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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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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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42  
43 **Word count:** 2972 (excluding title page, references, figures)  
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11 published and unpublished research in international registries and  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.  
50

### 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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13 ▪ Subgroup and sensitivity analyses will provide implications for  
14 clinically relevant questions for later research directions.  
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18 ▪ This method synthesizes the data comprehensively and provides a  
19 clinically useful summary that can guide the development of a clinical  
20 prescription system.  
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## 24 25 **Introduction**

### 26 27 **Description of the condition**

28  
29 Osteoarthritis (OA) is a degenerative disease that is also known as  
30 degenerative arthritis or senile arthritis.<sup>1</sup> Increased obesity, age, trauma to  
31 joint areas, excessive manual labour, and decreased muscle strength and  
32 joint stability are important risk factors for OA.<sup>2-5</sup> The main clinical  
33 manifestations of OA are chronic pain, joint instability, stiffness, joint  
34 deformity and reduced imaging of the joint space, and these  
35 manifestations eventually lead to progressive disability and reduce the  
36 patient's quality of life.<sup>1,6</sup> OA, particularly OA of the knee and hip joints,  
37 is one of the leading causes of disability in the world among the elderly,  
38 and it is estimated that the global age-standardized incidence rates are 3.8%  
39 in the knee and 0.85% in the hip.<sup>7-8</sup> The impact of this disease is  
40 widespread and serious, and there are currently no effective interventions  
41 to prevent the development of OA.<sup>1</sup>  
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3 Cartilage destruction, subchondral bone remodelling and synovitis are the  
4 major pathological features of OA. Changes in the internal environment  
5 of various tissue structures within the joint cavity are the main causes of  
6 these pathological features and include anabolic and catabolic imbalance,  
7 especially an increase in articular cartilage catabolism leading to a  
8 decrease in the regeneration ability of cartilage.<sup>9-10</sup> Previous studies have  
9 shown that many factors may interfere with chondrocyte homeostasis,  
10 including abnormal mechanical loading of proinflammatory mediators  
11 and oxidative stress.<sup>11-12</sup> These mediators can cause inflammation, which,  
12 in addition to promoting serious chondrocyte apoptosis and articular  
13 cartilage damage, can also stimulate the sensory nerves in the synovium  
14 and surrounding tissues. This nerve stimulation leads to the peripheral  
15 and central sensitization of the adjacent tissues, which further leads to  
16 chronic pain.<sup>13</sup>

### 30 **Description of the intervention**

31  
32  
33 Pain is the most relevant symptom of OA; as the degree of pain increases,  
34 patient mobility is decreased and the degree of disability increases.<sup>14-15</sup> A  
35 previous study showed that because of pain and functional limitations, the  
36 quality of life of patients with OA is even worse than those of patients  
37 with gastrointestinal or chronic respiratory system disorders.<sup>16</sup>

38  
39  
40 Therefore, alleviating pain, preventing muscle atrophy, and reducing joint  
41 deformity, stiffness and other complications are the main therapeutic  
42 targets of OA.<sup>17-18</sup> Currently, the treatment modalities for OA include  
43 invasive surgery, non-drug therapy and drug therapy.

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45  
46 Invasive surgery includes intra-articular injections and surgery. Intra-  
47 articular injections of agents such as hyaluronic acid (HA),  
48 corticosteroids, ozone, and platelet-rich plasma (PRP) are used for the  
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3 treatment of OA, and these treatments have been proven to be effective.<sup>19-</sup>  
4  
5 <sup>22</sup> 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.<sup>23-24</sup>  
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.<sup>25</sup> 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.<sup>26-28</sup>

26  
27 Drugs for the treatment of OA pain primarily include non-steroidal anti-  
28  
29 inflammatory drugs (NSAIDs) and opioid drugs.<sup>29</sup> 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.<sup>30-31</sup> 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.<sup>32</sup>

### 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.<sup>10,29</sup> 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.<sup>33</sup>  
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## 23 **Objectives**

24  
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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31

## 32 **METHODS**

### 33 **Criteria for the included studies**

#### 34 **Types of studies**

35  
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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.  
17  
18  
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### 23 24 **Types of outcome measures**

#### 25 26 **Primary outcomes**

27  
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 studies<sup>34-35</sup> and extract data  
31 according to the hierarchy. The detailed scale hierarchy is presented in  
32 **Table 1.**  
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#### 39 40 **Secondary outcomes**

41  
42 To assess the safety of opioids, we will extract the proportion of  
43 participants who experienced adverse events. We will define adverse  
44 effects as nausea, constipation, drug addiction or dependence, cessation  
45 of drug use, extended length of hospitalization, hospitalization, life-  
46 threatening complications, or death.<sup>29</sup>  
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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.<sup>10,29</sup> For the strategies that will be used in this review, see  
9 **Appendix 1.**

### 16 17 **Searching other resources**

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

### 32 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.

### 46 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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6  
7 -Patient characteristics (average age, gender, duration of symptoms, and  
8 the type of joint affected);

9  
10  
11  
12 -Details of the intervention, including the route of administration, dosage,  
13 and frequency of the drug therapies and the treatment duration;

14  
15  
16 -Types of measures used and pain- or function-related outcomes;

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18  
19 -Type of adverse effects related to the outcome;

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21  
22 -Outcome data for each endpoint of interest;

23  
24  
25 -Duration of the follow up;

26  
27  
28 -Trial design (including eligibility criteria of patients);

29  
30  
31 -Trial size;

32  
33  
34 -Publication status; and

35  
36  
37 -The type and source of financial support.

38  
39 We will use the results from the intention-to-treat analyses whenever  
40 possible.<sup>36</sup> 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.<sup>37</sup>  
51 Disagreements will be resolved by negotiation. We will systematically  
52 evaluate bias across six domains<sup>38</sup> 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.<sup>37</sup>  
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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.<sup>39</sup> 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.<sup>35,40</sup> If some necessary data are not  
25 available, we will use approximations as previously described.<sup>35</sup> 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.<sup>40</sup> 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.<sup>40-41</sup> 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.<sup>42-45</sup> 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.<sup>46-47</sup>

### 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.<sup>48</sup>

### 26 **Data analysis**

27  
28  
29  
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.<sup>49</sup>

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.<sup>50-51</sup> A Bayesian random-effects  
39  
40 model will be used because this model completely retains the within-trial  
41  
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.<sup>51-</sup>

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<sup>52</sup> The between-trial variance of the treatment effects ( $\tau^2$ ) 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  
4  
5 Markov chains will be considered to be achieved if the Gelman-Rubin  
6  
7 diagnostic plots indicate that the widths of the pooled runs and individual  
8  
9 runs stabilize around the same value and their ratio is approximately  
10  
11 one.<sup>53</sup>  
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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).  
20  
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### 24 25 **Assessment of statistical heterogeneity**

26  
27 We will use  $I^2$  statistics and p-values to assess the statistical heterogeneity  
28  
29 of each pairwise comparison.<sup>54</sup> In the Bayesian meta-analysis, we will  
30  
31 calculate the heterogeneity of the treatment effects estimated from the  
32  
33 posterior median between-trial variance ( $\tau^2$ ). Global heterogeneity will be  
34  
35 assessed using the  $I^2$  statistic.  
36  
37

### 38 39 **Assessment of statistical inconsistency**

40  
41 We will evaluate the inconsistencies locally in the network using the  
42  
43 loop-specific approach.<sup>55</sup> The design-by-treatment interaction model will  
44  
45 also be used to calculate the consistency throughout the entire network.<sup>56</sup>  
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### 48 49 **Subgroup analyses**

50  
51 To explore the robustness of the results, we will include the  
52  
53 characteristics of the trials as covariates in the Bayesian meta-analysis to  
54  
55 assess the primary outcomes based on the clinical characteristics, risk of  
56  
57 bias and trial size. A random-effects meta-regression model<sup>57</sup> 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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26  
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**

35  
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.<sup>58</sup> Additionally, a comparison-  
40 adjusted funnel plot will be drawn to detect any major publication bias in  
41 the Bayesian network meta-analysis.<sup>59</sup>  
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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.  
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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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## 16 17 18 **DISCUSSION**

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21 This systematic review and Bayesian network meta-analysis will provide  
22 an assessment of opioid therapies in patients with knee or hip OA.  
23  
24 Whether opioids can be used as a routine treatment for knee or hip OA is  
25 controversial. Our results will rank the efficacy and safety of opioids in  
26 the treatment of OA, which has not been included in previous studies.  
27  
28 The conclusions of this study may be beneficial for patients with knee or  
29 hip OA, clinicians and policy makers. The proposed systematic review  
30 and network meta-analysis may have some potential limitations. The  
31 different routes of administration (oral or transdermal), durations and  
32 frequencies may cause considerable heterogeneity. Another limitation  
33 may be differences in the quality of the included studies, which will limit  
34 the ability of this work to reach high-confidence conclusions.  
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53 **Collaborators:** None  
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2  
3 **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 ML and LY will be responsible for assessing bias and the data synthesis  
7 and analysis. All the authors have approved the publication of the  
8 protocol.  
9

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16 commercial or not-for-profit organization.  
17

18  
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20

21  
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23 for excellent language assistance.  
24  
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## 26 REFERENCES

- 27 1. Chen K, Yan Y, Li C, et al. Increased 15-lipoxygenase-1 expression in  
28 chondrocytes contributes to the pathogenesis of osteoarthritis. *Cell death & disease*  
29 2017; 8(10): e3109.  
30
- 31 2. Cooper C, Inskip H, Croft P, et al. Individual risk factors for hip osteoarthritis:  
32 obesity, hip injury and physical activity. *American journal of epidemiology* 1998;  
33 147(6): 516-522.  
34
- 35 3. Blagojevic M, Jinks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the  
36 knee in older adults: a systematic review and meta-analysis. *Osteoarthritis and*  
37 *cartilage* 2010; 18(1): 24-33.  
38
- 39 4. Jørgensen K T, Pedersen B V, Nielsen N M, et al. Socio-demographic factors,  
40 reproductive history and risk of osteoarthritis in a cohort of 4.6 million Danish women  
41 and men. *Osteoarthritis and cartilage* 2011; 19(10): 1176-1182.  
42
- 43 5. Dekker J, van Dijk G M, Veenhof C. Risk factors for functional decline in  
44 osteoarthritis of the hip or knee. *Current opinion in rheumatology* 2009; 21(5): 520-  
45 524.  
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2  
3 6. Guilak F. Biomechanical factors in osteoarthritis. *Best practice & research Clinical*  
4 *rheumatology* 2011; 25(6): 815-823.  
5
- 6  
7 7. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis:  
8 estimates from the global burden of disease 2010 study. *Annals of the rheumatic*  
9 *diseases* 2014: annrheumdis-2013-204763.  
10
- 11  
12 8. Holden M A, Burke D L, Runhaar J, et al. Subgrouping and targeted exercise  
13 programmes for knee and hip osteoarthritis (STEER OA): a systematic review update  
14 and individual participant data meta-analysis protocol. *BMJ open* 2017; 7(12):  
15 e018971.doi:10.1136/bmjopen-2017-018971.  
16
- 17  
18 9. Dunlop D D, Semanik P, Song J, et al. Risk factors for functional decline in older  
19 adults with arthritis. *Arthritis & Rheumatology* 2005; 52(4): 1274-1282.  
20
- 21  
22 10. Cepeda M S, Camargo F, Zea C, et al. Tramadol for osteoarthritis. *The Cochrane*  
23 *Library*, 2006, Issue 3. Art. No: CD005522. DOI:10.1002/14651858.CD005522.pub2.  
24
- 25  
26 11. Goldring M B, Otero M, Tsuchimochi K, et al. Defining the roles of inflammatory  
27 and anabolic cytokines in cartilage metabolism. *Annals of the rheumatic diseases*  
28 2008; 67(Suppl 3): iii75-iii82.  
29
- 30  
31 12. Hui W, Young DA, Rowan AD, Xu X, Cawston TE, Proctor CJ. Oxidative  
32 changes and signalling pathways are pivotal in initiating age-related changes in  
33 articular cartilage. *Ann Rheum Dis* 2016; 75: 449-458.  
34
- 35  
36 13. Kean W F, Kean R, Buchanan W W. Osteoarthritis: symptoms, signs and source  
37 of pain. *Inflammopharmacology* 2004; 12(1): 3-31.  
38
- 39  
40 14. Bjordal J M, Ljunggren A E, Klovning A, et al. Non-steroidal anti-inflammatory  
41 drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-  
42 analysis of randomised placebo controlled trials. *BMJ* 2004; 329(7478): 1317.  
43
- 44  
45 15. Dieppe P A, Lohmander L S. Pathogenesis and management of pain in  
46 osteoarthritis. *The Lancet* 2005; 365(9463): 965-973.  
47
- 48  
49 16. Reginster J Y. The prevalence and burden of arthritis. *Rheumatology* 2002;  
50 41(suppl\_1): 3-6.  
51  
52  
53  
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56  
57  
58  
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60

17. Odding E, Valkenburg H A, Algra D, et al. Associations of radiological osteoarthritis of the hip and knee with locomotor disability in the Rotterdam Study. *Annals of the rheumatic diseases* 1998; 57(4): 203-208.
18. Towheed TE, Judd MJ, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *The Cochrane Library* 2003; Issue2. DOI:10.1002/14651858.CD004257. pub2
19. Jevsevar D S, Brown G A, Jones D L, et al. The American Academy of Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the knee. *JBJS* 2013; 95(20): 1885-1886.
20. McAlindon T E, Bannuru R R, Sullivan M C, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and cartilage* 2014; 22(3): 363-388.
21. Hashemi M, Jalili P, Mennati S, Koosha A, Rohanifar R, Madadi F, et al. The effects of prolotherapy with hypertonic dextrose versus prolozone (intraarticular Ozone) in patients with knee osteoarthritis. *Anesth Pain Med* 2015; 5, e27585.
22. Cugat R, Cuscó X, Seijas R, et al. Biologic enhancement of cartilage repair: The role of platelet-rich plasma and other commercially available growth factors. *Arthroscopy* 2015; 31(4): 777-783.
23. Emkey R, Rosenthal N, Wu S C, et al. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. *The Journal of rheumatology* 2004; 31(1): 150-156.
24. Towheed T E, Hochberg M C. Health-related quality of life after total hip replacement. *Seminars in arthritis and rheumatism*. WB Saunders 1996; 26(1): 483-491.
25. Zhang W, Moskowitz R W, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis and cartilage* 2008; 16(2): 137-162.

- 1  
2  
3 26. Chodosh J, Morton S C, Mojica W, et al. Meta-analysis: chronic disease self-  
4 management programs for older adults. *Annals of internal medicine* 2005; 143(6):  
5 427-438.  
6  
7  
8  
9 27. Warsi A, LaValley M P, Wang P S, et al. Arthritis self-management education  
10 programs: A meta-analysis of the effect on pain and disability. *Arthritis &*  
11 *Rheumatology* 2003; 48(8): 2207-2213.  
12  
13  
14 28. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for  
15 osteoarthritis of the knee? A systematic review. *Annals of the rheumatic diseases*  
16 2005; 64(4): 544-548.  
17  
18  
19 29. da Costa BR, Nuesch E, Kasteler R, Husni E, Welch V, Rutjes AWS, Juni P. Oral  
20 or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database of*  
21 *Systematic Reviews* 2014; Issue 9. Art. No.: CD003115. DOI:  
22 10.1002/14651858.CD003115.pub4.  
23  
24  
25  
26 30. Rashad S, Hemingway A, Rainsford K, et al. Effect of non-steroidal anti-  
27 inflammatory drugs on the course of osteoarthritis. *The Lancet* 1989; 334(8662): 519-  
28 522.  
29  
30  
31  
32 31. Herman J H, Appel A M, Khosla R C, et al. The in vitro effect of select classes of  
33 nonsteroidal antiinflammatory drugs on normal cartilage metabolism. *The Journal of*  
34 *rheumatology* 1986; 13(6): 1014-1018.  
35  
36  
37  
38 32. Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis:  
39 a meta-analysis of randomized controlled trials. *Osteoarthritis and Cartilage* 2007;  
40 15(8): 957-965.  
41  
42  
43  
44 33. Caldwell D M, Ades A E, Higgins J P T. Simultaneous comparison of multiple  
45 treatments: combining direct and indirect evidence. *BMJ* 2005; 331(7521): 897.  
46  
47  
48 34. Juni P, Reichenbach S, Dieppe P. Osteoarthritis: rational approach to treating the  
49 individual. *Best Practice & Research Clinical Rheumatology*, 2006, 20(4): 721-740.  
50  
51  
52 35. Reichenbach S, Sterchi R, Scherer M, et al. Meta-analysis: chondroitin for  
53 osteoarthritis of the knee or hip. *Annals of internal medicine* 2007; 146(8): 580-590.  
54  
55  
56  
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- 1  
2  
3 36. Nüesch E, Trelle S, Reichenbach S, et al. The effects of excluding patients from  
4 the analysis in randomised controlled trials: meta-epidemiological study. *BMJ* 2009;  
5 339: b3244.  
6  
7  
8 37. Higgins J, Green S, editors. Chapter 8: Assessing risk of bias in included studies.  
9 *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane  
10 Collaboration. Version 5.1.0 (updated March 2011); 2011; 2001;323(7303):42–6  
11  
12  
13 38. Palmer SC, Mavridis D, Navaresem E, et al. Comparative efficacy and safety of  
14 blood pressure-lowering agents in adults with diabetes and kidney disease: a network  
15 meta-analysis. *Lancet* 2015; 385: 2047–56.  
16  
17  
18 39. Zhou X, Qin B, Whittington C, et al. Comparative efficacy and tolerability of  
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.  
22  
23  
24 40. Follmann D, Elliott P, Suh I L, et al. Variance imputation for overviews of clinical  
25 trials with continuous response. *Journal of clinical epidemiology* 1992; 45(7): 769-  
26 773.  
27  
28 41. Da Costa B R, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-  
29 inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network  
30 meta-analysis. *The Lancet* 2017; 390(10090): e21-e33.  
31  
32 42. Eberle E, Oetillinger B. Clinically relevant change and clinically relevant  
33 difference in knee osteoarthritis. *Osteoarthritis and cartilage* 1999; 7(5): 502-503.  
34  
35 43. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically  
36 important differences of rehabilitation intervention with their implications for  
37 required sample sizes using WOMAC and SF-36 quality of life measurement  
38 instruments in patients with osteoarthritis of the lower extremities. *Arthritis Care &*  
39 *Research* 2001; 45(4): 384-391.  
40  
41 44. Angst F, Aeschlimann A, Michel B A, et al. Minimal clinically important  
42 rehabilitation effects in patients with osteoarthritis of the lower extremities. *The*  
43 *Journal of rheumatology* 2002; 29(1): 131-138.  
44  
45  
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49  
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56  
57  
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60

- 1  
2  
3 45. Salaffi F, Stancati A, Silvestri C A, et al. Minimal clinically important changes in  
4 chronic musculoskeletal pain intensity measured on a numerical rating scale.  
5  
6 European  
7  
8  
9 46. Bellamy N. Outcome measurement in osteoarthritis clinical trials. *The Journal of*  
10 *rheumatology*. Supplement 1995; 43: 49-51. *journal of pain* 2004; 8(4): 283-291.  
11  
12 47. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic  
13 reviews. *BMJ* 1994; 309(6964): 1286.  
14  
15  
16 48. Salanti G, Ades A E, Ioannidis J P A. Graphical methods and numerical  
17 summaries for presenting results from multiple-treatment meta-analysis: an overview  
18 and tutorial. *Journal of clinical epidemiology* 2011; 64(2): 163-171.  
19  
20  
21 49. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials*  
22 1986; 7(3): 177-188.  
23  
24  
25 50. Salanti G, Higgins J P T, Ades A E, et al. Evaluation of networks of randomized  
26 trials. *Statistical methods in medical research* 2008; 17(3): 279-301.  
27  
28  
29 51. Lu G, Ades A E. Combination of direct and indirect evidence in mixed treatment  
30 comparisons. *Statistics in medicine* 2004; 23(20): 3105-3124.  
31  
32  
33 52. Cooper N J, Sutton A J, Lu G, et al. Mixed comparison of stroke prevention  
34 treatments in individuals with nonrheumatic atrial fibrillation. *Archives of internal*  
35 *medicine* 2006; 166(12): 1269-1275.  
36  
37  
38 53. Brooks S P, Gelman A. General methods for monitoring convergence of iterative  
39 simulations. *Journal of computational and graphical statistics* 1998; 7(4): 434-455.  
40  
41  
42 54. White I R, Barrett J K, Jackson D, et al. Consistency and inconsistency in network  
43 meta-analysis: model estimation using multivariate meta-regression. *Research*  
44 *synthesis methods* 2012; 3(2): 111-125.  
45  
46  
47 55. Higgins J P T, Jackson D, Barrett J K, et al. Consistency and inconsistency in  
48 network meta-analysis: concepts and models for multi-arm studies. *Research*  
49 *synthesis methods* 2012; 3(2): 98-110.  
50  
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3 56. Higgins JPT, Jackson D, Barret JK, Lu G, Ades AE, White IR. Consistency and  
4 inconsistency in network meta-analysis: concepts and models for multiarm studies.  
5 Res Syn Meth 2012; 3: 98-110.  
6  
7

8 57. Dias S, Sutton AJ, Welton NJ, et al. Evidence synthesis for decision making 3:  
9 heterogeneity-subgroups, meta-regression, bias, and bias-adjustment. Med Decis  
10 Making 2013; 33:618-40.-176.  
11  
12

13 58. Abe H, Minatoguchi S, Ohashi H, et al. Renoprotective effect of the addition of  
14 losartan to ongoing treatment with an angiotensin converting enzyme inhibitor in  
15 type-2 diabetic patients with nephropathy. Hypertension Research 2007; 30(10): 929.  
16  
17

18 59. Estacio R O, Coll J R, Tran Z V, et al. Effect of intensive blood pressure control  
19 with valsartan on urinary albumin excretion in normotensive patients with type 2  
20 diabetes. American journal of hypertension 2006; 19(12): 1241-1248.  
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**Table 1** Hierarchy of osteoarthritis pain and function measurement scales<sup>34-35</sup>

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

WOMAC, Western Ontario and McMaster Universities.



**Table 2** Assessment of the risk of bias in the six domains<sup>39</sup>

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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?

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## 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  
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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  
17 68.ketobemidone.tw.  
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  
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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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34 114  
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39 116.20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30  
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41 117.1 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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43  
44 or 17 or 18 or 19  
45

46  
47 118.115 and 116 and 117  
48

49 119.animal/  
50

51 120.animal/ and human/  
52

53  
54 121.119 not 120  
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56  
57 122.118 not 121  
58

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.  
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.  
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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 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
- 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
- 50 68. TX diphenoxylate
- 51
- 52 69. TX dipipanone
- 53
- 54
- 55 70. TX enadoline
- 56
- 57 71. TX ethylketazocine
- 58
- 59 72. TX ethylmorphine
- 60



1  
2  
3 73. TX etonitazene  
4

5 74. TX etorphine  
6  
7

8 75. TX fentanyl  
9

10 76. TX heroin  
11  
12

13 77. TX hydrocodone  
14

15 78. TX hydromorphin\$  
16  
17

18 79. TX hydromorphone  
19  
20

21 80. TX ketazocine  
22

23 81. TX ketobemidone  
24  
25

26 82. TX lefetamine  
27  
28

29 83. TX levomethadon  
30  
31

32 84. TX levomethadyl  
33

34 85. TX levomethorphan\$  
35  
36

37 86. TX levorphanol  
38  
39

40 87. TX loperamide  
41  
42

43 88. TX meperidine  
44  
45

46 89. TX meptazinol  
47  
48

49 90. TX methadone  
50  
51

52 91. TX methadyl  
53  
54

55 92. TX methylmorphine  
56  
57

58 93. TX morphin\$  
59  
60

94. TX nalbuphine

95. TX narcotic\$

- 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  
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  
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  
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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
<b>ADMINISTRATIVE INFORMATION</b>		
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>
<b>INTRODUCTION</b>		
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)
<b>METHODS</b>		
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 $\tau$ )
	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
Date Submitted by the Author:	09-Jul-2018
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<b>Primary Subject Heading</b>:	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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Manuscripts

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2  
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  
6  
7

8  
9 Jun Wang,<sup>1</sup> Yin Wang,<sup>2</sup> Hui Zhang,<sup>1</sup> Ming Lu,<sup>1</sup> Weilu Gao,<sup>1</sup> Li Yin,<sup>1</sup>  
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37 Medical University, Anhui, China  
38  
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  
53  
54  
55  
56  
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1  
2  
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.  
6  
7

8  
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.  
25  
26  
27  
28  
29  
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39

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.  
44  
45  
46  
47  
48

49 **Trial registration number:** PROSPERO CRD42018085503.  
50

### 51 **Strengths and limitations of this study**

52  
53

54 •While conventional paired meta-analyses focus on direct comparisons of  
55 single interventions, this Bayesian network meta-analysis will combine  
56  
57  
58  
59  
60

1  
2  
3 direct evidence with indirect evidence to assess the interrelationships  
4 between all treatments in multiple treatment comparisons.  
5

- 6  
7 ▪ Subgroup and sensitivity analyses will provide implications for  
8 clinically relevant questions for later research directions.  
9
- 10  
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.  
14
- 15  
16 ▪ The different routes of administration (oral or transdermal), durations  
17 and frequencies may cause considerable heterogeneity.  
18  
19  
20  
21  
22

## 23 **Introduction**

### 24 **Description of the condition**

25  
26  
27  
28 Osteoarthritis (OA), also known as degenerative arthritis or senile  
29 arthritis, is a degenerative disease.<sup>1</sup> 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.<sup>2-5</sup> 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.<sup>1,6</sup> Worldwide, OA, particularly OA of the knee and hip joints, is one  
36 of the leading causes of disability among the elderly.<sup>7-8</sup> 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.<sup>9</sup> 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.<sup>10</sup> 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.<sup>1</sup>  
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10  
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.<sup>11-12</sup> 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.<sup>13-14</sup> 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.<sup>15</sup>  
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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.<sup>16-17</sup>  
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.<sup>18</sup>  
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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.<sup>19-20</sup> 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.<sup>21-24</sup> Surgery mainly includes total hip and knee replacement, which can improve health-related quality of life in the late stage of OA.<sup>25-26</sup> 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.<sup>27</sup> Non-drug therapies include weight reduction, exercise, changes in lifestyle and other physical therapy measures designed to slow the progression of OA.<sup>28-30</sup>

Drugs for the treatment of OA pain primarily include non-steroidal anti-inflammatory drugs (NSAIDs), opioid drugs, paracetamol, capsaicin and duloxetine.<sup>31</sup> 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.<sup>32-34</sup> Opioids may be a viable alternative for patients who do not adequately respond to routine treatment and when other analgesics are contraindicated.<sup>35</sup>

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

Several systematic reviews have investigated the effectiveness of the agents used to treat OA.<sup>12,31</sup> However, previous studies have considered

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2  
3 only direct evidence from head-to-head comparisons and did not aim to  
4 synthesise all the available evidence. As a result, determining the best  
5 treatment based on previous studies is often difficult. Indirect  
6 comparisons are usually required to establish a 'ranking' (occasionally  
7 referred to as a “league table”) of interventions. The Bayesian network  
8 meta-analysis method allows for the coinstantaneous comparison of  
9 multiple opioid drug interventions in a unitary analysis and ranks the  
10 interventions accordingly. This approach provides estimates of treatment  
11 differences and uses the heterogeneities and inconsistencies found in the  
12 tests to evaluate the uncertainties in the resultant estimates. Therefore,  
13 this approach is particularly useful in situations involving many different  
14 intervention measures.<sup>36</sup>

## 25 26 **Objectives**

27  
28 To systematically review, compare in terms of efficacy and safety and  
29 rank opioid analgesics for hip or knee OA.

## 30 31 **METHODS**

### 32 33 **Study design**

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35 This protocol follows the Preferred Reporting Items for Systematic  
36 Reviews and Meta-Analyses Protocols, see **Supplementary file 1**.<sup>37</sup>

### 37 38 **Criteria for the included studies**

#### 39 40 **Types of studies**

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

### Types of participants

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

### Types of interventions

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

### Types of outcome measures

#### Primary outcomes

The primary outcomes will include pain and function. If data from more than one pain or function scale are provided in a single trial, we will follow the method described in previous studies<sup>38-39</sup> and extract data according to the hierarchy. The detailed scale hierarchy is presented in **Table 1**.

**Table 1** Hierarchy of osteoarthritis pain and function measurement scales<sup>38-39</sup>

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.<sup>10,29,12,31</sup> For the  
6 strategies that will be used in this review, see **Supplementary file 2**.  
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9

### 10 11 **Searching other resources**

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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.<sup>40</sup> 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.<sup>41</sup> Disagreements will be resolved by negotiation. We will systematically evaluate bias across six domains<sup>42</sup> as illustrated in **Table 2**. All included

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3 trials will be classified into the following categories: low risk, high risk,  
4 and unclear.<sup>41</sup>  
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7 **Table 2** Assessment of the risk of bias in the six domains<sup>43</sup>  
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9	1 Was there adequate sequence generation (selection bias)?
10	
11	2 Was allocation adequately concealed (selection bias)?
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13	3 Was knowledge of the allocated interventions adequately prevented
14	during the study (detection bias)?
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16	4 Were incomplete outcome data adequately addressed (attrition bias)?
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18	5 Are reported of the study free of selective reporting (reporting bias)?
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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  
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6 understood similarly to confidence interval (CIs), and at the conventional  
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8 statistical significance level, a two-sided  $p < 0.05$  can be assumed if the 95%  
9  
10 CrIs do not include 0.<sup>43</sup> 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.<sup>39,44</sup> If some necessary data are not  
15  
16 available, we will use approximations as previously described.<sup>35</sup> 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.<sup>44</sup> 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  
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30 10-cm VAS.<sup>44-45</sup> Additionally, we will compare the effects with a pre-  
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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  
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36 patients with OA and corresponds to 0.9 cm on a 10-cm VAS.<sup>46-49</sup> 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.<sup>50-51</sup>

### 43 44 45 46 47 48 49 50 51 52 **Relative treatment ranking**

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3 Each intervention and each outcome will be systematically evaluated and  
4 ranked. We will determine a treatment hierarchy using the surface under  
5 the cumulative ranking curve (SUCRA) and the mean ranks.<sup>52</sup>  
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## 8 9 **Data analysis**

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12 First, we will conduct paired meta-analyses by synthesising the studies  
13 that compare interventions head-to-head using a random-effects model.<sup>53</sup>  
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16 Then, we will use a Bayesian network meta-analysis to compare the  
17 different classes of oral or transdermal opioid treatments based on the  
18 median of the posterior distribution.<sup>54-55</sup> A Bayesian random-effects  
19 model will be used because this model completely retains the within-trial  
20 randomised treatment comparisons of each study while combining all  
21 available comparisons between treatments and accounting for multiple  
22 comparisons within a trial in cases with more than two treatment arms.<sup>55-</sup>  
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<sup>56</sup> The between-trial variance of the treatment effects ( $\tau^2$ ) 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.<sup>57</sup>

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.<sup>58</sup> In the Bayesian meta-analysis, we will calculate the heterogeneity of the treatment effects estimated from the posterior median between-trial variance ( $\tau^2$ ). 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.<sup>59</sup> The design-by-treatment interaction model will also be used to calculate the consistency throughout the entire network.<sup>60</sup>

### **Subgroup analyses**

To explore the robustness of the results, we will include the characteristics of the trials as covariates in the Bayesian meta-analysis to assess the primary outcomes based on the clinical characteristics, risk of bias and trial size. A random-effects meta-regression model<sup>61</sup> will be used to determine whether the treatment effects are affected by the following factors: (1) treatment duration (short-term  $\leq 1$  month and long-term  $> 1$  month); (2) trial size (small-scale: allocated participants  $\leq 200$ , 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.<sup>62</sup> Additionally, a  
23 comparison-adjusted funnel plot will be drawn to detect any major  
24 publication bias in the Bayesian network meta-analysis.<sup>63</sup>  
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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.<sup>64</sup> 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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2  
3 ability of this work to reach high-confidence conclusions.  
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8 **Collaborators:** None  
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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.  
15  
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20 commercial or not-for-profit organisation.  
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26  
27

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30  
31

## 32 REFERENCES

- 33  
34  
35 1. Chen K, Yan Y, Li C, et al. Increased 15-lipoxygenase-1 expression in  
36 chondrocytes contributes to the pathogenesis of osteoarthritis. *Cell death & disease*  
37 2017; 8(10): e3109.  
38  
39  
40  
41 2. Cooper C, Inskip H, Croft P, et al. Individual risk factors for hip osteoarthritis:  
42 obesity, hip injury and physical activity. *American journal of epidemiology* 1998;  
43 147(6): 516-522.  
44  
45  
46  
47 3. Blagojevic M, Jinks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the  
48 knee in older adults: a systematic review and meta-analysis. *Osteoarthritis and*  
49 *cartilage* 2010; 18(1): 24-33.  
50  
51  
52  
53 4. Jørgensen K T, Pedersen B V, Nielsen N M, et al. Socio-demographic factors,  
54 reproductive history and risk of osteoarthritis in a cohort of 4.6 million Danish women  
55 and men. *Osteoarthritis and cartilage* 2011; 19(10): 1176-1182.  
56  
57  
58  
59



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2  
3 5. Dekker J, van Dijk G M, Veenhof C. Risk factors for functional decline in  
4 osteoarthritis of the hip or knee. *Current opinion in rheumatology* 2009; 21(5): 520-  
5 524.  
6  
7
- 8  
9 6. Guilak F. Biomechanical factors in osteoarthritis. *Best practice & research Clinical*  
10 *rheumatology* 2011; 25(6): 815-823.  
11
- 12  
13 7. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis:  
14 estimates from the global burden of disease 2010 study. *Annals of the rheumatic*  
15 *diseases* 2014; annrheumdis-2013-204763.  
16  
17
- 18  
19 8. Holden M A, Burke D L, Runhaar J, et al. Subgrouping and targeted exercise  
20 programmes for knee and hip osteoarthritis (STEER OA): a systematic review update  
21 and individual participant data meta-analysis protocol. *BMJ open* 2017; 7(12):  
22 e018971.doi:10.1136/bmjopen-2017-018971.  
23  
24
- 25  
26 9. Bijlsma J W J, Knahr K. Strategies for the prevention and management of  
27 osteoarthritis of the hip and knee. *Best practice & research Clinical rheumatology*  
28 2007; 21(1): 59-76.  
29  
30
- 31  
32 10. Hunter D J, Schofield D, Callander E. The individual and socioeconomic impact  
33 of osteoarthritis. *Nature Reviews Rheumatology* 2014; 10(7): 437-441.  
34
- 35  
36 11. Dunlop D D, Semanik P, Song J, et al. Risk factors for functional decline in older  
37 adults with arthritis. *Arthritis & Rheumatology* 2005; 52(4): 1274-1282.  
38
- 39  
40 12. Cepeda M S, Camargo F, Zea C, et al. Tramadol for osteoarthritis. *The Cochrane*  
41 *Library*, 2006, Issue 3. Art. No: CD005522. DOI:10.1002/14651858.CD005522.pub2.  
42
- 43  
44 13. Goldring M B, Otero M, Tsuchimochi K, et al. Defining the roles of inflammatory  
45 and anabolic cytokines in cartilage metabolism. *Annals of the rheumatic diseases*  
46 2008; 67(Suppl 3): iii75-iii82.  
47  
48
- 49  
50 14. Hui W, Young DA, Rowan AD, Xu X, Cawston TE, Proctor CJ. Oxidative  
51 changes and signalling pathways are pivotal in initiating age-related changes in  
52 articular cartilage. *Ann Rheum Dis* 2016; 75: 449-458.  
53
- 54  
55 15. Kean W F, Kean R, Buchanan W W. Osteoarthritis: symptoms, signs and source  
56 of pain. *Inflammopharmacology* 2004; 12(1): 3-31.  
57  
58  
59

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2  
3 16. Bjordal J M, Ljunggren A E, Klovning A, et al. Non-steroidal anti-inflammatory  
4 drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-  
5 analysis of randomised placebo controlled trials. *BMJ* 2004; 329(7478): 1317.  
6  
7  
8 17. Dieppe P A, Lohmander L S. Pathogenesis and management of pain in  
9 osteoarthritis. *The Lancet* 2005; 365(9463): 965-973.  
10  
11 18. Reginster J Y. The prevalence and burden of arthritis. *Rheumatology* 2002;  
12 41(suppl\_1): 3-6.  
13  
14 19. Odding E, Valkenburg H A, Algra D, et al. Associations of radiological  
15 osteoarthritis of the hip and knee with locomotor disability in the Rotterdam Study.  
16 *Annals of the rheumatic diseases* 1998; 57(4): 203-208.  
17  
18 20. Towheed TE, Judd MJ, Hochberg MC, Wells G. Acetaminophen for osteoarthritis.  
19 *The Cochrane Library* 2003; Issue2. DOI:10.1002/14651858.CD004257. pub2  
20  
21 21. Jevsevar D S, Brown G A, Jones D L, et al. The American Academy of  
22 Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the  
23 knee. *JBJS* 2013; 95(20): 1885-1886.  
24  
25 22. McAlindon T E, Bannuru R R, Sullivan M C, et al. OARSI guidelines for the non-  
26 surgical management of knee osteoarthritis. *Osteoarthritis and cartilage* 2014; 22(3):  
27 363-388.  
28  
29 23. Hashemi M, Jalili P, Mennati S, Koosha A, Rohanifar R, Madadi F, et al. The  
30 effects of prolotherapy with hypertonic dextrose versus prolozone (intraarticular  
31 Ozone) in patients with knee osteoarthritis. *Anesth Pain Med* 2015; 5, e27585.  
32  
33 24. Cugat R, Cuscó X, Seijas R, et al. Biologic enhancement of cartilage repair: The  
34 role of platelet-rich plasma and other commercially available growth factors.  
35 *Arthroscopy* 2015; 31(4): 777-783.  
36  
37 25. Emkey R, Rosenthal N, Wu S C, et al. Efficacy and safety of  
38 tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in  
39 subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter,  
40 randomized, double-blind, placebo-controlled trial. *The Journal of rheumatology* 2004;  
41 31(1): 150-156.  
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3 26. Towheed T E, Hochberg M C. Health-related quality of life after total hip  
4 replacement. *Seminars in arthritis and rheumatism*. WB Saunders 1996; 26(1): 483-  
5 491.  
6  
7  
8  
9 27. Zhang W, Moskowitz R W, Nuki G, et al. OARSI recommendations for the  
10 management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert  
11 consensus guidelines. *Osteoarthritis and cartilage* 2008; 16(2): 137-162.  
12  
13  
14 28. Chodosh J, Morton S C, Mojica W, et al. Meta-analysis: chronic disease self-  
15 management programs for older adults. *Annals of internal medicine* 2005; 143(6):  
16 427-438.  
17  
18  
19 29. Warsi A, LaValley M P, Wang P S, et al. Arthritis self-management education  
20 programs: A meta-analysis of the effect on pain and disability. *Arthritis &*  
21 *Rheumatology* 2003; 48(8): 2207-2213.  
22  
23  
24  
25 30. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for  
26 osteoarthritis of the knee? A systematic review. *Annals of the rheumatic diseases*  
27 2005; 64(4): 544-548.  
28  
29  
30  
31 31. da Costa BR, Nüesch E, Kasteler R, Husni E, Welch V, Rutjes AWS, Jüni P. Oral  
32 or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database of*  
33 *Systematic Reviews* 2014; Issue 9. Art. No.: CD003115. DOI:  
34 10.1002/14651858.CD003115.pub4.  
35  
36  
37  
38 32. Rashad S, Hemingway A, Rainsford K, et al. Effect of non-steroidal anti-  
39 inflammatory drugs on the course of osteoarthritis. *The Lancet* 1989; 334(8662): 519-  
40 522.  
41  
42  
43  
44 33. Herman J H, Appel A M, Khosla R C, et al. The in vitro effect of select classes of  
45 nonsteroidal antiinflammatory drugs on normal cartilage metabolism. *The Journal of*  
46 *rheumatology* 1986; 13(6): 1014-1018.  
47  
48  
49  
50 34. Harirforoosh S, Jamali F. Renal adverse effects of nonsteroidal anti-inflammatory  
51 drugs. *Expert opinion on drug safety* 2009; 8(6): 669-681.  
52  
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3 35. Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis:  
4 a meta-analysis of randomized controlled trials. *Osteoarthritis and Cartilage* 2007;  
5 15(8): 957-965.  
6  
7  
8 36. Caldwell D M, Ades A E, Higgins J P T. Simultaneous comparison of multiple  
9 treatments: combining direct and indirect evidence. *BMJ* 2005; 331(7521): 897.  
10  
11  
12 37. Moher D , Shamseer L , Clarke M, et al. Preferred reporting items for systematic  
13 review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1  
14  
15 38. Jüni P, Reichenbach S, Dieppe P. Osteoarthritis: rational approach to treating the  
16 individual. *Best Practice & Research Clinical Rheumatology*, 2006, 20(4): 721-740.  
17  
18 39. Reichenbach S, Sterchi R, Scherer M, et al. Meta-analysis: chondroitin for  
19 osteoarthritis of the knee or hip. *Annals of internal medicine* 2007; 146(8): 580-590.  
20  
21 40. Nüesch E, Trelle S, Reichenbach S, et al. The effects of excluding patients from  
22 the analysis in randomised controlled trials: meta-epidemiological study. *BMJ* 2009;  
23 339: b3244.  
24  
25 41. Higgins J, Green S, editors. Chapter 8: Assessing risk of bias in included studies.  
26 *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane  
27 Collaboration. Version 5.1.0 (updated March 2011); 2011; 2001;323(7303):42–6  
28  
29 42. Palmer SC, Mavridis D, Navaresem E, et al. Comparative efficacy and safety of  
30 blood pressure-lowering agents in adults with diabetes and kidney disease: a network  
31 meta-analysis. *Lancet* 2015; 385: 2047–56.  
32  
33 43. Zhou X, Qin B, Whittington C, et al. Comparative efficacy and tolerability of  
34 first-generation and newer-generation antidepressant medications for depressive  
35 disorders in children and adolescents: study protocol for a systematic review and  
36 network meta-analysis. *BMJ open* 2015; 5(9): e007768.  
37  
38 44. Follmann D, Elliott P, Suh I L, et al. Variance imputation for overviews of clinical  
39 trials with continuous response. *Journal of clinical epidemiology* 1992; 45(7): 769-  
40 773.  
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3 45. Da Costa B R, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-  
4 inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network  
5 meta-analysis. *The Lancet* 2017; 390(10090): e21-e33.  
6  
7
- 8 46. Eberle E, Ottilinger B. Clinically relevant change and clinically relevant  
9 difference in knee osteoarthritis. *Osteoarthritis and cartilage* 1999; 7(5): 502-503.  
10
- 11 47. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically  
12 important differences of rehabilitation intervention with their implications for  
13 required sample sizes using WOMAC and SF-36 quality of life measurement  
14 instruments in patients with osteoarthritis of the lower extremities. *Arthritis Care &*  
15 *Research* 2001; 45(4): 384-391.  
16  
17
- 18 48. Angst F, Aeschlimann A, Michel B A, et al. Minimal clinically important  
19 rehabilitation effects in patients with osteoarthritis of the lower extremities. *The*  
20 *Journal of rheumatology* 2002; 29(1): 131-138.  
21  
22
- 23 49. Salaffi F, Stancati A, Silvestri C A, et al. Minimal clinically important changes in  
24 chronic musculoskeletal pain intensity measured on a numerical rating scale.  
25 *European*  
26
- 27 50. Bellamy N. Outcome measurement in osteoarthritis clinical trials. *The Journal of*  
28 *rheumatology*. Supplement 1995; 43: 49-51. *journal of pain* 2004; 8(4): 283-291.  
29  
30
- 31 51. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic  
32 reviews. *BMJ* 1994; 309(6964): 1286.  
33  
34
- 35 52. Salanti G, Ades A E, Ioannidis J P A. Graphical methods and numerical  
36 summaries for presenting results from multiple-treatment meta-analysis: an overview  
37 and tutorial. *Journal of clinical epidemiology* 2011; 64(2): 163-171.  
38  
39
- 40 53. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials*  
41 1986; 7(3): 177-188.  
42  
43
- 44 54. Salanti G, Higgins J P T, Ades A E, et al. Evaluation of networks of randomized  
45 trials. *Statistical methods in medical research* 2008; 17(3): 279-301.  
46  
47
- 48 55. Lu G, Ades A E. Combination of direct and indirect evidence in mixed treatment  
49 comparisons. *Statistics in medicine* 2004; 23(20): 3105-3124.  
50  
51  
52  
53  
54  
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3 56. Cooper N J, Sutton A J, Lu G, et al. Mixed comparison of stroke prevention  
4 treatments in individuals with nonrheumatic atrial fibrillation. *Archives of internal*  
5 *medicine* 2006; 166(12): 1269-1275.  
6  
7  
8 57. Brooks S P, Gelman A. General methods for monitoring convergence of iterative  
9 simulations. *Journal of computational and graphical statistics* 1998; 7(4): 434-455.  
10  
11 58. White I R, Barrett J K, Jackson D, et al. Consistency and inconsistency in network  
12 meta-analysis: model estimation using multivariate meta-regression. *Research*  
13 *synthesis methods* 2012; 3(2): 111-125.  
14  
15 59. Higgins J P T, Jackson D, Barrett J K, et al. Consistency and inconsistency in  
16 network meta-analysis: concepts and models for multi-arm studies. *Research*  
17 *synthesis methods* 2012; 3(2): 98-110.  
18  
19 60. Higgins JPT, Jackson D, Barret JK, Lu G, Ades AE, White IR. Consistency and  
20 inconsistency in network meta-analysis: concepts and models for multiarm studies.  
21 *Res Syn Meth* 2012; 3: 98-110.  
22  
23 61. Dias S, Sutton AJ, Welton NJ, et al. Evidence synthesis for decision making 3:  
24 heterogeneity-subgroups, meta-regression, bias, and bias-adjustment. *Med Decis*  
25 *Making* 2013; 33:618-40.-176.  
26  
27 62. Abe H, Minatoguchi S, Ohashi H, et al. Renoprotective effect of the addition of  
28 losartan to ongoing treatment with an angiotensin converting enzyme inhibitor in  
29 type-2 diabetic patients with nephropathy. *Hypertension Research* 2007; 30(10): 929.  
30  
31 63. Estacio R O, Coll J R, Tran Z V, et al. Effect of intensive blood pressure control  
32 with valsartan on urinary albumin excretion in normotensive patients with type 2  
33 diabetes. *American journal of hypertension* 2006; 19(12): 1241-1248.  
34  
35 64. Smith S R, Deshpande B R, Collins J E, et al. Comparative pain reduction of oral  
36 non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic  
37 analytic review. *Osteoarthritis and cartilage* 2016; 24(6): 962-972.  
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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
<b>ADMINISTRATIVE INFORMATION</b>		
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>
<b>INTRODUCTION</b>		
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)
<b>METHODS</b>		
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 $\tau$ )
	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  
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.alpha-prodine.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 43.bremazocine.tw.  
10

11 44.carfentan\$.tw.  
12

13 45.codeine.tw.  
14

15 46.contin.tw.  
16

17 47.dextromoramide.tw.  
18

19 48.dextropropoxyphene.tw.  
20

21 49.dezocine.tw.  
22

23 50.diacetylmorphine.tw.  
24

25 51.diamorphine.tw.  
26

27 52.dihydrocodeine.tw.  
28

29 53.dihydromorphine.tw.  
30

31 54.dihydromorphone.tw.  
32

33 55.diphenoxylate.tw.  
34

35 56.dipipanone.tw.  
36

37 57.enadoline.tw.  
38

39 58.ethylketazocine.tw.  
40

41 59.ethylmorphine.tw.  
42

43 60.etonitazene.tw.  
44

45 61.etorphine.tw.  
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47 62.fentanyl.tw.  
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3 63.heroin.tw.  
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5  
6 64.hydrocodone.tw.  
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8 65.hydromorphin\$.tw.  
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10  
11 66.hydromorphone.tw.  
12

13  
14 67.ketazocine.tw.  
15

16  
17 68.ketobemidone.tw.  
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.  
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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.  
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53  
54 83.nicocodeine.tw.  
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56  
57 84.nicomorphine.tw.  
58

59 85.normorphine.tw.  
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- 2
- 3 86.noscapin\$.tw.
- 4
- 5
- 6 87.ohmefantanyl.tw.
- 7
- 8 88.opiate\$.tw.
- 9
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- 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.
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- 36 99.peronine.tw.
- 37
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- 39 100. pethidine.tw.
- 40
- 41 101.phenazocine.tw.
- 42
- 43 102.phencyclidine.tw.
- 44
- 45
- 46 103.pholcodine.tw.
- 47
- 48 104.piritramid\$.tw.
- 49
- 50
- 51 105.prodine.tw.
- 52
- 53 106.promedol.tw.
- 54
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- 56 107.propoxyphene.tw.
- 57
- 58
- 59 108.remifentanil.tw.
- 60

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3 109.sufentanil.tw.  
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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  
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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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34 114  
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39 116.20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30  
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41 117.1 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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43  
44 or 17 or 18 or 19  
45

46  
47 118.115 and 116 and 117  
48

49 119.animal/  
50

51 120.animal/ and human/  
52

53  
54 121.119 not 120  
55

56  
57 122.118 not 121  
58

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.

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2  
3 21.gonarthro\$.ab,sh,ti.  
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5 22.coxarthriti\$.ab,sh,ti.  
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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.  
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18  
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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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- 6 44.dextromoramide.tw.
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- 8 45.dextropropoxyphene.tw.
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- 11 46.dezocine.tw.
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- 13 47.diacetylmorphine.tw.
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- 16 48.diamorphine.tw.
- 17
- 18 49.dihydrocodeine.tw.
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- 20
- 21 50.dihydromorphine.tw.
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- 23
- 24 51.dihydromorphone.tw.
- 25
- 26 52.diphenoxylate.tw.
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- 29 53.dipipanone.tw.
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- 31 54.enadoline.tw.
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- 34 55.ethylketazocine.tw.
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- 54 63.hydromorphone.tw.
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- 57 64.ketazocine.tw.
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- 60 65.ketobemidone.tw.

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- 3 66.lefetamine.tw.
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- 8 68.levomethadyl.tw.
- 9
- 10
- 11 69.levomethorphan\$.tw.
- 12
- 13 70.levorphanol.tw.
- 14
- 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
- 47 83.noscapin\$.tw.
- 48
- 49 84.ohmefentanyl.tw.
- 50
- 51
- 52 85.opiate\$.tw.
- 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
- 41 104.propoxyphene.tw.
- 42
- 43
- 44 105.remifentanil.tw.
- 45
- 46 106.sufentanil.tw.
- 47
- 48
- 49 107.tapentadol.tw.
- 50
- 51 108.thebaine.tw.
- 52
- 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
- 11 9. TX (trebl\$ n25 blind\$)
- 12
- 13 10. TX (trebl\$ n25 mask\$)
- 14
- 15
- 16 11. TX (tripl\$ n25 blind\$)
- 17
- 18 12. TX (tripl\$ n25 mask\$)
- 19
- 20
- 21 13. (MH “Placebos”)
- 22
- 23
- 24 14. TX placebo\$
- 25
- 26 15. TX random\$
- 27
- 28
- 29 16. (MH “Study Design+”)
- 30
- 31 17. (MH “Comparative Studies”)
- 32
- 33
- 34 18. (MH “Evaluation Research”)
- 35
- 36 19. (MH “Prospective Studies+”)
- 37
- 38
- 39 20. TX (control\$ or prospectiv\$ or volunteer\$)
- 40
- 41 21. S1 or S2 or (...) or S20
- 42
- 43

#### 44 **Search terms for Osteoarthritis**

- 45
- 46 22. osteoarthriti\$
- 47
- 48
- 49 23. (MH “Osteoarthritis”)
- 50
- 51
- 52 24. TX osteoarthro\$
- 53
- 54 25. TX gonarthriti\$
- 55
- 56
- 57 26. TX gonarthro\$
- 58
- 59 27. TX coxarthriti\$
- 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 74. TX etorphine  
6  
7

8 75. TX fentanyl  
9

10 76. TX heroin  
11  
12

13 77. TX hydrocodone  
14

15 78. TX hydromorphin\$  
16  
17

18 79. TX hydromorphone  
19  
20

21 80. TX ketazocine  
22

23 81. TX ketobemidone  
24  
25

26 82. TX lefetamine  
27  
28

29 83. TX levomethadon  
30  
31

32 84. TX levomethadyl  
33

34 85. TX levomethorphan\$  
35  
36

37 86. TX levorphanol  
38  
39

40 87. TX loperamide  
41  
42

43 88. TX meperidine  
44  
45

46 89. TX meptazinol  
47  
48

49 90. TX methadone  
50  
51

52 91. TX methadyl  
53  
54

55 92. TX methylmorphine  
56  
57

58 93. TX morphin\$  
59  
60

94. TX nalbuphine

95. TX narcotic\$



- 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
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- 41
- 42 111. TX percocet
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- 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  
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  
50  
51 Trials

### 52 **Search terms for Opioids**

53  
54  
55 #3. MeSH descriptor Analgesics, Opioid explode all trees  
56

57 #4. MeSH descriptor Narcotics explode all trees  
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  
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26  
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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  
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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022142.R2
Article Type:	Protocol
Date Submitted by the Author:	23-Aug-2018
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<b>Primary Subject Heading</b>:	Complementary medicine
Secondary Subject Heading:	Medical management
Keywords:	opioid, osteoarthritis, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Hip < ORTHOPAEDIC & TRAUMA SURGERY, opioids, osteoarthritis, knee, hip

SCHOLARONE™  
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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9 4 Jun Wang,<sup>1</sup> Yin Wang,<sup>2</sup> Hui Zhang,<sup>1</sup> Ming Lu,<sup>1</sup> Weilu Gao,<sup>1</sup> Li Yin,<sup>1</sup>  
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37  
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39  
40 17 **Keywords:** opioids, osteoarthritis, knee, hip

41  
42  
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.<sup>1</sup> 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.<sup>2-5</sup> 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.<sup>1,6</sup> Worldwide, OA, particularly OA of the knee and hip joints, is one  
22 of the leading causes of disability among the older adults.<sup>7-8</sup>  
23 Research has shown that around one third of older adults have OA.<sup>9</sup> 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.<sup>10</sup>

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.<sup>11-12</sup> Previous studies have  
13 6 decrease in the regeneration ability of cartilage.<sup>11-12</sup> 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.<sup>13-14</sup> These mediators can cause inflammation, which,  
19 9 and oxidative stress.<sup>13-14</sup> 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.<sup>15</sup>  
29 14 pain.<sup>15</sup>

### 30 15 **Description of the intervention**

31  
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.<sup>16-17</sup>

35 18 Because of pain and functional limitations, the quality of life of patients  
36 19 with OA is even worse than that of patients with gastrointestinal or  
37 20 chronic respiratory system disorders.<sup>18</sup>

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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.<sup>19-20</sup> Currently, the treatment modalities for OA include  
46 24 invasive surgery, non-drug therapy and drug therapy.

47  
48  
49  
50  
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.<sup>21-</sup>  
2  
3  
4 24 Surgery mainly includes total hip and knee replacement, which can  
5  
6 improve health-related quality of life in the late stage of OA.<sup>25-26</sup> However,  
7  
8 surgery is not the first choice of treatment for OA in clinical practice due  
9  
10 to the limited lifespan of an artificial prosthesis. Furthermore, if a  
11  
12 prosthesis fails, the patient may face a second revision operation, and the  
13  
14 risk of failure in such operations is high due to the loss of bone mass.  
15  
16 Therefore, joint surgery is often considered the ultimate treatment for OA.  
17  
18 Non-drug therapy is important for reducing pain and improving the  
19  
20 physiological function of OA patients.<sup>27</sup> Non-drug therapies include  
21  
22 weight reduction, exercise, changes in lifestyle and other physical therapy  
23  
24 measures designed to slow the progression of OA.<sup>28-30</sup>

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Drugs for the treatment of OA pain primarily include non-steroidal anti-inflammatory drugs (NSAIDs), opioid drugs, paracetamol, capsaicin and duloxetine.<sup>31</sup> 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.<sup>32-34</sup> Opioids may be a viable alternative for patients who do not adequately respond to routine treatment and when other analgesics are contraindicated.<sup>35</sup>

## 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.<sup>12,31</sup> 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.<sup>36</sup>

## 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.<sup>37</sup>

### 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 studies<sup>38-39</sup> 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 scales<sup>38-39</sup>

<b>Hierarchy</b>	<b>Pain measurement scales</b>	<b>Function measurement scales</b>
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.<sup>10,29,31</sup> 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](http://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);

- 1 -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.<sup>40</sup> 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.<sup>41</sup> Disagreements will be resolved by negotiation. We will systematically evaluate bias across six domains<sup>42</sup> as illustrated in **Table 2**. All included trials will be classified into the following categories: low risk, high risk, and unclear.<sup>41</sup>

**Table 2** Assessment of the risk of bias in the six domains<sup>43</sup>

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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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22  
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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40 **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.<sup>43</sup> 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.<sup>39,44</sup> If some necessary data are not  
4 available, we will use approximations as previously described.<sup>35</sup> 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.<sup>44</sup> 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.<sup>44-45</sup> 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.<sup>46-49</sup> 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.<sup>50-51</sup>

## 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.<sup>52</sup>

## 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.<sup>53</sup>

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.<sup>54-55</sup> 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.<sup>55-</sup>

10 <sup>56</sup> The between-trial variance of the treatment effects ( $\tau^2$ ) 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.<sup>57</sup>

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.<sup>58</sup> In the Bayesian meta-analysis, we will  
3 calculate the heterogeneity of the treatment effects estimated from the  
4 posterior median between-trial variance ( $\tau^2$ ). 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.<sup>59</sup> The design-by-treatment interaction model will  
9 also be used to calculate the consistency throughout the entire network.<sup>60</sup>

## 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 model<sup>61</sup> will be used  
15 to determine whether the treatment effects are affected by the following  
16 factors: (1) treatment duration (short-term  $\leq 1$  month and long-term  $> 1$   
17 month); (2) trial size (small-scale: allocated participants  $\leq 200$ , 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.<sup>62</sup> Additionally, a  
10 comparison-adjusted funnel plot will be drawn to detect any major  
11 publication bias in the Bayesian network meta-analysis.<sup>63</sup>

#### 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.<sup>64</sup> 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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18 8 **Competing interests:** None declared.  
19

20  
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23  
24

## 25 11 REFERENCES

26  
27  
28 12 1. Chen K, Yan Y, Li C, et al. Increased 15-lipoxygenase-1 expression in  
29 chondrocytes contributes to the pathogenesis of osteoarthritis. *Cell death & disease*  
30 2017; 8(10): e3109.  
31

32  
33 15 2. Cooper C, Inskip H, Croft P, et al. Individual risk factors for hip osteoarthritis:  
34 obesity, hip injury and physical activity. *American journal of epidemiology* 1998;  
35 147(6): 516-522.  
36  
37

38  
39 18 3. Blagojevic M, Jinks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the  
40 knee in older adults: a systematic review and meta-analysis. *Osteoarthritis and*  
41 *cartilage* 2010; 18(1): 24-33.  
42  
43

44  
45 21 4. Jørgensen K T, Pedersen B V, Nielsen N M, et al. Socio-demographic factors,  
46 reproductive history and risk of osteoarthritis in a cohort of 4.6 million Danish women  
47 and men. *Osteoarthritis and cartilage* 2011; 19(10): 1176-1182.  
48  
49

50  
51 24 5. Dekker J, van Dijk G M, Veenhof C. Risk factors for functional decline in  
52 osteoarthritis of the hip or knee. *Current opinion in rheumatology* 2009; 21(5): 520-  
53 524.  
54  
55

- 1 6. Guilak F. Biomechanical factors in osteoarthritis. *Best practice & research Clinical*  
2 *rheumatology* 2011; 25(6): 815-823.
- 3 7. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis:  
4 estimates from the global burden of disease 2010 study. *Annals of the rheumatic*  
5 *diseases* 2014: annrheumdis-2013-204763.
- 6 8. Holden M A, Burke D L, Runhaar J, et al. Subgrouping and targeted exercise  
7 programmes for knee and hip osteoarthritis (STEER OA): a systematic review update  
8 and individual participant data meta-analysis protocol. *BMJ open* 2017; 7(12):  
9 e018971.doi:10.1136/bmjopen-2017-018971.
- 10 9. Bijlsma J W J, Knahr K. Strategies for the prevention and management of  
11 osteoarthritis of the hip and knee. *Best practice & research Clinical rheumatology*  
12 2007; 21(1): 59-76.
- 13 10. Hunter D J, Schofield D, Callander E. The individual and socioeconomic impact  
14 of osteoarthritis. *Nature Reviews Rheumatology* 2014; 10(7): 437-441.
- 15 11. Dunlop D D, Semanik P, Song J, et al. Risk factors for functional decline in older  
16 adults with arthritis. *Arthritis & Rheumatology* 2005; 52(4): 1274-1282.
- 17 12. Cepeda M S, Camargo F, Zea C, et al. Tramadol for osteoarthritis. *The Cochrane*  
18 *Library*, 2006, Issue 3. Art. No: CD005522. DOI:10.1002/14651858.CD005522.pub2.
- 19 13. Goldring M B, Otero M, Tsuchimochi K, et al. Defining the roles of inflammatory  
20 and anabolic cytokines in cartilage metabolism. *Annals of the rheumatic diseases*  
21 2008; 67(Suppl 3): iii75-iii82.
- 22 14. Hui W, Young DA, Rowan AD, Xu X, Cawston TE, Proctor CJ. Oxidative  
23 changes and signalling pathways are pivotal in initiating age-related changes in  
24 articular cartilage. *Ann Rheum Dis* 2016; 75: 449-458.
- 25 15. Kean W F, Kean R, Buchanan W W. Osteoarthritis: symptoms, signs and source  
26 of pain. *Inflammopharmacology* 2004; 12(1): 3-31.
- 27 16. Bjordal J M, Ljunggren A E, Klovning A, et al. Non-steroidal anti-inflammatory  
28 drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-  
29 analysis of randomised placebo controlled trials. *BMJ* 2004; 329(7478): 1317.

- 1  
2  
3 17. Dieppe P A, Lohmander L S. Pathogenesis and management of pain in  
4 osteoarthritis. *The Lancet* 2005; 365(9463): 965-973.  
5  
6  
7 18. Reginster J Y. The prevalence and burden of arthritis. *Rheumatology* 2002;  
8 41(suppl\_1): 3-6.  
9  
10  
11 19. Odding E, Valkenburg H A, Algra D, et al. Associations of radiological  
12 osteoarthritis of the hip and knee with locomotor disability in the Rotterdam Study.  
13 *Annals of the rheumatic diseases* 1998; 57(4): 203-208.  
14  
15  
16 20. Towheed TE, Judd MJ, Hochberg MC, Wells G. Acetaminophen for osteoarthritis.  
17 *The Cochrane Library* 2003; Issue2. DOI:10.1002/14651858.CD004257. pub2  
18  
19  
20 21. Jevsevar D S, Brown G A, Jones D L, et al. The American Academy of  
21 Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the  
22 knee. *JBJS* 2013; 95(20): 1885-1886.  
23  
24  
25 22. McAlindon T E, Bannuru R R, Sullivan M C, et al. OARSI guidelines for the non-  
26 surgical management of knee osteoarthritis. *Osteoarthritis and cartilage* 2014; 22(3):  
27 363-388.  
28  
29  
30 23. Hashemi M, Jalili P, Mennati S, Koosha A, Rohanifar R, Madadi F, et al. The  
31 effects of prolotherapy with hypertonic dextrose versus prolozone (intraarticular  
32 Ozone) in patients with knee osteoarthritis. *Anesth Pain Med* 2015; 5, e27585.  
33  
34  
35 24. Cugat R, Cuscó X, Seijas R, et al. Biologic enhancement of cartilage repair: The  
36 role of platelet-rich plasma and other commercially available growth factors.  
37 *Arthroscopy* 2015; 31(4): 777-783.  
38  
39  
40 25. Emkey R, Rosenthal N, Wu S C, et al. Efficacy and safety of  
41 tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in  
42 subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter,  
43 randomized, double-blind, placebo-controlled trial. *The Journal of rheumatology* 2004;  
44 31(1): 150-156.  
45  
46  
47 26. Towheed T E, Hochberg M C. Health-related quality of life after total hip  
48 replacement. *Seminars in arthritis and rheumatism*. WB Saunders 1996; 26(1): 483-  
49 491.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 1 27. Zhang W, Moskowitz R W, Nuki G, et al. OARSI recommendations for the  
4 2 management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert  
5 3 consensus guidelines. *Osteoarthritis and cartilage* 2008; 16(2): 137-162.  
6  
7  
8 4 28. Chodosh J, Morton S C, Mojica W, et al. Meta-analysis: chronic disease self-  
9 5 management programs for older adults. *Annals of internal medicine* 2005; 143(6):  
10 6 427-438.  
11  
12  
13 7 29. Warsi A, LaValley M P, Wang P S, et al. Arthritis self- management education  
14 8 programs: A meta- analysis of the effect on pain and disability. *Arthritis &*  
15 9 *Rheumatology* 2003; 48(8): 2207-2213.  
16  
17  
18 10 30. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for  
19 11 osteoarthritis of the knee? A systematic review. *Annals of the rheumatic diseases*  
20 12 2005; 64(4): 544-548.  
21  
22  
23 13 31. da Costa BR, Nüesch E, Kasteler R, Husni E, Welch V, Rutjes AWS, Jüni P. Oral  
24 14 or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database of*  
25 15 *Systematic Reviews* 2014; Issue 9. Art. No.: CD003115. DOI:  
26 16 10.1002/14651858.CD003115.pub4.  
27  
28  
29 17 32. Rashad S, Hemingway A, Rainsford K, et al. Effect of non-steroidal anti-  
30 18 inflammatory drugs on the course of osteoarthritis. *The Lancet* 1989; 334(8662): 519-  
31 19 522.  
32  
33  
34 20 33. Herman J H, Appel A M, Khosla R C, et al. The in vitro effect of select classes of  
35 21 nonsteroidal antiinflammatory drugs on normal cartilage metabolism. *The Journal of*  
36 22 *rheumatology* 1986; 13(6): 1014-1018.  
37  
38  
39 23 34. Harirforoosh S, Jamali F. Renal adverse effects of nonsteroidal anti-inflammatory  
40 24 drugs. *Expert opinion on drug safety* 2009; 8(6): 669-681.  
41  
42  
43 25 35. Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis:  
44 26 a meta-analysis of randomized controlled trials. *Osteoarthritis and Cartilage* 2007;  
45 27 15(8): 957-965.  
46  
47  
48 28 36. Caldwell D M, Ades A E, Higgins J P T. Simultaneous comparison of multiple  
49 29 treatments: combining direct and indirect evidence. *BMJ* 2005; 331(7521): 897.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 1 37. Moher D , Shamseer L , Clarke M, et al. Preferred reporting items for systematic  
4 2 review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1  
5  
6 3 38. Jüni P, Reichenbach S, Dieppe P. Osteoarthritis: rational approach to treating the  
7 4 individual. *Best Practice & Research Clinical Rheumatology*, 2006, 20(4): 721-740.  
8  
9 5 39. Reichenbach S, Sterchi R, Scherer M, et al. Meta-analysis: chondroitin for  
10 6 osteoarthritis of the knee or hip. *Annals of internal medicine* 2007; 146(8): 580-590.  
11  
12 7 40. Nüesch E, Trelle S, Reichenbach S, et al. The effects of excluding patients from  
13 8 the analysis in randomised controlled trials: meta-epidemiological study. *BMJ* 2009;  
14 9 339: b3244.  
15  
16 10 41. Higgins J, Green S, editors. Chapter 8: Assessing risk of bias in included studies.  
17 11 *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane  
18 12 Collaboration. Version 5.1.0 (updated March 2011); 2011; 2001;323(7303):42–6  
19  
20 13 42. Palmer SC, Mavridis D, Navaresem E, et al. Comparative efficacy and safety of  
21 14 blood pressure-lowering agents in adults with diabetes and kidney disease: a network  
22 15 meta-analysis. *Lancet* 2015; 385: 2047–56.  
23  
24 16 43. Zhou X, Qin B, Whittington C, et al. Comparative efficacy and tolerability of  
25 17 first-generation and newer-generation antidepressant medications for depressive  
26 18 disorders in children and adolescents: study protocol for a systematic review and  
27 19 network meta-analysis. *BMJ open* 2015; 5(9): e007768.  
28  
29 20 44. Follmann D, Elliott P, Suh I L, et al. Variance imputation for overviews of clinical  
30 21 trials with continuous response. *Journal of clinical epidemiology* 1992; 45(7): 769-  
31 22 773.  
32  
33 23 45. Da Costa B R, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-  
34 24 inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network  
35 25 meta-analysis. *The Lancet* 2017; 390(10090): e21-e33.  
36  
37 26 46. Eberle E, Ottilinger B. Clinically relevant change and clinically relevant  
38 27 difference in knee osteoarthritis. *Osteoarthritis and cartilage* 1999; 7(5): 502-503.  
39  
40 28 47. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically  
41 29 important differences of rehabilitation intervention with their implications for  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1 required sample sizes using WOMAC and SF-36 quality of life measurement  
2 instruments in patients with osteoarthritis of the lower extremities. *Arthritis Care &*  
3 *Research* 2001; 45(4): 384-391.
- 4 48. Angst F, Aeschlimann A, Michel B A, et al. Minimal clinically important  
5 rehabilitation effects in patients with osteoarthritis of the lower extremities. *The*  
6 *Journal of rheumatology* 2002; 29(1): 131-138.
- 7 49. Salaffi F, Stancati A, Silvestri C A, et al. Minimal clinically important changes in  
8 chronic musculoskeletal pain intensity measured on a numerical rating scale.  
9 *European*
- 10 50. Bellamy N. Outcome measurement in osteoarthritis clinical trials. *The Journal of*  
11 *rheumatology*. Supplement 1995; 43: 49-51. *Journal of pain* 2004; 8(4): 283-291.
- 12 51. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic  
13 reviews. *BMJ* 1994; 309(6964): 1286.
- 14 52. Salanti G, Ades A E, Ioannidis J P A. Graphical methods and numerical  
15 summaries for presenting results from multiple-treatment meta-analysis: an overview  
16 and tutorial. *Journal of clinical epidemiology* 2011; 64(2): 163-171.
- 17 53. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials*  
18 1986; 7(3): 177-188.
- 19 54. Salanti G, Higgins J P T, Ades A E, et al. Evaluation of networks of randomized  
20 trials. *Statistical methods in medical research* 2008; 17(3): 279-301.
- 21 55. Lu G, Ades A E. Combination of direct and indirect evidence in mixed treatment  
22 comparisons. *Statistics in medicine* 2004; 23(20): 3105-3124.
- 23 56. Cooper N J, Sutton A J, Lu G, et al. Mixed comparison of stroke prevention  
24 treatments in individuals with nonrheumatic atrial fibrillation. *Archives of internal*  
25 *medicine* 2006; 166(12): 1269-1275.
- 26 57. Brooks S P, Gelman A. General methods for monitoring convergence of iterative  
27 simulations. *Journal of computational and graphical statistics* 1998; 7(4): 434-455.

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2  
3 1 58. White I R, Barrett J K, Jackson D, et al. Consistency and inconsistency in network  
4 2 meta- analysis: model estimation using multivariate meta- regression. Research  
5 3 synthesis methods 2012; 3(2): 111-125.  
6  
7  
8 4 59. Higgins J P T, Jackson D, Barrett J K, et al. Consistency and inconsistency in  
9 5 network meta- analysis: concepts and models for multi- arm studies. Research  
10 6 synthesis methods 2012; 3(2): 98-110.  
11  
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13 7 60. Higgins JPT, Jackson D, Barret JK, Lu G, Ades AE, White IR. Consistency and  
14 8 inconsistency in network meta-analysis: concepts and models for multiarm studies.  
15 9 Res Syn Meth 2012; 3: 98-110.  
16  
17  
18 10 61. Dias S, Sutton AJ, Welton NJ, et al. Evidence synthesis for decision making 3:  
19 11 heterogeneity-subgroups, meta-regression, bias, and bias-adjustment. Med Decis  
20 12 Making 2013; 33:618-40.-176.  
21  
22  
23 13 62. Abe H, Minatoguchi S, Ohashi H, et al. Renoprotective effect of the addition of  
24 14 losartan to ongoing treatment with an angiotensin converting enzyme inhibitor in  
25 15 type-2 diabetic patients with nephropathy. Hypertension Research 2007; 30(10): 929.  
26  
27  
28 16 63. Estacio R O, Coll J R, Tran Z V, et al. Effect of intensive blood pressure control  
29 17 with valsartan on urinary albumin excretion in normotensive patients with type 2  
30 18 diabetes. American journal of hypertension 2006; 19(12): 1241-1248.  
31  
32  
33 19 64. Smith S R, Deshpande B R, Collins J E, et al. Comparative pain reduction of oral  
34 20 non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic  
35 21 analytic review. Osteoarthritis and cartilage 2016; 24(6): 962-972.  
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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
<b>ADMINISTRATIVE INFORMATION</b>		
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>
<b>INTRODUCTION</b>		
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)
<b>METHODS</b>		
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 $\tau$ )
	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  
2  
3 18.prospective studies.sh.  
4

5 19.(control\$ or prospectiv\$ or volunteer\$).ab,ti.  
6  
7

8 **Search terms for Osteoarthritis**  
9

10 20.exp osteoarthritis/  
11

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

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

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

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

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

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

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

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

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

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

32 **Search terms for Opioids**  
33

34 31.exp Analgesics, Opioid/  
35

36 32.exp Narcotics/  
37

38 33.acetyldihydrocodeine.tw.  
39

40 34.alfentanil.tw.  
41

42 35.allylprodine.tw.  
43

44 36.alphamethylfentanyl.tw.  
45

46 37.alphaprodine.tw.  
47

48 38.benzylmorphine.tw.  
49  
50  
51  
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1  
2  
3 39.betaprodine.tw.  
4

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.  
29

30  
31 50.diacetylmorphine.tw.  
32

33 51.diamorphine.tw.  
34

35  
36 52.dihydrocodeine.tw.  
37

38 53.dihydromorphine.tw.  
39

40 54.dihydromorphone.tw.  
41

42  
43 55.diphenoxylate.tw.  
44

45  
46 56.dipipanone.tw.  
47

48 57.enadoline.tw.  
49

50  
51 58.ethylketazocine.tw.  
52

53 59.ethylmorphine.tw.  
54

55  
56 60.etonitazene.tw.  
57

58  
59 61.etorphine.tw.  
60



1  
2  
3 62.fentanyl.tw.  
4

5  
6 63.heroin.tw.  
7

8  
9 64.hydrocodone.tw.  
10

11  
12 65.hydromorphin\$.tw.  
13

14  
15 66.hydromorphone.tw.  
16

17  
18 67.ketazocine.tw.  
19

20  
21 68.ketobemidone.tw.  
22

23  
24 69.lefetamine.tw.  
25

26  
27 70.levomethadon.tw.  
28

29  
30 71.levomethadyl.tw.  
31

32  
33 72.levomethorphan\$.tw.  
34

35  
36 73.levorphanol.tw.  
37

38  
39 74.loperamide.tw.  
40

41  
42 75.meperidine.tw.  
43

44  
45 76.meptazinol.tw.  
46

47  
48 77.methadone.tw.  
49

50  
51 78.methadyl.tw.  
52

53  
54 79.methylmorphine.tw.  
55

56  
57 80.morphin\$.tw.  
58

59  
60 81.nalbuphine.tw.

82.narcotic\$.tw.

83.nicocodeine.tw.

84.nicomorphine.tw.

1  
2  
3 85.normorphine.tw.  
4

5 86.noscapin\$.tw.  
6

7  
8 87.ohmefentanyl.tw.  
9

10 88.opiate\$.tw.  
11

12  
13 89.opioid\$.tw.  
14

15 90.opium.tw.  
16

17  
18 91.oripavine.tw.  
19

20 92.oxycodone.tw.  
21

22  
23 93.oxycontin.tw.  
24

25 94.oxymorphone.tw.  
26

27  
28 95.papaveretum.tw.  
29

30 96.papaverin.tw.  
31

32  
33 97.pentazocine.tw.  
34

35 98.percocet.tw.  
36

37  
38 99.peronine.tw.  
39

40 100. pethidine.tw.  
41

42  
43 101.phenazocine.tw.  
44

45 102.phencyclidine.tw.  
46

47  
48 103.pholcodine.tw.  
49

50 104.piritramid\$.tw.  
51

52  
53 105.prodine.tw.  
54

55 106.promedol.tw.  
56

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58 107.propoxyphene.tw.  
59  
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1  
2  
3 108.remifentanil.tw.  
4

5 109.sufentanil.tw.  
6

7 110.tapentadol.tw.  
8  
9

10 111.thebaine.tw.  
11

12 112.tilidine.tw.  
13

14 113.tramadol.sh,tw.  
15

16 114.ultracet.sh,tw.  
17  
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19  
20  
21 **Combining terms**  
22

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  
24

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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27 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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29 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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31 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  
32

33 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or  
34

35 114  
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

39 117.1 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  
40

41 or 17 or 18 or 19  
42

43 118.115 and 116 and 117  
44

45 119.animal/  
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47 120.animal/ and human/  
48

49 121.119 not 120  
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51 122.118 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**

9

10  
11 1.randomized controlled trial.sh.  
12

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/  
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63  
64 18.osteoarthriti\$.ab,sh,ti.  
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67 19.osteoarthro\$.ab,sh,ti.  
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3 20.gonarthriti\$.ab,sh,ti.  
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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  
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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.  
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35 33.alphamethylfentanyl.tw.  
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37 34.alphaprodine.tw.  
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39 35.benzylmorphine.tw.  
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41 36.betaprodine.tw.  
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43 37.bezitriamide.tw.  
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45 38.buprenorphine.tw.  
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47 39.butorphanol.tw.  
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49 40.bremazocine.tw.  
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51 41.carfentan\$.tw.  
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3 42.codeine.tw.  
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6 43.contin.tw.  
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9 44.dextromoramide.tw.  
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11 45.dextropropoxyphene.tw.  
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14 46.dezocine.tw.  
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16 47.diacetylmorphine.tw.  
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19 48.diamorphine.tw.  
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21 49.dihydrocodeine.tw.  
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24 50.dihydromorphine.tw.  
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26 51.dihydromorphone.tw.  
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29 52.diphenoxylate.tw.  
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31 53.dipipanone.tw.  
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34 54.enadoline.tw.  
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36 55.ethylketazocine.tw.  
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39 56.ethylmorphine.tw.  
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41 57.etonitazene.tw.  
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44 58.etorphine.tw.  
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46 59.fentanyl.tw.  
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49 60.heroin.tw.  
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51 61.hydrocodone.tw.  
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54 62.hydromorphin\$.tw.  
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57 63.hydromorphone.tw.  
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59 64.ketazocine.tw.  
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3 65.ketobemidone.tw.  
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6 66.lefetamine.tw.  
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9 67.levomethadon.tw.  
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15 69.levomethorphan\$.tw.  
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18 70.levorphanol.tw.  
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24 72.meperidine.tw.  
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33 75.methadyl.tw.  
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36 76.methylmorphine.tw.  
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39 77.morphin\$.tw.  
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42 78.nalbuphine.tw.  
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44  
45 79.narcotic\$.tw.  
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48 80.nicocodeine.tw.  
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51 81.nicomorphine.tw.  
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54 82.normorphine.tw.  
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57 83.noscapin\$.tw.  
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59  
60 84.ohmefentanyl.tw.

85.opiate\$.tw.

86.opioid\$.tw.

87.opium.tw.

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- 2
- 3 88.oripavine.tw.
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- 5 89.oxycodone.tw.
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- 8 90.oxycontin.tw.
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- 13 92.papaveretum.tw.
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- 16 93.papaverin.tw.
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- 18 94.pentazocine.tw.
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- 21 95.percocet.tw.
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- 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.
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- 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



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3 111.ultracet.sh,tw.  
4  
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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
- 11 8. TX (doubl\$ n25 mask\$)
- 12
- 13 9. TX (trebl\$ n25 blind\$)
- 14
- 15
- 16 10. TX (trebl\$ n25 mask\$)
- 17
- 18 11. TX (tripl\$ n25 blind\$)
- 19
- 20
- 21 12. TX (tripl\$ n25 mask\$)
- 22
- 23 13. (MH “Placebos”)
- 24
- 25
- 26 14. TX placebo\$
- 27
- 28
- 29 15. TX random\$
- 30
- 31 16. (MH “Study Design+”)
- 32
- 33 17. (MH “Comparative Studies”)
- 34
- 35 18. (MH “Evaluation Research”)
- 36
- 37 19. (MH “Prospective Studies+”)
- 38
- 39 20. TX (control\$ or prospectiv\$ or volunteer\$)
- 40
- 41
- 42 21. S1 or S2 or (...) or S20
- 43
- 44
- 45

#### 46 **Search terms for Osteoarthritis**

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

- 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

29 129. S21 and S43 and S128  
30  
31

## 32 **CENTRAL** 33

### 34 **Search terms for Osteoarthritis** 35

36 #1. MeSH descriptor Osteoarthritis explode all trees  
37

38 #2. (osteoarthritis\* OR osteoarthro\* OR gonarthriti\* OR gonarthro\* OR coxarthriti\*  
39 OR coxarthro\* OR arthros\* OR arthrot\* OR ((knee\* OR hip\* OR joint\*) near/3  
40 (pain\* OR ach\* OR discomfort\*)) OR ((knee\* OR hip\* OR joint\*) near/3 stiff\*)) in  
41 Trials  
42

### 43 **Search terms for Opioids** 44

45 #3. MeSH descriptor Analgesics, Opioid explode all trees  
46

47 #4. MeSH descriptor Narcotics explode all trees  
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  
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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  
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