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Exploring incidence and risk factors for persistent postoperative opioid use in adult surgical patients: a systematic review protocol

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Abstract

Objective: To determine the incidence of persistent postsurgical use of opioids in adult patients and the risk factors associated.

Introduction: Surgery has been identified as an independent risk factor for unwarranted chronic opioid use, contributing to opioid-related harm in the community. Persistent opioid use after surgery is associated with morbidity and mortality from opioid-related adverse events, indicating a significant yet mitigable public health concern. There is substantial variation in the reported incidence and risk factors for postoperative opioid use, which require evaluation for future evidence-based risk reduction strategies.

Inclusion criteria: This review will include studies investigating the persistent use of opioids after 90 postoperative days in adult (≥18 years) patients undergoing surgery of any type, including cancer pain patients. Selected evidence must report on opioid use prior to surgery. Included study designs are analytical and descriptive observational studies, and experimental and quasi-experimental studies, published in the last decade.

Methods: The proposed study methods follow guidance from the JBI Methodology for Systematic Reviews of Prevalence and Incidence. A systematic search will include PubMed, EMBASE, CINAHL, Cochrane Central, Web of Science, and the gray literature. Study selection, critical appraisal, and data extraction are to be performed by two independent reviewers, aided by relevant JBI systematic review tools. We aim to produce a narrative synthesis of results and conduct a meta-analysis where feasible, in addition to subgroup analyses of suitable populations. The results are intended to promote safe, evidence-based postoperative opioid prescribing when considering risk factors for persistent postoperative opioid use.

Keywords: Opioid; Incidence; Postoperative; Pain.

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Introduction

For centuries, opioids have successfully alleviated pain and suffering for patients, including those undergoing surgery.[1] Over the past two decades, prescription rates for opioids have increased sharply in the United States (US), where the "opioid epidemic" is said to have originated,[3] with many other nations following this trend, including the United Kingdom (UK).[4, 5] However, despite their strengths, prescription opioids carry significant potential for abuse and addiction similar to non-prescription opioids, and the risk of transition towards illicit opioid use has been documented.[6] As a result, health, societal, and economic burden from inappropriate opioid prescribing is increasing, resulting in significant morbidity, mortality, and public health expenditure.[1, 3, 7] In the UK, between 1998 and 2016, opioid prescription counts rose by 34%, compounded by a 127% increase in the average oral morphine equivalent (OME) dose prescribed (mg day^{-1}),[1] and it is now estimated that 5% of the UK population take opioids regularly.[8] Consequently, these data have prompted issues of warning by the Chief Medical Officer and numerous UK pain associations to promote evidence-based, judicious prescribing of opioids.[1, 2]

Highlighting opioid-related harm, a Cochrane systematic review of 18,679 randomized patients found that chronic opioid use, compared with placebo, caused a higher risk of experiencing any adverse event (risk ratio (RR) 1.42, 95% confidence interval (CI) 1.22-1.66) or serious adverse event (RR 2.75, 95% CI 2.06-3.67).[9] Notable serious opioid-related adverse events (ORAEs) include dependence, hospitalization, death or hypoxia via opioid-induced ventilatory impairment, and fatal or non-fatal overdose.[1, 3] More recently, evidence suggests that surgery is an isolated risk factor for developing chronic opioid consumption, a phenomenon termed persistent postoperative opioid use (PPOU),[1, 7, 10] which is associated with morbidity and mortality from ORAEs.[2] The definition of PPOU varies within the literature;[11] however, the most recent national and international guidelines define PPOU as ≥1 opioid prescription (OP) in postoperative days 90-365 for patients opioid-naïve prior to surgery, and any baseline increase in OME from the 90 days preceding surgery to postoperative days 90-365 for presurgical users.[1, 7, 12] Depending on the selected definition, the reported risk of developing PPOU from US observational research ranges from 0.6-26% for opioid-naïve patients to 35-77% for presurgical chronic opioid users.[13] Moreover, the responsibility held by surgeons, anesthetists and other disciplines in mitigating this risk is increasingly evident, with clinical and research interest in perioperative opioid stewardship gaining significantly.[2, 12]

PPOU has been reported in recent observational studies for patients undergoing both major and

minor surgery, regardless of preoperative opioid exposure. Therefore, all patients undergoing surgery are currently deemed at risk.[14-16] Successful harm reduction strategies, such as gradual preoperative opioid tapering, will require targeting patient risk factors and modifying potential drivers of PPOU where possible via supportive evidence.[17] In attempt to facilitate this, many observational studies have characterized the relationship between patient baseline characteristics as risk factors and PPOU.[14, 15] For example, Chaudhary *et al.* performed a retrospective case-control study in 86,356 adult surgical patients, where 6,365 (7.4%) met criteria for PPOU, and found that the strongest risk factors were preoperative sustained opioid use (odds ratio (OR) 13.00, 95% CI 11.88-14.23), preoperative opioid exposure (OR 3.21, 95% CI 2.96-3.47), and nonhome discharge (OR 2.14, 95% CI 1.62-2.83).[15] In comparison, Khazi and colleagues found that in 12,038 adult patients undergoing total shoulder arthroplasty, continued OPs at 12 months were most associated preoperative chronic opioid use (OR 10.32, 95% CI 8.69-12.3), preoperative opioid exposure (OR 2.54, 95% CI 1.89-3.39), and concurrent chronic lung disease (OR 2.14, 95% CI 1.62-2.82).[18] Therefore, variation in estimates of PPOU incidence, and the magnitude of risk factors contributing, warrants an evidence synthesis for clinicians to aid accurate risk stratification in surgical patients who may transition to long-term opioid therapy.[1]

A preliminary search of PROSPERO, PubMed, the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* was conducted. PubMed revealed three systematic reviews investigating PPOU across multiple surgical disciplines;[12, 19, 20] one was confined to the US and Canada,[12] and another confined to Europe.[19] The former review did not create a pooled estimate of risk factors but only assessed the quality of evidence for studies that mentioned them;[12] the latter only assessed incidence and found insufficient evidence to make robust conclusions on the current extent of PPOU.[19] The third review examined both incidence and risk factors of PPOU with no geographical limitations to studies, but included historical data dating back to 1995 in a fast-changing health issue, and excluded cancer patients.[20] Despite excluding a large proportion of the opioid-using population and thus reducing generalizability, some studies exclude cancer patients due to their inherent differences in pain management, particularly as many may be palliative.[5] Interestingly, use of historical data and handling of cancer diagnoses were among the greatest methodological weaknesses found in an analysis of current prescription opioid safety research.[21] It is suggested that examining the effect or interaction due to cancer patients, rather than excluding them or simply combining the pooled estimates, will help inform whether separate opioid safety guidelines may or may not be required for cancer-related postsurgical pain.[21]

Our proposed review will include cancer patients and enable geographical comparisons of incidence and risk factors of PPOU, to evaluate whether data from the US may be used cautiously to aid decision-making where raw data is still scarce.[16] Additionally, owing to both the rapidly changing picture of the opioid epidemic and the recent surge in research interest,[15, 16] we believe an updated review of existing evidence is warranted. The objective of this review is to measure the incidence of PPOU across existing literature and determine the overall risk of individual patient characteristics contributing to PPOU in adult surgical patients, thus contributing to the knowledge of opioid prescription safety. This will help evidence local policy decisions enforcing opioid stewardship practices and facilitate the identification and management of surgical patients susceptible to opioid-related harm.

Review question

1. What is the incidence of persistent postoperative opioid use in adult surgical patients in varying populations and backgrounds?
2. What are the pooled estimates of risk factors for persistent postoperative opioid use?

Inclusion criteria

The inclusion criteria outlined utilizes the Population, Condition, Context (PCC) structure for the first research question, and the Population, Exposure, Outcome (PEO) structure for the second research question, as described by the JBI Methodology for Systematic Reviews.[22] The Population criteria for both questions are synonymous.

Population

This review will consider studies that include surgical patients aged 18 years or older requiring any formulation or duration of opioid-based analgesia postoperatively. This includes operations for cancer diagnoses. Contrary to existing reviews, no minimum participant number applies, permitting inclusion of smaller studies. The intervention in this review will include any form of major or minor: elective, emergency, day-case, or reoperative surgery, given sufficient postdischarge data is presented. Consistent with other literature, studies involving ≥75% of participants meeting inclusion criteria will be accepted in the event of mixed populations.[23]

Condition

This review will consider studies evaluating PPOU, including a limited variety of associated definitions. Currently, no standardized definition for PPOU exists, which remains an issue with current research.[1, 12] For inclusion, studies investigating PPOU must attempt to quantify postoperative opioid consumption at least 90 days after discharge; studies mentioning PPOU but measuring OPs received or prescribed only at discharge, or before 90 postoperative days, will not meet the definition requirements and are therefore excluded.[16] This threshold is frequently agreed in existing evidence and is in line with the definition of persistent postsurgical pain.[12, 20] Similarly, studies failing to provide details on the timing of opioid initiation or duration are excluded. Studies with postdischarge data limited to 90 days are included if OP data is indexed to the corresponding surgical event.

Context

This review will consider studies conducted in any cultural, racial, or gender-based contexts. There are no geographical or temporal limitations for included studies, provided they were published in the last decade.

Exposure

The exposure of interest is preoperative opioid use, including patients that were: opioid-naïve (defined as no OPs in the year preceding surgery), opioid-exposed (≥1 OP in the year preceding surgery), or chronic users (≥60 days duration of OPs in the year preceding surgery) prior to admission. Potential candidate studies must include opioids that are indicated and prescribed for pain; unless specifically indicated for pain, studies investigating opioids regularly prescribed for other purposes are excluded. There are no exclusions regarding medication formulation or route. Further exposures of interest include patient characteristics that have been examined in included studies, such as depression and concurrent benzodiazepine use, among others. To facilitate comparisons between patients that are either opioid-naïve or experienced prior to surgery, studies with mixed cohorts which prevent subgroup analyses of these exposures are excluded.

Outcome

The outcome of interest for the pooled rates of risk factors is PPOU.

Types of studies

This review will consider analytical observational studies including prospective and retrospective cohort studies, case-control studies, and cross-sectional studies. Additionally, descriptive observational study designs that may contribute to incidence data will be considered. Similarly, experimental and quasi-experimental studies, including *post hoc* analyses of these, will be included if they contribute toward incidence data or test an intervention where the outcome directly addresses postsurgical opioid use and meets the criteria.[24] Further, conference proceedings will be searched for contributable incidence data given the scarcity of available published information. Studies in English will be included for feasibility purposes, despite potential language bias and the possibility of an incomplete dataset.[25] Qualitative studies will be excluded.

Methods

The methodology proposed in this protocol will be conducted in accordance with the JBI Methodology for Systematic Reviews of Prevalence and Incidence,[22] and adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[26] This protocol has been registered in PROSPERO (CRD42022320691).

Search strategy

The search strategy will retrieve both published and unpublished literature. The first stage of the search strategy is an initial search of PubMed to identify articles and relevant key terms. The second stage involves creating a full search strategy developed for PubMed, using text words identified from the titles and abstracts of relevant articles and associated index terms (Appendix I). The full search strategy, with all identified keywords and index terms, will be adapted for searching additional databases, including CINAHL (EBSCOhost), CENTRAL (Cochrane Library), EMBASE (Ovid), and Web of Science (Clarivate). Sources of unpublished studies and gray literature will be searched, including Google Scholar and ClinicalTrials.gov. As the final stage of the strategy, additional studies will be sought by hand-searching bibliographies of relevant articles that were selected for critical appraisal. The results of all searches, including the number of results and the date each search was performed, in addition to any limits applied to each database, will be recorded as a supplement, to develop a fully reproducible search and improve transparency.[26] Studies published from 1 January 2012 until present will be included to better capture recent trends in incidence and ensure that the most

relevant studies will be analyzed.

Study selection

Upon completion of the full search strategy, all identified citations will be collated and uploaded into EndNote 20 (Clarivate Analytics, Philadelphia, USA), with duplicates removed. The final search results and retrieved studies will be imported into the JBI System for the Unified Management, Assessment and Review of Information (SUMARI).[27] Following an initial pilot test, two independent reviewers will screen titles and abstracts for compliance with the inclusion criteria described previously. The two reviewers will then undergo full-text screening of relevant citations to determine their compatibility with the inclusion criteria. Reasons for exclusion of full-text studies will be recorded in SUMARI and reported in the review. Any disagreements that occur between the reviewers at each stage of the study selection process will be recorded and resolved through either discussion or consultation with a third reviewer. The results of the search, study selection and inclusion process will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram.[28]

Assessment of methodological quality

Two independent reviewers will critically appraise candidate studies for methodological quality using standardized critical appraisal instruments from JBI for experimental, quasi-experimental, and observational studies within SUMARI.[22] As with the selection process, disagreements between reviewers will be recorded and resolved by consensus or with the help of a third reviewer. Included studies and their corresponding results for each critical appraisal criterion (yes, no, or unclear) will be reported in a table with an accompanying narrative. Studies that meet ≥50% of the criteria in the JBI critical appraisal checklist for studies reporting incidence data will be included for improved quality of contributing studies. Authors will be contacted for missing or additional data where required.

Data extraction

Data extraction from included studies will be performed by two independent reviewers using the standardized JBI data extraction tools.[27] The data extracted will include specific details about the populations, study methods, exposures, and outcomes of significance to the review question. This

includes study design, sample size, follow-up duration, type of surgical admission, and selected PPOU and preoperative opioid use definitions. Additionally, data will be organized into categories relating to PPOU risk factors, such as sociodemographic information, comorbid status, and preoperative opioid use status. Studies reporting odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs) for risk factors are included since no limitations to extracted effect measurements apply. Finally, sources of study funding, such as pharmaceutical companies or research funding institutions, will be analyzed. Authors of papers will be contacted to request missing or additional data, where required.

Data synthesis

Estimates of incidence will, where possible, be pooled with statistical meta-analysis using JBI SUMARI.[27] Incidence data will be transformed using Freeman-Tukey transformation and subsequently used to calculate a summary proportion using a random effects model.[29] Since the overall prevalence of risk factors is expected to be low, we will regard ORs and RRs as equivalent measures; pooled rates of HRs will undergo a separate analysis.[20] Effect sizes of PPOU risk factors will be expressed as ORs and their 95% confidence intervals (CIs) for dichotomous variables and as standardized mean differences (SMD) with 95% CIs for continuous variables, using a random effects model. Included studies will be assessed for clinical, methodological, and statistical heterogeneity; the latter will involve the standard χ^2, τ^2, and I^2 tests.[22] Subgroup analyses will be conducted to explore any clinical heterogeneity where there are sufficient data concerning study, participant, and exposure characteristics previously mentioned. Examples of this include cancer diagnosis, type of surgical admission, extent of preoperative opioid use, and study location. As substantial variation in PPOU definitions is expected, a sensitivity analysis of the pooled odds ratios is planned, testing different definition thresholds in addition to our primary analysis. It is likely that significant heterogeneity will prohibit meta-analysis as often seen in reviews of prevalence and incidence.[22] In this instance, the findings will be presented in narrative form including tables and figures to aid in data presentation, where appropriate. In the event of low heterogeneity between studies, a funnel plot will be generated to assess publication bias if 10 or more studies are included in a meta-analysis. Statistical tests for funnel plot asymmetry, including the Egger regression-based test, will be performed if necessary.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, adapted for prognostic studies, for grading the certainty of evidence, will be followed.[30] The Summary of Findings will be created using GRADEpro GDT (McMaster University, ON, Canada) and present the following information where appropriate: incidence rates, pooled estimates of risk, and a ranking of the quality of the evidence based on methodological bias assessment, directness, heterogeneity, precision, and risk of publication bias of the review results.

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Appendix I: Search strategy

Search conducted on 07 July 2022 in PubMed.

Search	**Query**	**Records retrieved**
Condition	(“Persistent postoperative opioid use”[All Fields] OR opioid use prolonged postoperative[All Fields] OR postoperative opioid dependence[All Fields] OR opioid dependence surgery[All Fields] OR persistent opioid use surgery[All Fields] OR chronic opioid use surgery[All Fields] OR opioid use postsurgical[All Fields] OR postoperative chronic opioid use[All Fields] OR postoperative opioid use[All Fields])	1,358
Exposure	((“opioid”[MeSH] OR “opioid”[All Fields]) OR (“codeine”[MeSH] OR “codeine”[All Fields]) OR (“morphine”[MeSH] OR “morphine”[All Fields]) OR (“tramadol”[MeSH] OR “tramadol”[All Fields]) OR (“oxycodone”[MeSH] OR “oxycodone”[All Fields]) OR (“dihydrocodeine”[MeSH] OR “dihydrocodeine”[All Fields]) OR (“hydromorphone”[MeSH] OR “hydromorphone”[All Fields]) OR (“oxymorphone”[MeSH] OR “oxymorphone”[All Fields]) OR (“fentanyl”[MeSH] OR “fentanyl”[All Fields]) OR (“hydrocodone”[MeSH] OR “hydrocodone”[All Fields]) OR (“tapentadol”[MeSH] OR “tapentadol”[All Fields]) OR (anagles*[All Fields] AND	71,759

	"opioid"[All Fields]) OR ("levorphanol"[MeSH] OR "levorphanol"[All Fields]) OR ("meperidine"[MeSH] OR "meperidine"[All Fields]) OR ("pentazocine"[MeSH] OR "pentazocine"[All Fields]) OR ("levopropoxyphene"[MeSH] OR "levopropoxyphene"[All Fields]) OR ("propoxyphene"[MeSH] OR "propoxyphene"[All Fields]) OR ("dextropropoxyphene"[MeSH] OR "dextropropoxyphene"[All Fields]) OR ("sufentanil"[MeSH] OR "sufentanil"[All Fields]) OR ("buprenorphine"[MeSH] OR "buprenorphine"[All Fields]))	
Context	("Postoperative"[All Fields] OR "postsurgical"[All Fields] OR ("minor"[All Fields] AND "surgery"[All Fields] OR "operative"[All Fields] OR "procedure"[All Fields]) OR ("major"[All Fields] AND "surgery"[All Fields] OR "operative"[All Fields] OR "procedure"[All Fields]) OR "surgical procedures"[All Fields] OR "minor surgical procedures"[MeSH] OR "major surgical procedures"[MeSH] OR "general surgery"[All Fields] OR "elective surgery"[All Fields] OR emergen* surgery[All Fields] OR "day-case surgery"[All Fields] OR reoperative surgery[All Fields] OR "operative"[All Fields] OR "surgical"[All Fields] OR "surgery"[All Fields] NOT ("animals"[MeSH] NOT "humans"[MeSH]) NOT ((child[MeSH] OR adolescent[MeSH]) NOT adult[MeSH]))	1,865,709
#4	#1 AND #2 AND #3	1,181
Limited to studies published from 1 January 2012.		

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