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Observational Study

# Association Between Opioid Use and the Development of Diverticulitis

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This Observational Study is being conducted by the Canadian Network for Observational Drug Effect Studies (CNODES) through the Post-Market Drug Evaluation CoLab Network.

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# Abbreviations

| | |
|---|---|
| **CI** | confidence interval |
| **CNODES** | Canadian Network for Observational Drug Effect Studies |
| **CPRD** | Clinical Practice Research Datalink |
| **ED** | emergency department |
| **IPCW** | inverse probability of censoring weights |
| **IPTW** | inverse probability of treatment weights |
| **SMD** | standardized mean difference |

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# Amendments and Updates

The following amendments were made during the implementation of analyses.

### Table 1: Protocol Version Tracking

| Section heading | Amendment | Rationale |
|---|---|---|
| Objective, research methods, and limitations | Edits made to include the part 2 comparative analyses | Included the components of the comparative analyses and decisions based on results of the feasibility analysis in Ontario and findings in CPRD |
| Research methods | Removed use of stabilized odds weights | Stabilizing the stratified odds weights was resulting in covariate imbalance |
| Research methods | Limited the comparative analysis within the CPRD to a smaller selection of surgical interventions | Needed to create a sufficiently small cohort to download from CPRD |
| Research methods | Added discussion of removing sites with too few events to generate bootstrapped confidence limits | Noticed during the analysis that small numbers of events at some sites within as-treated analyses of severe diverticulitis generated misleading confidence limits when bootstrapping |
| Research methods | Limited contributions of some sites in the data sources section | Timelines limited the scope of analyses that could be performed |

CPRD = Clinical Practice Research Datalink.

# Abstract

While opioid use has been established as a risk factor for diverticulitis, there is limited evidence on the association between opioid analgesics and diverticulitis. The overall aim of this study is to evaluate the feasibility of, and subsequently conduct, an observational study evaluating whether short-term and sustained opioid use are associated with elevated risks of diverticulitis in patients with an indication for treatment with opioids. Using data from 5 Canadian provinces, the UK, and the US, we will create 3 separate cohorts of adults with an indication for opioid therapy, including postsurgical, trauma, and other pain indications, between 2004 and 2020. Within each indication cohort, we will estimate the incidence rate ratios, incidence rate differences, risk ratios, and risk differences of diverticulitis and severe diverticulitis comparing opioid new users to opioid nonusers and opioid new users to prevalent opioid users, respectively. Follow-up will be defined using both an intention-to-treat and an as-treated approach (with inverse probability of censoring weights [IPCW]). Analyses will be conducted using inverse probability of treatment weights (IPTW) and odds weights. Subgroup and sensitivity analyses will be conducted. Site-specific results will be pooled using random-effects meta-analysis.

## Background and Rationale

Opioids have long been used to treat pain. Since morphine was originally extracted from poppies and then successfully marketed by Merck at the start of the 19th century, there has been a wide array of opioid derivatives introduced including completely synthetic opioid products.[1] 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.[2,3] Treating opioid-induced constipation while maintaining the patient on opioids to relieve pain can be extremely difficult. Whether constipation occurs due to opioid use or because of other factors, protracted constipation can lead to a diverse array of complications. These can include severe pain, hemorrhoids, and longer-term bowel damage.[3]

One important unanswered question is whether opioids, presumably through opioid-induced constipation, increase the risk of diverticulitis, an illness caused by inflammation and/or infection of small sacs within the large intestine called diverticula.[4-9] While many cases of diverticulitis are mild and can be treated with antibiotics at home, it can also be life-threatening. There is a biologically plausible mechanism to explain this whereby opioids induce constipation that increases pressure in the colon and creates more diverticula, at which point the increased length of exposure of these diverticula to bowel contents increases risk of diverticulitis.[3] Randomized controlled trials of opioid therapies have been too small to show an increase in the rate of this rare outcome, especially among younger adults, who are at low baseline risk of diverticulitis. As a result, the majority of the evidence on any association between opioids and diverticulitis has come from observational studies.[5-9] In addition to being limited by potential confounding bias, these studies also have to contend with the fact that the primary symptom of diverticulitis is severe abdominal pain, which in turn is often treated with opioids. If not accounted for, this can result in protopathic bias that spuriously increases the observed risk of diverticulitis in opioid users relative to nonusers. By identifying new users of opioids following a clearly recorded indication for opioid treatment (e.g., surgery, trauma, dental procedure, or other defined indications) and comparing them to noninitiators following the same indication, we could mitigate the chance of observing such protopathic bias. Additional comparisons between new users and prevalent users following the indication could help identify differences in underlying risk between the 2 populations and help avoid the biases associated with prevalent users that are frequently observed in studies that combine new users and prevalent users into 1 exposure category.

## 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 Plus]) more at risk?
3. Does the risk of diverticulitis change according to the indication for opioid use?

## Policy Impact

Health Canada will use the findings to better understand these risks and determine whether regulatory actions are required.

## Research Questions

1. What is the risk of diverticulitis in adult patients after exposure to opioids?
2. Does the risk of diverticulitis vary by age, sex, and indication?

## Objectives

The overall aim of this study is to evaluate the feasibility of, and subsequently conduct, an observational study evaluating whether short-term and sustained opioid use are associated with elevated risks of diverticulitis in patients with an indication for treatment with opioids.

This query will be conducted in 2 parts: a feasibility study and a comparative safety study.

### Feasibility Study Objectives

1. To describe the patient characteristics and prevalence of new use, prevalent use, and nonuse of opioids within a variety of indications for opioid therapy.
2. To evaluate the incidence rates of diverticulitis according to 5 different administrative health data case definitions selected to represent increasing severity of diverticulitis within each of these indication-specific cohorts.

### Comparative Safety Study Objectives

1. To describe patient characteristics and prevalence of new use, prevalent use, and nonuse of opioids within the 90 days preceding and 7 days (for postsurgical pain) and 30 days (for trauma or other pain indications) following the inciting event, hereafter referred to as the landmark period.
2. To compare estimates of the incidence rate ratio, incidence rate difference, risk ratio, and risk difference at 30, 180, and 730 days for diverticulitis and severe diverticulitis comparing new users of opioids, prevalent users of opioids, and nonusers of opioids before and after adjusting for confounding variables.

# Research Methods

## Study Design

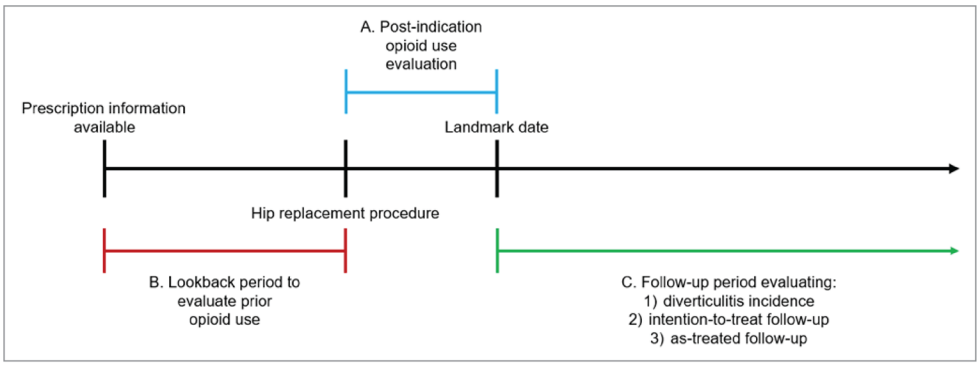
### Feasibility Study

This multicentre retrospective descriptive cohort study will explore the feasibility of a landmark-style comparative study contrasting new users of opioids, prevalent users of opioids, and nonusers of opioids following surgery, pain after trauma, dental pain, and other indications for opioid use. A landmark-style comparative study considers exposures in the time window between a signal index event creating a potential indication for opioid use (e.g., surgery leading to postsurgical pain) and a set landmark time (typically a set time postindex event) as exposed. The number of individuals within each exposure group and outcome rates for a wide spectrum of outcome definitions will be determined. We will also explore how varying study parameters such as landmark date, lookback period, and type of as-treated follow-up might influence the size and composition of the study cohorts and variation in these impacts across the different sites.

### Comparative Safety Study

The comparative safety study will be a multicentre retrospective cohort study comparing new users of opioids, prevalent users of opioids, and nonusers of opioids following defined indications for opioid therapy including postsurgical pain, trauma, and select other indications. The study design diagram for the comparative safety study is depicted in Figure 1.

## Figure 1: Study Design Diagram




## Study Population and Setting

This study will be conducted by the Canadian Network for Observational Drug Effect Studies (CNODES).[10,11] The study population will consist of individuals who had an indication for opioid use (subsequently described) between April 1, 2004, and March 31, 2020, in 5 Canadian provinces (Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan), the UK, and the US. We selected 2004 as the beginning of the study period as this marks the introduction of the International Classification of Diseases, 10th Revision, with Canadian enhancement and Canadian Classification of Health Interventions coding schemes in Canada. We selected March 2020 as the end of the study period as this marks the beginning of the COVID-19 pandemic, during which access to many health services was limited for an extended period.

For the feasibility study, separate study cohorts for each of the 4 potential study indications: postsurgical pain, pain after trauma, dental pain, and other pain indications for opioids with specific encounter dates will be constructed. The criteria for these indications will be adapted from the stepwise approach employed by Pasricha et al.[12] and will be identified using inpatient and outpatient health care encounter procedure and diagnosis codes. Each indication cohort will include several subclasses. For example, the postsurgical indication cohort will include common excisions, hip and knee replacements, hernia repairs, Caesarean sections, and a mix of other less frequent elective surgical procedures. Note that the other surgery subclass will not be included in the Clinical Practice Research Datalink (CPRD) for the postsurgical indication cohort due to CPRD limitations regarding the size of data extractions.

Individuals aged 18 years and older will be eligible for inclusion as of their date of eligibility for health care coverage in their administrative database and will enter the study cohort on the date they first meet the criteria for entry into each indication cohort. For cohorts defined by inpatient diagnosis or procedure codes, the cohort entry date will be the date of hospital discharge. For outpatient surgical procedures, cohort entry will be the date of the procedure. Patients will not be permitted to enter the cohort multiple times for a given indication but could enter multiple indication cohorts during the accrual period provided they meet the criteria for cohort entry.

For the comparative safety study, individuals who meet the entry criteria for multiple subclasses within an indication cohort on the same date will be randomly assigned to a subclass (except in MarketScan, where they will be allowed to contribute to multiple subclasses). Ultimately, based on the results of the feasibility analysis in Ontario, the final indications for the comparative safety study will be postsurgical pain, pain after trauma, and other indications for opioid use combined (excluding dental pain). We decided to exclude dental pain rather than combine it with the other indication category because the numbers for the dental pain indication were very small and the other indications are based on more longer-term chronic indications than treatment with opioids following a shorter-term indication such as a dental procedure.

## Study Variables

### Exposures

After meeting the criteria for a given indication, patients will be followed until their designated landmark date to determine whether they are dispensed (or prescribed for CPRD) an opioid. Multiple landmark dates were evaluated in the feasibility study (7, 14, and 30 days). Because the feasibility analysis in Ontario data suggested minimal opioid initiation between 7 days and 30 days following the surgery date, we will use a 7-day landmark period for the postsurgical cohort to ensure proximity to the indication. We will use a 30-day landmark for the trauma and other pain indication cohorts due to more patients initiating within the 7- to 30-day window in the feasibility analyses.

Patients will then be subclassified as opioid nonusers, new opioid users, and prevalent opioid users. Those with no opioid prescription records by the landmark date will be classified as nonusers. Those with opioid prescription records (insurance claims in North American databases, prescription orders in the UK CPRD) by the landmark date will be classified as new or prevalent users depending on their previous opioid exposure

history. New users of opioids will be defined as those without any opioid prescription records within a 90-day lookback before their indication. Those with at least 1 opioid prescription record within that lookback will be defined as prevalent users of opioids. We will separate new users from prevalent users of opioids to avoid healthy adherer and prevalent user biases (which could bias short-term results toward the null if the risk is higher in the early stages of opioid use) and ensure better alignment of the start of the hypothetical intervention and the start of follow-up.[13] Multiple lookback periods were assessed in the feasibility study (90, 180, and 365 days). A 90-day lookback will be used for all indication cohorts (postsurgical, trauma, and other pain) as extending the lookback period to 365 days in the feasibility analyses did not greatly alter the distribution of prevalent and new users. In the comparative safety study, all patients will be required to have at least 1 year of continuous health coverage before the cohort entry date, and those who die or otherwise leave the cohort before the landmark date will be excluded from the analysis. Gaps of 30 days or fewer will be considered as continuous health care coverage whether before and after the landmark date.

Exposure will be defined using both an intention-to-treat approach and an as-treated approach. In the intention-to-treat approach, patients will be followed from the landmark date (day 7 or 30, as appropriate) until occurrence of death, end of health insurance coverage (or leaving the general practice in the CPRD), end of data availability, or end of the study period (March 31, 2020), whichever occurs first, irrespective of whether they change their initial exposure status. In the as-treated approach, new users and prevalent users will be considered continuous users until the preceding events or they discontinue opioid therapy, defined as a gap of 30 days or longer beyond the end of the days supplied in their last continuous prescription. No censoring will be applied for patients switching between different types or dosages of opioids. Nonusers will be followed similarly to the intention-to-treat follow-up but will be censored upon initiation of opioid therapy.

## Outcomes

The outcome of interest is diverticulitis. Follow-up for the outcome will begin after the 7- or 30-day landmark date, as appropriate for the indication. The feasibility study explored 5 outcome definitions for diverticulitis:

1. an emergency department (ED) or inpatient primary discharge diagnosis for diverticulitis
2. an ED diagnosis for diverticulitis accompanied by a scan (CT or MRI) within the same ED visit
3. an inpatient primary discharge diagnosis for diverticulitis accompanied by a scan (CT or MRI) within the same hospitalization (referred hereafter as inpatient visit with a scan)
4. an inpatient visit with a scan and subsequent surgery during hospitalization
5. an inpatient visit with a scan and subsequent mortality.

Two specific outcome definitions of differing severity will be evaluated in the comparative safety study: an ED or inpatient primary discharge diagnosis of diverticulitis (the first outcome from the feasibility analysis), and more severe diverticulitis defined as an inpatient visit with a scan (the third outcome from the feasibility analysis). These outcome definitions were selected based on the feasibility analysis which showed the more severe diverticulitis case definitions (i.e., those including surgery or mortality) to have too few events to be feasible. The less severe diverticulitis outcome of a diverticulitis coded as an ED visit with a CT scan was

considered, but ultimately dropped due to inconsistent access to physician billing data for CT scans and/or ED records across the study sites. This means that the sensitivity and specificity of the first outcome have not been formally validated and it picks up an unknown number of cases that are not truly diverticulitis events. Due to the requirement for a CT scan, the second outcome will be more specific, but it may also be less sensitive and omit cases of diverticulitis that can be treated at home.

For the diverticulitis outcomes involving hospitalization, the outcome event date will be defined as the date of hospital admission. Risk of diverticulitis will be assessed at 30, 180, and 730 days after the appropriate landmark date for the opioid indication (i.e., 7 or 30 days). When estimating incidence rates, patients will be permitted to experience multiple outcome events provided they are separated by at least 30 days (meaning the ED visit or admission date for the inpatient encounter defining a subsequent outcome is occurring at least 30 days after the ED visit or inpatient encounter discharge date defining the previous outcome).

### Covariates

Patient characteristics will be assessed as of the date of cohort entry. The covariates will include sociodemographic characteristics, including age, sex at birth, and socioeconomic status (using site-specific definitions). We will capture several gastrointestinal risk factors for diverticulitis, including history of irritable bowel syndrome, Crohn disease, diverticulitis, and diverticulosis, as well as the following elements of the Deyo-Charlson Comorbidity Index:[14,15] myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, transient ischemic attack, dementia, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, chronic kidney disease, and current tumour (excluding nonmelanoma skin cancer). Comorbidities will be assessed in the year before cohort entry using both outpatient and inpatient diagnosis codes in all Canadian provinces and the US Merative MarketScan as is conventional for insurance claims data, whereas in the UK CPRD these will be assessed as ever before (i.e., using all available data before cohort entry date with a minimum of 1-year lookback) as is the convention for analyzing the general practitioner data due to the generally longer follow-up periods and, in the absence of studies attempting to examine temporal trends, a more sensitive approach to capturing potential confounding variables than shorter lookback durations.[16] While the 1-year lookback period may sometimes miss historical cases of some covariates, it will be used to avoid issues of unequal lookback between patients in US commercial claims and public insurance in Canada and enhance comparability of covariates across those data sources. Additional covariates that are not routinely available in administrative health data will be included in the UK CPRD, which contains electronic health records data: race, ethnicity, smoking status, and body mass index.

## Data Analysis

### Control for Confounding

Patients who initiate opioids (or are prevalent users of opioids) after experiencing a compelling indication may differ systematically from those who do not take any opioids after the same indication, resulting in potential confounding bias. To address this bias in the comparative safety analyses, **odds weights** (also referred to as standardized morbidity ratio weights) will be used to estimate the **effect specifically in opioid new users**, or the average treatment effect in the treated.[17]

We will first estimate a propensity score using multivariable logistic regression based on baseline covariates (previously mentioned) and then use the estimated propensity score to calculate the odds weights. The estimation of this propensity score will be stratified by indication subclass. New users will be assigned a weight of 1. The weights for nonusers will be determined by combining the nonuser cohort with the opioid new user cohort, and then estimating conditional probabilities of being in the opioid new user group. The nonusers will receive weights equal to their conditional odds of being in the opioid new user group, or the probability divided by 1 minus the probability. This will then be repeated with the prevalent users replacing the nonusers to calculate their weights. This analysis will be performed specifically to evaluate potential prevalent user bias and unmeasured confounding if new and prevalent users are treated as 1 exposure group. Standardized mean differences (SMDs) will be calculated comparing the new users with the nonusers and with prevalent users and weights will be recreated if these differences exceed 0.100.

To explore whether treatment effects would differ with a target population of **all individuals with the indication** (rather than new users of opioids following the indication) **IPTW** will be created for each indication subclass and exposure group to estimate effects in the overall population, or the average treatment effect.[18] Logistic regression will be applied to estimate propensity scores for each exposure group conditional on the baseline covariates (previously mentioned) and then used to calculate the IPTW. For each exposure group, individuals will be assigned a weight corresponding to the probability of the treatment they received divided by the conditional probability of the treatment they received. For example, new users will be assigned a weight corresponding to being a new user divided by the probability of being a new user, or 1 divided by the probability. This will then be repeated with the prevalent users and then nonusers. SMDs will be calculated, and weights will be recreated if these differences exceed 0.100.

If there are persistent issues with the SMDs exceeding 0.100 after modifying the terms in the propensity score, the weights will be truncated (meaning weights with stabilized value greater than 10 will be set to a value of 10) to reduce the influence of large weights on treatment effect estimates and avoid large weights resulting in poor covariate balance.

## Control for Selection Bias

Intention-to-treat and as-treated analyses will both be conducted. While the administrative censoring in the intention-to-treat analysis is unlikely to generate meaningful selection bias, censoring nonusers who initiate and users who discontinue treatment in the as-treated analysis is much more likely to cause bias. To help evaluate the potential for (and address) this selection bias, IPCW will be created based on baseline covariates for the as-treated analyses.[19] To create these IPCW, a Cox proportional hazards model will be fitted to predict the hazard ratio for censoring (meaning a gap in 30 days of days supply for opioid users and receipt of an opioid prescription for opioid nonusers) based on key predictors of sustained opioid use measured at baseline including age, sex, prior diverticulitis, and economic deprivation factors (where available). The coefficients from this Cox regression model will be used to generate a covariate-conditional probability of remaining uncensored for each individual. Patients will then receive an IPCW equal to the inverse of this value. This IPCW will then be combined with odds or IPTW weights to simultaneously control for both confounding and selection bias.

## Descriptive Analysis

Descriptive statistics will be used to summarize patient characteristics in each indication cohort overall in the feasibility analysis and before and after weighting in the comparative safety analysis. Continuous variables will be described as mean (standard deviation) and categorical variables as frequencies and percentages. Baseline characteristics will be weighted using odds and ITPW weights in separate analyses. In addition, these will be combined with IPCW in the as-treated analyses. Covariate balance between the exposure groups will be assessed using SMDs, with an absolute value of less than 0.100 considered good balance.[20] Crude and weighted incidence rates of diverticulitis (per 10,000 person-years) and corresponding 95% confidence intervals (CIs) will be estimated within each exposure group. In the comparative safety study, the risk of diverticulitis at 30, 180, and 730 days will be estimated (with a focus on risks at 30 and 730 days to capture short-term and long-term risks), while the feasibility study includes additional risk estimates at 90 and 365 days.

## Comparative Analyses

Within each indication cohort, we will estimate incidence rate ratios and rate differences, as well as 30-, 180-, and 730-day risk ratios and risk differences comparing opioid new users to opioid nonusers and opioid new users to prevalent opioid users, respectively. Crude and weighted values will be estimated. The corresponding 95% CIs for these comparative measures will be estimated using 1,000 bootstrap replicates, with the lower and upper confidence limits taken from the 2.5 and 97.5 percentiles, respectively, of the bootstrap estimates, with missing results omitted from the calculation of the percentiles. The new users will be determined to be significantly different from the nonusers if these 95% confidence limits do not include 1 (for the rate ratio and risk ratio) or 0 (for the rate difference and risk difference), and similarly for the new users and prevalent users. If the number of events at a site is too small for bootstrapping to generate accurate 95% confidence limits in a particular analysis, their findings will not be included in the meta-analysis.

For each indication cohort, we will conduct the 3 following subgroup analyses using the as-treated follow-up: by indication subclass, by age at initial event (18 to 39 years, 40 to 64 years, and 65 years and older), and by sex. The analyses by age subgroup will be repeated using the intention-to-treat follow-up. Lastly, we will conduct a sensitivity analysis excluding new users and prevalent users who received opioids used in opioid maintenance therapy. These include buprenorphine, buprenorphine-naloxone combinations, and methadone.

## Meta-Analysis

For the feasibility study, the site-specific results will be pooled to understand the size and characteristics of the overall sample. We will also sum the person-years and event counts to calculate a pooled incidence rate for each outcome and calculate pooled risks based on the weighted average across the sites. For the comparative safety study, site-specific incidence rate ratios, incidence rate differences, risk ratios, and risk differences for the severe diverticulitis outcome will be pooled for each indication cohort (and, where appropriate, each potential subgroup) using DerSimonian and Laird random-effects meta-analysis.[21] The standard error of each comparative measure at each site will be obtained by taking the width of the CI (for

difference comparisons) or the width of the log CI (for ratio comparisons) and dividing by 3.92. Between-site heterogeneity will be assessed using the $I^2$ statistic.

### Data Sources

We will be using administrative health databases from 5 Canadian provinces (Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan), the UK CPRD (Aurum), and the US Merative MarketScan. Briefly, the databases contain health insurance registries, prescription drug claims, medical service claims, hospitalization records, and ED records (where available). The UK CPRD Aurum is a primary care database which contains the records of 40 million individuals (including 14 million individuals currently registered) from 1,370 general practices in the UK.[22] The UK CPRD database will be linked to the Hospital Episode Statistics database, which contains hospital admission information and is available for approximately 90% of the participating practices in CPRD. UK CPRD data will also be linked to national death registrations from the Office of National Statistics; this linkage is available for general practices in England who have consented to the linkage. The US Merative MarketScan database includes more than 70 million individuals covered by large employer health insurance plans in the US, and government and public organizations. Due to timeline constraints, UK CPRD and US Merative MarketScan will only contribute to the surgical analysis, and British Columbia only to the surgical and trauma analyses.

## Limitations

The central limitation of the pooled intention-to-treat analyses will be the potential for residual confounding when comparing opioid users and nonusers. While this cannot be dismissed, we will be able to balance a broad swathe of covariates associated with general health status as well as risk factors for diverticulitis. Moreover, by conducting a new user versus nonuser comparison, rather than a user versus nonuser comparison, the potential for residual confounding by exposure history or prevalent user bias will be eliminated. That said, intention-to-treat estimates may not be generalizable to other populations that have different patterns of adherence and persistence (e.g., those initiating opioids for chronic pain), limiting their broader applicability. If almost everyone discontinues the treatment, or most of the population who does not initiate by day 7 eventually begins using it, the comparison can also become less useful.

To help combat this limitation, the as-treated analyses will require patients to maintain opioid use (or nonuse) after the initial landmark period. While this approach ensures we are only treating patients using opioids as exposed during windows where they are likely to be physically exposed to the drug and when a link between opioid use and diverticulitis is most biologically plausible, the fact that some individuals are censored from the analysis and that those individuals may have a differing risk of the outcome can potentially generate selection bias. In the case of this specific study, this type of bias may lead to overestimation of the risk of diverticulitis if the new users who continue using opioids are older and less healthy or more susceptible to diverticulitis than those who do not. While IPCW will be used to control this potential source of bias, only baseline covariates will be used in the censoring models; any changes in the patients' status over time that may predict their continued use or nonuse of opioids will not be captured. For example, the inability to

capture postsurgical complications in the censoring weights which may be strongly associated with lack of mobility (and thus, constipation and potential diverticulitis) could bias results.

Finally, the reliance on routinely collected data to generate the study samples means that there may be a susceptibility to measurement error in the exposure (e.g., patients receiving discharge prescriptions free of charge from the hospital may be misclassified as nonusers, people filling prescriptions who ultimately never take them, or issues with not being able to detect prescriptions prescribed by specialists or provided for free), covariates (e.g., not identifying older diverticulitis or diverticulosis diagnoses or claims data lacking sensitivity for these conditions), and the outcome (e.g., imperfect sensitivity and specificity). Fortunately, missing data are infrequent in these routinely collected administrative data.

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