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Preoperative opioid use and complications following total joint replacement: A protocol for a systematic review and meta-analysis.

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ABSTRACT

Introduction:

Mounting evidence now indicates that preoperative opioid use is associated with an array of complications following total joint replacement (TJR). However, evidence of these risks remains fragmented. A comprehensive and well-integrated understanding of this body of evidence is necessary to appropriately inform treatment decisions, the allocation of limited healthcare resources, and the direction of future clinical research. The proposed systematic review and meta-analysis aims to identify and synthesize the available evidence of an association between opioid use prior to TJR and postoperative complications, categorized by complication type.

Methods and Analysis:

We will search MEDLINE, EMBASE, CINAHL, PsycINFO, Web of Science, and Google Scholar from inception to September 2019. Observational and experimental studies that compare either preoperative opioid users or chronic preoperative opioid users who have undergone elective total joint replacement (TJR) to opioid naïve TJR patients will be included. The primary outcomes will be postoperative complications, which will be categorized as either mortality, morbidity, or joint-related complications. The secondary outcomes will be persistent postoperative opioid use, readmission, and length of stay. Individual study quality will be assessed using the relevant NIH-NHLBI Study Quality Assessment Tools. Findings will be reported in narrative and tabular form, and, where possible, risk ratios (dichotomous outcomes) or standardized mean differences (continuous outcomes) will be reported with 95% confidence intervals. Where appropriate, random effect meta-analyses will be conducted for each outcome, and heterogeneity will be quantified using I^2 statistic. This study will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines.

Ethics and dissemination:

Ethics approval will not be required as no primary or private data is being collected. Findings will be disseminated through peer-reviewed publication and presentation at academic conferences.

Protocol registration:

PROSPERO (Submitted - Awaiting confirmation)

Keywords: Opioid, Total Joint Replacement, Complications, Systematic review, Meta-analysis

Article Summary: Strengths and Limitations of this Study

- This systematic review will be the first to identify complications that are associated with preoperative opioid use among TJR patients.
- The comprehensive *a priori* categorization of complications will ensure that this review highlights specific areas in which further research is needed.
- The search strategy has been designed using key terms, synonyms, and database specific vocabulary across a range of carefully selected databases to ensure comprehensive coverage of both peer reviewed and grey literature.
- The recent nature of much of the research in this domain may limit the amount of data available for some of the pre-defined outcome categories.

BACKGROUND

Total joint replacement is a safe and effective surgery, which aims to restore physical function and offer long-term pain relief to patients suffering from severe arthritis.[1-3] In recent decades, the number of total joint replacements (TJRs) performed each year has risen substantially. Between 2000 and 2014, the number of total hip replacement (THR) and total knee replacement (TKR) surgeries performed annually in the United States more than doubled.[4] Over a similar period, opioid use has become more prevalent among patients presenting for TJR. Data from Australia indicate that the prevalence of preoperative opioid use increased between 2001 and 2012 from 37% to 49% in TKR patients and 44% to 54% in THR patients.[5] In the United States, where opioid misuse has been declared a public health emergency,[6] this trend is likely even more pronounced; with one recent study reporting that more than 87% of commercially-insured TJR patients had received an opioid prescription in the year leading up to their procedure.[7]

There is now mounting evidence that opioid use prior to TJR is associated with an array of surgical complications.[8-11] Despite this, a number of recent reviews[12-14] have failed to report that preoperative opioid use is associated with an increased risk of certain serious complications among TJR patients. In a 2016 systematic review, Kunutsor and colleagues did not report preoperative opioid use as a risk factor for periprosthetic infections following TJR.[12] Similarly, a 2016 scoping review conducted by Jasper and colleagues, which aimed to identify factors associated with revision following TKR, did not identify preoperative opioid use as a relevant risk factor.[14] There is now evidence that preoperative opioid use places patients at an increased risk of experiencing the specific outcomes examined in both of these reviews.[10][11] These omissions are largely due to the relatively recent nature of much of the evidence linking preoperative opioid use with these important complications. Nonetheless, this underreporting within the review literature suggests that the risks associated with preoperative opioid use among TJR patients remains underrecognized.

In addition to being underreported in reviews examining specific complications, the more general evidence of an association between preoperative opioid use and complications following TJR remains fragmented. To date, no systematic reviews have examined the evidence of such an association. The only systematic review specifically examining the impact of preoperative opioid use on outcomes following TJR focused exclusively on patient reported pain and function outcomes.[15] This review, which was conducted by Goplen and colleagues,[15] found that preoperative opioid users experienced worse pain and function improvements between 6 and 58 months following TJR, when compared to opioid-naïve patients. While pain and function outcomes are undoubtedly central to decisions made about TJR procedures,[16] prudent decision-making requires that such factors be weighed against all risks associated with the procedure.

A comprehensive and well-integrated understanding of complications associated with opioid use prior to TJR is necessary to appropriately inform treatment decisions, the allocation of limited healthcare resources, and the direction of future clinical research. Awareness of these potential complications also allows clinicians to appropriately inform patients who are using opioids about the risks of their procedure. Importantly, such awareness may also encourage surgeons and patients to treat preoperative opioid use as a modifiable risk factor that can be targeted to improve the quality and safety of surgical care. With these considerations in mind, the proposed systematic review and meta-analysis seeks to identify and synthesize available evidence of an association between opioid use prior to TJR and postoperative complications, categorized by complication type.

METHODS AND ANALYSIS:

This protocol was developed in accordance with 'Preferred Reporting Items for Systematic reviews and Meta-Analysis - Protocol' (PRIMSA-P)[17, 18] and 'Meta-analysis of Observational Studies in Epidemiology' (MOOSE)[19] guidelines. The review has been prospectively registered with the PROSPERO database (registration number) Throughout the process of conducting this review, disagreement will be resolved through discussion between these independent reviewers (CS and DG) where possible. When consensus cannot be achieved through discussion, a third author (MD) will be consulted.

Criteria for consideration in this review.

Types of Studies

This systematic review will include both descriptive (e.g. case series, cross-sectional) and analytic (e.g. retrospective cohort, prospective cohort, case-control) observational studies, as well as experimental studies (e.g. randomized controlled trials, quasi-experimental designs). Although we will include studies using experimental designs, we expect that most – if not all – of the data will be drawn from observational studies. Case

reports, editorials, commentaries, qualitative studies, and literature reviews will be excluded. However, reference lists from relevant literature reviews identified in the initial screening process will be searched to identify additional original studies. We will only include studies published in English.

Type of Population

Adult patients (≥ 18 years of age) who have undergone elective total joint replacement (TJR). Total hip, knee, shoulder, elbow, ankle, and wrist replacement patients will be included in this review. Studies exclusively examining patients who have undergone partial joint replacement will be excluded. In the instance that a study does not clearly distinguish between total and partial joint replacement, the study will be included in the primary analysis given that a vast majority of all such procedures are for total joint replacements.[20, 21] The impact of including these studies will be tested through sensitivity analyses. Studies specifically examining patients who have undergoing non-elective TJR will be excluded. Study that do not clearly distinguish between elective and non-elective procedures will be included in the primary analysis. The impact of including these studies will also evaluated through sensitivity analyses. Studies of surgical populations that include patients undergoing procedures other than joint replacement will only be included only if sufficient data is available to isolate measures of association for TJR patients.

Type of Exposure

The two exposures of interest are *preoperative opioid use* and *chronic preoperative opioid use*. As there is no standard definition of preoperative opioid use in the literature, we expect this concept to be characterized heterogeneously between studies. For this reason, studies will be included in our analysis of preoperative opioid use if they report that the patient has been prescribed opioids at any time prior to admission for TJR. Studies will be excluded if they determine patients' exposure status based upon less than 30 days of preoperative data. Informed by the *Centre for Disease Control's*

recommendation that long-term opioid therapy be reviewed at least every three months,[22] chronic preoperative opioid use will be defined as ongoing use for ≥ 90 days prior to presenting for surgery. Findings related to preoperative use and chronic preoperative use will be reported and analyzed separately.

Opioid use in the perioperative period (i.e. once a patient been admitted for surgery) will not be considered a relevant exposure. Studies examining preemptive analgesia will also be excluded, as will studies explicitly examining the impact of preoperative opioid abuse, addiction, or dependence. To this end, studies specifically examining patients who used buprenorphine or methadone before surgery will not be included, as these medications are predominately prescribed for the treatment of opioid use disorder.[23]

Type of Comparison

The comparison of interest is adult (≥ 18 years of age) total joint replacement patients who have not used or been prescribed opioids in the lead up to admission for surgery (i.e. opioid naïve patients). Studies will only be included if they consider patients opioid naïve based on at least the 30 days immediately before presenting for surgery. Studies that only compare preoperative opioid use with the use of other medications (e.g. benzodiazepines) will be excluded.

Types of Outcome Measure

The primary outcomes of interest in this systematic review are complications, which provide a direct measure of the patient's physical or psychological health following the indexed procedure. Informed by Australian national quality and safety measures[24] and previously published work examining complications associated with preoperative smoking[25] and alcohol consumption,[26] the primary outcomes will be categorized as follows:

- **Mortality:** Any measure of mortality within one year of the indexed procedure will be included in our analysis; however, analyses of mortality will be stratified by the timeframe examined (e.g. 30-days, 90-days, 1-year).
- **Morbidity:** Measures of morbidity occurring within either 30 or 90-days of the indexed procedure will be categorized as: general complications, medication-related complications, wound complications, general infections, pulmonary complications, cardiovascular complications, neurological complications, gastrointestinal complications, renal/urinary complication, falls resulting in fracture or intracranial injury, unplanned returns to theatre or additional invasive interventions, bleedings, unplanned ICU admissions, and other complications.
- **Joint-related complications:** Any complications that are specific to the TJR procedure (e.g. revision, joint infection, or stiffness requiring manipulation under anesthetic)[27, 28] will be reported separately where possible. As these complications are necessarily tied to the indexed procedure, no time restrictions will be placed on measures relating to these outcomes.

The secondary outcomes of interest for this review provide valuable, but indirect, measures of the patient's course of recovery following the indexed procedure.

- **Persistent postoperative opioid use:** Any measure which includes patients receiving a prescription of opioids ≥ 90 days after the indexed procedure will be included in the analysis. This was informed by the CDC's recommendation that long-term opioid therapy be reviewed at least every three months.[22]
- **Unplanned readmission:** Measures of readmission within 90-days of discharge will be included in our analysis; however, all analyses of readmission will be stratified by the timeframe examined (e.g. 30-day, 90-day).
- **Length of stay:** Studies examining length of hospital stay following surgery will be included in our analysis.

Despite the importance of information about pain and function to decisions regarding TJR, to avoid duplicating work done in a recent systematic review by Goplen and colleagues,[15] patient reported pain and function outcomes will be excluded from this review.

Search Strategy

A comprehensive literature search of MEDLINE, EMBASE, CINAHL, PsycINFO, and Web of Science from inception to September 2019 will be conducted. These databases have been selected to maximize the coverage of the literature search.[29] The search strategy will be formulated by two authors (CS and DG) in consultation with an external research librarian. The search will be tailored to each database using keywords, database-specific vocabulary (e.g. Medical Subject Headings), and relevant Boolean operators to cover the following conceptual groups: (1) opioids; and (2) total joint replacement; and (3) risk or outcomes or complications or mortality or morbidity. See Table 1 for the full search MEDLINE search strategy. A narrower supplementary search will be conducted using Google Scholar, as this has been shown to regularly capture eligible studies not returned by other databases.[29, 30] Articles which referenced ("forward citation tracking") or were referenced by ("backwards citation tracking") included studies and relevant published literature reviews will be searched to identify additional eligible studies.[31]

Table 1: Full Medline Search Strategy via OVID

1	exp Narcotics/ or exp Analgesics, Opioid/ or opioid*.mp. or opiate*.mp. or narcotic*.mp.
2	exp Arthroplasty/ or (arthroplasty or joint replacement or shoulder replacement or knee replacement or hip replacement or elbow replacement or wrist replacement or ankle replacement).mp.
3	exp Treatment Outcome/ or exp "Outcome Assessment (Health Care)"/ or outcome*.mp.

4	exp Health Risk Behaviors/ or exp Risk/ or exp Risk Factors/ or risk*.mp.
5	morbidity.mp. or exp Morbidity/ or mortality.mp. or exp Mortality/or exp Intraoperative Complications/ or exp Postoperative Complications/ or complication*.mp.
Final Search: 1 and 2 and (3 or 4 or 5)	

Data Collection and Management

To avoid issues with the export functionality of Google Scholar, Harzing's Publish or Perish (V.7) will be used to extract relevant information from the supplementary search. Covidence will be used for deduplication, screening, and data extraction. Statistical analysis will be conducted using Review Manager software.

Study Selection

Two reviewers (CS and DG) will independently screen the titles and abstracts of all items identified through the search process. After 10% of studies have been screened, the selection process will be reviewed to ensure that eligibility criteria are consistently applied. The full text documents of potentially relevant studies will then be compiled and reviewed against the inclusion and exclusion criteria by two reviewers (CS and DG). Forward and backward citation tracking of all studies that remain after full text screening will be used to identify additional potentially eligible studies. The full text of studies identified through this final stage of the search will then be independently assessed for inclusion by two reviewers (CS and DG). The study selection process will be reported using a PRISMA flow diagram.[32]

Data Extraction

Data will be extracted independently by two reviewers (CS and DG) using a standardized data collection form. The following details will be extracted from all included articles:

- Publication details: First author, year of publication, title, publication venue
- Study design: Study design, data source, sample size, funding source.
- Clinical setting: Location, public/private/veterans' institution
- Population characteristics: Demographic information (e.g. age, sex, BMI), comorbidities
- Surgery type: Primary/revision/undefined, hip/knee/shoulder/elbow/ankle/wrist, indication for surgery, TJR clearly defined, elective TJR clearly defined.
- Exposure: Preoperative opioid use definition, prolonged preoperative opioid use definition.
- Outcomes: Outcome class, outcome definition
- Results summary: Relative risk or standard mean difference and 95% confidence intervals for each outcome measure, degree of effect size adjustment.

Where adjusted and unadjusted measures are reported for a given outcome, the most comprehensively adjusted outcome measures will be used. Where outcomes are measured at multiple time points, the effects measured at the longest relevant time points will be recorded. Missing values will be calculated whenever there is sufficient data available to do so. Study authors will be contacted to obtain missing data, and response rates will be reported in the published review.

Individual Study Quality Assessment

The quality of all included studies will be independently assessed by two reviewers (CS and DG) using the appropriate NIH/NHLBI *Study Quality Assessment Tool*.[33] The appropriate tool will be determined for each included study based upon the research design that was used. These tools include items to evaluate potential flaws in study method or implementation, including sources of bias, study power, confounding, and other factors. In response to each item included in these tools, reviewers will select "yes," "no," or "cannot determine/not reported/not applicable". Responses to each of these items will inform a judgment of each study as either of "good," "fair," or "poor"

quality. Where studies are deemed to be of poor quality, explicit justification will be offered and reported in the published review.

Data synthesis and subgroup analysis.

The characteristics of all included studies will be reported in narrative and tabular form. Where the outcomes reported are considered sufficiently similar from a clinical and methodological perspective,[34] meta-analyses will be conducted for each of the predefined primary and secondary outcome categories. In all instances, outcomes associated with preoperative opioid use and chronic preoperative use will be analyzed and reported separately. For data that can be meaningfully pooled, a random effect model will be used for meta-analysis as we expect significant between study heterogeneity.[35] For dichotomous outcomes, relative risk (RR) will be reported and standardized mean difference (SMD) will be used for the analysis of continuous outcome variables. 95% confidence intervals will be reported for all effect estimates. Sensitivity analysis will explore the impact of including both unadjusted and adjusted effect size estimates in our analysis, and wherever possible adjusted effect sizes will be reported alongside overall pooled effect sizes. Sensitivity analyses will also be conducted to evaluate the impact of including studies of imprecisely defined populations. To account for expected heterogeneity, which will be assessed visually and using the I^2 statistic, subgroup analyses will be conducted where possible. Planned subgroup analyses include: geographic location, type of surgery, and preoperative opioid use categorization. Where meta-analysis is deemed inappropriate for a given outcome variable, the results will be included in a narrative synthesis. In the instance that no studies have reported on an outcome relevant to one of the predefined outcome categories, this will be explicitly reported during the narrative synthesis.

Meta-bias assessment

We have aimed to minimize the effect of publication bias on the findings of this review by placing no restrictions on the inclusion of ‘grey literature’.[36] Furthermore, our

search strategy has been designed to ensure comprehensiveness by drawing upon a database that is commonly overlooked by systematic reviewers (i.e. Google Scholar), despite having been shown to be effective at capturing grey literature.[29, 30] To investigate the potential residual effects of publication bias, funnel plots will be generated for meta-analyses that include ten or more studies.[37] Where significant asymmetry is detected in the funnel plot, potential sources of this asymmetry will be explored and, if deemed appropriate, the trim and fill method may be used to account for the possibility of publication bias.[37, 38]

Confidence in cumulative evidence

Two reviewers (CS and DG) will independently assess the quality of cumulative evidence in relation to each reported outcome measures using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.[39-41] The five GRADE considerations – study limitations, imprecision, inconsistency, indirectness, and publication bias – will be used to assess each study before reporting the quality of evidence as high, moderate, low, or very low.[41] The results of the cumulative quality assessment will be presented in a Summary of Findings table.[41, 42] Care will be taken to include all outcome categories specified in this protocol in this table, to ensure that the absence of evidence relating to particular types of complications is reported clearly and consistently.

Ethics and dissemination

Ethics approval will not be required for the proposed study, as it draws on previously published data and will not impact upon the privacy of any individual patients. The results of the systematic review will be disseminated through publication in a peer-reviewed journal, and through presentation at relevant academic conferences. It will also be disseminated to members of the *Consortium Against the overuse of Opiates in Surgery* (CAOS), which is a recently formed multinational initiative that aims to address issues relating to opioid use among surgical patients.

DISCUSSION

As it currently stands, the available research examining the impact of opioid use prior to TJR on postoperative complications remains fragmented. Not only does this mean that the scope of the available evidence is difficult to interpret, it has also resulted in some serious risks associated with opioid use prior to TJR potentially remaining underrecognized. The proposed systematic review and meta-analysis aims to provide some much-needed order and clarity to the growing body of research in this domain. By providing a comprehensive and well-integrated understanding of complications associated with opioid use prior to TJR, this review will allow clinicians to inform preoperative opioid users about the risks of their procedure more appropriately. The findings of the proposed review will also offer insight that is necessary if both clinicians and patients are to make prudent treatment decisions. Finally, and perhaps most importantly, the information gleaned from this review will clarify the extent to which targeting preoperative opioid use may improve the quality and safety of surgical care for patients undergoing total joint replacement.

Contributions:

All authors contributed to the conception and design of the protocol; CS wrote the first draft; All authors contributed to revising the manuscript for critically important intellectual content, and read and approved the submitted version. CS is the guarantor of this review.

Competing interests:

Dr. Dowsey reports personal fees from Pfizer and grants from Medacta, outside the submitted work; Dr. Choong reports personal fees from Stryker, Johnson & Johnson, and Kluwer, and grants from Medacta, outside the submitted work. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REFERENCES

1. Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, et al. Knee replacement. Lancet. 2012;379(9823):1331-40.
2. Ng CY, Ballantyne JA, Brenkel IJ. Quality of life and functional outcome after primary total hip replacement. A five-year follow-up. J Bone Joint Surg Br. 2007;89(7):868-73.
3. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. Lancet. 2007;370(9597):1508-19.
4. Sloan M, Premkumar A, Sheth NP. Projected Volume of Primary Total Joint Arthroplasty in the U.S., 2014 to 2030. J Bone Joint Surg Am. 2018;100(17):1455-60.
5. Inacio MCS, Cashman K, Pratt NL, Gillam MH, Caughey G, Graves SE, et al. Prevalence and changes in analgesic medication utilisation 1 year prior to total joint replacement in an older cohort of patients. Osteoarthritis Cartilage. 2018;26(3):356-62.
6. Haffajee RL, Frank RG. Making the Opioid Public Health Emergency Effective. JAMA Psychiatry. 2018;75(8):767-8.
7. Kim SC, Choudhry N, Franklin JM, Bykov K, Eikermann M, Lii J, et al. Patterns and predictors of persistent opioid use following hip or knee arthroplasty. Osteoarthritis Cartilage. 2017;25(9):1399-406.
8. Huang J, Bin Abd Razak HR, Yeo SJ. Incidence of postoperative delirium in patients undergoing total knee arthroplasty-an Asian perspective. Ann Transl Med. 2017;5(16):321.
9. Kim SC, Jin Y, Lee YC, Lii J, Franklin PD, Solomon DH, et al. Association of Preoperative Opioid Use With Mortality and Short-term Safety Outcomes After Total Knee Replacement. JAMA Netw Open. 2019;2(7):e198061.

10. Bell KL, Shohat N, Goswami K, Tan TL, Kalbian I, Parvizi J. Preoperative Opioids Increase the Risk of Periprosthetic Joint Infection After Total Joint Arthroplasty. J Arthroplasty. 2018;33(10):3246-51 e1.
11. Ben-Ari A, Chansky H, Rozet I. Preoperative Opioid Use Is Associated with Early Revision After Total Knee Arthroplasty: A Study of Male Patients Treated in the Veterans Affairs System. J Bone Joint Surg Am. 2017;99(1):1-9.
12. Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD, Team I. Patient-Related Risk Factors for Periprosthetic Joint Infection after Total Joint Arthroplasty: A Systematic Review and Meta-Analysis. PLoS One. 2016;11(3):e0150866.
13. Prokopetz JJ, Losina E, Bliss RL, Wright J, Baron JA, Katz JN. Risk factors for revision of primary total hip arthroplasty: a systematic review. BMC Musculoskelet Disord. 2012;13(1):251.
14. Jasper LL, Jones CA, Mollins J, Pohar SL, Beaupre LA. Risk factors for revision of total knee arthroplasty: a scoping review. BMC Musculoskelet Disord. 2016;17:182.
15. Goplen CM, Verbeek W, Kang SH, Jones CA, Voaklander DC, Churchill TA, et al. Preoperative opioid use is associated with worse patient outcomes after Total joint arthroplasty: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2019;20(1):234.
16. Szawlowski S, Choong PFM, Li J, Nelson E, Nikpour M, Scott A, et al. How do surgeons' trade-off between patient outcomes and risk of complications in total knee arthroplasty? a discrete choice experiment in Australia. BMJ Open. 2019;9(7):e029406.
17. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.
18. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.
19. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.
20. Bolognesi MP, Greiner MA, Attarian DE, Watters TS, Wellman SS, Curtis LH, et al. Unicompartmental knee arthroplasty and total knee arthroplasty among Medicare beneficiaries, 2000 to 2009. J Bone Joint Surg Am. 2013;95(22):e174.

21. Australian Orthopaedic Association National Joint Replacment Registry. Hip, Knee & Shoulder Arthroplasty: 2019 Annual Report. AOA, 2019. [Avaliable from: aoanjrr.sahmri.com/documents/ 10180/668596/Hip%2C+Knee+%26+Shoulder+Arthroplasty/c287d2a3-22df-a3bb-37a2-91e6c00bfcf0]

22. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. JAMA. 2016;315(15):1624-45.

23. Srivastava A, Kahan M, Nader M. Primary care management of opioid use disorders Abstinence, methadone, or buprenorphine-naloxone? Can Fam Physician. 2017;63(3):200-5.

24. Australian Commission on Safety and Quality in Health Care . National Safety and Quality Health Service Standards: Guide for Hospitals. ACSQHC, 2017. [Available from: https://www.safetyandquality .gov.au/sites/default/files/migrated/National-Safety-and-Quality-Health-Service-Standards-Guide-for-Hospitals.pdf]

25. Gronkjaer M, Eliasen M, Skov-Ettrup LS, Tolstrup JS, Christiansen AH, Mikkelsen SS, et al. Preoperative smoking status and postoperative complications: a systematic review and meta-analysis. Ann Surg. 2014;259(1):52-71.

26. Eliasen M, Gronkjaer M, Skov-Ettrup LS, Mikkelsen SS, Becker U, Tolstrup JS, et al. Preoperative alcohol consumption and postoperative complications: a systematic review and meta-analysis. Ann Surg. 2013;258(6):930-42.

27. Iorio R, Della Valle CJ, Healy WL, Berend KR, Cushner FD, Dalury DF, et al. Stratification of standardized TKA complications and adverse events: a brief communication. Clin Orthop Relat Res. 2014;472(1):194-205.

28. Healy WL, Iorio R, Clair AJ, Pellegrini VD, Della Valle CJ, Berend KR. Complications of Total Hip Arthroplasty: Standardized List, Definitions, and Stratification Developed by The Hip Society. Clin Orthop Relat Res. 2016;474(2):357-64.

29. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. Syst Rev. 2017;6(1):245.

30. Haddaway NR, Collins AM, Coughlin D, Kirk S. The Role of Google Scholar in Evidence Reviews and Its Applicability to Grey Literature Searching. PLoS One. 2015;10(9):e0138237.

31. Kuper H, Nicholson A, Hemingway H. Searching for observational studies: what does citation tracking add to PubMed? A case study in depression and coronary heart disease. BMC Med Res Methodol. 2006;6(1):4.

32. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339(4):b2535.
33. National Institutes of Health, National Heart, Lung, and Blood Institute. Study quality assessment tools. NIH- NHLBI 2017 [Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.]
34. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2011.
35. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010;1(2):97-111.
36. Song F, Hooper, Loke Y. Publication bias: what is it? How do we measure it? How do we avoid it? Open Access Journal of Clinical Trials. 2013;2013(5):71-81.
37. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds) Cochrane handbook for systematic reviews of interventions version 6.0 (Updated July 2019). Cochrane 2019 [Available from: www.training.cochrane.org/handbook.]
38. Weinhandl ED, Duval S. Generalization of trim and fill for application in meta-regression. Res Synth Methods. 2012;3(1):51-67.
39. Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ. 2015;350:h870.
40. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
41. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.
42. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158-72.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments			
	#4	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	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	10
Sponsor	#5b	Provide name for the review funder and / or sponsor	10
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	10
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	3-4

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	#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	4-6
Information sources	#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	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	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)	7-8
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	8

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6, 8
Risk of bias in individual studies	#14	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	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8-9
Data synthesis	#15b	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 I2, Kendall's τ)	9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	9

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

BMJ Open

Preoperative opioid use and complications following total joint replacement: A protocol for a systematic review and meta-analysis.

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Preoperative opioid use and complications following total joint replacement: A protocol for a systematic review and meta-analysis.

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ABSTRACT

Introduction:

Mounting evidence now indicates that preoperative opioid use is associated with an array of complications following total joint replacement (TJR). However, evidence of these risks remains fragmented. A comprehensive and well-integrated understanding of this body of evidence is necessary to appropriately inform treatment decisions, the allocation of limited healthcare resources, and the direction of future clinical research. The proposed systematic review and meta-analysis aims to identify and synthesize the available evidence of an association between opioid use prior to TJR and postoperative complications, categorized by complication type.

Methods and Analysis:

We will search MEDLINE, EMBASE, CINAHL, PsycINFO, and Web of Science from inception to April 2020. Observational and experimental studies that compare preoperative opioid users who have undergone elective total joint replacement (TJR) to opioid naïve TJR patients will be included. The primary outcomes will be postoperative complications, which will be categorized as either mortality, morbidity, or joint-related complications. The secondary outcomes will be persistent postoperative opioid use, readmission, and length of stay. Individual study quality will be assessed using the relevant NIH-NHLBI Study Quality Assessment Tools. Findings will be reported in narrative and tabular form, and, where possible, odds ratios (dichotomous outcomes) or standardized mean differences (continuous outcomes) will be reported with 95% confidence intervals. Where appropriate, random effect meta-analyses will be conducted for each outcome, and heterogeneity will be quantified using the I^2 statistic and Cochran's Q test. This study will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines.

Ethics and dissemination:

Ethics approval will not be required as no primary or private data is being collected. Findings will be disseminated through peer-reviewed publication and presentation at academic conferences.

Protocol registration:

PROSPERO (CRD42020153047)

Keywords: Opioid, Total Joint Replacement, Complications, Systematic review, Meta-analysis

Article Summary: Strengths and Limitations of this Study

- This systematic review will be the first to identify complications that are associated with preoperative opioid use among TJR patients.
- The comprehensive *a priori* categorization of complications will ensure that this review highlights specific areas in which further research is needed.
- The search strategy has been designed using key terms, synonyms, and database specific vocabulary across a range of carefully selected databases to ensure comprehensive coverage of both peer reviewed and grey literature.
- The recent nature of much of the research in this domain may limit the amount of data available for some of the pre-defined outcome categories.
- As most included studies are expected to rely upon observational study methods, the strength of the conclusions drawn from this review will be limited by the quality of the evidence presented in the included studies.

BACKGROUND

Total joint replacement is a safe and effective surgery, which aims to restore physical function and offer long-term pain relief to patients suffering from severe arthritis.[1-3] In recent decades, the number of total joint replacements (TJRs) performed each year has risen substantially. Between 2000 and 2014, the number of total hip replacement (THR) and total knee replacement (TKR) surgeries performed annually in the United States more than doubled.[4] Over a similar period, opioid use has become more prevalent among patients presenting for TJR. Data from Australia indicate that the prevalence of preoperative opioid use increased between 2001 and 2012 from 37% to 49% in TKR patients and 44% to 54% in THR patients.[5] In the United States, where opioid misuse has been declared a public health emergency,[6] this trend is likely even more pronounced; with one recent study reporting that more than 87% of commercially-

insured TJR patients had received an opioid prescription in the year leading up to their procedure.[7]

There is now mounting evidence that opioid use prior to TJR is associated with an array of surgical complications.[8-14] In 2017, Ben-Ari and colleagues were among the first to report that chronic opioid use was associated with an increased risk of early revision following TKR.[8] A study conducted by Bell and colleagues, published in 2018, was the first to highlight that preoperative opioid use may be a risk factor for peri-prosthetic infection following TJR.[9] Several other recent studies have supported these findings [10-12] while also demonstrating links between opioid use prior to TJR and opioid overdose,[10] systemic infection,[11] unplanned readmission,[12] postoperative delirium,[13] and in-hospital complications.[14] Given the recency of these findings, the evidence of an association between preoperative opioid use and complications following TJR remains fragmented. To date, no systematic review has examined the evidence of such an association, which may be contributing to risks associated with preoperative opioid use being under-recognized. The only systematic review specifically examining the impact of preoperative opioid use on outcomes following TJR focused exclusively on patient reported pain and function outcomes.[15] This review, which was conducted by Goplen and colleagues,[15] found that preoperative opioid users experienced worse pain and function improvements between 6 and 58 months following TJR, when compared to opioid-naïve patients. While pain and function outcomes are undoubtedly central to decisions made about TJR procedures,[16] prudent decision-making requires that such factors be weighed against all risks associated with the procedure.

A comprehensive and well-integrated understanding of complications associated with opioid use prior to TJR is necessary to appropriately inform treatment decisions, the allocation of limited healthcare resources, and the direction of future clinical research. Awareness of these potential complications also allows clinicians to appropriately inform

patients who are using opioids about the risks of their procedure. Importantly, such awareness may also encourage surgeons and patients to treat preoperative opioid use as a modifiable risk factor that can be targeted to improve the quality and safety of surgical care. With these considerations in mind, the proposed systematic review and meta-analysis seeks to identify and synthesize available evidence of an association between opioid use prior to TJR and postoperative complications, categorized by complication type.

METHODS AND ANALYSIS:

This protocol was developed in accordance with 'Preferred Reporting Items for Systematic reviews and Meta-Analysis - Protocol' (PRIMSA-P)[17, 18] and 'Meta-analysis of Observational Studies in Epidemiology' (MOOSE)[19] guidelines. The review has been prospectively registered with the PROSPERO database (CRD42020153047)

Criteria for consideration in this review.

Types of Studies

This systematic review will include both descriptive (e.g. case series, cross-sectional) and analytic (e.g. retrospective cohort, prospective cohort, case-control) observational studies, as well as experimental studies (e.g. randomized controlled trials, quasi-experimental designs). Although we will include studies using experimental designs, we expect that the majority of the data will be drawn from observational studies. Studies reported in conference abstracts and other forms of grey literature will also be included in this review. Case reports, editorials, commentaries, qualitative studies, and literature reviews will be excluded. However, reference lists from relevant literature reviews identified in the initial screening process will be searched to identify additional original studies. We will only include studies published in English.

Type of Population

The population of interest will be adult patients (≥ 18 years of age) who have undergone elective total joint replacement. Total hip, knee, shoulder, elbow, ankle, and wrist replacement patients will be included in this review. Studies exclusively examining patients who have undergone partial joint replacement will be excluded. In the instance that a study does not clearly distinguish between total and partial joint replacement, the study will be included in the primary analysis given that a vast majority of all such procedures are for total joint replacements.[20, 21] The impact of including these studies will be tested through sensitivity analyses. Studies specifically examining patients who have undergone non-elective TJR will be excluded. Studies that do not clearly distinguish between elective and non-elective procedures will be included in the primary analysis. The impact of including these studies will also be evaluated through sensitivity analyses. Studies of surgical populations that include patients undergoing procedures other than TJR will be included only if sufficient data is available to isolate measures of association for TJR patients.

Type of Exposure

The two exposures of interest are *preoperative opioid use* and *chronic preoperative opioid use*. As there is no standard definition of preoperative opioid use in the literature, we expect this concept to be characterized heterogeneously between studies. For this reason, studies will be included in our analysis of preoperative opioid use if they report that the patient has been prescribed opioids at any time prior to admission for TJR. Studies that rely upon patient reporting to identify preoperative opioid exposure will be included in this more inclusive exposure group, unless patients specifically reported chronic preoperative opioid use. Informed by the *Centre for Disease Control's* recommendation that long-term opioid therapy be reviewed at least every three months,[22] chronic preoperative opioid use will be defined as ongoing use for ≥ 90 days prior to presenting for surgery. Given the lack of a common definition, studies that define chronic use more restrictively than this (e.g. by requiring 12 months of preoperative use) will be included in our analyses of chronic use. The impact of different

definitions of chronic use will be assessed in sub-group analyses where possible, as will the inclusion of studies relying on patient reported exposure status. Findings related specifically to chronic preoperative use will be reported and analyzed separately to findings related to preoperative use more generally.

Opioid use in the perioperative period (i.e. once a patient has been admitted for surgery) will not be considered a relevant exposure. Studies examining preemptive analgesia will also be excluded, as will studies explicitly examining the impact of preoperative opioid abuse, addiction, or dependence. To this end, studies will be excluded if they specifically examine patients who have been prescribed buprenorphine or methadone to treat opioid use disorder before surgery.[23]

Type of Comparison

The comparison of interest is adult (≥ 18 years of age) total joint replacement patients who have not used or been prescribed opioids in the lead up to admission for surgery (i.e. opioid naïve patients). Studies that only compare preoperative opioid use with the use of other medications (e.g. benzodiazepines) will be excluded.

Types of Outcome Measure

The primary outcomes of interest in this systematic review are complications, which provide a direct measure of the patient's physical or psychological health following the index procedure. Informed by Australian national quality and safety measures[24] and previously published work examining complications associated with preoperative smoking[25] and alcohol consumption,[26] the primary outcomes will be categorized as follows:

- **Mortality:** Any measure of mortality within one year of the index procedure will be included in our analysis; however, analyses of mortality will be stratified by the timeframe examined (e.g. 30-days, 90-days, 1-year).

- **Morbidity:** Measures of morbidity occurring within either 30 or 90-days of the index procedure will be categorized as: general complications, medication-related complications, wound complications, general infections, pulmonary complications, cardiovascular complications, neurological complications, gastrointestinal complications, renal/urinary complication, falls resulting in fracture or intracranial injury, unplanned returns to theatre or additional invasive interventions, bleedings, unplanned ICU admissions, and other complications.
- **Joint-related complications:** Any complications that are specific to the TJR procedure (e.g. revision, joint infection, or stiffness requiring manipulation under anesthesia)[27, 28] will be reported separately where possible. As these complications are necessarily tied to the index procedure, no time restrictions will be placed on measures relating to these outcomes.

The secondary outcomes of interest for this review provide valuable, but indirect, measures of the patient's course of recovery following the index procedure.

- **Persistent postoperative opioid use:** Any measure that includes patients receiving a prescription of opioids ≥ 90 days after the index procedure will be included in the analysis. This was informed by the CDC's recommendation that long-term opioid therapy be reviewed at least every three months.[22]
- **Unplanned readmission:** Measures of readmission within 90-days of initial discharge will be included in our analysis; however, all analyses of readmission will be stratified by the timeframe examined (e.g. 30-day, 90-day).
- **Length of stay:** Studies examining length of hospital stay following surgery will be included in our analysis.

Despite the importance of information about pain and function to decisions regarding TJR, to avoid duplicating work done in a recent systematic review by Goplen and colleagues,[15] patient reported pain and function outcomes will be excluded from this review.

Search Strategy

A comprehensive literature search of MEDLINE, EMBASE, CINAHL, PsycINFO, and Web of Science from inception to April 2020 will be conducted. These databases have been selected to maximize the coverage of the literature search.[29] The search strategy has been formulated in consultation with two external research librarians. The search will be tailored to each database using keywords, database-specific vocabulary (e.g. Medical Subject Headings), and relevant Boolean operators to cover the conceptual groups “opioids” (i.e. the exposure of interest) and “total joint replacement” (i.e. the population of interest). In accordance with widely accepted recommendations,[30] this strategy does not aim to narrow the scope of the search by including specific conceptual groups for the outcomes or comparisons of interest. This will ensure that the search strategy is sufficiently sensitive given the breadth of outcomes that we are seeking to include in this review and the lack of an established lexicon to describe the comparison of interest. See the supplementary materials for details of the full search strategy.

A narrower set of supplementary searches will be conducted using Google Scholar, as this has been shown to regularly capture eligible studies not returned by other databases.[29, 31] To account for difficulties with replicating searches conducted in Google Scholar, all results from this search that were not returned by our searches of other databases will be reported in a supplement to the published review. Articles which referenced (“forward citation tracking”) or were referenced by (“backwards citation tracking”) included studies and relevant published literature reviews will be searched to identify additional eligible studies.[32]

Data Collection and Management

To avoid issues with the export functionality of Google Scholar, Harzing’s Publish or Perish (V.7) will be used to extract relevant information from the supplementary search.

DistillSR will be used for deduplication, screening, and data extraction. Statistical analysis will be conducted using Stata (V.16). Three reviewers (CS, DG and SR) will be involved in the screening, study selection, data extraction, and quality assessment process. Each study will be independently assessed by two of these reviewers at each stage of this process. Disagreement will be resolved through discussion between these reviewers where possible. When consensus cannot be achieved through discussion, a fourth author (MD) will be consulted. Inter-rater agreement (kappa statistics) on the study selection process will be reported.[30]

Study Selection

The titles and abstracts of all items identified through the search process will be independently screened. After 10% of studies have been screened, the selection process will be reviewed to ensure that eligibility criteria are consistently applied. The full text documents of potentially relevant studies will then be compiled and reviewed against the eligibility criteria. Forward and backward citation tracking of all studies that remain after full text screening will be used to identify additional potentially eligible studies. The full text of studies identified through this final stage of the search will then be assessed for inclusion. The study selection process will be reported using a PRISMA flow diagram.[33]

Data Extraction

Data will be extracted using a standardized data collection form. The following details will be extracted from all included articles:

- Publication details: Authors, year of publication, title, publication venue
- Study design: Study design, data source(s), sample size, funding source.
- Clinical setting: Location (e.g. public/private/veterans' institution)
- Population characteristics: Demographic information (e.g. age, sex, BMI), comorbidities

- Surgery type: Primary/revision/undefined, hip/knee/shoulder/elbow/ankle/wrist, indication for surgery, TJR clearly defined, elective TJR clearly defined.
- Exposure: Preoperative opioid use definition, chronic preoperative opioid use definition.
- Outcomes: Outcome class, outcome definition.
- Results summary: Odd ratio or standard mean difference and 95% confidence intervals for each outcome measure, use of univariate/multivariate analysis, variables included in multivariate analysis.

Where adjusted and unadjusted measures are reported for a given outcome, the most comprehensively adjusted outcome measures will be used. Where outcomes are measured at multiple time points, the effects measured at the longest relevant time points will be recorded. Missing values will be calculated whenever there is sufficient data available to do so. Study authors will be contacted to obtain missing data, and response rates will be reported in the published review.

Individual Study Quality Assessment

The quality of all included studies will be assessed using the appropriate NIH/NHLBI *Study Quality Assessment Tool*.[34] The appropriate tool will be determined for each included study based upon the research design that was used. These tools include items to evaluate potential flaws in study methodology or implementation, including sources of bias, study power, confounding, and other factors. In response to each item included in these tools, reviewers will select "yes," "no," or "cannot determine/not reported/not applicable". Responses to each of these items will inform a judgment of each study as being of either "good," "fair," or "poor" quality. Where studies are deemed to be of poor quality, explicit justification will be offered and reported in the published review.

Data synthesis and subgroup analysis.

Where the outcomes reported are considered sufficiently similar from a clinical and methodological perspective, and where sufficient data is available to calculate a common effect size,[30] meta-analyses will be conducted for each of the predefined primary and secondary outcome categories. The primary meta-analyses reported for each outcome will only include adjusted effect sizes as residual confounding is likely to significantly impact unadjusted estimates. Outcomes associated with preoperative opioid use and chronic preoperative use will be analyzed and reported separately. For data that can be meaningfully pooled, a random effect model will be used for meta-analysis as we expect significant between study heterogeneity.[35] For dichotomous outcomes, odds ratios (OR) will be reported. Standardized mean difference (SMD) will be used for the analysis of continuous outcome variables. 95% confidence intervals will be reported for all effect estimates. Where outcomes are reported as risk ratios without sufficient data available to manually compute the odds ratio, the odds ratio will be computed using the formula described by Zhang and Yu.[36] The characteristics of all eligible studies, including those not suitable for meta-analysis, will be reported in narrative and tabular form.

Sensitivity analyses will explore the impact of including both unadjusted and adjusted effect size estimates in our meta-analyses, and assess the impact of including studies that rely on patient reported measures of opioid exposure. Sensitivity analyses will also be conducted to evaluate the impact of including studies of imprecisely defined populations (i.e. where it is not clear if the population also contains partial or non-elective joint replacement patients). Heterogeneity will be assessed using the I^2 statistic and Cochran's Q test. An I^2 statistic of greater than 50% will trigger investigation of potential causes of heterogeneity through subgroup analyses.[30] Planned subgroup analyses will be based on differences in study quality, geographic location, type of surgery, and opioid exposure definitions. In the instance that no studies have reported on an outcome relevant to one of the predefined outcome categories, this will be explicitly reported in the narrative synthesis.

Meta-bias assessment

We have aimed to minimize the effect of publication bias on the findings of this review by placing no restrictions on the inclusion of 'grey literature'.[37] Furthermore, our search strategy has been designed to ensure comprehensiveness by drawing upon a database that is commonly overlooked by systematic reviewers (i.e. Google Scholar), despite having been shown to be effective at capturing grey literature.[31] To investigate the potential residual effects of publication bias, funnel plots will be generated for meta-analyses that include ten or more studies.[34] Where significant asymmetry is detected in the funnel plot, potential sources of this asymmetry will be explored and, if deemed appropriate, the trim and fill method may be used to account for the possibility of publication bias.[30, 38]

Confidence in cumulative evidence

The quality of cumulative evidence in relation to each reported outcome measures will be assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.[39-41] The five GRADE considerations – study limitations, imprecision, inconsistency, indirectness, and publication bias – will be used to assess each study before reporting the quality of evidence as high, moderate, low, or very low.[41] The results of the cumulative quality assessment will be presented in a Summary of Findings table.[41, 42] Care will be taken to include all outcome categories specified in this protocol in this table, to ensure that the absence of evidence relating to particular types of complications is reported clearly and consistently.

Ethics and dissemination

Ethics approval will not be required for the proposed study, as it draws on previously published data and will not impact upon the privacy of any individual patients. The results of the systematic review will be disseminated through publication in a peer-reviewed journal, and through presentation at relevant academic conferences. It will also be disseminated to members of the *Consortium Against the overuse of Opioids in*

Surgery (CAOS), which is a recently formed multinational initiative that aims to address issues relating to opioid use among surgical patients.

Patient and Public Involvement:

No patients were involved in the planning or conduct of this review. The findings of this review will be shared with members of the Centre for Research Excellence in Total Joint Replacement's newly formed Arthritis Consumer and Community Involvement Programme (ACCIP). Translation of these findings into future clinical trials will be informed by members of ACCIP.

DISCUSSION

As it currently stands, the available research examining the impact of opioid use prior to TJR on postoperative complications remains fragmented. Not only does this mean that the scope of the available evidence is difficult to interpret, it has also potentially led to serious risks associated with opioid use prior to TJR remaining underrecognized. The proposed systematic review and meta-analysis aims to provide some much-needed order and clarity to the growing body of research in this domain. By providing a comprehensive and well-integrated understanding of complications associated with opioid use prior to TJR, this review will allow clinicians to more appropriately inform potential TJR patients who have been prescribed opioids about the risks associated with their procedure. The findings of the proposed review will also offer insights that are necessary for both clinicians and patients to make prudent treatment decisions. However, as is the case with all systematic reviews, the strength of the conclusions that can be drawn from this review will be determined by the quality of the available evidence. Although we will only include adjusted estimates in our primary meta-analyses, the possibility of residual confounding (e.g. confounding by indication) in the included studies may limit the strength of the conclusions that can be drawn about the links between the exposures and outcomes of interest.[43]Finally, and perhaps most

importantly, the knowledge gleaned from this review will clarify the extent to which targeting preoperative opioid use may improve the quality and safety of surgical care for patients undergoing total joint replacement.

Contributions:

CS, DG, XC, JK, ST, YZ, MD, PC originally conceived of this project. CS, DG, MD, PC initially refined the scope of the project. CS wrote the first draft. CS, DG, XC, JK, SR, ST, YZ, MD, PC contributed to revising various drafts of the protocol for critically important intellectual content. ST provided statistical advice on the final protocol. CS, SR, and DG were responsible for designing the final search strategy. CS, DG, XC, JK, SR, ST, YZ, MD, PC read and approved the submitted version. CS will be the guarantor of this review.

Competing interests:

Dr. Dowsey reports personal fees from Pfizer and grants from Medacta, outside the submitted work; Dr. Choong reports personal fees from Stryker, Johnson & Johnson, and Kluwer, and grants from Medacta, outside the submitted work. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REFERENCES

1. Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, et al. Knee replacement. Lancet. 2012;379(9823):1331-40.
2. Ng CY, Ballantyne JA, Brenkel IJ. Quality of life and functional outcome after primary total hip replacement. A five-year follow-up. J Bone Joint Surg Br. 2007;89(7):868-73.
3. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. Lancet. 2007;370(9597):1508-19.
4. Sloan M, Premkumar A, Sheth NP. Projected Volume of Primary Total Joint Arthroplasty in the U.S., 2014 to 2030. J Bone Joint Surg Am. 2018;100(17):1455-60.
5. Inacio MCS, Cashman K, Pratt NL, Gillam MH, Caughey G, Graves SE, et al. Prevalence and changes in analgesic medication utilisation 1 year prior to total joint replacement in an older cohort of patients. Osteoarthritis Cartilage. 2018;26(3):356-62.
6. Haffajee RL, Frank RG. Making the Opioid Public Health Emergency Effective. JAMA Psychiatry. 2018;75(8):767-8.
7. Kim SC, Choudhry N, Franklin JM, Bykov K, Eikermann M, Lii J, et al. Patterns and predictors of persistent opioid use following hip or knee arthroplasty. Osteoarthritis Cartilage. 2017;25(9):1399-406.
8. Ben-Ari A, Chansky H, Rozet I. Preoperative Opioid Use Is Associated with Early Revision After Total Knee Arthroplasty: A Study of Male Patients Treated in the Veterans Affairs System. J Bone Joint Surg Am. 2017;99(1):1-9

9. Bell KL, Shohat N, Goswami K, Tan TL, Kalbian I, Parvizi J. Preoperative Opioids Increase the Risk of Periprosthetic Joint Infection After Total Joint Arthroplasty. J Arthroplasty. 2018;33(10):3246-51 e1.

10. Kim SC, Jin Y, Lee YC, Lii J, Franklin PD, Solomon DH, et al. Association of Preoperative Opioid Use With Mortality and Short-term Safety Outcomes After Total Knee Replacement. JAMA Netw Open. 2019;2(7):e198061

11. Jain N, Brock JL, Malik AT, Phillips FM, Khan SN. Prediction of complications, readmission, and revision surgery based on duration of preoperative opioid use: analysis of major joint replacement and lumbar fusion. J Bone Joint Surg Am. 2019;101(5):384-91.

12. Blevins Peratikos M, Weeks HL, Pisansky AJ, Yong RJ, Stringer EA. Effect of preoperative opioid use on adverse outcomes, medical spending, and persistent opioid use following elective total joint arthroplasty in the United States: a large retrospective cohort study of administrative claims data. Pain Medicine. 2020;21(3):521-31.

13. Huang J, Bin Abd Razak HR, Yeo SJ. Incidence of postoperative delirium in patients undergoing total knee arthroplasty-an Asian perspective. Ann Transl Med. 2017;5(16):321.

14. Rozell JC, Courtney PM, Dattilo JR, Wu CH, Lee GC. Preoperative opiate use independently predicts narcotic consumption and complications after total joint arthroplasty. The Journal of arthroplasty. 2017;32(9):2658-62.

15. Goplen CM, Verbeek W, Kang SH, Jones CA, Voaklander DC, Churchill TA, et al. Preoperative opioid use is associated with worse patient outcomes after Total joint arthroplasty: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2019;20(1):234.

16. Szawlowski S, Choong PFM, Li J, Nelson E, Nikpour M, Scott A, et al. How do surgeons' trade-off between patient outcomes and risk of complications in total knee arthroplasty? a discrete choice experiment in Australia. BMJ Open. 2019;9(7):e029406.

17. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

18. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.

19. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.

20. Bolognesi MP, Greiner MA, Attarian DE, Watters TS, Wellman SS, Curtis LH, et al. Unicompartmental knee arthroplasty and total knee arthroplasty among Medicare beneficiaries, 2000 to 2009. J Bone Joint Surg Am. 2013;95(22):e174.

21. Australian Orthopaedic Association National Joint Replacment Registry. Hip, Knee & Shoulder Arthroplasty: 2019 Annual Report. AOA, 2019. [Avaliable from: aoanjrr.sahmri.com/documents/10180/668596/Hip%2C+Knee+%26+Shoulder+Arthroplasty/c287d2a3-22df-a3bb-37a2-91e6c00bfcf0]

22. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. JAMA. 2016;315(15):1624-45.

23. Srivastava A, Kahan M, Nader M. Primary care management of opioid use disorders Abstinence, methadone, or buprenorphine-naloxone? Can Fam Physician. 2017;63(3):200-5.

24. Australian Commission on Safety and Quality in Health Care . National Safety and Quality Health Service Standards: Guide for Hospitals. ACSQHC, 2017. [Available from: https://www.safetyandquality .gov.au/sites/default/files/migrated/National-Safety-and-Quality-Health-Service-Standards-Guide-for-Hospitals.pdf]

25. Gronkjaer M, Eliasen M, Skov-Ettrup LS, Tolstrup JS, Christiansen AH, Mikkelsen SS, et al. Preoperative smoking status and postoperative complications: a systematic review and meta-analysis. Ann Surg. 2014;259(1):52-71.

26. Eliasen M, Gronkjaer M, Skov-Ettrup LS, Mikkelsen SS, Becker U, Tolstrup JS, et al. Preoperative alcohol consumption and postoperative complications: a systematic review and meta-analysis. Ann Surg. 2013;258(6):930-42.

27. Iorio R, Della Valle CJ, Healy WL, Berend KR, Cushner FD, Dalury DF, et al. Stratification of standardized TKA complications and adverse events: a brief communication. Clin Orthop Relat Res. 2014;472(1):194-205.

28. Healy WL, Iorio R, Clair AJ, Pellegrini VD, Della Valle CJ, Berend KR. Complications of Total Hip Arthroplasty: Standardized List, Definitions, and Stratification Developed by The Hip Society. Clin Orthop Relat Res. 2016;474(2):357-64.

29. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. Syst Rev. 2017;6(1):245.

30. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds) Cochrane handbook for systematic reviews of interventions version 6.0 (Updated July 2019). Cochrane 2019 [Available from: www.training.cochrane.org/handbook.]

31. Haddaway NR, Collins AM, Coughlin D, Kirk S. The Role of Google Scholar in Evidence Reviews and Its Applicability to Grey Literature Searching. PLoS One. 2015;10(9):e0138237.

32. Kuper H, Nicholson A, Hemingway H. Searching for observational studies: what does citation tracking add to PubMed? A case study in depression and coronary heart disease. BMC Med Res Methodol. 2006;6(1):4.

33. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339(4):b2535.

34. National Institutes of Health, National Heart, Lung, and Blood Institute. Study quality assessment tools. NIH- NHLBI 2017 [Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.]

35. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010;1(2):97-111.

36. Zhang J, Yu KF. What's the relative risk?: A method of correcting the odds ratio in cohort studies of common outcomes. Jama. 1998;280(19):1690-1.

37. Song F, Hooper, Loke Y. Publication bias: what is it? How do we measure it? How do we avoid it? Open Access Journal of Clinical Trials. 2013;2013(5):71-81.

38. Weinhandl ED, Duval S. Generalization of trim and fill for application in meta-regression. Res Synth Methods. 2012;3(1):51-67.

39. Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ. 2015;350:h870.

40. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

41. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.

42. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158-72.

43. Miettinen OS. The need for randomization in the study of intended effects. Stat Med 1983;2:267-71.

Supplementary Material

Planned search strategies for primary databases

#	Medline
1	exp Analgesics, Opioid/
2	exp Narcotics/
3	(opioid* or opiate* or narcotic*).mp.
4	(Bezitramide or Burgodin or Bezitramida or Buprenorphine or Buprenorfina or Buprenex or Prefin or Subutex or Buprex or Temgesic or Butorphanol or Butorfanol or Beforal or Moradol or Stadol or Torbugesic or Apo-Butorphanol or Dolorex or Codeine or Codeinum or Methylmorphine or N-Methylmorphine or Isocodeine or Ardinex or Dextromoramide or Palphium or Pyrrolamidol or Pyrrolamidol or D-Moramide or D Moramide or Palfium or Dextropropoxyphene or Propoxyphene or D-Propoxyphene or Darvon or Dezocine or Dihydrocodeine or paramol or Rikodeine or Tiamon or Tosidrin or Contugesic or Dicodin or Paracodin or Paracodina or Fentanyl or Fentanil or Phentanyl or Fentanest or Sublimaze or Transmucosal or Duragesic or Durogesic or Fentora or Hydrocodone or Dihydrocodeinone or Hydrocodon or Hydrocone or Hydroconum or Idrocodone or Dicodid or Robidone or Hycodan or Hycon or Hydromorphone or Dihydromorphinone or Dimorphone or Hydromorphon or Palladone or Laudacon or Dilaudid or Ketobemidone or Cetobemidon or Levorphanol or Levodroman or Levorphan or Levo-Dromoran or Levo Dromoran or LevoDromoran or L-Dromoran or L Dromoran or Meperidine or Isonipecaine or Pethidine or Isonipecain or Dolsin or Dolosal or Dolin or Operidine or Dolantin or Dolargan or Lidol or Lydol or Demerol or Dolcontral or Meptazinol or Meptid or Methadone or Biodone or Dolophine or Metadol or Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict or Methadyl acetate or Acetylmethadol or Alphacetylmethadol or Amidolacetate or Dimepheptanol or Levomethadyl or Levoacetylmethadol or Levomethadyl or Methadol or Acemethadone or Morphine or Morphia or Morphium or Contin or Oramorph or Duramorph or Nalbuphine or Nubain or Nicomorphine or Vilan or Opium or Papaveretum or Omnopon or Pantopon or Oxycodone or Dihydrohydroxycodeinone or Dihydroxycodeinone or Oxymorphone or Dihydrohydroxymorphinone or Dihydroxymorphinone or Oximorphonum or Numorphan or Opana or Pentazocine or Talwin or Fortral or Lexir or Phenazocine or Phenethylazocine or Phenbenzorphan or Narphen or Piritramide or Piritramid or Dipidolor or Dipydolor or Tapentadol or Nucynta of Tilidine or Tilidate or Tilidin or Valoron or Valerone or Tramadol* or Tramundin or Biodalgic or Jutadol or MTW-Tramadol or MTWTramadol or Nobligan or Prontofort or Zytram or Takadol or Theradol or Tiral or Topalgic or Tradol or Tradol-Puren or TradolPuren or Tradonal or Tralgiol or Trama AbZ or Trama KD or Trama-Dorsch or Trama Dorsch or TramaDorsch or Biokanol or Tramabeta or Tramadin or Tramadoc or Ranitidin or Trama or Trasedal or Ultram or Xymel or Zamudol or Zumalgic or Zydol or Tramadura or Tramagetic or Tramagit or Tramake or Tramal or Tramex or Adolonta or Contramal or Amadol).mp.
5	1 or 2 or 3 or 4
6	Arthroplasty, Replacement/
7	Arthroplasty, Replacement, Ankle/
8	Arthroplasty, Replacement, Elbow/
9	Arthroplasty, Replacement, Hip/
10	Arthroplasty, Replacement, Knee/
11	Arthroplasty, Replacement, Shoulder/
12	((joint or shoulder or knee or hip or elbow or wrist or ankle) adj3 (replacement* or arthroplast*)).mp.
13	6 or 7 or 8 or 9 or 10 or 11 or 12
14	5 and 13

#	Embase
1	exp narcotic analgesic agent/
2	exp narcotic agent/

3	(opioid* or opiate* or narcotic*).mp.
4	(Bezitramide or Burgodin or Bezitramida or Buprenorphine or Buprenorfina or Buprenex or Prefin or Subutex or Buprex or Temgesic or Butorphanol or Butorfanol or Beforal or Moradol or Stadol or Torbugesic or Apo-Butorphanol or Dolorex or Codeine or Codeinum or Methylmorphine or N-Methylmorphine or Isocodeine or Ardinex or Dextromoramide or Palphium or Pyrrolamidol or Pyrrolamidol or D-Moramide or D Moramide or Palfium or Dextropropoxyphene or Propoxyphene or D-Propoxyphene or Darvon or Dezocine or Dihydrocodeine or paramol or Rikodeine or Tiamon or Tosidrin or Contugesic or Dicodin or Paracodin or Paracodina or Fentanyl or Fentanil or Phentanyl or Fentanest or Sublimaze or Transmucosal or Duragesic or Durogesic or Fentora or Hydrocodone or Dihydrocodeinone or Hydrocodon or Hydrocone or Hydroconum or Idrocodone or Dicodid or Robidone or Hycodan or Hycon or Hydromorphone or Dihydromorphinone or Dimorphone or Hydromorphon or Palladone or Laudacon or Dilaudid or Ketobemidone or Cetobemidon or Levorphanol or Levodroman or Levorphan or Levo-Dromoran or Levo Dromoran or LevoDromoran or L-Dromoran or L Dromoran or Meperidine or Isonipecaine or Pethidine or Isonipecain or Dolsin or Dolosal or Dolin or Operidine or Dolantin or Dolargan or Lidol or Lydol or Demerol or Dolcontral or Meptazinol or Meptid or Methadone or Biodone or Dolophine or Metadol or Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict or Methadyl acetate or Acetylmethadol or Alphacetylmethadol or Amidolacetate or Dimepheptanol or Levomethadyl or Levoacetylmethadol or Levomethadyl or Methadol or Acemethadone or Morphine or Morphia or Morphium or Contin or Oramorph or Duramorph or Nalbuphine or Nubain or Nicomorphine or Vilan or Opium or Papaveretum or Omnopon or Pantopon or Oxycodone or Dihydrohydroxycodeinone or Dihydroxycodeinone or Oxymorphone or Dihydrohydroxymorphinone or Dihydroxymorphinone or Oximorphonum or Numorphan or Opana or Pentazocine or Talwin or Fortral or Lexir or Phenazocine or Phenethylazocine or Phenbenzorphan or Narphen or Piritramide or Piritramid or Dipidolor or Dipydolor or Tapentadol or Nucynta of Tilidine or Tilidate or Tilidin or Valoron or Valerone or Tramadol* or Tramundin or Biodalgic or Jutadol or MTW-Tramadol or MTWTramadol or Nobligan or Prontofort or Zytram or Takadol or Theradol or Tiral or Topalgic or Tradol or Tradol-Puren or TradolPuren or Tradonal or Tralgiol or Trama AbZ or Trama KD or Trama-Dorsch or Trama Dorsch or TramaDorsch or Biokanol or Tramabeta or Tramadin or Tramadoc or Ranitidin or Trama or Trasedal or Ultram or Xymel or Zamudol or Zumalgic or Zydol or Tramadura or Tramagetic or Tramagit or Tramake or Tramal or Tramex or Adolonta or Contramal or Amadol).mp.
5	1 or 2 or 3 or 4
6	replacement arthroplasty/
7	ankle replacement/ or ankle arthroplasty/
8	elbow replacement/ or elbow arthroplasty/
9	hip replacement/ or hip arthroplasty/
10	knee replacement/ or knee arthroplasty/
11	shoulder arthroplasty/ or reverse shoulder arthroplasty/ or shoulder replacement/
12	((joint or shoulder or knee or hip or elbow or wrist or ankle) adj3 (replacement* or arthroplast*)).mp.
13	6 or 7 or 8 or 9 or 10 or 11 or 12
14	5 and 13

#	Web of Science
1	TS=(narcotic* OR opioid* OR opiate*)
2	TS=(Bezitramide or Burgodin or Bezitramida or Buprenorphine or Buprenorfina or Buprenex or Prefin or Subutex or Buprex or Temgesic or Butorphanol or Butorfanol or Beforal or Moradol or Stadol or Torbugesic or Apo-Butorphanol or Dolorex or Codeine or Codeinum or Methylmorphine or N-Methylmorphine or Isocodeine or Ardinex or Dextromoramide or Palphium or Pyrrolamidol or Pyrrolamidol or D-Moramide or D Moramide or Palfium or Dextropropoxyphene or Propoxyphene or D-Propoxyphene or Darvon or Dezocine or Dihydrocodeine or paramol or Rikodeine or Tiamon or Tosidrin or Contugesic or Dicodin or Paracodin or Paracodina or Fentanyl or Fentanil or Phentanyl or Fentanest or Sublimaze or Transmucosal or Duragesic or Durogesic or Fentora or Hydrocodone or Dihydrocodeinone or Hydrocodon or Hydrocone or Hydroconum or Idrocodone or Dicodid or Robidone or Hycodan or Hycon or Hydromorphone or Dihydromorphinone or Dimorphone or Hydromorphon or Palladone or Laudacon or Dilaudid or Ketobemidone or Cetobemidon or Levorphanol or Levodroman or Levorphan or Levo-Dromoran or Levo Dromoran or LevoDromoran or L-Dromoran or L Dromoran or Meperidine or Isonipecaine or Pethidine or Isonipecain or Dolsin or Dolosal or Dolin or Operidine or Dolantin or Dolargan or Lidol or Lydol or Demerol or Dolcontral or Meptazinol or Meptid or Methadone or Biodone or Dolophine or Metadol or Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict or

	Methadyl acetate or Acetylmethadol or Alphacetylmethadol or Amidolacetate or Dimepheptanol or Levomethadyl or Levoacetylmethadol or Levomethadyl or Methadol or Acemethadone or Morphine or Morphia or Morphium or Contin or Oramorph or Duramorph or Nalbuphine or Nubain or Nicomorphine or Vilan or Opium or Papaveretum or Omnopon or Pantopon or Oxycodone or Dihydrohydroxycodeinone or Dihydroxycodeinone or Oxymorphone or Dihydrohydroxymorphinone or Dihydroxymorphinone or Oximorphonum or Numorphan or Opana or Pentazocine or Talwin or Fortral or Lexir or Phenazocine or Phenethylazocine or Phenbenzorphan or Narphen or Piritramide or Piritramid or Dipidolor or Dipydolor or Tapentadol or Nucynta of Tilidine or Tilidate or Tilidin or Valoron or Valerone or Tramadol* or Tramundin or Biodalgic or Jutadol or MTW-Tramadol or MTWTramadol or Nobligan or Prontofort or Zytram or Takadol or Theradol or Tiral or Topalgic or Tradol or Tradol-Puren or TradolPuren or Tradonal or Tralgiol or Trama AbZ or Trama KD or Trama-Dorsch or Trama Dorsch or TramaDorsch or Biokanol or Tramabeta or Tramadin or Tramadoc or Ranitidin or Trama or Trasedal or Ultram or Xymel or Zamudol or Zumalgic or Zydol or Tramadura or Tramagetic or Tramagit or Tramake or Tramal or Tramex or Adolonta or Contramal or Amadol)
3	#1 OR 2
4	TS=((joint or shoulder or knee or hip or elbow or wrist or ankle) NEAR/3 (replacement* or arthroplast*))
5	#3 AND #4

#	PsychINFO
1	exp narcotic drugs/
2	exp Opiates
3	(opioid* or opiate* or narcotic*).mp.
4	(Bezitramide or Burgodin or Bezitramida or Buprenorphine or Buprenorfina or Buprenex or Prefin or Subutex or Buprex or Temgesic or Butorphanol or Butorfanol or Beforal or Moradol or Stadol or Torbugesic or Apo-Butorphanol or Dolorex or Codeine or Codeinum or Methylmorphine or N-Methylmorphine or Isocodeine or Ardinex or Dextromoramide or Palphium or Pyrrolamidol or Pyrrolamidol or D-Moramide or D Moramide or Palfium or Dextropropoxyphene or Propoxyphene or D-Propoxyphene or Darvon or Dezocine or Dihydrocodeine or paramol or Rikodeine or Tiamon or Tosidrin or Contugesic or Dicodin or Paracodin or Paracodina or Fentanyl or Fentanil or Phentanyl or Fentanest or Sublimaze or Transmucosal or Duragesic or Durogesic or Fentora or Hydrocodone or Dihydrocodeinone or Hydrocodon or Hydrocone or Hydroconum or Idrocodone or Dicodid or Robidone or Hycodan or Hycon or Hydromorphone or Dihydromorphinone or Dimorphone or Hydromorphon or Palladone or Laudacon or Dilaudid or Ketobemidone or Cetobemidon or Levorphanol or Levodroman or Levorphan or Levo-Dromoran or Levo Dromoran or LevoDromoran or L-Dromoran or L Dromoran or Meperidine or Isonipecaine or Pethidine or Isonipecain or Dolsin or Dolosal or Dolin or Operidine or Dolantin or Dolargan or Lidol or Lydol or Demerol or Dolcontral or Meptazinol or Meptid or Methadone or Biodone or Dolophine or Metadol or Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict or Methadyl acetate or Acetylmethadol or Alphacetylmethadol or Amidolacetate or Dimepheptanol or Levomethadyl or Levoacetylmethadol or Levomethadyl or Methadol or Acemethadone or Morphine or Morphia or Morphium or Contin or Oramorph or Duramorph or Nalbuphine or Nubain or Nicomorphine or Vilan or Opium or Papaveretum or Omnopon or Pantopon or Oxycodone or Dihydrohydroxycodeinone or Dihydroxycodeinone or Oxymorphone or Dihydrohydroxymorphinone or Dihydroxymorphinone or Oximorphonum or Numorphan or Opana or Pentazocine or Talwin or Fortral or Lexir or Phenazocine or Phenethylazocine or Phenbenzorphan or Narphen or Piritramide or Piritramid or Dipidolor or Dipydolor or Tapentadol or Nucynta of Tilidine or Tilidate or Tilidin or Valoron or Valerone or Tramadol* or Tramundin or Biodalgic or Jutadol or MTW-Tramadol or MTWTramadol or Nobligan or Prontofort or Zytram or Takadol or Theradol or Tiral or Topalgic or Tradol or Tradol-Puren or TradolPuren or Tradonal or Tralgiol or Trama AbZ or Trama KD or Trama-Dorsch or Trama Dorsch or TramaDorsch or Biokanol or Tramabeta or Tramadin or Tramadoc or Ranitidin or Trama or Trasedal or Ultram or Xymel or Zamudol or Zumalgic or Zydol or Tramadura or Tramagetic or Tramagit or Tramake or Tramal or Tramex or Adolonta or Contramal or Amadol).mp.
5	1 or 2 or 3 or 4
6	((joint or shoulder or knee or hip or elbow or wrist or ankle) adj3 (replacement* or arthroplast*)).mp.
7	5 and 6

#	CINAHL Complete Search
1	MH ("Analgesics, Opioid+" OR "Narcotics+") OR (TX (“opioid*” OR “opiate*” OR “narcotic*” OR “Bezitramide” OR “Burgodin” OR “Bezitramida” OR “Buprenorphine” OR “Buprenorfina” OR “Buprenex” OR “Prefin” OR “Subutex” OR “Buprex” OR “Temgesic” OR

"Butorphanol" OR "Butorfanol" OR "Beforal" OR "Moradol" OR "Stadol" OR "Torbugesic" OR "Apo-Butorphanol" OR "Dolorex" OR "Codeine" OR "Codeinum" OR "Methylmorphine" OR "N-Methylmorphine" OR "Isocodeine" OR "Ardinex" OR "Dextromoramide" OR "Palphium" OR "Pyrrolamidol" OR "Pyrrolamidol" OR "D-Moramide" OR "D Moramide" OR "Palfium" OR "Dextropropoxyphene" OR "Propoxyphene" OR "D-Propoxyphene" OR "Darvon" OR "Dezocine" OR "Dihydrocodeine" OR "paramol" OR "Rikodeine" OR "Tiamon" OR "Tosidrin" OR "Contugesic" OR "Dicodin" OR "Paracodin" OR "Paracodina" OR "Fentanyl" OR "Fentanil" OR "Phentanyl" OR "Fentanest" OR "Sublimaze" OR "Transmucosal" OR "Duragesic" OR "Durogesic" OR "Fentora" OR "Hydrocodone" OR "Dihydrocodeinone" OR "Hydrocodon" OR "Hydrocone" OR "Hydroconum" OR "Idrocodone" OR "Dicodid" OR "Robidone" OR "Hycodan" OR "Hycon" OR "Hydromorphone" OR "Dihydromorphinone" OR "Dimorphone" OR "Hydromorphon" OR "Palladone" OR "Laudacon" OR "Dilaudid" OR "Ketobemidone" OR "Cetobemidon" OR "Levorphanol" OR "Levodroman" OR "Levorphan" OR "Levo-Dromoran" OR "Levo Dromoran" OR "LevoDromoran" OR "L-Dromoran" OR "L Dromoran" OR "Meperidine" OR "Isonipecaine" OR "Pethidine" OR "Isonipecain" OR "Dolsin" OR "Dolosal" OR "Dolin" OR "Operidine" OR "Dolantin" OR "Dolargan" OR "Lidol" OR "Lydol" OR "Demerol" OR "Dolcontral" OR "Meptazinol" OR "Meptid" OR "Methadone" OR "Biodone" OR "Dolophine" OR "Metadol" OR "Metasedin" OR "Symoron" OR "Methadose" OR "Methex" OR "Phenadone" OR "Physeptone" OR "Phymet" OR "Pinadone" OR "Amidone" OR "Methaddict" OR "Methadyl acetate" OR "Acetylmethadol" OR "Alphacetylmethadol" OR "Amidolacetate" OR "Dimepheptanol" OR "Levomethadyl" OR "Levoacetylmethadol" OR "Levomethadyl" OR "Methadol" OR "Acemethadone" OR "Morphine" OR "Morphia" OR "Morphium" OR "Contin" OR "Oramorph" OR "Duramorph" OR "Nalbuphine" OR "Nubain" OR "Nicomorphine" OR "Vilan" OR "Opium" OR "Papaveretum" OR "Omnopon" OR "Pantopon" OR "Oxycodone" OR "Dihydrohydroxycodeinone" OR "Dihydroxycodeinone" OR "Oxymorphone" OR "Dihydrohydroxymorphinone" OR "Dihydroxymorphinone" OR "Oximorphonum" OR "Numorphan" OR "Opana" OR "Pentazocine" OR "Talwin" OR "Fortral" OR "Lexir" OR "Phenazocine" OR "Phenethylazocine" OR "Phenbenzorphan" OR "Narphen" OR "Piritramide" OR "Piritramid" OR "Dipidolor" OR "Dipydolor" OR "Tapentadol" OR "Nucynta of Tilidine" OR "Tilidate" OR "Tilidin" OR "Valoron" OR "Valerone" OR "Tramadol*" OR "Tramundin" OR "Biodalgic" OR "Jutadol" OR "MTW-Tramadol" OR "MTWTramadol" OR "Nobligan" OR "Prontofort" OR "Zytram" OR "Takadol" OR "Theradol" OR "Tiral" OR "Topalgic" OR "Tradol" OR "Tradol-Puren" OR "TradolPuren" OR "Tradonal" OR "Tralgiol" OR "Trama AbZ" OR "Trama KD" OR "Trama-Dorsch" OR "Trama Dorsch" OR "TramaDorsch" OR "Biokanol" OR "Tramabeta" OR "Tramadin" OR "Tramadoc" OR "Ranitidin" OR "Trama" OR "Trasedal" OR "Ultram" OR "Xymel" OR "Zamudol" OR "Zumalgic" OR "Zydol" OR "Tramadura" OR "Tramagetic" OR "Tramagit" OR "Tramake" OR "Tramal" OR "Tramex" OR "Adolonta" OR "Contramal" OR "Amadol"))

2 TX (("joint" OR "shoulder" OR "knee" OR "hip" OR "elbow" OR "wrist" OR "ankle") n3 ("replacement*" OR "arthroplast*")) OR (MH ("Arthroplasty, replacement" OR "Arthroplasty, Replacement, Elbow" OR "Arthroplasty, Replacement, Shoulder" OR "Arthroplasty, Replacement, Ankle" OR "Arthroplasty, Replacement, Knee" OR "Arthroplasty, Replacement, Hip"))

3 1 AND 2

Planned search strategy for supplementary database

#	Google Scholar searches
1	("preoperative narcotic" OR "preoperative opioid" OR "preoperative opiate") AND ("total joint arthroplasty" OR "total knee arthroplasty" OR "total hip arthroplasty" OR "total ankle arthroplasty")
2	("preoperative narcotic" OR "preoperative opioid" OR "preoperative opiate") AND ("total elbow arthroplasty" OR "total shoulder arthroplasty" OR "total wrist arthroplasty")
3	("preoperative narcotic" OR "preoperative opioid" OR "preoperative opiate") AND ("total joint replacement" OR "total knee replacement" OR "total hip replacement" OR "total ankle replacement")
4	("preoperative narcotic" OR "preoperative opioid" OR "preoperative opiate") AND ("total elbow replacement" OR "total shoulder replacement" OR "total wrist replacement")

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11
Amendments			
	#4	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	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	11
Sponsor	#5b	Provide name for the review funder and / or sponsor	11
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	11
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	3-4

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	#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	4-6
Information sources	#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	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	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)	7-8
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	7-8

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6, 8
Risk of bias in individual studies	#14	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	8-9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8-9
Data synthesis	#15b	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 I2, Kendall's τ)	9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	9

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9-10