Periods of altered risk for non-fatal drug overdose: a self-controlled case series

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Summary

Background Being recently released from prison or discharged from hospital, or being dispensed opioids, benzodiazepines, or antipsychotics have been associated with an increased risk of fatal drug overdose. This study aimed to examine the association between these periods and non-fatal drug overdose using a within-person design.

Methods In this self-controlled case series, we used data from the provincial health insurance client roster to identify a 20% random sample of residents (aged ≥10 years) in British Columbia, Canada between Jan 1, 2015, and Dec 31, 2017 (n=921 346). Individuals aged younger than 10 years as of Jan 1, 2015, or who did not have their sex recorded in the client roster were excluded. We used linked provincial health and correctional records to identify a cohort of individuals who had a non-fatal overdose resulting in medical care during this time period, and key exposures, including periods of incarceration, admission to hospital, emergency department care, and supply of medications for opioid use disorder (MOUD), opioids for pain (unrelated to MOUD), benzodiazepines, and antipsychotics. Using a self-controlled case series, we examined the association between the time periods during and after each of these exposures and the incidence of non-fatal overdose with case-only, conditional Poisson regression analysis. Sensitivity analyses included recurrent overdoses and pre-exposure risk periods.

Findings We identified 4149 individuals who had a non-fatal overdose in 2015–17. Compared with unexposed periods (ie, all follow-up time that was not part of a designated risk period for each exposure), the incidence of non-fatal overdose was higher on the day of admission to prison (adjusted incidence rate ratio [aIRR] 2·76 [95% CI 1·51–5·04]), at 1–2 weeks (2·92 [2·37–3·61]), and 3–4 weeks (1·34 [1·01–1·78]) after release from prison, 1–2 weeks after discharge from hospital (1·35 [1·11–1·63]), when being dispensed opioids for pain (after ≥4 weeks) or benzodiazepines (entire use period), and from 3 weeks after discontinuing antipsychotics. The incidence of non-fatal overdose was reduced during use of MOUD (aIRRs ranging from 0·33 [0·26–0·42] to 0·41 [0·25–0·67]) and when in prison (0·12 [0·08–0·19]).

Interpretation Expanding access to and increasing support for stable and long-term medication for the management of opioid use disorder, improving continuity of care when transitioning between service systems, and ensuring safe prescribing and medication monitoring processes for medications that reduce respiratory function (eg, benzodiazepines) could decrease the incidence of non-fatal overdose.

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Introduction

Overdose is a large and growing public health crisis. The Global Burden of Disease study estimated that there were 109 500 deaths from opioid overdose worldwide in 2017.[1] Non-fatal overdose is estimated to be 20–30 times more common than fatal overdose,[2] and is associated with a range of short-term and long-term health impacts.[3,4] Having one non-fatal overdose increases the risk of having subsequent overdoses, both non-fatal[5,6] and fatal.[7]

The incidence of fatal and non-fatal overdoses in British Columbia, Canada, has been particularly high, primarily because of the introduction of fentanyl and fentanyl analogues into the illegal drug supply.[8] Since 2015, fatal overdoses have been the leading cause of unnatural death in British Columbia.[9] The rising incidence of overdose resulted in the Government of British Columbia declaring a public health emergency in April, 2016,[10] and led to an increased focus on overdose prevention and response, including the creation of supervised consumption sites, increased provision of take-home naloxone, increased availability of medications for opioid use disorder (MOUD),[11] and changes to the guidance for opioid and benzodiazepine prescribing.[12]

The risk of overdose is influenced by complex, overlapping social determinants of health.[13] Factors such as incarceration, mental and physical health conditions, and the treatments prescribed for these conditions can all affect the risk of overdose.[13,14] For example, time periods when MOUD are dispensed are associated with a reduction in the risk of fatal overdose and all-cause mortality, whereas periods of transition between the use and discontinuation of MOUD have been associated with

Research in context

Evidence before this study

We searched PubMed on June 15, 2020, using the search terms "overdos*", "over dos*", or "poison*" (in titles, abstracts, or both); OR "drug overdose" or "overdose" (medical subject headings); AND "self-control*", "case-crossover", "case-cross-over", "own control", "case-time-control", "case-case-time", "case-only", "within-individual", "within-person", or "within-case" (in titles, abstracts, or both). We searched for primary research or reviews published in English between database inception and June 15, 2020. Our search yielded 39 studies. We excluded 32 articles because they were not done in humans (n=4), did not contain quantitative data (n=1), did not examine drug overdose as an outcome (n=25), or did not use a self-controlled method (n=2). The remaining seven studies met our inclusion criteria. Of these studies, four used a case-crossover design, one used quadratic growth models, and two used a modified self-controlled case series. Two studies examined the association between external factors (hot and cold temperatures) and risk of fatal drug overdose, three studies examined the association between proximate drug use factors (ie, drugs taken and route of administration) and non-fatal overdose, and two studies examined periods of medication use, including gabapentinoids, acamprosate, naltrexone, buprenorphine, and methadone, and accidental overdose. The study that examined buprenorphine and methadone use found that the risk of accidental overdose decreased during periods of buprenorphine use and increased during periods of methadone use. These studies show that a self-controlled design can be applied to examine overdose. However, to our knowledge, a self-controlled design has never been used to examine the association between use of prescribed opioids for pain, benzodiazepines, antipsychotics, incarceration, medical service use, and non-fatal drug overdose. These factors have previously been individually associated with drug overdose in studies using cohort and case-control designs, although often these studies used selected samples limited to people who use drugs.

Added value of this study

Using a large, representative sample of people who had a non-fatal overdose that resulted in medical care in British Columbia, Canada, we examined potential risk periods for this outcome in a self-controlled case-series. Compared with unexposed periods, the incidence of non-fatal overdose was higher on the day of admission to a provincial correctional centre, in the 4 weeks following release from prison, in the 2 weeks after discharge from hospital, during periods when people had a supply of prescription benzodiazepine or opioid medication, or both, and following the discontinuation of antipsychotic use. The incidence of non-fatal overdose was lower during periods when people were taking medications for opioid use disorder (MOUD) and when they were in prison. In contrast to previous studies, we did not find an increased incidence of non-fatal overdose compared with baseline after discontinuation of MOUD. Using a self-controlled design addresses some limitations of previous studies by accounting for potential bias from unmeasured, static, person-level confounders.

Implications of all the available evidence

Our findings provide further evidence for the existence of distinct, identifiable periods of heightened and reduced risk for non-fatal drug overdose. These risk periods have policy relevance, particularly in the context of fiscal austerity when investment in targeted prevention is typically constrained by time and resources. Our findings can be used to target responses and programmes to ensure that: (1) people are given additional support during periods of heightened overdose risk; and (2) measures that reduce the risk and associated harm of overdose (eg, MOUD and take-home naloxone) are made widely available, particularly in periods of increased risk such as following release from prison and discharge from hospital.

increased mortality.[15] Recent (ie, within 4 weeks) release from prison,[16] recent (ie, within 90 days) discharge from hospital,[17] concurrent use of opioids and benzodiazepines,[18] and times when a person is supplied antipsychotics[19] have also been identified as potential periods when the risk of fatal overdose might be increased. The reasons for the increased risk are varied, and they include, but are not limited to, a reduced drug tolerance due to extended periods of abstinence or reduced drug consumption (eg, while incarcerated or admitted to hospital),[20,14] disrupted social networks, housing and financial instability, stress associated with changing drug-use patterns, a reduced capacity to practise safer drug use,[14,21] interrupted treatment, and the increased risk of overdose associated with concomitant use of medications such as benzodiazepines and opioids.[18] However, research on how these factors affect the risk of non-fatal overdose is inconsistent. For example, a meta-analysis examining non-fatal overdose in people who inject drugs found no evidence of an association between recent incarceration and non-fatal overdose.[22] However, individual studies have identified an increased risk of non-fatal overdose following release from incarceration.[5,23] The inconsistency between study findings could be due to the reliance on self-reported non-fatal overdose in many studies, thus reducing the ability to accurately determine the time-dependent nature of the association between exposure and the non-fatal overdose.

Self-controlled research designs allow for the examination of the effect of transient risk factors on acute outcomes, such as non-fatal overdose. These methods inherently account for the effects of unmeasured, static confounding factors.[24] As such, this approach can be useful in studies examining exposures, such as incarceration or medication use, in which people who have these exposures might differ from others in ways that are difficult to measure.[25]

In a large random sample linked to administrative health and correctional records in British Columbia, Canada, this study aimed to: (1) describe the patterns of incarceration, hospital admissions, emergency department use, MOUD use, and the use of other medications in people who had a non-fatal overdose resulting in medical care; and (2) examine the association between these time-varying exposures (incarceration, medical service use, MOUD use, and other medication use) and non-fatal overdose resulting in medical care.

Methods

Study design and population

In this self-controlled case series, we included a 20% random sample of British Columbia residents registered for provincial health insurance in the British Columbia Ministry of Health Provincial Client Roster between Jan 1, 2015, and Dec 31, 2017.[26] In a series of deterministic and probabilistic linkage algorithms, ambulance and emergency department overdose surveillance, hospital, provincial poison control hotline, primary care, community pharmacy dispensing, provincial corrections, coroner, and death records for cohort members were linked by the British Columbia Ministry of Health using the person's name, date of birth, sex, and provincial health number.[26] Linked data were available from all datasets between Jan 1, 2015, and Dec 31, 2017. Additional linked data for Jan 1, 2010 to Dec 31, 2014, were available for medication, hospital, emergency department admission, and correctional records. Details of the client roster and linked datasets are provided in the appendix (p 1). Our study cohort consisted of all people aged 10 years or older on Jan 1, 2015, who had a record of a non-fatal overdose during the study period.

The 2016 British Columbia public health emergency declaration under the *Public Health Act,* and subsequent orders issued by the Provincial Health Officer, facilitated the formation of the provincial overdose cohort. Institutional ethics approval and informed consent for this project was not required, as the creation of the cohort was authorised through the emergency declaration, and the work was was completed as part of the British Columbia Centre for Disease Control's core public health mandate.

Overdose ascertainment

Non-fatal overdose episodes were identified through emergency department, hospital, primary care, and poison control hotline records by use of source-specific case definitions. The case definitions, including International Classification Of Diseases, 10th edition codes, are provided in the appendix (p 1) and detailed elsewhere.[26] Some datasets only ascertained overdoses recorded as involving opioids, but other datasets included overdoses involving a range of substances or those for which the substance involved was unknown. Therefore, although most overdoses were likely to have involved opioids,[27] overdose ascertainment was not limited to opioid overdoses only. Overdose episodes that resulted in death were defined as fatal overdoses and were excluded, because self-controlled case series require censoring to be independent of the outcome.[28] Self-controlled case-series analysis also requires recurrent outcome events to be independent. Given that having had a previous non-fatal overdose is associated with subsequent overdose,[5] recurrent overdoses are likely to be dependent. Therefore, we followed recommended practice and limited the analysis to the first non-fatal overdose occurring during the study period.[29–31]

Exposure measures

We examined risk periods associated with incarceration,[16] discharge from hospital and the emergency department,[17] and dispensations of MOUD (ie, methadone, buprenorphine, or slow-release oral morphine prescribed for opioid substitution),[15] opioids prescribed for pain,[32] benzodiazepines,[33] and antipsychotics.[19] We chose MOUD, opioids for pain, and benzodiazepines as they have been examined in previous cohort studies but not in a self-controlled case series. We chose antipsychotics, as some research has suggested a potential association between antipsychotics and overdose,[19] but this association has not been thoroughly investigated. A detailed description of the creation of each exposure measure is provided in the appendix (pp 2–4). As overdose-specific databases were only available from Jan 1, 2015, the study period was limited to Jan 1, 2015 to Dec 31, 2017. However, we used all available data (ie, from 2010–17) to create risk periods to ensure that initial exposure status was correctly classified. From the client roster records, we extracted data on sex and calculated age at the start of the study period using date of birth.

See Online for appendix

We created episodes of incarceration, hospital admission, and emergency department care by combining overlapping events, nested events, and events that began on the day of discharge or release from the previous event of the same exposure type, into single episodes starting from the earliest admission date and ending on the latest discharge or release date within the episode. All hospital admissions and emergency department presentations were included, regardless of the reason for presentation. We used provincial incarceration records to identify episodes of incarceration in which people were remanded or serving a sentence of up to 2 years less a day. As such, periods of time in federal prison in which people served a sentence of over 2 years were not identified, as these data were not available (appendix p 2).

MOUD, opioid, benzodiazepine, and antipsychotic dispensing were defined by use of drug identification numbers or product identification numbers (appendix p 4). Episodes of medication use were constructed using the "service date" and "days supplied" fields. There was no minimum number of supplies or days of supply.

Consistent with previous research[34] and based on clinical guidelines for reversion to initation dosing,[35] we defined

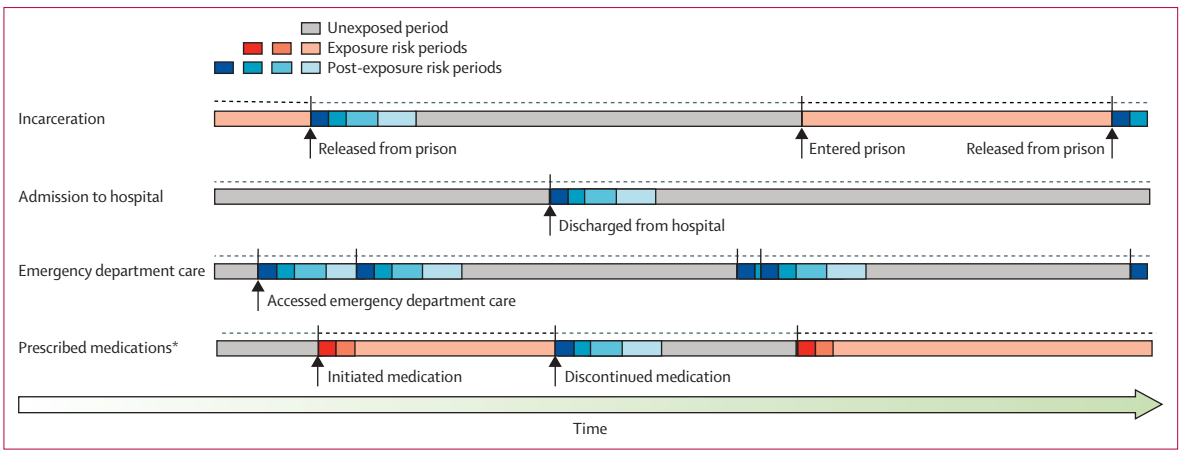

Figure 1: **Potential risk periods for non-fatal drug overdose in the self-controlled case series**
Risk periods for different exposures (eg, incarceration and medication supply risk periods) could occur simultaneously. MOUD=medications for opioid use disorder. *Prescribed medications included MOUD, opioids for pain (unrelated to MOUD), benzodiazepines, and antipsychotics; each type of medication was examined separately.

MOUD discontinuation as a gap in supply lasting 5 days or more for methadone or slow release oral morphine, and 6 days or more for buprenorphine. Because MOUD dispensing is highly controlled and often dispensed daily, we assumed that people began using each new supply on the day that it was dispensed. If a person was dispensed two different MOUD on the same day, we used the longer discontinuation gap.

For opioids for pain, benzodiazepines, and antipsychotics, we used a discontinuation gap of at least 7 days. As used in previous studies,[33] the period of use began on the day of supply of a medication and continued to the end of the supply, as determined by the number of days' supplied. If an additional prescription for the same drug and dose was dispensed, the number of days of the new prescription was added to the remaining number of days available from the previous dispensing of the drug. If a person was supplied a different drug or dose, the number of days' supply of the new medication replaced the remaining number of days supplied from the previous dispensing. For long-acting antipsychotics, we adjusted the number of days of supply to reflect the expected length of action of a dose, where this information was in the dispensing notes. Switching medication within the same class was considered as a continuation of the same episode. The date of discontinuation was designated as the last day of any supply of medication.

As we did not have records of medication dispensing during hospital stays, we assumed that the person was supplied their medication by the hospital during their stay and that they did not use any of their personal supply.

Data analysis

We calculated descriptive statistics for all measures and compared the occurrence of these exposures in our study cohort (ie, people who had a non-fatal overdose) to the entire 20% random sample. We calculated incidence rate ratios (IRRs) of non-fatal overdose using conditional Poisson models, comparing the incidence of non-fatal overdose during specified risk periods for each exposure to the unexposed period (ie, all follow-up time that was not part of a designated risk period for each exposure) for each individual.[28,36]

Figure 1 provides a pictorial representation of the creation of risk periods for the analysis. For incarceration, the risk periods were the day of admission, the period of time in prison (excluding the day of admission and the day of release), the day of release from prison, and weeks 1–2, 3–4, 5–8, and 9–12 after release from prison. For medication exposures the risk periods were the day of initiation, weeks 1–2 and 3–4 of use, the remainder of medication use episode, and weeks 1–2, 3–4, 5–8, and 9–12 post-discontinuation. For emergency department visits and hospital admissions, the risk periods were weeks 1–2, 3–4, 5–8, and 9–12 after discharge. As hospital admission and emergency department presentation were used to identify overdose episodes, periods in hospital and in the emergency department were not included as risk periods. Post-discharge risk periods began the day after discharge.

An indicator of calendar year was also created, as calendar year could act as a proxy for policy changes affecting both exposures (eg, eligibility for MOUD) and outcomes (eg, changing drug supply). Time from the start of the study period to the date of death or the end of the study period (whichever occurred first), including time after the first non-fatal overdose, was included in the analysis. We did univariable analyses for each exposure, adjusted for calendar year only, and a multivariable analysis that adjusted for all exposures. Only individuals who changed exposure status during follow-up contributed directly to an estimate. However, all other individuals contributed indirectly to the multivariable models through the estimates of the other covariates.

For the sensitivity analyses, we altered several study criteria: excluding people with a first episode of non-fatal

	Entire 20% random sample* (number of individuals [n=921 346])	Non-fatal drug overdose cohort				
		Number of individuals (n=4149)†	Number of episodes	Median number of episodes (IQR)	Median duration of episode (IQR), days	Number of days of exposure during the study period (n=4 452 963)
Sex						
Female	465 797 (50·6%)	1351 (32·6%)	..	..	..	..
Male	455 549 (49·4%)	2798 (67·4%)	..	..	..	..
Age at baseline, years	44 (27–59)	34 (25–46)	..	..	..	..
Incarceration						
Exposed	6581 (0·7%)	1055 (25·4%)	3979	2 (1–5)	18 (6–47)	172 323 (3·9%)
Not exposed	914 765 (99·3%)	3094 (74·6%)	..	..	..	..
Admitted to hospital						
Exposed	254 348 (27·6%)	2425 (58·4%)	7992	2 (1–4)	3 (2–8)	67 103 (1·5%)
Not exposed	666 998 (72·4%)	1724 (41·6%)	..	..	..	..
Received emergency department care						
Exposed	318 297 (34·5%)	3737 (90·1%)	35 886	5 (2–11)	1 (1–1)	43 158 (1·0%)
Not exposed	603 049 (65·5%)	412 (9·9%)	..	..	..	..
Dispensed MOUD						
Exposed	5501 (0·6%)	1664 (40·1%)	6380	3 (1–5)	21 (6–88)	570 307 (12·8%)
Not exposed	915 845 (99·4%)	2485 (59·9%)	..	..	..	..
Dispensed opioids for pain (unrelated to MOUD)						
Exposed	228 851 (24·8%)	2127 (51·3%)	6761	2 (1–4)	10 (4–30)	492 716 (11%)
Not exposed	692 495 (75·2%)	2022 (48·7%)	..	..	..	..
Dispensed benzodiazepines						
Exposed	100 904 (11·0%)	1533 (36·9%)	4677	2 (1–4)	14 (7–34)	298 124 (7%)
Not exposed	820 442 (89·0%)	2616 (63·1%)	..	..	..	..
Dispensed antipsychotics						
Exposed	35 110 (3·8%)	1697 (40·9%)	5178	2 (1–4)	33 (14–102)	543 737 (12%)
Not exposed	886 236 (96·2%)	2452 (59·1%)	..	..	..	..

Data are n (%) or median (IQR). MOUD=medications for opioid use disorder. *Includes cases of non-fatal drug overdose. †For time-varying exposures, the number of individuals exposed at least once during the study period is shown.

Table 1: **Exposures in the entire sample and in those who had a non-fatal drug overdose in 2015–17**

overdose but who later died of a fatal overdose; including all recurrent, non-fatal overdose events; limiting the cohort to people who had their first non-fatal overdose after Jan 1, 2016 (ie, people who had at least 1 year with no previous drug overdose resulting in medical care); and excluding people with intermittent prison sentences (in which individuals are released to the community in order to continue employment during weekdays, but return to prison at weekends). We also altered the construction of medication episodes, by increasing the interval that defined medication discontinuation and removing the assumption that hospitals supplied medication to patients during their hospital stay (appendix p 7). In the analysis that included all recurrent, non-fatal overdose events, we included a pre-exposure risk period to reduce the risk of bias due to the outcome affecting the short-term likelihood of experiencing each exposure.[36] To examine if the association differed by age, we conducted age-stratified analyses (<25 years, 25–39 years, and ≥40 years). The details of and rationale for all sensitivity analyses are provided in the appendix (p 7).

All analyses were done using SAS Enterprise Guide, release 7.1.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The entire 20% random sample of residents consisted of 921 346 people, 4149 (0·5%) of whom had at least one non-fatal overdose and 688 (0·1%) of whom died from a fatal overdose between Jan 1, 2015, and Dec 31, 2017. Among the 4149 people who had a non-fatal overdose, there were a total of 6938 non-fatal overdose events, with 1152 (27·8%)

people who had more than one non-fatal overdose and 141 (3·4%) people who died from a fatal overdose during follow-up. The median length of follow-up was 3 years (5–95th percentile 2·7–3·0 years).

Compared with the entire 20% random sample, people who had a non-fatal overdose were approximately 10 years younger and more likely to be male, and a greater proportion had been incarcerated, been admitted to hospital, and received emergency department care (table 1). 1351 (32·6%) people who had a non-fatal overdose were female, and the median age at first non-fatal overdose was 35 years (IQR 26–48). Accessing emergency department care was the most common exposure; 3737 (90·1%) of the cohort had received emergency department care at least once between 2015 and 2017, with a median number of five (IQR 2–11) visits per person over the 3-year follow-up period. However, of the 4452963 days of exposure during the study period, MOUD (570307 [12·8%] days) and

	Non-fatal overdose (n=4149)*	IRR (95% CI)†	Adjusted IRR (95% CI)‡	Adjusted IRR (95% CI)§
Incarceration				
Unexposed	3785 (91·2%)	1 (ref)	1 (ref)	1 (ref)
Day of incarceration	11 (0·3%)	3·03 (1·66–5·52)	2·95 (1·62–5·40)	2·76 (1·51–5·04)
In prison	22 (0·5%)	0·11 (0·07–0·12)	0·10 (0·07–0·16)	0·12 (0·08–0·19)
Day of release	5 (0·1%)	1·40 (0·57–3·37)	1·36 (0·56–3·28)	1·45 (0·60–3·51)
Weeks 1–2 post-release	126 (3·0%)	2·91 (2·36–3·58)	2·84 (2·30–3·50)	2·92 (2·37–3·61)
Weeks 3–4 post-release	56 (1·3%)	1·41 (1·06–1·87)	1·38 (1·04–1·83)	1·34 (1·01–1·78)
Weeks 5–8 post-release	80 (1·9%)	1·22 (0·96–1·56)	1·19 (0·94–1·52)	1·15 (0·90–1·46)
Week 9–12 post-release	64 (1·5%)	1·20 (0·92–1·56)	1·17 (0·90–1·53)	1·15 (0·88–1·50)
Admission to hospital				
Unexposed	3632 (87·5%)	1 (ref)	1 (ref)	1 (ref)
Weeks 1–2 post-discharge	140 (3·4%)	1·59 (1·33–1·90)	1·55 (1·29–1·85)	1·35 (1·11–1·63)
Weeks 3–4 post-discharge	104 (2·5%)	1·25 (1·02–1·54)	1·22 (1·00–1·49)	1·16 (0·90–1·38)
Weeks 5–8 post-discharge	149 (3·6%)	1·04 (0·88–1·24)	1·02 (0·86–1·21)	0·97 (0·81–1·16)
Weeks 9–12 post-discharge	124 (3·0%)	1·01 (0·84–1·21)	0·98 (0·82–1·18)	0·96 (0·80–1·17)
Emergency department care				
Unexposed	2814 (67·8%)	1 (ref)	1 (ref)	1 (ref)
Weeks 1–2 post-contact	413 (10·0%)	1·37 (1·22–1·54)	1·31 (1·17–1·47)	1·10 (0·97–1·24)
Weeks 3–4 post-contact	287 (6·9%)	1·22 (1·08–1·39)	1·17 (1·03–1·34)	1·06 (0·93–1·21)
Weeks 5–8 post-contact	365 (8·8%)	1·03 (0·91–1·15)	0·99 (0·88–1·11)	0·93 (0·82–1·05)
Weeks 9–12 post-contact	270 (6·5%)	0·99 (0·87–1·13)	0·96 (0·84–1·09)	0·94 (0·92–1·07)
Use of MOUD				
Unexposed	3460 (83·4%)	1 (ref)	1 (ref)	1 (ref)
Day of initiation	12 (0·3%)	1·80 (1·02–3·20)	1·59 (0·90–2·83)	1·57 (0·88–2·79)
Weeks 1–2 of use	182 (4·4%)	0·40 (0·32–0·51)	0·30 (0·24–0·39)	0·33 (0·26–0·42)
Weeks 3–4 of use	16 (0·4%)	0·43 (0·26–0·72)	0·39 (0·24–0·65)	0·41 (0·25–0·67)
Remainder of MOUD use episode	154 (3·7%)	0·40 (0·32–0·50)	0·38 (0·31–0·48)	0·40 (0·33–0·50)
Weeks 1–2 post-discontinuation	91 (2·2%)	1·23 (0·98–1·55)	1·09 (0·86–1·37)	0·96 (0·76–1·21)
Weeks 3–4 post-discontinuation	71 (1·7%)	1·33 (1·03–1·70)	1·17 (0·91–1·51)	1·10 (0·85–1·41)
Weeks 5–8 post-discontinuation	99 (2·4%)	1·26 (1·01–1·56)	1·13 (0·91–1·40)	1·08 (0·87–1·34)
Weeks 9–12 post-discontinuation	64 (1·5%)	1·06 (0·82–1·34)	0·96 (0·74–1·25)	0·94 (0·73–1·23)
Use of opioids for pain (unrelated to MOUD)				
Unexposed	3454 (83·2%)	1 (ref)	1 (ref)	1 (ref)
Day of initiation	13 (0·3%)	2·37 (1·37–4·12)	2·46 (1·42–4·26)	1·94 (1·11–3·77)
Weeks 1–2 of use	153 (3·7%)	1·49 (1·17–1·90)	1·47 (1·15–1·87)	1·25 (0·97–1·60)
Weeks 3–4 of use	23 (0·6%)	1·21 (0·79–1·87)	1·31 (0·85–2·01)	1·12 (0·73–1·72)
Remainder of opioid use episode	165 (4·0%)	1·33 (1·05–1·68)	1·53 (1·21–1·93)	1·30 (1·02–1·65)
Week 1–2 post-discontinuation	81 (2·0%)	1·15 (0·91–1·45)	1·19 (0·94–1·51)	1·08 (0·85–1·36)
Weeks 3–4 post-discontinuation	68 (1·6%)	1·09 (0·85–1·40)	1·13 (0·98–1·44)	1·06 (0·83–1·37)
Weeks 5–8 post-discontinuation	116 (2·8%)	1·16 (0·95–1·41)	1·19 (0·98–1·44)	1·16 (0·95–1·41)
Weeks 9–12 post-discontinuation	76 (1·8%)	0·89 (0·70–1·13)	0·91 (0·72–1·15)	0·91 (0·72–1·15)

(Table 2 continues on next page)

	Non-fatal overdose (n=4149)*	IRR (95% CI)†	Adjusted IRR (95% CI)‡	Adjusted IRR (95% CI)§
(Continued from previous page)				
Use of benzodiazepines				
Unexposed	3545 (85·4%)	1 (ref)	1 (ref)	1 (ref)
Day of initiation	20 (0·5%)	5·84 (3·73–9·15)	6·09 (3·88–9·54)	5·19 (3·28–8·21)
Weeks 1–2 of use	154 (3·7%)	1·98 (1·55–2·53)	1·96 (1·53–2·52)	1·76 (1·37–2·27)
Weeks 3–4 of use	32 (0·8%)	2·08 (1·44–3·00)	2·26 (1·56–3·26)	2·05 (1·41–2·96)
Remainder of benzodiazepine use episode	150 (3·6%)	1·54 (1·21–1·95)	1·79 (1·41–2·28)	1·65 (1·29–2·10)
Week 1–2 post-discontinuation	52 (1·3%)	1·18 (0·88–1·57)	1·23 (0·92–1·64)	1·12 (0·83–1·49)
Weeks 3–4 post-discontinuation	53 (1·3%)	1·34 (1·01–1·78)	1·39 (1·04–1·84)	1·27 (0·96–1·70)
Weeks 5–8 post-discontinuation	86 (2·1%)	1·31 (1·04–1·64)	1·34 (1·07–1·68)	1·27 (1·01–1·60)
Weeks 9–12 post-discontinuation	57 (1·4%)	1·01 (0·77–1·32)	1·03 (0·78–1·35)	0·99 (0·75–1·30)
Use of antipsychotics				
Unexposed	3358 (80·9%)	1 (ref)	1 (ref)	1 (ref)
Day of initiation	7 (0·2%)	1·77 (0·84–3·74)	1·72 (0·81–3·63)	1·29 (0·61–2·77)
Weeks 1–2 of use	245 (5·9%)	1·32 (1·07–1·63)	1·14 (0·92–1·42)	1·20 (0·97–1·64)
Weeks 3–4 of use	38 (0·9%)	1·17 (0·84–1·64)	1·16 (0·83–1·62)	1·17 (0·83–1·64)
Remainder of antipsychotics use episode	229 (5·5%)	1·04 (0·86–1·26)	1·06 (0·88–1·28)	1·09 (0·90–1·32)
Week 1–2 post-discontinuation	52 (1·3%)	1·08 (0·81–1·44)	1·05 (0·79–1·40)	1·01 (0·75–1·35)
Weeks 3–4 post-discontinuation	66 (1·6%)	1·66 (1·29–2·15)	1·63 (1·26–2·11)	1·58 (1·22–2·05)
Weeks 5–8 post-discontinuation	83 (2·0%)	1·35 (1·08–1·71)	1·33 (1·05–1·57)	1·28 (1·02–1·62)
Weeks 9–12 post-discontinuation	71 (1·7%)	1·42 (1·11–1·81)	1·38 (1·08–1·77)	1·37 (1·07–1·80)
Calendar year				
2015	1104 (26·6%)	1 (ref)	..	1 (ref)
2016	1441 (34·7%)	1·37 (1·27–1·48)	..	1·41 (1·30–1·53)
2017	1604 (38·7%)	1·60 (1·48–1·73)	..	1·72 (1·59–1·87)

IRR=incidence rate ratio. MOUD=medications for opioid use disorder. *Includes first non-fatal overdose episodes only. †Univariable analysis. ‡Adjusted for calendar year only. §Adjusted for all exposure variables.

Table 2: **Association between potential risk periods and the incidence of non-fatal drug overdose**

antipsychotic (543 737 [12·2%] days) dispensing episodes covered the greatest number of days. Of all MOUD dispensing episodes (n=6380), 4131 (64·7%) contained at least one supply of methadone, 2437 (38·2%) contained at least one supply of buprenorphine, and 116 (1·8%) contained at least one supply of slow-release oral morphine. 6080 (95·3%) of MOUD dispensing episodes included a single type of MOUD.

In the multivariable analysis, compared with unexposed periods, the incidence of non-fatal overdose was higher on the day of admission to prison, for the first 4 weeks after release from prison, for the first 2 weeks after discharge from hospital, on the day of initiating opioids for pain and during long-term (>4 week) use, during the entire period of being dispensed benzodiazepines, and from 2 weeks after discontinuation of antipsychotics (table 2 and figures 2, 3). The incidence of non-fatal overdose was reduced during supply of MOUD and when in prison compared with unexposed periods. The incidence of non-fatal overdose in the cohort increased with each calendar year (table 2). Results for multivariable analyses, stratified by age group (<25 years, 25–39 years, and ≥40 years) are presented in the appendix (pp 9–10).

The results for the sensitivity analyses, in which the criteria used to create the medication use episodes were altered, were broadly similar to the results from the main analysis (appendix pp 10–13). However, when the cohort was limited to people who had their first non-fatal overdose after Dec 31, 2015, the incidence of non-fatal overdose was increased in the first 8 weeks after discontinuation of MOUD compared with the unexposed period. There was also an increased incidence of non-fatal overdose in the first 2 weeks after initiating antipsychotics when compared with the unexposed period, but no association between periods of using opioid for pain and non-fatal overdose. In further sensitivity analyses including all non-fatal overdose events (ie, including both first and recurrent episodes), the point estimate for the day of incarceration IRR attenuated toward the null and was non-significant. By contrast, several periods emerged as having significantly increased risk of non-fatal overdose events (compared with non-exposed periods) that were not evident in the primary analysis, particularly weeks 5–12 after release from prison, up to 12 weeks post-discharge from emergency department care, the period post-discontinuation of MOUD, and weeks 1–2 post-discontinuation of benzodiazepine.

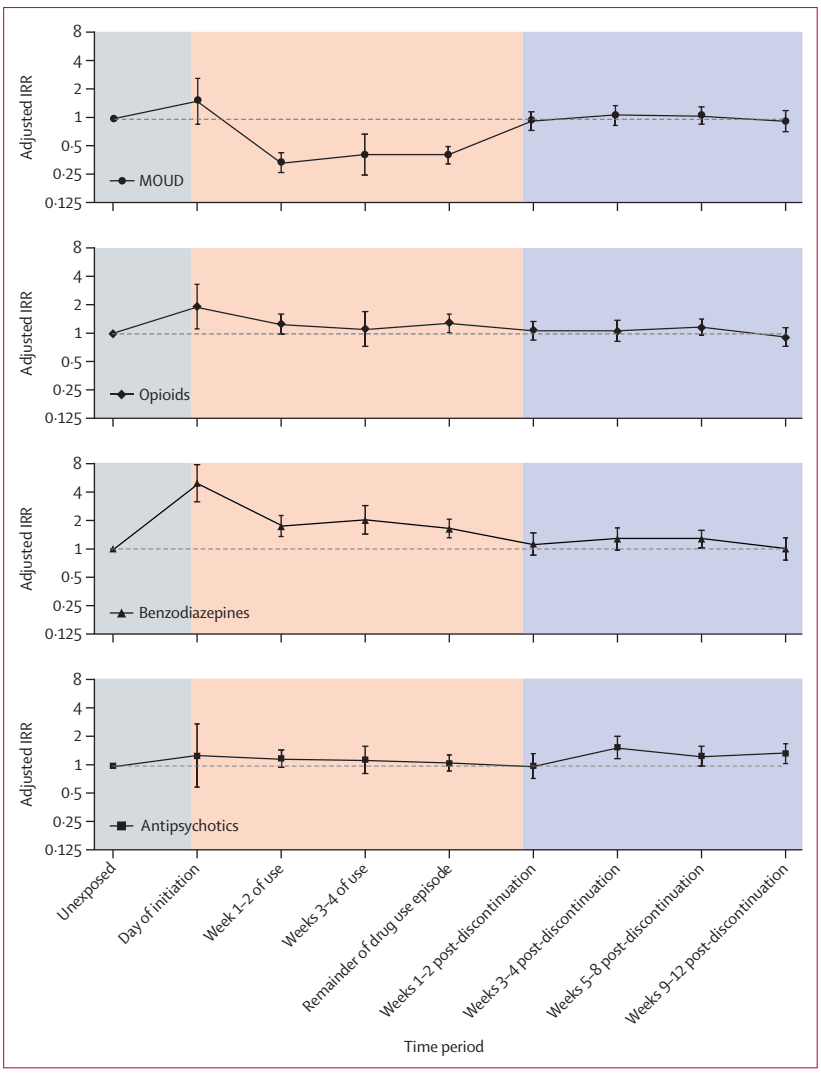

Figure 2: **Multivariable analysis of the association between risk periods of medication use and non-fatal drug overdose**
The multivariable model included use of MOUD, opioids for pain (unrelated to MOUD), benzodiazepines, and antipsychotics, emergency department care, admission to hospital, incarceration, and calendar year. The unexposed period was used as the reference period. MOUD=medications for opioid use disorder. IRR=incidence rate ratio.

Discussion

Our study found that, compared with unexposed periods, the incidence of non-fatal overdose decreased while using MOUD and while in prison. We observed an increase in the risk of non-fatal overdose during some periods of treatment with opioids for pain and during all periods of benzodiazepine use, in the 4 weeks after being released from prison, in the 2 weeks after being discharged from hospital, on the day of admission to prison, and after discontinuation of antipsychotics.

The substantial decrease in incidence of non-fatal overdose observed during periods of MOUD use is consistent with previous studies.[15] However, in our primary analyses there was no increase in risk during the first 4 weeks of MOUD use, or in the 4 weeks after discontinuation of MOUD. As our study focused solely on non-fatal overdose events, we cannot exclude the possibility of survivor bias; overdose events after discontinuation might be more likely to be fatal, thus reducing the number of non-fatal events. However, the considerable and immediate decrease in risk during MOUD use shown in our study emphasises the importance of removing barriers to initiating and ensuring continuity of MOUD in people with an opioid use disorder.[37]

Previous studies have suggested that, when used as a treatment for opioid use disorder, buprenorphine could be more effective than methadone for reducing both all-cause and drug-related mortality.[15] Further research using self-controlled study designs and disaggregating by type of MOUD is recommended to establish differences in the effects of buprenorphine, methadone, and other MOUD on overdose, while controlling for static confounders.

Given that the 4-week period after release from prison has been associated with an increased risk in both fatal and non-fatal overdose events,[16,23] it is essential to ensure that people have access to MOUD, alcohol treatment, and other drug treatments while in prison, and that this care continues uninterrupted after release from prison, to reduce the occurrence of overdose during this period. Our study also found an increased risk of non-fatal overdose on the day of incarceration. To our knowledge, this association has not been examined previously and warrants further research. This association could suggest that people are being arrested while under the influence of drugs, resulting in a need for overdose-related care while in police custody, or that people are being arrested for drug-related offences originating from the non-fatal overdose itself. Many people who have or who witness an overdose are reluctant to seek care because of the perceived risk of arrest.[38] The decriminalisation of drug use and drug possession for individual use might increase people's willingness to seek care for drug overdose. In responding to the incidence of non-fatal overdose on admission to prison, as in all overdose response, engaging meaningfully with people who use drugs to establish how social and medical institutions can be adapted to meet the needs of and improve safety for people who use drugs is essential.[39]

Our finding that the risk of non-fatal overdose is increased in the 2 weeks following discharge from hospital is consistent with that of Merrall and colleagues.[17] Hospital-based interventions and consultations designed to connect people leaving hospital to community services have been found to improve treatment access and substance use-related outcomes after discharge.[40] As of December, 2020, take-home naloxone kits are available in 86 hospital and emergency departments in British Columbia.[41] Providing take-home naloxone to people discharged from hospital with opioid or benzodiazepine prescriptions, providing training on the use of naloxone to the families of these individuals or their housemates, and initiating long-term buprenorphine treatment during

hospitalisation could also reduce the risk of overdose in the weeks following hospital discharge.[42,43]

The increased risk of non-fatal overdose associated with benzodiazepine use shows the exacerbating role of polydrug use in overdose. Even though our study examined opioid and benzodiazepine use separately, our results emphasise the high risk associated with benzodiazepine use, suggesting that caution is needed when prescribing benzodiazepines for people who are concurrently prescribed opioid medications, who might engage in illicit opioid use, or who fulfil both criteria. Not only can polydrug use increase the risk of overdose,[6] treatments such as naloxone might also be less effective in the context of polydrug overdose.[44] Prescribing practices need to consider the risk associated with the concurrent use of benzodiazepines and opioids, and overdose prevention and treatment programmes need to ensure that they can recognise and respond appropriately to polydrug overdoses.

We noted an increased incidence of non-fatal overdose following discontinuation of antipsychotics. Co-occurring substance use disorders, which are common in people with psychotic disorders,[45] have been associated with poorer medication adherence and higher rates of relapse compared with people with a psychotic disorder alone.[46] Antipsychotics can also be used off-label for sleep disorders, obsessive-compulsive disorder, depression, post-traumatic stress disorder, anxiety, and other conditions, all of which can also be risk factors for overdose. Integrated services providing treatment for substance use disorder and mental health care are likely to be essential for improving health outcomes, including reducing the risk of overdose.[47]

Our study identified non-fatal overdose systematically through many sources, increasing the number of overdoses that were identified compared with using a single type of medical care. However, the use of medical records underestimates non-fatal overdose, as up to 50% of overdose events might not result in medical care.[48] It is possible that some people in our cohort had a non-fatal overdose before 2015, which could be a potential confounder. However, the results of the sensitivity analysis, in which people who had an overdose in 2015 were excluded, suggests that this factor did not substantially affect the results. We limited the analysis to the first non-fatal overdose event only, which could produce conservative effect estimates for some exposures, particularly if an exposure affects the risk of a subsequent overdose more than the risk of the first overdose.[49]

Using a self-controlled design, we accounted for unmeasured, static, person-level characteristics. However, there were some potential time-varying confounders, such as transitions in housing status, access to naloxone, use of illicit or non-prescribed drugs, and residential drug treatment, that we were unable to adjust for because they were not present in the administrative datasets. Future research could examine the effects of these important time-varying factors on the risk of non-fatal overdose.

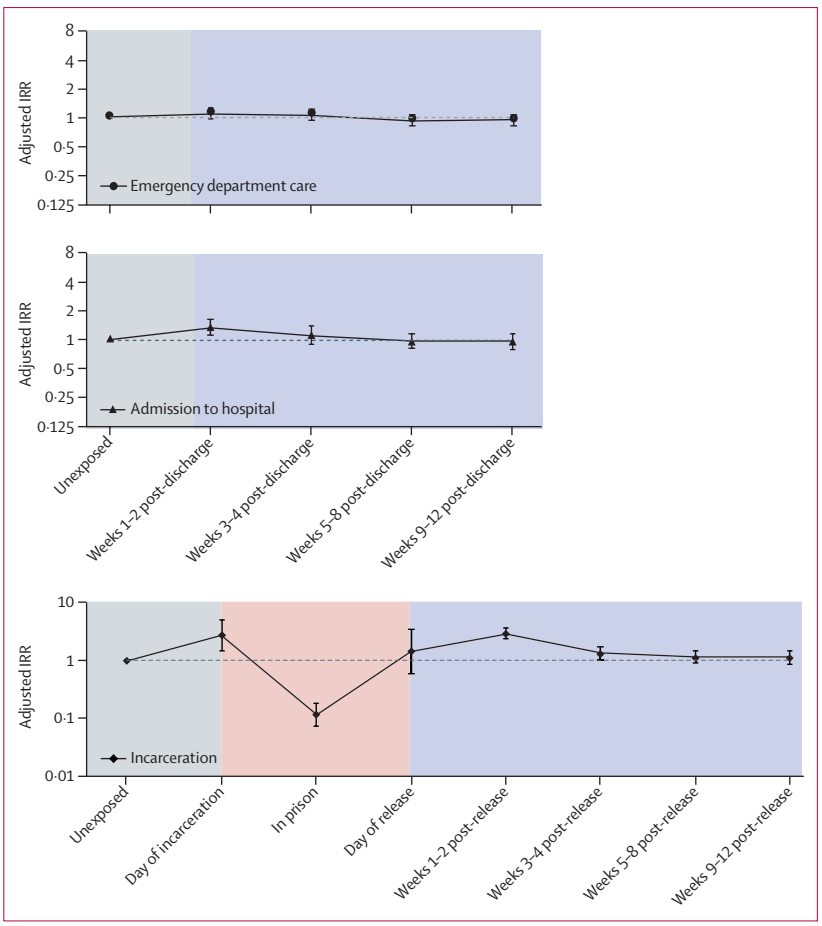

Figure 3: **Multivariable analysis of the association between hospital discharge, emergency department care, and incarceration risk periods and non-fatal drug overdose**
The multivariable model included use of MOUD, opioids for pain (unrelated to MOUD), benzodiazepines, and antipsychotics, emergency department care, admission to hospital, incarceration, and calendar year. The unexposed period was used as the reference period. MOUD=medications for opioid use disorder. IRR=incidence rate ratio.

One important limitation is that we do not know if people used medications as prescribed. However, the consistency across sensitivity analyses, in which durations of medication use episodes were altered, suggests that our results are robust to the assumptions we made when creating medication use episodes. We also do not know the reasons for medication prescribing, which could have resulted in some medications being misclassified. For example, hydromorphone might have been used off-label as a treatment for opioid use disorder, rather than to treat pain.

The database used to capture emergency department care does not record all emergency department admissions in rural areas of British Columbia, resulting in some periods of emergency department use being classified as unexposed and producing conservative effect estimates for this exposure. We also did not have information on federal incarcerations, which could mean that some time periods when people were recorded as being in prison were misclassified as time in the community.

Although this study was limited to analysis of non-fatal overdose, there are modifications to self-controlled case-series study designs that allow the analysis of fatal outcomes.[50] Further research examining fatal overdose using these modified study designs would provide greater insight into the association between the exposure periods examined in this study and overdose, and allow risk periods for fatal and non-fatal overdose events to be compared. Future research could also investigate the role of other medications, such as stimulants,[27] and examine the effect of dose or taking multiple medications (such as opioids and benzodiazepines) concomitantly.

There are unique, time-dependent effects of release from prison, discharge from hospital, and opioid, benzodiazepine, antipsychotic, and MOUD dispensation patterns, on the risk of non-fatal overdose. Policies that increase continuity of care during periods of hospitalisation or incarceration, and in periods of transition from, or between, health and correctional services might reduce the risk of overdose. Interactions with health services, including hospital and primary care physicians and health-care services within correctional facilities, provide key opportunities to prevent overdose or offer treatment, such as MOUD and take-home naloxone. The prescribing of benzodiazepines to people who use opioids needs to be carefully considered and monitored. Expanding access to and increasing support for long-term MOUD could reduce the risk of non-fatal overdose.

Contributors

CK developed the original research proposal and methodology, with contributions from JTY, SAK, KS, and AKS. CK developed and did the statistical analyses, with contributions from WG, and BZ. CK wrote the initial draft of the manuscript. CK, JTY, WG, BZ, SAK, KS, and AKS contributed substantially to the interpretation and synthesis of the results and were involved in the development of the final submitted manuscript. CK, SAK, AKS, BZ, and WG had full access to the raw data in the study. Due to international data sharing agreements, JTY and KS had access only to aggregate results data. CK, WG, and BZ accessed and verified the data. All authors approved the final manuscript and had final responsibility for the decision to submit this manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The data used in this study is not publicly available due to privacy considerations. However, researchers can request access to the Provincial Overdose Cohort via annual calls for proposals through Population Data BC.

For the **Population Data BC** see https://www.popdata.bc.ca/data

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