



## Patterns and history of prescription drug use among opioid-related drug overdose cases in British Columbia, Canada, 2015–2016

Kate Smolina<sup>a,b,\*</sup>, Alexis Crabtree<sup>a,b</sup>, Mei Chong<sup>a</sup>, Bin Zhao<sup>a</sup>, Mina Park<sup>a</sup>, Christopher Mill<sup>c</sup>, Christian G. Schütz<sup>d,e</sup>

<sup>a</sup> BC Centre for Disease Control, 655 W 12th Avenue, Vancouver, BC, V5Z 4R4 Canada

<sup>b</sup> School of Population and Public Health, University of British Columbia, 2206 East Mall, Vancouver, BC, V6T 1Z3, Canada

<sup>c</sup> Public Health Agency of Canada, Government of Canada, 130 Colonnade Road, Ottawa, ON, K1A 0K9, Canada

<sup>d</sup> Institute of Mental Health, Department of Psychiatry, University of British Columbia, 2255 Westbrook Mall, Vancouver, BC, V6T 2A1, Canada

<sup>e</sup> The Burnaby Centre for Mental Health & Addiction, 3405 Willingdon Avenue, Burnaby, BC, V5G 3H4, Canada

### ARTICLE INFO

#### Keywords:

Overdose  
Opioids  
Prescribing  
Administrative data  
Fentanyl  
OAT

### ABSTRACT

**Background:** British Columbia is the epicenter of the current fentanyl-related overdose crisis in Canada. Our study characterizes prescribing histories of people who had an opioid-related overdose compared to matched controls.

**Methods:** We examined linked administrative data for individuals who overdosed between January 1, 2015 and November 30, 2016. Past prescriptions over five years were assessed for opioids for pain, opioid agonist therapy, benzodiazepines/z-drugs, antidepressants, antipsychotics, gabapentinoids, mood stabilizers and anti-epileptics, muscle relaxants, and other sedating medications. Prescribing history of 9964 cases was compared with that of 49,820 matched controls.

**Results:** Overdose cases were more likely to be prescribed opioids for pain and to have used prescription opioids on a long-term basis in the previous five years compared to controls. However, at the time of overdose, 92% of men and 86% of women did not have an active opioid for pain prescription, and approximately half had not filled one in the past five years. Those who overdosed tended to have more prescriptions for psychotropic substances than controls. Fewer than 10% of cases had an active prescription for opioid agonist therapy and most were not on treatment in the past.

**Conclusions:** Low prevalence of active prescriptions for opioids for pain at the time of overdose suggests that opioid prescribing plays a limited short-term impact in the current fentanyl-related crisis of overdoses. While liberal opioid prescribing practices may have contributed to the development of the current overdose crisis, regulation and enforcement of clinicians' prescribing practices will likely have limited impact in reducing overdoses.

### 1. Introduction

Drug overdoses involving opioids have been dramatically increasing in North America since 2000, with a more rapid rise in the last several years (Fischer et al., 2018; Rudd et al., 2016a,b). Opioid overdoses have been described as occurring in the context of an intertwined epidemic driven by increasing availability of prescribed and diverted opioids since the 1990s (Slavova et al., 2017; Unick et al., 2013). More recently, statistics show an unprecedented increase in drug overdose deaths that have been linked to the replacement of heroin and diverted pharmaceutical opioids with fentanyl and its analogues, extremely potent opioids, into the illegal drug supply (European Monitoring Centre for

Drugs and Drug Addiction, 2017; Seth et al., 2018; Vivolo-Kantor et al., 2018).

British Columbia (BC), Canada, has been the epicenter of the current fentanyl-related overdose crisis in Canada, leading to the declaration of a public health emergency in April 2016 (Government of British Columbia, 2016). Estimates indicate that illicitly-manufactured fentanyl is the main driver of current crisis in BC; the proportion of illicit drug overdose deaths with detected fentanyl rose from 4% in 2012 to more than 80% in 2017 and 2018 (British Columbia Coroners Service, 2018). These increases parallel the surge in overdose events and overdose deaths seen in recent years (British Columbia Coroners Service, 2017). While the contribution of patients' own prescribed medications

\* Corresponding author at: BC Centre for Disease Control, 2101-655 W 12th Avenue, Vancouver, BC, V5Z 4R4, Canada.

E-mail address: [kate.smolina@bccdc.ca](mailto:kate.smolina@bccdc.ca) (K. Smolina).

<https://doi.org/10.1016/j.drugalcdep.2018.09.019>

Received 15 June 2018; Received in revised form 24 September 2018; Accepted 25 September 2018

Available online 25 October 2018

0376-8716/ © 2018 Published by Elsevier B.V.

to the risk of opioid overdose is well studied, these analyses have focused on patients receiving prescribed opioids (Bohnert et al., 2011; Glanz et al., 2018; Larochelle et al., 2016; Nadpara et al., 2017; Ray et al., 2016; Zedler et al., 2014), thereby limiting our ability to generalize findings to the broader population of individuals experiencing opioid-related overdoses.

Specifically, there are gaps in our understanding of the patterns of use of prescribed medications among people using illegal opioids. Survey data on prescription drug use before overdose are often self-reported, generally conducted on high-risk urban populations, and collected on non-fatal cases only (Chahua et al., 2014; Fischer et al., 2004; Kerr et al., 2007; Silva et al., 2013). Coroners' studies using toxicology results generally report substances detected in biological samples, but do not differentiate between those that were prescribed or obtained illegally (Boscarino et al., 2016; Groot et al., 2016; Shah et al., 2008). Other studies with coroners' data have excluded overdoses due to illegal opioids such as heroin (Hall et al., 2008; Johnson et al., 2013) or, among the studies focused specifically on individuals experiencing illegal drug overdoses, have generally examined only a limited set of medications over a short time period before overdose (Madadi et al., 2013; Spies et al., 2015).

Despite this limited information, one of the common actions implemented by many jurisdictions to combat the recent surge in overdose deaths has been restriction and regulation of clinicians' prescribing of opioids, such as introduction of new prescribing standards by the College of Physicians and Surgeons of British Columbia, 2016; Dowell et al., 2016). Our study uses a large linked administrative dataset to examine the prevalence and past history of use of a range of prescription medications among men and women who experienced an opioid-related drug overdose in BC.

## 2. Materials and methods

### 2.1. Data sources

BC has universal healthcare service coverage and each resident of BC holds a unique Personal Health Number, thus allowing for virtually complete capture of healthcare services use by BC residents. The BC Provincial Overdose Cohort includes linked administrative data on healthcare utilization for individuals experiencing an opioid overdose in BC. Briefly, individuals experiencing opioid-related overdoses were identified using data from the BC Ambulance Service (BCAS), Drug and Poison Information Centre (DPIC), BC Coroners Service (BCGS), case-based reporting from emergency departments (ED), National Ambulatory Care Reporting System (NACRS), Discharge Abstract Database (DAD) and Medical Services Plan (MSP). Five years of health history for each patient were then appended through linkage across datasets on unique personal identifiers from hospital discharge summaries, ED visits, visits to physicians on fee-for-service billing system (the majority of physicians in BC), and all prescriptions dispensed in community pharmacies, regardless of insurance status or mode of payment.

### 2.2. Study population

The cohort includes individuals who experienced a drug-related overdose event between January 1, 2015 and November 30, 2016. This period captures a rapid rise in unintentional opioid-related drug deaths in BC. Based on data availability, individuals meeting any of the following criteria were considered to have experienced an opioid-related drug overdose: administration of the opioid antagonist naloxone by paramedics, call to DPIC with an opioid-related event, physician-diagnosed opioid overdose in the ED (from case-based reporting), coroner determined illicit drug overdose death, visit to hospital, ED or physician with an associated opioid overdose (poisoning) diagnosis code (from

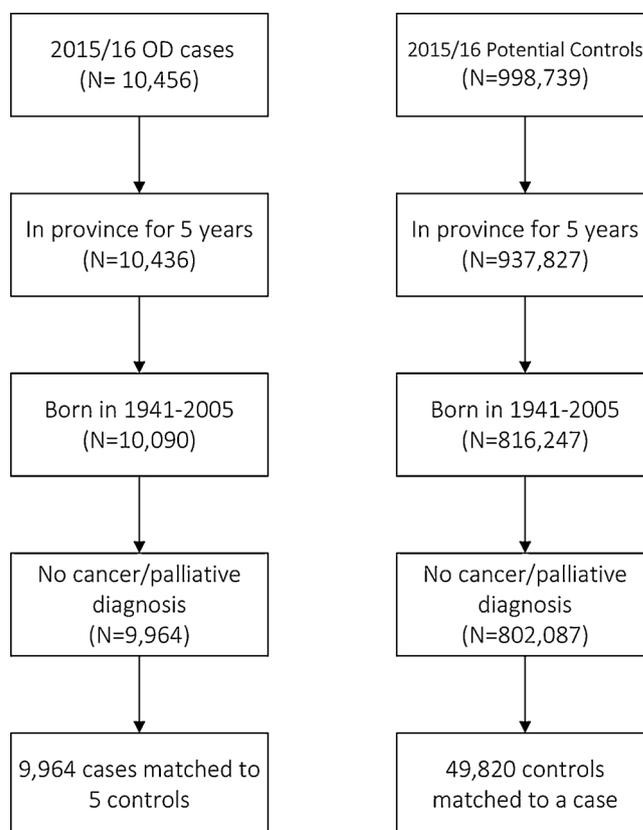


Fig. 1. Flow diagram of selection of study cohort.

DAD, NACRS and MSP) (see supplementary material for more details on case ascertainment). Related events present in multiple data sets and occurring within 24 h of each other (e.g., a single overdose involving ambulance response, transport to emergency department, and admission to hospital) were grouped into a single overdose episode to prevent double counting of overdoses.

Controls were selected from a 20% random sample of the 2016 BC population (overdose cases removed). Cases were matched 1:5 without replacement to controls based on birth year, sex, and local health area of residence (there are 89 areas in BC). For each case, prescription drug history was examined at the time of first recorded overdose and during the previous five years; for controls, comparisons were made over the same time frame based on a generated index date that corresponded with the first overdose date of the matched case.

Cases and controls were included if they were present in the provincial patient roster for each year for the past five years prior to first overdose/index date and if they were born between 1941 and 2005 inclusive (i.e., age inclusion 10–75 years). Cases and controls were excluded if they had at least one hospitalization for cancer or palliative care in the past five years prior to the overdose/index date (Fig. 1). Nonfatal and fatal overdoses were grouped because 1) there were not enough fatal cases to provide enough statistical power for some comparisons and 2) we found few clinically meaningful differences in prescribing history and comorbidities between the two groups. Previous analyses using this cohort also showed few differences in healthcare utilization patterns between fatal and non-fatal cases (Otterstatter et al., 2018).

### 2.3. Concept definitions

Prescribing histories of cases and controls spanning five years before the index date were assessed for the following classes of medications: opioids for pain, opioid agonist therapy (OAT), benzodiazepines/z-

drugs, antidepressants, antipsychotics, gabapentinoids, mood stabilizers and anti-epileptics, muscle relaxants, stimulants, and other sedating medications (nabilone, chloral hydrate, and phenobarbital). These classes were chosen to encompass the most common psychoactive medications dispensed to cases and controls. A full list of medications included in each class is available in the supplementary material. To best capture medications that are primarily self-administered, all non-injection formulations were included (i.e., oral, buccal, intranasal, rectal, and transdermal). Long-acting injectable formulations of antipsychotics were also included. Opioids for cough suppression were excluded, as were low dose codeine formulations (i.e., < 30 mg codeine per tablet, therefore including Tylenol 3s and equivalents but excluding weaker formulations). OAT medications (i.e., methadone and buprenorphine/suboxone used to treat opioid use disorder) were identified in the dataset through OAT-specific fees codes; all other opioid prescriptions were classified as opioids for pain. Medications from each class that had sedating properties were identified (e.g., sedating antidepressants) (Clinical Handbook of Psychotropic Drugs, 2015). Non-prescription (over-the-counter) medications were not captured.

The period of active prescription was defined as the time between the day on which the medication was dispensed and the day on which the prescription would have run out if taken every day based on recorded number of days' supply dispensed. Daily dose was calculated as follows. First, medications in each class were converted to a standard measure that allowed comparison across medications within the class. For opioids, doses were converted to morphine equivalents (ME) (Nielsen et al., 2016); all other medications were converted to daily defined doses (DDDs) (World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology, 2018). The daily dose of each dispensation was calculated as the total amount dispensed divided by the number of days supplied. Overlapping prescriptions (i.e., prescriptions in which additional medication was dispensed before the end of the days' supply of the previous dispensation) were treated by summing the doses on the overlapping days, using MEs or DDDs to combine medications within classes.

For "opioids for pain" drugs only, episodes were defined based on a group of one or more dispensations with less than 182 days gap from the last day of supply of the previous dispensation to the next dispensation date (Smolina et al., 2016). Episode duration was defined from the first dispensation date to the date of the last day of supply among a sequential group of dispensations. Episodes were categorized as short-term (episode duration  $\leq 90$  calendar days) and long-term (episode duration  $> 90$  calendar days). Long-term episodes were further divided into four groups based on intensity of opioid use during the episode, using the percentage of days on which there was medication supply: occasional ( $< 20\%$  days on therapy), intermittent ( $20 - < 50\%$  days on therapy), chronic ( $50 - < 90\%$  days on therapy), and every day ( $\geq 90\%$  days on therapy).

Recent initiation on opioids for pain was defined as occurring when there was an active prescription of opioids for pain on the index date and an episode was started within four weeks before the index date. Recent discontinuation from opioids for pain was assessed for the population of chronic and everyday long-term users only. Recent discontinuation was defined as occurring when a long-term episode with  $\geq 50\%$  of days on therapy ended within six weeks before the index date. To identify instances of potentially inappropriate prescribing, we identified individuals who had evidence of multi-doctoring ( $\geq 3$  different physicians prescribing opioids for pain, OAT, benzodiazepines/z-drug, and/or stimulants in the 28 days before the index date) or multi-pharmacy ( $\geq 3$  different pharmacies dispensing medications from the aforementioned classes in the 28 days before the index date). Potentially inappropriate prescribing was identified when an individual met criteria for both multi-doctoring and multi-pharmacy for opioid for pain medications (Gomes et al., 2014).

ICD9/10 codes from inpatient and outpatient health service records were used to derive mental and physical health diagnoses received in

the past year prior to overdose. Mental health conditions under consideration were the following: substance use disorder, alcohol use disorder, major depressive and related disorders, anxiety disorders, adjustment disorder, schizophrenia, bipolar disorder, personality disorders, attention-deficit/hyperactivity disorder (ADHD), and developmental disorders (including intellectual disabilities and fetal alcohol spectrum disorder). A full list of ICD codes and algorithms used to derive mental health diagnoses can be found in the supplementary material. Physical health diagnoses that were assessed as risk factors included chronic pain, cardiovascular disease (including angina, hypertension, ischemic heart disease, and myocardial infarction), and respiratory disease (including asthma and chronic obstructive pulmonary disorder). Physical health diagnoses were based on case definitions used by the BC Ministry of Health (British Columbia Centre for Disease Control, 2018), with the exception of chronic pain, which was based on a validated algorithm (Tian et al., 2013; Tonelli et al., 2015). Additionally, we considered if an individual was flagged as being an intravenous drug user in the past year using two versions of a validated algorithm (Janjua et al., 2018). The more sensitive algorithm identifies people who inject drugs through diagnostic codes for substance use. A more specific version of the algorithm additionally requires diagnostic codes for injection-related infections such as cellulitis and endocarditis (Janjua et al., 2018).

#### 2.4. Statistical analyses

Pearson's chi-squared tests were used to compare prescription use and prevalence of diagnosed mental/physical health comorbidities between cases and controls, separately by sex. All comparisons were performed at two different time frames, at the time of overdose/index date for prescription use and based on five years of history. For comorbidity analyses, both one year and five-year time frames were assessed. All analyses were performed using SAS Enterprise Guide V7.1 with statistical significance level set at 0.01.

### 3. Results

The overall study sample yielded 9964 cases that were matched to 49,820 controls (Fig. 1). The majority of cases (67%) were men, and 11% of cases experienced a fatal overdose event during the study period. The mean (median) age was 39 (37) for men and 39 (36) for women. Since birth year was one of the matching variables, the age distribution was similar among controls.

Table 1 summarizes prescription drug classes active at the time of overdose for cases and at the index date for controls, as well as history of use of these drug classes at any point in the previous five years. Generally, both current and past use of selected medications was significantly higher among cases than controls. However, despite a relatively higher level of use of certain prescription medications, the majority of cases did not have active prescriptions at the time of overdose.

#### 3.1. Active prescriptions

Among all active prescriptions at the time of overdose, antidepressants were the most common (men 17%; women 32%), followed by benzodiazepines/z-drugs (men 12%; women 22%) and antipsychotics (men 12%; women 17%). Overall, almost half of all female cases and a third of all male cases had an active prescription for at least one sedating medication. Compared to controls, all cases received significantly higher daily doses of non-opioid and non-benzodiazepine/z-drug sedating medications (Fig. 2).

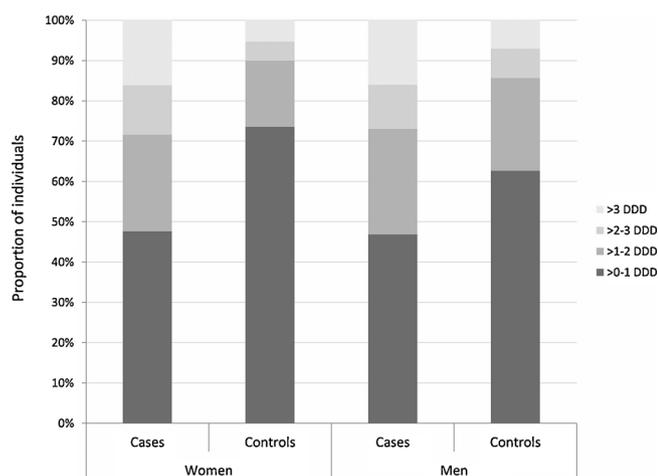
Active opioid for pain prescriptions were uncommon. Among men, 7.7% of cases vs 0.9% of controls had an active opioid for pain prescription on the day of overdose. Among women, the figures were 14% for cases and 1.1% for controls.

For both cases and controls with an active prescription for an opioid

**Table 1**  
Active and previous history of prescription drug use by drug class and sex for cases and controls.

	Active prescription at first overdose/index date				Past five year history			
	Men		Women		Men		Women	
	All cases (N = 6672)	Matched controls (N = 33,360)	All cases (N = 3292)	Matched controls (N = 16,460)	All cases (N = 6672)	Matched controls (N = 33,360)	All cases (N = 3292)	Matched controls (N = 16,460)
Opioid for pain	514(7.7%)	292(0.9%)	446(14%)	188(1.1%)	3034(46%)	5472(16%)	1821(55%)	3162(19%)
Short-term episode	73(1.4%)	34(1.2%) †	58(1.3%)	26(1.4%) †	N/A		N/A	
Long-term episode	441(86%)	258(88%)	388(87%)	162(86%)				
Dose < 90ME	251(49%)	190(65%)	253(57%)	146(78%)	N/A		N/A	
Dose 90-200ME	156(30%)	54(19%)	110(25%)	28(15%)				
Dose > 200ME	107(21%)	48(16%)	83(19%)	14(7.4%)				
Recent initiation of opioid for pain	53(0.79%)	26(0.08%)	33(1.0%)	20(0.12%)	N/A		N/A	
Recent discontinuation from long-term opioid therapy	90(1.3%)	37(0.11%)	59(1.8%)	27(0.16%)	N/A		N/A	
OAT	528(7.9%)	283(0.85%)	272(8.3%)	82(0.50%)	2291(34%)	484(1.5%)	1090(33%)	148(0.90%)
Benzos/Z-drugs	803(12%)	610(1.8%)	720(22%)	458(2.8%)	3291(49%)	4629(14%)	2190(67%)	3654(22%)
Antidepressants	1153(17%)	1609(4.8%)	1059(32%)	1455(8.8%)	3822(57%)	5017(15%)	2480(75%)	3955(24%)
Antipsychotics	808(12%)	606(1.8%)	558(17%)	244(1.5%)	2799(42%)	1667(5.0%)	1616(49%)	744(4.5%)
Gabapentin/Pregabalin	469(7.0%)	275(0.82%)	368(11%)	175(1.1%)	1636(25%)	1408(4.2%)	1024(31%)	860(5.2%)
Mood stabilizers/anti-epileptics	228(3.4%)	327(1.0%)	197(6.0%)	197(1.2%)	773(12%)	725(2.2%)	637(19%)	456(2.8%)
Muscle relaxants	147(2.2%)	127(0.38%)	164(5.0%)	100(0.61%)	1696(25%)	3486(10.4%)	1134(34%)	1967(12%)
Stimulants	126(1.9%)	174(0.52%)	55(1.7%)	79(0.48%)	589(8.8%)	704(2.1%)	266(8.1%)	282(1.7%)
Other sedating drugs <sup>1</sup>	32(0.5%)	31(0.090%)	31(0.94%)	11(0.07%)	286(4.3%)	147(0.44%)	200(6.1%)	69(0.42%)
Any sedating drugs	2246(34%)	2014(6.0%)	1540(47%)	1250(7.6%)	5427(81%)	11,408(34%)	2901(88%)	6830(42%)
Any sedating drugs excluding opioid	1773(27%)	1687(5.1%)	1331(40%)	1126(6.8%)	4905(74%)	8847(27%)	2742(83%)	5606(34%)
Multi-doctoring and multi-pharmacy	265(4.0%)	31(0.090%)	144(4.4%)	16(0.10%)	N/A		N/A	

<sup>1</sup> This class contains nabilone, chloral hydrate, and phenobarbital; all comparisons are statistically significant (< 0.01) unless indicated by †.



**Fig. 2.** Defined daily doses (DDDs) of sedating medications active on the overdose/index date, other than opioids or benzodiazepines/z-drugs.

for pain, the majority were in a long-term episode of use. Among cases, 6.0% of men and 10% of women were chronic opioid users at the time of overdose. Cases tended to have higher-dose prescriptions compared with controls. Few cases and controls experienced a recent initiation into opioid for pain therapy or a recent discontinuation from long-term chronic opioid therapy. These patterns were similar among men and women.

Fewer than 10% of cases had a prescription for OAT at the time of overdose and fewer than 5% of cases were seeking opioids for pain from multiple doctors or multiple pharmacies.

### 3.2. Past five-year history

The level of exposure to selected medication classes was

substantially higher when the time frame was expanded to the past five years. Similar to the patterns observed for active prescriptions, the most common medications were antidepressants (men 57%; women 75%), followed by benzodiazepines/z-drugs (men 49%; women 67%) and antipsychotics (men 42%; women 49%). Approximately a third of cases had a history of OAT (men 34%; women 33%) and many had been prescribed gabapentin and/or pregabalin (men 25%; women 31%). Overall, almost all cases had a history of use of at least one sedating medication.

History of opioid for pain use was prevalent in both groups, but significantly more common among cases than controls. Among men, 46% of cases vs 16% of controls had at least one past opioid for pain prescription, while for women, the figures were 55% for cases and 19% for controls.

Table 2 provides more details regarding patterns of past opioid for pain use among the study populations. Cases tended to have more long-term episodes of use compared with controls, as the majority of the latter group took opioids for pain on a short-term basis only. Among long-term users of opioids for pain, approximately 67% of cases and 45% of controls took opioids on a chronic basis, i.e., at least every other day or more often. The patterns were similar for men and women. Of all individuals who experienced an overdose during the study period, 14% of men and 20% of women had used opioids for pain on a chronic basis at some point in the past five years. In comparison, only 1.5% of men and 1.8% of women fell into this category among controls.

### 3.3. Morbidity burden

The higher level of use of selected prescription medications among cases can be at least partially explained by the significantly higher burden of prevalent mental health conditions in this population, as illustrated in Table 3.

With the exception of developmental disorders and cardiovascular disease for men, the prevalence of all comorbidities assessed both

**Table 2**  
Five-year history<sup>1</sup> of long-term/short-term use of opioids for pain (OAT therapy not included) by sex, comparing cases and controls.

Measure	Category	Men				Women			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
Number of people with past episodes of opioid use		6672		33,360		3292		16,460	
	No past episodes	3638	54.5	27888	83.6	1471	44.7	13298	80.8
	1 + past episodes	3034	45.5	5472	16.4	1821	55.3	3162	19.2
Episode types among people with at least 1 episode		3,034		5,472		1,821		3,162	
	Short-term use only	1638	54.0	4351	79.5	827	45.4	2496	78.9
	Long-term use only	893	29.4	729	13.3	636	34.9	427	13.5
	Short- & long-term use	503	16.6	392	7.2	358	19.7	239	7.6
Highest episode intensity <sup>2</sup> among people with at least one long-term episode		1,396		1,121		994		666	
	Occasional	210	15.0	320	28.5	163	16.4	183	27.5
	Intermittent	231	16.5	299	26.7	181	18.2	188	28.2
	Chronic	556	39.8	318	28.4	361	36.3	189	28.4
	Every day	399	28.6	184	16.4	289	29.1	106	15.9

<sup>1</sup> Includes active prescriptions at the time of overdose/index date <sup>2</sup>Episode intensity is based on the percentage of days on which there was medication supply: occasional (< 20% days on therapy), intermittent (20- < 50% days on therapy), chronic (50- < 90% days on therapy), and every day (≥90% days on therapy).

during the past year and past five years was significantly higher among cases. Approximately half of all cases had a recorded diagnosis of substance use disorder in the five years prior to overdose for both sexes. Other common morbidities were intravenous drug use (men 35%; women 40%), anxiety disorder (men 30%; women 45%), major depressive and related disorders (men 34%; women 52%), and alcohol use disorder (men 18%; women 21%). The five-year prevalence of diagnosed chronic pain was relatively low, at 10% for men and 14% for women for cases and approximately 3% for controls.

**4. Discussion**

This analysis examined select prescription drug histories among 9964 people who experienced an opioid-related drug overdose in 2015 and 2016 in British Columbia. We found that cases were more likely to have had a prescription for an opioid for pain and to have used prescription opioids on a long-term basis at some point over the past five years compared with matched controls. However, at the time of overdose, most people did not have an active prescription for an opioid for pain and approximately half had not filled any opioid prescriptions for pain in the past five years. The results also show that those who overdosed tended to have substantially more prescriptions for psychotropic

substances compared with controls. Current or past use of medications to treat opioid use disorder was not common among cases – the vast majority was not on OAT treatment at the time of overdose and most did not have any history of OAT therapy in the past five years.

It is widely thought that medical prescribers have directly contributed to the current crisis through increased prescribing of opioid medications over the last two decades and thus increased population exposure to these substances. In addition, several qualitative studies suggest some individuals may move from prescribed to illegal opioids if they are cut off from therapy (Daniulaityte et al., 2006; Harocopos and Allen, 2015; Kendall, 2017; Mars et al., 2014; Mui et al., 2014). We found few active long-term prescription “opioid for pain” users among our cases; of these active users, almost all were still continuing their therapy and did not experience any discontinuation in their prescription just prior to or at the time of overdose. These results suggest that interruption of opioid medications among chronic users is unlikely to have greatly contributed to the rise in fentanyl-related deaths. However, more individuals have used opioids on a long-term basis over the past five years compared with the number of cases who were active users, suggesting that previous exposure to opioids may still play an important role in shaping the current crisis. Specifically, it is possible that an increase in opioid prescribing over the past three decades may

**Table 3**  
Prevalence of diagnosed mental health and physical health comorbidities among cases and controls.

	Past year prevalence				Past five year prevalence			
	Men		Women		Men		Women	
	All cases	Matched controls	All cases	Matched controls	All cases	Matched controls	All cases	Matched controls
Major depressive and related disorders	904(14%)	866(2.6%)	690(21%)	726(4.4%)	2278(34%)	2619(7.9%)	1701(52%)	2181(13%)
Anxiety disorder	850(13%)	722(2.2%)	645(20%)	614(3.7%)	1979(30%)	2263(6.8%)	1488(45%)	1826(11%)
Adjustment disorder	411(6.2%)	225(0.67%)	313(9.5%)	193(1.2%)	1077(16%)	786(2.4%)	836(25%)	781(4.7%)
Bipolar	418(6.3%)	274(0.82%)	363(11%)	171(1.0%)	926(14%)	724(2.2%)	751(23%)	474(2.9%)
Schizophrenia	467(7.0%)	309(0.93%)	241(7.3%)	63(0.38%)	768(12%)	536(1.6%)	387(12%)	145(0.88%)
Personality disorder	218(3.3%)	53(0.16%)	171(5.2%)	26(0.16%)	504(7.6%)	180(0.54%)	354(11%)	108(0.66%)
ADHD	125(1.9%)	117(0.35%)	40(1.2%)	50(0.30%)	329(4.9%)	363(1.1%)	109(3.3%)	136(0.83%)
Developmental disorders	9(0.13%)	3(0.01%)	20(0.61%)	5(0.03%)	34(0.51%)	30(0.09%)	39(1.2%)	18(0.11%)
Substance use disorder	2407(36%)	572(1.7%)	1242(37%)	129(0.78%)	3448(52%)	1102(3.3%)	1740(53%)	325(2.0%)
Alcohol use disorder	570(8.5%)	143(0.43%)	314(9.5%)	31(0.19%)	1222(18%)	500(1.5%)	684(21%)	145(0.88%)
IDU	1217(18%)	162(0.49%)	720(22%)	39(0.24%)	2335(35%)	509(1.5%)	1331(40%)	169(1.0%)
IDU + IRI	423(6.3%)	36(0.11%)	258(7.8%)	9(0.05%)	1048(16%)	138(0.41%)	638(19%)	46(0.28%)
Cardiovascular disease	337(5.1%) <sup>†</sup>	1514(4.5%)	193(5.9%)	643(3.9%)	681(10%)	3072(9.2%)	409(12%)	1348(8.2%)
Respiratory disease	278(4.2%)	574(1.7%)	277(8.4%)	336(2.0%)	659(9.9%)	1451(4.3%)	590(18%)	967(5.9%)
Chronic pain	279(4.2%)	320(0.96%)	218(6.6%)	195(1.2%)	671(10%)	1059(3.2%)	471(14%)	621(3.8%)

All comparisons between cases and matched controls in Table 3 are statistically significant (p < 0.01) unless marked by “†”; ADHD = attention deficit hyperactivity disorder; IDU = injection drug use; IRI = injecting-related infections.

have indirectly contributed to the development of the current surge in illicit drug overdose deaths by increasing the number of individuals who have used opioid drugs and who thus may be at risk of overdose.

It is important to keep in mind that regulating opioid prescribing results in a lower level of availability of high quality prescription medications, with two opposite effects: while some prescription-opioid related deaths may have been prevented, a lower level of pharmaceutical drug supply available for diversion leads some individuals who use drugs to turn to illicitly-produced opioids (Martin et al., 2018), thus possibly exposing them to products contaminated with fentanyl and in turn increasing their risk of opioid overdose. Unfortunately, the extent to which these forces play out in BC has not been quantified. However, the finding that most individuals experiencing an overdose did not have an active prescription for opioids at the time of overdose suggests that regulating opioid prescribing may have a limited, short-term impact on the current crisis of unprecedented increases in drug-related overdoses fueled by contamination of the illegal drug supply.

Our study is among the first to examine the patterns of use of various classes of prescription medications among individuals experiencing an opioid-related overdose during the current epidemic. Comparisons with other study populations are complicated by the heterogeneity of research on drug overdoses – e.g., variability in case definitions to include or exclude non-opioid overdoses, prescription-only overdoses, and/or intentional overdoses – and the rapidly changing nature of the opioid overdose crisis across jurisdictions. Importantly, prior studies have focused on fatal overdose deaths or on prescription drug-related opioid overdoses, which represent only a minority of all current drug overdoses, and thus results from such studies may not be generalizable to all overdose events.

Our findings are generally comparable to those from previous studies. Among Canadian sources, a study from Ontario examining opioid-related accidental deaths from 2006 to 2008 found that 33% had a prescription for an opioid for chronic pain and 7.2% had a prescription for acute pain (Johnson et al., 2013). Research from BC on opioid-related deaths (excluding OAT medications) in 2013 reported that 54% of women and 29% of men had an active opioid prescription in the 60 days before death (Gladstone et al., 2015). Both of these analyses predate the current crisis and included a relatively small number of deaths, largely capturing prescription-opioid related deaths. Among all people experiencing opioid-related overdose in a large American health network between 2005 and 2015, 68% had been prescribed opioids in the previous 12 months (Boscarino et al., 2016). An epidemiological analysis of prescription histories of individuals experiencing a fentanyl-related drug overdose death in Ohio in 2014 found that 28% received a prescription opioid in the month prior to death (Spies et al., 2015).

Compared to controls, cases were more likely to be prescribed sedating medications, and, if prescribed, received higher doses. Sedating medications can act both as possible contributors to overdose (e.g., through synergistic respiratory depression when combined with other medications (Gomes et al., 2017; Park et al., 2015; Sun et al., 2017) and as potential therapies (e.g., treatment of underlying mental illness such as anxiety, depression, and psychosis, the symptoms of which also commonly include sleep disturbances). A particularly high-risk situation for overdose is the combination of sedating prescription medications with illegal opioids, as this also adds a lack of physician knowledge of co-ingestion to the underlying risk associated with the variable potency of the illegal drug supply.

While our analysis did not specifically evaluate sex differences, there were notable differences in prescription drug use and comorbidities between men and women. At the time of overdose, female cases had approximately twice as high levels of active prescriptions for opioids for pain, antidepressants, and benzodiazepines/z-drugs compared with male cases. However, there were not substantial dose differences among those who had at least one sedating medication. Past exposures for many psychotropic drugs remained higher for women, but with smaller differences. Similarly, prevalence of diagnosed anxiety

and depressive disorders was higher for females than males for both cases and controls.

In our cohort, benzodiazepines and z-drugs were the most commonly prescribed non-opioid sedating medication, although sedating anti-depressants, antipsychotics, gabapentinoids, and mood stabilizers/anti-epileptics were all more frequently prescribed to cases than controls. It is therefore important to consider the potential additive or synergistic role of prescribed medications from these classes in contributing to overdose (Gomes et al., 2017; Lyndon et al., 2017; Oliva et al., 2017; Zedler et al., 2014). As these medications have therapeutic indications; however, it is essential that their use not be framed solely in terms of risk, lest patients lose access to beneficial and necessary therapies. This last point is of particular concern as, similar to illegally produced opioids such as fentanyl, there is increasing availability of illegally produced benzodiazepines and theoretical risk of displacement of patients to the illegal market (Abouchedid et al., 2018; Häkkinen et al., 2014; Arens et al., 2016).

It is likely that the higher level of use of the examined prescription medication classes among cases can be at least partially explained by the significantly higher burden of psychiatric comorbidities in this population. The prevalence of all analyzed mental disorders was approximately five to ten times higher in the population with a history of overdose compared to controls; the differences in substance use disorders and alcohol use disorder were even more pronounced. This is in keeping with a systematic review of risk factors for overdose on prescription opioids, which found a four-fold increase in risk associated with psychiatric disorders and a five-fold increase with substance use disorders (Brady et al., 2017). In recent years, coordination or integration of treatment of substance use disorders, mental disorders and physical disorders have been increasingly recommended. Such an integrated approach may not only help improve outcomes, but also to avoid other adverse events, such as overdoses (Canadian Centre on Substance Abuse, 2009).

An indicator of high-risk and severe substance use is injection drug use (IDU). The prevalence of being identified as using injection drugs among those who had an overdose was almost as high as being identified as having a substance use disorder – approximately half of cases were identified as IDU in the five years previous to the overdose. The number of IDU was low in the control population and much lower than the prevalence of substance use disorder, suggesting less severe and less risky use of substances among controls.

These findings reflect the importance of considering the indication for underlying mental health conditions when examining rates of prescription medications in people who overdose, especially for substance use disorders. It is therefore not surprising that OAT use is higher among cases than controls, or that one in three people who experience an overdose have been prescribed OAT in the preceding five years. The proportion of individuals receiving active OAT therapy is similar to the frequency of OAT use (8.6%) observed among people who died of fatal overdose in Canada in 2006–2008 (Madadi et al., 2013). Thus, our results provide reassurance that OAT alone or in combination with other medications is not a major component of the current opioid overdose crisis, and supports the US Food and Drug Administration's call not to deny OAT to individuals currently receiving other CNS depressants (U.S. Food and Drug Administration, 2016). While approximately one third of cases had been dispensed OAT in the previous five years in our study, less than 10% were still receiving it at the time of overdose. Receiving OAT is associated with a substantially reduced risk of mortality (Bell et al., 2009; Larochelle et al., 2018). The response to the opioid overdose crisis must therefore identify and address patient, provider, and system-level reasons for not initiating and for discontinuing therapy, with a goal of lessening and removing barriers to treatment. It must also be recognized that not all individuals who use opioids are eligible, ready or interested in OAT, and developing alternative public health strategies to reach them is critical.

Similar to mental health diagnoses, we found that prevalence of

chronic pain was significantly higher among cases than controls, which may help explain higher levels of use of opioids for pain among cases. Prevalence estimates in our study were lower than what was reported through surveys of the general Canadian population (Reitsma et al., 2012; Schopflocher et al., 2011); however, our cohort was younger and predominantly male, while chronic pain diagnoses tend to be more common among older women. Nevertheless, our five-year prevalence results of 10% for men and 14% for women among cases are consistent with 2007/08 figures from the Canadian Community Health Survey, which reported prevalence of 9% for men and 12% for women aged 12 to 44 years. However, chronic pain diagnosis is poorly captured by administrative data and we may have underestimated the true prevalence among our study population (Ramage-Morin and Gilmour, 2010).

This study has several limitations. The majority of overdose events were identified based on administrative data, which do not capture any events that occurred without contact with medical, emergency, or coroners' services. This would tend to exclude people with even fewer encounters with health services and less access to opioid prescriptions. Inconsistent coding standards and varying ways of information collection across contributing data sources may have resulted in misclassification or misidentification of some overdose events. Our data sources also did not allow us to distinguish between overdose cases that were related to prescription opioids vs illicit opioids. While fatal overdose cases are restricted to those obtained illicitly, we were unable to exclude prescription-only overdoses from non-fatal cases. However, BC Coroners reported relatively stable rates of prescription-opioid related deaths in BC of approximately 75 deaths per year (McLarnon, 2017), compared with a recent rapid rise to 1446 illicit drug overdose deaths in 2017, with 81% having fentanyl detected (British Columbia Coroners Service, 2017). Personal communication with the BC Coroner's Office has confirmed that prescription-opioid related deaths in BC have been relatively stable between 2010 and 2016. We estimate that less than 5% of all fatal drug overdose deaths in BC were related to prescription opioids in 2016. Given the correlation between fatal and non-fatal overdoses, most of the overdose events captured in our dataset are likely related to illegal drug supply. Further, the demographic characteristics of the study population (mostly young males) are consistent with the population at risk of illicit drug overdoses, rather than prescription opioid overdoses, who tend to be older individuals and more likely to be women. Only medications dispensed in community pharmacies could be assessed; prescriptions written but not filled, and medications dispensed in hospital were not captured. Additionally, dispensed medications are not necessarily consumed, and therefore the results may overestimate consumption. On the other hand, we were also unable to capture use of diverted prescription opioids and thus may have underestimated consumption. Because we relied on fee codes to identify OAT, these results may slightly overestimate opioids for pain and underestimate OAT in the situation where opioids without an OAT fee code (e.g., long-acting oral morphine, hydromorphone) were used off-label to treat opioid use disorder. Lastly, this study presents descriptive results only, precluding attribution of association or causality between covariates and risk of overdose.

In conclusion, we found that active opioid for pain prescriptions are not common among people who experienced an opioid-related drug overdose. While overdose cases were more likely to fill opioid for pain prescriptions, the majority did not have an active opioid medication prescription at the time of overdose, and almost half did not have a history of any opioid prescriptions in the past five years. These findings suggest that while regulation and enforcement of healthcare providers' prescribing practices may improve appropriate prescribing and reduce the use of opioids for management of chronic pain, it will likely have limited short-term impact on reducing the fentanyl-related overdose burden and could have the unintended consequences of pushing people to seek illegal and unregulated supplies. Future research should focus on quantifying the relative contribution of any prescription-related risk

factors to illegal drug overdose.

## Role of the Funding Source

Nothing declared.

## Contributors

Kate Smolina originated the study concept and drafted the manuscript. Alexis Crabtree advised on all aspects of the study and contributed to manuscript preparation and revisions. Mei Chong, Bin Zhao and Mina Park conducted statistical analyses and reviewed drafts of the manuscript. Christopher Mill contributed to manuscript preparation and revisions. Christian Schuetz advised on all aspects of the study and provided critical revision of the manuscript. All authors approved the final version for publication.

## Conflict of interest

No conflict declared.

## Acknowledgements

The authors thank the British Columbia Overdose Surveillance Task Group for their guidance throughout the development of the Provincial Overdose Cohort and for collective interpretation of results. The cohort was assembled by the Provincial Overdose Cohort Design Group and analysis-ready data was generated by the Data Preparation Team. Data for this publication was provided by the BC Coroner's Service, the BC Emergency Health Services, the BC Drug and Poison Information Centre, the BC Ministry of Health (PharmaNet, Medical Services Plan, the National Ambulatory Care and R Network (NACRS) and the BC Discharge Abstract Database) and Emergency Departments in Interior, Island and Northern Health Authorities. The authors also thank other members of the Prescribing Patterns Analytic Team (Tim Chu, Vancouver Coastal Health; Andrew Pacey, First Nations Health Authority) for contributions to development of metrics and concepts related to this analysis. The authors would also like to thank Mark Tyndall of the BC Centre for Disease Control for critical review of this manuscript. Mental health diagnoses were based on algorithms developed by the BC Ministry of Health Mental Health Working Group wherever available.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugalcdep.2018.09.019>.

## References

- Aboucheid, R., Gilks, T., Dargan, P.I., Archer, J.R.H., Wood, D.M., 2018. Assessment of the availability, cost, and motivations for use over time of the new psychoactive substances-benzodiazepines diclazepam, flubromazepam, and pyrazolam-in the UK. *J. Med. Toxicol.* 14, 134–143.
- Arens, A.M., van Wijk, X.R., Vo, K.T., Lynch, K.L., Wu, A.B., Smolin, C.G., 2016. Adverse effects from counterfeit alprazolam tablets. *JAMA Intern. Med.* 176, 1554–1555.
- Bell, J.R., Butler, B., Lawrance, A., Batey, R., Salmelainen, P., 2009. Comparing overdose mortality associated with methadone and buprenorphine treatment. *Drug Alcohol Depend.* 104, 73–77.
- Bohnert, A.S., Valenstein, M., Bair, M.J., Ganoczy, D., McCarthy, J.F., Ilgen, M.A., Blow, F.C., 2011. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA* 305, 1315–1321.
- Boscarino, J.A., Kirchner, H.L., Pitcavage, J.M., Nadipelli, V.R., Ronquest, N.A., Fitzpatrick, M.H., Han, J.J., 2016. Factors associated with opioid overdose: a 10-year retrospective study of patients in a large integrated health care system. *Subst. Abuse Rehabil.* 7, 131–141.
- Brady, J.E., Giglio, R., Keyes, K.M., DiMaggio, C., Li, G., 2017. Risk markers for fatal and non-fatal prescription drug overdose: a meta-analysis. *Inj. Epidemiol.* 4, 24.
- British Columbia Centre for Disease Control, 2018. Chronic Disease Dashboard Case Definitions. <http://www.bccdc.ca/health-info/disease-system-statistics/chronic>

- disense-dashboard#Case-Definitions.
- British Columbia Coroners Service, 2018. **Fentanyl-Detected Illicit Drug Overdose Deaths.** <https://www2.gov.bc.ca/assets/gov/public-safety-and-emergency-services/death-investigation/statistical/fentanyl-detected-overdose.pdf>.
- British Columbia Coroners Service, 2017. **Illicit Drug Overdose Deaths in BC, January 1, 2007 - December 31, 2016.** Office of the Chief Coroner, Burnaby, BC.
- Canadian Centre on Substance Abuse, 2009. **Substance Abuse in Canada: Concurrent Disorders.** Canadian Centre on Substance Abuse, Ottawa, ON.
- Chahua, M., Sordo, L., Barrio, G., Domingo-Salvany, A., Brugal, M.T., Molist, G., de la Fuente, L., Bravo, M.J., 2014. Non-fatal opioid overdose and major depression among street-recruited young heroin users. *Eur. Addict. Res.* 20, 1–7.
- Clinical Handbook of Psychotropic Drugs, 2015. **Clinical Handbook of Psychotropic Drugs**, 21st edition ed. Hogrefe Publishing, Toronto, Canada.
- College of Physicians and Surgeons of British Columbia, 2016. **Professional Standards and Guidelines – Safe Prescribing of Drugs With Potential for Misuse/Diversion.**
- Daniulaityte, R., Carlson, R.G., Kenne, D.R., 2006. Initiation to pharmaceutical opioids and patterns of misuse: preliminary Qualitative findings obtained by the Ohio Substance Abuse Monitoring Network. *J. Drug Issues* 36, 787–808.
- Dowell, D., Haegerich, T.M., Chou, R., 2016. **CDC Guideline for prescribing opioids for chronic pain—United States, 2016.** *JAMA* 315, 1624–1645.
- European Monitoring Centre for Drugs and Drug Addiction, 2017. **Statistical Bulletin 2017.**
- Fischer, B., Brissette, S., Brochu, S., Bruneau, J., El-Guebaly, N., Noël, L., Rehm, J., Tyndall, M., Wild, C., Mun, P., Haydon, E., Baliunas, D., 2004. Determinants of overdose incidents among illicit opioid users in 5 Canadian cities. *CMAJ* 171, 235–239.
- Fischer, B., Vojtila, L., Rehm, J., 2018. The 'fentanyl epidemic' in Canada - some cautionary observations focusing on opioid-related mortality. *Prev. Med.* 107, 109–113.
- Gladstone, E.J., Smolina, K., Weymann, D., Rutherford, K., Morgan, S.G., 2015. Geographic variations in prescription opioid dispensations and deaths among women and men in British Columbia. *Canada. Med. Care* 53, 954–959.
- Glanz, J.M., Narwaney, K.J., Mueller, S.R., Gardner, E.M., Calcaterra, S.L., Xu, S., Breslin, K., Binswanger, I.A., 2018. Prediction model for two-year risk of opioid overdose among patients prescribed chronic opioid therapy. *J. Gen. Intern. Med.* 33, 1646–1653.
- Gomes, T., Juurlink, D., Yao, Z., Camacho, X., Paterson, J.M., Singh, S., Dhalla, I., Sproule, B., Mamdani, M., 2014. Impact of legislation and a prescription monitoring program on the prevalence of potentially inappropriate prescriptions for monitored drugs in Ontario: A time series analysis. *CMAJ Open* 2, E256–E261.
- Gomes, T., Juurlink, D.N., Antoniou, T., Mamdani, M.M., Paterson, J.M., van den Brink, W., 2017. Gabapentin, opioids, and the risk of opioid-related death: a population-based nested case-control study. *PLoS Med.* 14, e1002396.
- Government of British Columbia, 2016. **Provincial Health Officer Declares Public Health Emergency.** Government of British Columbia, Victoria, BC.
- Groot, E., Kouyoumdjian, F.G., Kiefer, L., Madadi, P., Prevost, B., Jhirad, R., Huyer, D., Snowdon, V., Persaud, N., 2016. Drug toxicity deaths after release from incarceration in Ontario, 2006–2013: review of Coroner's Cases. *PLoS One* 11, e0157512.
- Häkkinen, M., Vuori, E., Kalso, E., Gergov, M., Ojanperä, I., 2014. Profiles of pregabalin and gabapentin abuse by postmortem toxicology. *Forensic Sci. Int.* 241, 1–6.
- Hall, A.J., Logan, J.E., Toblin, R.L., Kaplan, J.A., Kraner, J.C., Bixler, D., Crosby, A.E., Paulozzi, L.J., 2008. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA* 300, 2613–2620.
- Harocopos, A., Allen, B., 2015. Routes into opioid analgesic misuse: emergent typologies of initiation. *J. Drug Issues* 45, 385–395.
- Janjua, N.Z., Islam, N., Kuo, M., Yu, A., Wong, S., Butt, Z.A., Gilbert, M., Buxton, J., Chapinal, N., Samji, H., Chong, M., Alvarez, M., Wong, J., Tyndall, M.W., Krajden, M., Team, B.C., Hepatitis Testers Cohort Team, 2018. Identifying injection drug use and estimating population size of people who inject drugs using healthcare administrative datasets. *Int. J. Drug Policy* 55, 31–39.
- Johnson, E.M., Lanier, W.A., Merrill, R.M., Crook, J., Porucznik, C.A., Rolfs, R.T., Sauer, B., 2013. Unintentional prescription opioid-related overdose deaths: description of decedents by next of kin or best contact, Utah, 2008–2009. *J. Gen. Intern. Med.* 28, 522–529.
- Kendall, P., 2017. **BC opioid substitution treatment system: performance measures 2014/2015–2015/2016.** British Columbia Office of the Provincial Health Officer.
- Kerr, T., Fairbairn, N., Tyndall, M., Marsh, D., Li, K., Montaner, J., Wood, E., 2007. Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. *Drug Alcohol Depend.* 87, 39–45.
- Laroche, M.R., Liebschutz, J.M., Zhang, F., Ross-Degnan, D., Wharam, J.F., 2016. **Opioid Prescribing After Nonfatal Overdose and Association With Repeated Overdose: A Cohort Study.** *Ann. Intern. Med.* 164, 1–9.
- Laroche, M.R., Bernson, D., Land, T., Stopka, T.J., Wang, N., Xuan, Z., Bagley, S.M., Liebschutz, J.M., Walley, A.Y., 2018. Medication for opioid use disorder after non-fatal opioid overdose and association with mortality: a cohort study. *Ann. Intern. Med.* 169, 137–145.
- Lyndon, A., Audrey, S., Wells, C., Burnell, E.S., Ingle, S., Hill, R., Hickman, M., Henderson, G., 2017. Risk to heroin users of polydrug use of pregabalin or gabapentin. *Addiction* 112, 1580–1589.
- Madadi, P., Hildebrandt, D., Lauwers, A.E., Koren, G., 2013. Characteristics of opioid-users whose death was related to opioid-toxicity: a population-based study in Ontario, Canada. *PLoS One* 8, e60600.
- Mars, S.G., Bourgeois, P., Karandinos, G., Montero, F., Ciccarone, D., 2014. Every' never' I ever said came true': transitions from opioid pills to heroin injecting. *Int. J. Drug Policy* 25, 257.
- Martin, J., Cunliffe, J., Decary-Hetu, D., Aldridge, J., 2018. Effect of restricting the legal supply of prescription opioids on buying through online illicit marketplaces. *Interrupted time series analysis.* *BMJ* 361, k2270.
- McLarnon, M., 2017. **Preventing Pharmaceutical Opioid-associated Mortality in British Columbia: a Review of Prescribed Opioid Overdose Deaths, 2009–2013.** British Columbia Ministry of Health, Victoria, B.C.
- Mui, H.Z., Sales, P., Murphy, S., 2014. Everybody's doing it: initiation to prescription drug misuse. *J. Drug Issues* 44, 236–253.
- Nadpara, P.A., Joyce, A.R., Murrelle, E.L., Carroll, N.W., Carroll, N.V., Barnard, M., Zedler, B.K., 2017. Risk factors for serious prescription opioid-induced respiratory depression or overdose: comparison of commercially insured and Veterans Health Affairs populations. *Pain Med.* 19, 79–96.
- Nielsen, S., Degenhardt, L., Hoban, B., Gisev, N., 2016. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidemiol. Drug Saf.* 25, 733–737.
- Oliva, E.M., Oliva, E.M., Bowe, T., Tavakoli, S., Martins, S., 2017. Development and applications of the Veterans Health Administration's Stratification Tool for Opioid Risk Mitigation (STORM) to improve opioid safety and prevent overdose and suicide. *Psychol. Serv.* 14, 34–49.
- Otterstatter, M.C., Crabtree, A., Dobrer, S., Kinniburgh, B., Klar, S., Leamon, A., May-Hadford, J., Mill, C., Park, M., Tu, A.W., Zheng, L., 2018. Patterns of health care utilization among people who overdosed from illegal drugs: A descriptive analysis using the BC Provincial Overdose Cohort. *Health Promot. Chronic Dis. Prev. Can.* 38, 328–333.
- Park, T.W., Saitz, R., Ganoczy, D., Ilgen, M.A., Bohnert, A.S., 2015. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics. *Case-cohort study.* *BMJ* 350, h2698.
- Ramage-Morin, P.L., Gilmour, H., 2010. Chronic pain at ages 12 to 44. *Health Rep.* 21, 53.
- Ray, W.A., Chung, C.P., Murray, K.T., Hall, K., Stein, C.M., 2016. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. *JAMA* 315, 2415–2423.
- Reitsma, M.L., Tranmer, J.E., Buchanan, D.M., VanDenKerkhof, E.G., 2012. The epidemiology of chronic pain in Canadian men and women between 1994 and 2007: results from the longitudinal component of the National Population Health Survey. *Pain Res. Manag.* 17, 166–172.
- Rudd, R.A., Aleshire, N., Zibbell, J.E., Gladden, R.M., 2016a. Increases in drug and opioid overdose deaths—United States, 2000–2014. *MMWR Morb. Mortal. Wkly. Rep.* 64, 1378–1382.
- Rudd, R.A., Seth, P., David, F., Scholl, L., 2016b. Increases in drug and opioid-involved overdose deaths — united States, 2010–2015. *MMWR Morb. Mortal. Wkly. Rep.* 65, 1445–1452.
- Schopflocher, D., Taenzer, P., Jovey, R., 2011. The prevalence of chronic pain in Canada. *Pain Res. Manag.* 16, 445–450.
- Seth, P., Rudd, R.A., Noonan, R.K., Haegerich, T.M., 2018. Quantifying the epidemic of prescription opioid overdose deaths. *Am. J. Public Health* 108, 500–502.
- Shah, N.G., Lathrop, S.L., Reichard, R.R., Landen, M.G., 2008. Unintentional drug overdose death trends in New Mexico, USA, 1990–2005: combinations of heroin, cocaine, prescription opioids and alcohol. *Addiction* 103, 126–136.
- Silva, K., Schragger, S.M., Keckojevic, A., Lankenau, S.E., 2013. Factors associated with history of non-fatal overdose among young nonmedical users of prescription drugs. *Drug Alcohol Depend.* 128, 104–110.
- Slavova, S., Costich, J.F., Bunn, T.L., Luu, H., Singleton, M., Hargrove, S.L., Triplett, J.S., Quesinberry, D., Ralston, W., Ingram, V., 2017. Heroin and fentanyl overdoses in Kentucky: epidemiology and surveillance. *Int. J. Drug Policy* 46, 120–129.
- Smolina, K., Gladstone, E.J., Rutherford, K., Morgan, S.G., 2016. Patterns and trends in long-term opioid use for non-cancer pain in British Columbia, 2005–2012. *Can. J. Public Health* 107, e404–e409.
- Spies, E.P.A., Garcia-Williams, A., Halpin, J., Gladden, R.M., Zibbell, J., McCarty, C.L., 2015. **Undetermined Risk Factors for Fentanyl-related Overdose Death - Ohio, 2015 (EpiAid 2016-003).** Centre for Disease Control and Prevention (CDC), Atlanta, GA.
- Sun, E.C., Dixit, A., Humphreys, K., Darnall, B.D., Baker, L.C., Mackey, S., 2017. Association between concurrent use of prescription opioids and benzodiazepines and overdose. *Retrospective analysis.* *BMJ* 356, j760.
- Tian, T.Y., Zlateva, I., Anderson, D.R., 2013. Using electronic health records data to identify patients with chronic pain in a primary care setting. *J. Am. Med. Inform. Assoc.* 20, e275–280.
- Tonelli, M., Wiebe, N., Fortin, M., Guthrie, B., Hemmelgarn, B.R., James, M.T., Klarenbach, S.W., Lewanczuk, R., Manns, B.J., Ronksley, P., Sargious, P., Straus, S., Quan, H., Alberta Kidney Disease Network, 2015. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med. Inform. Decis. Mak.* 15, 31.
- U.S. Food & Drug Administration, 2016. **FDA Drug Safety Communication: FDA Urges Caution About Withholding Opioid Addiction Medications From Patients Taking Benzodiazepines or CNS Depressants: Careful Medication Management Can Reduce Risks.** <https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm>.
- Unick, G.J., Rosenblum, D., Mars, S., Ciccarone, D., 2013. Intertwined epidemics: national demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993–2009. *PLoS One* 8, e54496.
- Vivolo-Kantor, A.M., Seth, P., Gladden, R.M., Mattson, C.L., Baldwin, G.T., Kite-Powell, A., Coletta, M.A., 2018. Vital signs: trends in emergency department visits for suspected opioid overdoses - United States, July 2016–September 2017. *MMWR Morb. Mortal. Wkly. Rep.* 67, 279–285.
- World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology, 2018. **Definitions and General Considerations.** [https://www.whocc.no/ddd/definition\\_and\\_general\\_considera/](https://www.whocc.no/ddd/definition_and_general_considera/).
- Zedler, B., Xie, L., Wang, L., Joyce, A., Vick, C., Kariburyo, F., Rajan, P., Baser, O., Murrelle, L., 2014. Risk factors for serious prescription opioid-related toxicity or overdose among Veterans Health Administration patients. *Pain Med.* 15, 1911–1929.