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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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Manuscripts

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3 Comparative efficacy and safety of oral or transdermal opioids in the
4 treatment of knee or hip osteoarthritis: A systematic review and Bayesian
5 network meta-analysis protocol
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40 **Keywords:** opioids, osteoarthritis, knee, hip
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44

45 46 **ABSTRACT** 47

48 **Introduction:** Osteoarthritis is a common degenerative joint disease with
49 mobility pain and disorders as the main symptoms, eventually leading to
50 disability and poor quality of life. If the patient has severe pain or other
51 analgesics are contraindicated, opioids may be a viable treatment option.
52 To evaluate and compare the efficacy and safety of opioids in the
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3 treatment of knee or hip osteoarthritis, we will integrate the direct and
4 indirect evidence using a Bayesian network meta-analysis to establish
5 hierarchies of these drugs.
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9 **Methods and analysis:** We will search the Medicine, Embase, CINAHL,
10 Cochrane Library, Web of Science, and PsycINFO databases as well as
11 published and unpublished research in international registries and
12 websites of regulatory agencies for osteoarthritis reports published prior
13 to January 5, 2018. There will be no restrictions on the language.
14 Randomized clinical trials that compare oral or transdermal opioids with
15 other various opioids, placebo or no treatment for patients with knee or
16 hip osteoarthritis will be included. The primary outcomes of efficacy will
17 be pain and function. We will use pain and function scales to evaluate the
18 main outcomes. The secondary outcomes of safety will be defined as the
19 proportion of patients who have stopped treatment due to side effects.
20 Pairwise meta-analyses and Bayesian network meta-analyses will be
21 performed for all related outcome measures. We will conduct subgroup
22 analyses and sensitivity analyses to assess the robustness of our findings.
23 The GRADE framework will be used to assess the quality of the evidence
24 contributing to each network assessment.
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40 **Ethics and dissemination:** This study does not require formal ethical
41 approval as individual patient data will not be included. The findings will
42 be disseminated through peer-reviewed publications or conference
43 presentations.
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49 **Trial registration number:** PROSPERO CRD42018085503.
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51 **Strengths and limitations of this study**

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54 •While conventional paired meta-analyses focus on direct comparisons of
55 single interventions, this Bayesian network meta-analysis will combine
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3 direct evidence with indirect evidence to assess the interrelationships
4 between all treatments in multiple treatment comparisons.
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- 7 ▪ There is controversy over the efficacy and safety of the use of opioids in
8 the treatment of knee or hip osteoarthritis. We will rank the efficacy and
9 safety of the available opioid drugs.
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- 12 ▪ Subgroup and sensitivity analyses will provide implications for
13 clinically relevant questions for later research directions.
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- 16 ▪ This method synthesizes the data comprehensively and provides a
17 clinically useful summary that can guide the development of a clinical
18 prescription system.
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25 **Introduction**

26 **Description of the condition**

27
28 Osteoarthritis (OA) is a degenerative disease that is also known as
29 degenerative arthritis or senile arthritis.¹ Increased obesity, age, trauma to
30 joint areas, excessive manual labour, and decreased muscle strength and
31 joint stability are important risk factors for OA.²⁻⁵ The main clinical
32 manifestations of OA are chronic pain, joint instability, stiffness, joint
33 deformity and reduced imaging of the joint space, and these
34 manifestations eventually lead to progressive disability and reduce the
35 patient's quality of life.^{1,6} OA, particularly OA of the knee and hip joints,
36 is one of the leading causes of disability in the world among the elderly,
37 and it is estimated that the global age-standardized incidence rates are 3.8%
38 in the knee and 0.85% in the hip.⁷⁻⁸ The impact of this disease is
39 widespread and serious, and there are currently no effective interventions
40 to prevent the development of OA.¹
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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

1
2
3 treatment of OA, and these treatments have been proven to be effective.¹⁹⁻
4
5 ²² Surgery mainly includes total hip and knee replacement, which can
6
7 improve the health-related quality of life in the late stage of OA.²³⁻²⁴
8
9 However, surgery is not the first choice of treatment for OA in clinical
10
11 practice due to the limited lifetime of an artificial prosthesis. Furthermore,
12
13 if a prosthesis fails, the patient may face a second revision operation, and
14
15 the risk of failure in such operations is high due to the loss of bone mass.
16
17 Therefore, joint surgery is often considered as the ultimate treatment for
18
19 OA. Non-drug therapy is important for reducing pain and improving the
20
21 physiological function of OA patients.²⁵ Non-drug therapies include
22
23 weight reduction, exercise, changes in lifestyle and other physical therapy
24
25 measures designed to slow the progression of OA.²⁶⁻²⁸

26
27 Drugs for the treatment of OA pain primarily include non-steroidal anti-
28
29 inflammatory drugs (NSAIDs) and opioid drugs.²⁹ Currently, the use of
30
31 NSAID drugs for the treatment of OA pain is preferred in the clinic.
32
33 However, NSAID use may cause serious adverse cardiovascular and
34
35 gastrointestinal events.³⁰⁻³¹ Opioids may be a viable alternative for
36
37 patients who do not adequately respond to routine treatment and when
38
39 other analgesics are contraindicated.³²

40 41 **Why it is important to perform this review**

42
43
44 Several systematic reviews have investigated the effectiveness of the
45
46 agents used to treat OA.^{10,29} However, previous studies only considered
47
48 direct evidence from head-to-head comparisons and did not aim to
49
50 synthesize all the available evidence. Moreover, the authors of these
51
52 previous studies have often refrained from conducting meta-analyses due
53
54 to differences in the outcome measures reported in individual trials, thus
55
56 limiting their use to inform clinical practice. As a result, it often difficult
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3 to determine the best treatment based on previous studies. Indirect
4 comparisons are usually required to establish a 'ranking' (occasionally
5 referred to as a "league table") of interventions. The Bayesian network
6 meta-analysis method allows for the coinstantaneous comparison of
7 multiple opioids drug interventions in a unitary analysis and ranks the
8 interventions accordingly. This approach provides estimates of treatment
9 differences and uses the heterogeneities and inconsistencies found in the
10 tests to evaluate the uncertainties in the resultant estimates. Therefore,
11 this approach is particularly useful in situations involving many different
12 intervention measures.³³
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23 **Objectives**

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25
26 To systematically analyse the efficacy and safety of opioid medications
27 against those of other opioids, placebos or interventions in the treatment
28 of knee or hip OA.
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32 **METHODS**

33 **Criteria for the included studies**

34 **Types of studies**

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38 All randomized controlled trials (RCTs) comparing oral or transdermal
39 opioid therapies with other opioids, placebos, or no intervention in
40 patients with knee or hip OA will be included. Trials only published as
41 abstracts will be excluded. We will not apply limits based on the
42 language of the publication.
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51 **Types of participants**

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3 Trials with mixed populations of patients with OA of the knee or hip
4 must either report the results separately or must have included at least 75%
5 of the patients in the relevant comparisons to be eligible for inclusion.
6
7

8 9 **Types of interventions**

10
11 Comparisons of oral or transdermal opioid drugs with any type of opioid
12 drug, placebo or no intervention will be included. Trials comparing the
13 same type of opioid at different therapeutic doses will be considered as a
14 different node in the Bayesian network analysis. Consequently, the
15 following comparisons are eligible: opioid vs. opioid, placebo vs. opioid,
16 and no intervention vs. opioid.
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23 24 **Types of outcome measures**

25 26 **Primary outcomes**

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28 The primary outcomes will include pain and function. If data from more
29 than one pain or function scale are provided in a single trial, we will
30 follow the method described in previous studies³⁴⁻³⁵ and extract data
31 according to the hierarchy. The detailed scale hierarchy is presented in
32 **Table 1.**
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38 39 **Secondary outcomes**

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41 To assess the safety of opioids, we will extract the proportion of
42 participants who experienced adverse events. We will define adverse
43 effects as nausea, constipation, drug addiction or dependence, cessation
44 of drug use, extended length of hospitalization, hospitalization, life-
45 threatening complications, or death.²⁹
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52 53 **Data sources and search strategy**

54 55 **Electronic searches**

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

16 **Searching other resources**

17
18 International registries of published and unpublished articles and the
19 websites of regulatory agencies will be searched in our review. These
20 sources include the following: the WHO International Clinical Trials
21 Registry Platform, clinicaltrials.gov, the UMIN-Clinical Trials Registry,
22 the American College of Rheumatology (ACR), the European League
23 Against Rheumatism (EULAR), and U.S. Food and Drug Administration
24 (FDA) reports. No language limitations will be applied.

33 **Study selection**

34
35 Two independent reviewers (YW and HZ) will evaluate all relevant titles
36 and abstracts. The reviewers will use uniform standards to independently
37 extract key study parameters, and any disagreements will be resolved by
38 the third review (JW). There will be no language restrictions. If multiple
39 studies describe the same experiment, the study with the most relatively
40 complete data will be used in the analyses.

47 **Data extraction and management**

48
49 Two review authors (YW and HZ) will extract the trial information
50 independently via a single purpose-built electronic database. Any
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3 differences will be resolved by consensus or discussion with the third
4 author (JW). The following information will be extracted:

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7 -Patient characteristics (average age, gender, duration of symptoms, and
8 the type of joint affected);

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12 -Details of the intervention, including the route of administration, dosage,
13 and frequency of the drug therapies and the treatment duration;

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16 -Types of measures used and pain- or function-related outcomes;

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19 -Type of adverse effects related to the outcome;

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22 -Outcome data for each endpoint of interest;

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25 -Duration of the follow up;

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28 -Trial design (including eligibility criteria of patients);

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31 -Trial size;

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34 -Publication status; and

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37 -The type and source of financial support.

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39 We will use the results from the intention-to-treat analyses whenever
40 possible.³⁶ If we cannot calculate the effect size, we will contact the study
41 authors for additional data. Research from non-English language journals
42 will be electronically translated before assessment.
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47 **Assessment of the risk of bias in the included studies**

48
49 Two review authors (ML and LY) will independently use the risk of bias
50 assessment tools generated by the Cochrane Collaboration.³⁷
51 Disagreements will be resolved by negotiation. We will systematically
52 evaluate bias across six domains³⁸ as illustrated in **Table 2**. All included
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3 trials will be classified into three categories: low risk, high risk, and
4 unclear.³⁷
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7 **Data synthesis and analysis**

8 **Measures of treatment effects**

9 **Relative treatment effects**

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16 We will estimate the continuous variables using the standardized mean
17 difference (SMD) with 95% credible intervals (CrIs). For the categorical
18 outcomes, odds ratios (ORs) with 95% CrIs will be calculated for the
19 analyses. In the presence of minimally informative priors, CrIs can be
20 understood similarly to confidence interval (CIs), and at the conventional
21 statistical significance level, a two-sided $p < 0.05$ can be assumed if the 95%
22 CrIs do not include 0.³⁹ If standard deviations (SDs) are not provided, we
23 will calculate them from the standard errors, CIs, or p-values using a
24 method described in previous studies.^{35,40} If some necessary data are not
25 available, we will use approximations as previously described.³⁵ To
26 visually explain the pooled effects, we will transform the effect sizes into
27 differences on a 10-cm visual analogue scale (VAS) based on a median
28 pooled SD of 2.5 cm as found in large-scale OA trials that have used 10-
29 cm VASs to assess pain.⁴⁰ SMDs of -0.20 correspond to approximate
30 differences in pain scores between the experimental and control groups of
31 0.5 on a 10-cm VAS, -0.50 of 1.25 on a 10-cm VAS, and -0.80 of 2 on a
32 10-cm VAS.⁴⁰⁻⁴¹ Additionally, we will compare the effects with a pre-
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4 specified minimal clinically important difference based on the median
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6 pooled SD of 0.37 units, which has been utilized in recent studies of
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8 patients with OA and corresponds to 0.9 cm on a 10-cm VAS.⁴²⁻⁴⁵ We
9
10 will also transform the SMDs for function to a Western Ontario and
11
12 McMaster Universities Osteoarthritis Index (WOMAC) score based on a
13
14 median pooled SD of 2.1 units as observed in large-scale OA trials.⁴⁶⁻⁴⁷

17 **Relative treatment ranking**

18
19
20 Each intervention and each outcome will be systematically evaluated and
21
22 ranked. We will determine a treatment hierarchy using the surface under
23
24 the cumulative ranking curve (SUCRA) and the mean ranks.⁴⁸

26 **Data analysis**

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30 First, we will conduct paired meta-analyses by synthesizing the studies
31
32 that compare interventions head-to-head using a random-effects model.⁴⁹

33
34 Then, we will use a Bayesian network meta-analysis to compare the
35
36 different classes of oral or transdermal opioid treatments based on the
37
38 median of the posterior distribution.⁵⁰⁻⁵¹ A Bayesian random-effects
39
40 model will be used because this model completely retains the within-trial
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42 randomized treatment comparisons of each study while combining all
43
44 available comparisons between treatments and accounting for multiple
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46 comparisons within a trial in cases with more than two treatment arms.⁵¹⁻

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⁵² The between-trial variance of the treatment effects (τ^2) will be
estimated from the posterior distribution. Pooled estimates will be

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3 performed with Markov chain Monte Carlo methods. Convergence of the
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5 Markov chains will be considered to be achieved if the Gelman-Rubin
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7 diagnostic plots indicate that the widths of the pooled runs and individual
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9 runs stabilize around the same value and their ratio is approximately
10
11 one.⁵³
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15 The analyses will be performed with Stata 14.0 software (StataCorp,
16
17 College Station, TX, USA) and WinBUGS (MRC Biostatistics Unit 2007,
18
19 Version 1.4.3 Cambridge, UK).
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24 25 **Assessment of statistical heterogeneity**

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27 We will use I^2 statistics and p-values to assess the statistical heterogeneity
28
29 of each pairwise comparison.⁵⁴ In the Bayesian meta-analysis, we will
30
31 calculate the heterogeneity of the treatment effects estimated from the
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33 posterior median between-trial variance (τ^2). Global heterogeneity will be
34
35 assessed using the I^2 statistic.
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38 39 **Assessment of statistical inconsistency**

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41 We will evaluate the inconsistencies locally in the network using the
42
43 loop-specific approach.⁵⁵ The design-by-treatment interaction model will
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45 also be used to calculate the consistency throughout the entire network.⁵⁶
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48 49 **Subgroup analyses**

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51 To explore the robustness of the results, we will include the
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53 characteristics of the trials as covariates in the Bayesian meta-analysis to
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55 assess the primary outcomes based on the clinical characteristics, risk of
56
57 bias and trial size. A random-effects meta-regression model⁵⁷ will be used
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3 to determine whether the treatment effects are affected by the following
4 factors: (1) treatment duration (short-term \leq 1 month and long-term $>$ 1
5 month); (2) trial size (small-scale: allocated participants \leq 200, and large-
6 scale: allocated participants $>$ 200); (3) high methodological quality as
7 defined by adequate concealment of the allocation (adequate versus
8 inadequate or unclear); (4) adequate blinding of the patients (adequate
9 versus inadequate or unclear); (5) intention-to-treat analysis (yes versus
10 no or unclear); (6) source of funding (independent of the pharmaceutical
11 industry or unclear versus no); (7) type of OA (hip only versus knee only
12 versus mixed); (8) type of opioid (oral versus transdermal); and (9) type
13 of trial (published versus unpublished).
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24 **Sensitivity analyses**

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

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36 The GRADE framework, which characterizes the quality of evidence
37 based on the study limitations, publication bias, indirectness, imprecision
38 and inconsistency in the primary outcomes, will be used to evaluate the
39 quality of evidence in each network.⁵⁸ Additionally, a comparison-
40 adjusted funnel plot will be drawn to detect any major publication bias in
41 the Bayesian network meta-analysis.⁵⁹
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49 **Ethics and dissemination**

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52 This systematic review and Bayesian meta-analysis does not require
53 formal ethical approval as individual patient data are not included. The
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3 results will provide a general review of and evidence for the efficacy and
4 safety of oral or transdermal opioids in the treatment of knee or hip OA.
5
6 The findings will be disseminated through peer-reviewed publications or
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8 conference presentations. The basic protocol amendments will be
9
10 recorded in the full review.
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17 **DISCUSSION**

18
19 This systematic review and Bayesian network meta-analysis will provide
20 an assessment of opioid therapies in patients with knee or hip OA.
21 Whether opioids can be used as a routine treatment for knee or hip OA is
22 controversial. Our results will rank the efficacy and safety of opioids in
23 the treatment of OA, which has not been included in previous studies.
24 The conclusions of this study may be beneficial for patients with knee or
25 hip OA, clinicians and policy makers. The proposed systematic review
26 and network meta-analysis may have some potential limitations. The
27 different routes of administration (oral or transdermal), durations and
28 frequencies may cause considerable heterogeneity. Another limitation
29 may be differences in the quality of the included studies, which will limit
30 the ability of this work to reach high-confidence conclusions.
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52 **Collaborators:** None
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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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15 meta-analysis. *Lancet* 2015; 385: 2047–56.
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19 first-generation and newer-generation antidepressant medications for depressive
20 disorders in children and adolescents: study protocol for a systematic review and
21 network meta-analysis. *BMJ open* 2015; 5(9): e007768.
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30 meta-analysis. *The Lancet* 2017; 390(10090): e21-e33.
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33 difference in knee osteoarthritis. *Osteoarthritis and cartilage* 1999; 7(5): 502-503.
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42 rehabilitation effects in patients with osteoarthritis of the lower extremities. *The*
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48 network meta-analysis: concepts and models for multi-arm studies. *Research*
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Table 1 Hierarchy of osteoarthritis pain and function measurement scales³⁴⁻³⁵

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 domains³⁹

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 treb1\$ or trip1\$) 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.

1
2
3 19.(control\$ or prospectiv\$ or volunteer\$).ab,ti.
4
5

6 **Search terms for Osteoarthritis**
7

8 20.exp osteoarthritis/
9

10
11 21.osteoarthriti\$.ab,sh,ti.
12

13 22.osteoarthro\$.ab,sh,ti.
14

15
16 23.gonarthriti\$.ab,sh,ti.
17

18 24.gonarthro\$.ab,sh,ti.
19

20
21 25.coxarthriti\$.ab,sh,ti.
22

23 26.coxarthro\$.ab,sh,ti.
24

25
26 27.arthros\$.ab,ti.
27

28 28.arthrot\$.ab,ti.
29

30
31 29.((knee\$ or hip\$ or joint\$) adj3 (pain\$ or ach\$ or discomfort\$)).ab,ti.
32

33 30.((knee\$ or hip\$ or joint\$) adj3 stiff\$).ab,ti.
34
35

36 **Search terms for Opioids**
37

38
39 31.exp Analgesics, Opioid/
40

41 32.exp Narcotics/
42

43 33.acetyldihydrocodeine.tw.
44

45
46 34.alfentanil.tw.
47

48
49 35.allyprodine.tw.
50

51 36.alpha-methylfentanyl.tw.
52

53
54 37.alphaprodine.tw.
55

56
57 38.benzylmorphine.tw.
58

59 39.betaprodine.tw.
60

1
2
3 40.bezitriamide.tw.
4

5 41.buprenorphine.tw.
6

7 42.butorphanol.tw.
8
9

10 43.bremazocine.tw.
11

12 44.carfentanil.tw.
13

14 45.codeine.tw.
15

16 46.contin.tw.
17

18 47.dextromoramide.tw.
19

20 48.dextropropoxyphene.tw.
21

22 49.dezocine.tw.
23

24 50.diacetylmorphine.tw.
25

26 51.diamorphine.tw.
27

28 52.dihydrocodeine.tw.
29

30 53.dihydromorphine.tw.
31

32 54.dihydromorphone.tw.
33

34 55.diphenoxylate.tw.
35

36 56.dipipanone.tw.
37

38 57.enadoline.tw.
39

40 58.ethylketazocine.tw.
41

42 59.ethylmorphine.tw.
43

44 60.etonitazene.tw.
45

46 61.etorphine.tw.
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48 62.fentanyl.tw.
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1
2
3 63.heroin.tw.
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5
6 64.hydrocodone.tw.
7

8 65.hydromorphin\$.tw.
9

10
11 66.hydromorphone.tw.
12

13
14 67.ketazocine.tw.
15

16 68.ketobemidone.tw.
17

18
19 69.lefetamine.tw.
20

21 70.levomethadon.tw.
22

23
24 71.levomethadyl.tw.
25

26 72.levomethorphan\$.tw.
27

28
29 73.levorphanol.tw.
30

31 74.loperamide.tw.
32

33
34 75.meperidine.tw.
35

36 76.meptazinol.tw.
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38
39 77.methadone.tw.
40

41 78.methadyl.tw.
42

43
44 79.methylmorphine.tw.
45

46 80.morphin\$.tw.
47

48
49 81.nalbuphine.tw.
50

51 82.narcotic\$.tw.
52

53
54 83.nicocodeine.tw.
55

56
57 84.nicomorphine.tw.
58

59 85.normorphine.tw.
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- 1
- 2
- 3 86.noscapin\$.tw.
- 4
- 5 87.ohmefantanyl.tw.
- 6
- 7
- 8 88.opiate\$.tw.
- 9
- 10 89.opioid\$.tw.
- 11
- 12
- 13 90.opium.tw.
- 14
- 15 91.oripavine.tw.
- 16
- 17 92.oxycodone.tw.
- 18
- 19 93.oxycontin.tw.
- 20
- 21 94.oxymorphone.tw.
- 22
- 23 95.papaveretum.tw.
- 24
- 25 96.papaverin.tw.
- 26
- 27 97.pentazocine.tw.
- 28
- 29 98.percocet.tw.
- 30
- 31 99.peronine.tw.
- 32
- 33 100. pethidine.tw.
- 34
- 35 101.phenazocine.tw.
- 36
- 37 102.phencyclidine.tw.
- 38
- 39 103.pholcodine.tw.
- 40
- 41 104.piritramid\$.tw.
- 42
- 43 105.prodine.tw.
- 44
- 45 106.promedol.tw.
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- 47 107.propoxyphene.tw.
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- 49 108.remifentanil.tw.
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3 109.sufentanil.tw.
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5 110.tapentadol.tw.
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7

8 111.thebaine.tw.
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10 112.tilidine.tw.
11
12

13 113.tramadol.sh,tw.
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15

16 114.ultracet.sh,tw.
17

18 **Combining terms**
19

20
21 115.31 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
22

23 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
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25 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
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27 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
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29 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
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31 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or
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33 114
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36 116.20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
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39 117.1 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
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42 or 17 or 18 or 19
43
44

45 118.115 and 116 and 117
46
47

48 119.animal/
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50 120.animal/ and human/
51
52

53 121.119 not 120
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56 122.118 not 121
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59 123.remove duplicates from 122
60

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 doub1\$ or treb1\$ or trip1\$) 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.

1
2
3 21.gonarthro\$.ab,sh,ti.
4

5 22.coxarthriti\$.ab,sh,ti.
6

7 23.coxarthro\$.ab,sh,ti.
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9

10 24.arthros\$.ab,ti.
11

12 25.arthrot\$.ab,ti.
13

14 26.((knee\$ or hip\$ or joint\$) adj3 (pain\$ or ach\$ or discomfort\$)).ab,ti.
15

16 27.((knee\$ or hip\$ or joint\$) adj3 stiff\$).ab,ti.
17

18
19
20
21 **Search terms for Opioids**
22

23 28.exp Analgesics, Opioid/
24

25 29.exp Narcotic Analgesic Agent/
26

27 30.acetyldihydrocodeine.tw.
28

29 31.alfentanil.tw.
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31 32.allyprodine.tw.
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33 33.alpha-methylfentanyl.tw.
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35 34.alphaprodine.tw.
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37 35.benzylmorphine.tw.
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39 36.betaprodine.tw.
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41 37.bezitriamide.tw.
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43 38.buprenorphine.tw.
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45 39.butorphanol.tw.
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- 13 47.diacetylmorphine.tw.
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- 16 48.diamorphine.tw.
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- 57 110.tramadol.sh,tw.
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- 59 111.ultracet.sh,tw.
- 60

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\$)

- 1
- 2
- 3 6. TX (sing\$ n25 mask\$)
- 4
- 5 7. TX (doubl\$ n25 blind\$)
- 6
- 7
- 8 8. TX (doubl\$ n25 mask\$)
- 9
- 10 9. TX (trebl\$ n25 blind\$)
- 11
- 12 10. TX (trebl\$ n25 mask\$)
- 13
- 14 11. TX (tripl\$ n25 blind\$)
- 15
- 16 12. TX (tripl\$ n25 mask\$)
- 17
- 18 13. (MH "Placebos")
- 19
- 20 14. TX placebo\$
- 21
- 22 15. TX random\$
- 23
- 24 16. (MH "Study Design+")
- 25
- 26 17. (MH "Comparative Studies")
- 27
- 28 18. (MH "Evaluation Research")
- 29
- 30 19. (MH "Prospective Studies+")
- 31
- 32 20. TX (control\$ or prospectiv\$ or volunteer\$)
- 33
- 34 21. S1 or S2 or (...) or S20
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44 **Search terms for Osteoarthritis**

- 45
- 46 22. osteoarthriti\$
- 47
- 48 23. (MH "Osteoarthritis")
- 49
- 50 24. TX osteoarthro\$
- 51
- 52 25. TX gonarthriti\$
- 53
- 54 26. TX gonarthro\$
- 55
- 56 27. TX coxarthriti\$
- 57
- 58
- 59
- 60

- 1
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- 3 28. TX coxarthro\$
- 4
- 5 29. TX arthros\$
- 6
- 7
- 8 30. TX arthrot\$
- 9
- 10
- 11 31. TX knee\$ n3 pain\$
- 12
- 13 32. TX hip\$ n3 pain\$
- 14
- 15
- 16 33. TX joint\$ n3 pain\$
- 17
- 18 34. TX knee\$ n3 ach\$
- 19
- 20
- 21 35. TX hip\$ n3 ach\$
- 22
- 23 36. TX joint\$ n3 ach\$
- 24
- 25
- 26 37. TX knee\$ n3 discomfort\$
- 27
- 28
- 29 38. TX hip\$ n3 discomfort\$
- 30
- 31 39. TX joint\$ n3 discomfort\$
- 32
- 33
- 34 40. TX knee\$ n3 stiff\$
- 35
- 36 41. TX hip\$ n3 stiff\$
- 37
- 38
- 39 42. TX joint\$ n3 stiff\$
- 40
- 41
- 42 43. S22 or S23 or S24(...)or S42
- 43

44 **Search terms for Opioids**

- 45
- 46 44. MH “ Analgesics, Opioid”
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- 48
- 49 45. MH “Narcotics”
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- 51
- 52 46. TX acetyldihydrocodeine
- 53
- 54 47. TX alfentanil
- 55
- 56
- 57 48. TX allylprodine
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- 59 49. TX alphamethylfentanyl
- 60

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- 3 50. TX alphaprodine
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- 6 51. TX benzylmorphine
- 7
- 8 52. TX betaprodine
- 9
- 10
- 11 53. TX bezitriamide
- 12
- 13 54. TX buprenorphine
- 14
- 15
- 16 55. TX butorphanol
- 17
- 18 56. TX bremazocine
- 19
- 20
- 21 57. TX carfentan\$
- 22
- 23 58. TX codeine
- 24
- 25
- 26 58. TX contin
- 27
- 28
- 29 60. TX dextromoramide
- 30
- 31 61. TX dextropropoxyphene
- 32
- 33
- 34 62. TX dezocine
- 35
- 36 63. TX diacetylmorphine
- 37
- 38
- 39 64. TX diamorphine
- 40
- 41
- 42 65. TX dihydrocodeine
- 43
- 44 66. TX dihydromorphine
- 45
- 46
- 47 67. TX dihydromorphone
- 48
- 49 68. TX diphenoxylate
- 50
- 51
- 52 69. TX dipipanone
- 53
- 54 70. TX enadoline
- 55
- 56
- 57 71. TX ethylketazocine
- 58
- 59 72. TX ethylmorphine
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3 73. TX etonitazene
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5 74. TX etorphine
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8 75. TX fentanyl
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10 76. TX heroin
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13 77. TX hydrocodone
14

15 78. TX hydromorphin\$
16
17

18 79. TX hydromorphone
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21 80. TX ketazocine
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23 81. TX ketobemidone
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26 82. TX lefetamine
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29 83. TX levomethadon
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32 84. TX levomethadyl
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34 85. TX levomethorphan\$
35
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37 86. TX levorphanol
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40 87. TX loperamide
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42

43 88. TX meperidine
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45

46 89. TX meptazinol
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48

49 90. TX methadone
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51

52 91. TX methadyl
53
54

55 92. TX methylmorphine
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57

58 93. TX morphin\$
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94. TX nalbuphine

95. TX narcotic\$

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- 2
- 3 96. TX nicocodeine
- 4
- 5 97. TX nicomorphine
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- 7
- 8 98. TX normorphine
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- 11 99. TX noscapin\$
- 12
- 13 100. TX ohmefentanyl
- 14
- 15
- 16 101. TX opiate\$
- 17
- 18 102. TX opioid\$
- 19
- 20
- 21 103. TX opium
- 22
- 23
- 24 104. TX oripavine
- 25
- 26 105. TX oxycodone
- 27
- 28
- 29 106. TX oxycontin
- 30
- 31 107. TX oxymorphone
- 32
- 33
- 34 108. TX papaveretum
- 35
- 36 109. TX papaverin
- 37
- 38
- 39 110. TX pentazocine
- 40
- 41
- 42 111. TX percocet
- 43
- 44 112. TX peronine
- 45
- 46
- 47 113. TX pethidine
- 48
- 49 114. TX phenazocine
- 50
- 51
- 52 115. TX phencyclidine
- 53
- 54 116. TX pholcodine
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- 56
- 57 117. TX piritramid\$
- 58
- 59 118. TX prodine
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3 119. TX promedol
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5 120. TX propoxyphene
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8 121. TX remifentanyl
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10 122. TX sufentanyl
11
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13 123. TX tapentadol
14
15

16 124. TX thebaine
17
18

19 125. TX tilidine
20
21

22 126. TX tramadol
23
24

25 127. TX ultracet
26
27

28 128. S44 or S45 or(...)S127
29

30 **Combining terms**

31 129. S21 and S43 and S128
32
33
34
35

36 **CENTRAL**

37 **Search terms for Osteoarthritis**

38
39
40
41
42 #1. MeSH descriptor Osteoarthritis explode all trees
43

44 #2. (osteoarthritis* OR osteoarthro* OR gonarthriti* OR gonarthro* OR coxarthriti*
45 OR coxarthro* OR arthros* OR arthrot* OR ((knee* OR hip* OR joint*) near/3
46 (pain* OR ach* OR discomfort*)) OR ((knee* OR hip* OR joint*) near/3 stiff*)) in
47
48
49 Trials
50

51 **Search terms for Opioids**

52
53
54 #3. MeSH descriptor Analgesics, Opioid explode all trees
55

56
57 #4. MeSH descriptor Narcotics explode all trees
58
59
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3 #5. (acetyldihydrocodeine OR alfentanil OR allylprodine OR alphamethylfentanyl OR
4 alphaprodine OR benzylmorphine OR betaprodine OR bezitriamide OR
5 buprenorphine OR butorphanol ORbremazocine OR carfentan* OR codeine OR
6
7
8 contin ORdextromoramide OR dextropropoxyphene OR dezocine OR
9
10 diacetylmorphine OR diamorphine OR dihydrocodeine OR dihydromorphine OR
11 dihydromorphone OR diphenoxylate OR dipipanone OR enadoline OR
12 ethylketazocine OR ethylmorphine OR etonitazene OR etorphine OR fentanyl OR
13 heroin OR hydrocodone OR hydromorphin* OR hydromorphone OR ketazocine OR
14 ketobemidone OR lefetamine OR levomethadon OR levomethadyl OR
15 levomethorphan* OR levorphanol OR loperamide OR meperidine OR meptazinol OR
16 methadone OR methadyl OR methylmorphine OR morphin* OR nalbuphine OR
17 narcotic* OR nicocodeine OR nicomorphine OR normorphine OR noscapin* OR
18 ohmefentanyl OR opiate* OR opioid* OR opium OR oripavine OR oxycodone OR
19 oxycontin OR oxymorphone OR papaveretum OR papaverin OR pentazocine OR
20 percocet OR peronine OR pethidine OR phenazocine OR phencyclidine OR
21 pholcodine OR piritramid* OR prodine OR promedol OR propoxyphene OR
22 remifentanil OR sufentanil OR tapentadol OR thebaine OR tilidine OR tramadol OR
23 ultracet) in Trials

Combining terms

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37 #6. (#1 OR #2)

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40 #7. (#3 OR #4 OR #5)

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43 #8. (#6 AND #7) in Clinical Trials
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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	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	<i>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</i>
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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022142.R1
Article Type:	Protocol
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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

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3 Comparative efficacy and safety of oral or transdermal opioids in the
4 treatment of knee or hip osteoarthritis: A systematic review and Bayesian
5 network meta-analysis protocol
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39

40 **Keywords:** opioids, osteoarthritis, knee, hip
41

42
43 **Word count:** 3086 (excluding title page, references, figures)
44

45 46 **ABSTRACT** 47

48 **Introduction:** Osteoarthritis is a common degenerative joint disease that
49 eventually leads to disability and poor quality of life. The main symptoms
50 are mobility pain and disorders. If the patient has severe pain or other
51 analgesics are contraindicated, opioids may be a viable treatment option.
52 To evaluate and compare the efficacy and safety of opioids in the
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3 treatment of knee or hip osteoarthritis, we will integrate direct and
4 indirect evidence using a Bayesian network meta-analysis to establish
5 hierarchies of these drugs.
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9 **Methods and analysis:** We will search the Medicine, Embase, CINAHL,
10 Cochrane Library, Web of Science, and PsycINFO databases as well as
11 published and unpublished research in international registries and
12 regulatory agency websites for osteoarthritis reports published prior to
13 January 5, 2018. There will be no restrictions on the language.
14 Randomised clinical trials that compare oral or transdermal opioids with
15 other various opioids, placebo or no treatment for patients with knee or
16 hip osteoarthritis will be included. The primary outcomes of efficacy will
17 be pain and function. We will use pain and function scales to evaluate the
18 main outcomes. The secondary outcomes of safety will be defined as the
19 proportion of patients who have stopped treatment due to side effects.
20 Pairwise meta-analyses and Bayesian network meta-analyses will be
21 performed for all related outcome measures. We will conduct subgroup
22 analyses and sensitivity analyses to assess the robustness of our findings.
23 The GRADE framework will be used to assess the quality of the evidence
24 contributing to each network assessment.
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40 **Ethics and dissemination:** This study does not require formal ethical
41 approval because individual patient data will not be included. The
42 findings will be disseminated through peer-reviewed publications or
43 conference presentations.
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49 **Trial registration number:** PROSPERO CRD42018085503.
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51 **Strengths and limitations of this study**

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54 •While conventional paired meta-analyses focus on direct comparisons of
55 single interventions, this Bayesian network meta-analysis will combine
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3 direct evidence with indirect evidence to assess the interrelationships
4 between all treatments in multiple treatment comparisons.
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7 ▪ Subgroup and sensitivity analyses will provide implications for
8 clinically relevant questions for later research directions.
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11 ▪ This method synthesises the data comprehensively and provides a
12 clinically useful summary that can guide the development of a clinical
13 prescription system.
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16 ▪ The different routes of administration (oral or transdermal), durations
17 and frequencies may cause considerable heterogeneity.
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23 **Introduction**

24 **Description of the condition**

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28 Osteoarthritis (OA), also known as degenerative arthritis or senile
29 arthritis, is a degenerative disease.¹ Increased obesity, age, trauma to joint
30 areas, excessive manual labour, and decreased muscle strength and joint
31 stability are important risk factors for OA.²⁻⁵ The main clinical
32 manifestations of OA are chronic pain, joint instability, stiffness, joint
33 deformity and reduced imaging of the joint space; these manifestations
34 eventually lead to progressive disability and reduce patient quality of
35 life.^{1,6} Worldwide, OA, particularly OA of the knee and hip joints, is one
36 of the leading causes of disability among the elderly.⁷⁻⁸ In a Dutch study,
37 the prevalence of symptomatic hip OA was 5.9% in adults aged 45-54
38 years and 17% in adults aged 75 years and older; the prevalence of knee
39 OA in adults aged 55 years and older was 15.6% in men and 30.5% in
40 women.⁹ This highly prevalent disease and the accompanying disability
41 have terrible effects on individuals and society. The burden of disease of
42 OA is usually measured by direct and indirect economic costs, including
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3 less explicit intangibles such as pain and reduced quality of life.¹⁰ In
4 general, the impact of this disease is widespread and serious, and there
5 are currently no effective interventions to prevent the development of
6 OA.¹
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11 Cartilage destruction, subchondral bone remodelling and synovitis are the
12 major pathological features of OA. Changes in the internal environment
13 of various tissue structures within the joint cavity are the main causes of
14 these pathological features and include anabolic and catabolic imbalance,
15 especially an increase in articular cartilage catabolism leading to a
16 decrease in the regeneration ability of cartilage.¹¹⁻¹² Previous studies have
17 shown that many factors may interfere with chondrocyte homeostasis,
18 including abnormal mechanical loading of proinflammatory mediators
19 and oxidative stress.¹³⁻¹⁴ These mediators can cause inflammation, which,
20 in addition to promoting serious chondrocyte apoptosis and articular
21 cartilage damage, can stimulate the sensory nerves in the synovium and
22 surrounding tissues. This nerve stimulation leads to the peripheral and
23 central sensitisation of the adjacent tissues, which further leads to chronic
24 pain.¹⁵
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39 **Description of the intervention**

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42 Pain is the most relevant symptom of OA; as the degree of pain increases,
43 patient mobility is decreased, and the degree of disability increases.¹⁶⁻¹⁷
44 Because of pain and functional limitations, the quality of life of patients
45 with OA is even worse than that of patients with gastrointestinal or
46 chronic respiratory system disorders.¹⁸
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52 Therefore, alleviating pain, preventing muscle atrophy, and reducing joint
53 deformity, stiffness and other complications are the main therapeutic
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3 targets of OA.¹⁹⁻²⁰ Currently, the treatment modalities for OA include
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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, capsaicin and duloxetine.³¹ Currently, the use of NSAIDs for the treatment of OA pain is preferred in the clinic. However, NSAID use may cause serious adverse cardiovascular, gastrointestinal and renal events.³²⁻³⁴ Opioids may be a viable alternative for patients who do not adequately respond to routine treatment and when other analgesics are contraindicated.³⁵

Why it is important to perform this review

Several systematic reviews have investigated the effectiveness of the agents used to treat OA.^{12,31} However, previous studies have considered

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

Objectives

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

METHODS

Study design

This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols, see **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 studies³⁸⁻³⁹ 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 scales³⁸⁻³⁹

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 alгоfunctional score	Lequesne osteoarthritis index global score
8	Lequesne osteoarthritis index global score	Other alгоfunctional scale
9	Other alгоfunctional 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

1
2
3 EBSCO. We will also search the Web of Science and PsycINFO
4 databases. All databases will be searched from implementation to January
5 5, 2018 using a previously reported search strategy.^{10,29,12,31} For the
6 strategies that will be used in this review, see **Supplementary file 2**.
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10 11 **Searching other resources**

12
13 International registries of published and unpublished articles and the
14 websites of regulatory agencies will be searched in our review. These
15 sources include the following: the World Health Organization (WHO)
16 International Clinical Trials Registry Platform, clinicaltrials.gov, the
17 University hospital Medical Information Network (UMIN)-Clinical Trials
18 Registry, the American College of Rheumatology (ACR), the European
19 League Against Rheumatism (EULAR), and U.S. Food and Drug
20 Administration (FDA) reports. No language limitations will be applied.
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29 30 **Study selection**

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32 Two independent reviewers (YW and HZ) will evaluate all relevant titles
33 and abstracts. The reviewers will use uniform standards to independently
34 extract key study parameters, and any disagreements will be resolved by
35 the third review (JW). There will be no language restrictions. If multiple
36 studies describe the same experiment, the study with the most relatively
37 complete data will be used in the analyses.
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44 45 **Data extraction and management**

46
47 Two review authors (YW and HZ) will extract the trial information
48 independently via a single purpose-built electronic database. Any
49 differences will be resolved by consensus or discussion with the third
50 author (JW). The following information will be extracted:
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- 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 domains⁴² as illustrated in **Table 2**. All included

1
2
3 trials will be classified into the following categories: low risk, high risk,
4 and unclear.⁴¹
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7 **Table 2** Assessment of the risk of bias in the six domains⁴³
8

9	1 Was there adequate sequence generation (selection bias)?
10	
11	2 Was allocation adequately concealed (selection bias)?
12	
13	3 Was knowledge of the allocated interventions adequately prevented
14	during the study (detection bias)?
15	
16	4 Were incomplete outcome data adequately addressed (attrition bias)?
17	
18	5 Are reported of the study free of selective reporting (reporting bias)?
19	
20	6 Was the study apparently free of other problems that could put it at a
21	risk of bias?
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41 **Data synthesis and analysis**

42 **Measures of treatment effects**

43 **Relative treatment effects**

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50 We will estimate continuous variables using the standardised mean
51 difference (SMD) with 95% credible intervals (CrIs). For categorical
52 outcomes, odds ratios (ORs) with 95% CrIs will be calculated for the
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4 analyses. In the presence of minimally informative priors, CrIs can be
5
6 understood similarly to confidence interval (CIs), and at the conventional
7
8 statistical significance level, a two-sided $p < 0.05$ can be assumed if the 95%
9
10 CrIs do not include 0.⁴³ If standard deviations (SDs) are not provided, we
11
12 will calculate them from the standard errors, CIs, or p-values using a
13
14 method described in previous studies.^{39,44} If some necessary data are not
15
16 available, we will use approximations as previously described.³⁵ To
17
18 visually explain the pooled effects, we will transform the effect sizes into
19
20 differences on a 10-cm visual analogue scale (VAS) based on a median
21
22 pooled SD of 2.5 cm, as found in large-scale OA trials that have used 10-
23
24 cm VASs to assess pain.⁴⁴ SMDs of -0.20 correspond to approximate
25
26 differences in pain scores between the experimental and control groups of
27
28 0.5 on a 10-cm VAS, -0.50 of 1.25 on a 10-cm VAS, and -0.80 of 2 on a
29
30 10-cm VAS.⁴⁴⁻⁴⁵ Additionally, we will compare the effects with a pre-
31
32 specified minimal clinically important difference based on the median
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34 pooled SD of 0.37 units, which has been utilised in recent studies of
35
36 patients with OA and corresponds to 0.9 cm on a 10-cm VAS.⁴⁶⁻⁴⁹ We
37
38 will also transform the SMDs for function to a Western Ontario and
39
40 McMaster Universities Osteoarthritis Index (WOMAC) score based on a
41
42 median pooled SD of 2.1 units as observed in large-scale OA trials.⁵⁰⁻⁵¹

43 44 45 46 47 48 49 50 51 52 **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 model⁶¹ 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

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3 versus mixed); (8) type of opioid (oral versus transdermal); and (9) type
4 of trial (published versus unpublished).
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7 **Sensitivity analyses**

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

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18 The Grading of Recommendations, Assessment, Development and
19 Evaluations (GRADE) framework, which characterises the quality of
20 evidence based on the study limitations, publication bias, indirectness,
21 imprecision and inconsistency in the primary outcomes, will be used to
22 evaluate the quality of evidence in each network.⁶² Additionally, a
23 comparison-adjusted funnel plot will be drawn to detect any major
24 publication bias in the Bayesian network meta-analysis.⁶³
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34 **Ethics and dissemination**

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

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3 ability of this work to reach high-confidence conclusions.
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8 **Collaborators:** None
9

10 **Contributors:** JW conceived the review and wrote the first draft of the
11 protocol. WLG and ZSY revised the protocol. YW and HZ are
12 responsible for the development of the search strategy and data extraction.
13 ML and LY will be responsible for assessing bias and data synthesis and
14 analysis. All the authors have approved the publication of the protocol.
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18

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21
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26
27

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30
31

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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	<i>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</i>
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

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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 (if 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 treb1\$ or trip1\$) 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.

1
2
3 19.(control\$ or prospectiv\$ or volunteer\$).ab,ti.
4

5 **Search terms for Osteoarthritis**

6
7
8 20.exp osteoarthritis/
9

10
11 21.osteoarthriti\$.ab,sh,ti.
12

13 22.osteoarthro\$.ab,sh,ti.
14

15 23.gonarthriti\$.ab,sh,ti.
16

17 24.gonarthro\$.ab,sh,ti.
18

19 25.coxarthriti\$.ab,sh,ti.
20

21 26.coxarthro\$.ab,sh,ti.
22

23 27.arthros\$.ab,ti.
24

25 28.arthrot\$.ab,ti.
26

27 29.((knee\$ or hip\$ or joint\$) adj3 (pain\$ or ach\$ or discomfort\$)).ab,ti.
28

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

31 **Search terms for Opioids**

32 31.exp Analgesics, Opioid/
33

34 32.exp Narcotics/
35

36 33.acetyldihydrocodeine.tw.
37

38 34.alfentanil.tw.
39

40 35.allyprodine.tw.
41

42 36.alpha-methylfentanyl.tw.
43

44 37.alphaprodine.tw.
45

46 38.benzylmorphine.tw.
47

48 39.betaprodine.tw.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 40.bezitriamide.tw.
4

5
6 41.buprenorphine.tw.
7

8 42.butorphanol.tw.
9

10
11 43.bremazocine.tw.
12

13 44.carfentanil.tw.
14

15
16 45.codeine.tw.
17

18 46.contin.tw.
19

20
21 47.dextromoramide.tw.
22

23 48.dextropropoxyphene.tw.
24

25
26 49.dezocine.tw.
27

28
29 50.diacetylmorphine.tw.
30

31 51.diamorphine.tw.
32

33
34 52.dihydrocodeine.tw.
35

36 53.dihydromorphine.tw.
37

38
39 54.dihydromorphone.tw.
40

41 55.diphenoxylate.tw.
42

43
44 56.dipipanone.tw.
45

46
47 57.enadoline.tw.
48

49 58.ethylketazocine.tw.
50

51
52 59.ethylmorphine.tw.
53

54 60.etonitazene.tw.
55

56
57 61.etorphine.tw.
58

59 62.fentanyl.tw.
60

1
2
3 63.heroin.tw.
4

5
6 64.hydrocodone.tw.
7

8 65.hydromorphin\$.tw.
9

10
11 66.hydromorphone.tw.
12

13
14 67.ketazocine.tw.
15

16 68.ketobemidone.tw.
17

18
19 69.lefetamine.tw.
20

21 70.levomethadon.tw.
22

23
24 71.levomethadyl.tw.
25

26 72.levomethorphan\$.tw.
27

28
29 73.levorphanol.tw.
30

31 74.loperamide.tw.
32

33
34 75.meperidine.tw.
35

36 76.meptazinol.tw.
37

38
39 77.methadone.tw.
40

41 78.methadyl.tw.
42

43
44 79.methylmorphine.tw.
45

46 80.morphin\$.tw.
47

48
49 81.nalbuphine.tw.
50

51 82.narcotic\$.tw.
52

53
54 83.nicocodeine.tw.
55

56
57 84.nicomorphine.tw.
58

59 85.normorphine.tw.
60

- 1
- 2
- 3 86.noscapin\$.tw.
- 4
- 5
- 6 87.ohmefantanyl.tw.
- 7
- 8 88.opiate\$.tw.
- 9
- 10
- 11 89.opioid\$.tw.
- 12
- 13 90.opium.tw.
- 14
- 15
- 16 91.oripavine.tw.
- 17
- 18 92.oxycodone.tw.
- 19
- 20
- 21 93.oxycontin.tw.
- 22
- 23 94.oxymorphone.tw.
- 24
- 25
- 26 95.papaveretum.tw.
- 27
- 28 96.papaverin.tw.
- 29
- 30
- 31 97.pentazocine.tw.
- 32
- 33
- 34 98.percocet.tw.
- 35
- 36 99.peronine.tw.
- 37
- 38
- 39 100. pethidine.tw.
- 40
- 41 101.phenazocine.tw.
- 42
- 43 102.phencyclidine.tw.
- 44
- 45
- 46 103.pholcodine.tw.
- 47
- 48
- 49 104.piritramid\$.tw.
- 50
- 51 105.prodine.tw.
- 52
- 53 106.promedol.tw.
- 54
- 55
- 56 107.propoxyphene.tw.
- 57
- 58
- 59 108.remifentanil.tw.
- 60

1
2
3 109.sufentanil.tw.
4

5
6 110.tapentadol.tw.
7

8
9 111.thebaine.tw.
10

11
12 112.tilidine.tw.
13

14
15 113.tramadol.sh,tw.
16

17
18 114.ultracet.sh,tw.
19

20 **Combining terms**

21 115.31 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
22

23 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
24

25 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
26

27 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
28

29 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
30

31 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or
32

33
34 114
35

36
37 116.20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
38

39
40 117.1 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
41

42
43 or 17 or 18 or 19
44

45
46 118.115 and 116 and 117
47

48
49 119.animal/
50

51
52 120.animal/ and human/
53

54
55 121.119 not 120
56

57
58 122.118 not 121
59

60 123.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 doub1\$ or treb1\$ or trip1\$) 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.

1
2
3 21.gonarthro\$.ab,sh,ti.
4

5 22.coxarthriti\$.ab,sh,ti.
6

7 23.coxarthro\$.ab,sh,ti.
8

9 24.arthros\$.ab,ti.
10

11 25.arthrot\$.ab,ti.
12

13 26.((knee\$ or hip\$ or joint\$) adj3 (pain\$ or ach\$ or discomfort\$)).ab,ti.
14

15 27.((knee\$ or hip\$ or joint\$) adj3 stiff\$).ab,ti.
16

17
18
19
20
21 **Search terms for Opioids**
22

23 28.exp Analgesics, Opioid/
24

25 29.exp Narcotic Analgesic Agent/
26

27 30.acetyldihydrocodeine.tw.
28

29 31.alfentanil.tw.
30

31 32.allyprodine.tw.
32

33 33.alpha-methylfentanyl.tw.
34

35 34.alphaprodine.tw.
36

37 35.benzylmorphine.tw.
38

39 36.betaprodine.tw.
40

41 37.bezitriamide.tw.
42

43 38.buprenorphine.tw.
44

45 39.butorphanol.tw.
46

47 40.bremazocine.tw.
48

49 41.carfentan\$.tw.
50

51 42.codeine.tw.
52
53
54
55
56
57
58
59
60

- 1
- 2
- 3 43.contin.tw.
- 4
- 5
- 6 44.dextromoramide.tw.
- 7
- 8 45.dextropropoxyphene.tw.
- 9
- 10
- 11 46.dezocine.tw.
- 12
- 13 47.diacetylmorphine.tw.
- 14
- 15
- 16 48.diamorphine.tw.
- 17
- 18 49.dihydrocodeine.tw.
- 19
- 20
- 21 50.dihydromorphine.tw.
- 22
- 23
- 24 51.dihydromorphone.tw.
- 25
- 26 52.diphenoxylate.tw.
- 27
- 28
- 29 53.dipipanone.tw.
- 30
- 31 54.enadoline.tw.
- 32
- 33
- 34 55.ethylketazocine.tw.
- 35
- 36 56.ethylmorphine.tw.
- 37
- 38
- 39 57.etonitazene.tw.
- 40
- 41 58.etorphine.tw.
- 42
- 43
- 44 59.fentanyl.tw.
- 45
- 46
- 47 60.hero in.tw.
- 48
- 49 61.hydrocodone.tw.
- 50
- 51
- 52 62.hydromorphin\$.tw.
- 53
- 54 63.hydromorphone.tw.
- 55
- 56
- 57 64.ketazocine.tw.
- 58
- 59
- 60 65.ketobemidone.tw.

- 1
- 2
- 3 66.lefetamine.tw.
- 4
- 5
- 6 67.levomethadon.tw.
- 7
- 8 68.levomethadyl.tw.
- 9
- 10
- 11 69.levomethorphan\$.tw.
- 12
- 13
- 14 70.levorphanol.tw.
- 15
- 16 71.loperamide.tw.
- 17
- 18 72.meperidine.tw.
- 19
- 20
- 21 73.meptazinol.tw.
- 22
- 23
- 24 74.methadone.tw.
- 25
- 26 75.methadyl.tw.
- 27
- 28
- 29 76.methylmorphine.tw.
- 30
- 31 77.morphin\$.tw.
- 32
- 33
- 34 78.nalbuphine.tw.
- 35
- 36 79.narcotic\$.tw.
- 37
- 38
- 39 80.nicocodeine.tw.
- 40
- 41 81.nicomorphine.tw.
- 42
- 43
- 44 82.normorphine.tw.
- 45
- 46 83.noscapin\$.tw.
- 47
- 48
- 49 84.ohmefentanyl.tw.
- 50
- 51 85.opiate\$.tw.
- 52
- 53
- 54 86.opioid\$.tw.
- 55
- 56
- 57 87.opium.tw.
- 58
- 59 88.oripavine.tw.
- 60

- 1
- 2
- 3 89.oxycodone.tw.
- 4
- 5 90.oxycontin.tw.
- 6
- 7
- 8 91.oxymorphone.tw.
- 9
- 10
- 11 92.papaveretum.tw.
- 12
- 13 93.papaverin.tw.
- 14
- 15
- 16 94.pentazocine.tw.
- 17
- 18 95.percocet.tw.
- 19
- 20
- 21 96.peronine.tw.
- 22
- 23 97.pethidine.tw.
- 24
- 25
- 26 98.phenazocine.tw.
- 27
- 28
- 29 99.phencyclidine.tw.
- 30
- 31 100. pholcodine.tw.
- 32
- 33 101.piritramid\$.tw.
- 34
- 35
- 36 102.prodine.tw.
- 37
- 38
- 39 103.promedol.tw.
- 40
- 41
- 42 104.propoxyphene.tw.
- 43
- 44 105.remifentanil.tw.
- 45
- 46
- 47 106.sufentanil.tw.
- 48
- 49 107.tapentadol.tw.
- 50
- 51
- 52 108.thebaine.tw.
- 53
- 54 109.tilidine.tw.
- 55
- 56
- 57 110.tramadol.sh,tw.
- 58
- 59 111.ultracet.sh,tw.
- 60

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\$)

- 1
- 2
- 3
- 4 6. TX (sing\$ n25 mask\$)
- 5
- 6 7. TX (doubl\$ n25 blind\$)
- 7
- 8 8. TX (doubl\$ n25 mask\$)
- 9
- 10 9. TX (trebl\$ n25 blind\$)
- 11
- 12 10. TX (trebl\$ n25 mask\$)
- 13
- 14 11. TX (tripl\$ n25 blind\$)
- 15
- 16 12. TX (tripl\$ n25 mask\$)
- 17
- 18 13. (MH “Placebos”)
- 19
- 20 14. TX placebo\$
- 21
- 22 15. TX random\$
- 23
- 24 16. (MH “Study Design+”)
- 25
- 26 17. (MH “Comparative Studies”)
- 27
- 28 18. (MH “Evaluation Research”)
- 29
- 30 19. (MH “Prospective Studies+”)
- 31
- 32 20. TX (control\$ or prospectiv\$ or volunteer\$)
- 33
- 34 21. S1 or S2 or (...) or S20
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43

44 **Search terms for Osteoarthritis**

- 45
- 46 22. osteoarthriti\$
- 47
- 48 23. (MH “Osteoarthritis”)
- 49
- 50 24. TX osteoarthro\$
- 51
- 52 25. TX gonarthriti\$
- 53
- 54 26. TX gonarthro\$
- 55
- 56 27. TX coxarthriti\$
- 57
- 58
- 59
- 60

- 1
- 2
- 3 28. TX coxarthro\$
- 4
- 5 29. TX arthros\$
- 6
- 7
- 8 30. TX arthrot\$
- 9
- 10
- 11 31. TX knee\$ n3 pain\$
- 12
- 13 32. TX hip\$ n3 pain\$
- 14
- 15
- 16 33. TX joint\$ n3 pain\$
- 17
- 18 34. TX knee\$ n3 ach\$
- 19
- 20
- 21 35. TX hip\$ n3 ach\$
- 22
- 23 36. TX joint\$ n3 ach\$
- 24
- 25
- 26 37. TX knee\$ n3 discomfort\$
- 27
- 28
- 29 38. TX hip\$ n3 discomfort\$
- 30
- 31 39. TX joint\$ n3 discomfort\$
- 32
- 33
- 34 40. TX knee\$ n3 stiff\$
- 35
- 36 41. TX hip\$ n3 stiff\$
- 37
- 38
- 39 42. TX joint\$ n3 stiff\$
- 40
- 41
- 42 43. S22 or S23 or S24(...)or S42
- 43

44 **Search terms for Opioids**

- 45
- 46 44. MH “ Analgesics, Opioid”
- 47
- 48
- 49 45. MH “Narcotics”
- 50
- 51
- 52 46. TX acetyldihydrocodeine
- 53
- 54 47. TX alfentanil
- 55
- 56
- 57 48. TX allylprodine
- 58
- 59 49. TX alphamethylfentanyl
- 60

- 1
- 2
- 3 50. TX alphaprodine
- 4
- 5
- 6 51. TX benzylmorphine
- 7
- 8 52. TX betaprodine
- 9
- 10
- 11 53. TX bezitriamide
- 12
- 13 54. TX buprenorphine
- 14
- 15
- 16 55. TX butorphanol
- 17
- 18 56. TX bremazocine
- 19
- 20
- 21 57. TX carfentan\$
- 22
- 23 58. TX codeine
- 24
- 25
- 26 58. TX contin
- 27
- 28
- 29 60. TX dextromoramide
- 30
- 31 61. TX dextropropoxyphene
- 32
- 33
- 34 62. TX dezocine
- 35
- 36 63. TX diacetylmorphine
- 37
- 38
- 39 64. TX diamorphine
- 40
- 41
- 42 65. TX dihydrocodeine
- 43
- 44 66. TX dihydromorphine
- 45
- 46
- 47 67. TX dihydromorphone
- 48
- 49 68. TX diphenoxylate
- 50
- 51
- 52 69. TX dipipanone
- 53
- 54 70. TX enadoline
- 55
- 56
- 57 71. TX ethylketazocine
- 58
- 59 72. TX ethylmorphine
- 60

1
2
3 73. TX etonitazene
4

5
6 74. TX etorphine
7

8
9 75. TX fentanyl
10

11
12 76. TX heroin
13

14
15 77. TX hydrocodone
16

17
18 78. TX hydromorphin\$
19

20
21 79. TX hydromorphone
22

23
24 80. TX ketazocine
25

26
27 81. TX ketobemidone
28

29
30 82. TX lefetamine
31

32
33 83. TX levomethadon
34

35
36 84. TX levomethadyl
37

38
39 85. TX levomethorphan\$
40

41
42 86. TX levorphanol
43

44
45 87. TX loperamide
46

47
48 88. TX meperidine
49

50
51 89. TX meptazinol
52

53
54 90. TX methadone
55

56
57 91. TX methadyl
58

59
60 92. TX methylmorphine
61

62
63 93. TX morphin\$
64

65
66 94. TX nalbuphine
67

68
69 95. TX narcotic\$
70

- 1
- 2
- 3 96. TX nicocodeine
- 4
- 5 97. TX nicomorphine
- 6
- 7
- 8 98. TX normorphine
- 9
- 10
- 11 99. TX noscapin\$
- 12
- 13 100. TX ohmefentanyl
- 14
- 15
- 16 101. TX opiate\$
- 17
- 18 102. TX opioid\$
- 19
- 20
- 21 103. TX opium
- 22
- 23
- 24 104. TX oripavine
- 25
- 26 105. TX oxycodone
- 27
- 28
- 29 106. TX oxycontin
- 30
- 31 107. TX oxymorphone
- 32
- 33
- 34 108. TX papaveretum
- 35
- 36 109. TX papaverin
- 37
- 38
- 39 110. TX pentazocine
- 40
- 41
- 42 111. TX percocet
- 43
- 44 112. TX peronine
- 45
- 46
- 47 113. TX pethidine
- 48
- 49 114. TX phenazocine
- 50
- 51
- 52 115. TX phencyclidine
- 53
- 54 116. TX pholcodine
- 55
- 56
- 57 117. TX piritramid\$
- 58
- 59 118. TX prodine
- 60

1
2
3 119. TX promedol
4

5 120. TX propoxyphene
6
7

8 121. TX remifentanyl
9

10 122. TX sufentanyl
11
12

13 123. TX tapentadol
14
15

16 124. TX thebaine
17
18

19 125. TX tilidine
20
21

22 126. TX tramadol
23
24

25 127. TX ultracet
26
27

28 128. S44 or S45 or(...)S127
29

30 **Combining terms**

31 129. S21 and S43 and S128
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33
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36 **CENTRAL**

37 **Search terms for Osteoarthritis**

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39 #1. MeSH descriptor Osteoarthritis explode all trees
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42 #2. (osteoarthritis* OR osteoarthro* OR gonarthriti* OR gonarthro* OR coxarthriti*
43 OR coxarthro* OR arthros* OR arthrot* OR ((knee* OR hip* OR joint*) near/3
44 (pain* OR ach* OR discomfort*)) OR ((knee* OR hip* OR joint*) near/3 stiff*)) in
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Trials

52 **Search terms for Opioids**

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54 #3. MeSH descriptor Analgesics, Opioid explode all trees
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57 #4. MeSH descriptor Narcotics explode all trees
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3 #5. (acetyldihydrocodeine OR alfentanil OR allylprodine OR alphamethylfentanyl OR
4 alphaprodine OR benzylmorphine OR betaprodine OR bezitriamide OR
5 buprenorphine OR butorphanol OR bremazocine OR carfentan* OR codeine OR
6 contin OR dextromoramide OR dextropropoxyphene OR dezocine OR
7 diacetylmorphine OR diamorphine OR dihydrocodeine OR dihydromorphine OR
8 dihydromorphone OR diphenoxylate OR dipipanone OR enadoline OR
9 ethylketazocine OR ethylmorphine OR etonitazene OR etorphine OR fentanyl OR
10 heroin OR hydrocodone OR hydromorphin* OR hydromorphone OR ketazocine OR
11 ketobemidone OR lefetamine OR levomethadon OR levomethadyl OR
12 levomethorphan* OR levorphanol OR loperamide OR meperidine OR meptazinol OR
13 methadone OR methadyl OR methylmorphine OR morphin* OR nalbuphine OR
14 narcotic* OR nicocodeine OR nicomorphine OR normorphine OR noscapin* OR
15 ohmefentanyl OR opiate* OR opioid* OR opium OR oripavine OR oxycodone OR
16 oxycontin OR oxymorphone OR papaveretum OR papaverin OR pentazocine OR
17 percocet OR peronine OR pethidine OR phenazocine OR phencyclidine OR
18 pholcodine OR piritramid* OR prodine OR promedol OR propoxyphene OR
19 remifentanil OR sufentanil OR tapentadol OR thebaine OR tilidine OR tramadol OR
20 ultracet) in Trials
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35 **Combining terms**

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37 #6. (#1 OR #2)

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39 #7. (#3 OR #4 OR #5)

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42 #8. (#6 AND #7) in Clinical Trials
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BMJ Open

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

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Manuscripts

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3 1 Comparative efficacy and safety of oral or transdermal opioids in the
4 2 treatment of knee or hip osteoarthritis: A systematic review and Bayesian
5 3 network meta-analysis protocol

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40 17 **Keywords:** opioids, osteoarthritis, knee, hip

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43 18 **Word count:** 3086 (excluding title page, references, figures)

44 45 19 **ABSTRACT**

46
47
48 20 **Introduction:** Osteoarthritis is a common degenerative joint disease that
49 21 eventually leads to disability and poor quality of life. The main symptoms
50 22 are joint pain and mobility disorders. If the patient has severe pain or
51 23 other analgesics are contraindicated, opioids may be a viable treatment
52 24 option. To evaluate and compare the efficacy and safety of opioids in the

1 treatment of knee or hip osteoarthritis, we will integrate direct and
2 indirect evidence using a Bayesian network meta-analysis to establish
3 hierarchies of these drugs.

4 **Methods and analysis:** We will search the Medicine, Embase, CINAHL,
5 Cochrane Library, Web of Science, and PsycINFO databases as well as
6 published and unpublished research in international registries and
7 regulatory agency websites for osteoarthritis reports published prior to
8 January 5, 2018. There will be no restrictions on the language.
9 Randomised clinical trials that compare oral or transdermal opioids with
10 other various opioids, placebo or no treatment for patients with knee or
11 hip osteoarthritis will be included. The primary outcomes of efficacy will
12 be pain and function. We will use pain and function scales to evaluate the
13 main outcomes. The secondary outcomes of safety will be defined as the
14 proportion of patients who have stopped treatment due to side effects.
15 Pairwise meta-analyses and Bayesian network meta-analyses will be
16 performed for all related outcome measures. We will conduct subgroup
17 analyses and sensitivity analyses to assess the robustness of our findings.
18 The GRADE framework will be used to assess the quality of the evidence
19 contributing to each network assessment.

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

24 **Trial registration number:** PROSPERO CRD42018085503.

25 **Strengths and limitations of this study**

26 ▪ While previous conventional paired meta-analyses focused on direct
27 comparisons between opioid analgesics and placebo for OA, this

1 Bayesian network meta-analysis will combine direct evidence with
2 indirect evidence to assess the interrelationships between a wide range of
3 opioid analgesics, placebo and no treatment in multiple treatment
4 comparisons.

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

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

10 ▪ The different routes of administration (oral or transdermal), durations
11 and frequencies may cause considerable heterogeneity.

12 **Introduction**

13 **Description of the condition**

14 Osteoarthritis (OA), also known as degenerative arthritis or senile
15 arthritis, is a degenerative disease.¹ Increased obesity, age, trauma to joint
16 areas, excessive manual labour, and decreased muscle strength and joint
17 stability are important risk factors for OA.²⁻⁵ The main clinical
18 manifestations of OA are chronic pain, joint instability, stiffness, joint
19 deformity and reduced imaging of the joint space; these manifestations
20 eventually lead to progressive disability and reduce patient quality of
21 life.^{1,6} Worldwide, OA, particularly OA of the knee and hip joints, is one
22 of the leading causes of disability among the older adults.⁷⁻⁸
23 Research has shown that around one third of older adults have OA.⁹ This
24 highly prevalent disease and the accompanying disability have terrible
25 effects on individuals and society. The burden of OA is usually measured
26 by direct and indirect economic costs, including less explicit intangibles
27 such as pain and reduced quality of life.¹⁰

1
2
3 1 Cartilage destruction, subchondral bone remodelling and synovitis are the
4 major pathological features of OA. Changes in the internal environment
5 2 major pathological features of OA. Changes in the internal environment
6 of various tissue structures within the joint cavity are the main causes of
7 3 of various tissue structures within the joint cavity are the main causes of
8 these pathological features and include anabolic and catabolic imbalance,
9 4 these pathological features and include anabolic and catabolic imbalance,
10 especially an increase in articular cartilage catabolism leading to a
11 5 especially an increase in articular cartilage catabolism leading to a
12 decrease in the regeneration ability of cartilage.¹¹⁻¹² Previous studies have
13 6 decrease in the regeneration ability of cartilage.¹¹⁻¹² Previous studies have
14 shown that many factors may interfere with chondrocyte homeostasis,
15 7 shown that many factors may interfere with chondrocyte homeostasis,
16 including abnormal mechanical loading of proinflammatory mediators
17 8 including abnormal mechanical loading of proinflammatory mediators
18 and oxidative stress.¹³⁻¹⁴ These mediators can cause inflammation, which,
19 9 and oxidative stress.¹³⁻¹⁴ These mediators can cause inflammation, which,
20 in addition to promoting serious chondrocyte apoptosis and articular
21 10 in addition to promoting serious chondrocyte apoptosis and articular
22 cartilage damage, can stimulate the sensory nerves in the synovium and
23 11 cartilage damage, can stimulate the sensory nerves in the synovium and
24 surrounding tissues. This nerve stimulation leads to the peripheral and
25 12 surrounding tissues. This nerve stimulation leads to the peripheral and
26 central sensitisation of the adjacent tissues, which further leads to chronic
27 13 central sensitisation of the adjacent tissues, which further leads to chronic
28 pain.¹⁵
29 14 pain.¹⁵

30 15 **Description of the intervention**

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32
33 16 Pain is the most relevant symptom of OA; as the degree of pain increases,
34 17 patient mobility is decreased, and the degree of disability increases.¹⁶⁻¹⁷
35 17 patient mobility is decreased, and the degree of disability increases.¹⁶⁻¹⁷
36 Because of pain and functional limitations, the quality of life of patients
37 18 Because of pain and functional limitations, the quality of life of patients
38 with OA is even worse than that of patients with gastrointestinal or
39 19 with OA is even worse than that of patients with gastrointestinal or
40 chronic respiratory system disorders.¹⁸
41 20 chronic respiratory system disorders.¹⁸

42
43 21 Therefore, alleviating pain, preventing muscle atrophy, and reducing joint
44 22 deformity, stiffness and other complications are the main therapeutic
45 23 targets of OA.¹⁹⁻²⁰ Currently, the treatment modalities for OA include
46 24 invasive surgery, non-drug therapy and drug therapy.

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51 25 Invasive surgery includes intra-articular injections and surgery. Intra-
52 26 articular injections of agents such as hyaluronic acid (HA),
53 27 corticosteroids, ozone, and platelet-rich plasma (PRP) are used for the

1 treatment of OA, and these treatments have been proven to be effective.²¹⁻
2
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5 24 Surgery mainly includes total hip and knee replacement, which can
6
7 improve health-related quality of life in the late stage of OA.²⁵⁻²⁶ However,
8
9 surgery is not the first choice of treatment for OA in clinical practice due
10
11 to the limited lifespan of an artificial prosthesis. Furthermore, if a
12
13 prosthesis fails, the patient may face a second revision operation, and the
14
15 risk of failure in such operations is high due to the loss of bone mass.
16
17 Therefore, joint surgery is often considered the ultimate treatment for OA.
18
19 Non-drug therapy is important for reducing pain and improving the
20
21 physiological function of OA patients.²⁷ Non-drug therapies include
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23 weight reduction, exercise, changes in lifestyle and other physical therapy
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25 measures designed to slow the progression of OA.²⁸⁻³⁰

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13 Drugs for the treatment of OA pain primarily include non-steroidal anti-
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15 inflammatory drugs (NSAIDs), opioid drugs, paracetamol, capsaicin and
16
17 duloxetine.³¹ Currently, the use of NSAIDs for the treatment of OA pain
18
19 is preferred in the clinic. However, NSAID use may cause serious
20
21 adverse cardiovascular, gastrointestinal and renal events.³²⁻³⁴ Opioids may
22
23 be a viable alternative for patients who do not adequately respond to
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25 routine treatment and when other analgesics are contraindicated.³⁵

20 **Why it is important to perform this review**

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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

1 meta-analysis method allows for the coinstantaneous comparison of
2 multiple opioid drug interventions in a unitary analysis and ranks the
3 interventions accordingly. This approach provides estimates of treatment
4 differences and uses the heterogeneities and inconsistencies found in the
5 tests to evaluate the uncertainties in the resultant estimates. Therefore,
6 this approach is particularly useful in situations involving many different
7 intervention measures.³⁶

8 **Objectives**

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

11 **METHODS**

12 **Study design**

13 This protocol follows the Preferred Reporting Items for Systematic
14 Reviews and Meta-Analyses Protocols, see Supplementary file 1.³⁷

15 **Criteria for the included studies**

16 **Types of studies**

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

22 **Types of participants**

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

4 **Types of interventions**

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

11 **Types of outcome measures**

12 **Primary outcomes**

13 The primary outcomes will include pain and function. If data from more
 14 than one pain or function scale are provided in a single trial, we will
 15 follow the method described in previous studies³⁸⁻³⁹ and extract data
 16 according to the hierarchy. The detailed scale hierarchy is presented in

17 **Table 1.**

Table 1 Hierarchy of osteoarthritis pain and function measurement scales³⁸⁻³⁹

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.

1

2 **Secondary outcomes**

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

5 **Data sources and search strategy**

6 **Electronic searches**

7 We will search the Medical Literature Analysis and Retrieval System
8 Online (MEDLINE) and Excerpta Medica database (EMBASE) databases
9 via the Ovid platform, the Cochrane Central Register of Controlled Trials
10 (CENTRAL) database via the Cochrane Library, and the Cumulative
11 Index to Nursing and Allied Health Literature (CINAHL) database via
12 EBSCO. We will also search the Web of Science and PsycINFO
13 databases. All databases will be searched from implementation to January

1 5, 2018 using a previously reported search strategy.^{10,29,31} For the
2 strategies that will be used in this review, see **Supplementary file 2**.

3 **Searching other resources**

4 International registries of published and unpublished articles and the
5 websites of regulatory agencies will be searched in our review. These
6 sources include the following: the World Health Organization (WHO)
7 International Clinical Trials Registry Platform, clinicaltrials.gov, the
8 University hospital Medical Information Network (UMIN)-Clinical Trials
9 Registry, the American College of Rheumatology (ACR), the European
10 League Against Rheumatism (EULAR), and U.S. Food and Drug
11 Administration (FDA) reports. No language limitations will be applied.

12 **Study selection**

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

19 **Data extraction and management**

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

24 -Patient characteristics (average age, gender, duration of symptoms, and
25 the type of joint affected);

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3 1 -Details of the intervention, including the route of administration, dosage
4 (different doses of the same drug will be divided into different nodes),
5 2
6 3 and frequency of the drug therapies and the treatment duration;
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9 4 -Types of measures used and pain- or function-related outcomes;
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12 5 -Type of adverse effects related to the outcome;
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15 6 -Outcome data for each endpoint of interest;
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18 7 -Duration of the follow up;
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20 8 -Trial design (including eligibility criteria of patients);
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23 9 -Trial size;
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26 10 -Publication status; and
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29 11 -The type and source of financial support.
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31 We will use the results from intention-to-treat analyses whenever
32 possible.⁴⁰ If we cannot calculate the effect size, we will contact the study
33 authors for additional data. Research from non-English language journals
34 will be electronically translated before assessment.
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40 **Assessment of the risk of bias in the included studies**

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42 17 Two review authors (ML and LY) will independently use the risk of bias
43 assessment tools generated by the Cochrane Collaboration.⁴¹
44 18 Disagreements will be resolved by negotiation. We will systematically
45 19 evaluate bias across six domains⁴² as illustrated in **Table 2**. All included
46 20 trials will be classified into the following categories: low risk, high risk,
47 21 and unclear.⁴¹
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54 **Table 2** Assessment of the risk of bias in the six domains⁴³

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3 1 Was there adequate sequence generation (selection bias)?
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6 2 Was allocation adequately concealed (selection bias)?
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11 3 Was knowledge of the allocated interventions adequately prevented
12 during the study (detection bias)?
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18 4 Were incomplete outcome data adequately addressed (attrition bias)?
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23 5 Are reported of the study free of selective reporting (reporting bias)?
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28 6 Was the study apparently free of other problems that could put it at a
29 risk of bias?
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34 2 **Data synthesis and analysis**

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37 3 **Measures of treatment effects**

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39 4 **Relative treatment effects**

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43 5 We will estimate continuous variables using the standardised mean
44 difference (SMD) with 95% credible intervals (CrIs). For categorical
45 6 outcomes, odds ratios (ORs) with 95% CrIs will be calculated for the
46 7 analyses. In the presence of minimally informative priors, CrIs can be
47 8 understood similarly to confidence interval (CIs), and at the conventional
48 9 statistical significance level, a two-sided $p < 0.05$ can be assumed if the 95%
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1 CrIs do not include 0.⁴³ If standard deviations (SDs) are not provided, we
2 will calculate them from the standard errors, CIs, or p-values using a
3 method described in previous studies.^{39,44} If some necessary data are not
4 available, we will use approximations as previously described.³⁵ To
5 visually explain the pooled effects, we will transform the effect sizes into
6 differences on a 10-cm visual analogue scale (VAS) based on a median
7 pooled SD of 2.5 cm, as found in large-scale OA trials that have used 10-
8 cm VASs to assess pain.⁴⁴ SMDs of -0.20 correspond to approximate
9 differences in pain scores between the experimental and control groups of
10 0.5 on a 10-cm VAS, -0.50 of 1.25 on a 10-cm VAS, and -0.80 of 2 on a
11 10-cm VAS.⁴⁴⁻⁴⁵ Additionally, we will compare the effects with a pre-
12 specified minimal clinically important difference based on the median
13 pooled SD of 0.37 units, which has been utilised in recent studies of
14 patients with OA and corresponds to 0.9 cm on a 10-cm VAS.⁴⁶⁻⁴⁹ We
15 will also transform the SMDs for function to a Western Ontario and
16 McMaster Universities Osteoarthritis Index (WOMAC) score based on a
17 median pooled SD of 2.1 units as observed in large-scale OA trials.⁵⁰⁻⁵¹

18 **Relative treatment ranking**

19 Each intervention and each outcome will be systematically evaluated and
20 ranked. We will determine a treatment hierarchy using the surface under
21 the cumulative ranking curve (SUCRA) and the mean ranks.⁵²

22 **Data analysis**

1 First, we will conduct paired meta-analyses by synthesising the studies
2 that compare interventions head-to-head using a random-effects model.⁵³

3 Then, we will use a Bayesian network meta-analysis to compare the
4 different classes of oral or transdermal opioid treatments based on the
5 median of the posterior distribution.⁵⁴⁻⁵⁵ A Bayesian random-effects
6 model will be used because this model completely retains the within-trial
7 randomised treatment comparisons of each study while combining all
8 available comparisons between treatments and accounting for multiple
9 comparisons within a trial in cases with more than two treatment arms.⁵⁵⁻

10 ⁵⁶ The between-trial variance of the treatment effects (τ^2) will be
11 estimated from the posterior distribution. Pooled estimates will be
12 performed with Markov chain Monte Carlo methods. Convergence of the
13 Markov chains will be considered to be achieved if the Gelman-Rubin
14 diagnostic plots indicate that the widths of the pooled runs and individual
15 runs stabilise around the same value and their ratio is approximately
16 one.⁵⁷

17 The analyses will be performed with Stata 14.0 software (StataCorp,
18 College Station, TX, USA) and WinBUGS (MRC Biostatistics Unit 2007,
19 Version 1.4.3 Cambridge, UK).

20 **Assessment of statistical heterogeneity**

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

6 **Assessment of statistical inconsistency**

7 We will evaluate the inconsistencies locally in the network using the
8 loop-specific approach.⁵⁹ The design-by-treatment interaction model will
9 also be used to calculate the consistency throughout the entire network.⁶⁰

10 **Subgroup analyses**

11 To explore the robustness of the results, we will include the
12 characteristics of the trials as covariates in the Bayesian meta-analysis to
13 assess the primary outcomes based on the clinical characteristics, risk of
14 bias and trial size. A random-effects meta-regression model⁶¹ will be used
15 to determine whether the treatment effects are affected by the following
16 factors: (1) treatment duration (short-term ≤ 1 month and long-term > 1
17 month); (2) trial size (small-scale: allocated participants ≤ 200 , and large-
18 scale: allocated participants > 200); (3) high methodological quality as
19 defined by adequate concealment of the allocation (adequate versus
20 inadequate or unclear); (4) adequate blinding of the patients (adequate
21 versus inadequate or unclear); (5) intention-to-treat analysis (yes versus
22 no or unclear); (6) source of funding (independent of the pharmaceutical
23 industry or unclear versus no); (7) type of OA (hip only versus knee only
24 versus mixed); (8) type of opioid (oral versus transdermal); and (9) type
25 of trial (published versus unpublished).

26 **Sensitivity analyses**

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

4 **Other analyses**

5 The Grading of Recommendations, Assessment, Development and
6 Evaluations (GRADE) framework, which characterises the quality of
7 evidence based on the study limitations, publication bias, indirectness,
8 imprecision and inconsistency in the primary outcomes, will be used to
9 evaluate the quality of evidence in each network.⁶² Additionally, a
10 comparison-adjusted funnel plot will be drawn to detect any major
11 publication bias in the Bayesian network meta-analysis.⁶³

12 **Ethics and dissemination**

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

20 **Patient and public involvement**

21 No patients or the public participated in the study.

23 **DISCUSSION**

1 This systematic review and Bayesian network meta-analysis will provide
2 an assessment of opioid therapies in patients with knee or hip OA.
3 Currently, NSAIDs remain the first-line drugs for OA treatment. Whether
4 opioids can be used as a routine treatment for knee or hip OA is
5 controversial. One review compared the efficacy of NSAIDs and opioids
6 in the treatment of knee OA and found that the efficacy is essentially the
7 same.⁶⁴ To date, no systematic review on opioids for OA has carried out a
8 network meta-analysis to compare efficacy and safety across different
9 opioid analgesics. Our results will rank the efficacy and safety of opioids
10 in the treatment of OA, which has not been included in previous studies.
11 The conclusions of this study may be beneficial for patients with knee or
12 hip OA, clinicians and policy makers. We will perform subgroup analysis
13 to explore whether our findings are consistent across subgroups and
14 explore the sources of heterogeneity. The proposed systematic review and
15 network meta-analysis may have some potential limitations. The different
16 routes of administration (oral or transdermal), durations and frequencies
17 may cause considerable heterogeneity. Another limitation may be
18 differences in the quality of the included studies, which will limit the
19 ability of this work to reach high-confidence conclusions.

20
21 **Collaborators:** None

1
2
3 1 **Contributors:** JW conceived the review and wrote the first draft of the
4 protocol. WLG and ZSY revised the protocol. YW and HZ are
5 responsible for the development of the search strategy and data extraction.
6
7 ML and LY will be responsible for assessing bias and data synthesis and
8 analysis. All the authors have approved the publication of the protocol.
9

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11
12
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15
16

17
18 8 **Competing interests:** None declared.
19

20
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23
24

25 REFERENCES

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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	<i>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</i>
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 (see 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.

1
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3 18.prospective studies.sh.
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5 19.(control\$ or prospectiv\$ or volunteer\$).ab,ti.
6
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8 **Search terms for Osteoarthritis**
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10 20.exp osteoarthritis/
11

12
13 21.osteoarthriti\$.ab,sh,ti.
14

15 22.osteoarthro\$.ab,sh,ti.
16

17 23.gonarthriti\$.ab,sh,ti.
18

19 24.gonarthro\$.ab,sh,ti.
20

21 25.coxarthriti\$.ab,sh,ti.
22

23 26.coxarthro\$.ab,sh,ti.
24

25 27.arthros\$.ab,ti.
26

27 28.arthrot\$.ab,ti.
28

29 29.((knee\$ or hip\$ or joint\$) adj3 (pain\$ or ach\$ or discomfort\$)).ab,ti.
30

31 30.((knee\$ or hip\$ or joint\$) adj3 stiff\$).ab,ti.
32

33 **Search terms for Opioids**
34

35 31.exp Analgesics, Opioid/
36

37 32.exp Narcotics/
38

39 33.acetyldihydrocodeine.tw.
40

41 34.alfentanil.tw.
42

43 35.allylprodine.tw.
44

45 36.alphamethylfentanyl.tw.
46

47 37.alphaprodine.tw.
48

49 38.benzylmorphine.tw.
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3 39.betaprodine.tw.
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5
6 40.bezitriamide.tw.
7

8 41.buprenorphine.tw.
9

10 42.butorphanol.tw.
11

12
13 43.bremazocine.tw.
14

15
16 44.carfentan\$.tw.
17

18 45.codeine.tw.
19

20
21 46.contin.tw.
22

23 47.dextromoramide.tw.
24

25
26 48.dextropropoxyphene.tw.
27

28 49.dezocine.tw.
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30
31 50.diacetylmorphine.tw.
32

33 51.diamorphine.tw.
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35
36 52.dihydrocodeine.tw.
37

38 53.dihydromorphine.tw.
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40 54.dihydromorphone.tw.
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43 55.diphenoxylate.tw.
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46 56.dipipanone.tw.
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48 57.enadoline.tw.
49

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51 58.ethylketazocine.tw.
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53 59.ethylmorphine.tw.
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56 60.etonitazene.tw.
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59 61.etorphine.tw.
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3 62.fentanyl.tw.
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6 63.heroin.tw.
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9 64.hydrocodone.tw.
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12 65.hydromorphin\$.tw.
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15 66.hydromorphone.tw.
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18 67.ketazocine.tw.
19

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21 68.ketobemidone.tw.
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24 69.lefetamine.tw.
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26
27 70.levomethadon.tw.
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30 71.levomethadyl.tw.
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33 72.levomethorphan\$.tw.
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36 73.levorphanol.tw.
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39 74.loperamide.tw.
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42 75.meperidine.tw.
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45 76.meptazinol.tw.
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48 77.methadone.tw.
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51 78.methadyl.tw.
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54 79.methylmorphine.tw.
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57 80.morphin\$.tw.
58

59
60 81.nalbuphine.tw.

82.narcotic\$.tw.

83.nicocodeine.tw.

84.nicomorphine.tw.

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3 85.normorphine.tw.
4

5 86.noscapin\$.tw.
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8 87.ohmefentanyl.tw.
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10 88.opiate\$.tw.
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13 89.opioid\$.tw.
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15 90.opium.tw.
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18 91.oripavine.tw.
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20 92.oxycodone.tw.
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23 93.oxycontin.tw.
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25 94.oxymorphone.tw.
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28 95.papaveretum.tw.
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30 96.papaverin.tw.
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33 97.pentazocine.tw.
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35 98.percocet.tw.
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38 99.peronine.tw.
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40 100. pethidine.tw.
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43 101.phenazocine.tw.
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45 102.phencyclidine.tw.
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48 103.pholcodine.tw.
49

50 104.piritramid\$.tw.
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52
53 105.prodine.tw.
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55 106.promedol.tw.
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58 107.propoxyphene.tw.
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1
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3 108.remifentanil.tw.
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5 109.sufentanil.tw.
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8 110.tapentadol.tw.
9

10 111.thebaine.tw.
11
12

13 112.tilidine.tw.
14

15 113.tramadol.sh,tw.
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18 114.ultracet.sh,tw.
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21 **Combining terms**
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23 115.31 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
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25 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
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28 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
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30 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
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33 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
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35 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or
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40 116.20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
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43 117.1 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
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46 or 17 or 18 or 19
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48 118.115 and 116 and 117
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50 119.animal/
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53 120.animal/ and human/
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56 121.119 not 120
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59 122.118 not 121
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3 123.remove duplicates from 122
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6 **Ovid EMBASE**

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8 **Search terms for design**

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10
11 1.randomized controlled trial.sh.
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13
14 2.randomization.sh.
15

16
17 3.double blind procedure.sh.
18

19
20 4.single blind procedure.sh.
21

22
23 5.exp clinical trials/
24

25
26 6.(clin\$ adj25 trial\$.ab,ti.
27

28
29 7.((singl\$ or doubl\$ or treb1\$ or tripl\$) adj25 (blind\$ or mask\$)).ab,ti.
30

31
32 8.placebo.sh.
33

34
35 9.placebo\$.ab,ti.
36

37
38 10.random\$.ab,ti.
39

40
41 11.methodology.sh.
42

43
44 12.comparative study.sh.
45

46
47 13.exp evaluation studies/
48

49
50 14.follow up.sh.
51

52
53 15.prospective study.sh.
54

55
56 16.(control\$ or prospectiv\$ or volunteer\$).ab,ti.
57

58 **Search terms for Osteoarthritis**

59

60
61 17.exp osteoarthritis/
62

63
64 18.osteoarthriti\$.ab,sh,ti.
65

66
67 19.osteoarthro\$.ab,sh,ti.
68

1
2
3 20.gonarthriti\$.ab,sh,ti.
4

5 21.gonarthro\$.ab,sh,ti.
6

7 22.coxarthriti\$.ab,sh,ti.
8

9 23.coxarthro\$.ab,sh,ti.
10

11 24.arthros\$.ab,ti.
12

13 25.arthrot\$.ab,ti.
14

15 26.((knee\$ or hip\$ or joint\$) adj3 (pain\$ or ach\$ or discomfort\$)).ab,ti.
16

17 27.((knee\$ or hip\$ or joint\$) adj3 stiff\$).ab,ti.
18

19
20
21
22
23 **Search terms for Opioids**
24

25 28.exp Analgesics, Opioid/
26

27 29.exp Narcotic Analgesic Agent/
28

29 30.acetyldihydrocodeine.tw.
30

31 31.alfentanil.tw.
32

33 32.allylprodine.tw.
34

35 33.alphamethylfentanyl.tw.
36

37 34.alphaprodine.tw.
38

39 35.benzylmorphine.tw.
40

41 36.betaprodine.tw.
42

43 37.bezitriamide.tw.
44

45 38.buprenorphine.tw.
46

47 39.butorphanol.tw.
48

49 40.bremazocine.tw.
50

51 41.carfentan\$.tw.
52
53
54
55
56
57
58
59
60

1
2
3 42.codeine.tw.
4

5
6 43.contin.tw.
7

8
9 44.dextromoramide.tw.
10

11 45.dextropropoxyphene.tw.
12

13
14 46.dezocine.tw.
15

16 47.diacetylmorphine.tw.
17

18
19 48.diamorphine.tw.
20

21 49.dihydrocodeine.tw.
22

23
24 50.dihydromorphine.tw.
25

26 51.dihydromorphone.tw.
27

28
29 52.diphenoxylate.tw.
30

31 53.dipipanone.tw.
32

33
34 54.enadoline.tw.
35

36 55.ethylketazocine.tw.
37

38
39 56.ethylmorphine.tw.
40

41 57.etonitazene.tw.
42

43
44 58.etorphine.tw.
45

46 59.fentanyl.tw.
47

48
49 60.heroin.tw.
50

51 61.hydrocodone.tw.
52

53
54 62.hydromorphin\$.tw.
55

56
57 63.hydromorphone.tw.
58

59 64.ketazocine.tw.
60

1
2
3 65.ketobemidone.tw.
4

5 66.lefetamine.tw.
6

7
8 67.levomethadon.tw.
9

10
11 68.levomethadyl.tw.
12

13 69.levomethorphan\$.tw.
14

15
16 70.levorphanol.tw.
17

18 71.loperamide.tw.
19

20
21 72.meperidine.tw.
22

23 73.meptazinol.tw.
24

25
26 74.methadone.tw.
27

28
29 75.methadyl.tw.
30

31 76.methylmorphine.tw.
32

33
34 77.morphin\$.tw.
35

36 78.nalbuphine.tw.
37

38
39 79.narcotic\$.tw.
40

41 80.nicocodeine.tw.
42

43
44 81.nicomorphine.tw.
45

46 82.normorphine.tw.
47

48
49 83.noscapin\$.tw.
50

51 84.ohmefentanyl.tw.
52

53
54 85.opiate\$.tw.
55

56
57 86.opioid\$.tw.
58

59 87.opium.tw.
60

- 1
- 2
- 3 88.oripavine.tw.
- 4
- 5 89.oxycodone.tw.
- 6
- 7
- 8 90.oxycontin.tw.
- 9
- 10
- 11 91.oxymorphone.tw.
- 12
- 13 92.papaveretum.tw.
- 14
- 15
- 16 93.papaverin.tw.
- 17
- 18 94.pentazocine.tw.
- 19
- 20
- 21 95.percocet.tw.
- 22
- 23
- 24 96.peronine.tw.
- 25
- 26 97.pethidine.tw.
- 27
- 28
- 29 98.phenazocine.tw.
- 30
- 31 99.phencyclidine.tw.
- 32
- 33
- 34 100. pholcodine.tw.
- 35
- 36 101.piritramid\$.tw.
- 37
- 38
- 39 102.prodine.tw.
- 40
- 41
- 42 103.promedol.tw.
- 43
- 44 104.propoxyphene.tw.
- 45
- 46
- 47 105.remifentanil.tw.
- 48
- 49 106.sufentanil.tw.
- 50
- 51
- 52 107.tapentadol.tw.
- 53
- 54 108.thebaine.tw.
- 55
- 56
- 57 109.tilidine.tw.
- 58
- 59 110.tramadol.sh,tw.
- 60

1
2
3 111.ultracet.sh,tw.
4
5

6 **Combining terms**
7

8 112 .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
9
10 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
11
12 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
13
14 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
15
16 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
17
18 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111
19
20

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

24 114.1 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
25
26

27 115.112 and 113 and 114
28
29

30 116.animal/
31
32

33 117.animal/ and human/
34
35

36 118.116 not 117
37
38

39 119.115 not 118
40
41

42 120.remove duplicates from 119
43
44
45

46 **CINAHL through EBSCOhost**
47
48

49 **Search terms for design**
50
51

52 1. (MH "Clinical Trials+")
53
54

55 2. (MH "Random Assignment")
56
57

58 3. (MH "Double-Blind Studies") or (MH"Single-Blind Studies")
59
60

60 4. TX (clin\$ n25 trial\$)

- 1
- 2
- 3 5. TX (sing\$ n25 blind\$)
- 4
- 5 6. TX (sing\$ n25 mask\$)
- 6
- 7
- 8 7. TX (doubl\$ n25 blind\$)
- 9
- 10 8. TX (doubl\$ n25 mask\$)
- 11
- 12 9. TX (trebl\$ n25 blind\$)
- 13
- 14 10. TX (trebl\$ n25 mask\$)
- 15
- 16 11. TX (tripl\$ n25 blind\$)
- 17
- 18 12. TX (tripl\$ n25 mask\$)
- 19
- 20 13. (MH “Placebos”)
- 21
- 22 14. TX placebo\$
- 23
- 24 15. TX random\$
- 25
- 26 16. (MH “Study Design+”)
- 27
- 28 17. (MH “Comparative Studies”)
- 29
- 30 18. (MH “Evaluation Research”)
- 31
- 32 19. (MH “Prospective Studies+”)
- 33
- 34 20. TX (control\$ or prospectiv\$ or volunteer\$)
- 35
- 36 21. S1 or S2 or (...) or S20
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
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- 60

Search terms for Osteoarthritis

22. osteoarthriti\$
23. (MH “Osteoarthritis”)
24. TX osteoarthro\$
25. TX gonarthriti\$
26. TX gonarthro\$

- 1
- 2
- 3 27. TX coxarthriti\$
- 4
- 5 28. TX coxarthro\$
- 6
- 7
- 8 29. TX arthros\$
- 9
- 10 30. TX arthrot\$
- 11
- 12
- 13 31. TX knee\$ n3 pain\$
- 14
- 15 32. TX hip\$ n3 pain\$
- 16
- 17 33. TX joint\$ n3 pain\$
- 18
- 19 34. TX knee\$ n3 ach\$
- 20
- 21 35. TX hip\$ n3 ach\$
- 22
- 23 36. TX joint\$ n3 ach\$
- 24
- 25 37. TX knee\$ n3 discomfort\$
- 26
- 27 38. TX hip\$ n3 discomfort\$
- 28
- 29 39. TX joint\$ n3 discomfort\$
- 30
- 31 40. TX knee\$ n3 stiff\$
- 32
- 33 41. TX hip\$ n3 stiff\$
- 34
- 35 42. TX joint\$ n3 stiff\$
- 36
- 37 43. S22 or S23 or S24(...)or S42
- 38
- 39 **Search terms for Opioids**
- 40
- 41 44. MH “ Analgesics, Opioid”
- 42
- 43 45. MH “Narcotics”
- 44
- 45 46. TX acetyldihydrocodeine
- 46
- 47 47. TX alfentanil
- 48
- 49 48. TX allylprodine
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- 1
- 2
- 3 49. TX alphamethylfentanyl
- 4
- 5
- 6 50. TX alphaprodine
- 7
- 8 51. TX benzylmorphine
- 9
- 10
- 11 52. TX betaprodine
- 12
- 13 53. TX bezitriamide
- 14
- 15
- 16 54. TX buprenorphine
- 17
- 18 55. TX butorphanol
- 19
- 20
- 21 56. TX bremazocine
- 22
- 23
- 24 57. TX carfentan\$
- 25
- 26 58. TX codeine
- 27
- 28 58. TX contin
- 29
- 30
- 31 60. TX dextromoramide
- 32
- 33
- 34 61. TX dextropropoxyphene
- 35
- 36 62. TX dezocine
- 37
- 38
- 39 63. TX diacetylmorphine
- 40
- 41 64. TX diamorphine
- 42
- 43 65. TX dihydrocodeine
- 44
- 45 66. TX dihydromorphine
- 46
- 47 67. TX dihydromorphone
- 48
- 49 68. TX diphenoxylate
- 50
- 51 69. TX dipipanone
- 52
- 53 70. TX enadoline
- 54
- 55 71. TX ethylketazocine
- 56
- 57
- 58
- 59
- 60

1
2
3 72. TX ethylmorphine
4

5 73. TX etonitazene
6

7
8 74. TX etorphine
9

10
11 75. TX fentanyl
12

13
14 76. TX heroin
15

16 77. TX hydrocodone
17

18 78. TX hydromorphin\$
19

20
21 79. TX hydromorphone
22

23 80. TX ketazocine
24

25
26 81. TX ketobemidone
27

28
29 82. TX lefetamine
30

31 83. TX levomethadon
32

33
34 84. TX levomethadyl
35

36 85. TX levomethorphan\$
37

38
39 86. TX levorphanol
40

41 87. TX loperamide
42

43
44 88. TX meperidine
45

46 89. TX meptazinol
47

48
49 90. TX methadone
50

51 91. TX methadyl
52

53
54 92. TX methylmorphine
55

56
57 93. TX morphin\$
58

59 94. TX nalbuphine
60

- 1
- 2
- 3 95. TX narcotic\$
- 4
- 5 96. TX nicocodeine
- 6
- 7
- 8 97. TX nicomorphine
- 9
- 10
- 11 98. TX normorphine
- 12
- 13 99. TX noscapin\$
- 14
- 15
- 16 100. TX ohmefentanyl
- 17
- 18 101. TX opiate\$
- 19
- 20
- 21 102. TX opioid\$
- 22
- 23
- 24 103. TX opium
- 25
- 26 104. TX oripavine
- 27
- 28
- 29 105. TX oxycodone
- 30
- 31 106. TX oxycontin
- 32
- 33
- 34 107. TX oxymorphone
- 35
- 36 108. TX papaveretum
- 37
- 38
- 39 109. TX papaverin
- 40
- 41
- 42 110. TX pentazocine
- 43
- 44 111. TX percocet
- 45
- 46 112. TX peronine
- 47
- 48
- 49 113. TX pethidine
- 50
- 51
- 52 114. TX phenazocine
- 53
- 54 115. TX phencyclidine
- 55
- 56
- 57 116. TX pholcodine
- 58
- 59 117. TX piritramid\$
- 60

1
2
3 118. TX prodine
4

5 119. TX promedol
6

7 120. TX propoxyphene
8
9

10 121. TX remifentanil
11

12 122. TX sufentanil
13

14 123. TX tapentadol
15

16 124. TX thebaine
17

18 125. TX tilidine
19

20 126. TX tramadol
21

22 127. TX ultracet
23

24 128. S44 or S45 or(...)S127
25
26

27 **Combining terms**

28 129. S21 and S43 and S128
29
30

31 **CENTRAL**

32 **Search terms for Osteoarthritis**

33 #1. MeSH descriptor Osteoarthritis explode all trees
34

35 #2. (osteoarthritis* OR osteoarthro* OR gonarthriti* OR gonarthro* OR coxarthriti*
36 OR coxarthro* OR arthros* OR arthrot* OR ((knee* OR hip* OR joint*) near/3
37 (pain* OR ach* OR discomfort*)) OR ((knee* OR hip* OR joint*) near/3 stiff*)) in
38 Trials
39

40 **Search terms for Opioids**

41 #3. MeSH descriptor Analgesics, Opioid explode all trees
42

43 #4. MeSH descriptor Narcotics explode all trees
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 #5. (acetyldihydrocodeine OR alfentanil OR allylprodine OR alphamethylfentanyl OR
4 alphaprodine OR benzylmorphine OR betaprodine OR bezitriamide OR
5 buprenorphine OR butorphanol OR bremazocine OR carfentan* OR codeine OR
6 contin OR dextromoramide OR dextropropoxyphene OR dezocine OR
7 diacetylmorphine OR diamorphine OR dihydrocodeine OR dihydromorphine OR
8 dihydromorphone OR diphenoxylate OR dipipanone OR enadoline OR
9 ethylketazocine OR ethylmorphine OR etonitazene OR etorphine OR fentanyl OR
10 heroin OR hydrocodone OR hydromorphin* OR hydromorphone OR ketazocine OR
11 ketobemidone OR lefetamine OR levomethadon OR levomethadyl OR
12 levomethorphan* OR levorphanol OR loperamide OR meperidine OR meptazinol OR
13 methadone OR methadyl OR methylmorphine OR morphin* OR nalbuphine OR
14 narcotic* OR nicocodeine OR nicomorphine OR normorphine OR noscapin* OR
15 ohmefentanyl OR opiate* OR opioid* OR opium OR oripavine OR oxycodone OR
16 oxycontin OR oxymorphone OR papaveretum OR papaverin OR pentazocine OR
17 percocet OR peronine OR pethidine OR phenazocine OR phencyclidine OR
18 pholcodine OR piritramid* OR prodine OR promedol OR propoxyphene OR
19 remifentanil OR sufentanil OR tapentadol OR thebaine OR tilidine OR tramadol OR
20 ultracet) in Trials
21
22
23
24
25
26
27
28
29
30
31
32
33

34 35 **Combining terms**

36
37 #6. (#1 OR #2)

38
39 #7. (#3 OR #4 OR #5)

40
41
42 #8. (#6 AND #7) in Clinical Trials
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60