Observational Study

Association Between Opioid Use and the Development of Diverticulitis: Draft Project Protocol

Publication Date: August 31, 2023
Report Length: 10 Pages

Protocol

Authors: Michael Webster Clark, Laura Targownik, David Juurlink, Michael Paterson, Matt Dahl, Carolina Moriello, Greg Carney, Tyrone Harrison, James Zhang, Donica Janzen, Xinya Lu, Amani Hamad, Fangyun Wu, Chris Cameron, Devin Manning, Antonios Douros, Christopher Filliter, Robert Platt

This work was supported by CADTH and its Post-Market Drug Evaluation Program, through funding provided by Health Canada.

Table of Contents

Abbreviations

CNODES	Canadian Network for Observational Drug Effect Studies
CPRD	Clinical Practice Research Datalink

Background

Opioids have long been used as a means to treat pain. Since morphine was originally extracted from poppies and then successfully marketed by Merck at the start of the 19th century, there have been a wide array of opioid derivatives introduced — including completely synthetic opioid products. Opioids act on opioid receptors to dull pain, but they also slow the movement of food and increase water absorption within the gastrointestinal tract. This can lead to constipation, even during a relatively short course of opioid treatment.[1,2] Treating opioid-induced constipation while maintaining the patient on opioids to relieve pain can be extremely difficult. To date, only 1 gastrointestinal-sparing opioid has been developed and approved in Canada, although there has been minimal uptake by patients and clinicians. Whether it occurs due to opioid use or as a result of other factors, constipation (particularly protracted constipation) can lead to a diverse array of complications. These complications include severe pain, hemorrhoids, an increased susceptibility to bowel infection, and longer-term bowel damage.[2]

One potential gastrointestinal complication that is not as well understood is whether opioids and opioid-induced constipation increase the risk of diverticulitis, an illness caused by the infection of small sacs within the large intestine (called diverticula) that is most common in older adults.[3-8] Many cases of diverticulitis are fairly mild and can be treated with antibiotics at home, but it can also be life-threatening. There is a biologically plausible mechanism: opioids induce constipation which in turn leads to pressure in the colon and more diverticula, and the increased length of exposure of these diverticula to bowel contents increases risk of infection.[2]

Rationale

Opioid use is a risk factor for diverticulitis, but there is limited evidence on the association between opioid analgesics and diverticulitis.

Policy Questions

1. Are adult patients who are exposed to opioids more likely to develop diverticulitis?
2. Is there a specific group of patients (emphasis on Sex- and Gender-Based Analysis Plus [SGBA+]) more at risk?
3. Does the risk of diverticulitis change according to the indication for opioids use?

Policy Impact

Health Canada will use the findings to better understand this risk and determine if additional regulatory activities are required, including but not limited to drug labelling.

Objectives

This study aims to determine whether short-term and sustained opioid use are associated with an elevated risk of diverticulitis in patients indicated for opioid treatment for various indications, associated rates of new use, nonuse, and prevalent use of opioids.

The query will be conducted in 2 parts.

Part 1 objectives:

1. Evaluate population characteristics and the prevalence of new use, prevalent use, and nonuse of opioids within a variety of indications across participating sites.
2. Evaluate the incidence rates of 5 different definitions of diverticulitis of increasing severity within each of those indications.

Part II objective:

3. Compare estimates of the incidence rate ratio, incidence rate difference, risk ratios, and risks for diverticulitis and severe diverticulitis for new and prevalent users of opioids with nonusers.

Deliverables

This study is being conducted by the Canadian Network for Observational Drug Effect Studies (CNODES). We will carry out separate population-based cohort studies using administrative health databases from 6 Canadian provinces, the UK, and the US. We will also combine the results from the separate sites to provide an overall assessment of the risk of developing diverticulitis with opioid use.

The following deliverables are planned:

- a scientific protocol
- a presentation of results to the query submitter (as needed)
- a scientific report.

Methods

Population

The population is individuals who had 1 of 3 indications for opioid use (described subsequently) between April 1, 2004, and March 31, 2020.

The individuals included in the study will have prescription drug and health data available in their respective provincial administrative data repositories, MarketScan (MScan), or Clinical Practice Research Datalink

(CPRD). For the feasibility study, we identified our broad classes of potential indications based on the work done in Ontario by Pasricha et al.[9] These classes include:

- postsurgical pain
- pain after trauma
- other indications for opioids with a specific encounter date
- dental indications

Based on preliminary results from Ontario, we will limit ourselves to the postsurgical pain, pain after trauma, and other indications classes for the comparative analyses due to an inadequate sample size for the dental indications class.

Study Design

This study is a multicentre, retrospective, cohort study comparing new users and prevalent users of opioids versus nonusers with defined indications for opioid therapy.

Inclusion Criteria

We will include individuals aged 18 years and older who meet the criteria for the indication classes.

Data Sources

We will use data from the administrative health databases in British Columbia, Alberta, Saskatchewan, Nova Scotia, Manitoba, and Ontario, as well as MScan and CPRD data. Each of these sources has information on inpatient and outpatient procedures and diagnoses as well as outpatient prescriptions.

Exposure

Individuals will be divided into opioid nonusers, new users, and prevalent users based on prescriptions for opioid analgesics by various landmark dates following an indication for opioid use (to separate users from nonusers) and prescriptions within a look-back period before the indication for opioid use (to separate new users from prevalent users).

Outcomes of Interest

Five different definitions of diverticulitis (1 based on diagnosis codes in both emergency department and inpatient encounters and another based on inpatient encounters with associated CT scans) will be evaluated. The risk of diverticulitis will be assessed at 30, 180, and 730 days after the indication for opioid use. The incidence rate will also be assessed.

Analyses Overview

Three indication cohorts for opioid treatment (i.e., patients with postsurgical pain, patients with trauma pain, and patients with other indications) between 2004 and 2020 will be created. Analyses will be conducted using inverse probability of treatment weights and odds weights separately. We will describe patient characteristics and the prevalence of opioid use (new use, prevalent use, and nonuse) for each indication. We will estimate the incidence rate ratios and differences as well as risk ratios and differences for diverticulitis among prevalent and nonusers of opioids compared with new users. Follow-up will be defined using both an intention-to-treat and an as-treated approach (with inverse probability of censoring weights). If feasible, we will conduct subgroup analyses by sex or gender, age, and subclass of surgical indication. Patients with prevalent or new use of opioid maintenance therapy will be excluded in a sensitivity analysis. Site-specific results will be pooled using random effects meta-analysis if sample size permits.

Limitations

The primary limitation in this study is the risk of confounding by indication which could affect the validity of the comparisons between nonusers, prevalent users, and new users. New users could differ from the other groups in terms of their risk for diverticulitis in ways that cannot be identified based on measured patient characteristics in the databases (for example, frailty or risk of constipation). Therefore, an association between opioid new use and nonuse may be observed despite the absence of a causal effect or a null association may be observed despite the presence of a causal effect. The comparative analyses among multiple opioid indication–based patient cohorts will reduce this potential bias.

Additionally, we need to consider potential misclassification of exposure (some patients may use old supplies of opioids and be falsely categorized as nonusers), outcomes (some patients may have “rule-out” diagnoses of diverticulitis), and covariates (not all covariates may be measured perfectly).

The as-treated analyses evaluating the effect of sustained opioid use will also need to consider possible bias from systematic differences between opioid new users and prevalent users who do and do not take opioids for a sustained period of time.

Opportunities for Stakeholder Feedback

Stakeholders — including patient groups, medical associations, clinicians, clinical experts and/or peer reviewers, and pharmaceutical industry — will be given the opportunity to provide feedback on the proposed protocol and the draft report through public postings on the CADTH website.

Areas for Potential Amendments

If amendments are required at any time during the study, reasons for the changes will be recorded in a study file and subsequently reported within the final study report.

References

1. Shaikh A KA, Le A, Kaye AJ, Ahlawat S. Pre-existing Opioid Use Worsens Outcomes in Patients With Diverticulitis. *Cureus* 2023;15(2):e34624. doi:10.7759/cureus.34624
2. Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. *Am J Gastroenterol*. May 2011;106(5):835-42; quiz 843. doi:10.1038/ajg.2011.30
3. Gravante G, Yahia S. Medical influences, surgical outcomes: role of common medications on the risk of perforation from untreated diverticular disease. *World J Gastroenterol*. Sep 28 2013;19(36):5947-52. doi:10.3748/wjg.v19.i36.5947
4. Humes DJ, Fleming KM, Spiller RC, West J. Concurrent drug use and the risk of perforated colonic diverticular disease: a population-based case-control study. *Gut*. Feb 2011;60(2):219-24. doi:10.1136/gut.2010.217281
5. Piekarek K, Israelsson LA. Perforated colonic diverticular disease: the importance of NSAIDs, opioids, corticosteroids, and calcium channel blockers. *Int J Colorectal Dis*. Dec 2008;23(12):1193-7. doi:10.1007/s00384-008-0555-4
6. Morris CR, Harvey IM, Stebbings WS, Speakman CT, Kennedy HJ, Hart AR. Anti-inflammatory drugs, analgesics and the risk of perforated colonic diverticular disease. *Br J Surg*. Oct 2003;90(10):1267-72. doi:10.1002/bjs.4221
7. Kvasnovsky CL, Papagrigoriadis S, Bjarnason I. Increased diverticular complications with nonsteriodal anti-inflammatory drugs and other medications: a systematic review and meta-analysis. *Colorectal Dis*. Jun 2014;16(6):O189-96. doi:10.1111/codi.12516
8. Awad AK, Varney J, Motawea KR, et al. OPIOID INDUCED COLONIC DIVERTICULAR DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS. presented at: Abstract published at SHM Converge 2022 Abstract G8 Journal of Hospital Medicine; 2022; https://shmabstracts.org/abstract/opioid-induced-colonic-diverticular-disease-a-systematic-review-and-meta-analysis/
9. Pasricha SV, Tadrous M, Khuu W, et al. Clinical indications associated with opioid initiation for pain management in Ontario, Canada: a population-based cohort study. *Pain*. Aug 2018;159(8):1562-1568. doi:10.1097/j.pain.0000000000001242