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Concurrent prescriptions for opioids and benzodiazepines and risk of opioid overdose: protocol for a retrospective cohort study using linked administrative data

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ABSTRACT

Introduction: Opioid overdoses have increased substantially over the last 20 years, with over 700,000 deaths in North America. While opioid prescribing has been a target of research, benzodiazepine and opioid co-intoxication has emerged as a potential risk factor. Our aim is to assess the risk of opioid overdose associated with concurrent use of opioids and benzodiazepines relative to opioids alone.

Methods and analysis: A retrospective cohort study will be conducted using medical claims data from adult residents of Montréal, Canada. We will create a cohort of new users of opioids (i.e., no opioid dispensations in prior year) in 2000-2014 from people with at least two years of continuous health insurance. Those with any diagnosis or hospitalization for cancer or palliative care in the two-years before their first opioid dispensation will be excluded. On each person-day of follow-up, exposure status will be classified into one of four mutually-exclusive categories: i) opioid-only, ii) benzodiazepine-only, iii) both opioid and benzodiazepine (concurrent use), or iv) neither. Opioid overdose will be measured using diagnostic codes documented in the hospital discharge abstract database, physician billing claims from emergency department visits, and death records. Using a marginal structural Cox proportional hazards model, we will compare the hazard of overdose during intervals of concurrent opioid and benzodiazepine use to intervals of opioid use alone, adjusted for socio-demographics, medical and psychiatric comorbidities, and substance use disorders.

Ethics and dissemination: This study is approved by the McGill Faculty of Medicine Institutional Review Board and the *Commission d'access à l'information* (Québec privacy commission). Results will be relevant to clinicians, policymakers, and other researchers interested in co-prescribing practices of opioids and benzodiazepines. Study findings will be disseminated at relevant conferences and published in biomedical and epidemiological peer-reviewed journals.

ARTICLE SUMMARY

Strengths and Limitations of this study

- Our study will contribute evidence to an important public health question. Given the high prescribing rates of opioids and benzodiazepines, any risk of overdose from their concurrent use would have a large impact at a population level. It is thus crucial that we assess the association between concurrent drug use and risk of overdose.
- A strength in our study is the use of rigorous design features that were chosen to reduce bias. Restricting our cohort to new opioid users instead of prevalent users reduces the chance for selection bias because prevalent opioid users will be more tolerant of the medication. We will also use a validated outcome definition, and by modelling exposure as time-varying, we will reduce misclassification bias.
- The use of causal inference methods in our main analysis is both scientifically rigorous and novel for this area of research. By employing a marginal structural Cox proportional hazards model, we can control both time-fixed and time-varying confounders, reducing confounding bias. Conducting observational studies with varied statistical techniques in diverse populations will strengthen the evidence base regarding this issue.
- This will be the first study outside the USA to investigate this research question. Our study in a Canadian sample can inform whether previous results are robust across different healthcare systems, types of prescribing behaviour, and drug insurance policies.
- A potential limitation is that our results may not be generalizable to all opioid users, as we are restricted to individuals insured through the public drug plan. The drug plan is limited to all persons 65 years or older, those on social assistance, and those without employer-based access to drug insurance. However, given that we are measuring a biological drug effect and population-level variation in drug metabolism is unlikely to differ substantially, our results should be generalizable to most patients prescribed these medications.

INTRODUCTION

Morbidity and mortality attributable to opioid use has increased sharply in North America over the last 20 years. In the USA, deaths from opioid overdose increased threefold from 1999 to 2015[1], while in Canada, hospitalizations rose by 53% from 2007 to 2017[2], and 12,800 people have died from opioid overdose from January 2016 to March 2019[3]. Since the number of opioid overdoses remains high and they affect younger age groups disproportionately, these alarming trends demand effective and immediate public health actions.

Substantial research activity has focused on the role of prescription opioids in these overdoses and deaths.[4–7] Increasingly though, the co-prescribing of opioids and benzodiazepines and their potential role in causing overdose is receiving attention.[8–11] Up to 30% of prescription opioid overdose deaths involved benzodiazepines[12] and this prevalence has increased over time, from 16.8% in 2002-03 to 27.9% in 2014-15.[13] In comparison, the prevalence of other concurrent prescriptions such as antidepressants has remained constant. During this period, outpatient co-prescribing rates for these two drugs has increased, from 0.5% (95% CI 0.3 to 0.7) of visits to 2.0% (95% CI 1.4 to 27)[14] and amongst all opioid users, the proportion with a concurrent benzodiazepine prescription rose from 7% in 2002 to 10% in 2014[15]. In this context, the extent of the role of benzodiazepines in the opioid overdose epidemic demands further research.

Benzodiazepines are a class of anticonvulsant/anxiolytic medications used to treat anxiety, depression, panic disorders, insomnia, seizure disorders, alcohol dependence, and musculoskeletal pain.[16] When consumed alone, benzodiazepines do not cause respiratory depression, the main consequence of drug overdose. But animal studies have shown that the risk of respiratory depression is elevated when benzodiazepines are taken concurrently with opioids.[17] This interaction is due to the presence of receptors for both opioids (mu and delta) and benzodiazepines (GABA) in the brain region responsible for respiratory control.[18] Since benzodiazepines act on the inhibitory pathway for respiration and opioids inhibit the excitatory receptors, the activation of both pathways can reduce the respiratory drive more than the activation of either pathway alone. Whether this reduction is a consequence of an additive effect of both drugs inhibiting the respiratory system or an amplification of benzodiazepines on the effects of opioids is unknown. Nevertheless, the biological mechanism suggests greater harm from their combined use, and there is a need to understand if these effects are sufficient to cause respiratory depression at therapeutic doses.

To date, three epidemiologic studies conducted in population-based samples of adults have examined the risk of overdose associated with concurrent use of opioids and benzodiazepines. All of these retrospective studies were based in United States and used health insurance claims data. They reported effects ranging from hazard ratio (HR)=1.2 (95% CI 1.16 to 1.34; Cho et al)[19], odds ratio (OR)=2.14 (95% CI 2.05 to 2.24; Sun et al)[20], to HR=5.05 (95% CI 3.68 to 6.93; Hernandez et al)[21] when comparing concurrent opioid and benzodiazepine use to opioid use alone. However, potential methodological limitations make these results difficult to interpret. In Hernandez et al, the exclusion of cohort members based on non-benzodiazepine sedatives use after cohort entry[21] could induce selection bias, with an unknown effect on the point estimate if concurrent users are more, or less, likely to be dispensed these medications. A potential source of selection bias in Sun et al is restriction to prevalent opioid users[20] since this would limit the sample to those who tolerated their opioid medication long enough to continue its use. Bias from exposure misclassification is also a concern. In the retrospective cohort study conducted by Hernandez et al, comparing concurrent use in the 1-90 days before overdose to

opioid-only use in the 1 day before means concurrent users had more opportunity (up to 90 days) for opioid exposure. Longer opportunity for opioid use means concurrent users are more likely to be chronic opioid users,[15,22] which independently increases the risk for overdose. The resultant effect would be an over-estimation of the association. In Sun et al, misclassification bias from inclusion of person-years of non-opioid use in the reference group could have also overestimated the association. Periods of non-opioid use are less likely to lead to opioid overdose, which would artificially underestimate the rate of overdose in the reference group. Immortal time bias[23] due to misclassification of person-time could have manifested in the retrospective cohort study conducted by Cho et al[19]. In their main analysis, use of a time-fixed exposure means patients who initiated opioids and later added a benzodiazepine to their opioid regimen would have their opioid-only (and, by definition, event-free) person-time misclassified as concurrent drug use. This misclassification would bias the estimate downward, under-estimating the risk.

In summary, the current evidence base could be affected by important bias. As such, there remains uncertainty about the magnitude of the risk of overdose due to the concurrent use of opioids and benzodiazepines. To reduce this uncertainty, we propose a retrospective cohort study using population-based data sources.

Prescription opioid use has more than doubled in North America from 2001 to 2013, and combined with Europe and Oceania, these three continents account for 95.7% of worldwide use.[24] Benzodiazepine use is also high in these regions, with the USA reporting 5.2% of adults filling a prescription in 2008[25], 4.9% amongst those 45 years and older in Canada in 2002[26], 17.7% prevalence of use in France in 2012[27] and 2.4% of Australians from 2002 to 2007[28]. Evidently, the use of prescription opioids and benzodiazepines is highly prevalent in many countries. An accurate estimate of the risk of overdose associated with their concurrent use is important for setting public health policy in this area.

METHODS AND ANALYSIS

Data source

This study will use anonymized population-based administrative data from Montréal, Québec to define our cohort and measure all study variables. The source population consists of 1.4 million people representing a 25% random sample of health-insured Montréal residents sampled from January 1, 1998 to December 31, 2014. For each individual, data on their physician services and community pharmacy drug dispensations comes from the *Régie de l'assurance maladie du Québec* (RAMQ), the provincial health authority that reimburses all publicly-insured medical and pharmacy services. Data on hospitalizations is provided by the *Ministère de la santé et des services sociaux* (MSSS), and mortality data comes from the *Institut de la statistique du Québec* (ISQ). As such, we have linked information on each person's demographics, inpatient and outpatient medical services, hospitalizations, emergency department (ED) visits, and the date and causes of death from the time they were sampled until the time that an individual loses health insurance through death or emigration from province. Half of residents are also insured for prescription drugs through the RAMQ if they are welfare recipients, aged 65 years or older, or lack other drug insurance coverage (e.g., through their employer). Thus, data on dispensed drugs in the community (including the date, chemical name, dose, and duration), the prescribing physician, and dispensing pharmacist are available for approximately 50% of Montréal residents. The data sources have been validated previously[29] and used extensively for research[30–33].

Study population

New opioid users with RAMQ drug insurance will form our study population. These are drug-insured Montréal residents aged ≥18 who started using opioids between 2000 and 2014. We chose to include new users starting on January 1, 2000 to allow a two-year lookback period for exclusion criteria. A new opioid user will be defined as a person with no opioid dispensations for at least one year before their first opioid dispensation in this interval. A new user design was chosen to reduce the chance for selection bias, as prevalent drug users are limited to those that tolerated the drug well enough to continue its use.[34] The date of their first opioid dispensation will define the cohort entry date, and opioid users will be followed from this date until the occurrence of the outcome (defined below) or censoring due to i) death, ii) cancer diagnosis, iii) palliative care admission, iv) loss of drug or health insurance, or v) end of study period (December 31, 2014). Since patients with cancer and those undergoing palliative care will have a different risk-benefit ratio when using opioids, cohort members will be excluded if they have at least one cancer or palliative-care related diagnostic code in the two years prior to cohort entry. Patients whose first opioid dispensation is methadone or buprenorphine likely have a history of illicit opioid use, as these medications are indicated for an opioid use disorder. Given that we will be adjusting for history of opioid substance abuse, these patients will remain in the study.

Outcome

An opioid overdose occurs when opioids, possibly together with other substances, cause sedation, leading to loss of consciousness and respiratory depression.[35] We chose to study events where the use of opioids alone or in combination with benzodiazepines induces respiratory depression severe enough to require medical attention. To identify these events, we will use *International Classification of Diseases* (ICD) codes for opioid poisoning (ICD-9 codes E8500-E8502, 96500-96509 and ICD-10 codes T400-T404, T4060, T4069 and X42) and acute effects of opioids (E9350-E9352 and Y450) (Table E1, Appendix I). The presence of any one of these codes in medical service claims, hospital discharge abstracts, or vital statistics data during follow-up will define an event, and follow-up will be censored on this date. We chose to use ICD codes related to opioid poisoning and acute effects of opioids because there are no codes specific to drug overdose. However, validation studies comparing opioid poisoning codes to physician chart review have found positive predictive values ranging from 70.0% to 84.6%[36–38]. As such, this outcome definition will provide a high specificity in capturing the mechanism of interest (e.g., respiratory depression caused by medication).

Exposure

To ascertain each person's opioid and benzodiazepine status, we will calculate their average daily dose using information on the drug type (Table E2, Appendix I), the date the prescription was filled, the dose, quantity dispensed, and duration of the prescription. To account for different combinations of use and non-use, we will model our exposure using a time-varying approach. On each day of follow-up, exposure status will be classified into one of four mutually-exclusive categories: i) opioid-only, ii) benzodiazepine-only, iii) both opioid and benzodiazepine (concurrent use), or iv) neither (Figure 1). Since opioid overdose is an acute event, we will consider exposure status on the day before the event as the primary etiologic window of interest.

To ensure equivalency across opioid types, we will use published conversion factors to calculate each drug's oral morphine milligram equivalent (MME).[2,39] To calculate MME, we will use the standard method of multiplying the average daily dose by its conversion factor:

$$Dosage\ per\ pill\ in\ mg \times \frac{\#\ of\ pills}{Duration\ of\ prescription\ in\ days} \times MME\ conversion\ factor$$

To standardize benzodiazepine potencies, we will use the defined daily dose (DDD) methodology as recommended by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC).[40] The DDD is the "the assumed average maintenance dose per day for a drug used for its main indication in adults" and is calculated as follows:

$$\frac{Total\ \#\ pills}{Duration\ of\ prescription\ in\ days} \times \frac{Dosage\ per\ pill\ in\ mg}{WHO\ recommended\ daily\ dose\ in\ mg}$$

Each drug's Anatomical Therapeutic Chemical (ATC) category and route of administration has its own recommended daily dose, and values will be obtained from the WHOCC website.

Confounders

Confounding can occur in our study if we fail to adjust for factors that differ between opioid users and concurrent users, and these factors independently affect one's risk for overdose. Opioid users additionally prescribed a benzodiazepine are often older[15,20,41], more likely to be women[15,20,41,42], require social assistance[14,21], be a chronic opioid user[15], have more pain conditions[41], use more potent opioids[41,43], use other central nervous system medications[19,42], and are more likely to have comorbidities[19,20], mental health[19,21,41,42] and substance use disorders[20,41,42]. Concurrent users are also more likely to seek out multiple prescribers and pharmacies in a given time period[21,43,44]. Since these characteristics are also associated with overdose in studies on opioid prescribing patterns,[45] it is important that they are adjusted for in this study.

Across all statistical analyses, we will adjust for the following confounders (Table 1): demographic factors such as age, sex, drug insurance type and neighborhood income quintile, medical comorbidities such as history of myocardial infarction, dementia, and chronic pulmonary disease, mental health comorbidities such as diagnoses and prescriptions for anxiety, depression, and mood disorders, opioid use disorders, non-opioid substance abuse/misuse such as alcohol or nicotine dependence and measures of drug-seeking behaviour such as the number of distinct prescribers and pharmacies used in past 30 days. Receipt of concurrent muscle relaxants or Z-drugs will also be adjusted for since these medications can also depress the respiratory system.

Values of covariates will be measured in the baseline period (1-year before cohort entry), and every 30 days during follow-up. For age, sex, drug insurance type, neighborhood income quintile and history of opioid poisoning, the baseline values will remain fixed throughout follow-up. For medical comorbidities, mental health conditions, opioid use disorder, and substance use disorders, once a patient is diagnosed, we will assume these conditions persist. All other covariate values will be updated every 30 days during follow-up.

Statistical analyses

Main analysis

Time-varying confounding is a concern when both exposure and confounder values are likely to change over the study period and affect each other.[46] Given that opioids and benzodiazepines are often used intermittently, bias could occur if there are factors that both predict a change in benzodiazepine status (e.g., development of drug misuse disorders or mental health exacerbation) and independently increase the risk for overdose. The three previous epidemiological studies assessing concurrent use and risk of overdose measured confounders at baseline only.[19–21] This approach assumes, often implicitly, that comorbidities and drugs used at baseline remain the same throughout follow-up and that changes in comorbidities and concomitant drugs that occur during follow-up do not impact subsequent exposure to concurrent opioid and benzodiazepines. However, for studies with long follow-up periods and transient exposures, such as our study, this assumption will likely be violated.

To adjust for changes in confounder status without adjusting for variables on the causal pathway, we will employ a marginal structural Cox model with inverse probability of treatment weights (IPTW).[47] These models re-weight study participants based on their inverse probability of treatment, conditional on history of opioid and benzodiazepine use, and previous confounders. To construct these weights, we will first develop a multinomial logistic regression (exposure model) for the 4 exposure categories. Covariates used to generate the exposure model will include all time-varying confounders listed in Table 1. These weights will be re-estimated during study follow-up using updated covariate values from the past 30 days. For values that do not change, the previous value will be carried forward. Indicator variables will be used for all categorical covariates and continuous covariates will be tested for non-linear effects using Akaike Information Criterion (AIC) to determine the optimal form. Once we convert the log odds into predicted probabilities, P(A|W), for each exposure category, we can calculate stabilized weights [P(A)/P(A|W), where P(A) is the observed probability exposed to the specific opioid/benzodiazepine category, and P(A|W) is the predicted probability estimated from the exposure model as this approach is more efficient than using un-stabilized weights, which are simply 1/ P(A|W).[47,48] To check for positivity violations, we will assess the mean distribution of weights which should be close to 1, and the robustness of our results will be assessed after removing extreme weights (e.g. 99th, 95th, and 90th percentile values).

The final Cox proportional hazards regression model will estimate the hazard ratio for time to first overdose event, when comparing events during concurrent opioid and benzodiazepine person-time to opioid-only person time, adjusted for baseline confounders, and weighted according to each person's vector of IPTWs. We will use bootstrapping to construct 95% confidence intervals.

Secondary analyses

To identify patient characteristics that may modify the opioid and benzodiazepine association with overdose, we will undertake the following secondary analyses. We will stratify the primary analyses by sex (males vs female), age (≥76 vs 65 to 75 years among everyone on the 65+ drug insurance plan), social deprivation (drug insurance for welfare recipients vs all other), presence of an opioid use disorder or substance use disorder (ever/never), presence of a mental health condition (ever/never), and number and type of distinct opioid prescribers (e.g., surgeon, dentist or family physician). To assess potential differential effects by drug characteristics, we will also stratify analyses by cumulative days, and standardized dose of

opioid and benzodiazepine supply in the 7 and 30 days prior to overdose. Individuals who have a greater supply of or more potent forms of medication will have more opportunity to over-use. We intend these analyses to be hypothesis generating for future researchers to identify high-risk patient groups.

Sensitivity analyses

To account for the biological half-lives[49] of opioids and benzodiazepines, and the fact that many patients may take their medications on an 'as needed' (or "PRN") basis, we will introduce a grace period into our exposure assessment, where an additional 7 and 30 days of drug duration will be added to the end of each prescription. This is to account for situations where some patients may dispense their drug but keep it in their medicine cabinets until it is required. Since chronic opioid users have more medication in supply, this also increases their chance for overdose if they ingest more than the recommended dose at once. Although opioid and benzodiazepine-induced overdose is an acute effect, we will assess the 30-day period before the event date as a secondary etiological window of interest. To address the possibility that prevalent benzodiazepine users may be less susceptible to respiratory depression due to tolerance, we will perform another sensitivity analysis restricting our cohort to those with no use of benzodiazepines in the 1 year before cohort entry. Finally, given the challenges of attributing causality in drug poisoning, we will repeat our primary analyses using the broader definition of any drug poisoning to account for outcome measurement error.

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

ETHICS AND DISSEMINATION

This study is approved by the McGill Faculty of Medicine Institutional Review Board, and the *Commission d'access à l'information* (Québec privacy commission). Since we will be using pseudo-anonymized data, no consent is required.

Our findings will be important to researchers, public health, and medical communities in Canada and abroad, and this will be reflected in our dissemination plan. We plan to first present our findings at pharmacoepidemiology (e.g. the International Conference on Pharmacoepidemiology & Therapeutic Risk Management) and public health/health services conferences (e.g. the Canadian Association for Health Services and Policy Research and Public Health). We hope to elicit feedback from our scientific and clinical colleagues at these venues. As our methods are novel and other epidemiologists may benefit from learning about our experience applying these methods, we will also be submitting abstracts to the Society for Epidemiology's Annual Meeting and the Canadian Society for Epidemiology and Biostatistics conference. Our partners at the National Institute of Public Health of Québec (INSPQ) and Canadian Institutes of Health Research (CIHR)'s Drug Safety and Effectiveness Network (DSEN) will be important knowledge users. We anticipate our work will inform decisions around implementing prescription monitoring programs and guidelines on prescribing of opioids and benzodiazepines. We will reach out to our public health partners to present this work in their organizational seminars.

After integrating feedback from conference peers, we will submit our manuscript to peer-reviewed biomedical journals (e.g. BMJ, AJPM) as primary care physicians are responsible for the majority of opioid and benzodiazepine prescriptions. All publications will be reported in accordance with the REporting of studies Conducted using Observational Routinely collected health Data specific to pharmacoepidemiological research (RECORD-PE).[50]

AUTHOR CONTRIBUTIONS

This study was conceived by EYL and all authors contributed to the design, analysis and interpretation of the data. EYL drafted the manuscript and DLB, RT, KBF revised it critically for important intellectual content. All authors gave final approval of the version to be published and EYL will be the guarantor of the work.

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DATA STATEMENT

The data sharing agreements governing use of our data restricts access to members of the research team only. However, technical information used for this study (e.g. drug and disease codes) is available and will be provided in an appendix. DOI: [include DOI for appendix here].

COMPETING INTERESTS STATEMENT

The authors have no conflicts of interest relevant to this manuscript to disclose.

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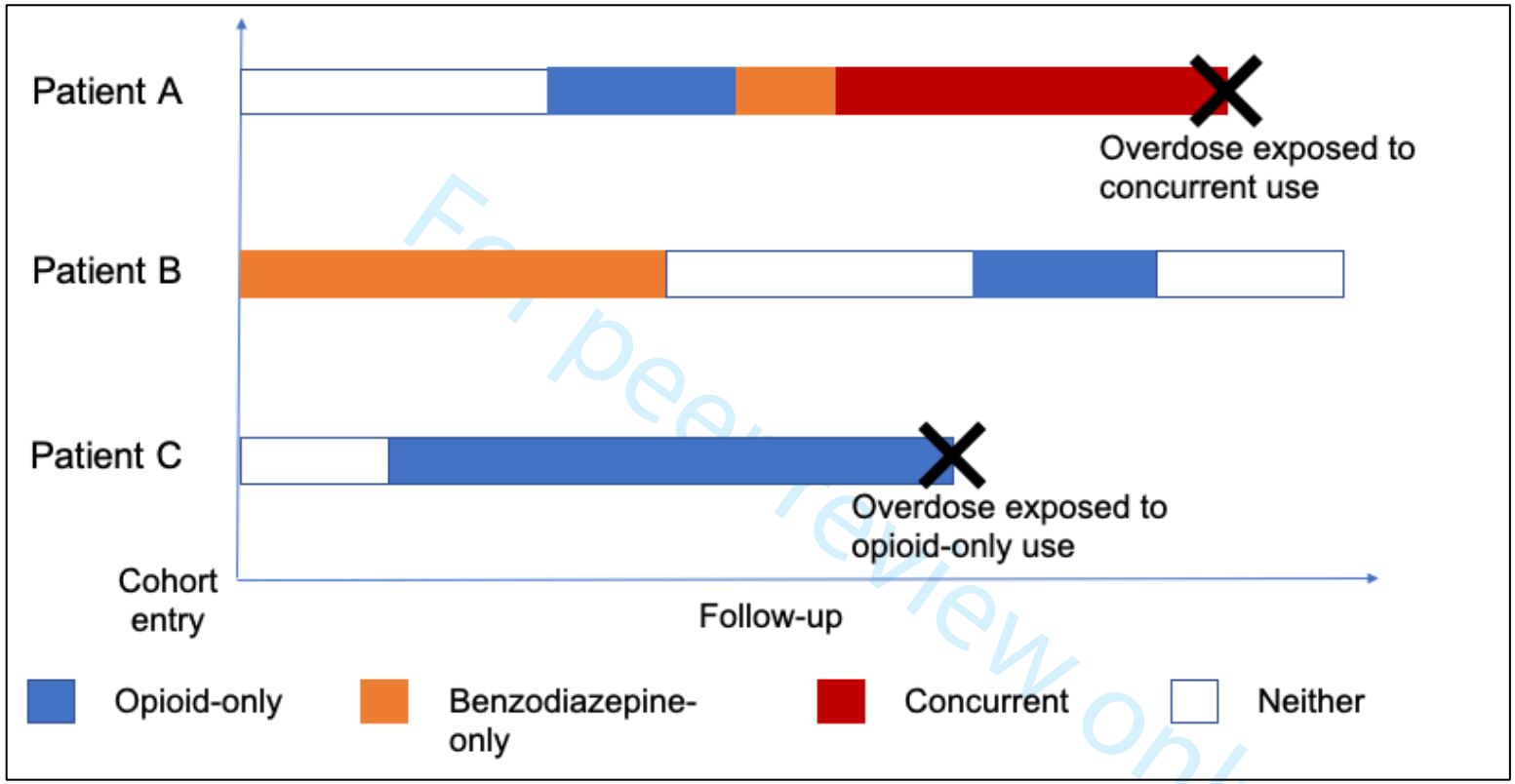
Table 1: Confounders under study

Covariate	**Measured at baseline only**
Age	18-45, 46-64, >64
Sex	Male or Female
Neighborhood income quintile	Q1-Q5; Calculated using results from the 2016 Canadian Census
Drug insurance type	Those who require social assistance vs all other. A measure of social deprivation.
History of opioid poisoning	Ever/never hospital or emergency department visit for an opioid poisoning in previous year. These are patients who experienced an overdose from non-prescription sources of opioids, or from opioids dispensed > 1 year before cohort entry.
	Measured at baseline and every 30 days during follow-up
Mental health diagnoses	Diagnoses for depression, anxiety disorders, personality disorders, mood disorders, schizophrenic and psychotic disorders, and all other mental health disorders
Mental health medications	Dispensations for anti-depressants, anti-psychotics, and mood stabilizing drugs
Opioid abuse/dependence diagnoses	Diagnoses for opioid abuse, opioid dependence, or mental/behavioural disorders due to opioid use
Opioid use disorder medications	Dispensations for methadone or buprenorphine
Non-opioid substance use disorders	Diagnoses for alcohol and nicotine dependence/abuse.
Substance use disorder treatments	Dispensations for nicotine or alcohol dependence medication
Drug seeking behaviour	Number of unique opioid prescribers and pharmacies used in given time period
Muscle relaxant or z-drug use	Ever/never use. These are non-benzodiazepine sedatives that could also potentiate the effect of opioids.
Comorbidities	Diagnoses for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes (with or without complications), hemiplegia or paraplegia, renal disease, cancer, moderate or severe liver disease, metastatic solid tumour or AIDS/HIV.

Figure 1: Examples of opioid and benzodiazepine utilization patterns to illustrate how exposure will be assigned



The purpose of this figure is to show how exposure will be assigned using three fictitious patients to illustrate. **Patient (A)** enters the cohort with no opioid and benzodiazepine use as shown by the section in white. Then, they receive their opioid prescription (blue), which ends right before they begin their benzodiazepine prescription (orange). During their period of benzodiazepine use, however, they receive another opioid prescription that overlaps this benzodiazepine period (red). Since they were using both drugs the day before an overdose, this patient's event would be exposed to concurrent drug use. **Patient (B)** enters our study already using benzodiazepines (orange), then stops for a period of time (white) before receiving a short prescription for opioids (blue) and then continues their period of non-use (white). **Patient (C)** enters the study using neither drug (white), but then begins a long duration of opioid-only use (blue) before experiencing the event. Since they were exposed to opioids only in the day before overdose, their event would be considered unexposed to concurrent drug use.

APPENDIX I

Table E1: ICD-9 and ICD-10 codes included in outcome definition

Opioid poisoning	Code	Description
	E8500	Accidental poisoning by heroin
	E8501	Accidental poisoning by methadone
	E8502	Accidental poisoning by other opiates and related narcotics
	96500	Poisoning by opium (alkaloids) unspecified
	96501	Poisoning by heroin
	96502	Poisoning by methadone
	96509	Poisoning by other opiates and related narcotics
	T400	Poisoning by opium
	T401	Poisoning by heroin
	T402	Poisoning by other opioids
	T403	Poisoning by methadone
	T404	Poisoning by other synthetic narcotic
	T406	Poisoning by other and unspecified narcotics
	X42	Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified
Adverse effects of opioids	E9350	Heroin causing adverse effects in therapeutic use
	E9351	Methadone causing adverse effects in therapeutic use
	E9352	Other opiates and related narcotics causing adverse effects in therapeutic use
	Y450	Drugs, medicaments and biological substances causing adverse effects in therapeutic use: Opioids and related analgesics

*The first occurrence of any one code will define presence of the event

Table E2: Prescription opioids and benzodiazepines under study

Opioid type	ATC codes
ANILERIDINE	N01AH05
BUPRENORPHINE	N02AE01, N07BC51
BUTORPHANOL	N02AF01
CODEINE	N02AA59, N02AA79, N02AJ06, N02BE51, R05DA04
FENTANYL	N01AH01, N02AB03
HYDROCODONE	R05DA03
HYDROMORPHONE	N02AA03
MEPERIDINE / PETHIDINE	N02AB02
METHADONE	N07BC02
MORPHINE	N02AA01
OPIUM	N02AA02
OXYCODONE	N02AA05, N02AA55, N02AJ17
PENTAZOCINE	N02AD01

TAPENTADOL	N02AX06
TRAMADOL	N02AJ13, N02AX02
Benzodiazepine type	**ATC codes**
ALPRAZOLAM	N05BA12
BROMAZEPAM	N05BA08
CHLORDIAZEPOXIDE	N05BA02
CLOBAZAM	N05BA09
CLONAZEPAM	N03AE01
DIAZEPAM	N05BA01
FLURAZEPAM	N05CD01
LORAZEPAM	N05BA06
MIDAZOLAM	N05CD08
NITRAZEPAM	N05CD02
OXAZEPAM	N05BA04
TEMAZEPAM	N05CD07
TRIAZOLAM	N05CD05

*Includes combination versions of the molecule of interest

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Concurrent prescriptions for opioids and benzodiazepines and risk of opioid overdose: protocol for a retrospective cohort study using linked administrative data

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ABSTRACT

Introduction: Opioid overdoses have increased substantially over the last 20 years, with over 400,000 deaths in North America. While opioid prescribing has been a target of research, benzodiazepine and opioid co-intoxication has emerged as a potential risk factor. Our aim is to assess the risk of opioid overdose associated with concurrent use of opioids and benzodiazepines relative to opioids alone.

Methods and analysis: A retrospective cohort study will be conducted using medical claims data from adult residents of Montréal, Canada. We will create a cohort of new users of opioids (i.e., no opioid dispensations in prior year) in 2000-2014 from people with at least two years of continuous health insurance. Those with any diagnosis or hospitalization for cancer or palliative care in the two-years before their first opioid dispensation will be excluded. On each person-day of follow-up, exposure status will be classified into one of four mutually-exclusive categories: i) opioid-only, ii) benzodiazepine-only, iii) both opioid and benzodiazepine (concurrent use), or iv) neither. Opioid overdose will be measured using diagnostic codes documented in the hospital discharge abstract database, physician billing claims from emergency department visits, and death records. Using a marginal structural Cox proportional hazards model, we will compare the hazard of overdose during intervals of concurrent opioid and benzodiazepine use to intervals of opioid use alone, adjusted for socio-demographics, medical and psychiatric comorbidities, and substance use disorders.

Ethics and dissemination: This study is approved by the McGill Faculty of Medicine Institutional Review Board and the *Commission d'access à l'information* (Québec privacy commission). Results will be relevant to clinicians, policymakers, and other researchers interested in co-prescribing practices of opioids and benzodiazepines. Study findings will be disseminated at relevant conferences and published in biomedical and epidemiological peer-reviewed journals.

ARTICLE SUMMARY

Strengths and Limitations of this study

- Our choice to conduct our study in new opioid users reduces the chance for selection bias because prevalent opioid users will be more tolerant of the medication.
- Other strengths in this study includes the use of a validated outcome definition and modelling exposure as time-varying, which will reduce misclassification bias.
- The use of a marginal structural Cox proportional hazards model can control both time-fixed and time-varying confounders, therefore reducing confounding bias.
- Our study in a Canadian sample can inform whether previous results are robust across different healthcare systems, types of prescribing behaviour, and drug insurance policies.
- A potential limitation is that our results may not be generalizable to all opioid users, as we are restricted to individuals insured through the public drug plan.

INTRODUCTION

Morbidity and mortality attributable to opioid use has increased sharply in North America over the last 20 years. In the USA, deaths from drug overdose increased from 6.1 per 100,000 in 1999 to 20.7 in 2018,[1] with 446,032 of these deaths involving opioid use.[2] In Canada, hospitalizations related to opioid overdose rose by 53% from 2007 to 2017,[3] with a national rate of 15.5 per 100,000 in 2019.[4] Deaths related to opioids also remains high, with Canada's public health agency recording 1,634 deaths from January 2016 to March 2020.[5] Since harm from opioid overdoses persist, and they affect younger age groups disproportionately, these alarming trends demand effective and immediate public health actions.

Substantial research conducted in North America has focused on the role of prescription opioids in these overdoses and deaths.[6-9] Increasingly though, the co-prescribing of opioids and benzodiazepines and their potential role in causing overdose is receiving attention.[10-13] Studies in Canada and USA showed that 27.6% and 30% of opioid overdose deaths involved benzodiazepines, respectively.[14,15] This has paralleled high rates of concurrent use of both medications. A 2017 Alberta study showed that 17.6% of opioid users had overlapping dispensations with a benzodiazepine,[16] and a 2014 study using USA pharmacy claims estimated the prevalence to be 10%.[17] What is concerning is that the prevalence of concurrent use increased by 41% from 2002 to 2014, despite guidelines from both countries cautioning against combining their use.[18,19] In this context, the extent of the role of benzodiazepines in the opioid overdose epidemic demands further research.

Benzodiazepines are a class of anticonvulsant/anxiolytic medications used to treat anxiety, depression, panic disorders, insomnia, seizure disorders, alcohol dependence, and musculoskeletal pain.[20] When consumed alone, benzodiazepines do not cause respiratory depression, the main consequence of drug overdose. But animal studies have shown that the risk of respiratory depression is elevated when benzodiazepines are taken concurrently with opioids.[21] This interaction is due to the presence of receptors for both opioids (mu and delta) and benzodiazepines (GABA) in the brain region responsible for respiratory control.[22] Since benzodiazepines act on the inhibitory pathway for respiration and opioids inhibit the excitatory receptors, the activation of both pathways can reduce the respiratory drive more than the activation of either pathway alone. Whether this reduction is a consequence of an additive effect of both drugs inhibiting the respiratory system or an amplification of benzodiazepines on the effects of opioids is unknown. Nevertheless, the biological mechanism suggests greater harm from their combined use, and there is a need to understand if these effects are sufficient to cause respiratory depression at therapeutic doses.

To date, three epidemiologic studies conducted in population-based samples of adults have examined the risk of overdose associated with concurrent use of opioids and benzodiazepines. We considered other studies on concurrent use and overdose risk, but due to their use of distinct subpopulations such as veterans,[23,24] we precluded them from our literature review as their generalizability is unclear.

The three relevant studies were all retrospective analyses based in United States that used health insurance claims data. They reported effects ranging from hazard ratio (HR)=1.2 (95% CI 1.16 to 1.34; Cho et al),[25] odds ratio (OR)=2.14 (95% CI 2.05 to 2.24; Sun et al),[26] to HR=5.05 (95% CI 3.68 to 6.93; Hernandez et al),[27] when comparing concurrent opioid and benzodiazepine use to opioid use alone. However, potential methodological limitations make these results difficult to interpret. In Hernandez et al, the exclusion of cohort members based on non-benzodiazepine sedatives use after cohort entry could induce selection bias, with an

unknown effect on the point estimate if concurrent users are more, or less, likely to be dispensed these medications. A potential source of selection bias in Sun et al is restriction to prevalent opioid users, since this would limit the sample to those who tolerated their opioid medication long enough to continue its use. Bias from exposure misclassification is also a concern. In the retrospective cohort study conducted by Hernandez et al, comparing concurrent use in the 1-90 days before overdose to opioid-only use in the 1 day before means concurrent users had more opportunity (up to 90 days) for opioid exposure. Longer opportunity for opioid use means concurrent users are more likely to be chronic opioid users,[16,17] which independently increases the risk for overdose. The resultant effect would be an over-estimation of the association. In Sun et al, misclassification bias from inclusion of person-years of non-opioid use in the reference group could have also overestimated the association. Periods of non-opioid use are less likely to lead to opioid overdose, which would artificially underestimate the rate of overdose in the reference group. Immortal time bias[28] due to misclassification of person-time could have manifested in the retrospective cohort study conducted by Cho et al. In their main analysis, use of a time-fixed exposure means patients who initiated opioids and later added a benzodiazepine to their opioid regimen would have their opioid-only (and, by definition, event-free) person-time misclassified as concurrent drug use. This misclassification would bias the estimate downward, under-estimating the risk.

In summary, the current evidence base could be affected by important bias. As such, there remains uncertainty about the magnitude of the risk of overdose due to the concurrent use of opioids and benzodiazepines. To reduce this uncertainty, we propose a retrospective cohort study using population-based data sources.

Prescription opioid use has more than doubled in North America from 2001 to 2013, and combined with Europe and Oceania, these three continents account for 95.7% of worldwide use.[29] Benzodiazepine use is also high in these regions, with the USA reporting 5.2% of adults filling a prescription in 2008,[30] 4.9% amongst those 45 years and older in Canada in 2002,[31] 17.7% prevalence of use in France in 2012,[32] and 2.4% of Australians from 2002 to 2007.[33] Evidently, the use of prescription opioids and benzodiazepines is highly prevalent in many countries. An accurate estimate of the risk of overdose associated with their concurrent use is important for setting public health policy in this area.

METHODS AND ANALYSIS

Data source

This study will use anonymized population-based administrative data from Montréal, Québec to define our cohort and measure all study variables. The source population consists of 1.4 million people representing a 25% random sample of health-insured Montréal residents sampled from January 1, 1998 to December 31, 2014. For each individual, data on their physician services and community pharmacy drug dispensations comes from the *Régie de l'assurance maladie du Québec* (RAMQ), the provincial health authority that reimburses all publicly-insured medical and pharmacy services. Data on hospitalizations is provided by the *Ministère de la santé et des services sociaux* (MSSS), and mortality data comes from the *Institut de la statistique du Québec* (ISQ). As such, we have linked information on each person's demographics, inpatient and outpatient medical services, hospitalizations, emergency department (ED) visits, and the date and causes of death from the time they were sampled until the time that an individual loses health insurance through death or emigration from province. Half of residents are also insured for prescription drugs through the RAMQ if they are welfare recipients, aged 65

years or older, or lack other drug insurance coverage (e.g., through their employer). Thus, data on dispensed drugs in the community (including the date, chemical name, dose, and duration), the prescribing physician, and dispensing pharmacist are available for approximately 50% of Montréal residents. The data sources have been validated previously,[34] and used extensively for research.[35-38]

Study population

New opioid users with RAMQ drug insurance will form our study population. These are drug-insured Montréal residents aged ≥18 who started using opioids between 2000 and 2014. We chose to include new users starting on January 1, 2000 to allow a two-year lookback period for exclusion criteria. A new opioid user will be defined as a person with no opioid dispensations for at least one year before their first opioid dispensation in this interval. A new user design was chosen to reduce the chance for selection bias, as prevalent drug users are limited to those that tolerated the drug well enough to continue its use.[39] The date of their first opioid dispensation will define the cohort entry date, and opioid users will be followed from this date until the occurrence of the outcome (defined below) or censoring due to i) death, ii) cancer diagnosis, iii) palliative care admission, iv) loss of drug or health insurance, or v) end of study period (December 31, 2014). Since patients with cancer and those undergoing palliative care will have a different risk-benefit ratio when using opioids, cohort members will be excluded if they have at least one cancer or palliative-care related diagnostic code in the two years prior to cohort entry. Patients whose first opioid dispensation is methadone or buprenorphine likely have a history of illicit opioid use, as these medications are indicated for an opioid use disorder. Given that we will be adjusting for history of opioid substance abuse, these patients will remain in the study.

Outcome

An opioid overdose occurs when opioids, possibly together with other substances, cause sedation, leading to loss of consciousness and respiratory depression.[40] We chose to study events where the use of opioids alone or in combination with benzodiazepines induces respiratory depression severe enough to require medical attention. To identify these events, we will use *International Classification of Diseases* (ICD) codes for opioid poisoning (ICD-9 codes E8500-E8502, 96500-96509 and ICD-10 codes T400-T404, T4060, T4069 and X42) and acute effects of opioids (E9350-E9352 and Y450) (Table E1, Appendix I). The presence of any one of these codes in medical service claims, hospital discharge abstracts, or vital statistics data during follow-up will define an event, and follow-up will be censored on this date. We chose to use ICD codes related to opioid poisoning and acute effects of opioids because there are no codes specific to drug overdose. However, validation studies comparing opioid poisoning codes to physician chart review have found positive predictive values ranging from 70.0% to 84.6%.[41-43] As such, this outcome definition will provide a high specificity in capturing the mechanism of interest (e.g., respiratory depression caused by medication).

Exposure

To ascertain each person's opioid and benzodiazepine status, we will calculate their average daily dose using information on the drug type (Table E2, Appendix I), the date the prescription was filled, the dose, quantity dispensed, and duration of the prescription. To account for different combinations of use and non-use, we will model our exposure using a time-varying approach. On each day of follow-up, exposure status will be classified into one of four mutually-

exclusive categories: i) opioid-only, ii) benzodiazepine-only, iii) both opioid and benzodiazepine (concurrent use), or iv) neither (Figure 1). Since opioid overdose is an acute event, we will consider exposure status on the day before the event as the primary etiologic window of interest.

To ensure equivalency across opioid types, we will use published conversion factors to calculate each drug's oral morphine milligram equivalent (MME).[3,44] To calculate MME, we will use the standard method of multiplying the average daily dose by its conversion factor:

$$Dosage\ per\ pill\ in\ mg \times \frac{\#\ of\ pills}{Duration\ of\ prescription\ in\ days} \times MME\ conversion\ factor$$

To standardize benzodiazepine potencies, we will use the defined daily dose (DDD) methodology as recommended by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC).[45] The DDD is the "the assumed average maintenance dose per day for a drug used for its main indication in adults" and is calculated as follows:

$$\frac{Total\ \#\ pills}{Duration\ of\ prescription\ in\ days} \times \frac{Dosage\ per\ pill\ in\ mg}{WHO\ recommended\ daily\ dose\ in\ mg}$$

Each drug's Anatomical Therapeutic Chemical (ATC) category and route of administration has its own recommended daily dose, and values will be obtained from the WHOCC website.

Confounders

Confounding can occur in our study if we fail to adjust for factors that differ between opioid users and concurrent users, and these factors independently affect one's risk for overdose. Opioid users additionally prescribed a benzodiazepine are often older,[17,26,46] more likely to be women,[17,23,26,46] require social assistance,[27,47] be a chronic opioid user,[16,17] have more pain conditions,[46] use more potent opioids,[46,48] use other central nervous system medications,[23,25] and are more likely to have comorbidities,[25,26] mental health,[23,25,27,46] and substance use disorders.[23,26,46] Concurrent users are also more likely to seek out multiple prescribers and pharmacies in a given time period.[27,48,49] Since these characteristics are also associated with overdose in studies on opioid prescribing patterns,[50] it is important that they are adjusted for in this study.

Across all statistical analyses, we will adjust for the following confounders (Table 1): demographic factors such as age, sex, drug insurance type and neighborhood income quintile, medical comorbidities such as history of myocardial infarction, dementia, and chronic pulmonary disease, mental health comorbidities such as diagnoses and prescriptions for anxiety, depression, and mood disorders, opioid use disorders, non-opioid substance abuse/misuse such as alcohol or nicotine dependence and measures of drug-seeking behaviour such as the number of distinct prescribers and pharmacies used in past 30 days. Receipt of concurrent muscle relaxants, gabapentinoids, or Z-drugs will also be adjusted for since these medications can also depress the respiratory system.

To ascertain confounder status, we will check for its associated diagnostic or service code(s) in the defined time period. Values of covariates will be measured in the baseline period (1-year before cohort entry), and every 30 days during follow-up. For age, sex, drug insurance type, neighborhood income quintile and history of opioid poisoning, the baseline values will remain fixed throughout follow-up. For medical comorbidities, mental health conditions, opioid

use disorder, and substance use disorders, once a patient is diagnosed, we will assume these conditions persist. All other covariate values will be updated every 30 days during follow-up.

Statistical analyses

Descriptive analysis

We will first perform descriptive analyses to better understand our study participants. This will include comparing concurrent and non-concurrent users with respect to baseline covariates such as those listed in Table 1. Continuous variables will be compared using means and medians, and categorical variables using frequency distributions and proportions.

Primary analysis

Time-varying confounding

Time-varying confounding is a concern when both exposure and confounder values are likely to change over the study period and affect each other.[51] Given that opioids and benzodiazepines are often used intermittently, bias could occur if there are factors that both predict a change in benzodiazepine status (e.g., development of drug misuse disorders or mental health exacerbation) and independently increase the risk for overdose. The three previous epidemiological studies assessing concurrent use and risk of overdose measured confounders at baseline only.[25-27] This approach assumes, often implicitly, that comorbidities and drugs used at baseline remain the same throughout follow-up and that changes in comorbidities and concomitant drugs that occur during follow-up do not impact subsequent exposure to concurrent opioid and benzodiazepines. However, for studies with long follow-up periods and transient exposures, such as our study, this assumption will likely be violated.

To adjust for changes in confounder status without adjusting for variables on the causal pathway, we will employ a marginal structural Cox model with inverse probability of treatment weights (IPTW).[52] These models re-weight study participants based on their inverse probability of exposure to each treatment group, conditional on past use, and all confounders.

Logistic regression for calculation of weights

To construct these weights, we will first develop a multinomial logistic regression (exposure model) for the 4 exposure categories. Given A = exposure and W = Covariates, the goal is to estimate P(A|W), which is the predicted probability of being exposed to i) opioid-only, ii) benzodiazepine-only, iii) both opioid and benzodiazepine (concurrent use), or iv) neither, as a function of covariates. Covariates used to generate the exposure model will include all time-varying confounders listed in Table 1. These weights will be re-estimated during study follow-up using updated covariate values from the past 30 days. For values that do not change, the previous value will be carried forward. Indicator variables will be used for all categorical covariates and continuous covariates will be tested for non-linear effects using Akaike Information Criterion (AIC) to determine the optimal form. Once we convert the log odds into predicted probabilities, P(A|W), we can calculate stabilized weights [P(A)/P(A|W)]. This is achieved by dividing P(A), the proportion of the cohort exposed to each opioid and/or benzodiazepine category, by P(A|W), the predicted probability estimated from the exposure model. Use of stabilized weights is recommended because it leads to smaller variance as compared to un-stabilized weights, which are simply the inverse of P(A|W).[52,53] This ensures that results do not depend on a few individuals with extremely large weights. Similarly, we will truncate any extreme values (e.g. 99th or 95th percentiles) and verify that the mean distribution of weights is close to 1 to ensure the robustness of our weights.

Cox proportional hazards regression to estimate effect on overdose

The final Cox proportional hazards regression model will estimate the hazard ratio for time to first overdose event, when comparing events during concurrent opioid and benzodiazepine person-time to opioid-only person time, adjusted for baseline confounders, and weighted according to each person's vector of IPTWs. We will use bootstrapping to construct 95% confidence intervals.

Subgroup analyses

To identify patient characteristics that may modify the opioid and benzodiazepine association with overdose, we will undertake the following secondary analyses. We will stratify the primary analysis by sex (males vs female), age (≥76 vs 65 to 75 years among everyone on the 65+ drug insurance plan), social deprivation (drug insurance for welfare recipients vs all other), presence of an opioid use disorder or substance use disorder (ever/never), presence of a mental health condition (ever/never), and number and type of distinct opioid prescribers (e.g., surgeon, dentist or family physician). To assess differential effects by duration or potency of drug use, we will also stratify the analysis by cumulative days, and standardized dose of opioid and benzodiazepines. To address the possibility that prevalent benzodiazepine users may be less susceptible to respiratory depression due to increased tolerance, we will repeat the primary analysis restricted to those with no use of benzodiazepines at baseline.

In these secondary analyses, the stratification variables will be omitted from the multinomial regression model used to calculate IPTWs. Instead, they will be used to separate the cohort into subgroups and each subgroup will be fit with their own Cox regression model to obtain strata-specific estimates. We intend these analyses to be hypothesis generating for future researchers to identify high-risk patient groups.

Sensitivity analyses

Exposure measurement error

To account for the biological half-lives of opioids and benzodiazepines,[54] and the fact that many patients may take their medications on an 'as needed' (or "PRN") basis, we will introduce a grace period into our exposure assessment, where an additional 7 and 30 days of drug duration will be added to the end of each prescription. This is to account for situations where some patients may dispense their drug but keep it in their medicine cabinets until it is required. Since chronic opioid users have more medication in supply, this also increases their chance for overdose if they ingest more than the recommended dose at once.

Timing of exposure

Although opioid and benzodiazepine-induced overdose is an acute effect, we will assess the 30-day period before the event date as a secondary etiological window of interest.

Outcome measurement error

Given the challenges of attributing causality in drug poisoning, we will repeat our primary analysis using the broader definition of 'any drug poisoning' to account for outcome measurement error. Additionally, we will analyze fatal and non-fatal overdoses separately, and given the potential for overdose deaths to be misclassified, we will also assess all-cause mortality as a secondary outcome.

STRENGTHS AND LIMITATIONS

Our study will contribute evidence to an important public health question. Given the high prescribing rates of opioids and benzodiazepines, any risk of overdose from their concurrent use would have a large impact at a population level.

We believe our study has several strengths. Restricting our cohort to new opioid users reduces the chance for selection bias because prevalent opioid users will be more tolerant of the medication. Our use of a validated outcome measure will reduce misclassification bias and the sensitivity analysis using the broadened definition can test robustness of our results. By modelling use of opioids and benzodiazepines as time-varying, we will reduce exposure misclassification bias. This is particularly important since prescriptions for these two medications tend to be intermittent in nature. By employing a marginal structural Cox proportional hazards model, we can reduce bias from both time-fixed and time-varying confounders. Conducting observational studies with varied statistical techniques in diverse populations will strengthen the evidence base regarding this issue. Finally, our study in a Canadian sample can inform whether previous results are robust across different healthcare systems, types of prescribing behaviour, and drug insurance policies.

A limitation is that our results may not be generalizable to all opioid users, as we are restricted to individuals insured through the public drug plan. The drug plan is limited to all persons 65 years or older, those on social assistance, and those without employer-based access to drug insurance. However, given that we are measuring a biological drug effect and population-level variation in drug metabolism is unlikely to differ substantially, our results should be generalizable to most patients prescribed these medications. Another limitation is that exposure to non-prescribed sources of opioids and benzodiazepines, such as those obtained illicitly, or from friends and family, will be missing in our analysis. We believe any misclassification will be minimal, though, since our exposure contrast includes prescription opioid use in both the exposed (concurrent opioid and benzodiazepine) and reference (opioid-only) groups. Moreover, population-based surveys such as the Canadian Tobacco, Alcohol and Drugs Survey show that in 2015, 2.3% of Canadians aged 15 and older reported any non-cannabis, illicit drug use in the past year, and 0.3% had abused pharmaceutical pain relievers.[55] This small percentage of illicit opioid use in the population, in addition to the fact that our study period (2000-2014) predates the rise of synthetic, illicit opioids (e.g. fentanyl) and their involvement in overdose deaths[56] means it should not impact our study findings greatly.

PATIENT AND PUBLIC INVOLVEMENT

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

ETHICS AND DISSEMINATION

This study is approved by the McGill Faculty of Medicine Institutional Review Board, and the *Commission d'access à l'information* (Québec privacy commission). Since we will be using pseudo-anonymized data, no consent is required.

Our findings will be important to researchers, public health, and medical communities in Canada and abroad, and this will be reflected in our dissemination plan. We plan to first present our findings at pharmacoepidemiology (e.g. the International Conference on Pharmacoepidemiology & Therapeutic Risk Management) and public health/health services

conferences (e.g. the Canadian Association for Health Services and Policy Research and Public Health). We hope to elicit feedback from our scientific and clinical colleagues at these venues. As our methods are novel and other epidemiologists may benefit from learning about our experience applying these methods, we will also be submitting abstracts to the Society for Epidemiology's Annual Meeting and the Canadian Society for Epidemiology and Biostatistics conference. Our partners at the National Institute of Public Health of Québec (INSPQ) and Canadian Institutes of Health Research (CIHR)'s Drug Safety and Effectiveness Network (DSEN) will be important knowledge users. We anticipate our work will inform decisions around implementing prescription monitoring programs and guidelines on prescribing of opioids and benzodiazepines. We will reach out to our public health partners to present this work in their organizational seminars.

After integrating feedback from conference peers, we will submit our manuscript to peer-reviewed biomedical journals (e.g. BMJ, AJPM) as primary care physicians are responsible for the majority of opioid and benzodiazepine prescriptions. All publications will be reported in accordance with the REporting of studies Conducted using Observational Routinely collected health Data specific to pharmacoepidemiological research (RECORD-PE).[57]

AUTHOR CONTRIBUTIONS

This study was conceived by EYL and all authors contributed to the design, analysis and interpretation of the data. EYL drafted the manuscript and DLB, RT, KBF revised it critically for important intellectual content. All authors gave final approval of the version to be published and EYL will be the guarantor of the work.

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DATA STATEMENT

The data sharing agreements governing use of our data restricts access to members of the research team only. However, technical information used for this study (e.g. drug and disease codes) is available and will be provided in an appendix. DOI: [include DOI for appendix here].

COMPETING INTERESTS STATEMENT

The authors have no conflicts of interest relevant to this manuscript to disclose.

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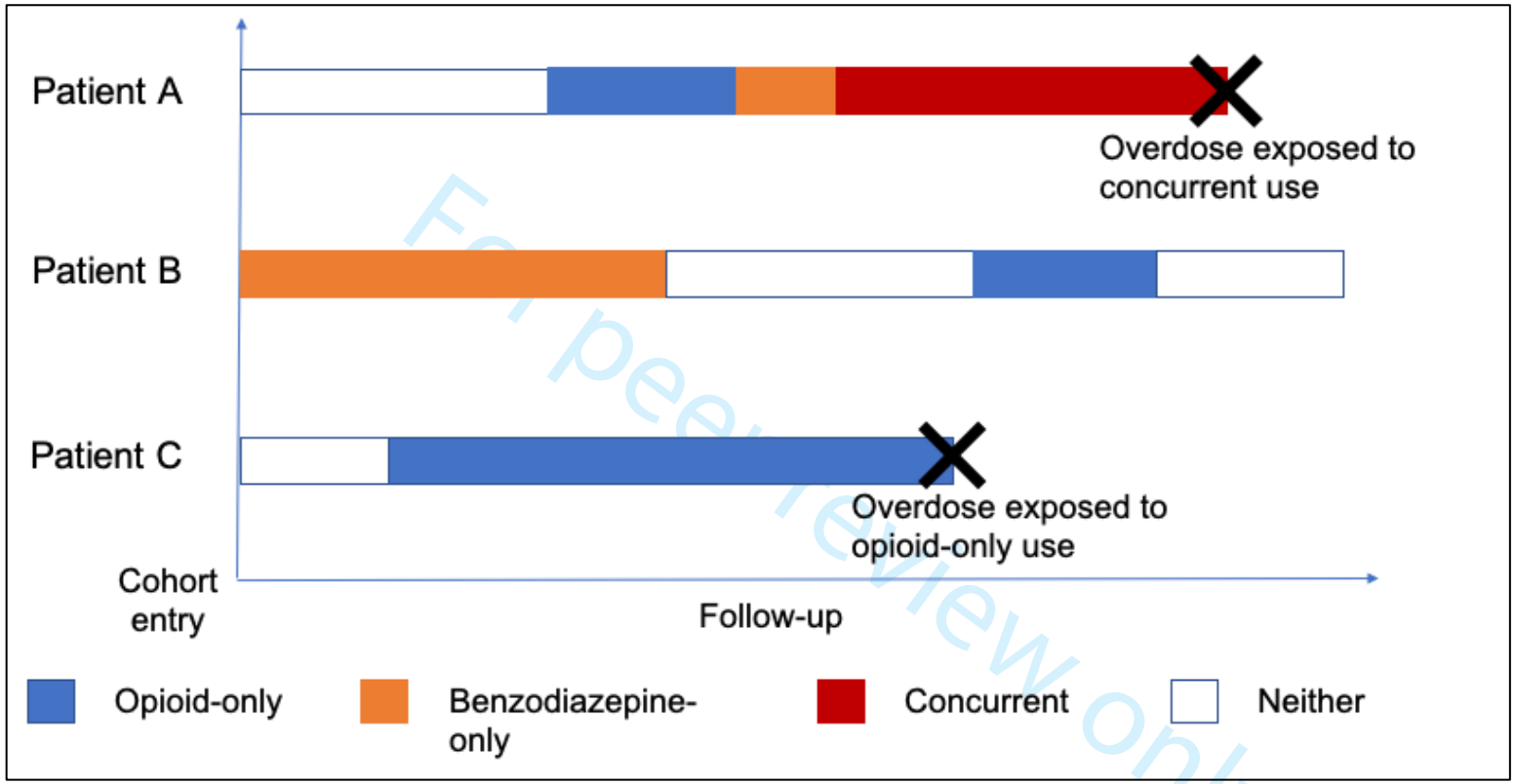
Table 1: Confounders under study

Covariate	**Measured at baseline only**
Age	18-45, 46-64, >64
Sex	Male or Female
Neighborhood income quintile	Calculated using results from the 2011 National Household Survey and 2011 Canadian Census
Drug insurance type	Those who require social assistance vs all other. A measure of social deprivation.
History of opioid poisoning	Ever/never hospital or emergency department visit for an opioid poisoning or acute effect of opioid in previous year. These are patients who experienced an overdose from non-prescription sources of opioids, or from opioids dispensed > 1 year before cohort entry.
	Measured at baseline and every 30 days during follow-up
Mental health diagnoses	Diagnoses for depression, anxiety disorders, personality disorders, mood disorders, schizophrenic and psychotic disorders, and all other mental health disorders
Mental health medications	Dispensations for anti-depressants, anti-psychotics, and mood stabilizing drugs
Opioid abuse/dependence diagnoses	Diagnoses for opioid abuse, opioid dependence, or mental/behavioural disorders due to opioid use
Opioid use disorder medications	Dispensations for methadone or buprenorphine
Non-opioid substance use disorders	Diagnoses for alcohol and nicotine dependence/abuse.
Substance use disorder treatments	Dispensations for nicotine or alcohol dependence medication
Drug seeking behaviour	Number of unique opioid prescribers and pharmacies used in given time period
Muscle relaxant, gabapentinoid, or z-drug use	Ever/never use. These are non-benzodiazepine sedatives that could also potentiate the effect of opioids.
Comorbidities	Diagnoses for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes (with or without complications), hemiplegia or paraplegia, renal disease, cancer, moderate or severe liver disease, metastatic solid tumour or AIDS/HIV.

Figure 1 caption
The purpose of this figure is to show how exposure will be assigned using three fictitious patients to illustrate. **Patient (A)** enters the cohort with no opioid and benzodiazepine use as shown by the section in white. Then, they receive their opioid prescription (blue), which ends right before they begin their benzodiazepine prescription (orange). During their period of benzodiazepine use, however, they receive another opioid prescription that overlaps this benzodiazepine period (red). Since they were using both drugs the day before an overdose, this patient's event would be exposed to concurrent drug use. **Patient (B)** enters our study already using benzodiazepines (orange), then stops for a period of time (white) before receiving a short prescription for opioids (blue) and then continues their period of non-use (white). **Patient (C)** enters the study using neither drug (white), but then begins a long duration of opioid-only use (blue) before experiencing the event. Since they were exposed to opioids only in the day before overdose, their event would be considered unexposed to concurrent drug use.

Figure 1: Opioid and benzodiazepine utilization patterns to illustrate how exposure will be assigned



APPENDIX I

Table E1: ICD-9 and ICD-10 codes included in outcome definition

Opioid poisoning	Code	Description
	E8500	Accidental poisoning by heroin
	E8501	Accidental poisoning by methadone
	E8502	Accidental poisoning by other opiates and related narcotics
	96500	Poisoning by opium (alkaloids) unspecified
	96501	Poisoning by heroin
	96502	Poisoning by methadone
	96509	Poisoning by other opiates and related narcotics
	T400	Poisoning by opium
	T401	Poisoning by heroin
	T402	Poisoning by other opioids
	T403	Poisoning by methadone
	T404	Poisoning by other synthetic narcotic
	T406	Poisoning by other and unspecified narcotics
	X42	Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified
Adverse effects of opioids	E9350	Heroin causing adverse effects in therapeutic use
	E9351	Methadone causing adverse effects in therapeutic use
	E9352	Other opiates and related narcotics causing adverse effects in therapeutic use
	Y450	Drugs, medicaments and biological substances causing adverse effects in therapeutic use: Opioids and related analgesics

*The first occurrence of any one code will define presence of the event

Table E2: Prescription opioids and benzodiazepines under study

Opioid type	ATC codes
ANILERIDINE	N01AH05
BUPRENORPHINE	N02AE01, N07BC51
BUTORPHANOL	N02AF01
CODEINE	N02AA59, N02AA79, N02AJ06, N02BE51, R05DA04
FENTANYL	N01AH01, N02AB03
HYDROCODONE	R05DA03
HYDROMORPHONE	N02AA03
MEPERIDINE / PETHIDINE	N02AB02
METHADONE	N07BC02
MORPHINE	N02AA01
OPIUM	N02AA02
OXYCODONE	N02AA05, N02AA55, N02AJ17
PENTAZOCINE	N02AD01

TAPENTADOL	N02AX06
TRAMADOL	N02AJ13, N02AX02
Benzodiazepine type	**ATC codes**
ALPRAZOLAM	N05BA12
BROMAZEPAM	N05BA08
CHLORDIAZEPOXIDE	N05BA02
CLOBAZAM	N05BA09
CLONAZEPAM	N03AE01
DIAZEPAM	N05BA01
FLURAZEPAM	N05CD01
LORAZEPAM	N05BA06
MIDAZOLAM	N05CD08
NITRAZEPAM	N05CD02
OXAZEPAM	N05BA04
TEMAZEPAM	N05CD07
TRIAZOLAM	N05CD05

*Includes combination versions of the molecule of interest