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Drugs Health Technologies Health Systems

Drug Utilization Study

Trends in Opioid Prescribing and Associated Harms in Canada, 2018 to 2022: Study Protocol

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This drug utilization study is being conducted by the Ontario Drug Policy Research Network (ODPRN) through the Post-Market Drug Evaluation CoLab Network.

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Abbreviations

BUP-ER	buprenorphine extended-release
BUP-IMP	implantable buprenorphine
CIHI	Canadian Institute for Health Information
CSizeMIZ	community size and metropolitan influence zones
CSize	community size
DIN	drug information number
DAD	Discharge Abstract Database
ED	emergency department
ICD-10	International Classification of Diseases, 10th Revision
MME	milligrams of morphine equivalent
NMS	Narcotics Monitoring System
NPDUIS	National Prescription Drug Utilization Information System
NACRS	National Ambulatory Care Reporting System
OAT	opioid agonist therapy
OUD	opioid use disorder
PIN	product identification number
PCCF+	Postal Code Conversion File Plus
RAMQ	Régie de l'assurance maladie du Québec

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Amendments and Updates

If amendments are required at any time during the study, the reasons for changes will be tracked in Table 1 and reported within the final study report.

Table 1: Protocol Version Tracking

Version	Version date	Location (e.g., heading or page)	Amendment description and rationale
Version 2	July 23, 2024	Objective 2 analyses	We updated DINs for objective 2 analyses to include SROM in definitions of prior opioid dispensing, but we categorized it separately in a stratified analysis by opioid type due to its mixed indication. This change was made to capture the true prevalence of prior opioid dispensing more accurately.
Version 2	July 23, 2024	Objective 2 analyses	We updated the definition of active opioid dispensations to capture individuals receiving daily-dispensed methadone or oral buprenorphine who experienced an opioid-related toxicity event before receiving their observed OAT dose on the day of their toxicity event.

DIN = drug information number; OAT = opioid agonist therapy; SROM = slow-release oral morphine.

Abstract

The opioid toxicity crisis is an ongoing public health issue in Canada. However, little is known about national trends in prescription opioid use and opioid prescribing patterns before opioid toxicity. This study will characterize prescription opioid use for pain and opioid agonist therapy (OAT), as well as the contribution of prescription opioids to opioid toxicity events over time in Canada. We will conduct a population-based cross-sectional study using administrative health data from Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia. Findings from this study will help inform future policy development.

Background and Rationale

Canada is experiencing an ongoing opioid toxicity crisis; between January 2016 and March 2023, there were a total of 38,514 apparent opioid toxicity deaths and 37,697 hospitalizations related to opioid poisoning.[1] The majority of these opioid-related deaths and hospitalizations occurred in British Columbia, Alberta, and Ontario, with the illicit, unregulated drug market (primarily fentanyl) being responsible for the vast majority of deaths in recent years.[1] Although data are available nationally on patterns of opioid-related toxicity events, information about prescription opioid use for pain and treatment of opioid use disorder (OUD) is limited to regional analyses in some parts of the country. Furthermore, available reports generally do not characterize national trends in prescription opioid use and access to treatment beyond 2018 and, as such, do not provide context on how these patterns have been affected by the COVID-19 pandemic. Given the effectiveness of OAT in treating OUD, it is essential to determine whether patterns in OAT dispensations have changed

since the beginning of the pandemic, particularly given COVID-19–related changes to OAT programs and treatment disruptions.[2-5]

To inform future policy development, policy-makers would like to determine the trends in opioid prescriptions dispensed for pain and OAT over time, as well as opioid dispensing patterns preceding opioid-related toxicities to assess the changing role of pharmaceutical opioids in these events. This will include determining patient profiles, including differences by region, sex, age group, and socioeconomic status. This information will further our understanding of the variation in opioid dispensing for pain and OAT across the country.

Policy Questions

1. How have trends in opioid prescriptions dispensed for pain and OAT changed across Canada, and do these trends vary geographically or across sociodemographic groups?
2. What is the prevalence of recent pharmaceutical opioid dispensing before opioid toxicity events in Canada, and how has this changed over time?

Policy Impact

Policy-makers will use the findings to inform policy and programming decisions around opioid use and OUD across Canada, and to inform the government's response to opioid-related harms.

Research Questions

1. What is the rate of new and overall use of prescription opioids for pain and OAT in Canada annually between 2018 and 2022 (before and during the COVID-19 pandemic), overall and stratified by patient characteristics, geography, and exposure characteristics?
2. What is the prevalence of prescription opioid use for pain and OAT before opioid toxicity inpatient hospitalizations and emergency department (ED) visits annually between 2018 and 2022 (before and during the COVID-19 pandemic), overall and stratified by patient characteristics, geography, and opioid type?

Note that prescription dispensing data will be used as a proxy for prescription opioid use. However, we are unable to determine if individuals used the medication as prescribed.

Objectives

Objective 1:

- to estimate the number and rate of new users of prescription opioids for pain and OAT in Canada annually between 2018 and 2022 (before and during the COVID-19 pandemic), overall and stratified by patient characteristics, geography, and exposure characteristics
- to estimate the number and rate of overall users of prescription opioids for pain and OAT in Canada annually between 2018 and 2022 (before and during the COVID-19 pandemic), overall and stratified by patient characteristics, geography, and exposure characteristics.

Objective 2:

- to report the number and proportion of opioid toxicity inpatient hospitalizations and ED visits with active (within ≤ 100 days, supply overlapping hospitalization or ED visit) and recent (within ≤ 30 or ≤ 180 days of hospitalization or ED visit with nonoverlapping supply) prescription opioid dispensations at the time of toxicity in Canada annually between 2018 and 2022 (before and during the COVID-19 pandemic), overall and stratified by patient characteristics and opioid type.

Data Sources

Objective 1 will use dispensing data from the following 6 provinces: British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, and Quebec, where coverage of community pharmacy-dispensed prescription drug data are readily available. Together, these provinces represent the vast majority of the total population in Canada. We will identify prescription medications dispensed across the provinces of interest using the Canadian Institute for Health Information (CIHI)'s National Prescription Drug Utilization Information System (NPDUIS), the Ontario Narcotics Monitoring System, the Alberta Pharmaceutical Information Network, and the Régie de l'assurance maladie du Québec (RAMQ). The databases contain all claims for prescription opioids dispensed from community pharmacies — regardless of method of payment — with the exception of RAMQ, which contains claims for those insured by Quebec's public drug insurance plan only (Table 2). Data captured also includes drug identification numbers (DINs), unique patient identifiers, dispensing date, dose dispensed, and days' supply of prescription claims. We will use the Postal Code Conversion File Plus (PCCF+) to determine geographic characteristics, including neighbourhood income quintiles, rurality, and community size and metropolitan influence zones (CSizeMiz) across each province (with the exception of Quebec where is not available).

Objective 2 will link the prescription databases described previously to the CIHI Discharge Abstract Database (DAD) and CIHI National Ambulatory Care Reporting System (NACRS), which contain records of inpatient hospitalizations and ED visits, respectively, using unique patient identifiers derived from health card numbers. For Quebec, we will link to comparable provincial databases — the Maintenance et exploitation des données pour l'étude de la clientèle hospitalière and Banque de données communes des urgences. Full coverage of inpatient hospitalization data are available for all 6 provinces described in objective 1, while ED visit data are only available in British Columbia, Alberta, Saskatchewan, Ontario, and Quebec. Manitoba

will not be included in ED analyses due to the unavailability of data on diagnosis codes required to identify opioid-related toxicities over the study period. Coverage of ED data in British Columbia and Saskatchewan through NACRS is limited to a subset of all ED facilities in these provinces. Moreover, facilities in British Columbia had limited the submission of ED discharge diagnoses over the study period (i.e., not mandated at the highest level of detail). For Saskatchewan, we will restrict the study period for the ED analyses to April 2021 onward, reflecting the beginning of mandatory submission of full diagnosis codes from the International Classification of Diseases, 10th revision (ICD-10), Canadian Edition to NACRS. Data sources and coverage in each province have been summarized in Table 2.

Table 2: Data Sources for Proposed Study

Province	Databases and data coverage		
	Prescription drug claims	Hospital records	ED records
British Columbia	CIHI NPDUIS (all, regardless of payer)	CIHI NACRS (all)	CIHI DAD (partial coverage)
Alberta	Pharmaceutical Information Network (all, regardless of payer)	CIHI NACRS (all)	CIHI DAD (all)
Saskatchewan	CIHI NPDUIS (all, regardless of payer)	CIHI NACRS (all)	CIHI DAD (partial coverage captured from April 2021 onwards)
Manitoba	CIHI NPDUIS (all, regardless of payer)	CIHI NACRS (all)	NA
Ontario	Narcotics Monitoring System (all [for opioids], regardless of payer)	CIHI NACRS (all)	CIHI DAD (all)
Quebec	RAMQ (coverage for people aged 65 years and older, people receiving social assistance, and people without a private insurance plan, representing approximately 46% of Quebec's population)	Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (all)	Banque de données communes des urgences (all)

CIHI = Canadian Institute for Health Information; DAD = Discharge Abstract Database; ED = emergency department; NA = not available; NACRS = National Ambulatory Care Reporting System; NPDUIS = National Prescription Drug Utilization Information System; RAMQ = Régie de l'assurance maladie du Québec.

Identification of Opioids

Throughout this study, we will only be considering opioids with indications for pain or OAT. We will not include opioids that are generally used as antitussives (i.e., cough suppressants) or for antidiarrheal indications in definitions of opioid use and in lookback periods for incident use or prior exposure. The list of opioid drug classes that will be included in our analyses is reported in Appendix 1, Table 3.

Opioids for pain: We will use a universal DIN list to capture opioids indicated to treat pain consistently across provinces and supplement with product identification numbers (PINs) to account for province-specific product coding. To help harmonize data across the provinces, and due to heterogeneity in the availability of over-the-counter medications across Canada, low-dose codeine products (i.e., ≤ 8 mg of codeine per tablet or ≤ 20 mg of codeine per 30 mL of liquid product) will be excluded.

Opioid agonist therapy: DINs for prescription opioids indicated for OAT — including methadone and buprenorphine alone or in combination with naloxone (i.e., buprenorphine-naloxone, subcutaneous buprenorphine extended-release [BUP-ER] [Sublocade; first marketed in Canada on February 3, 2020], or implantable buprenorphine [BUP-IMP] [Probuphine; first marketed in Canada on November 22, 2018]) — will be used to identify products available on 1 or more provincial formularies from start through the end of an observation period of interest. We will supplement with PINs to capture province-specific coding of OAT products.

Slow-release oral morphine (SROM): In objective 1, we will report SROM (Kadian) separately, as it is commonly used for both pain and OAT. In objective 2, SROM will be included in definitions of prior opioid dispensing, but will be categorized separately due to its mixed indication.

Research Methods (Objective 1)

Study Design

We will conduct a population-based repeated cross-sectional study to describe trends in new and overall use of prescription opioids for pain and OAT across 6 Canadian provinces between **January 1, 2018, and December 31, 2022**.

Study Cohort and Setting

Objective 1: New Users (Incidence Cohorts)

We will identify individuals newly initiating prescription opioids for pain and OAT across provinces in the time period of interest (i.e., month or year). The cohort entry or index date will be the date of the first opioid for pain or OAT dispense in the time period of interest.

New users of opioids for pain will be defined as those with no claim for any opioids indicated for pain or OAT dispensed in, or overlapping with, the 365 days before the cohort entry date. To do this, we will look back for any dispenses in the 455 (365 + 90) days before index and use days' supply to identify any prescriptions overlapping with the 365 days before index. When determining overlapping dispenses, we will subtract 1 from the days' supply to account for the assumption that medication was taken on the day it was supplied (i.e., dispense date + days' supply – 1).

New users of OAT will be defined as individuals initiating either methadone or buprenorphine alone or in combination with naloxone, with no prior dispensation claim for the specific OAT dispensed in, or overlapping with (as specified), a predefined period before the cohort entry or index date (first prescription in a given month or year). We will use shorter lookback periods for more regularly dispensed forms of OAT (i.e., methadone and buprenorphine-naloxone) and longer lookbacks for longer-acting (less frequently dispensed) forms of OAT (i.e., BUP-ER and BUP-IMP), as follows:

- **Methadone** includes those with no methadone claim dispensed in, or overlapping with, the 30 days before the index date. To do this, we will look back for any dispenses in the 90 days before index

and use days' supply to identify any prescriptions overlapping with the 30 days before index. When determining overlapping dispenses, we will subtract 1 from the days' supply to account for the assumption that medication was taken on the day it was supplied (i.e., use dispense date + days' supply − 1).

- **Buprenorphine-naloxone** includes those with no buprenorphine-naloxone claim dispensed in, or overlapping with, the 30 days before the index date. To do this, we will look back for any dispenses in the 90 days before index and use days' supply to identify any prescriptions overlapping the 30 days before index. When determining overlapping dispenses, subtract 1 from the days' supply to account for the assumption that medication was taken on the day it was supplied (i.e., use dispense date + days' supply − 1).
- **BUP-ER** includes those with no BUP-ER claim in the 90 days before the index date.
- **BUP-IMP** includes those with no BUP-IMP claim in the 270 days before the index date.

Objective 1: Prevalence Cohorts

We will identify overall users of prescription opioids for pain, OAT, and SROM across provinces in the time period of interest.

Prevalent users of opioids for pain will be defined as individuals with any prescription claim for an opioid for pain dispensed in the time period of interest.

Prevalent users of OAT will be defined as individuals with any claim for methadone or buprenorphine (alone or in combination with naloxone) dispensed in the time period of interest.

Prevalent users of SROM will be defined as individuals with any claim for SROM each year over the study period.

Exclusion Criteria

We will apply the following general exclusion criteria when defining the cohorts described previously:

- Step 1: Individuals who do not meet definitions of incident use defined previously (for incidence cohorts only)
- Step 2: Individuals with missing or invalid patient identifiers, or missing age or sex
- Step 3: Individuals residing out of province on the cohort entry date
- Step 4: Individuals with data quality issues, defined as having a negative age or age older than 105 years

Analysis Overview (Objective 1)

Trends

We will report trends of new and overall use of prescription opioids between January 2018 and December 2022. Each unique individual will only be represented once in each time period of interest (i.e., month or year). For new user cohorts, we will select only one new course of treatment (earliest by date) per unique individual and for overall user cohorts, we will select the first dispense. The following measures will be reported:

- number and rate (per 1,000 population) of new users of prescription of opioids in each province, reported monthly
- number and rate (per 1,000 population) of new users of OAT in each province, reported monthly
- number and rate (per 1,000 population) of overall users of prescription for opioids for pain in each province, reported monthly
- number and rate (per 1,000 population) of overall users of OAT in each province, reported monthly
- number and rate (per 1,000 population) of overall users of SROM in each province, reported yearly.

Note: Rate per 1,000 will be calculated using monthly interpolated population estimates from Statistics Canada as denominators. In Quebec, we will use the population eligible for the public drug insurance plan as the denominator.

Stratification

We will report new and overall use of prescription opioids for pain and OAT separately for the years 2018, 2020, and 2022. Further stratified analyses will be conducted in each province annually for the years 2018, 2020, and 2022 for each of the new and overall cohorts of opioids for pain and OAT (i.e., 4 cohorts). We will report stratifications by demographic characteristics (age, sex, and neighbourhood income quintile), geography (rural or urban location of residence, and community size and metropolitan influence zone [CSizeMIZ]). Furthermore, the distribution of opioid type dispensed among overall users of opioids for pain and OAT, and initial opioid dose among new users of opioids for pain will be reported. The first new treatment initiation or first dispense for each individual in each year will be selected for the reporting of the new user and overall user indicators respectively (unless stated otherwise). All characteristics will be captured at index.

The stratification categories and measures are described as follows:

- Age group (N, rate per 1,000): 24 years or younger, 25 to 44 years, 45 to 55 years, 65 to 74 years, 75 years and older
  - Numerator: number of new or overall users of opioids for pain or OAT in each age category
  - Denominator: annual population estimates in each age category or number of people covered by the public drug plan in each age category (for Quebec only)
- Sex (N, rate per 1,000): male, female
  - Numerator: number of new or overall users of opioids for pain or OAT in each sex category

    - Denominator: annual population estimates in each sex category or number of people covered by the public drug plan in each sex category (for Quebec only)
- Neighbourhood income quintile (N, rate per 1,000): lowest quintile, medium-low quintile, middle quintile, medium-high quintile, highest quintile, missing
    - Numerator: number of new or overall users of opioids for pain or OAT in each income quintile
    - Denominator: annual population estimates in each income quintile

  Note that this variable is based on neighbourhood income per person equivalent (in Census Metropolitan Area or Census Agglomeration [CMACA] before tax) in PCCF+.
- Location of residence (N, rate per 1,000): urban, rural
    - Numerator: number of new or overall users of opioids for pain or OAT in each income quintile
    - Denominator: annual population estimates in each income quintile

  Note that this variable is based on community size (CSize) in PCCF+.
- CSizeMIZ (N, %): large urban areas (500,000 or more), medium urban areas (100,000 to 499,999), small urban areas (10,000 to 99,999), non-CMACA; strong metropolitan influence zone (MIZ), non-CMACA; moderate MIZ, non-CMACA; weak or no MIZ; territories outside of any census agglomeration (CA), non-CMACA; unknown MIZ, missing (unknown if CMACA or not)
    - Numerator: number of new or overall users of opioids for pain or OAT in each CSizeMIZ category
    - Denominator: total number of new or overall users of opioids for pain or OAT

  Note that this variable is based on CSizeMIZ in PCCF+.
- Opioid type (N, %): In contrast with the other stratifications, to conduct this analysis, we will extract all prescription dispensations for opioids for pain and OAT in each year outlined. We will count unique drug classes by unique individual identifier in each year to report the percentage of all opioid recipients in the year who are dispensed at least 1 of each of the opioid types described as follows:
    - Opioids for pain: oxycodone, morphine, codeine, hydromorphone, fentanyl, and other
        - Numerator: number of unique individuals dispensed each type of opioid for pain
        - Denominator: total number of overall users of opioids for pain
    - OAT: methadone, buprenorphine (alone or with naloxone)
        - Numerator: number of unique individuals dispensed each type of OAT
        - Denominator: total number of overall users of OAT
- Initial opioid daily dose (N, %): We will report the number of unique individuals newly dispensed at least 1 opioid indicated to treat pain with a daily dose of 50 milligrams of morphine equivalent (MME) or less and greater than 50 MME at the time of initiation. Initial opioid dose will be reported as 50 MME or less, greater than 50 MME, and “not estimable” (i.e., those with any dispenses with an invalid MME conversion factor).

- Numerator: number of new users of opioids for pain in each initial daily dose category in the year of interest
- Denominator: total number of new users of opioids for pain the year of interest

Note: Calculations will be limited to initial daily dose dispensed among new users of oral opioid formulations and transdermal fentanyl only.

Research Methods (Objective 2)

Study Design

We will conduct a population-based repeated cross-sectional study of opioid dispensing patterns before opioid toxicity inpatient hospitalizations and ED visits between **January 1, 2018, and December 31, 2022,** in Canada (where data are available).

Study Cohort and Setting

Inpatient Hospitalization

We will identify all episodes of acute opioid toxicity inpatient hospitalizations regardless of intention (i.e., accidental, intentional, undetermined, or unknown). Opioid toxicity will be defined using the ICD-10 diagnosis codes provided in Appendix 1, Table 4. We will flag the intention of toxicity using accompanying ICD-10 external cause codes (E-codes) (Appendix 1, Table 4). All episodes of admissions will be captured over the time period of interest, meaning that an individual can be included in the cohort multiple times. We will use diagnosis code types to determine that the opioid-related toxicity was present on admission, rather than a toxicity event that happened during hospitalization. Only episodes with confirmed diagnoses will be included. We will exclude repeated inpatient hospital visits within the same episode of care (e.g., transfers across multiple institutions were counted as 1 hospitalization) in provinces where possible.

ED Visits

We will identify all episodes of opioid toxicity ED visits, regardless of intention, over the time period of interest, defined using ICD-10 diagnosis codes (NACRS) (Appendix 1, Table 4). The intention of toxicity will be flagged using accompanying ICD-10 E-codes (Appendix 1, Table 4). We will use all diagnosis types to determine ED visits and only confirmed diagnoses will be included. All episodes of ED visits will be captured over the time period of interest; thus, the same individual may contribute to the cohort each time they have a unique episode of hospitalization. We will include episodes of ED visits that lead to inpatient hospitalization, as well as those in which a person left the ED without being seen. We will exclude repeated ED visits within the same episode of care (e.g., transfers across multiple institutions were counted as 1 ED visit) in provinces where possible.

The index date will be defined as the admission date (for inpatient hospitalizations) or registration date (for ED visits).

Exclusion Criteria

We will apply the following general exclusion criteria when defining the cohorts defined previously:

- Step 1: Episodes with “suspected” but unconfirmed diagnoses
- Step 2: Individuals with missing or invalid patient identifiers, or missing age or sex
- Step 3: Individuals residing out of province
- Step 4: Individuals with data quality issues (i.e., negative age, age > 105 years)

Exposure

We will define prior opioid exposure among all episodes of opioid toxicity inpatient hospitalization and ED visits separately, in 3 ways:

1. Active opioid prescription, defined as those with an opioid prescription dispensed in the 100 days before hospital admission or ED visit, with a duration (days’ supply) overlapping the admission date (i.e., dispense date + days’ supply – 1 ≥ index date and dispense date < index date) or those that had any methadone or any oral buprenorphine dispensed on the day before the index date (i.e., dispense date = index date − 1). When determining overlapping dispenses, we will subtract 1 from the days’ supply to account for the assumption that medication was taken on the day it was supplied (i.e., dispense date + days’ supply – 1).
2. Recently dispensed opioid prescription in the previous 30 days (not including the index date).
3. Recently dispensed opioid prescription in the previous 180 days (not including the index date).

The aforementioned definitions are complementary approaches to broadly identify opioid exposure before opioid toxicity inpatient hospitalizations and ED visits. We incorporated a definition with a longer lookback to allow sufficient duration to capture opioid exposure considering that people may use opioids intermittently (i.e., as needed) or for extended periods (especially those indicated for pain).

Note: We focused on the dispensing of opioids for pain, OAT (i.e., methadone and buprenorphine-containing products [either alone or in combination with naloxone]), and SROM. Refer to the Identification of Opioids section for opioids included in the lookback for prior exposure.

Analysis Overview (Objective 2)

Yearly Trends

We will report trends annually as follows:

- Number of opioid toxicity inpatient hospitalization and ED visits, by intention of toxicity. Report **per year** (2018 to 2022) in each province:
  - overall (i.e., regardless of intention)
  - accidental

    - intentional
    - other.
- Number and percentage of opioid toxicity inpatient hospitalizations with recent and active opioid dispensations. Report per year (2018 to 2022) in each province:
    - primary: active opioid dispensations
    - recent opioid dispensations in the past 30 days
    - recent opioid dispensations in the past 180 days.
- Number and percentage of opioid toxicity ED visits with recent and active opioid dispensations. Report per year (2018 to 2022) in each province:
    - active opioid dispensations
    - recent opioid dispensations in the past 30 days
    - recent opioid dispensations in the past 180 days.

Stratification

Report the proportions of opioid-related inpatient hospitalization and ED visits with active opioid dispensations within each province, stratified by age, sex, and opioid type dispensed, for the years 2018, 2020, and 2022 only. The stratification categories are described as follows:

- Age group (N, %): 24 years or younger, 25 to 44 years, 45 to 64 years, 65 to 74 years, and 75 years or older
    - Numerator: number of episodes of opioid-related toxicity with an active opioid exposure in each age strata
    - Denominator: total number of episodes of opioid-related toxicity in each age strata
- Sex (N, %): male, female
    - Numerator: number of episodes of opioid-related toxicity with an active opioid exposure in each sex strata
    - Denominator: total number of episodes of opioid-related toxicity in each sex strata
- Opioid type: For any active opioid prescriptions, define as follows:
    - Opioids for pain (N, %): any opioid for pain, oxycodone, morphine, codeine, hydromorphone, fentanyl, other
        - Numerator: total number of episodes of opioid-related toxicity with an active opioid exposure to each type of opioid for pain
        - Denominator: total number of episodes of opioid-related toxicity
    - OAT (N, %): any opioid for OAT, methadone, buprenorphine (alone or in combination with naloxone) (if sufficient sample size)

        - Numerator: total number of episodes of opioid-related toxicity with an active opioid exposure to each type of OAT
        - Denominator: total number of episodes of opioid-related toxicity
    - SROM (N, %): any SROM
        - Numerator: total number of episodes of opioid-related toxicity with an active opioid exposure to SROM
        - Denominator: total number of episodes of opioid-related toxicity

    Note: Episodes can be captured in several opioid type categories if multiple opioids were dispensed over the time period.

Limitations

The primary strength of this proposed study is the use of linked population-based databases across several provinces to help characterize national trends in opioid use and opioid-related harms. However, there are some notable limitations to this project.

- Population-level opioid dispensing data are not available across all provinces and territories, and data linkage to inpatient hospitalizations and ED visits is only available in some provinces. Therefore, the trends presented will not characterize the entirety of Canada, with particular gaps in data in Atlantic Canada, meaning that this project will be unable to capture the full extent of trends in opioid dispensing and opioid-related harms in the Canadian context.
- We are using prescription dispensing data from community pharmacies, and we are therefore unable to determine if individuals adhered to the medications as prescribed.
- Our inclusion criteria for OAT are limited to methadone and buprenorphine (alone or in combination with naloxone), excluding SROM, which is increasingly used as a second-line treatment for OAT. Additionally, we are not able to separate immediate release (IR) hydromorphone used for safer opioid supply (SOS) from that used for pain. Although it is anticipated that the majority of SROM and IR hydromorphone prescribing across Canada is for a pain indication, our inability to separate this out in the analysis is an important limitation to consider. For this reason, the findings related to trends in dispensing of these 2 medications should be interpreted with caution, as any changes in trajectory in more recent years may be influenced by their use among people with OUD.
- We will assume that any methadone oral liquid or buprenorphine products dispensed are for the indication of OAT, although they may sometimes be used for pain.
- For opioid dispensing patterns before opioid-related harms, we were unable to specifically examine fatal toxicity events due to unavailability of linked coroner's data across provinces of interest. Therefore, analyses will be limited to ED and inpatient hospital data that is consistently available across the country (which will include fatal toxicities where the person is treated in a hospital setting before death). Additionally, it is important to note that many opioid toxicity events do not present in

hospital settings and will not be captured in this analysis. Thus, the findings of this study are only generalizable to toxicity events treated in a hospital.

- We will not have access to hospital laboratory records at admission; therefore, we cannot determine whether an opioid toxicity event was a direct result of pharmaceutical opioids, nonpharmaceutical opioids, or a combination of these.

References

1. Federal, provincial, and territorial Special Advisory Committee on the Epidemic of Opioid Overdoses *Opioid- and Stimulant-related Harms in Canada.* Ottawa: Public Health Agency of Canada; September, 2023. https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants/#fn1
2. Gomes T, Campbell TJ, Kitchen SA, et al. Association Between Increased Dispensing of Opioid Agonist Therapy Take-Home Doses and Opioid Overdose and Treatment Interruption and Discontinuation. *JAMA.* 2022;327(9):846-855. PubMed
3. Garg R, Kitchen SA, Men S, et al. Impact of the COVID-19 pandemic on the prevalence of opioid agonist therapy discontinuation in Ontario, Canada: A population-based time series analysis. *Drug and Alcohol Dependence.* 2022;236:109459. PubMed
4. Kitchen SA, Campbell TJ, Men S, et al. Impact of the COVID-19 pandemic on the provision of take-home doses of opioid agonist therapy in Ontario, Canada: A population-based time-series analysis. (1873-4758 (Electronic)).
5. Russell C, Ali F, Nafeh F, Rehm J, LeBlanc S, Elton-Marshall T. Identifying the impacts of the COVID-19 pandemic on service access for people who use drugs (PWUD): A national qualitative study. *Journal of Substance Abuse Treatment.* 2021;129:108374. PubMed

Appendix 1: Supplementary Information on Methods

Table 3: List of Drug Classes Included in Analyses

Opioid type	Drug class
Opioids for pain	• Oxycodone • Morphine • Codeine • Hydromorphone • Fentanyl • Other (buprenorphine [pain], butorphanol, dextropropoxyphene, meperidine, methadone [pain], nalbuphine, oxymorphone, pentazocine, tapentadol, or tramadol)
Opioid agonist therapy	• Methadone • Buprenorphine (buprenorphine-naloxone, subcutaneous buprenorphine extended-release [Sublocade], or implantable buprenorphine [Probuphine])
Slow-release oral morphine	• Slow-release oral morphine (Kadian 24-hour formulation)

Table 4: Diagnosis Codes and Parameters for Opioid Toxicity

Condition	Data source	Codes	Parameters
Opioid-related toxicity	CIHI DAD, CIHI NACRS, and Quebec	**ICD-10 (DAD, NACRS):** **T400:** Poisoning by opium **T401:** Poisoning by heroin **T402:** Poisoning by other opioids **T403:** Poisoning by methadone **T404:** Poisoning by other synthetic narcotics **T406:** Poisoning by unspecified and other narcotics **Intention of toxicity (using E-codes on the same record):** Accidental (X42) Intentional (X62) Unknown (all others)	**Inpatient hospitalization:** For type of diagnosis, use admission diagnosis types **ED visit:** Use all types of diagnosis

CIHI = Canadian Institute for Health Information; DAD = Discharge Abstract Database; ED = emergency department; ICD-10 = International Classification of Diseases, 10th Revision; NACRS = National Ambulatory Care Reporting System.

For more information on CoLab and its work, visit colab.cda-amc.ca.

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