Adverse drug events and cost components related to the use of opioids in post-operative pain: a scoping review protocol

Érica Brandão de Moraes¹,²,³,⁴ • Ana Karine Brum¹,² • Julia Darte Martins¹ • Juliane de Macedo Antunes¹,³

¹Aurora de Afonso Costa Nursing School, Federal Fluminense University, Niterói, Rio de Janeiro, Brazil, ²Brazilian Society for Quality of Care and Patient Safety – SOBRASP, Rio de Janeiro, Brazil, ³Brazilian Society for the Study of Pain – SBED, São Paulo, Brazil, and ⁴The Brazilian Centre for Evidence-based Healthcare: A JBI Centre of Excellence

ABSTRACT

Objective: The objective of this review is to map the available evidence on adverse drug events and costs related to the use of opioids in hospitalized patients with post-operative pain.

Introduction: Post-operative pain is the most prevalent type of acute pain, affecting 80% of patients undergoing surgery. The main drug used in the treatment of post-operative pain is the opioid analgesic. These alleviate pain but cause adverse drug events. These events may result in lack of expected improvement in health status, the emergence of a new pathology, change in an organic function, or a harmful response due to the use of medicament.

Inclusion criteria: This review will consider studies that include adult (18 years or over) post-operative patients experiencing pain from any type of surgery. Patients must be hospitalized in tertiary hospitals and taking opioid analgesics by any route of administration. Studies must report adverse events and associated costs of adverse drug events. Quantitative and qualitative studies, theses, and text and opinion papers will be considered. Only studies published in English, Spanish, and Portuguese will be included, with no date limit.

Methods: A three-step search strategy will be utilized for this review. The databases to be searched include MEDLINE (PubMed), CINAHL, LILACS, Scopus, Embase, and Google Scholar. Studies published in English, Spanish, and Portuguese will be included. The extracted data will be presented in diagrammatic or tabular form in a manner that aligns with the objective of this scoping review, and a narrative summary will be provided.

Keywords adverse drug event; health care costs; opioids; patient safety; post-operative pain


Introduction

Pain is a protective reaction that enables people to detect, and subsequently avoid, harmful physical and chemical stimuli. This definition conceptualizes pain as a harrowing experience associated with current or potential tissue injury involving sensory, emotional, cognitive, and social components.¹,³ Pain after surgery is both common and expected. Post-operative pain is the most prevalent type of acute pain, affecting 80% of patients undergoing surgery. It represents an autonomic and behavioral response due to a complex physiological reaction to tissue injury.⁴ The time after surgery directly influences the frequency and intensity of pain, which is higher in the first post-operative days.⁴,⁸

Effective management of pain is a priority of care, and it is a patient’s right.⁹,¹⁰ When it is not properly controlled, the patient becomes predisposed to the chronicity of post-operative pain, which has a significant impact on quality of life.⁶ An additional consideration is patient safety and the fundamental principle of not causing harm.¹¹ Despite the high prevalence of acute pain in health services, there is still a lack of knowledge on how to assess and treat pain. Inadequate pain management in the post-operative period is considered an adverse event.¹²,¹³
The main class of medication used in the treatment of post-operative pain is opioid analgesics. Opioid analgesics alleviate pain, reduce the possibility of peripheral and central sensitization, but cause many adverse drug events. Every year patients experience the adverse consequences of poor acute pain management, including the overuse of opioids, which are serious and include an increased risk of complications, longer hospitalizations, opioid-use disorder, and death.\textsuperscript{14-17}

An adverse drug event is defined as any injury or harm caused by improper or inadequate use, or lack of access to necessary drugs. Adverse drug events may occur due to unintended effects or medication errors. Unintended effects concern the risk inherent in the use of otherwise appropriate medicinal products. Medication errors, however, are considered preventable failures in the treatment process. The most common adverse opioid effects include nausea, vomiting, sedation, pruritus, urinary retention, constipation, and respiratory depression (the latter of which accounts for less than 1% of adverse effects).\textsuperscript{11,13,14}

These adverse drug events may result in a lack of expected improvement in health status, the emergence of a new pathology, a change in an organic function, or a harmful response due to the use of medication. In turn, these may have significant health and economic consequences, including the increased use of health services, preventable medication-related hospital admissions, and death. It has been estimated that in some countries approximately 6% to 7% of hospital admissions appear to be medication related, with over two-thirds of these considered avoidable and, as such, due to errors.\textsuperscript{18-20}

Adverse events attributable to opioid use are among the 10 most common events, contributing to patients’ withdrawal from treatment, and fear of prescription and administration by health professionals.\textsuperscript{11,13} Globally, the costs associated with adverse events are high, estimated at US$17 to $29 billion per year in the United States.\textsuperscript{18} Cost components are defined as all elements of health care expenditure, including costs to patients and/or family members and social cost. Costs related to adverse events can be classified as direct costs, which are those directly related to health services, or indirect costs, which are those related to changes in the productive capacity of the individual and family.\textsuperscript{19,21}

One study showed that 29% of avoidable adverse events were associated with opioid analgesics, with a significant impact on hospital length of stay (2.2 days), charges (US$6341), and costs (US$3244).\textsuperscript{18} Aside from the direct financial costs, there are also several indirect costs for patients and their caregivers, such as missed days of work, and morbidity, such as anxiety due to the adverse drug event episode. With advances in pain management, measures should be established to prevent or minimize adverse events related to the use of opioids in order to guarantee quality of treatment and safety while in care, as well as to promote an optimized and economical treatment. For these reasons, adverse events and costs are an urgent patient safety issue.\textsuperscript{20-22}

Primary studies on adverse drug events and costs associated with opioids have been published; however, there has been no mapping of these opioid-related adverse events and costs related to post-operative pain in a scoping review. A preliminary search of PROSPERO, MEDLINE (PubMed), the Cochrane Database of Systematic Reviews, and the JBI Database of Systematic Reviews and Implementation Reports was conducted, and no current or pending systematic or scoping reviews on the subject of adverse opioid events and costs in post-operative pain were identified. Awareness of opioid-related adverse events and the associated costs affords health care professionals greater knowledge for planning care, preventing and/or identifying these events early to ensure safer care for patients, and maintaining lower costs to the health service.

The scoping review will be a step in a future umbrella project on pain management. The project also outlines the dimensions of education, research, and extension, comprising activities in the Research Group Nucleus of Studies and Research in Citizenship and Management in Nursing (NECIGEN), and the LabQualiseg Extension Project – Laboratory of Innovative Educational Technologies in the Management of Patient Safety, Quality of Care and Risk Management for Health Teaching.

**Review question**

What are the adverse drug events and cost components related to the use of opioids in hospitalized patients with post-operative pain?

**Inclusion criteria**

**Participants**

The participants of this review will be post-operative patients experiencing pain. This review will consider...
studies that include adult patients, 18 years or over, undergoing any type of surgery. Patients must be taking opioid analgesics by any route of administration and have reported adverse events.

**Concept**
This review will consider studies that include opioid-related adverse events and associated costs to adverse drug events. For the opioid-related adverse event, the study will consider both adverse drug effects and medication errors. The costs will be classified into direct and indirect costs. Direct costs will be those directly related to health services; indirect costs refer to those related to changes in the productivity of the individual and the family.

**Context**
This scoping review will only consider studies that have been conducted with patients who are hospitalized in tertiary hospitals.

**Types of sources**
This scoping review will consider both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies, and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies, and cross-sectional studies will be considered for inclusion. This review will also consider descriptive observational study designs including case series and individual case reports, qualitative research, economic evidence, and clinical practice guidelines. Theses, and text and opinion papers will also be considered for inclusion in this scoping review.

**Methods**
The proposed scoping review will be conducted in accordance with JBI methodology.23

**Search strategy**
A three-step search strategy will be utilized for this review. An initial limited search of MEDLINE (PubMed) and CINAHL has been undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article.

A full secondary search will be performed across all included databases using the keywords and index terms identified from the initial limited search. A full search strategy for MEDLINE (PubMed) is included in Appendix I. To help identify any additional studies, a tertiary literature search will be performed by examining the reference lists of all literature meeting the inclusion criteria of this review. If relevant, the reviewers intend to contact the authors of the primary studies or reviews for further information.

Studies published in English, Spanish, or Portuguese will be included. The review will consider all relevant published studies, with no limit on the dates of publication.

**Information sources**
The databases to be searched include: MEDLINE (PubMed), CINAHL, LILACS, Scopus, Embase, and Google Scholar.

The search for unpublished literature will include: websites for pain organizations, the Agency for Healthcare Research and Quality, the Institute for Healthcare Improvement, the Networked Digital Library of Theses and Dissertations, and Internet search engines.

**Study selection**
Following the search, all identified citations will be collated and uploaded into EndNote (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full and their citation details imported into JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia) and included in the reference list. The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or with a third reviewer. The results of the search will be reported in full in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses for Scoping Review (PRISMA–ScR) flow diagram.24
**SYSTEMATIC REVIEW PROTOCOL**

**Data extraction**
Data will be extracted from papers included in the scoping review by two independent reviewers using a data extraction tool developed by the reviewers. The data extracted will include specific details about the population, concept, context, study methods, and key findings relevant to the review objective. A draft charting table is provided (Appendix II). Authors will pilot test the tool for three studies in order to become familiar with the extraction and the results. The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included study. Modifications will be detailed in the full scoping review report. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required.

**Data presentation**
The extracted data will be presented in diagrammatic or tabular form in a manner that aligns with the objective of this scoping review. Tables and mappings will report on the distribution of studies by surgery type, opioid-related adverse events, and associated costs. A narrative summary will accompany the tabulated and charted results, and will describe how the results relate to the review’s objective and question.

**References**
Research Datalink (CPRD) and Hospital Episode Statistics (HES). BMJ Open 2017;7:e017585.


# Appendix I: Search strategy

Search in MEDLINE (PubMed), conducted April 2019

<table>
<thead>
<tr>
<th>Search</th>
<th>Query</th>
<th>Records retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Search “Pain, Postoperative”[Mesh] OR “Postoperative Pain” OR “Postoperative Pains”</td>
<td>47,940</td>
</tr>
<tr>
<td>#3</td>
<td>Search “Analgesics, Opioid/adverse effects”[Mesh] OR “Opioid Analgesics” OR “Opioids” OR “Partial Opioid Agonists” OR “Agonists, Partial Opioid” OR “Opioid Agonists, Partial” OR “Opioid Partial Agonists” OR “Agonists, Opioid Partial” OR “Partial Agonists, Opioid” OR “Full Opioid Agonists” OR “Agonists, Full Opioid” OR “Opioid Agonists, Full” OR “Opioid Full Agonists” OR “Agonists, Opioid Full” OR “Full Agonists, Opioid” OR “Opioid Mixed Agonist-Antagonists” OR “Agonist-Antagonists, Opioid Mixed” OR “Mixed Agonist-Antagonists, Opioid” OR “Opioid Mixed Agonist Antagonists”</td>
<td>132,097</td>
</tr>
<tr>
<td>#4</td>
<td>Search ((#1) AND #2) AND #3</td>
<td>419</td>
</tr>
<tr>
<td></td>
<td>Filters: English; Portuguese; Spanish</td>
<td>383</td>
</tr>
</tbody>
</table>
## Appendix II: Data extraction instrument

<table>
<thead>
<tr>
<th>Study details and characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
</tr>
<tr>
<td>Primary author and year published</td>
</tr>
<tr>
<td>Related reference</td>
</tr>
<tr>
<td>Country</td>
</tr>
<tr>
<td>Study design</td>
</tr>
<tr>
<td>Purpose/objective</td>
</tr>
<tr>
<td>Sample/participants</td>
</tr>
<tr>
<td>Data collection methods</td>
</tr>
<tr>
<td>Analysis/key findings/summary of contents</td>
</tr>
<tr>
<td>Reviewers’ comments</td>
</tr>
<tr>
<td>Results extracted from study</td>
</tr>
<tr>
<td>Surgery type</td>
</tr>
<tr>
<td>Use of opioids</td>
</tr>
<tr>
<td>Opioid-related adverse event</td>
</tr>
<tr>
<td>Associated costs</td>
</tr>
</tbody>
</table>