

# Toxicology and prescribed medication histories among people experiencing fatal illicit drug overdose in British Columbia, Canada

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## ABSTRACT

**BACKGROUND:** Since 2015, illicit drug overdose has been one of British Columbia's most pressing public health issues. Our objective was to assess prescription history in the context of postmortem toxicology among people who had a fatal illicit drug overdose in BC.

**METHODS:** Toxicology results from drug overdose deaths involving 1 or more illicit drugs, as identified by the BC Coroners Service in 2015–2017, were linked to the prescription drug histories of individuals as recorded in BC's PharmaNet database for a descriptive analysis. Substances identified in toxicology were considered prescribed if the individual had an active

dispensation for a matching medication within 60 days before overdose.

**RESULTS:** There were 2872 deaths from illicit drug toxicity during the study period; 1789 (62.3%) were closed cases with toxicology results available. In 85.5% of cases, 1 or more opioids were found to be relevant to death. Prescribed opioids in the absence of nonprescribed opioids were detected in only 2.0% of cases, and 6.7% had a combination of prescribed and nonprescribed opioids. Among those with 1 or more nonprescribed opioids, 78.5% had fentanyl or fentanyl analogues detected. Medications used in

opioid agonist therapy (methadone and buprenorphine) were found to be relevant to death in 7.4% of cases, with methadone (130 cases) much more common than buprenorphine (< 5 cases). Stimulants were detected in 70.6% of cases.

**INTERPRETATION:** Our data show a high prevalence of nonprescribed fentanyl and stimulants, and a low prevalence of prescribed opioids detected on toxicology in people who died from illicit drug overdose. These results suggest that strategies to address the current overdose crisis in Canada must do much more than target deprescribing of opioids.

In British Columbia, overdose has been responsible for a devastating loss of life.<sup>1</sup> From 2014 to 2016, fatal drug overdose contributed to a decrease of 0.38 years<sup>2</sup> in the life expectancy of BC residents, and since 2015, fatal overdoses have been the province's leading cause of unnatural death.<sup>3</sup> The rising number of overdose deaths led the BC government to declare a public health emergency in April 2016.<sup>4</sup> Despite the tireless efforts of first responders, many of whom are themselves people with lived experience of drug use, and the rapid implementation of new medical and outreach services for people at risk of overdose, the rates of deaths attributed to illicit drug overdose remain unacceptably high in BC and exceed rates in other Canadian provinces.<sup>1,5,6</sup>

The opioid overdose crisis was initially primarily attributed to the misuse of prescription opioids. However, despite decreases in the prescribing of opioids in BC, the death rate from illicit drug toxicity has increased more than fourfold, from 7.8/100 000 in 2014 to

30.9/100 000 in 2018.<sup>3,7,8</sup> This unprecedented increase in overdose-related deaths has been primarily attributed to the introduction of fentanyl into the illicit drug supply.<sup>3,9</sup> From 2012 to 2018, the proportion of deaths from illicit drug overdose in BC in which fentanyl was detected rose from 4% to 87%.<sup>3</sup> Similar increases in fentanyl-attributed deaths have been observed in Alberta, the United States and, to a lesser extent, Ontario.<sup>10,11</sup> Similarly, stimulants have been increasingly implicated in deaths from drug overdose.<sup>12</sup>

With health professional organizations introducing guidelines to reduce prescribing of opioids and other controlled substances, understanding the relative contribution of prescribed substances and illicitly obtained substances to overdose deaths is key to developing effective programs to reduce overdose mortality. We used a linked population-based data set of overdose deaths to compare toxicology with active prescriptions at death to characterize the role of prescribed drugs in deaths from illicit drug overdose. While

the role of illegal fentanyl in the overdose crisis is well known, this study allows assessment at the individual level of the prescription status of substances that can be prescribed or obtained by other means, including opioids for pain, opioid agonist therapy, benzodiazepines and stimulants.

## Methods

### Data sources and definitions

The BC Provincial Overdose Cohort is a linked administrative database of medical, prescribing and postmortem data on people who have had a fatal or nonfatal overdose in the province of BC. A full description of case definitions and data sources for the Provincial Overdose Cohort is available from MacDougall and colleagues.<sup>13</sup>

For this analysis, cases were defined as all people who have had a fatal illicit drug overdose (at least 1 substance relevant to death was illegally produced or diverted), as determined by the BC Coroners Service. Investigations by the BC Coroners Service involve collection of postmortem samples for comprehensive toxicological and other laboratory testing, autopsy and review of available medical records. The coroner responsible for the case determines the substances that are relevant to death based on the levels found in blood and tissue, pharmacologic knowledge and other available data about the case. Data were available for the years 2015–2017. The sample was restricted to closed cases for which toxicology results were available.

Individuals were linked to their prescription medication histories using PharmaNet, a comprehensive electronic medical record system that contains information on dispensations from community pharmacies for all residents of BC. All included BC Coroners Service cases were linkable. We assessed for the presence of an active prescription within 60 days before overdose (with the period of active prescription defined as the day of medication dispensation until the supply end date as estimated by the pharmacist). Individuals were also linked to their medical histories to assess comorbidities in the year before overdose using the Discharge Abstract Database (for hospital admissions), Medical Services Plan billing data (for outpatient physician visits), and the National Ambulatory Care Reporting System (for emergency department visits), and using algorithms described by Smolina and colleagues.<sup>9</sup> Demographic information (sex and age) was drawn from the BC Ministry of Health Provincial Client Roster. All closed cases were linkable to these 4 data sets, and there was no missing demographic information.

Toxicology results were available to the BC Provincial Overdose Cohort only for substances determined by the BC Coroners Service to have been relevant to the death (i.e., not incidentally detected). Substances were considered prescribed if there was an exact match between prescription and toxicology (e.g., hydromorphone on prescription and toxicology) or a correspondence between a prescription and a metabolite on toxicology (e.g., fentanyl on prescription and norfentanyl on toxicology). Heroin was identified through detection of 6-monoacetylmorphine (a metabolite).

The following classes of medication were assessed: opioids, benzodiazepines and Z-drugs, stimulants, gabapentinoids, antidepressants and antipsychotics. A full list of the medications included in these classes is available in Appendix 1, available at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200191/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200191/-/DC1).

### Data analysis

Descriptive data analysis was conducted by the authors using SAS Enterprise Guide 7.1. Cell sizes less than 5 were suppressed in accordance with the information sharing agreement of the Provincial Overdose Cohort.

### Ethics approval

As this analysis was conducted as part of the surveillance and epidemiology functions of the BC Centre for Disease Control, ethics review was not required.

## Results

### Study population

A total of 2872 deaths from illicit drug overdose occurred in BC in 2015–2017. Of these, 1789 (62.3%) were closed cases with toxicology results available. In comparison, during the same period, 105 deaths occurred that were attributed to prescription drugs; the number is subject to change pending closure of investigations (Andrew Tu, BC Coroners Service, Burnaby, BC: personal communication, 2020). There were no clinically important differences

**Table 1: Characteristics of people who died from illicit drug overdose in British Columbia, 2015–2017**

Characteristic	No. (%) of people n = 1789
<b>Demographic characteristics</b>	
Age group, yr	
≤ 30	435 (24.3)
31–49	859 (48.0)
≥ 50	495 (27.7)
Sex, male	1440 (80.5)
<b>Active prescription for</b>	
Opioid for pain	149 (8.3)
Benzodiazepine or Z-drug	235 (13.1)
Antidepressant	272 (15.2)
Antipsychotic	47 (2.6)
Stimulant	36 (2.0)
Gabapentin	155 (8.7)
Antiepileptic	57 (3.2)
<b>Diagnoses in the past year</b>	
Cardiovascular disease	98 (5.5)
Respiratory disease	108 (6.0)
Substance use disorder	599 (33.5)
Alcohol use disorder	159 (8.9)
Schizophrenia, bipolar disorder or personality disorder*	223 (13)
Depression, anxiety or adjustment disorder†	310 (17)
*With or without co-occurring depression, anxiety or adjustment disorder.	
†Without co-occurring schizophrenia, bipolar or personality disorder.	

between closed and open cases (data available from author on request). Closed cases were more likely to have had overdose occur in 2015 and 2016 (96.8% and 91.6% of cases were closed, respectively) than in 2017 (34.7% were closed). A total of 80.5% of the people who died from illicit drug overdose during the study period were male, and the median age was 40 years (Table 1). In total, 33.5% of the people who died had a diagnosis of substance use disorder in the year before overdose.

Most deaths from illicit drug overdose in BC involved opioids (Table 2). Among cases with no opioids found relevant to death, the most common substances were cocaine (47.1%), methamphetamine (39.0%), amphetamines (34.0%) and alcohol (27.0%).

### Prescribed and nonprescribed opioids

A total of 120/1789 (6.7%) had a combination of prescribed and nonprescribed opioids relevant to death, and 36/1789 (2.0%) had only prescribed opioids found relevant to death (Table 2). Thus, of all the cases of deaths from illicit drug overdose in BC

from 2015 to 2017, 1374/1789 (76.8%) were found to have only nonprescribed opioids relevant to death. Of the individuals with 1 or more nonprescribed opioids found relevant to death, fentanyl and fentanyl analogues were found in more than twice as many cases as heroin (78.5% v. 33.1%) (Table 3).

### Methadone and buprenorphine

Methadone was found to be relevant to death more often than buprenorphine (130 cases v. < 5 cases) but was still only relevant in 130 (7.3%) of the illicit drug deaths for which toxicology was available. Of the cases for which methadone was relevant, 50 (38.5%) had no history of it being prescribed within 60 days before overdose, and 43 (33.1%) had no history of methadone prescribed within 365 days before overdose. Of people with an active methadone prescription on the day of overdose ( $n = 38$ ), 20 (52.6%) were prescribed a daily dose of less than 60 mg, and only 12 (31.6%) had doses of 80 mg or greater.<sup>14</sup> All of the people (< 5) whose death was related to buprenorphine had an active prescription within 60 days before overdose.

**Table 2: Prescription status\* of medication relevant to death among illicit drug overdose deaths in British Columbia, 2015–2017**

Prescription status	No. (%) of deaths by substance class and prescription status <i>n</i> = 1789	
		Substance class–related deaths, %
Any opioid relevant to death	1530 (85.5)	1530 (100)
Only prescribed opioids	36 (2.0)	36 (2.4)
Prescribed and nonprescribed opioids	120 (6.7)	120 (7.8)
Only nonprescribed opioids	1374 (76.8)	1374 (89.8)
Stimulants relevant to death	1263 (70.6)	1263 (100)
Only prescribed stimulants	< 5 (< 0.3)	< 5 (< 0.4)
Prescribed and nonprescribed stimulants	10 (0.6)	10 (0.8)
Only nonprescribed stimulants	1251 (70.0)	1251 (99.0)
Antidepressants relevant to death	122 (6.8)	122 (100)
Only prescribed antidepressants	82 (4.6)	82 (67.2)
Prescribed and nonprescribed antidepressants	13 (0.7)	13 (10.7)
Only nonprescribed antidepressants	27 (1.5)	27 (22.1)
Benzodiazepines and Z-drugs relevant to death	107 (6.0)	107 (100)
Only prescribed benzodiazepines or Z-drugs	35 (2.0)	35 (32.7)
Prescribed and nonprescribed benzodiazepines	5 (0.3)	5 (4.7)
Only nonprescribed benzodiazepines or Z-drugs	67 (3.7)	67 (62.6)
Antipsychotics relevant to death	46 (2.6)	46 (100)
Only prescribed antipsychotics	38 (2.2)	38 (82.6)
Prescribed and nonprescribed antipsychotics	0	0
Only nonprescribed antipsychotics	8 (0.4)	8 (17.4)
Gabapentinoids relevant to death	29 (1.6)	29 (100)
Only prescribed gabapentinoids	24 (1.3)	24 (82.8)
Prescribed and nonprescribed gabapentinoids	0	0
Only nonprescribed gabapentinoids	5 (0.3)	5 (17.2)

\*Active prescription within 60 days before overdose death.

**Table 3: Presence of fentanyl or fentanyl analogues and heroin among cases of fatal illicit drug overdose in British Columbia, 2015–2017**

Opioid class relevant to death	No. (%) of cases	
	Total among all illicit drug deaths <i>n</i> = 1789	Total among cases with ≥ 1 nonprescribed opioid <i>n</i> = 1494
Fentanyl or fentanyl analogue*	1174 (65.6)	1173 (78.5)
Heroin	494 (27.6)	494 (33.1)
No fentanyl analogue or heroin	409 (22.9)	115 (7.7)

\*3-Methylfentanyl, acetylfentanyl, carfentanil or furanylfentanyl.

### Benzodiazepines and Z-drugs

Only 107 (6.0%) fatal cases had benzodiazepines or Z-drugs relevant to death. In 67 (62.6%) of these cases, benzodiazepines and Z-drugs had not been prescribed within 60 days before overdose (Table 2). The most commonly detected nonprescribed benzodiazepines were alprazolam and diazepam (detected in 42 [62.7%] and 9 [13.4%], respectively, of cases with only nonprescribed benzodiazepines or Z-drugs).

### Other classes of medication

Other classes of medication that were assessed were stimulants, gabapentinoids, antidepressants and antipsychotics (Table 2). In total, 1263 (70.6%) of cases of fatal drug overdose had stimulants relevant to death. Among these people, very few had prescriptions for these medications (0.1%). Absolute numbers of cases with gabapentinoids, antidepressants and antipsychotics relevant to death were low (1.6%, 6.8%, 2.6%, respectively).

### Interpretation

We examined the postmortem toxicology of confirmed illicit drug-related deaths in relation to comprehensive prescription histories. Of cases with opioids found relevant to death, only 2.4% of cases had prescribed-only opioids found relevant in toxicology. A further 7.8% of cases had a combination of prescribed and nonprescribed opioids detected. Most people (90%) with opioids relevant to death had not been prescribed these substances. Of the cases with any nonprescribed opioids, fentanyl or fentanyl analogues were found relevant to death in 78.5% of cases. Opioid agonist therapy was relevant to only 7.4% of total illicit drug deaths, of which 38.5% of cases involving methadone had no active prescription at the time of death. Stimulants were found to be relevant to 70.6% of illicit drug deaths and, of these, less than 1.0% of people had been prescribed the stimulants detected. Finally, of the small number of cases in which benzodiazepines or Z-drugs were detected, more than half (62.6%) of these individuals had not obtained these substances through a prescription.

In BC, prescription-only overdose deaths have decreased as a relative percentage of all overdose deaths, with illegal overdose deaths 7–30 times as common as prescription-only overdose deaths in 2015–2017<sup>3</sup> and representing more than 96% of drug-

related deaths during the study period. Our findings underscore the declining role of prescription opioids and heroin in the overdose crisis and the rise of synthetic opioids and stimulants. Previous studies comparing toxicology and prescribing have found a much higher contribution of prescription drugs to overdose death, ranging from 29% to 67%, and further described oxycodone as the most prevalent opioid found on toxicology, with fentanyl accounting for less than 15% of deaths.<sup>15–17</sup> These studies generally occurred more than 5 years ago before the emergence of fentanyl and are not directly comparable because they excluded nonprescription opioid overdose deaths. We found prescribed opioids to be relevant to only 2.4% of opioid-related illicit drug deaths in BC between 2015 and 2017. Similar research from Ontario showed a decline in active opioid prescriptions associated with opioid overdose deaths from 2013 to 2016.<sup>7</sup>

Recent studies suggest that deaths from prescription opioids have been stable from 2009 to 2016, despite the precipitous rise in opioid overdose deaths.<sup>3,11,18</sup> The decreasing role of prescription opioids suggests that efforts at deprescribing opioids, and guidelines encouraging nonopioid management of chronic pain have led to reduced opioid prescriptions. Our findings suggest that prescribing policies are insufficient to address the current overdose crisis in Canada and additional strategies are needed. Physicians should be encouraged to practise patient-centred opioid prescribing. The risk of harms from these medications (including the harms of starting new long-term opioid therapy and the harms of continuing therapy instead of offering alternative therapies with better evidence of efficacy) must be balanced with the potential harms of nonconsensual discontinuation of opioids for long-term users, including increased pain, risk of suicide and risk of transition to the toxic illicit drug supply.<sup>19–22</sup>

Stimulants, overwhelmingly nonprescribed, were relevant to 71% of the illicit drug deaths in our sample, in keeping with the rise of unprescribed stimulant use across North America<sup>12</sup> and increasing methamphetamine use in BC.<sup>23</sup> The relation between stimulant use, opioid and other substance use, and risk of death is complex. Stimulants may be used to manage the sedation caused by opioids or benzodiazepines; opioids may be used to bring on sleep or manage anxiety among people using stimulants; and some people may choose to use them together because of preference for their joint effects.<sup>24</sup> The risk associated

with these types of use will be different depending on tolerance to the substances, with people who do not regularly use opioids (and therefore have lower tolerance than regular users) considered to be at higher risk of overdose when they do use opioids, including opioid-adulterated stimulants. Unintentional use may also contribute to our findings — it is unknown to what extent illegal stimulants are adulterated or contaminated with opioids, or vice versa. For people who have a stimulant use disorder there is no definitive gold standard of treatment, although a body of literature emphasizes the value of psychosocial interventions and an emerging role for sustained-release dexamphetamine.<sup>25–28</sup>

The use of methadone, and more recently buprenorphine, as opioid agonist therapy is known to be a safe and effective treatment for opioid use disorder.<sup>29–32</sup> We found that nonprescribed methadone was present in less than 2.0% of total illicit drug deaths, and that the methadone prescribed to people who fatally overdosed was generally at low doses that are less effective at preventing overdose.<sup>14</sup> Buprenorphine was present in less than 0.1% of illicit drug deaths, consistent with its known safety profile as a partial agonist with lower risk of respiratory depression than methadone.<sup>33–37</sup> This may also reflect its poorer retention rate and lower uptake in BC.<sup>35,38</sup> Our findings support the continued emphasis on decreasing barriers to medically supervised opioid agonist therapy, to provide a safer alternative to contaminated illegal drugs and diverted methadone. Supervised dosing, which is time-consuming and has limited evidence to support its use,<sup>39</sup> should be carefully considered as part of efforts to lower barriers to opioid agonist therapy. Use of nonprescribed methadone can be an important alternative for people who do not wish to access clinical opioid agonist therapy services and who wish to reduce reliance on the toxic drug supply.<sup>40</sup> Thus, supporting peer-based organizations and harm-reduction agencies can provide an opportunity to help people more safely manage non-medically supervised methadone use.

We found nonprescribed benzodiazepines to be more commonly associated with illicit drug deaths than prescribed benzodiazepines. With decreasing prescription of benzodiazepines in Canada and increasing detection globally of novel illegal benzodiazepines, attention should be given to supporting people with benzodiazepine use disorder.<sup>8,41–43</sup> This is particularly salient given that alprazolam was the most commonly detected nonprescribed benzodiazepine in our sample. Alprazolam is rarely prescribed in BC (only 2% of dispensations) but was the most commonly purchased benzodiazepine in the US in an analysis of online drug cryptomarkets (> 50% of sales).<sup>44,45</sup> Contamination of illegal opioids with benzodiazepines is also an increasing concern.<sup>46</sup> An important area for future study is the contribution of polypharmacy to overdose risk in populations using nonprescribed medications and, in particular, the contribution of stimulants and sedatives to overdose mortality.

### Limitations

A limitation of this analysis is that we were unable to identify the sources of medications that were consumed but not prescribed. For example, illicit methadone, whether diverted or imported, may have contributed to some of the fatal cases in which methadone

was detected. Diversion or illegal importation is also an issue for other classes of medication. It is possible that substances found on toxicology but not dispensed in the community could have been the result of provision of samples at physicians' offices; consumption of previously prescribed medication; provision of medication by first responders, in acute care settings or in prison; or contamination or adulteration of other illegal drugs. An additional limitation is the use of 6-monoacetylmorphine to detect heroin in toxicology. Since this molecule is relatively unstable and prone to degrade during transport, we expect some underestimation of heroin use in the sample. This study examines a period of rapid change in the illegal drug market; caution should therefore be exercised in generalizing to other provinces and to the present day.

### Conclusion

Among people who died from illicit drug overdose in BC in 2015–2017, 85.5% had opioids relevant to death on toxicology; of these, both prescribed-only opioids (2.4%) and a combination of prescribed and nonprescribed opioids (7.8%) were relatively rare. Stimulants were commonly found relevant to death (70.6%) and overwhelmingly nonprescribed. Few deaths (7.4%) involved opioid agonist therapy. Of the small number of deaths involving benzodiazepines (6.0% of illicit drug deaths), most (62.6%) were nonprescribed. Our findings highlight that overdose is more than an opioid prescribing problem and requires a multifaceted response beyond prescribing and the medical system.

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