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

Cade Shadbolt ,[1] Daniel Gould,[1] Ximena Camacho,[2] Josh Knight,[3] Siddharth Rele,[1,4] Sharmala Thuraisingam,[1,5] Yuting Zhang,[6] Michelle M Dowsey ,[1,7] Peter FM Choong[1,7]

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For numbered affiliations see end of article.

Correspondence to
Professor Peter FM Choong; sarcoma@bigpond.net.au

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 synthesise the available evidence of an association between opioid use prior to TJR and postoperative complications, categorised 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 TJR to opioid naïve TJR patients will be included. The primary outcomes will be postoperative complications, which will be categorised 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 standardised 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 are being collected. Findings will be disseminated through peer-reviewed publication and presentation at academic conferences.

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Strengths and limitations of this study

- This systematic review will be the first to identify complications that are associated with preoperative opioid use among total joint replacement patients.
- The comprehensive a priori categorisation 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 predefined outcome categories.
- As most included studies are expected to rely on 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 (TJR) 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 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 USA 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 USA, 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 periprosthetic 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-recognised. 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 with 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 synthesise available evidence of an association between opioid use prior to TJR and postoperative complications, categorised by complication type.

METHODS AND ANALYSIS

This protocol was developed in accordance with 'Preferred Reporting Items for Systematic reviews and Meta-Analysis—Protocol' (PRISMA-P)[17 18] and 'Meta-analysis of Observational Studies in Epidemiology' (MOOSE)[19] guidelines.

Criteria for consideration in this review

Types of studies

This systematic review will include both descriptive (eg, case series, cross-sectional) and analytic (eg, retrospective cohort, prospective cohort, case-control) observational studies as well as experimental studies (eg, randomised 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 the 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 TJR. Total hip, knee, shoulder, elbow, ankle, and wrist replacement 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 TJRs.[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 are 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 characterised 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 on 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 (CDC) recommendation that long-term opioid therapy be reviewed at least every 3 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 (eg, 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 subgroup 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 analysed separately to findings related to preoperative use more generally.

Opioid use in the perioperative period (ie, 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) TJR patients who have not used or been prescribed opioids in the lead up to admission for surgery (ie, opioid naïve patients). Studies that only compare preoperative opioid use with the use of other medications (eg, 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 categorised as follows:

- Mortality: any measure of mortality within 1 year of the index procedure will be included in our analysis; however, analyses of mortality will be stratified by the timeframe examined (eg, 30 days, 90 days, 1 year).
- Morbidity: measures of morbidity occurring within either 30 or 90 days of the index procedure will be categorised 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 intensive care unit admissions, and other complications.
- Joint-related complications: any complications that are specific to the TJR procedure (eg, revision, joint infection, or stiffness requiring manipulation under anaesthesia)[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 3 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 (eg, 30 days, 90 day).
- Length of stay: studies examining the 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 maximise 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 (eg, medical subject headings), and relevant Boolean operators to cover the conceptual groups 'opioids' (ie, the exposure of interest) and 'TJR' (ie, 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 online 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 that referenced ('forward citation tracking') or were referenced by ('backward citation tracking') included studies and relevant published literature reviews that 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. DistillerSR 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 (MMD) 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 trackings 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.[33]

Data extraction

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

- Publication details: authors, year of publication, title, and publication venue.
- Study design: study design, data source(s), sample size, and funding source.
- Clinical setting: location (eg, public/private/veterans' institution).
- Population characteristics: demographic information (eg, age, sex, BMI) and comorbidities.
- Surgery type: primary/revision/undefined, hip/knee/shoulder/elbow/ankle/wrist, indication for surgery, TJR clearly defined, and elective TJR clearly defined.
- Exposure: preoperative opioid use definition and chronic preoperative opioid use definition.
- Outcomes: outcome class and outcome definition.
- Result summary: odds ratio or standard mean difference and 95% confidence intervals for each outcome measure, use of univariate/multivariate analysis, and 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 are 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 on 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 judgement 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 are 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 analysed 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 will be reported. Standardised mean difference will be used for the analysis of continuous outcome variables. 95% confidence inervals 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 (ie, 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 minimise 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 on a database that is commonly overlooked by systematic reviewers (ie, 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 10 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 on 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, 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 the 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 underrecognised. 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 (eg, 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 TJR.

Author affiliations
[1]Department of Surgery, The University of Melbourne, St Vincent's Hospital, Melbourne, Victoria, Australia
[2]Centre for Digital Transformation of Health, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Melbourne, Victoria, Australia
[3]Centre for Health Policy, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia
[4]Melbourne Medical School, The University of Melbourne, Melbourne, Victoria, Australia
[5]Department of General Practice, The University of Melbourne, Melbourne, Victoria, Australia
[6]Melbourne Institute: Applied Economic & Social Research, Faculty of Business & Economics, The University of Melbourne, Melbourne, Victoria, Australia
[7]Department of Orthopaedics, St Vincent's Hospital, Melbourne, Fitzroy, Victoria, Australia

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Contributors CS, DG, XC, JK, ST, YZ, MMD and PFMC originally conceived of this project. CS, DG, MMD and PFMC initially refined the scope of the project. CS

wrote the first draft. CS, DG, XC, JK, SR, ST, YZ, MMD and PFMC 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, MMD and PFMC read and approved the submitted version. CS will be the guarantor of this review.

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Competing interests MMD reports personal fees from Pfizer and grants from Medacta, outside the submitted work; PFMC 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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ORCID iDs
Cade Shadbolt http://orcid.org/0000-0002-0937-2412
Michelle M Dowsey http://orcid.org/0000-0002-9708-5308

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