

Preventing Pharmaceutical Opioid-Associated Mortality in British Columbia:

A Review of Prescribed Opioid Overdose Deaths, 2009-2013

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Forward

Opioid related overdoses and deaths are tragic events and important indicators of the challenges and complexities of society's efforts to manage these naturally derived and synthetically produced substances. Pharmaceutical opioids are important therapeutic agents but can also have serious and potentially fatal health risks. This report describes information derived from a review of British Columbia Coroners Service investigations for the years 2009 to 2013 with respect to prescribed pharmaceutical opioid related deaths. The review was conducted in 2014, prior to the current opioid overdose public health emergency associated with illegally produced fentanyl and related analogues.

While being overshadowed by the recent epidemic associated with illegally produced opioids, this report demonstrates that deaths related to prescribed pharmaceutical opioids are also a concern, resulting in about 75 prescribed pharmaceutical opioid-associated deaths per year. This accounted for approximately 1 in 5 of the total number of accidental drug poisoning deaths in the province during the study period.

The results of this study help our understanding of this complex problem, point the way to further investigations of the risk factors and causes and suggest possible preventive actions. The rise in opioid use disorder over the past twenty years has been linked in part to prescribing practices, indicating a need to make prescribing safer and more effective. This includes being much more selective about opioid prescribing, avoiding combinations with sedatives, minimizing dosing and duration, and improving the opioid overdose/use disorder system of prevention and care.

We look forward to feedback on the report and suggestions for preventing these unfortunate deaths.

The collaboration and diligence of the staff of the Ministry of Health and the BC Coroners Service that made this study possible is most appreciated, and we especially want to thank Dr. Megan McLarnon for the hard work of pulling of all this information together, conducting the analysis and primarily writing the report.

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1 Executive Summary

Project description

Addressing morbidity and mortality associated with pharmaceutical opioids is a critical public health issue in British Columbia. This report presents key findings of an initial investigation of unintentional overdose deaths involving prescribed pharmaceutical opioids. The research design involved a retrospective review of pharmaceutical opioid-associated overdose fatalities of BC residents between 2009 and 2013 and linkage between BC Coroners Service file information and administrative health datasets, including prescription drug dispensation history, medical services utilization, and hospitalizations.

Purpose, key questions and scope

The primary goal of this work was to analyze information about people who died while taking prescribed opioids, as a distinct subset of all opioid overdose deaths, because the potential implications for overdose and death prevention may differ depending on whether or not the drugs were obtained and administered with the oversight of a health care provider. The objectives were to quantify and describe characteristics of unintentional prescribed pharmaceutical opioid overdose deaths in BC and any discernable trends over time, to explore the geographical distribution of deaths, to identify factors characterizing decedents, and to describe contexts and characteristics of fatal overdoses. Suicides, deaths involving illegal opioids, and deaths involving only pharmaceutical opioids taken without a valid prescription were out of scope.

Key findings

Annual Deaths and Mortality Rate

- There was an annual average of 74.5 prescribed pharmaceutical opioid-associated deaths in BC over the study period, corresponding to a mean annual age-standardized mortality rate of 1.51 per 100,000 population.
- Deaths involving prescribed pharmaceutical opioids account for 20.5%, or approximately 1 in 5, of the total number of accidental drug poisoning deaths in the province between 2009 and 2012

Socio-demographic Characteristics

- Overall fatal prescribed pharmaceutical opioid overdoses were more common among men than women (55.6 percent male, 44.4 percent female), but female fatalities slightly exceeded males for people less than 40 years of age.
- Women's risk for fatal overdose involving prescribed pharmaceutical opioids is comparatively higher than their risk for fatal overdose involving non-prescribed pharmaceutical opioids.
- Prescribed pharmaceutical opioid overdoses were most common among middle-aged British Columbians, with two thirds of deaths occurring among individuals between the ages of 40 and 59. On average, there was more than 35 years of potential life lost per individual death.

Geographic Distribution

- Consistent with previous reports, analyses showed regional variation across BC, with an elevated mortality rate in the Interior Health region and lower mortality in the Fraser Health region relative to the provincial average.
- The mortality rate in BC health authorities was variable between 2009 and 2012, potentially increasing in Vancouver Island and potentially decreasing in Interior Health. Based on earlier work by Interior Health the elevated rates were brought to the attention of the physicians in that region by the medical health

officer. It will be important to continue tracking mortality rates in each region over time to identify any potential trends.

- The highest mortality rates in the province were in the Okanagan and Thompson Cariboo Shuswap HSDAs, both in the Interior region, and in the North Vancouver Island HSDA in the Island region. The ASMR in each of these three HSDAs exceeded the provincial average.
- Further analysis to examine rates of drug prescribing, such as by geographic region, group of practitioners (by region/specialty etc.) or by individual practitioners to determine whether there is an association with a higher than expected number of decedents is warranted.

Context and Characteristics

- The vast majority of overdoses leading to death occurred in private residences.
- Approximately 15 percent of decedents received some form of medical intervention prior to death (e.g., ambulance services, hospital emergency room).
- In the vast majority of cases (97%), toxicology data showed that these fatal overdoses involved other substances in addition to prescribed pharmaceutical opioids.
- The pharmaceutical opioid involved in the greatest number of deaths was methadone prescribed for opioid substitution treatment, which was present in over 30% of fatalities. Almost 25% of deaths involved codeine.
- The presence of multiple prescribed pharmaceutical opioids was relatively uncommon (13% of cases); however in 24% of the fatalities toxicology testing detected the presence of a pharmaceutical opioid for which decedent did not hold an active prescription within 60 days of death, indicating that pharmaceutical opioids are being obtained from other sources and being consumed concurrently.
- Concurrent involvement of other pharmaceutical drug classes was common, with antidepressants detected in over 40 percent of cases and benzodiazepines detected in over 30 percent of cases.
- The anticonvulsant and antipsychotic drug classes were both notable in that a single medication accounted for most of the cases for the entire class. Gabapentin, which is classified as an anticonvulsant but is most commonly prescribed for chronic pain, accounted for approximately three-quarters of the cases in which an anticonvulsant was detected, while quetiapine, again often prescribed for chronic pain, accounted for two-thirds of the cases in which an antipsychotic was detected.
- Analysis by combinations of these drug classes would further help define potential problematic drug interactions.
- Alcohol was present in 11.4% of deaths in the study cohort.
- Illegal drugs were relatively uncommon, with the exception of cocaine, which was involved in approximately 38% of deaths. Given the potential pharmacological interactions between cocaine and opioids with respect to deaths consequent to heart arrhythmias, analyzing the opioid dose level in the cocaine associated group would be of interest.

Prescription drug dispensation history

- Among decedents prescribed pharmaceutical opioids for pain management, more than 25 percent were receiving daily doses exceeding 200 morphine milligram equivalents (MME), and 44 percent were receiving daily doses exceeding 120 MME. These dosages are the thresholds for increased risk outlined in clinical practice guidelines in BC and Washington State, respectively.
- Of the decedents on methadone maintenance treatment, 10% had initiated methadone treatment within two weeks of death. Overdose on initiation of methadone is a known risk; hence this finding indicates an opportunity to further improve methadone assisted treatment initiation, including having naloxone available as part of initiation.
- Most methadone-associated deaths occurred in individuals accessing methadone via daily witnessed ingestions, and thus within the context of daily contact with a health care provider (i.e., pharmacist).

Medical History

- Contact with the health care system was frequent for people who died of an overdose. On average, individuals who experienced a fatal overdose involving prescribed pharmaceutical opioids interacted with a health care professional approximately once a week in the year prior to death.
- Just over 40 percent of the cohort had been admitted to hospital at least once in the year prior to death. A subset of that group (7.5% of the overall cohort) had been hospitalized for a previous nonfatal overdose in the year prior to death. Additional analysis of these particular cases is important to determine why someone with a previous hospitalization due to overdose would overdose again due to prescribed drugs. Providing patients hospitalized due to an overdose with naloxone would be indicated.
- A high proportion of decedents (85%) saw a health professional for a mental disorder or substance use disorder in the year prior to death. Such contacts could facilitate safe and effective medication use, psychological support and substance use disorder treatment. Further analysis could examine whether these frequent contacts are resulting in meaningful therapeutic interventions.

Aboriginal Ethnicity

- People of Aboriginal ethnicity are disproportionately represented in this cohort of decedents.
- Given the age and geographic distribution of Aboriginal people in BC, the Aboriginal decedents did not differ notably from non-Aboriginal decedents on demographic or geographic measures, toxicology results, or prescribed opioid dosage.

2 Acknowledgments

This report is based on the work of and a report primarily prepared by:

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3 Definitions

3.1 Glossary

Administrative health regions: BC is divided into geographic health regions for administrative and data dissemination purposes. There are five regional health authorities (HAs) that are divided into 16 Health Service Delivery Areas (HSDAs) and further subdivided into 89 Local Health Areas (LHAs). Geographical analyses presented in this report are based on these administrative health regions.

Age standardized mortality rate: A measure of age-adjusted death rate standardized to a ‘standard’ population (1996 Canada Census) for the purpose of rate comparisons between genders, different time periods, or different geographic locations (BC Vital Statistics Agency, 2012).

Diversión: channeling of pharmaceuticals from legal sources to the illegal marketplace and/or unintended individuals (Larance et al., 2011).

“First Nations Client File” or “FNCF” means the data file containing the personal information needed to identify First Nations clients, established cooperatively and which the Parties to the Tripartite Data Quality and Sharing Agreement agree is the best method of access to accurate health information about the identifiable majority of First Nations clients residing in British Columbia, who are registered Indians and their entitled children. The First Nations Client File is created by means of a memorandum of understanding (MoU) between the Ministry of Health and Indigenous and Northern Affairs Canada authorizing and governing disclosure of information contained in the Indian Registry to the MoH and the Client Registry of the Public Health Insurance program of British Columbia. The First Nations Client File will be used in a process of record matching involving MoH administrative data on health, or BC Vital Statistics Agency data on vital events, or other research data, to produce First Nations Data.

Non-prescribed pharmaceutical opioid: a pharmaceutical opioid used without a valid prescription from an authorized health care professional.

Opioid analgesic: a drug with pharmacological effects resembling those of the alkaloids derived from the opium poppy plant and prescribed to relieve pain. Opioid analgesics include natural (codeine, morphine), semi-synthetic (buprenorphine, hydrocodone, hydromorphone, oxycodone) and synthetic (fentanyl, meperidine, methadone) forms (Warner et al., 2011). In BC, methadone and buprenorphine are used to treat opioid dependency as well as pain (see opioid substitution treatment).

Opioid use disorder: A problematic pattern of opioid use leading to clinically significant impairment or distress, with symptoms including unsuccessful efforts to control opioid use; cravings to use opioids; continued use despite adverse social, interpersonal, or health consequences; tolerance; and withdrawal (American Psychiatric Association, 2013).

Opioid substitution treatment: treatment approach for opioid use disorder involving the long-term prescribing of another opioid as an alternative to the opioid on which the client was dependent (CAMH, 2009), also known as maintenance treatment or medication assisted treatment. In BC, methadone, buprenorphine, diacetylmorphine and hydromorphone are prescribed for opioid substitution treatment.

Pharmaceutical opioid: any opioid drug that is eligible to be prescribed in BC. Heroin is not considered a pharmaceutical opioid in this report.

Pharmaceutical opioid-associated death: a drug poisoning death in which a pharmaceutical opioid was determined to be a relevant factor.

Potential years of life lost: a measure of the impact of premature mortality taking into account the number of years of life lost when a person dies before a specified age (Gardner & Sandborn, 1990). The present report uses 75 years as this specified age (BC Vital Statistics Agency, 2012).

Prescribed pharmaceutical opioid: a pharmaceutical opioid obtained via a prescription from an authorized health care professional. In this report, current prescription at time of death is operationally defined as a prescribed pharmaceutical opioid where the end date of the most recent dispensation is within 60 days of death.

Problematic pharmaceutical opioid use: Use of pharmaceutical opioids that is associated with an increased risk of harm for the user. This may include, for example, taking more of the drug than prescribed, using an alternate route of administration, using with alcohol or other substances, or using without a valid prescription. Not all individuals who engage in problematic pharmaceutical opioid use would meet criteria for an opioid use disorder; however, continued problematic use may develop into an opioid use disorder.

Toxicology: The study of the adverse effects of chemicals on living organisms, particularly the symptoms, mechanisms, treatments and detection of the poisoning of people (BC Coroners Service, 2015).

3.2 Abbreviations

ASMR	Age-standardized mortality rate
BCCS	British Columbia Coroners Service
DAD	Discharge Abstract Database
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
FNCF	First Nations Client File
HA	Health Authority
HSDA	Health Service Delivery Area
ICD-9	World Health Organization's International Classification of Diseases, Ninth Revision
ICD-10-CA	Canadian Enhancement of the World Health Organization's International Classification of Diseases, Tenth Revision
LHA	Local Health Area
MME	Morphine milligram equivalent dosage
MMT	Methadone maintenance treatment
MSP	Medical Services Plan
OST	Opioid substitution treatment
PHN	Personal health number
PYLL	Potential years of life lost

4 Introduction

Pharmaceutical opioids have important therapeutic uses in the management of pain and opioid use disorder. However, their increased rates of being prescribed in Canada and the US since the late 1990s have been paralleled by increases in associated morbidity and mortality. Canada has the second highest per capita opioid prescription rate in the world (International Narcotics Control Board, 2013); with recent data indicating that 15 percent of Canadian adults used a pharmaceutical opioid in the past year (Statistics Canada, 2015). Rates of dispensation and consumption of pharmaceutical opioids at the population level are strongly correlated to overdose mortality rates in British Columbia (Fischer et al., 2011; Gladstone et al., 2015b). The Provincial Health Officer and Chief Coroner of BC have identified pharmaceutical opioid-associated overdose as a significant cause of preventable death in BC and a critical public health issue. Research is urgently needed to better understand this complex public health issue and inform strategies for prevention and mitigation of harm.

4.1 Defining pharmaceutical opioid overdose

One challenge to understanding the harms associated with pharmaceutical opioids arises from the varying operational definitions used in the literature. There are numerous ways of classifying opioid-associated overdose deaths – for example, based on whether the overdoses were intentional (suicide) or unintentional and on whether the opioids involved were produced illegally or for medical purposes. Pharmaceutical opioid-associated deaths can be further differentiated based on whether the pharmaceutical opioids were obtained with a physicians’ prescription or through illegitimate channels (e.g., diversion from family or friends, pharmacy theft, online pharmacies). Within the existing body of literature, variability between studies and lack of clarity with respect to defining study cohorts makes it difficult to generalize and interpret results. For example, reported prevalence rates of opioid-related deaths differ widely between jurisdictions, but it is difficult to know to what extent these results reflect methodological differences between studies or true differences between jurisdictions. Similarly, the factors associated with risk for opioid overdose death may differ based on prescription status and intentional versus unintentional overdose.

A related consideration is that pharmaceutical opioid-related harms are frequently described within the context of “abuse,” “misuse,” or “nonmedical use” of these substances. While use of pharmaceutical opioids in ways that are inconsistent with prescribed guidelines increases the potential risks, pharmaceutical opioid-related harms, including overdose deaths, are not limited to cases of deliberate non-adherence to prescription regimens.

This report focuses on fatal overdoses involving pharmaceutical opioids for which decedents held current prescriptions. For the sake of clarity, this report uses the term “prescribed pharmaceutical opioid” as opposed to the more ambiguous “prescription opioid.” The latter is problematic as it may be interpreted narrowly as referring only to an opioid used with a valid prescription, or more broadly as any opioid *obtainable* by prescription, without specifying users’ prescription status.

4.2 Characteristics of pharmaceutical opioid overdoses

Taking into account the inconsistency in terminology in the literature, results of past studies suggest a number of factors associated with pharmaceutical opioid-associated mortality. Previous research in this area has focused on individual characteristics, prescriber behaviour and characteristics, drug characteristics, and contextual factors.

Studies suggest a gender difference in risk, with significantly more overall (i.e., prescribed and non-prescribed) pharmaceutical opioid-associated deaths among men as compared to women in BC and Ontario (Gladstone et al., 2015a; Gomes et al., 2014). While pharmaceutical opioid-associated overdose deaths can occur at any age, the

highest mortality rates are reported among middle-aged adults (CDC, 2011; Gomes et al., 2014; Johnson et al., 2013). Physical and mental health characteristics associated with risk include a history of substance use disorder or mental illness, enrolment in a methadone maintenance program, chronic illness or physical disability, and illegal drug use (King et al., 2014; Madadi et al., 2013; Johnson et al., 2013). There is a dearth of research on pharmaceutical opioid-associated overdose among Aboriginal Canadians, although many First Nations and Aboriginal communities have identified problematic prescription drug use as a priority concern (Fischer & Argento, 2012). In a review of drug overdose deaths in BC between 2001 and 2005, overdose rates and premature mortality were found to be disproportionately elevated among First Nations peoples in BC compared to the general population (Milloy et al., 2010).

While national-level data are unavailable in Canada, reports from the U.S. show dramatic regional variability in pharmaceutical opioid-associated mortality rates (Paulozzi & Ryan, 2006). A recent review found heterogeneity in terms of relationships between socio-demographic factors and overdose risk across the U.S. (King et al., 2014), indicating that generalizations across jurisdictions may not be valid.

Investigations of post-mortem toxicology results have repeatedly found that toxicity from multiple substances, particularly opioids combined with other drugs with depressant effects (King et al., 2014), is the most important factor in opioid overdose (Darke, 2014). Patterns of poly-substance toxicity may also differ by jurisdiction. Studies focusing on a variety of different populations have shown that risk for fatal pharmaceutical opioid overdose rises with increasing daily dosage (e.g., Bohnert et al., 2011; Dunn et al., 2010; Gwira Baumbblatt et al., 2014). The occurrence of overdoses at low to moderate doses has prompted controversy about what may constitute a threshold for a hazardous dose (King et al., 2014).

In 2011, the BC Coroners Service (BCCS) raised concern about the rate of pharmaceutical opioid-associated mortality in BC (Pederson et al., 2011), which was comparable to the rate of motor vehicle incident fatalities involving alcohol (BC Coroners Service, 2015). BCCS data also showed a significant elevation in the pharmaceutical opioid-associated mortality rate in the Interior Health region of BC relative to other regions. A subsequent investigation focusing on prescribed non-methadone opioid deaths in the Interior highlighted a number of potential risk factors, including chronic pain, mental health disorder diagnosis, and multiple adjuvant medications in addition to opioids (Corneil et al., 2012). In contrast to previous literature, high opioid dosages and contribution of alcohol use were found to be relevant in only a minority of cases. In light of these findings, a province-wide review was recommended to clarify patterns and predictors of prescribed pharmaceutical opioid-associated overdose deaths in BC.

4.3 Goals

Balancing the availability of pharmaceutical opioids for medical use with efforts to prevent or reduce problematic use and associated harms is a complex issue that requires a coordinated and evidence-based response. The present analysis explores patterns of unintentional pharmaceutical opioid-associated deaths in BC among individuals who held a prescription for these medications. We focussed on people who died while taking prescribed opioids because the potential implications for prevention of pharmaceutical drug-related mortality may differ depending on whether the drugs were obtained and administered with the oversight of a health care provider or not. This preliminary work may guide future efforts aimed at developing, implementing, and evaluating evidence-based strategies to prevent or reduce harms associated with pharmaceutical opioids.

4.3.1 Specific objectives and research questions

- To describe the prevalence and geographical distribution of unintentional prescribed pharmaceutical opioid overdose mortality in BC. Do prescribed pharmaceutical opioid-associated deaths vary by

geographical region across the province, and were there any identifiable trends over the duration of the study period?

- To identify potential factors characterizing individuals who experienced an unintentional fatal overdose involving pharmaceutical opioids prescribed to them by a health care provider. Are there individual-level factors, such as socio-demographic features, specific health conditions, or patterns of health service utilization, which may help to identify individuals at risk for overdose?
- To describe contexts and characteristics of fatal unintentional prescribed pharmaceutical opioid overdoses in BC. What specific pharmaceutical opioids are most implicated in fatal overdoses, and what other legal and illegal substances tend to be involved?

5 Methods

5.1 Case definition

Defined broadly, opioid-related overdose deaths include those associated with pharmaceutical opioids or illegal opioids (e.g., heroin) as well as intentional and unintentional overdoses. Pharmaceutical opioid-associated deaths can be further divided into cases where opioids were prescribed to the decedent or those where pharmaceutical opioids were taken without a valid prescription. The scope of the current analysis was limited to deaths meeting the following case definition:

An unintentional overdose fatality in BC between Jan 1st 2009-Dec 31st 2013 involving a pharmaceutical opioid prescribed to the decedent.

5.1.1 Inclusion criteria

Cases included in the study cohort met all of the following inclusion criteria:

- BC Coroners Service reported the cause of death as poisoning (overdose) involving one or more pharmaceutical opioids.
- Death classified as accidental (i.e., due to unintentional or unexpected injury; BC Coroners Service, 2014).
- Death occurring within the years 2009 to 2013, inclusive.
- One or more pharmaceutical opioids were detected through post-mortem serum toxicology.
- At least one pharmaceutical opioid involved in the overdose was prescribed to the decedent, with the end date of the prescription falling within 60 days of the date of death.
- Valid BC Personal Health Number (PHN) available, enabling linkages between datasets.

5.1.2 Exclusion criteria

The following exclusion criteria were used to limit the study cohort to cases of unintentional fatal overdose involving prescribed pharmaceutical opioids.

- Deaths classified by the BC Coroners Service as suicide, natural causes, or undetermined.
- Overdose deaths involving only illicit opioids (i.e., heroin, or pharmaceutical opioids for which the decedent was determined not to have held an active prescription dispensed in BC).

5.2 Sources of data

The BC Ministry of Health and the BC Coroners Service are the stewards of the data sets used in this analysis. Ministry of Health data was obtained through internal data requests. Data from the BC Coroners Service was obtained through a research agreement between the Ministry of Health and the BC Coroners Service. The data sources include BC Coroners Service case files, the provincial database of prescription drug dispensations in BC (PharmaNet), databases tracking publicly funded medical service utilization (MSP database) and hospital admissions (Discharge Abstract Database) in BC. These data sources are outlined in more detail in the following sub-sections.

5.2.1 Pharmaceutical opioid-associated deaths in BC

The BC Coroners Service (BCCS) mandate includes the responsibility of investigating all unnatural, sudden, and unexpected deaths in British Columbia (Coroners Act, 2007), including drug overdose deaths. Deaths reported to the BCCS undergo a thorough investigation of the circumstances surrounding the death and routinely involve pathology services and toxicological analysis if poisoning by alcohol or another drug is suspected as a relevant factor in the death (BC Coroners Service, 2014). Overdose fatalities in BC where pharmaceutical opioids are determined to be relevant to the death are coded as “Poisoning:Drugs:Rx” by the BC Coroners Service if the investigating coroner determines that the decedent had been prescribed the opioids involved in the fatal overdose. In cases where the coroner determines that the decedent did not hold a valid prescription for the opioids involved in the fatal overdose, the code “Poisoning:Drugs:Illicit” would be applied.

5.2.1.1 Case identification

Data used in this project were derived from a review of files obtained from a central registry maintained by the BCCS. This registry was used to identify cases of unintentional fatal poisonings in BC between 2009 and 2013 where a prescribed pharmaceutical opioid was determined to be a relevant factor in the cause of death. An initial dataset of 244 cases classified as “Poisoning:Drugs:Rx” was obtained from BCCS. As discussions with BCCS indicated that some deaths classified as “Poisoning:Drugs:Illicit” may have involved prescribed pharmaceutical opioids,¹ a second dataset of 832 cases was also provided. The process of applying the inclusion and exclusion criteria and determining the final study cohort from among these cases is described in section 5.3.

5.2.1.2 Data abstraction from BC Coroners Service records

Data on fatalities associated with prescribed opioids in British Columbia from 2009 to 2013 (i.e., the 244 “Poisoning:Drugs:Rx” cases) were abstracted from files provided by the BCCS and merged with existing BCCS electronic records. This process took place from May to July 2014. Information abstracted from BCCS records included:

1. Coroner’s Section 16 Report (cover form): This provides information on gender and age of decedents, date and time of death, type of location of death, cause of death details, and classification of death.

¹ This could happen for various reasons. Where illegal substances were involved in an overdose death along with pharmaceutical drugs, the “Poisoning:Drugs:Illicit” classification may have been applied. Alternately, the investigating coroner may have been unable to conclusively determine a decedent’s prescription status. A potential further analysis of subsets of the final study cohort based on involvement of illegal drugs in the fatal overdose is described in Appendices A and C.

2. **Verdict at Inquest:** The resulting document of the Coroner's Inquest that is held if the coroner determines that it would be beneficial in addressing community concern about a death, assisting in finding information about the deceased or circumstances around a death or drawing attention to a cause of death if such awareness can prevent future deaths. An inquest is mandatory if the deceased was in the care or control of a police officer or in a police lock-up at the time of their death. The Verdict includes a brief overview of the circumstances of the death, the evidence presented and the jury's findings and any recommendations.
3. **Toxicology Report:** This contains detailed information on toxicological findings – source of sample, drug/metabolite name, concentration of the drug/metabolite. BCCS conducts a toxicological examination for all deaths where drug poisoning is suspected. Routinely, a drug screen is performed first; if the drug screen is positive, more detailed analysis follows. The toxicologist drafts a short conclusion on probable cause of death based on the results of analysis.
4. **Autopsy Report:** This details the results of the autopsy.
5. **Medical Certificate of Death:** This contains personal and demographic information, medical cause of death, and specific circumstances and manner of death.
6. **Registration of Death:** This provides information on Personal Health Number and Social Insurance Number; address and postal code of residence, overdose, and death; marital status and occupation and occupation industry of the decedent. If some information is not available from the Registration of Death, the Medical Certificate of Death can be used.
7. **Form C – Interim Medical Report**
8. **Coroner's Investigative Protocol:** This contains a short narrative description of circumstances and location of death as well as the medical and alcohol/drug use history of the decedent that can provide data otherwise not captured by BCCS case files, such as the source of pharmaceutical opioids involved in fatal overdose, description of the overdose location, illegal drugs or paraphernalia found at the scene, etc.
9. **All relevant medical records in the Coroners file**
10. **Accidental Drug Overdose Protocol:** This provides information on known opioid overdose risk factors - recent changes in drug use; recent incarceration and release; circumstances of the fatal overdose (type of drug, mode of consumption, alcohol contributory, emergency medical intervention before death, administration of naloxone); enrollment in a methadone program; and, history of drug use and overdose.
11. **Electronic database of prescribed opioid-associated mortality cases in BC from 2009 to 2013 populated from the BCCS file, including relevant socio-demographic variables and case details.**

For the subset of the 832 "Poisoning:Drugs:Illicit" cases meeting criteria for inclusion in the analysis (n=142; see section 5.3.3), the electronic database and toxicology results were provided by BCCS in June 2015.

5.2.2 Prescription drug use history

PharmaNet is a centralized, real-time database that tracks every prescription dispensation occurring in community pharmacies and hospital outpatient pharmacies across BC, accounting for the vast majority of prescription dispensations in the province. It does not include prescription drugs dispensed to hospital inpatients; by the BC Cancer Agency, the BC Centre for Excellence in HIV/AIDS, the BC Transplant Society, or the BC Renal Agency; or as samples from health care practitioners (BC Ministry of Health, n.d.). The PharmaNet database is held by the Ministry of Health and was accessed through an internal data access request.

Data obtained from PharmaNet for this analysis included records of all pharmaceutical opioid dispensations to each decedent in the five years prior to death and records of all other prescription drug dispensations in the year prior to death. Each dispensation record included basic demographic details (e.g., the individual's PHN, date of birth, date of death, and geographical location in terms of HA, HSDA, and LHA), pharmacy location (in terms of HA, HSDA, and LHA), some prescriber information, and details about the type and amount of medication dispensed. For instance, a PharmaNet record for a single dispensation included the date of service, the name of the drug dispensed (e.g., chemical name and brand name), the quantity (e.g., 30 pills), the dosage (e.g., 20mg), and the number of days supply covered by that dispensation (e.g., 10 days). The end date of each dispensation was calculated based on the service date and the number of days' supply of drug dispensed.

5.2.2.1 Standardization of pharmaceutical opioids of varying strengths

PharmaNet dispensation records pertaining to the following specific pharmaceutical opioids were obtained: buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, and tramadol. While other pharmaceutical opioids are available by prescription in Canada (e.g., hydrocodone, propoxyphene, pentazocine), PharmaNet records indicated that these drugs were not dispensed to any decedents in the study cohort in the five years prior to death.

To account for variability in opioid strength, dosages of prescribed pharmaceutical opioids from the obtained PharmaNet records were converted to morphine milligram equivalent (MME) dosages using equivalence tables reported in Canadian and U.S. guidelines (Washington State Agency Medical Directors' Group, 2015; National Opioid Use Guideline Group, 2010b). See Appendix D for a table of conversion factors. These calculated MMEs were subsequently used in the study analyses examining dosages of prescribed pharmaceutical opioids among decedents. The exception to this process was methadone. Equianalgesic conversion factors for methadone are unreliable due to its non-linear pharmacokinetics, which are thought to result from its long half-life and tendency to accumulate with chronic dosing (Washington State Agency Medical Directors' Group, 2015). Methadone dosages are thus reported in terms of milligrams of methadone, taken directly from the dosage information obtained from PharmaNet records.

Canadian clinical practice guidelines consider 200 mg per day of morphine or equivalent (i.e., 200 MME per day) to be a "watchful dose," above which the risk for adverse effects is elevated (National Opioid Use Guideline Group, 2010a). Other jurisdictions employ alternate thresholds; for example, Washington State's guidelines recommend that prescribers seek consultation with pain specialists when escalating doses beyond 120 MME per day (Washington State Agency Medical Directors' Group, 2015). In the present analysis, proportions of decedents with daily dosages of higher than 120 MME and 200 MME are both reported.

5.2.3 Medical history and health care utilization

5.2.3.1 Medical Services Plan

The Medical Services Plan (MSP) covers BC residents for medically required services provided by physicians, surgeons, and supplementary health care practitioners, laboratory services, and diagnostic procedures. The MSP database is held by the Ministry of Health and was accessed through an internal data access request. Data obtained included medical services received, diagnoses, and details of claims (e.g., type of service, specialty of health care provider, location of services, and type of facility in which services were provided). Diagnoses in the MSP database were coded according to the World Health Organization's *International Classification of Diseases, Ninth Revision* (ICD-9) coding scheme.

5.2.3.2 Discharge Abstract Database

The Discharge Abstract Database (DAD) captures administrative, clinical and demographic information on hospital in-patient visits and day surgery interventions. Emergency room visits are not recorded within this database. DAD data was accessed through an internal Ministry of Health data access request. Data obtained included details of hospital visits (e.g., number and duration of admissions, type of facility, procedures or medical treatments received). The DAD also includes classification codes that describe the patient's diagnoses, conditions, and other relevant circumstances during the hospital stay. Diagnoses in the DAD were coded according to the Canadian Enhancement of the World Health Organization's *International Classification of Diseases, Tenth Revision* (ICD-10-CA; Canadian Institute for Health Information, 2001).

5.2.4 First Nations and Aboriginal ethnicity

A variable indicating Aboriginal or non-Aboriginal ethnicity was provided in BCCS records. According to the BCCS, a determination of Aboriginal ethnicity was made by the coroner investigating each death and could be based, for example, on interviews with associates of the deceased individual. Investigation of potential factors related to pharmaceutical opioid-associated mortality among Aboriginal and non-Aboriginal decedents in the present report are based on this BCCS coding.

Another source of information regarding First Nations status is the First Nations Client File (FNCF), a dataset containing demographic data of First Nations people residing in BC. It is constructed from data provided by Indigenous and Northern Affairs Canada as well as BC Ministry of Health sourced data, including the BC Client Registry and Vital Statistics. The study dataset was linked to the FNCF according to the process overseen by the Tripartite Data and Information Planning Committee (DIPC) based on an Internal Partners First Nations Client File Data Access Request (DAR) submitted by the research team. This DAR was completed in consultation with representatives from the First Nations Health Authority to ensure that use of the FNCF aligns with the priorities and principles outlined in the Tripartite Data Quality and Sharing Agreement and the Tripartite First Nations Health Plan.

5.2.5 Publicly available data

Publicly available data used in these analyses were drawn from BC Stats (BC Stats, 2011; 2013; 2014), the BC Vital Statistics Agency (BC Vital Statistics Agency, 2012), and the BC Coroners Service (BCCS, 2015).

Geographical location information available in BCCS records included the postal code and township for each decedent. These data were translated into their corresponding administrative health regions using BC Stats' *Translation of Place Names into Administrative Areas* (BC Stats, 2011).

Population estimates used in the calculation of mortality rates across geographical administrative health regions (HAs, HSDAs, and LHAs) were drawn from BC Stats' *Sub-Provincial Population Estimates* (BC Stats, 2013). Mortality

rates are expressed per 100,000 population. Calculations of age-standardized mortality rates (ASMR) and potential years of life lost (PYLL) were conducted according to methodology employed by the BC Vital Statistics Agency (BC Vital Statistics Agency, 2012). As complete data on prescribed pharmaceutical opioid-associated deaths for 2013 were unavailable due to ongoing investigation of deaths occurring in that year, results involving rate calculations are limited to 2009 to 2012.

5.3 Data linkage and cohort definition

As noted above, the BC Coroners Service (BCCS) provided the data that formed the starting point for the definition of the study cohort. The BCCS data included cases of unintentional fatal poisonings involving pharmaceutical opioids occurring in BC from January 1st 2009 to December 31st 2013. Data from 2013 were incomplete due to not all coroner's cases having been concluded. The process of refining the study cohort and linking the BCCS data to the other data sets of interest is described in the following sections and depicted in detail in section 5.4 (Figure 1).

5.3.1 Case identifier verification

BC residents enrolled in MSP are assigned a unique lifetime identifier for health care called a Personal Health Number (PHN). PHN is included within the MSP, DAD, and PharmaNet databases. A correct PHN is needed to link these distinct sets of data across individual decedents. In a substantial number of cases, the BCCS database was missing the PHN or had erroneous information (e.g., a PHN with an incorrect number of digits).² Analysts from the Ministry of Health Population Health Surveillance team employed a verification process to validate the information available from the BCCS database (i.e., PHN where available, name, date of birth, date of death) against the Ministry of Health's client roster, the "master list" or consolidated source of client demographic and geographic data (BC Ministry of Health, 2015). This resulted in PHN verification for 240 of 244 cases from the "Poisoning:Drugs:Rx" cohort (98.4%) and 760 of 832 cases from the "Poisoning:Drugs:Illicit" cohort (91.3%). Figure 1 depicts this step of the cohort definition process. Cases for which no correct PHN could be verified (n=76) were excluded from the study cohort, as no linkage could be carried out. Following PHN verification and subsequent data linkage, each case was assigned a unique anonymized code and all PHNs were deleted from the linked study database.

5.3.2 Prescription status verification

The current analysis focused on *prescribed pharmaceutical opioid-associated deaths* – that is, cases in which an individual experienced a fatal overdose involving a pharmaceutical opioid prescribed to him or her. Deaths involving only pharmaceutical opioids taken without a current prescription were excluded from the case definition. Linkage of the BCCS datasets to PharmaNet allowed for a determination of whether decedents had held an active prescription for a pharmaceutical opioid prior to death. Current (or active) prescription status was operationally defined based on having received a pharmaceutical opioid where the end date of the most recent dispensation was within 60 days of death, as per PharmaNet history. This approach is consistent with other recent research in BC (e.g., Gladstone et al., 2015b). As noted above, the end date of each dispensation was calculated based on the service date and number of days' supply provided.

Cases in which the decedent did not hold an active prescription for a pharmaceutical opioid within 60 days prior to death (as per PharmaNet dispensation records) were excluded from the study cohort. Active prescription status was confirmed for 199 of the remaining 240 cases from the "Poisoning:Drugs:Rx" cohort (82.9%) and 315 of the

² The correct PHN was absent in over 30 percent of cases. There were substantially more missing or inaccurate PHNs among the cohort of deaths coded as "Poisoning:Drugs:Illicit" as compared to those coded "Poisoning:Drugs:Rx".

remaining 760 cases from the “Poisoning:Drugs:Illicit” cohort (41.4%). Figure 1 depicts this step of the cohort definition process.

5.3.3 Cross-check with BC Coroners Service database

The final step of the cohort definition process involved comparing the BCCS toxicology data with decedents’ PharmaNet records to confirm whether the specific pharmaceutical opioid(s) involved in the overdose corresponded to the specific pharmaceutical opioid(s) that the decedent had been prescribed. For instance, if PharmaNet records showed that a decedent had held an active prescription for oxycodone prior to death, but toxicology indicated that the accidental overdose involved morphine, this individual would not meet the case definition and would be excluded from the study cohort.

If toxicology results showed the presence of multiple pharmaceutical opioids, and if the decedent held an active prescription within 60 days of death for at least one of those opioids, that individual was retained in the study cohort, with the involvement of both prescribed and non-prescribed pharmaceutical opioids noted accordingly.

Correspondence between pharmaceutical opioids dispensed to decedents and those detected through toxicology testing was confirmed for 191 of the remaining 199 cases from the “Poisoning:Drugs:Rx” cohort (96.0%) and 142 of the remaining 315 cases from the “Poisoning:Drugs:Illicit” cohort (45.1%), resulting in a final study cohort of 333 cases. Figure 1 depicts this step of the cohort definition process.

5.4 Inclusion/exclusion flow diagram

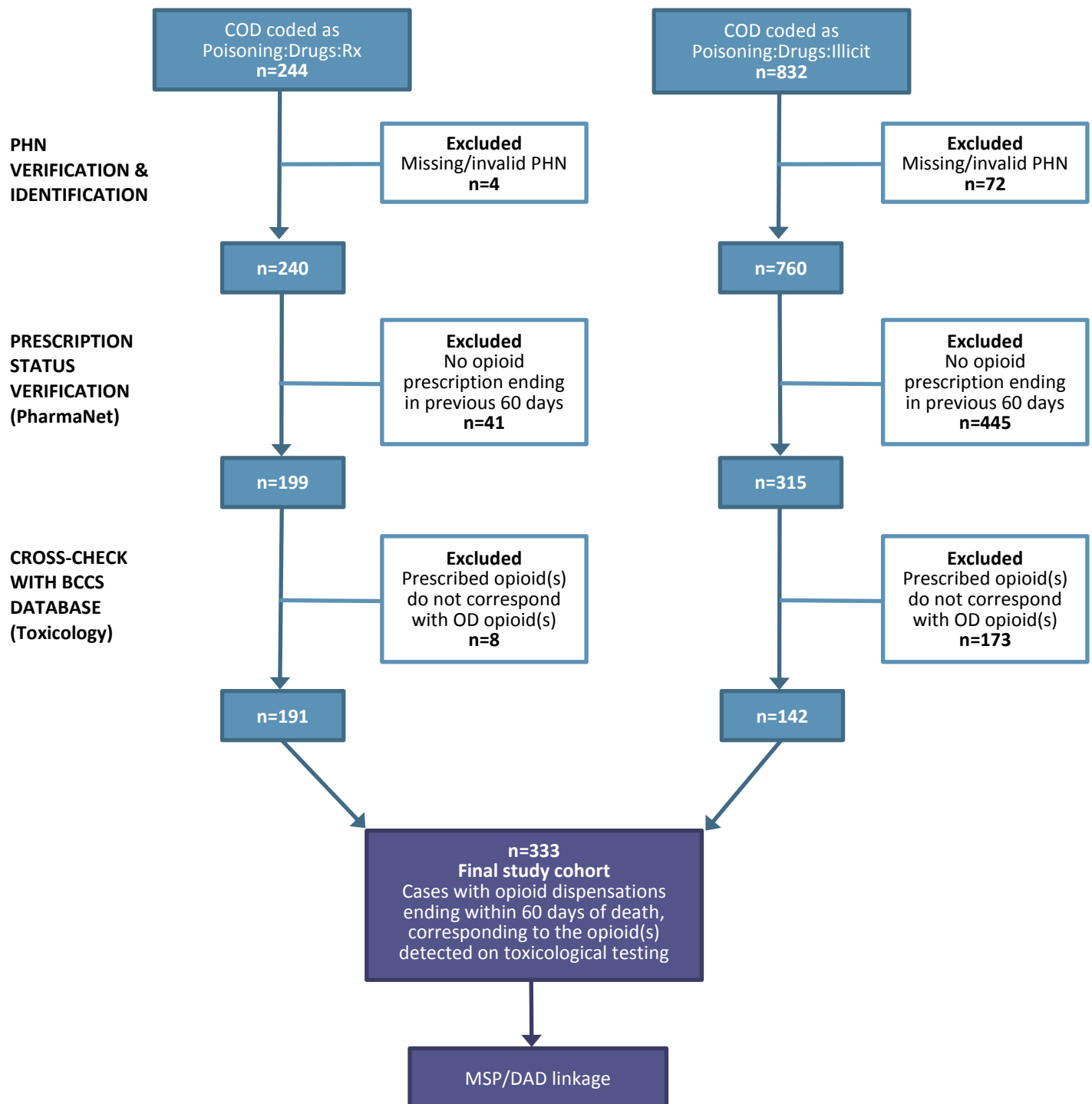


Figure 1. Inclusion/exclusion flow diagram illustrating the process of determining the study cohort of prescribed pharmaceutical opioid-associated deaths from January 1st 2009 to December 31st 2013. Data from 2013 were incomplete due to not all coroner's cases having been concluded.

5.5 Data security, privacy and confidentiality

As data linkage studies can pose a risk of identification of individuals or groups, safeguards were implemented to protect the privacy and confidentiality of the individuals included in this analysis. As noted, decedents were assigned a random number as a unique identifier and all personal information was stripped from the study database following data linkage and prior to analysis. In the present report, results based on small cell sizes are suppressed or aggregated, as appropriate, to avoid potential identification. This project was approved by the Office of the Chief Information Officer of BC through two Privacy Impact Assessments covering the abstraction of data from BCCS files (HLTH 14037) and the data linkage process (HLTH 14055). This project was also approved by the Human Research Ethics Board of the University of Victoria (Ethics Protocol Number 14-400).

5.6 Data analytic approach

BCCS, PharmaNet, MSP and DAD datasets were provided in Microsoft Excel or Excel CSV formats. All data were exported to SPSS (Version 15.0 for Windows; SPSS Inc., Chicago, Illinois, USA) for analysis. Data analysis included a combination of descriptive and inferential techniques. Descriptive analyses included the annual rate of prescribed pharmaceutical opioid-related mortality in BC, demographic features of decedents, geographic distribution of deaths across BC, and characteristics of overdoses (e.g., primary substances involved, findings of toxicological assessment). Statistical tests for inferential analysis were selected based on the variables under analysis (e.g., independent samples *t*-tests or Pearson *r* correlation for continuous variables, chi-square tests for categorical variables).³ A level of significance of $\alpha=0.05$ was used. Confidence intervals were calculated based on BC Vital Statistics methodology (BC Vital Statistics Agency, 2012). An exact sign test was used to compare prescriptions over 5 years vs. 1 year prior to death.

6 Results

6.1 Annual deaths and mortality rate

There were 333 unintentional overdose deaths associated with use of prescribed pharmaceutical opioids reported in BC from 2009 to 2013 (Figure 2). This is likely an underestimate of the true number of prescribed pharmaceutical opioid-associated deaths in BC during the study period, as data from an unknown number of ongoing investigations by the BC Coroners Service (i.e., open cases) were unavailable at the time these analyses were conducted. Furthermore, as noted above, 76 deaths occurring during the entire study period were excluded as no valid PHN could be identified, precluding linkage to other data sets.

³ In future analysis of this data, results of bivariate tests may be used to inform the development of multivariate models using appropriate statistical methods (e.g., logistic regression, cluster analysis).

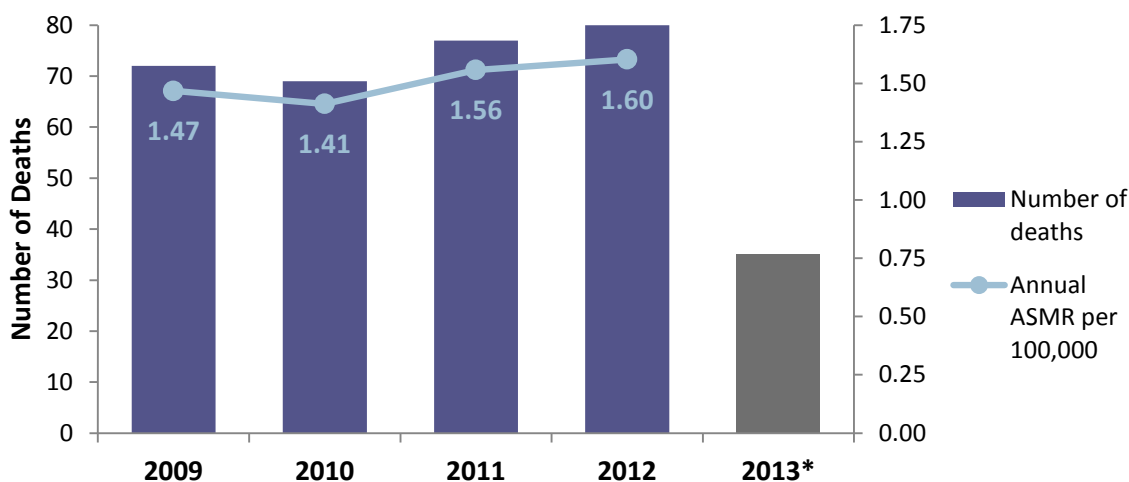


Figure 2. Annual prescribed pharmaceutical opioid-associated fatalities in BC, 2009 to 2013.

*Data were extracted in early 2014 so data for 2013 are incomplete due to incomplete coroner's cases.

The province-wide mean annual age-standardized mortality rate (ASMR) was 1.51 per 100,000 individuals from 2009 to 2012. The average number of prescribed pharmaceutical opioid-associated deaths per year over this period was 74.5 (SD 4.9). There was an annual average of 363.3 accidental drug poisoning deaths in BC between 2009 and 2011 (BCCS, 2015).⁴ This suggests that deaths involving prescribed pharmaceutical opioids account for 20.5%, or approximately 1 in 5, of the total number of accidental drug poisoning deaths in the province over this time period.

It is important to note that these deaths represent only a portion of all opioid-associated deaths in BC. Suicide deaths, deaths involving only illegal opioids, and deaths involving only pharmaceutical opioids administered without a prescription were excluded from the present analysis. Gladstone et al. (2015a) report an average mortality rate of 3.9 pharmaceutical opioid-associated deaths per 100,000 population in BC from 2004 to 2013, with no significant change over this time period. This rate includes all pharmaceutical opioid deaths, intentional and unintentional, as well as those involving pharmaceutical opioids taken with and without a prescription. This gives a broader sense of the overall impact of pharmaceutical opioid-associated mortality in BC; however, Gladstone et al. note that their findings, based on mortality data from BC Vital Statistics, may also underestimate the total number of pharmaceutical opioid deaths in the province.

Key Findings – Annual Deaths and Mortality Rate

- There was an annual average of 74.5 prescribed pharmaceutical opioid-associated deaths in BC over the study period, corresponding to a mean annual age-standardized mortality rate of 1.51 per 100,000 population.
- Deaths involving prescribed pharmaceutical opioids account for 20.5%, or approximately 1 in 5, of the total number of accidental drug poisoning deaths in the province between 2009 and 2012

⁴ This figure includes illegal drugs, prescription drugs (acquired legally or illegally), alcohol, and over-the-counter drugs (BCCS, 2015).

6.2 Socio-demographic characteristics

6.2.1 Sex of decedents

Decedents in the study cohort were 55.6 percent male and 44.4 percent female, although female deaths slightly exceeded male deaths for those under 40 years of age. The relative proportions of fatal prescribed pharmaceutical opioid-associated overdoses among men and women did not vary significantly by year from 2009 to 2013. Gladstone et al. (2015a) reported that men accounted for approximately two-thirds of all pharmaceutical opioid-associated deaths between 2004 and 2013 in BC. As a further comparison, recent data on illicit drug overdose trends in BC indicate that men and women account for approximately 70 and 30 percent of illicit drug deaths, respectively (British Columbia Coroners Service, 2015). This discrepancy between prescribed and illicit drug deaths suggests that women's risk for fatal overdose involving prescribed pharmaceutical opioids could be comparatively higher than their risk for overdose involving non-prescribed pharmaceutical opioids, or that more men use illegal substances, or that women are prescribed opioids at higher rates. Worryingly, recent data from the US suggest that the rate of pharmaceutical opioid-associated overdose death is increasing at a faster rate among women than among men (CDC, 2013).

6.2.2 Age of decedents

Decedents were largely middle-aged (Figure 3). The average age at which prescribed pharmaceutical opioid-associated death occurred between 2009 and 2013 was 48.5 years (SD 10.6; median 49.0), with two-thirds of deaths occurring among individuals aged 40 to 59 years. This parallels similar results from other jurisdictions, including Quebec (Gagné et al., 2013), Ontario (Ontario Drug Policy Research Network, 2014), and the United States (CDC, 2011). Over 90 percent of deaths occurred among individuals aged 30 to 69 years. There were no deaths among people less than 20 years old and fewer than two percent of deaths were among people over 70 years old. There was no overall significant mean difference in age of death between men and women.

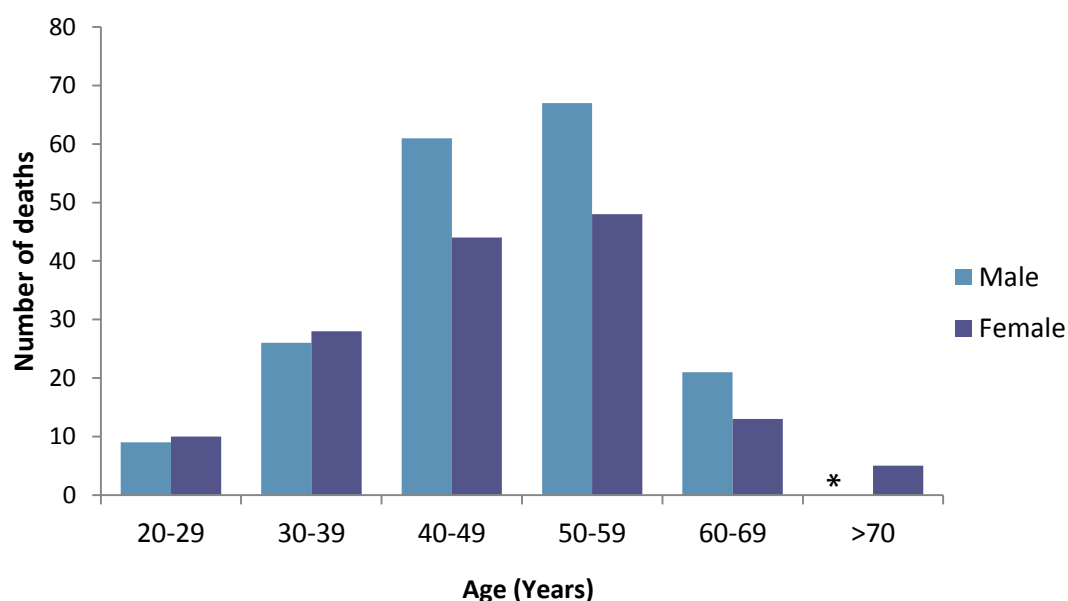


Figure 3. Prescribed pharmaceutical opioid deaths in BC by age group and sex, 2009 to 2013.

*Age groups with fewer than 5 cases are suppressed due to institutional privacy regulations.

6.2.3 Years of life lost

Potential years of life lost (PYLL) is a measure of the impact of premature mortality taking into account the age at which deaths occur (Gardner & Sandborn, 1990). PYLL for the cohort of prescribed pharmaceutical opioid-associated fatalities was calculated across age groups based a projected life expectancy of 75 years (BC Vital Statistics Agency, 2012). On average, PYLL was more than 35 years per individual (Table 1).

As noted above, the majority of deaths (66 percent) occurred among individuals aged 40 to 59 years. These groups accounted for approximately 62 percent of the total PYLL (Table 1). Although those aged 20 to 39 accounted for only 22 percent of the total number of deaths, these younger age groups together accounted for approximately 34 percent of the total years of life lost, a considerably greater burden than that observed when only considering mortality rates.

Table 1. Potential years of life lost due to prescribed pharmaceutical opioid-associated premature deaths, 2009 to 2013.

Age group	N	Mean PYLL	Total PYLL	Percent of total PYLL
20-29	19	47.74	907.06	10.24
30-39	54	38.92	2101.46	23.73
40-49	105	29.34	3080.40	34.78
50-59	115	20.73	2383.65	26.91
60-69	34	11.20	380.69	4.30
70+	6	0.54	3.22	0.04
Total	333	35.23	8856.48	100.00

Note. PYLL = potential years of life lost.

Key Findings – Socio-demographic Characteristics

- Overall fatal prescribed pharmaceutical opioid overdoses were more common among men than women (55.6 percent male, 44.4 percent female), but female fatalities slightly exceeded males for people less than 40 years of age.
- Women's risk for fatal overdose involving prescribed pharmaceutical opioids is comparatively higher than their risk for fatal overdose involving non-prescribed pharmaceutical opioids.
- Prescribed pharmaceutical opioid overdoses were most common among middle-aged British Columbians, with two thirds of deaths occurring among individuals between the ages of 40 and 59. On average, there was more than 35 years of potential life lost per individual death.

6.3 Geographical distribution

6.3.1 Distribution of deaths across regional Health Authorities

The mean annual ASMR across BC was 1.51 per 100,000 individuals from 2009 to 2012 (2013 was excluded due to incomplete data). As shown below in Figure 4 and Table 2, mortality rates varied across the five regional Health Authorities in BC over this time period, with the highest rate in the Interior region (2.73 per 100,000), significantly above the provincial average, and the lowest rate in the Fraser region (1.13 per 100,000), significantly below the provincial average.

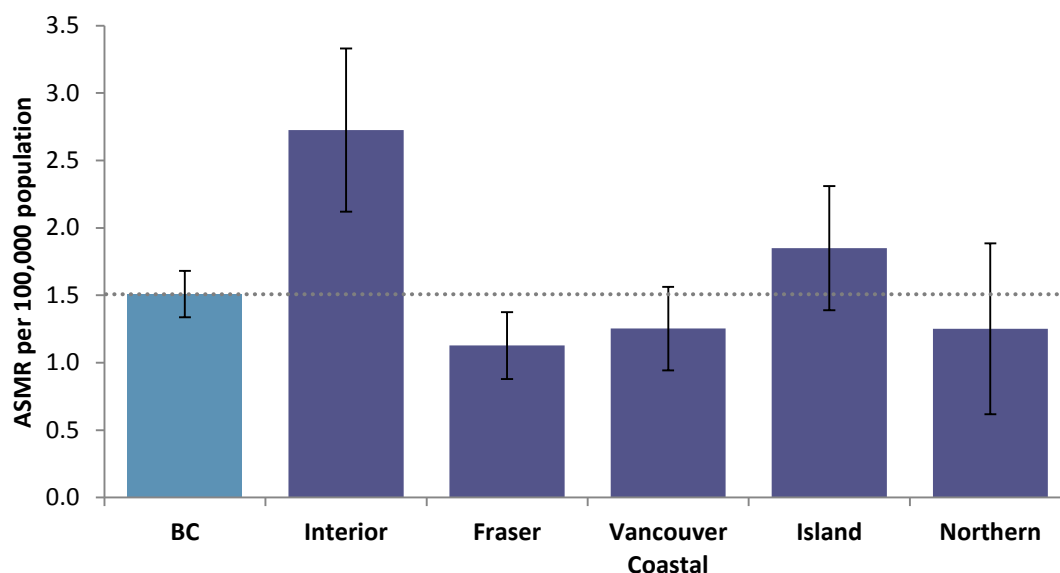


Figure 4. Mean annual age-standardized mortality rate by regional Health Authority, 2009 to 2012 (2013 was excluded due to incomplete data). These calculations are based on 298 prescribed pharmaceutical opioid-associated deaths occurring during this period. Error bars in this figure represent 95 percent confidence intervals. The dotted line represents the BC-wide age-standardized mortality rate. The mortality in the Interior region was significantly higher than the provincial average, while the mortality rate in the Fraser region was significantly lower.

Table 2. Mean annual deaths and age-standardized mortality rates associated with prescribed pharmaceutical opioids across BC regional Health Authorities, 2009 to 2012.

Regional Health Authority	Number of deaths (2009-12)	Mean annual deaths	Population (Mean 2009-12)	Mean annual ASMR per 100,000
Interior	78	19.50	720,861.25	2.73
Fraser	80	20.00	1,624,504.00	1.13
Vancouver Coastal	63	15.75	1,105,141.75	1.25
Island	62	15.50	747,092.75	1.85
Northern	15	3.75	282,162.75	1.25
BC Total	298	74.50	4,479,762.50	1.51

6.3.2 Changes over time in individual Health Authorities

The annual ASMR among the five regional Health Authorities in BC demonstrated variable patterns between 2009 and 2012 (Figure 5). For instance, the rate in the Island region increased substantially from 2011 to 2012 and the rate in the Interior region rose in 2011 before declining in 2012. While the four-year time period of this analysis is too brief to interpret these changes as indicative of meaningful trends, it will be important to continue tracking mortality rates in these regions over time to identify any potential patterns. Given the changes in mortality rate by year across Health Authorities depicted in Figure 5, the mean annual ASMR over multiple years (Figure 4) may obscure some of these variations.

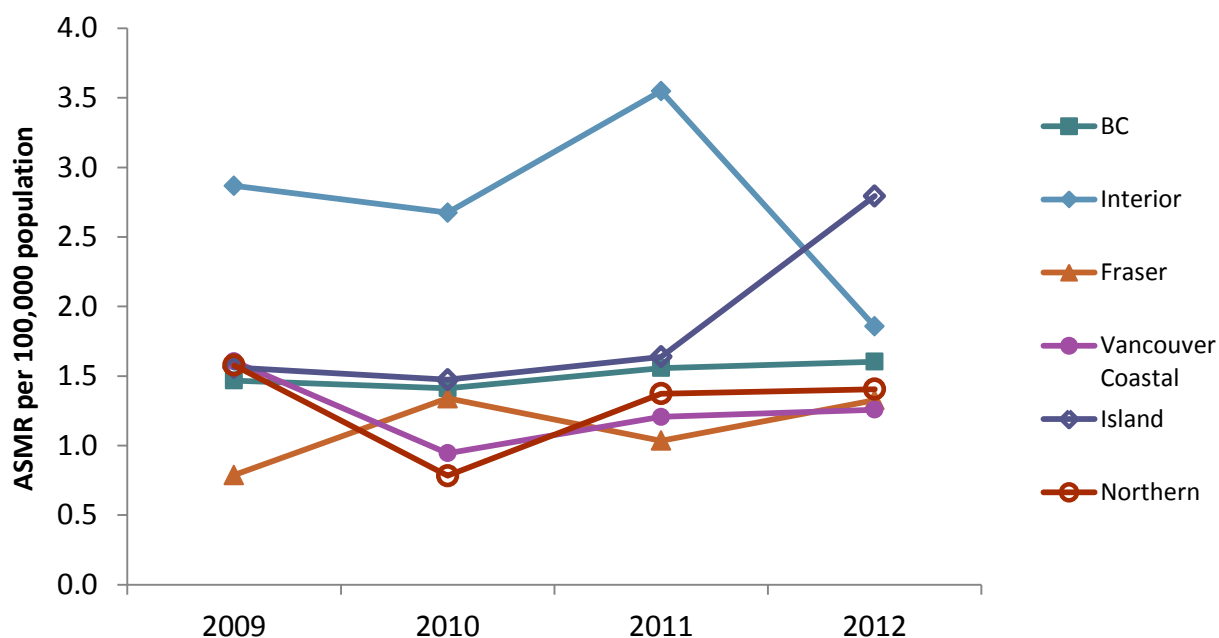


Figure 5. Prescribed pharmaceutical opioid-associated age-standardized mortality rate by regional Health Authority in BC and year, 2009 to 2012.

6.3.3 Distribution across Health Service Delivery Areas

The five regional Health Authorities in BC are subdivided into 16 Health Service Delivery Areas (HSDAs; see Table 4). Examination of specific HSDAs revealed substantial variability within Health Authorities. The highest mortality rates in the province were in the Okanagan and Thompson Cariboo Shuswap HSDAs, both in the Interior region, and in the North Vancouver Island HSDA in the Island region (Figure 6; Table 3). The ASMR in each of these three HSDAs exceeded the provincial average.

There were also three HSDAs with significantly lower ASMRs than the provincial average. These were the Fraser North, Fraser South, and Richmond HSDAs, all located within the greater Vancouver Lower Mainland area (Figure 6; Table 3).

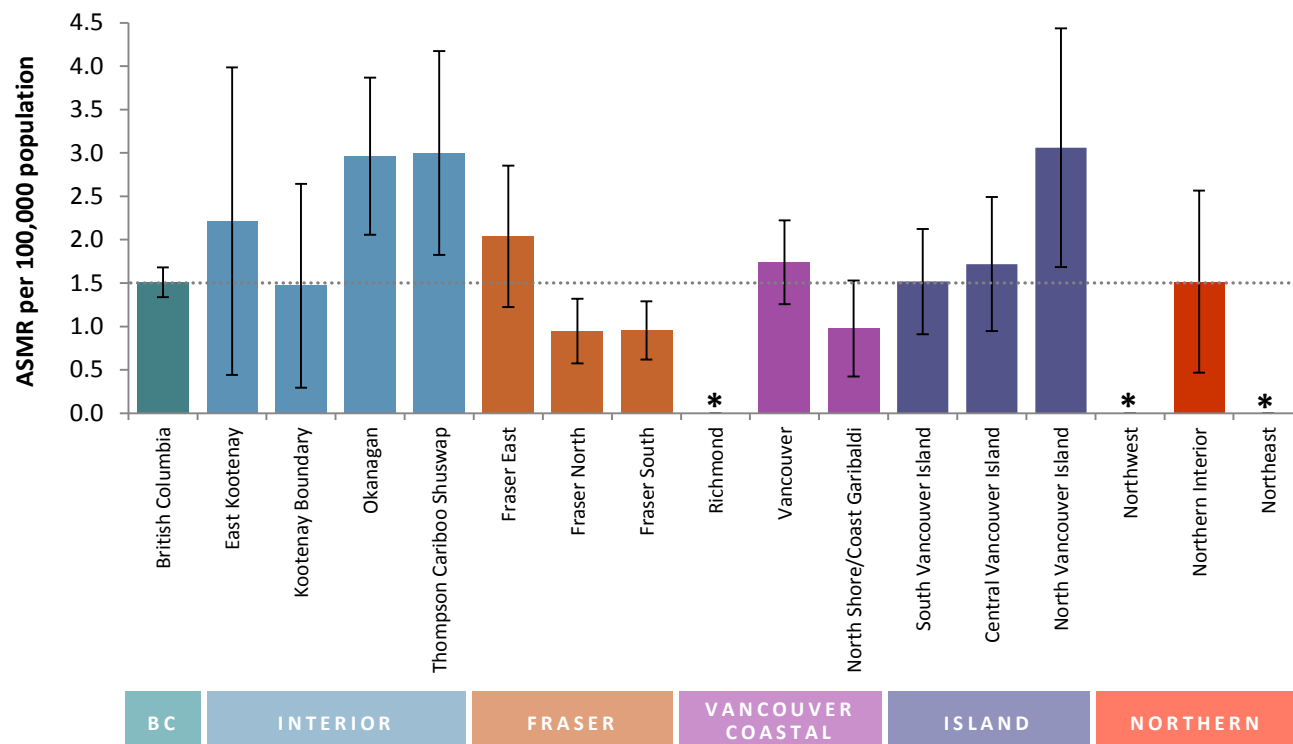


Figure 6. Mean annual age-standardized mortality rate by Health Service Delivery Area, 2009 to 2012. Error bars in this figure represent 95 percent confidence intervals. The dotted line represents the BC-wide ASMR. *HSDAs with fewer than 5 cases are suppressed due to institutional privacy regulations. The Richmond HSDA (suppressed) had a significantly lower ASMR than the provincial average.

Table 3. Mean annual age-standardized mortality rates related to prescribed pharmaceutical opioids by regional Health Service Delivery Areas in BC, 2009-2012.

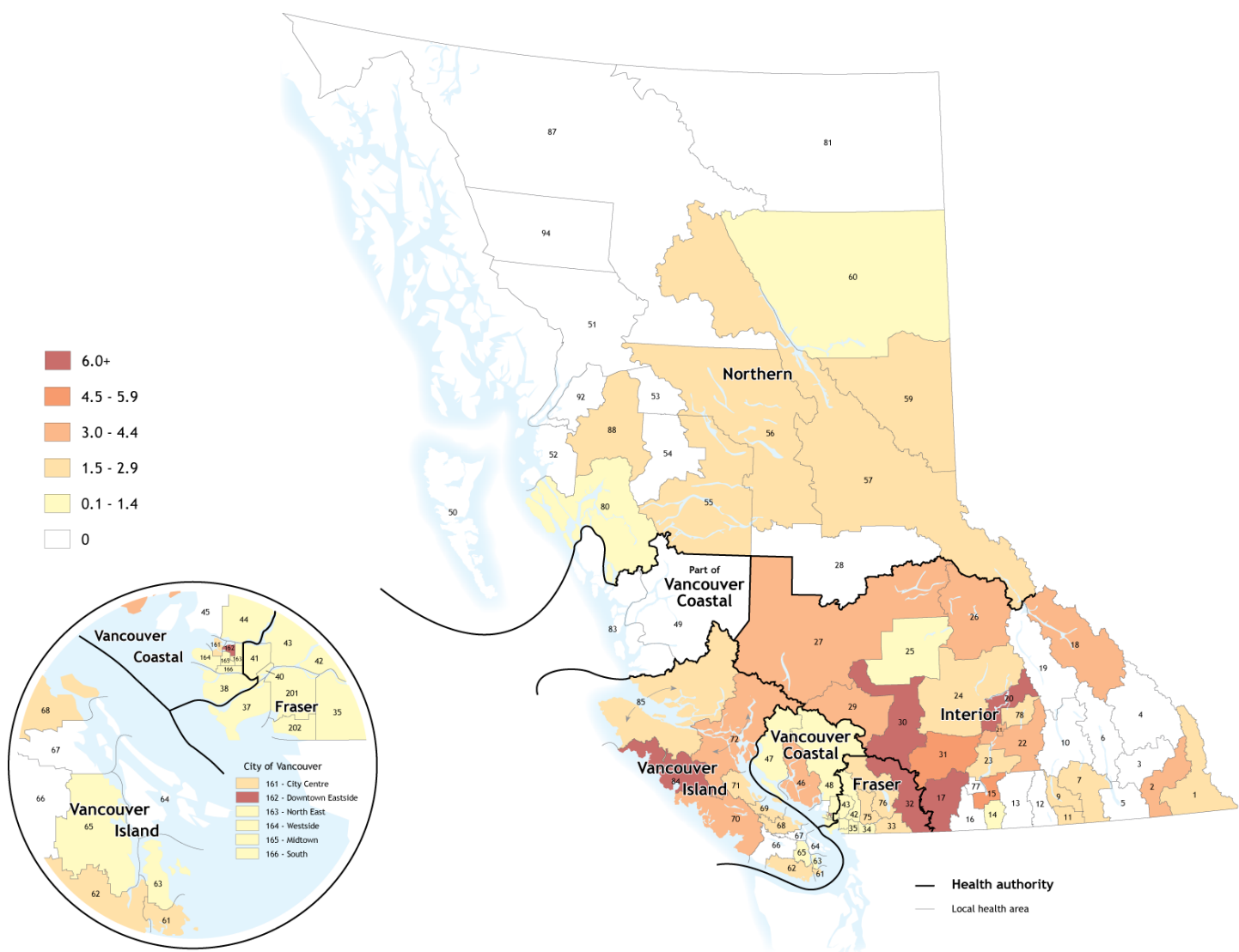
Health Service Delivery Area	Number of deaths (2009-2012)	Mean annual deaths	Population (Mean 2009-2012)	Mean annual ASMR per 100,000
East Kootenay	6	1.50	77,205.0	2.21
Kootenay Boundary	6	1.50	78,109.0	1.47
Okanagan	41	10.25	347,278.3	2.96
Thompson Cariboo	25	6.25	218,269.0	3.00
Fraser East	24	6.00	282,172.8	2.04
Fraser North	25	6.25	613,936.3	0.95
Fraser South	31	7.75	728,395.0	0.96
Richmond	*	*	195,635.8	*
Vancouver	50	12.50	633,958.5	1.74
North Shore/Coast	12	3.00	275,547.5	0.98
South Vancouver Island	24	6.00	366,516.0	1.52
Central Vancouver	19	4.75	261,012.0	1.72
North Vancouver Island	19	4.75	119,564.8	3.06

Northwest	*	*	73,644.8	*
Northern Interior	8	2.0	141,344.5	1.52
Northeast	*	*	67,173.5	*
BC Total	298	74.5	4,479,762.5	1.51

* Cells with 5 or fewer cases are suppressed due to institutional privacy regulations.

6.3.4 Distribution across Local Health Areas

British Columbia's HSDAs are further subdivided into 89 Local Health Areas (LHAs). Mean annual mortality rates in each LHA between 2009 and 2012 are depicted in terms of ranges on the map on the next page (Figure 7), with darker colours corresponding to higher rates. This map is presented for descriptive purposes; the darker shaded areas are not necessarily significantly different from the provincial average. For instance, the small population on the west coast of Vancouver Island resulted in the mortality rate being strongly influenced by a relatively small number of deaths. Table 4 on the following page lists the LHAs by name and number.



Map template courtesy of the Centre for Health Services and Policy Research, University of British Columbia. Used with permission.

Figure 7. Mean annual age-standardized rates of prescribed pharmaceutical opioid-associated mortality per 100,000 population by Local Health Areas in BC, 2009 to 2012. This map is presented for descriptive purposes and the darker shaded areas are not necessarily significantly different from the provincial average.

Table 4. British Columbia administrative health regions.

Heath Authority	HSDA	LHA	Heath Authority	HSDA	LHA	
Interior	East Kootenay	1 Fernie	Vancouver Coastal	Richmond	38 Richmond	
		2 Cranbrook		Vancouver	161 City Centre	
		3 Kimberley			162 Downtown Eastside	
		4 Windermere			163 North East	
		5 Creston			164 West Side	
		18 Golden			165 Midtown	
	Kootenay Boundary	6 Kootenay Lake			North Shore/Coast Garibaldi	166 South Vancouver
		7 Nelson		44 North Vancouver		
		9 Castlegar		45 West Vancouver-Bowen Island		
				46 Sunshine Coast		
				10 Arrow Lakes		47 Powell River
				11 Trail		48 Howe Sound
				12 Grand Forks		49 Bella Coola Valley
				13 Kettle Valley		83 Central Coast
	Okanagan		14 Southern Okanagan	Vancouver Island	61 Greater Victoria	
		15 Penticton	62 Sooke			
		16 Keremeos	63 Saanich			
		17 Princeton	64 Gulf Islands			
		21 Armstrong - Spallumcheen	Central Vancouver Island		65 Cowichan	
		22 Vernon			66 Lake Cowichan	
		23 Central Okanagan			67 Ladysmith	
		77 Summerland			68 Nanaimo	
	Thompson Cariboo Shuswap	78 Enderby	North Vancouver Island	69 Qualicum		
		19 Revelstoke		70 Alberni		
		20 Salmon Arm		North Vancouver Island	71 Courtenay	
		24 Kamloops			72 Campbell River	
		25 100 Mile House			84 Vancouver Island West	
		26 North Thompson			85 Vancouver Island North	
		27 Cariboo - Chilcotin		Northern	Northwest	50 Queen Charlotte
		29 Lillooet				51 Snow Country
	30 South Cariboo	52 Prince Rupert				
31 Merritt	53 Upper Skeena					
Fraser	Fraser East	32 Hope	54 Smithers			
		33 Chilliwack	80 Kitimat			
		34 Abbotsford	87 Stikine			
		75 Mission	88 Terrace			
		76 Agassiz - Harrison	92 Nisga'a			
	Fraser North	40 New Westminster	Northern Interior			94 Telegraph Creek
		41 Burnaby				28 Quesnel
		42 Maple Ridge		55 Burns Lake		
		43 Coquitlam		56 Nechako		
	Fraser South	35 Langley	Northeast	57 Prince George		
		37 Delta		59 Peace River South		
		201 Surrey		60 Peace River North		
		202 South Surrey/White Rock		81 Fort Nelson		
	Note. HSDA: Health Service Delivery Area. LHA: Local Health Area.					
Source: http://www.bcstats.gov.bc.ca/statisticsbysubject/geography/referencemaps/health.aspx						

Note. HSDA: Health Service Delivery Area. LHA: Local Health Area.

Source: <http://www.bcstats.gov.bc.ca/statisticsbysubject/geography/referencemaps/health.aspx>

Key Findings – Geographic Distribution

- Consistent with previous reports, analyses showed regional variation across BC, with an elevated mortality rate in the Interior Health region and lower mortality in the Fraser Health region relative to the provincial average.
- The mortality rate in BC health authorities was variable between 2009 and 2012, potentially increasing in Vancouver Island and potentially decreasing in Interior Health. Based on earlier work by Interior Health the elevated rates were brought to the attention of the physicians in that region by the medical health officer. It will be important to continue tracking mortality rates in each region over time to identify any potential trends.
- The highest mortality rates in the province were in the Okanagan and Thompson Cariboo Shuswap HSDAs, both in the Interior region, and in the North Vancouver Island HSDA in the Island region. The ASMR in each of these three HSDAs exceeded the provincial average.
- Further analysis to examine rates of drug prescribing, such as by geographic region, group of practitioners (by region/specialty etc.) or by individual practitioners to determine whether there is an association with a higher than expected number of decedents is warranted.

6.4 Contexts and characteristics of fatal prescribed pharmaceutical opioid overdoses

6.4.1 Location of overdoses and medical intervention

In the vast majority of cases, the fatal overdoses (83.5%) and deaths (77.5%) occurred in private residences. The discrepancy between these numbers is primarily accounted for by the 7.8% of deaths that occurred in hospitals or other medical facilities, including ambulances. Just over 10 percent occurred in a hotel, hostel, or rooming house. According to BCCS records, approximately 15 percent of decedents received some form of medical intervention prior to death,⁵ typically provided by ambulance services or hospital emergency rooms. The opioid antagonist naloxone was reportedly administered in only about 5 percent of cases.⁶

6.4.2 Poly-substance use patterns and overdose

Toxicological results were examined to determine the most common pharmaceutical opioids and other substances implicated in these deaths. Figure 8 shows the numbers of fatal overdoses involving various combinations of substances. In the overwhelming majority of cases (323 of 333; 97.0%), fatal overdoses involved other substances in addition to prescribed pharmaceutical opioids. Methadone accounted for almost all of the 10 prescribed pharmaceutical opioid-only overdoses. These categories of substances will be discussed in more detail in the following sections.

⁵ Based on 257 of 333 cases where information about medical intervention was available.

⁶ Based on 238 of 333 cases where information about naloxone administration was available.

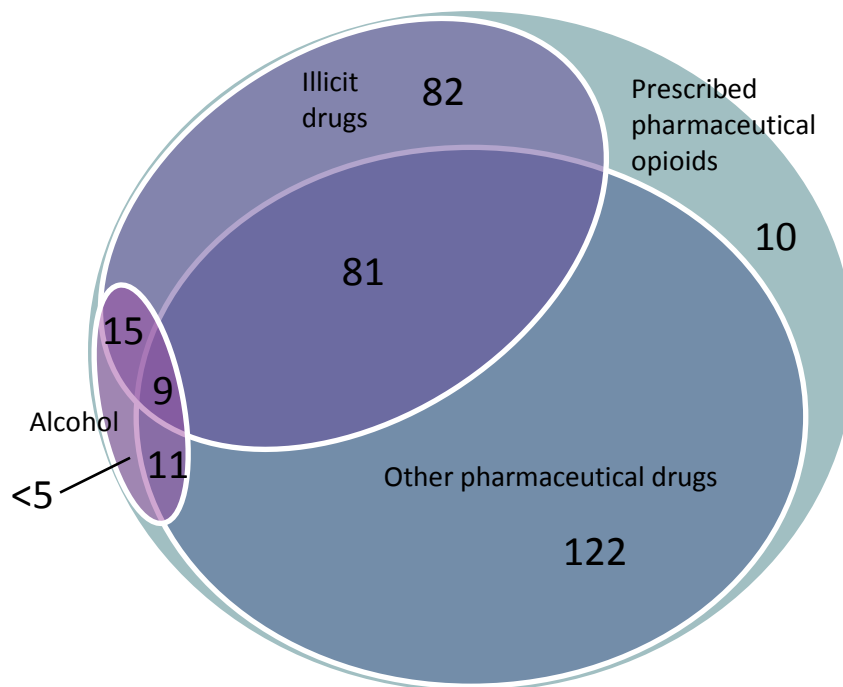


Figure 8. Number of prescribed pharmaceutical opioid-associated deaths in BC from 2009 to 2013 involving prescribed pharmaceutical opioids alone and in combination with other substances. Illicit drugs include illegal drugs as well as pharmaceutical opioids taken without an active prescription. Other pharmaceutical drugs include medications other than opioids detected through toxicology testing. The diagram is for illustrative purposes and is not to scale.

6.4.3 Prescribed pharmaceutical opioids

A variety of different pharmaceutical opioids were implicated in these overdose deaths. Figure 9 shows the specific prescribed pharmaceutical opioids that were implicated in fatal overdoses. Methadone prescribed for opioid substitution (maintenance) treatment is presented separately from methadone prescribed for pain management.

The pharmaceutical opioid involved in the greatest number of deaths was methadone prescribed for opioid substitution treatment, which was present in over 30 percent of fatalities (Figure 9). Almost 25 percent of deaths involved codeine, while morphine and oxycodone were each involved in about 20 percent of deaths.

Hydromorphone was present in about 10 percent of deaths, while methadone prescribed for pain management was present in just under 5 percent of deaths. Less than 1 percent of deaths involved the pharmaceutical opioids meperidine or tramadol. There were no deaths involving buprenorphine.

As noted in the previous section, toxicological analysis showed that the majority of these fatal overdoses involved other substances in addition to prescribed pharmaceutical opioids. However, according to toxicological analyses, presence of multiple prescribed pharmaceutical opioids was relatively uncommon. Eighty-seven percent of cases involved one prescribed pharmaceutical opioid, 12 percent of cases involved two prescribed pharmaceutical opioids, and less than 1 percent of cases involved more than two prescribed pharmaceutical opioids.

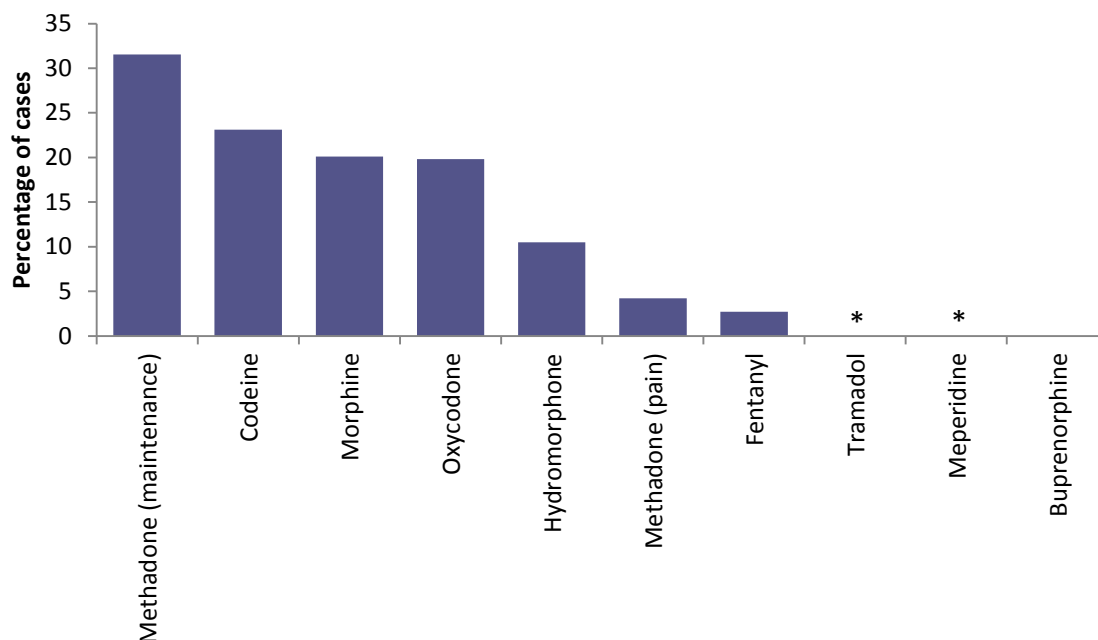


Figure 9. Involvement of specific pharmaceutical opioids in prescribed pharmaceutical opioid overdose deaths in BC, 2009 to 2013 ($n=333$). Relevance of specific opioids to overdose deaths was confirmed via BC Coroners Service records. The total adds to more than 100 percent due to the presence of multiple prescribed opioids in some cases. *Specific opioids involved in fewer than 5 deaths are suppressed due to institutional privacy regulations.

6.4.4 Non-prescribed pharmaceutical opioids

Review of decedents' prescription drug dispensation histories also allowed for identification of cases where a pharmaceutical opioid detected in post-mortem toxicology testing had not been dispensed to the decedent prior to death. This scenario would suggest use of non-prescribed, or diverted, pharmaceutical opioids in addition to prescribed pharmaceutical opioids.

In 79 of 333 deaths (23.7%) between 2009 and 2013, toxicology testing detected the presence of a pharmaceutical opioid for which decedent did not hold an active prescription within 60 days of death. The opioids detected were morphine (37 of 79 cases), codeine (20 of 79 cases), methadone (14 of 79 cases), fentanyl (9 of 79 cases), and oxycodone (fewer than 5 cases). Fewer than 5 cases involved more than one pharmaceutical opioid used without a valid prescription within 60 days of death. These findings are consistent with previous research showing that non-prescribed pharmaceutical opioids are frequently implicated in opioid overdose deaths (e.g., King et al., 2014).

As noted previously, a prescribed pharmaceutical opioid was defined as an opioid for which the decedent held an active prescription within 60 days of death. To explore whether these instances merely reflected use of opioids for which decedents had held prescriptions more than 60 days ago, decedents' opioid prescription histories over the past 5 years were examined. In 61 cases (18.3% of the overall cohort), the decedent had no record of ever having been dispensed the opioid in question in the 5 years prior to death. While this does not preclude the possibility that some decedents may have overdosed on an opioid that was dispensed to them in the more distant past, these data suggest that some fatal overdose cases involved administration of pharmaceutical opioids obtained without a prescription concurrently with prescribed pharmaceutical opioids.

6.4.5 Other pharmaceutical drugs

Concurrent involvement of other pharmaceutical drug classes was common. Review of toxicology findings showed that other pharmaceutical drugs were detected in addition to prescribed pharmaceutical opioids in 223 of 333 cases (70%). The most frequently co-occurring pharmaceutical drugs were antidepressants, which were present in 43.5 percent of cases (Figure 10). Review of PharmaNet history confirmed that the vast majority of these individuals (97.2%) held an active prescription for an antidepressant in the 60 days before death. The most common antidepressants detected were amitriptyline, citalopram, venlafaxine, and trazodone.

Benzodiazepines, including zopiclone, were detected in 33.6 percent of overdose deaths (Figure 10). Review of PharmaNet history confirmed that the vast majority of these individuals (96.4%) held an active prescription for a benzodiazepine or zopiclone in the 60 days before death. This finding is interesting in light of the results reported by Gladstone et al. (2015a), who found that the proportion of all pharmaceutical opioid-associated deaths in BC involving benzodiazepines rose from 2 percent in 2004 to 14 percent in 2013. Despite the increase over time, the concurrent presence of benzodiazepines in that study remains substantially lower than the present results. Gladstone et al. relied on mortality data drawn from BC Vital Statistics, suggesting that either the concurrent presence of benzodiazepines is a more salient factor in unintentional prescribed pharmaceutical-opioid associated deaths in BC (as opposed to pharmaceutical-opioid associated deaths more broadly), or perhaps that the role of benzodiazepines in opioid-associated overdose deaths may be underestimated in Vital Statistics data as compared to BC Coroners Service data.

Among prescribed pharmaceutical opioid-associated deaths in the present analysis, the anticonvulsant and antipsychotic drug classes were both notable in that a single medication accounted for most of the cases for the entire class. Gabapentin, which is classified as an anticonvulsant but is most commonly prescribed for chronic pain, accounted for approximately three-quarters of the cases in which an anticonvulsant was detected, while quetiapine, again often prescribed for chronic pain, accounted for two-thirds of the cases in which an antipsychotic was detected.

Many of the pharmaceutical drugs involved in these overdose deaths are known to present an increased risk of adverse effects when used concurrently with opioids (e.g., Jones et al., 2012).

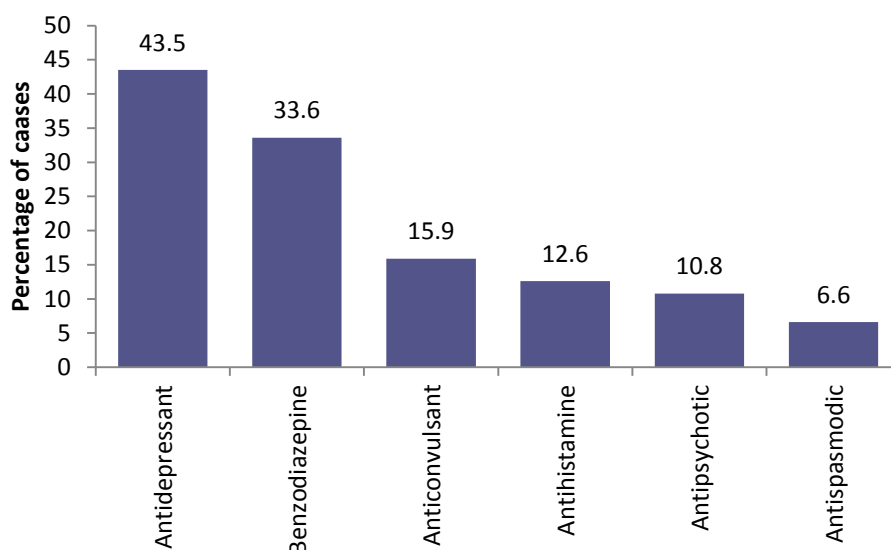


Figure 10. Presence of non-opioid pharmaceutical drug classes in prescribed opioid-associated deaths in BC, 2009 to 2013 ($n=333$). This figure includes only substances present in more than five percent of fatal prescribed pharmaceutical opioid overdoses. The benzodiazepine category includes zopiclone.

6.4.6 Alcohol and illegal drugs

Toxicology testing revealed that alcohol was present in 11.4 percent of prescribed pharmaceutical opioid-associated deaths in the study cohort (Table 5).⁷ As a comparison, alcohol was involved in approximately 22 percent of pharmaceutical opioid-related deaths in 2010 in the U.S. (Jones et al., 2014), and in approximately 40 percent of pharmaceutical opioid-related deaths in Ontario from 1990 to 2010 (Ontario Drug Policy Research Network, 2014).

An illegal drug was present in 45.6 percent of deaths (Table 5). Table 5 shows the percentages of cases in which specific illegal drugs were present. Most illegal drugs were relatively uncommon, with the exception of cocaine, which was involved in approximately 38 percent of deaths. In comparison, approximately 23 percent of pharmaceutical opioid-associated deaths in Ontario between 1990 and 2010 involved cocaine (Ontario Drug Policy Research Network, 2014). Cannabis toxicology was available for just over half of the deaths in this cohort, so the reported prevalence of marijuana may represent an under- or over-estimate of the actual involvement of marijuana in prescribed pharmaceutical opioid-associated deaths in BC during the study period.

Table 5. Proportions of prescribed pharmaceutical opioid-associated overdoses in BC involving alcohol and illegal drugs, 2009-2013.

Substance	<i>n</i> (%)
Cocaine	126 (37.8)
Alcohol	38 (11.4)
Heroin	20 (6.0)
Amphetamine/Methamphetamine	18 (5.4)
Cannabis*	9/192 (4.7)

⁷ This excludes three cases where alcohol was detected in postmortem toxicology testing, but where coroners' notes indicated that the alcohol was likely due to postmortem decomposition.

MDMA	<5 (<1)
Total	333
<i>Note.</i> Totals for cocaine and heroin include specific metabolites of these substances detected through toxicology analyses. MDMA: 3,4-methylenedioxymethamphetamine (ecstasy). *Cannabis toxicology was available for 192 of 333 cases.	

Key Findings – Context and Characteristics

- The vast majority of overdoses and deaths occurred in private residences.
- Approximately 15 percent of decedents received some form of medical intervention prior to death (e.g., ambulance services, hospital emergency room).
- In the vast majority of cases (97%), toxicology data showed that these fatal overdoses involved other substances in addition to prescribed pharmaceutical opioids.
- The pharmaceutical opioid involved in the greatest number of deaths was methadone prescribed for opioid substitution treatment, which was present in over 30% of fatalities. Almost 25% of deaths involved codeine.
- The presence of multiple prescribed pharmaceutical opioids was relatively uncommon (13% of cases), however in 24% of the fatalities toxicology testing detected the presence of a pharmaceutical opioid for which decedent did not hold an active prescription within 60 days of death, indicating that pharmaceutical opioids are being obtained from other sources and being consumed concurrently.
- Concurrent involvement of other pharmaceutical drug classes was common, with antidepressants detected in over 40 percent of cases and benzodiazepines detected in over 30 percent of cases.
- The anticonvulsant and antipsychotic drug classes were both notable in that a single medication accounted for most of the cases for the entire class. Gabapentin, which is classified as an anticonvulsant but is most commonly prescribed for chronic pain, accounted for approximately three-quarters of the cases in which an anticonvulsant was detected, while quetiapine, again often prescribed for chronic pain, accounted for two-thirds of the cases in which an antipsychotic was detected.
- Analysis by combinations of these drug classes would further help define potential problematic drug interactions.
- Alcohol was present in 11.4% of deaths in the study cohort.
- Illegal drugs were relatively uncommon, with the exception of cocaine, which was involved in approximately 38% of deaths. Given the potential pharmacological interactions between cocaine and opioids with respect to deaths consequent to heart arrhythmias, analyzing the opioid dose level in the cocaine associated group would be of interest. Comparing cocaine use in people on MMT to those not on MMT could be important if there are different patterns of cocaine use between people being treated for opioid disorder and people being treated for chronic pain.

6.5 Prescription drug dispensation history

The preceding sections focused on pharmaceutical opioids and other substances detected through post-mortem toxicology testing. Additional information about decedents' history of use of prescribed pharmaceutical opioid and other substances was obtained through review of prescription drug dispensation records. Opioids used for pain management are discussed separately from those used for opioid substitution treatment (OST) in the following sections. While not generally a first-line analgesic, methadone may be used to manage cancer pain or chronic non-cancer pain, in addition to its more common use for withdrawal management or maintenance treatment of opioid-dependent individuals (College of Physicians and Surgeons of BC, 2010). PharmaNet records were reviewed to determine whether methadone dispensed to decedents was prescribed for pain management or maintenance purposes.

Of 333 total overdose deaths, 228 cases (68.5%) involved pharmaceutical opioids prescribed for pain management. Ninety-two deaths (27.6%) involved OST, all of which were methadone maintenance treatment (MMT). Thirteen deaths (3.9%) involved both MMT and opioids prescribed for pain management.

6.5.1 Pharmaceutical opioids used for pain management

To account for variability in strength between different pharmaceutical opioids, the mean daily dosages of decedents' most recent opioids prescribed for pain management were converted into daily morphine milligram equivalent (MME) dosages. Table 6 lists the mean daily MME dosages among decedents receiving opioids for pain management only and among those receiving concurrent opioids for pain management and MMT.

Overall, almost half of decedents taking opioids for pain management (44%) were prescribed a mean daily dose exceeding 120 MME. More than a quarter of decedents taking opioids for pain management (27%) were prescribed a mean daily dose exceeding 200 MME. These dosages are the thresholds for increased risk outlined in clinical practice guidelines in BC and Washington State, respectively.

There were no significant relationships between decedents' sex or age and likelihood of receiving high-dose opioids, regardless of whether the threshold level for high-dose was set at 120 MME or 200 MME.

Table 6. Daily dosage of most recent pain management opioid prescription involved in prescribed pharmaceutical opioid-associated deaths in BC, 2009 to 2013.

	Daily dosage of most recent pharmaceutical opioid dispensation (MME) at date of death				Proportion receiving >120 MME per day	Proportion receiving >200 MME per day
	Minimum	Maximum	M (SD)	Median	n (%)	n (%)
Pain only (n=228)	4.5	1650.0	188.35 (263.40)	100.0	105 (46.1)	65 (28.5)
Pain and MMT (n=13)	10.0	180.0	47.62 (47.33)	28.5	*	0 (0.0)
Total (n=241)	4.5	1650.0	180.76 (258.36)	90.0	106 (44.0)	65 (27.0)

Note. "Pain only" refers to decedents receiving pharmaceutical opioids exclusively for pain management. "Pain and MMT" refers to decedents receiving pharmaceutical opioids concurrently for pain management and MMT. In cases where decedents held active prescriptions for more than one opioid for pain management at the time of death, and where toxicology testing showed that these opioids were involved in the fatal overdose, cumulative daily dosages are reported. In cases where decedents held active prescriptions for pharmaceutical opioids for pain management and MMT, MMEs reported in this table refer only to the daily dosage of opioids prescribed for pain management (i.e., MMT is not calculated within the cumulative total daily opioid dosage in this table). MME: morphine milligram equivalents. MMT: methadone maintenance treatment.

*Cells with fewer than 5 cases suppressed due to institutional privacy regulations.

There was variability both within and between regions in terms of mean opioid doses for pain management (Figure 11). The proportion of decedents prescribed opioid dosages higher than 200 MME for pain management varied from 15.4% in the Northern region to 37.8% in the Interior region, which also had the higher rates of overdose deaths. However, due to the large variability in opioid dosages within regions, and the small number of decedents, especially in the Northern region, these figures should not be interpreted as evidence of statistically significant differences.

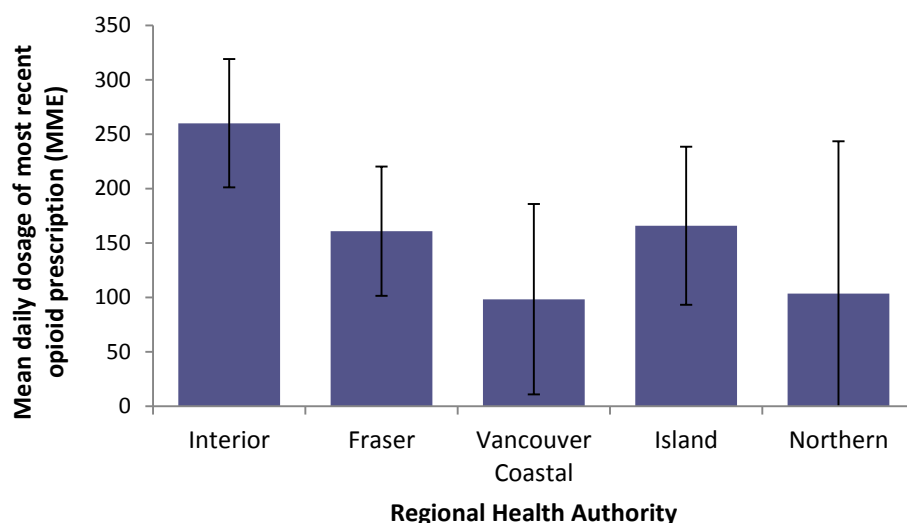


Figure 11. Mean daily dosage in morphine milligram equivalents (MME) of pharmaceutical opioids prescribed for pain management and involved in fatal overdoses in BC, 2009-2013. In cases where decedents held active prescriptions for more than one opioid for pain management at the time of death, and where toxicology testing showed that these opioids were involved in the fatal overdose, cumulative mean daily dosages are reported.

6.5.2 Opioid substitution treatment

Current options for opioid substitution treatment in BC include methadone, buprenorphine, and Suboxone, a buprenorphine and naloxone formulation (Nosyk et al., 2014). Within the total cohort of 333 deaths, there were 105 cases involving methadone where the decedent held an active prescription for methadone maintenance treatment (MMT) in the 60 days prior to death. Five decedents held a prescription for a buprenorphine formulation in the 60 days before death; however, as buprenorphine was not detected in toxicology results in any deaths, this section focuses on the 105 deaths involving MMT. As noted in section 4.2.2.1, daily dosages of methadone are reported in milligrams and are not converted into MME.

6.5.2.1 Methadone maintenance dosages among decedents

As shown in Table 7, most MMT-associated deaths (92 of 105; 87.6%) occurred among individuals receiving MMT and no other pharmaceutical opioids. A minority of MMT-associated deaths occurred among individuals receiving MMT and additional pharmaceutical opioids for pain management (13 of 105; 12.4%). Among decedents receiving opioid substitution treatment (OST), the mean daily dosage of methadone was 98.5 milligrams.

Table 7. Daily dosage of most recent methadone dispensation among methadone maintenance treatment-associated deaths in BC, 2009 to 2013.

	Daily dosage of most recent MMT dispensation (mg) at date of death			
	Minimum	Maximum	M (SD)	Median
MMT only (n=92)	2.0	450.0	102.88 (82.48)	90.0
Pain and MMT (n=13)	17.5	190.0	67.50 (49.52)	60.0
MMT total (n=105)	2.0	450.0	98.50 (79.83)	85.0

Note. “MMT only” refers to decedents receiving no pharmaceutical opioids other than MMT. “Pain and MMT” refers to decedents receiving pharmaceutical opioids concurrently for pain management and methadone maintenance treatment. In cases where decedents held active prescriptions for pharmaceutical opioids for pain management and MMT, dosages reported in this table refer only the daily dosage of methadone, not to the cumulative total daily opioid dosage. MMT: methadone maintenance treatment.

6.5.2.2 Patterns of methadone maintenance treatment

Clinical practice guidelines note an increased risk of fatal overdose during the initiation and dose titration phases of methadone treatment (College of Physicians and Surgeons of British Columbia, 2014; Washington State Agency Medical Directors' Group, 2015). PharmaNet records pertaining to service dates for dispensations involving MMT were examined to determine duration of treatment with methadone prior to death. Table 8 shows the duration of MMT use prior to MMT-related overdose deaths. A majority of these decedents (61.9%) initiated MMT four years or more prior to death. However, just over 10 percent of these decedents initiated MMT within two weeks of death.

In general, MMT users' prescription dispensation histories indicated they had received MMT on a regular basis. Regardless of the actual duration of treatment, 76 of 105 (72.4%) decedents had received MMT on at least 90 percent of days from the date MMT was first dispensed until the date of death. Intermittent MMT use was less common. Nineteen (18.1% of MMT deaths) had received MMT on 50 to 90 percent of days from the date MMT was first dispensed until the date of death. Ten decedents (9.5% of MMT deaths) had received MMT on fewer than 50 percent of days from the date of first dispensation until the date of death.

Prescription regimens for MMT include daily witnessed ingestions as well as doses that can be taken home and administered on a daily basis (“carries”). Among the 105 individuals whose fatal overdose involved MMT, the median days supply of methadone provided per dispensation (over the past 5 years) was 1 for the vast majority (78.1%). This indicates that most MMT-associated overdose deaths occurred among individuals accessing MMT via daily witnessed ingestions, and thus within the context of daily contact with a health care provider (i.e., pharmacist).

Table 8. Duration of methadone maintenance treatment among prescribed methadone-associated deaths in BC, 2009 to 2013.

Elapsed time between first MMT dispensation and date of death	n (%)
0 – 14 days	11 (10.5%)
15 days – 2 years	15 (14.3%)
2 – 4 years	14 (13.4%)
More than 4 years	65 (61.9%)
Total	105
MMT: methadone maintenance treatment	

Prescription drug dispensation history - Key Findings

- Among decedents prescribed pharmaceutical opioids for pain management, more than 25 percent were receiving daily doses exceeding 200 morphine milligram equivalents (MME), and 44 percent were receiving daily doses exceeding 120 MME. These dosages are the thresholds for increased risk outlined in clinical practice guidelines in BC and Washington State, respectively

- Of the decedents on methadone maintenance treatment, 10% had initiated methadone treatment within two weeks of death. Overdose on initiation of methadone is a known risk, hence this finding indicates an opportunity to further improve methadone assisted treatment initiation.
- Most methadone-associated deaths occurred in individuals accessing methadone via daily witnessed ingestions, and thus within the context of daily contact with a health care provider (i.e., pharmacist).

6.6 Medical history

Details of decedents' medical history were based on Medical Services Plan (MSP) and Discharge Abstract Database (DAD) records covering the year prior to death. MSP records were available for 330 of 333 decedents, with records for 329 decedents containing ICD-9 diagnostic codes. In this section, findings are reported separately for decedents receiving opioids exclusively for pain management and decedents receiving MMT. The majority of decedents were regular users of medical services.

6.6.1 Past year medical care

Service dates of MSP billing records were reviewed to investigate decedents' health care utilization in the year prior to death. Decedents saw a health care provider on an average of 48.5 different days (SD 34.5 days; median 40.0) in the year before death (range 3 to 256 days). This indicates that, on average, individuals who experienced a fatal overdose involving prescribed pharmaceutical opioids interacted with a health care professional approximately once a week in the year prior to death. The number of days on which a health care provider was seen was analyzed by quarter of the year prior to death: 0-3 months (M 12.8 days, SD 9.6); 3-6 months (M 12.4 days, SD 13.6), 6-9 months (M 11.4 days, SD 9.8), and 9-12 months (M 11.9 days, SD 9.9). These numbers indicate no apparent change, on average, in the frequency of medical visits in the months leading up to death.

On average, MMT recipients had more past-year medical service days than individuals receiving opioids exclusively for pain management. This may reflect the frequent interactions with health care providers among those receiving opioid substitution treatment. Taking into account the differences between MMT and pain management decedents, there was no significant difference between men and women in number of past-year MSP service days.

MSP records revealed that decedents in the study cohort had received services from health care providers in a range of different settings. Table 9 shows the proportions of decedents who had received care in various settings in the year prior to death.

Table 9. Number of decedents receiving medical care in various settings in the year prior to death, as per BC Medical Service Plan records, 2009-2013.

Service Location	n (%)
Practitioner's office – in community	322 (97.6)
Hospital – outpatient	238 (72.1)
Diagnostic facility	236 (71.5)
Hospital – emergency room (unscheduled patient)	215 (65.1)
Hospital inpatient	154 (46.7)
Practitioner's office – in publicly administered facility	50 (15.2)
Mental health centre	25 (7.6)

Hospital – day care (surgery)	24 (7.3)
Residential care/assisted living residence	13 (3.9)
Patient’s private home	10 (3.0)
Private medical/surgical facility	<5 (<2.0)
Other (e.g., accident site, ambulance, etc.)	<5 (<1.0)
Total	330

6.6.2 Physical health conditions

Diagnostic information obtained from decedents’ medical records showed that these individuals were frequently receiving treatment for a range of physical and mental health conditions. Detailed analysis of common physical health conditions among this cohort has not been done. However, review of MSP records from the year prior to death indicated that decedents receiving pharmaceutical opioids exclusively for pain management tended to have more diagnosed health conditions than decedents receiving MMT. Differences were particularly apparent for musculoskeletal conditions, injuries, and cardiovascular illness, which were all more common among decedents receiving opioids for pain management. Decedents receiving MMT were slightly more likely than those receiving opioids exclusively for pain management to have seen a health professional for an infectious disease in the year prior to death.

6.6.3 Mental health conditions

MSP records revealed that 85 percent of decedents saw a health professional for a mental disorder or substance use disorder in the year before death. Table 10 presents the proportions of decedents receiving opioids for pain management and MMT who had received various types of mental health diagnoses. Mood and anxiety disorders were common among both groups and exceeded estimated rates for these mental health conditions among the province as a whole (e.g., PHSA, 2010). In this cohort, rates of mood disorders were significantly higher among pain management decedents as compared to those receiving MMT (Table 10).

The high rate of drug use disorder (91%) among decedents receiving MMT is not unexpected, as an individual must be assessed as meeting DSM-IV-TR (APA, 2000) diagnostic criteria for opioid dependence prior to initiating MMT (College of Physicians and Surgeons of British Columbia, 2014). As shown in Table 10, 9 percent of decedents receiving MMT *did not* have a drug use disorder diagnosis noted in their MSP records in the previous year. These may represent cases in which the opioid dependence diagnosis was noted earlier in the decedents’ MSP records but not in the year prior to death.⁸

Table 10. Number of decedents diagnosed with various mental health conditions, as per past-year BC Medical Service Plan records.

Pain management <i>n</i> (%)	MMT <i>n</i> (%)	Significant difference (χ^2)
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⁸ The updated set of diagnostic criteria for opioid use disorder in the more recent DSM-V (APA, 2013) note that the criteria for tolerance and withdrawal (two symptoms typically associated with physical dependence on opioids) are not considered to be met for individuals using opioids solely under appropriate medical supervision. Thus, physicians using the DSM-V might not apply a diagnosis of opioid use disorder to patients receiving prescribed pharmaceutical opioids if no other symptoms of problematic opioid use are present. However, given that the mid-2013 publication date of the DSM-V coincides with the very late stages of the study period of the current investigation, it is unlikely that this would account for the 9% of decedents within the MMT group who did not have a drug-related disorder coded in their medical records in the year prior to death.

Alcohol-related disorder	22 (10%)	15 (14%)	No
Drug-related disorder	73 (33%)	95 (91%)	Yes ($p<.001$)
Mood disorder	127 (57%)	46 (44%)	Yes ($p<.05$)
Anxiety disorder	100 (45%)	43 (41%)	No
Psychosis	19 (9%)	11 (11%)	No
Total	224	105	

6.6.4 Hospitalization in the year prior to death

Hospitalization records for the year before death were obtained from the Discharge Abstract Database (DAD). Because hospitalizations occurring prior to death were of interest in this analysis, records for 7 decedents pertaining to hospitalizations for ultimately fatal overdoses were excluded from the present analysis.

A total of 136 of 333 decedents (40.8%) had been admitted to and discharged from hospital in the year before death. The number of hospitalizations ranged from 1 to 22 (M 2.29, SD 2.41). The median and modal numbers of past-year hospitalizations were both 1. Fourteen decedents (4.2%) had been discharged within a week of death. Thirty-three decedents (9.9%) had been discharged within 30 days of death.

There was no significant mean age difference between decedents who had been hospitalized in the year prior to death (M 49.21 years, SD 11.29) and those who had not (M 47.93 years, SD 10.02), $t(331)=1.093$, $p=.275$. There were no significant differences between the proportions of men (38.4%) and women (43.9%) who had been hospitalized in the past year, $\chi^2(1)=1.045$, $p=0.307$. Individuals receiving opioids exclusively for pain management (45.1%) were somewhat more likely to have been hospitalized in the year prior to death than those receiving MMT (31.8%), $\chi^2(1)=5.362$, $p=0.021$.

A review of ICD-10-CA classification codes within DAD hospitalization records in the year prior to death revealed that 25 of 333 decedents (7.5%) had been hospitalized with an associated diagnostic code of poisoning by drugs, medicaments and biological substances (ICD-10-CA codes T36-T50) or toxic effect of alcohol (ICD-10-CA code T51). There were no significant differences in terms of demographic variables or cohort (OST vs. pain management) between decedents who had or had not been hospitalized for a nonfatal poisoning incident in the year prior to death.

Key Findings – Medical History

- Contact with the health care system was frequent for people who died of an overdose. On average, individuals who experienced a fatal overdose involving prescribed pharmaceutical opioids interacted with a health care professional approximately once a week in the year prior to death.
- Just over 40 percent of the cohort had been admitted to hospital at least once in the year prior to death. A subset of that group (7.5% of the overall cohort) had been hospitalized for a previous nonfatal overdose in the year prior to death. Additional analysis of these particular cases is important to determine why someone with a previous hospitalization due to overdose would overdose again due to prescribed drugs.
- A high proportion of decedents (85%) saw a health professional for a mental disorder or substance use disorder in the year prior to death. Such contacts could facilitate safe and effective medication use, psychological support and substance use disorder treatment. Further analysis could examine whether these frequent contacts are resulting in meaningful therapeutic interventions.

6.7 Aboriginal Ethnicity

6.7.1 Identification of Aboriginal and First Nations decedents

An important goal of this project was to explore potential vulnerability factors for prescribed pharmaceutical opioid-associated overdose among Aboriginal British Columbians. According to BCCS records, 31 of 333 decedents (9.3%) from 2009 to 2013 were of Aboriginal ethnicity. Linkage of the current dataset with the First Nations Client File did not increase the numbers of people of First Nations status. Due to the small number no further analysis was conducted.

The proportion of decedents identified as Aboriginal in this cohort exceeds the 5.4 percent of the overall BC population made up of those reporting Aboriginal identity (Statistics Canada, 2013). Because of the small raw numbers of prescribed pharmaceutical opioid-associated deaths among Aboriginal British Columbians between 2009 and 2013, the following analyses should be considered with caution.

6.7.2 Characteristics of Aboriginal and non-Aboriginal decedents

The proportion of annual prescribed pharmaceutical opioid-associated deaths in BC identified as Aboriginal was consistent from 2009 to 2013, $X(1)^2=1.69$, $p=0.793$. On average, Aboriginal decedents tended to be somewhat younger (M 42.9 years, SD 10.4) than their non-Aboriginal counterparts (M 49.0 years, SD 10.4), $t(331)=3.08$, $p=0.002$. The majority of prescribed pharmaceutical opioid-associated deaths among Aboriginal people occurred between the ages of 30 and 49, while the majority of deaths among non-Aboriginal people occurred between the ages of 40 and 59. This is consistent with data at the provincial level showing that the average age of Aboriginal British Columbians is younger than that of non-Aboriginal British Columbians (BC Stats, 2006).

The proportion Aboriginal decedents who were female (58.1%) was somewhat higher than the proportion of non-Aboriginal female decedents (43.0%), but this difference was not statistically significant, $X(1)^2=2.57$, $p=0.109$.

There was significant variability by Health Authority of residence, $X(1)^2=12.77$, $p=0.012$, with the lowest proportion of deaths of individuals of Aboriginal ethnicity was in the Fraser region (5.3%), while the highest proportion of deaths of Aboriginal people was in the Northern region (33.3%). This variation is consistent with the relatively lower proportion of residents of Aboriginal ethnicity in the Fraser Health Authority and higher proportion of residents of Aboriginal ethnicity in the Northern Health Authority (BC Stats, 2006).

6.7.3 Substance use and pharmaceutical opioid prescription patterns among Aboriginal and non-Aboriginal decedents

Based on post-mortem toxicology testing, there were no differences between the proportions of Aboriginal and non-Aboriginal decedents where fatal overdoses involved prescribed pharmaceutical opioids in addition to alcohol, $X(1)^2=0.46$, $p=0.497$, illegal drugs, $X(1)^2=0.19$, $p=0.663$, or non-prescribed pharmaceutical opioids, $X(1)^2=0.03$, $p=0.875$. There were also no significant differences between the proportions of methadone deaths among Aboriginal and non-Aboriginal decedents, $X(1)^2=0.10$, $p=0.753$.

Among decedents who experienced an overdose on opioids prescribed for pain management, the mean daily dosage of the most recent opioid dispensed prior to death did not differ significantly between Aboriginal (M 178.91 MME, SD 316.70) and non-Aboriginal decedents (M 180.96 MME, SD 251.96), $t(26.32)=0.031$, $p=0.976$. Among decedents who experienced an overdose on methadone prescribed for maintenance, the mean daily

dosage of methadone did not differ significantly between Aboriginal (M 107.78mg, SD 118.93) and non-Aboriginal decedents, (M 97.63mg, SD 76.00), $t(103)=0.363$, $p=0.717$.

Key Findings

- People of Aboriginal ethnicity are disproportionately represented in this cohort of decedents.
- Given the age and geographic distribution of Aboriginal people in BC, the Aboriginal decedents did not differ notably from non-Aboriginal decedents on demographic or geographic measures, toxicology results, or prescribed opioid dosage.

7 Discussion

7.1 Summary

Harms relating to the use of pharmaceutical opioids have increasingly been recognized as a critical public health concern in British Columbia, and this report focuses on fatal overdoses involving pharmaceutical opioids for which decedents held current prescriptions. Focussing on prescribed pharmaceutical opioids has potential implications for prevention of prescribed pharmaceutical drug-related mortality, which may differ from deaths due to pharmaceutical drugs that are obtained illegally.

This investigation begins to address the need for province-wide data on the contexts and characteristics of such deaths to inform responses by examining prevalence and patterns of unintentional fatal overdoses involving prescribed pharmaceutical opioids in BC between 2009 and 2013. Details of overdose deaths drawn from the BC Coroners Service files were linked with population-based datasets containing prescription drug use history and medical services utilization to characterize factors associated with prescribed pharmaceutical opioid-associated death among British Columbians.

Terminology and definitions vary widely within the broader body of literature on problematic prescription drug use and prescription drug-related harms. Lack of clarity in terminology makes it difficult to interpret results, to compare findings across different studies, and to develop targeted strategies for prevention and intervention. In the current investigation, which focused specifically overdose deaths that were unintentional and associated with pharmaceutical opioids prescribed to the decedents, the research team prioritized the use of clear operational definitions in defining the study cohort. To facilitate the development of evidence-based policy and targeted strategies for prevention and intervention, future investigations of opioid-associated deaths should employ clear operational definitions and consistent terminology.

The first objective of this work was to describe the prevalence and geographical distribution of unintentional prescribed pharmaceutical opioid overdose mortality in BC. We found that these deaths have been happening at a rate of at least 75 deaths per year, they make up a substantial i.e. at least 20% of all accidental drug poisoning deaths, they are mostly impacting the young to middle age adults population, and that there is substantial geographic variation in these deaths. It is concerning that drugs which are prescribed to improve health are associated with this amount of mortality. The time period examined was not of sufficient duration to discern clear trends so additional monitoring of this situation is warranted.

We did not examine prescribing rates of these drugs by geographic area, so it is not known whether this mortality is associated with different prescribing patterns, or other factors. This is an avenue of investigation that warrants further attention.

The second objective was to identify potential factors characterizing individuals who experienced an unintentional fatal overdose involving pharmaceutical opioids prescribed to them by a health care provider. We found that, in contrast to illicit drug associated overdoses, women were represented more frequently, and exceeded representation by men in younger age groups. We did not examine prescribing rates by gender so this something that bears further investigation. Although numbers were small it also appears that Aboriginal patients are over-represented compared to non-Aboriginal patients.

The third objective was to describe the contexts and characteristics of fatal unintentional prescribed pharmaceutical opioid overdoses in BC. The vast majority of deaths occurred in private residences, indicating a substantial hazard related to taking these medications alone or without awareness of other members of a household about the risk to people taking these drugs.

Other psychoactive substances were detected in almost all fatalities, including pharmaceutical opioids which were not prescribed, indicating the importance of examining this problem as one of poly-drug use. Given the poly drug use noted, causation attribution to a particular drug is difficult and recognizing the cumulative or synergist effects is important. A particularly salient finding of this research was the high proportion of decedents whose deaths involved combinations of pharmaceutical opioids and other substances. Health care professionals should be aware of the medications that may act synergistically with opioids, including benzodiazepines and some antidepressants. This underscores the importance of physicians checking patients' PharmaNet records when prescribing opioids and other substances with known synergistic effects with opioids.

Almost a quarter of the deaths reviewed in this investigation involved concurrent use of non-prescribed and prescribed pharmaceutical opioids. Health care providers should be mindful of the risks of this risk and should invite their patients to discuss use of diverted medications and other problematic forms of opioid use in a non-judgmental, compassionate way.

Recent efforts to make naloxone more widely available throughout BC have prevented numerous deaths (Banjo et al., 2014), but have largely targeted illegal opioid users. Individuals using prescribed pharmaceutical opioids to treat chronic pain may be hesitant to request naloxone or accept it from a health care provider due to a tendency to underestimate the risk of overdose or a wish to avoid being perceived as a "drug user" (Banjo et al., 2014). Consideration should be given to making naloxone and education regarding its use available to all patients prescribed opioids for chronic pain management or opioid substitution treatment (Darke, 2014).

Methadone was found to be a substantial contributor to these deaths, as was codeine, although the latter is often being regarded as less risky. Shifting opioid substitution treatment to use buprenorphine as drug of choice may assist with reducing the impact of methadone. Closer examination of the role of codeine bears further investigation.

The high rates of concurrent involvement of antidepressants and benzodiazepines, as well as gabapentin and quetiapine, which are used to treat chronic pain, reinforces the concerns about polypharmacy of central nervous system acting drugs, and raises questions about the utility of co-prescribing compared to the risks of a fatal outcome. The high rates co-occurring mental health diagnoses in patients with pain conditions highlights the challenges in working with these patients to prescribed drugs for both conditions and avoid serious adverse events.

Contact with the health care system was frequent, and a high proportion of decedents being treated for pain saw a health professional for a mood, anxiety, or drug-related disorder. More detailed examination of the interaction with the health care system to identify risks, missed prevention opportunities, and potential ways to better intervene warrant examination.

The high rate of detection of cocaine was particularly notable, indicating that accessing the illegal market by these patients is not uncommon, and that perhaps cocaine is being used to counter the sedative effects of opioids. The association need further investigation.

High dose opioid prescribing was common, indicating the need for attention to risk of death as dose increases. Health care providers face a difficult challenge in balancing the provision of pharmaceutical opioids when indicated with efforts to minimize opioid-related harms. Opioids play an essential role in treating many medical conditions, including acute pain, cancer-related pain, and opioid dependence (e.g., Degenhardt et al., 2007; Mattick et al., 2009). Accumulating evidence suggests, however, that their utility in treating chronic pain may be limited and may be outweighed by their poor safety profile (Franklin, 2014). Further, evidence supports the efficacy of non-pharmacological treatments for chronic non-cancer pain, targeting pain itself or common comorbid issues such as depression or insomnia (e.g., Garland et al., 2013; Smith et al., 2005; Williams et al., 2013). Evidence-based non-pharmacological treatments, such as physical therapy and cognitive-behavioural therapy, should be considered part of a comprehensive and interdisciplinary approach to treating chronic pain. Removal of existing barriers (e.g., affordability, availability) to allow more patients to access non-opioid pain management services in BC is of critical importance.

Prescribed pharmaceutical opioid-associated deaths represent one aspect of the public health challenge related to opioids (CDC, 2011). To more fully understand this complex issue, it is important to situate the current findings within the broader context. A few of the many related concerns include: pharmaceutical opioid dispensations (e.g., changes in prescription rates, dosages, or durations), pharmaceutical opioid-associated morbidities, addition or removal of particular formulations of opioids from the provincial formulary (e.g., the discontinuation of OxyContin in 2012), diversion of prescribed opioids to non-prescribed users, access to opioid substitution treatment and harm reduction services, and availability of illegal opioids. An example of note is the recent increase in fentanyl-related overdose deaths in BC (BC Centre for Disease Control, 2015), which has been attributed to illegally-produced rather than pharmaceutical fentanyl (Burgmann, 2015). Although prescribed pharmaceutical opioid-associated overdose and illegal fentanyl-associated overdose may seem like distinct phenomena, evidence indicates that many individuals who use illegal opioids report a prior history of prescribed opioid use (Cicero et al., 2014).

To gain a more comprehensive perspective of opioid-related morbidity and mortality in BC, and to maximize the effective prevention and intervention strategies, prescribed pharmaceutical opioid-associated overdose deaths must be considered within the broader context of this critical public health concern.

Beyond the BC Ministry of Health and the BC Coroners Service, there are many stakeholders from sectors across BC involved in monitoring and surveillance, research, prevention, and intervention related to pharmaceutical opioid-associated harms. Partnerships between these diverse groups, which include other government agencies, health authorities, researchers, regulatory bodies, practitioners, non-profit/advocacy organizations, and patient groups are essential for maintaining a coordinated response to opioid-related harms. Collaborative relationships are critical for gathering and interpreting data, sharing resources, and developing evidence-based strategies to prevent and mitigate pharmaceutical opioid-related harms. Of particular note is the need for inclusion of Aboriginal organizations, including the First Nations Health Authority, the BC Association of Aboriginal Friendship Centres, and Métis Nation BC, to ensure that continued efforts in this area address the needs of First Nations and Aboriginal British Columbians.

Preliminary findings of this research were presented as part of a panel at the annual conference of the Canadian Public Health Association in May 2015 (McLarnon et al., 2015). This presentation drew a large and diverse audience of researchers, clinicians, and policymakers from across the country and resulted in an engaging discussion about opioid surveillance and strategies for prevention and harm reduction in Canada. While BC has long been innovative in its approach to harm reduction and is well positioned to be a leader in surveillance and monitoring of opioid-related harms, it is crucial to exchange knowledge and strategies with other jurisdictions to enhance our efforts at preventing and reducing harms related to pharmaceutical opioids. Encouragingly, plans for a national prescription drug monitoring system were announced in mid-2015 (Weeks, 2015), which may address the lack of countrywide data on this issue.

It is concerning that drugs which are prescribed to improve health are associated with this amount of mortality.

7.2 Strengths and Limitations

By linking information from coroners' investigations to relevant population-level datasets including prescription dispensation history, medical services utilization, and hospitalizations, this research gives new insight into the contexts and characteristics of prescribed pharmaceutical-opioid associated deaths in BC. However, some limitations should be taken into account when interpreting these findings.

Firstly, although comprehensive data on individual cases was available, the total number of deaths over the course of the study period was relatively small, precluding more detailed statistical analysis of subsets of the data (e.g., sub-provincial geographical areas). Similarly, the duration of the study period was limited to five years, with complete data available for only four years, limiting the ability to make inferences about longitudinal trends. While best efforts were employed to identify decedents' Personal Health Numbers (PHNs) in cases where the number was missing or invalid, in 76 cases, no PHN for the decedent could be identified. As a correct PHN was needed to link BCCS data with the other datasets of interest, absence of a PHN precluded data linkage and resulted in exclusion of these 76 cases from the study cohort. While some of these cases may represent deaths of non-BC residents (who would not be expected to have PHNs), any exclusion of cases otherwise meeting the cohort definition would suggest that the pharmaceutical opioid-associated mortality rate reported herein represents an underestimation of the actual rate in BC during the study period.

A unique aspect of this investigation is the inclusion of coroners' data, which contain extensive detail about the circumstances and contexts of prescribed pharmaceutical opioid-associated deaths. One tool used by BCCS to collect these data is the Accidental Drug Overdose Protocol form (Appendix B), which focuses on a variety of domains relevant to overdose risk (e.g., mode of drug administration, hazardous use of prescription medications, recent incarceration or abstinence from substance use, and medical intervention received prior to death). In many cases, this form was omitted or incomplete, limiting its use for detailed analysis in this investigation. While it is recognized that these data may not always be readily available to investigators, the Accidental Drug Overdose Protocol represents an invaluable source of information regarding the risk factors for prescribed pharmaceutical opioid-associated overdose in BC.

Another novel characteristic of this study was the attempt to ascertain, as accurately as possible, whether decedents had held prescriptions for the pharmaceutical opioids involved in these fatal overdoses. This was made possible by the availability of post-mortem toxicological analysis results and prescription dispensation history (see

section 4.3.3). Linking these datasets allowed for identification of cases meeting the cohort definition, with deaths involving prescribed pharmaceutical opioids included, and deaths associated with only non-prescribed opioids excluded. Further, in deaths involving multiple substances (the majority of cases) linking these datasets also allowed for determination of whether other pharmaceuticals involved were obtained with or without a prescription. The prescribed/non-prescribed determination is important, as the potential implications for prevention of pharmaceutical drug-related mortality may differ depending on whether the drugs were obtained and administered with the oversight of a health care provider or not.

While every effort was made to ensure the accuracy of this process, a number of caveats should be taken into account. Pharmaceutical opioids coded as non-prescribed may have originated from other legitimate sources not captured in PharmaNet (e.g., opioids dispensed in BC hospitals). Morphine detected through toxicology testing may have been the result of the metabolism of codeine to morphine (Häkkinen et al., 2012), rather than due to ingestion of pharmaceutical morphine (although careful review of coroners' records was undertaken to minimize this potential source of error). Finally, the data sources did not allow for determination of cases where a decedent may have taken the same pharmaceutical opioid both with and without a valid prescription. For example, if a decedent held a prescription for methadone, but obtained additional methadone through illegal channels, toxicology results would not distinguish these two sources.

The implications of this work are relevant to monitoring and surveillance of pharmaceutical opioid-associated harms as well as to clinical practice. It is hoped that the findings in this report will assist in developing recommendations and actions to prevent similar deaths in the future.

7.3 Future Directions

The findings described in this report represent preliminary and primarily descriptive analyses of a cohort of prescribed pharmaceutical opioid-associated deaths in BC from 2009 to 2013. The results indicate some potential risk factors for prescribed pharmaceutical opioid-associated mortality, which may guide future investigations in this area. Evidence-based prevention and intervention strategies depend on solid evidence specific to the BC context, and there is still much to learn about the social, contextual, and individual-level factors that may increase British Columbians' vulnerability for experiencing an overdose on prescribed pharmaceutical opioids. Further, the present findings provide baseline data for ongoing surveillance of pharmaceutical opioid-associated harms in BC, which may focus on tracking prevalence rate and trends over time. In addition to previously mentioned suggestions for further analysis, a list of suggested future analyses is outlined in Appendix C.

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9 Appendices

- A. Opioid conversion table
- B. BC Coroners Service Accidental Drug Overdose Protocol Form
- C. Future analyses
- D. Revised linkage flow diagram separating prescribed pharmaceutical opioid-associated deaths into two cohorts based on whether illicit substances were involved in the fatal overdose

APPENDIX A. Opioid conversion table

The table below was used to calculate morphine milligram equivalent dosage (MME). These equivalences refer to analgesic strength of oral opioids, and not psychoactive effects or effectiveness in relieving opioid withdrawal symptoms. Wide ranges have been reported in the literature, and the figures are based on the best data available in 2014-2015. References that informed this table are listed below.

<i>Equivalence to 1 mg of oral morphine</i>	
Opioid	Morphine Equivalent Conversion Factor*
Buprenorphine	80
Buprenorphine (transdermal) patch	2
Codeine	0.15
Fentanyl (transdermal) patch	4
Hydromorphone (injectable)	15
Hydromorphone (oral)	5
Morphine (injectable)	3
Morphine (oral)	1
Oxycodone (injectable)	2
Oxycodone (oral)	1.5
Tramadol	0.2
Meperidine	0.1
*The conversion factors are multiplied by the size of the unit whether that unit is measured in milligrams or micrograms/hour (e.g., for fentanyl and buprenorphine patches).	

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APPENDIX B. Accidental Drug Overdose Protocol

In the data abstracted from BC Coroners Service files, the following variables from the Accidental Drug Overdose Protocol form were included. This form was at least partially completed for 78.7% of the 333 cases in the cohort of prescribed pharmaceutical opioid-associated deaths; however, not all variables were always filled out, limiting its applicability for the present analysis. The information gathered in this form would be of use in understanding risk factors for fatal overdose among users of pharmaceutical opioids in BC.

Type of drug

- illicit/street
- over the counter
- prescription

If illicit, DTES? (yes/no)

If illicit, supervised injection site? (yes/no)

Mode of drug consumption (oral, smoked, snorted, injected, other)

- Name of drug consumed orally
- Name of drug smoked
- Name of drug snorted
- Name of drug injected
- Name of drug consumed in another way
- Consumption method

Drug taken in presence of others (yes/no)

Alcohol contributory to death (yes/no)

Medical intervention before death (yes/no)

If yes, intervention provided by?

Narcan administered (yes/no)

Drug use

- medical
- occasional/recreational
- chronic/addicted

Previous overdose events (yes/no)

If yes, provide OD event details

Factors in OTC or RX drug OD

- hoarding
- multidoctoring
- occasional overuse
- regular overuse
- use of other's medications
- other
- If other, specify factors

Recently abstinent from drug use (yes/no)

incarceration ending < 1 week ago

incarceration ending > 1 week ago

personal choice

rehab/detox

other, specify

If other, specify

Name of recent rehab program, if any

Duration of participation in rehab?

Time since rehab participation end

Registered in methadone maintenance program (yes/no)

If methadone program, physician name

If methadone program, pharmacy name

Compliant w methadone program (yes/no)

selling/sharing

use of street drugs

Recent termination of methadone maintenance program (yes/no)

Time since methadone maintenance termination

Medical history (yes/no)

HIV

Hep C

WorkSafe BC involvement

brain injury

chronic pain

disability

other relevant

If other relevant, specify

Current psychiatric diagnosis (yes/no)

bipolar

depression

schizophrenia/psychosis

other

If other diagnosis, specify

Current mental health treatment (yes/no)

community mental health team

family physician

medication

other

If other treatment, specify

Previous suicide attempt(s) (yes/no)

If yes, Accidental class rationale

Issues to address by recommendation

APPENDIX C. Future Analyses

The results described in this report represent preliminary descriptive analyses of cases of pharmaceutical opioid-associated mortality in BC between 2009 and 2013, limited to decedents holding current prescriptions within 60 days of death. While far from being a comprehensive list, the following points suggest a number of potentially important avenues for future analysis focusing on the current cohort.

- ***Providing additional context for mortality rates by considering population denominators.*** For example, this could include considering mortality rates by geographical region within the context of regional variation in prescription rates for various pharmaceutical opioids; regional variation in chronic pain and other relevant health conditions; availability of health services for chronic pain and/or opioid dependence by region; and socioeconomic factors.
- ***Separate analyses for distinct groups within the broader cohort.*** A priority for future analysis is to perform all analyses separately for opioid substitution treatment-associated deaths and those associated with opioids prescribed for pain management. Similarly, another priority is to perform separate analyses for overdose deaths involving only prescribed medications and those involving pharmaceutical opioids used concurrently with illegal substances (e.g., cocaine, heroin). A revised inclusion and exclusion flow diagram for this analysis is included in Appendix C (Figure 12).
- ***Exploratory analysis using a statistical technique such as cluster analysis*** is also a potentially useful empirical means of identifying meaningful subtypes within the broader cohort of prescribed pharmaceutical opioid-associated deaths. Greater understanding of heterogeneity within the overall cohort could assist in the development of targeted prevention and intervention strategies for those at risk of harms associated with pharmaceutical opioids.

An initial exploration using a two-step cluster analysis in SPSS, including demographics, geographic location, toxicological results, and diagnostic information as potential discriminating variables yielded two distinct clusters within the overall cohort. In addition to demographic differences, the two clusters differed in terms of mental health diagnoses, particularly depression and anxiety disorders.

- The BCCS ***Accidental Drug Overdose Protocol*** form (Appendix B) contains a potential wealth of information about relevant factors in prescribed pharmaceutical opioid associated deaths. Many of the pieces of data collected on this form have been linked to pharmaceutical opioid overdose risk in previous empirical research, including history of problematic substance use (e.g., King et al., 2014), medication overuse (e.g., Johnson et al., 2013; Lanier et al., 2012), alternate routes of administration (e.g., intranasal, intravenous; Madadi et al., 2013) and recent abstinence from substance use (e.g., Ravndal & Amundsen, 2010).

The Accidental Drug Overdose Protocol was partially or fully completed for 78.7% of the 333 deaths in the current cohort. Before proceeding with analysis of these data, it will be essential to determine whether the decedents for whom the form was completed are representative of the full cohort, and whether or not the missing data on the completed forms would preclude their analysis.

- ***Additional analyses of decedents' prescription drug dispensation histories.*** Review of PharmaNet records would allow for determination of any potentially meaningful patterns in pharmaceutical opioid or other prescription medication use, for example:
 - Any recent change in medication regimen or dosage prior to death
 - Total opioid exposure over time prior to death
 - Duration of prescribed opioid use over past 5 years (days dispensed)

- Chronic (long-term), acute, or sporadic use of opioids over past 5 years
- Dosage escalations among chronic opioid users
- Opioid characteristics (e.g., short-acting vs. extended release formulations)
- Prescription regimen: estimation of PRN (as-needed) vs. regularly scheduled dosages of opioids. PharmaNet does not specifically contain this information, but it could potentially be calculated based on service dates and days dispensed for refilled/ongoing prescriptions.
 - Consider looking at individuals taking daily opioids + additional PRN prescription
- Decedents obtaining pharmaceutical opioids from multiple physicians or pharmacies
 - Where other prescription drugs in addition to pharmaceutical opioids are relevant to overdose deaths, consider comparing toxicology results to prescription drug dispensation histories for other classes of medications to determine the extent to which non-prescribed pharmaceuticals from other drug classes (e.g., benzodiazepines) might be relevant.
- **Analysis of prescriber characteristics**, for example:
 - Context of prescription (e.g., family practice, community clinic, hospital)
 - Physician specialty or other health professional (e.g., dentist, nurse practitioner, or other health care provider)
 - Years practicing
 - Prescriber demographics
 - Were opioids prescribed consistent with clinical practice guidelines?
- **Physical and mental health**
 - More detailed physical and mental health diagnostic information from MSP and DAD
 - Any specific patterns of comorbidities that may be associated with increased risk
 - Future analysis of DAD to focus on identifying patterns in terms of reasons for hospitalization in the year prior to death, including physical and mental health diagnoses, other relevant signs and symptoms, acute and chronic conditions, and suicide attempts. Future analyses will also examine previous hospitalizations for poisonings in more detail to identify any potential patterns (e.g., specific substances involved).
 - Consider obtaining MSP/DAD history going back further than one year prior to death
- **Toxicology**
 - Can examination of toxicology findings provide insight into whether decedents were using their medications at prescribed therapeutic levels or whether there are indications of overuse?
 - Comparison of blood concentration in comparison to average lethal limit for each substance.
 - Comparison of opioid blood concentration to average lethal limit in the presence of other substances.
 - Quantitative toxicological analyses should exclude cases in which >2 days elapsed between death and autopsy (Buxton et al., 2006).

The analyses suggested above pertain to future investigation of the existing cohort. As this project proceeds, additional analyses will be important for gaining a more comprehensive understanding of pharmaceutical opioid-associated mortality in BC.

- **A case-control design** (e.g., with a matched cohort of pharmaceutical opioid users who did not experience fatal overdoses) would allow for potential inferences regarding risk factors for pharmaceutical opioid associated mortality.
- **Non-prescribed pharmaceutical opioid-associated deaths.** Over 1000 deaths were identified by the BC Coroners Service as involving pharmaceutical opioids between 2009 and 2013, of which only 333 were consistent with the inclusion criteria for the present analysis. Many of the excluded cases involved

pharmaceutical opioids that were likely taken without a prescription. A similar data linkage study could prove useful in informing strategies for prevention of overdose deaths among this group. For instance, is there any indication that individuals move from prescribed to non-prescribed opioid use, or seek non-prescribed opioids after discontinuing long- or short-term treatment with prescribed pharmaceutical opioids?

DRAFT

APPENDIX D. Revised Linkage Flow Diagram

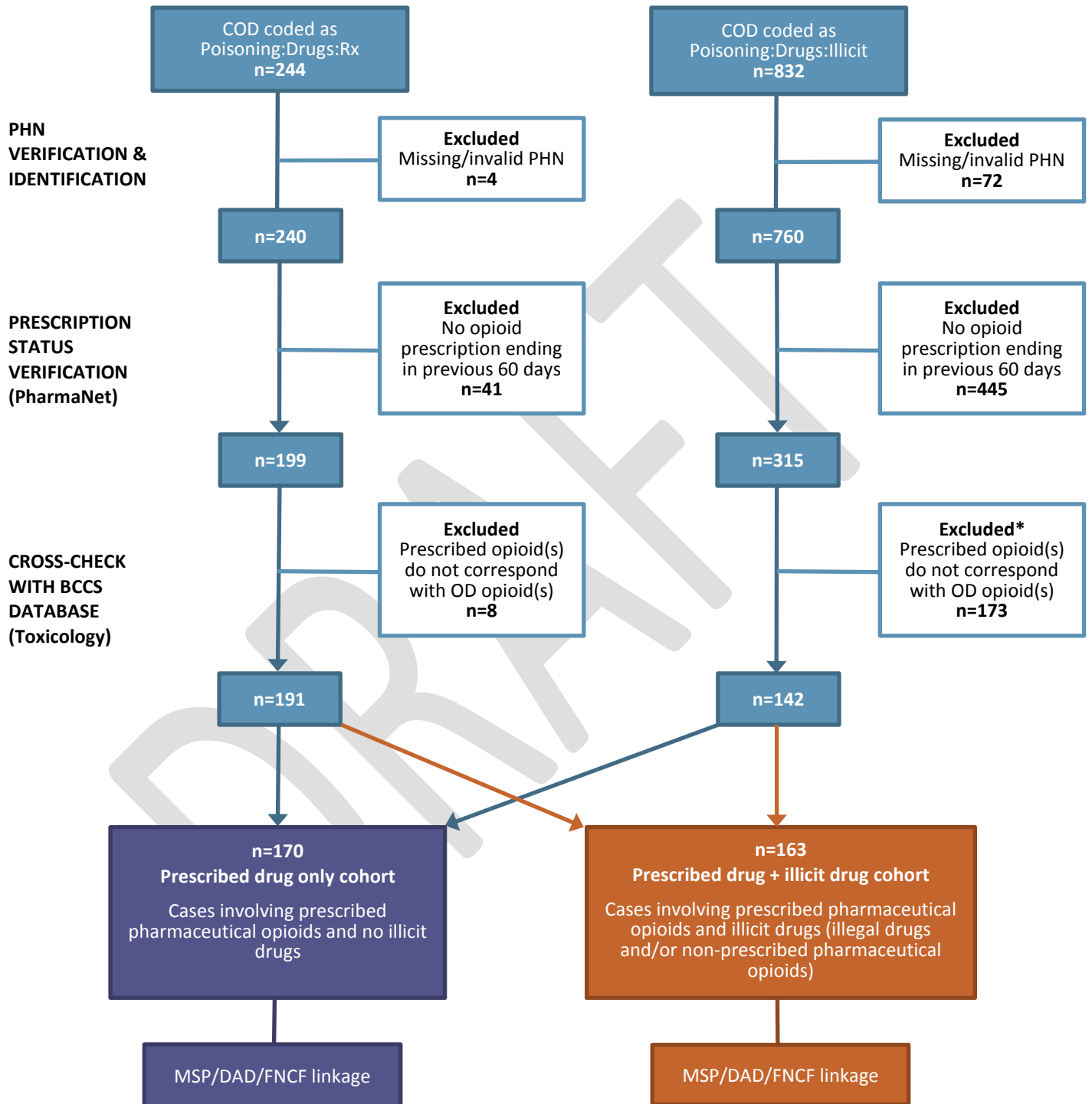


Figure 12. Linkage flow diagram revision, separating deaths associated with prescribed pharmaceutical opioids into two categories, 1) overdoses involving only prescribed pharmaceutical opioids and no illicit drugs, and 2) overdoses involving prescribed pharmaceutical opioids and illicit drugs (e.g., illegal drugs or non-prescribed pharmaceuticals).