti.

30.((knee$ or hip$ or joint$) adj3 stiff$).ab,ti.

Search terms for Opioids

31.exp Analgesics, Opioid/

32.exp Narcotics/

33.acetyldihydrocodeine.tw.

34.alfentanil.tw.

35.allylprodine.tw.

36.alphamethylfentanyl.tw.

37.alphaprodine.tw.

38.benzylmorphine.tw.

39.betaprodine.tw.

40.bezitriamide.tw.

41.buprenorphine.tw.

42.butorphanol.tw.

43.bremazocine.tw.

44.carfentan$.tw.

45.codeine.tw.

46.contin.tw.

47.dextromoramide.tw.

48.dextropropoxyphene.tw.

49.dezocine.tw.

50.diacetylmorphine.tw.

51.diamorphine.tw.

52.dihydrocodeine.tw.

53.dihydromorphine.tw.

54.dihydromorphone.tw.

55.diphenoxylate.tw.

56.dipipanone.tw.

57.enadoline.tw.

58.ethylketazocine.tw.

59.ethylmorphine.tw.

60.etonitazene.tw.

61.etorphine.tw.

62.fentanyl.tw.

63.heroin.tw.

64.hydrocodone.tw.

65.hydromorphin$.tw.

66.hydromorphone.tw.

67.ketazocine.tw.

68.ketobemidone.tw.

69.lefetamine.tw.

70.levomethadon.tw.

71.levomethadyl.tw.

72.levomethorphan$.tw.

73.levorphanol.tw.

74.loperamide.tw.

75.meperidine.tw.

76.meptazinol.tw.

77.methadone.tw.

78.methadyl.tw.

79.methylmorphine.tw.

80.morphin$.tw.

81.nalbuphine.tw.

82.narcotic$.tw.

83.nicocodeine.tw.

84.nicomorphine.tw.

85.normorphine.tw.

86.noscapin$.tw.

87.ohmefentanyl.tw.

88.opiate$.tw.

89.opioid$.tw.

90.opium.tw.

91.oripavine.tw.

92.oxycodone.tw.

93.oxycontin.tw.

94.oxymorphone.tw.

95.papaveretum.tw.

96.papaverin.tw.

97.pentazocine.tw.

98.percocet.tw.

99.peronine.tw.

100. pethidine.tw.

101.phenazocine.tw.

102.phencyclidine.tw.

103.pholcodine.tw.

104.piritramid$.tw.

105.prodine.tw.

106.promedol.tw.

107.propoxyphene.tw.

108.remifentanil.tw.

109.sufentanil.tw.

110.tapentadol.tw.

111.thebaine.tw.

112.tilidine.tw.

113.tramadol.sh,tw.

114.ultracet.sh,tw.

Combining terms

115.31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114

116.20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

117.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

118.115 and 116 and 117

119.animal/

120.animal/ and human/

121.119 not 120

122.118 not 121

123.remove duplicates from 122

Ovid EMBASE

Search terms for design

1.randomized controlled trial.sh.

2.randomization.sh.

3.double blind procedure.sh.

4.single blind procedure.sh.

5.exp clinical trials/

6.(clin$ adj25 trial$).ab,ti.

7.((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ab,ti.

8.placebo.sh.

9.placebo$.ab,ti.

10.random$.ab,ti.

11.methodology.sh.

12.comparative study.sh.

13.exp evaluation studies/

14.follow up.sh.

15.prospective study.sh.

16.(control$ or prospectiv$ or volunteer$).ab,ti.

Search terms for Osteoarthritis

17.exp osteoarthritis/

18.osteoarthriti$.ab,sh,ti.

19.osteoarthro$.ab,sh,ti.

20.gonarthriti$.ab,sh,ti.

21.gonarthro$.ab,sh,ti.

22.coxarthriti$.ab,sh,ti.

23.coxarthro$.ab,sh,ti.

24.arthros$.ab,ti.

25.arthrot$.ab,ti.

26.((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ab,ti.

27.((knee$ or hip$ or joint$) adj3 stiff$).ab,ti.

Search terms for Opioids

28.exp Analgesics, Opioid/

29.exp Narcotic Analgesic Agent/

30.acetyldihydrocodeine.tw.

31.alfentanil.tw.

32.allylprodine.tw.

33.alphamethylfentanyl.tw.

34.alphaprodine.tw.

35.benzylmorphine.tw.

36.betaprodine.tw.

37.bezitriamide.tw.

38.buprenorphine.tw.

39.butorphanol.tw.

40.bremazocine.tw.

41.carfentan$.tw.

42.codeine.tw.

43.contin.tw.

44.dextromoramide.tw.

45.dextropropoxyphene.tw.

46.dezocine.tw.

47.diacetylmorphine.tw.

48.diamorphine.tw.

49.dihydrocodeine.tw.

50.dihydromorphine.tw.

51.dihydromorphone.tw.

52.diphenoxylate.tw.

53.dipipanone.tw.

54.enadoline.tw.

55.ethylketazocine.tw.

56.ethylmorphine.tw.

57.etonitazene.tw.

58.etorphine.tw.

59.fentanyl.tw.

60.heroin.tw.

61.hydrocodone.tw.

62.hydromorphin$.tw.

63.hydromorphone.tw.

64.ketazocine.tw.

65.ketobemidone.tw.

66.lefetamine.tw.

67.levomethadon.tw.

68.levomethadyl.tw.

69.levomethorphan$.tw.

70.levorphanol.tw.

71.loperamide.tw.

72.meperidine.tw.

73.meptazinol.tw.

74.methadone.tw.

75.methadyl.tw.

76.methylmorphine.tw.

77.morphin$.tw.

78.nalbuphine.tw.

79.narcotic$.tw.

80.nicocodeine.tw.

81.nicomorphine.tw.

82.normorphine.tw.

83.noscapin$.tw.

84.ohmefentanyl.tw.

85.opiate$.tw.

86.opioid$.tw.

87.opium.tw.

88.oripavine.tw.

89.oxycodone.tw.

90.oxycontin.tw.

91.oxymorphone.tw.

92.papaveretum.tw.

93.papaverin.tw.

94.pentazocine.tw.

95.percocet.tw.

96.peronine.tw.

97.pethidine.tw.

98.phenazocine.tw.

99.phencyclidine.tw.

100. pholcodine.tw.

101.piritramid$.tw.

102.prodine.tw.

103.promedol.tw.

104.propoxyphene.tw.

105.remifentanil.tw.

106.sufentanil.tw.

107.tapentadol.tw.

108.thebaine.tw.

109.tilidine.tw.

110.tramadol.sh,tw.

111.ultracet.sh,tw.

Combining terms

112 .28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111

113.17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

114.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

115.112 and 113 and 114

116.animal/

117.animal/ and human/

118.116 not 117

119.115 not 118

120.remove duplicates from 119

CINAHL through EBSCOhost

Search terms for design

1. (MH "Clinical Trials+")

2. (MH "Random Assignment")

3. (MH "Double-Blind Studies") or (MH"Single-Blind Studies")

4. TX (clin$ n25 trial$)

5. TX (sing$ n25 blind$)

6. TX (sing$ n25 mask$)

7. TX (doubl$ n25 blind$)

8. TX (doubl$ n25 mask$)

9. TX (trebl$ n25 blind$)

10. TX (trebl$ n25 mask$)

11. TX (tripl$ n25 blind$)

12. TX (tripl$ n25 mask$)

13. (MH "Placebos")

14. TX placebo$

15. TX random$

16. (MH "Study Design+")

17. (MH "Comparative Studies")

18. (MH "Evaluation Research")

19. (MH "Prospective Studies+")

20. TX (control$ or prospectiv$ or volunteer$)

21. S1 or S2 or (…) or S20

Search terms for Osteoarthritis

22. osteoarthriti$

23. (MH "Osteoarthritis")

24. TX osteoarthro$

25. TX gonarthriti$

26. TX gonarthro$

27. TX coxarthriti$

28. TX coxarthro$

29. TX arthros$

30. TX arthrot$

31. TX knee$ n3 pain$

32. TX hip$ n3 pain$

33. TX joint$ n3 pain$

34. TX knee$ n3 ach$

35. TX hip$ n3 ach$

36. TX joint$ n3 ach$

37. TX knee$ n3 discomfort$

38. TX hip$ n3 discomfort$

39. TX joint$ n3 discomfort$

40. TX knee$ n3 stiff$

41. TX hip$ n3 stiff$

42. TX joint$ n3 stiff$

43. S22 or S23 or S24(…)or S42

Search terms for Opioids

44. MH " Analgesics, Opioid"

45. MH "Narcotics"

46. TX acetyldihydrocodeine

47. TX alfentanil

48. TX allylprodine

49. TX alphamethylfentanyl

50. TX alphaprodine

51. TX benzylmorphine

52. TX betaprodine

53. TX bezitriamide

54. TX buprenorphine

55. TX butorphanol

56. TX bremazocine

57. TX carfentan$

58. TX codeine

58. TX contin

60. TX dextromoramide

61. TX dextropropoxyphene

62. TX dezocine

63. TX diacetylmorphine

64. TX diamorphine

65. TX dihydrocodeine

66. TX dihydromorphine

67. TX dihydromorphone

68. TX diphenoxylate

69. TX dipipanone

70. TX enadoline

71. TX ethylketazocine

72. TX ethylmorphine

73. TX etonitazene

74. TX etorphine

75. TX fentanyl

76. TX heroin

77. TX hydrocodone

78. TX hydromorphin$

79. TX hydromorphone

80. TX ketazocine

81. TX ketobemidone

82. TX lefetamine

83. TX levomethadon

84. TX levomethadyl

85. TX levomethorphan$

86. TX levorphanol

87. TX loperamide

88. TX meperidine

89. TX meptazinol

90. TX methadone

91. TX methadyl

92. TX methylmorphine

93. TX morphin$

94. TX nalbuphine

95. TX narcotic$

96. TX nicocodeine

97. TX nicomorphine

98. TX normorphine

99. TX noscapin$

100. TX ohmefentanyl

101. TX opiate$

102. TX opioid$

103. TX opium

104. TX oripavine

105. TX oxycodone

106. TX oxycontin

107. TX oxymorphone

108. TX papaveretum

109. TX papaverin

110. TX pentazocine

111. TX percocet

112. TX peronine

113. TX pethidine

114. TX phenazocine

115. TX phencyclidine

116. TX pholcodine

117. TX piritramid$

118. TX prodine

119. TX promedol

120. TX propoxyphene

121. TX remifentanil

122. TX sufentanil

123. TX tapentadol

124. TX thebaine

125. TX tilidine

126. TX tramadol

127 .TX ultracet

128. S44 or S45 or(…)S127

Combining terms

129. S21 and S43 and S128

CENTRAL

Search terms for Osteoarthritis

#1. MeSH descriptor Osteoarthritis explode all trees

#2. (osteoarthritis* OR osteoarthro* OR gonarthriti* OR gonarthro* OR coxarthriti* OR coxarthro* OR arthros* OR arthrot* OR ((knee* OR hip* OR joint*) near/3 (pain* OR ach* OR discomfort*)) OR ((knee* OR hip* OR joint*) near/3 stiff*)) in Trials

Search terms for Opioids

#3. MeSH descriptor Analgesics, Opioid explode all trees

#4. MeSH descriptor Narcotics explode all trees

#5. (acetyldihydrocodeine OR alfentanil OR allylprodine OR alphamethylfentanyl OR alphaprodine OR benzylmorphine OR betaprodine OR bezitriamide OR buprenorphine OR butorphanol OR bremazocine OR carfentan* OR codeine OR contin ORdextromoramide OR dextropropoxyphene OR dezocine OR diacetylmorphine OR diamorphine OR dihydrocodeine OR dihydromorphine OR dihydromorphone OR diphenoxylate OR dipipanone OR enadoline OR ethylketazocine OR ethylmorphine OR etonitazene OR etorphine OR fentanyl OR heroin OR hydrocodone OR hydromorphin* OR hydromorphone OR ketazocine OR ketobemidone OR lefetamine OR levomethadon OR levomethadyl OR levomethorphan* OR levorphanol OR loperamide OR meperidine OR meptazinol OR methadone OR methadyl OR methylmorphine OR morphin* OR nalbuphine OR narcotic* OR nicocodeine OR nicomorphine OR normorphine OR noscapin* OR ohmefentanyl OR opiate* OR opioid* OR opium OR oripavine OR oxycodone OR oxycontin OR oxymorphone OR papaveretum OR papaverin OR pentazocine OR percocet OR peronine OR pethidine OR phenazocine OR phencyclidine OR pholcodine OR piritramid* OR prodine OR promedol OR propoxyphene OR remifentanil OR sufentanil OR tapentadol OR thebaine OR tilidine OR tramadol OR ultracet) in Trials

Combining terms

#6. (#1 OR #2)

#7. (#3 OR #4 OR #5)

#8. (#6 AND #7) in Clinical Trials

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022142.R2
Article Type:	Protocol
Date Submitted by the Author:	23-Aug-2018
Complete List of Authors:	Wang, Jun; The First Affiliated Hospital of Anhui Medical University, Anhui, China, Department of Orthopaedics Wang, Yin ; The Fourth Affiliated Hospital of Anhui Medical University, Anhui, China, Department of Plastic Surgery Zhang, Hui; The First Affiliated Hospital of Anhui Medical University, Anhui, China, Department of Orthopaedics Lu, Ming; The First Affiliated Hospital of Anhui Medical University, Anhui, China, Department of Orthopaedics Gao, Weilu; The First Affiliated Hospital of Anhui Medical University, Anhui, China, Department of Orthopaedics Yin, Li; The First Affiliated Hospital of Anhui Medical University, Anhui, China, Department of Orthopaedics Yin, Zongsheng
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Medical management
Keywords:	opioid, osteoarthritis, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Hip < ORTHOPAEDIC & TRAUMA SURGERY, opioids, osteoarthritis, knee, hip

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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Keywords: opioids, osteoarthritis, knee, hip

Word count: 3086 (excluding title page, references, figures)

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 Medicine, Embase, CINAHL, 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 January 5, 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 GRADE 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.

Trial registration number: PROSPERO CRD42018085503.

Strengths and limitations of this study

- While previous conventional paired meta-analyses focused on direct comparisons between opioid analgesics and placebo for OA, 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 (HA), corticosteroids, ozone, and platelet-rich plasma (PRP) 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 OA patients.[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, capsaisin 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 Supplementary file 1. [37]

Criteria for the included studies

Types of studies

All randomised controlled trials (RCTs) 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 vs. opioid, placebo vs. opioid, and no intervention vs. opioid.

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**.

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.

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 (MEDLINE) and Excerpta Medica database (EMBASE) databases via the Ovid platform, the Cochrane Central Register of Controlled Trials (CENTRAL) database via the Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database via EBSCO. We will also search the Web of Science and PsycINFO databases. All databases will be searched from implementation to January

5, 2018 using a previously reported search strategy.[10,2912,31] For the strategies that will be used in this review, see **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 World Health Organization (WHO) International Clinical Trials Registry Platform, clinicaltrials.gov, the University hospital Medical Information Network (UMIN)-Clinical Trials Registry, the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and U.S. Food and Drug Administration (FDA) 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- 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; and

-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.

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 domains[42] as illustrated in **Table 2**. All included trials will be classified into the following categories: low risk, high risk, and unclear.[41]

Table 2 Assessment of the risk of bias in the six domains[43]

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?

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, odds ratios (ORs) with 95% CrIs will be calculated for the analyses. In the presence of minimally informative priors, CrIs can be understood similarly to confidence interval (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 standard deviations (SDs) are not provided, we will calculate them from the standard errors, 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 pre-specified minimal clinically important difference based on the median pooled SD of 0.37 units, which has been utilised 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 (WOMAC) 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 (SUCRA) 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 with Stata 14.0 software (StataCorp, College Station, TX, USA) and WinBUGS (MRC Biostatistics Unit 2007, Version 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.[60]

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 model[61] 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 versus inadequate or unclear); (4) adequate blinding of the patients (adequate versus inadequate or unclear); (5) intention-to-treat analysis (yes versus no or unclear); (6) source of funding (independent of the pharmaceutical industry or unclear versus no); (7) type of OA (hip only versus knee only versus mixed); (8) type of opioid (oral versus transdermal); and (9) type of trial (published versus 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 (GRADE) 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.[62] Additionally, a comparison-adjusted funnel plot will be drawn to detect any major publication bias in the Bayesian network meta-analysis.[63]

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.[64] 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.

Collaborators: None

Contributors: JW conceived the review and wrote the first draft of the protocol. WLG and ZSY 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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Competing interests: None declared.

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Supplementary file 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No(page)	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1	Identify the report as a protocol of a systematic review
Update	NA	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	17	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	NA	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	17	Indicate sources of financial or other support for the review
Sponsor	NA	Provide name for the review funder and/or sponsor
Role of sponsor or funder	NA	*Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol*
INTRODUCTION		
Rationale	3-5	Describe the rationale for the review in the context of what is already known
Objectives	6	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	6-8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	8-9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage

Search strategy	8-9	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	8-10	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	8-10	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	8-10	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	15	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	7-8	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	9-10	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	11-13	Describe criteria under which study data will be quantitatively synthesised
	11-13	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	11-13	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	11-13	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	14	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	14	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (3e when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary file 2. MEDLINE, EMBASE, CINAHL, and CENTRAL

search strategy

Ovid MEDLINE

Search terms for design

1.randomized controlled trial.pt.

2.controlled clinical trial.pt.

3.randomized controlled trial.sh.

4.random allocation.sh.

5.double blind method.sh.

6.single blind method.sh.

7.clinical trial.pt.

8.exp clinical trial/

9.(clin$ adj25 trial$).ab,ti.

10.((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ab,ti.

11.placebos.sh.

12.placebo$.ab,ti.

13.random$.ab,ti.

14.research design.sh.

15.comparative study.sh.

16.exp evaluation studies/

17.follow up studies.sh.

18.prospective studies.sh.

19.(control$ or prospectiv$ or volunteer$).ab,ti.

Search terms for Osteoarthritis

20.exp osteoarthritis/

21.osteoarthriti$.ab,sh,ti.

22.osteoarthro$.ab,sh,ti.

23.gonarthriti$.ab,sh,ti.

24.gonarthro$.ab,sh,ti.

25.coxarthriti$.ab,sh,ti.

26.coxarthro$.ab,sh,ti.

27.arthros$.ab,ti.

28.arthrot$.ab,ti.

29.((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ab,ti.

30.((knee$ or hip$ or joint$) adj3 stiff$).ab,ti.

Search terms for Opioids

31.exp Analgesics, Opioid/

32.exp Narcotics/

33.acetyldihydrocodeine.tw.

34.alfentanil.tw.

35.allylprodine.tw.

36.alphamethylfentanyl.tw.

37.alphaprodine.tw.

38.benzylmorphine.tw.

39.betaprodine.tw.

40.bezitriamide.tw.

41.buprenorphine.tw.

42.butorphanol.tw.

43.bremazocine.tw.

44.carfentan$.tw.

45.codeine.tw.

46.contin.tw.

47.dextromoramide.tw.

48.dextropropoxyphene.tw.

49.dezocine.tw.

50.diacetylmorphine.tw.

51.diamorphine.tw.

52.dihydrocodeine.tw.

53.dihydromorphine.tw.

54.dihydromorphone.tw.

55.diphenoxylate.tw.

56.dipipanone.tw.

57.enadoline.tw.

58.ethylketazocine.tw.

59.ethylmorphine.tw.

60.etonitazene.tw.

61.etorphine.tw.

62.fentanyl.tw.

63.heroin.tw.

64.hydrocodone.tw.

65.hydromorphin$.tw.

66.hydromorphone.tw.

67.ketazocine.tw.

68.ketobemidone.tw.

69.lefetamine.tw.

70.levomethadon.tw.

71.levomethadyl.tw.

72.levomethorphan$.tw.

73.levorphanol.tw.

74.loperamide.tw.

75.meperidine.tw.

76.meptazinol.tw.

77.methadone.tw.

78.methadyl.tw.

79.methylmorphine.tw.

80.morphin$.tw.

81.nalbuphine.tw.

82.narcotic$.tw.

83.nicocodeine.tw.

84.nicomorphine.tw.

85.normorphine.tw.

86.noscapin$.tw.

87.ohmefentanyl.tw.

88.opiate$.tw.

89.opioid$.tw.

90.opium.tw.

91.oripavine.tw.

92.oxycodone.tw.

93.oxycontin.tw.

94.oxymorphone.tw.

95.papaveretum.tw.

96.papaverin.tw.

97.pentazocine.tw.

98.percocet.tw.

99.peronine.tw.

100. pethidine.tw.

101.phenazocine.tw.

102.phencyclidine.tw.

103.pholcodine.tw.

104.piritramid$.tw.

105.prodine.tw.

106.promedol.tw.

107.propoxyphene.tw.

108.remifentanil.tw.

109.sufentanil.tw.

110.tapentadol.tw.

111.thebaine.tw.

112.tilidine.tw.

113.tramadol.sh,tw.

114.ultracet.sh,tw.

Combining terms

115.31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114

116.20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

117.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

118.115 and 116 and 117

119.animal/

120.animal/ and human/

121.119 not 120

122.118 not 121

123.remove duplicates from 122

Ovid EMBASE

Search terms for design

1.randomized controlled trial.sh.

2.randomization.sh.

3.double blind procedure.sh.

4.single blind procedure.sh.

5.exp clinical trials/

6.(clin$ adj25 trial$).ab,ti.

7.((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ab,ti.

8.placebo.sh.

9.placebo$.ab,ti.

10.random$.ab,ti.

11.methodology.sh.

12.comparative study.sh.

13.exp evaluation studies/

14.follow up.sh.

15.prospective study.sh.

16.(control$ or prospectiv$ or volunteer$).ab,ti.

Search terms for Osteoarthritis

17.exp osteoarthritis/

18.osteoarthriti$.ab,sh,ti.

19.osteoarthro$.ab,sh,ti.

20.gonarthriti$.ab,sh,ti.

21.gonarthro$.ab,sh,ti.

22.coxarthriti$.ab,sh,ti.

23.coxarthro$.ab,sh,ti.

24.arthros$.ab,ti.

25.arthrot$.ab,ti.

26.((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ab,ti.

27.((knee$ or hip$ or joint$) adj3 stiff$).ab,ti.

Search terms for Opioids

28.exp Analgesics, Opioid/

29.exp Narcotic Analgesic Agent/

30.acetyldihydrocodeine.tw.

31.alfentanil.tw.

32.allylprodine.tw.

33.alphamethylfentanyl.tw.

34.alphaprodine.tw.

35.benzylmorphine.tw.

36.betaprodine.tw.

37.bezitriamide.tw.

38.buprenorphine.tw.

39.butorphanol.tw.

40.bremazocine.tw.

41.carfentan$.tw.

42.codeine.tw.

43.contin.tw.

44.dextromoramide.tw.

45.dextropropoxyphene.tw.

46.dezocine.tw.

47.diacetylmorphine.tw.

48.diamorphine.tw.

49.dihydrocodeine.tw.

50.dihydromorphine.tw.

51.dihydromorphone.tw.

52.diphenoxylate.tw.

53.dipipanone.tw.

54.enadoline.tw.

55.ethylketazocine.tw.

56.ethylmorphine.tw.

57.etonitazene.tw.

58.etorphine.tw.

59.fentanyl.tw.

60.heroin.tw.

61.hydrocodone.tw.

62.hydromorphin$.tw.

63.hydromorphone.tw.

64.ketazocine.tw.

65.ketobemidone.tw.

66.lefetamine.tw.

67.levomethadon.tw.

68.levomethadyl.tw.

69.levomethorphan$.tw.

70.levorphanol.tw.

71.loperamide.tw.

72.meperidine.tw.

73.meptazinol.tw.

74.methadone.tw.

75.methadyl.tw.

76.methylmorphine.tw.

77.morphin$.tw.

78.nalbuphine.tw.

79.narcotic$.tw.

80.nicocodeine.tw.

81.nicomorphine.tw.

82.normorphine.tw.

83.noscapin$.tw.

84.ohmefentanyl.tw.

85.opiate$.tw.

86.opioid$.tw.

87.opium.tw.

88.oripavine.tw.

89.oxycodone.tw.

90.oxycontin.tw.

91.oxymorphone.tw.

92.papaveretum.tw.

93.papaverin.tw.

94.pentazocine.tw.

95.percocet.tw.

96.peronine.tw.

97.pethidine.tw.

98.phenazocine.tw.

99.phencyclidine.tw.

100. pholcodine.tw.

101.piritramid$.tw.

102.prodine.tw.

103.promedol.tw.

104.propoxyphene.tw.

105.remifentanil.tw.

106.sufentanil.tw.

107.tapentadol.tw.

108.thebaine.tw.

109.tilidine.tw.

110.tramadol.sh,tw.

111.ultracet.sh,tw.

Combining terms

112 .28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111

113.17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

114.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

115.112 and 113 and 114

116.animal/

117.animal/ and human/

118.116 not 117

119.115 not 118

120.remove duplicates from 119

CINAHL through EBSCOhost

Search terms for design

1. (MH “Clinical Trials+”)

2. (MH “Random Assignment”)

3. (MH “Double-Blind Studies”) or (MH“Single-Blind Studies”)

4. TX (clin$ n25 trial$)

5. TX (sing$ n25 blind$)

6. TX (sing$ n25 mask$)

7. TX (doubl$ n25 blind$)

8. TX (doubl$ n25 mask$)

9. TX (trebl$ n25 blind$)

10. TX (trebl$ n25 mask$)

11. TX (tripl$ n25 blind$)

12. TX (tripl$ n25 mask$)

13. (MH "Placebos")

14. TX placebo$

15. TX random$

16. (MH "Study Design+")

17. (MH "Comparative Studies")

18. (MH "Evaluation Research")

19. (MH "Prospective Studies+")

20. TX (control$ or prospectiv$ or volunteer$)

21. S1 or S2 or (…) or S20

Search terms for Osteoarthritis

22. osteoarthriti$

23. (MH "Osteoarthritis")

24. TX osteoarthro$

25. TX gonarthriti$

26. TX gonarthro$

27. TX coxarthriti$

28. TX coxarthro$

29. TX arthros$

30. TX arthrot$

31. TX knee$ n3 pain$

32. TX hip$ n3 pain$

33. TX joint$ n3 pain$

34. TX knee$ n3 ach$

35. TX hip$ n3 ach$

36. TX joint$ n3 ach$

37. TX knee$ n3 discomfort$

38. TX hip$ n3 discomfort$

39. TX joint$ n3 discomfort$

40. TX knee$ n3 stiff$

41. TX hip$ n3 stiff$

42. TX joint$ n3 stiff$

43. S22 or S23 or S24(…)or S42

Search terms for Opioids

44. MH " Analgesics, Opioid"

45. MH "Narcotics"

46. TX acetyldihydrocodeine

47. TX alfentanil

48. TX allylprodine

49. TX alphamethylfentanyl

50. TX alphaprodine

51. TX benzylmorphine

52. TX betaprodine

53. TX bezitriamide

54. TX buprenorphine

55. TX butorphanol

56. TX bremazocine

57. TX carfentan$

58. TX codeine

58. TX contin

60. TX dextromoramide

61. TX dextropropoxyphene

62. TX dezocine

63. TX diacetylmorphine

64. TX diamorphine

65. TX dihydrocodeine

66. TX dihydromorphine

67. TX dihydromorphone

68. TX diphenoxylate

69. TX dipipanone

70. TX enadoline

71. TX ethylketazocine

72. TX ethylmorphine

73. TX etonitazene

74. TX etorphine

75. TX fentanyl

76. TX heroin

77. TX hydrocodone

78. TX hydromorphin$

79. TX hydromorphone

80. TX ketazocine

81. TX ketobemidone

82. TX lefetamine

83. TX levomethadon

84. TX levomethadyl

85. TX levomethorphan$

86. TX levorphanol

87. TX loperamide

88. TX meperidine

89. TX meptazinol

90. TX methadone

91. TX methadyl

92. TX methylmorphine

93. TX morphin$

94. TX nalbuphine

95. TX narcotic$

96. TX nicocodeine

97. TX nicomorphine

98. TX normorphine

99. TX noscapin$

100. TX ohmefentanyl

101. TX opiate$

102. TX opioid$

103. TX opium

104. TX oripavine

105. TX oxycodone

106. TX oxycontin

107. TX oxymorphone

108. TX papaveretum

109. TX papaverin

110. TX pentazocine

111. TX percocet

112. TX peronine

113. TX pethidine

114. TX phenazocine

115. TX phencyclidine

116. TX pholcodine

117. TX piritramid$

118. TX prodine

119. TX promedol

120. TX propoxyphene

121. TX remifentanil

122. TX sufentanil

123. TX tapentadol

124. TX thebaine

125. TX tilidine

126. TX tramadol

127 .TX ultracet

128. S44 or S45 or(…)S127

Combining terms

129. S21 and S43 and S128

CENTRAL

Search terms for Osteoarthritis

#1. MeSH descriptor Osteoarthritis explode all trees

#2. (osteoarthritis* OR osteoarthro* OR gonarthriti* OR gonarthro* OR coxarthriti* OR coxarthro* OR arthros* OR arthrot* OR ((knee* OR hip* OR joint*) near/3 (pain* OR ach* OR discomfort*)) OR ((knee* OR hip* OR joint*) near/3 stiff*)) in Trials

Search terms for Opioids

#3. MeSH descriptor Analgesics, Opioid explode all trees

#4. MeSH descriptor Narcotics explode all trees

#5. (acetyldihydrocodeine OR alfentanil OR allylprodine OR alphamethylfentanyl OR alphaprodine OR benzylmorphine OR betaprodine OR bezitriamide OR buprenorphine OR butorphanol OR bremazocine OR carfentan* OR codeine OR contin ORdextromoramide OR dextropropoxyphene OR dezocine OR diacetylmorphine OR diamorphine OR dihydrocodeine OR dihydromorphine OR dihydromorphone OR diphenoxylate OR dipipanone OR enadoline OR ethylketazocine OR ethylmorphine OR etonitazene OR etorphine OR fentanyl OR heroin OR hydrocodone OR hydromorphin* OR hydromorphone OR ketazocine OR ketobemidone OR lefetamine OR levomethadon OR levomethadyl OR levomethorphan* OR levorphanol OR loperamide OR meperidine OR meptazinol OR methadone OR methadyl OR methylmorphine OR morphin* OR nalbuphine OR narcotic* OR nicocodeine OR nicomorphine OR normorphine OR noscapin* OR ohmefentanyl OR opiate* OR opioid* OR opium OR oripavine OR oxycodone OR oxycontin OR oxymorphone OR papaveretum OR papaverin OR pentazocine OR percocet OR peronine OR pethidine OR phenazocine OR phencyclidine OR pholcodine OR piritramid* OR prodine OR promedol OR propoxyphene OR remifentanil OR sufentanil OR tapentadol OR thebaine OR tilidine OR tramadol OR ultracet) in Trials

Combining terms

#6. (#1 OR #2)

#7. (#3 OR #4 OR #5)

#8. (#6 AND #7) in Clinical Trials