Opioid Prescribing Patterns for Treatment of Acute and Chronic Pain in Rural and Urban British Columbia

by

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Abstract

Throughout Canada there has been an increase in both fatal and non-fatal opioid related overdoses, with British Columbia having some of the highest rates. In response to this increase, the Provincial Health Officer of British Columbia declared a public health emergency to mobilize resources to gather more robust data to better understand and respond to this increase. The current evidence has shown that there are differences between urban and rural health regions in British Columbia, which suggests that there may be unique drivers to fatal and non-fatal opioid related overdoses. The purpose of this research was to explore rural and urban differences in acute and chronic non-cancer pain, opioid prescription characteristics, the use of multiple prescribers and the associated risk of fatal and non-fatal overdoses. A systematic review examined the evidence for differences in opioid prescription characteristics between rural and urban areas. Two multivariate Cox regression analyses were conducted utilizing the British Columbia Provincial Overdose Cohort (Version 1) to examine rural and urban difference in chronic pain, opioid prescription characteristics and multiple prescribers, and risk of overdose. Chi-square tests with Cramer's V were utilized to examine opioid prescription dispensation characteristics between rural and urban residents. Chronic pain significantly increased the risk of experiencing an overdose; however, when prescription for opioids were included in the analysis, there was no longer an increase in risk for experiencing a fatal or non-fatal overdose associated with chronic pain. The risk for experiencing a fatal or non-fatal overdose when individuals had a prescription for opioids depended upon a diagnosed substance use disorder. Prescription opioids mitigated the risk of a fatal or non-fatal overdose for those individuals who had a diagnosis of a substance use disorder, and for those individuals who did not have a substance use disorder diagnosis it increased the risk. When examining geographic differences, opioid prescriptions and

related characteristics there were minimal variation, with the exception of a longer duration of opioid prescriptions for acute pain for individuals who lived in rural areas which was consistent to the findings of the systematic review. In addition, the overdose risk related to opioid prescriptions and their characteristics did not vary based on rural-urban geography. The use of multiple prescribers increased people's risk of overdose, however for individuals living in a rural area the use of multiple prescribers mitigated the risk of experiencing an overdose. The presented research highlights the complexity in understanding the risk of overdose. The findings from these studies highlight that reducing access to opioid prescriptions for the entire population may have mixed results; with those who do not have a substance use disorder diagnosis potentially benefiting from reduced access to opioid prescriptions, but potentially harming those individuals with a substance use disorder diagnosis. In the current study, the geographical differences in the rate of overdose were not explained by the differences in opioid prescribing practices; thus, further study is needed to understand the potential factors that will help explain the differences in overdose rates between rural and urban areas.

Preface

This thesis is an original work by Kari Ann Harder. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Health Research Ethics Board, Project Name "Opioid prescribing patterns for treatment of acute and chronic pain in rural and urban British Columbia", No. Pro00086411, dated November 25, 2018. Amendment approvals were provided November 4, 2019, reflecting changes in number of records being reviewed. Renewals were completed in 2019 and 2020, with new project numbers Pro00086411_REN1 and Pro00086411_REN2.

Kari Ann Harder conceptualized the study presented in this thesis and conducted all the research including developing research questions, procuring access to the data sources, analyzing the data, and composing the papers for this paper-based dissertation. All the papers within this dissertation were the initial work of Kari Ann Harder, with the supervisors and supervisory committee making contributions to the editing and organization of the final papers. The systematic review (Chapter 2), Toby Turner assisted with the screening of the articles for inclusion.

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Chapter 1: Introduction

The use of prescription opioids has increased worldwide in recent years, and North America has more than double the rate of prescription opioid consumption compared to the European Union or Australia (Fischer, Jones, & Rehm, 2014; Gomes, Mamdani, Paterson, Dhalla, & Juurlink, 2014). The increase in prescription opioid consumption has been followed by an increase in both medical and nonmedical prescription opioid use morbidity and mortality (Fischer & Argento, 2012; Keyes, Cerdá, Brady, Havens, & Galea, 2014). From 2000 – 2015 the illicit drug mortality rate in British Columbia remained stable with an average rate of 5.78 per 100,000; by 2016, the illicit drug overdose mortality rate increased 256% from the 15 year average to 20.6 per 100,000 (Office of the Chief Coroner, 2017b). In addition, the proportion of illicit drug overdose deaths, where opioids such as fentanyl were detected, increased by 131% from 2015 to 2016 (Office of the Chief Coroner, 2017a; Office of the Chief Coroner, 2017b). This increase in the mortality rate prompted the Provincial Health Officer of British Columbia in 2016 to declare a public health emergency, to take proactive action to protect people who use drugs (Government of British Columbia, 2016); this declaration is still in effect in 2021. However, even with the public health emergency declaration, the illicit drug overdose mortality rate and the proportion of deaths where illegal or illegally obtained opioids, such as fentanyl were detected, has continued to increase, with 2020 seeing the highest illicit drug overdose mortality rate ever in British Columbia (Office of the Chief Coroner, 2017a; Office of the Chief Coroner, 2021).

Prescription and the Opioid Emergency

It has been suggested that the increase in opioid related morbidity and mortality are associated with the increase in the use of long-term prescription opioids such as oxycodone,

fentanyl and hydrocodone for chronic non-cancer pain (Fischer et al., 2014; Seth, Rudd, Noonan, & Haegerich, 2018; Smolina, Gladstone, Rutherford, & Morgan, 2017). In response, new opioid prescription guidelines and standards have been developed. The British Columbia College of Physician and Surgeons developed a standard that requires physicians to have documented discussions regarding opioids and the treatment of chronic pain and directs them to review the patient's medication history prior to prescribing opioids (College of Physicians and Surgeons of British Columbia, 2016). In 2017 the new Canadian Guideline for Opioids for Chronic Non-Cancer Pain focused on initiation and dosing, rotation and tapering of opioids, expert guidance on prescribing opioids, and risk mitigation (Busse, 2017).

Impact of New Prescribing Guidelines and Standards in Canada

A report released by the Canadian Institute for Health Information (CIHI) shows that the changes in the prescribing guidelines and standards have influenced the rate of prescribed opioids. In Canada there has been a 10% drop in the rate of prescribed opioids between 2016 and 2017, which was more than double compared to the previous year's decline; British Columbia had a 14% drop in the rate of prescribed opioids, which was the largest decrease in Canada (Canadian Institute for Health Information, 2018). Specifically, for the period between 2013-2017, less Canadians started opioid therapy, and if they did start opioid therapy, they were prescribed weak opioids, or lower dose opioids, with a duration of less than a week (Canadian Institute for Health Information, 2019). In addition, the number of people starting long term opioid therapy also decreased and the evidence of people tapering off long-term opioid therapy increased between 2013-2017 (Canadian Institute for Health Information, 2019).

With the decline in opioid prescriptions in Canada, there has not a been an associated decrease in the morbidity and mortality related to opioids (Canadian Institute for Health

Information, 2019). British Columbia experienced the greatest drop in the rate of prescribed opioids, however the province had the second highest by province age-adjusted hospitalizations due to opioid poisoning in all of Canada, with 25.0 hospitalizations per 100,000 population, compared to the Canadian rate at 15.5 hospitalizations per 100,000 (Canadian Institute for Health Information, 2017). Some research has found that cessation of opioid therapy may cause some individuals to seek illicit opioids to manage their pain (Baldwin et al., 2018; Canadian Institute for Health Information, 2019; Murphy et al., 2018). This indicates that the opioid crisis is a complex issue and addressing opioid prescribing practices may only be a part of the solution (Canadian Institute for Health Information, 2019).

Rural/Urban Considerations

Where people live and the environment around them can have an impact on their health and health outcomes (Dummer, 2008). When defining what is rural many researchers use population size, population density, and distance to the nearest larger centre to identify the distinction between what is rural or urban (Hall, Kaufman, & Ricketts, 2006; Statistics Canada, 2017). These are also the features that planners used to determine where services will be provided (Deavers, 1992). Therefore, health services may be more likely to be in urban, highly populated areas leaving rural areas with minimal access to health services. In rural areas the variety and number of health services available may be limited. The limited access to health care services may result in underdiagnosis of health conditions, and/or an overuse of pharmaceuticals to treat patients as other alternative options are not available (Brookhart, Stürmer, Glynn, Rassen, & Schneeweiss, 2010). For example, individuals in urban areas may have access to physiotherapy to help with chronic pain, however, people in rural areas may not have access to

those services. This may cause the patient and/or physician to rely on pharmaceutical options to treat chronic pain, increasing the likelihood of experiencing an adverse outcome.

Regional Differences within British Columbia

There are observed variations of opioid related deaths within provinces. When reviewing the British Columbia Office of the Chief Coroner's (2021) report, the illicit drug toxicity drug death rates between the province's health authorities vary. The majority of health regions experienced a three to 10% increase in the illicit drug toxicity drug death rate from 2017 to 2020; however, the Northern Health Authority's rate of illegal drug deaths has increased by 93.6% between 2017 and 2020 (Office of the Chief Coroner, 2021). The reasons for these differences are unknown; there may be regional factors influencing the mortality rate.

Study rationale and significance

The differences in the illicit drug toxicity rate between the different regions across Canada and within British Columbia, suggest that there may be different drivers in the opioid crisis. These differences may require a variety of interventions to minimize the adverse health effects related to opioid use. During the opioid overdose public health crisis, much of the focus has been on urban areas or the province as a whole; however, there is a need for research exploring the potential epidemiological drivers in rural areas. The drivers of illicit drug overdoses and deaths between rural and urban areas need to be explored to ensure that appropriate interventions are implemented in response to the current public health crisis.

The goal of this research is to address the knowledge gap regarding the impact of opioid prescriptions in rural areas in British Columbia, and the possible effect this may have on fatal and non-fatal overdoses. The research to be presented in this dissertation provides a comprehensive longitudinal analysis of eight years of administrative health data, examining the

impact of chronic pain, opioid prescriptions, and prescription drug seeking behaviour have on the risk of experiencing a fatal or non-fatal illicit drug overdose in British Columbia. The results of this research are expected to help identify whether there is an association between chronic pain, opioid prescriptions, multiple prescribers, and the increase in illicit drug overdoses in British Columbia, and if they differ between rural and urban areas of the province. Understanding these associations may allow for more targeted interventions to address the opioid public health crisis.

The hypothesis of this research is that the differences in patterns in respect to fatal and non-fatal illicit drug overdose in rural and urban populations may be the result of distinct factors. These may include chronic pain, opioid prescription characteristics such as duration, and strength, or the use of multiple prescribers and/or pharmacies by patients. The factors that influence overdose potential may be different in rural populations compared to urban populations, and this would affect the likelihood of an individual experiencing a fatal and non-fatal illicit drug overdose.

Research Objectives

The objectives of this research are:

1. To conduct a systematic review of relevant literature related to characteristics of opioid prescriptions in rural areas.
2. To examine the impact chronic non-cancer pain has on the risk on experiencing a fatal or non-fatal overdose, and if differs between rural and urban populations.
3. To examine opioid prescriptions and characteristics between rural and urban populations in British Columbia among individuals who have experienced acute and/or chronic non-cancer pain.

4. To examine the opioid prescription characteristics and use multiple prescribers and/or pharmacies between rural and urban populations in British Columbia and the impact on the risk of experiencing a fatal and non-fatal overdose among individuals who have experienced acute and/or chronic non-cancer pain.

Author's Positioning

I am an epidemiologist within the Northern Health Authority (NHA) in British Columbia, which can be considered primarily rural. As part of my role, I have worked on the opioid public health emergency since prior to its declaration and work closely with those who are directly involved in responding to this emergency both at a provincial and local level. My position gives me a unique perspective in the types of questions being asked and the steps being taken to mitigate and prevent opioid related overdose in British Columbia

Dissertation Overview

This dissertation presents the results of four stand-alone manuscripts. Each chapter has its own introduction, methods, results, and discussion sections. Chapter 2 presents the results of a systematic review that examined existing literature on the difference in prescription opioid characteristics and fatal or non-fatal overdoses between rural and urban populations. Chapters 3 through 5 present the results of three retrospective cohort analyses utilizing the British Columbia Overdose and reference cohort. Since chapters 3 to 5 utilized the same data source, there is overlap in the chapters, specifically in description of study methods.

In Chapter 3, the British Columbia Overdose and reference cohort was utilized to examine the risk of experiencing a fatal or non-fatal overdose differed for those individuals who have experienced chronic pain. In chapter 4, prescription opioids were examined for those

individuals who had experienced either acute or chronic pain during study period, to investigate differences in opioid prescription characteristics between rural and urban areas. In chapter 5, the risk of overdose, opioid prescription characteristics and prescription drug seeking behaviour was assessed. Chapter 6 provides a general summary of the results and conclusions for the four studies and the strengths, limitations, and implications of the study are discussed.

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Chapter 2: Differences in Opioid Prescription Characteristics between Rural and Urban Areas and the Impact on Overdoses: A Systematic Review

Authors: Kari Harder MSc., Toby Turner, MSc.

Introduction

The use of prescription opioids has increased worldwide in recent years, and North America has more than double the rate of prescription opioid consumption compared to the European Union or Australia (Fischer, Jones, & Rehm, 2014). This increase in prescription opioid consumption has been followed by an increase in morbidity and mortality for both medical and nonmedical prescription opioid use (Fischer & Argento, 2012; Keyes, Cerdá, Brady, Havens, & Galea, 2014). The increase in opioid related morbidity and mortality has also been seen in British Columbia, Canada, which led the Provincial Health Officer of British Columbia on April 14, 2016 to declare a public health emergency to take proactive action to protect people who use drugs (Government of British Columbia, 2016), which is still in effect five years after it was declared.

The response to this public health emergency has included changing prescription guidelines for physicians. In 2017 the new Canadian "Guideline for Opioids for Chronic Non-Cancer Pain" was released. These guidelines focused on initiation and dosing, rotation and tapering of opioids, expert guidance on prescribing opioids, and risk mitigation (Busse, 2017). In 2016, US Center for Disease Control also introduced new opioid prescribing guidelines, however the results have been mixed. Two studies have shown that there has been a decline in the number opioid prescriptions which was seen in both rural and urban areas (Garcia et al., 2019; Lund et al., 2019), while the decrease in the number of opioid prescriptions has not resulted in a decline in fatal and non-fatal overdoses (Champagne-Langabeer, Madu, Giri, Stotts, & Langabeer, 2021).

Morbidity and mortality related to prescription opioids has increased at a greater rate in rural areas compared to urban areas, with rural region in the US state of Virginia seeing an 300%

increase in the drug overdose deaths in six years (Wunsch, Nakamoto, Behonick, & Massello, 2009). The reason for the difference in mortality between rural and urban areas is unknown as previous research has found that both prescription and illegal drug use occur at comparable rates in rural and urban areas (Cronk & Sarvela, 1997; Keyes et al., 2014; Wang, Becker, & Fiellin, 2013). When examining coroner reports for illicit drug poisoning Shah et al. (2012) found that deaths that occurred in rural areas were the result of prescription drug poisoning, whereas in urban areas were the result of illicit drug poisoning. The differences between rural and urban areas in fatal and non-fatal overdoses may be the result of variations in opioid prescribing. The purpose of this study was to perform a systematic literature review related to differences between rural and urban areas in opioid prescribing for pain.

Methods

A systematic search was conducted using Medline (OVID), PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Ebsco open dissertation and Psych Info (Ebsco and OVID), and a hand search of reference lists of all included articles was conducted to determine the extent of the existing research literature. Eligible for inclusion were articles published in English and reporting on human subjects; the last search was conducted July 17, 2020. A specific search strategy was used for each of the databases searched, the search strategy for OVID is shown in Table 6. The references in articles identified for inclusion were also screened. Eligibility of articles for inclusion was assessed by two independent reviewers (Table 1). Discrepancies were resolved by consensus. The Joanna Briggs Checklist for Analytical Cross Sectional Studies was used to assess study quality (Joanna Briggs Institute, 2020). The screening and data extraction tool Covidence (covidence.org) was used to manage the article reviews and data extraction. To report the results of this systematic review, the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach was used to report the findings (Page et al., 2021).

Data Synthesis

The methodology utilized in examining prescribing characteristics, and the population utilized were heterogenous, thus a meta-analysis was not deemed appropriate. Therefore, a narrative synthesis was used to summarize the study characteristics and findings.

Results

The systematic search identified 528 articles for initial screening; 518 from the database search and an additional 10 were identified from the reference list search. There were 204 duplicates, which were removed (Figure 1). Applying inclusion and exclusion criteria to the title and abstract review resulted in exclusion of 301 articles, leaving 23 articles that went on to full text screening, and 4 articles ultimately met the inclusion criteria for the study. Reasons for exclusion can be found in Table 2.

Study Characteristics

The study characteristics of included studies are found in Table 3. All four of the studies are retrospective studies; three are observational cohort studies, and one is a cross-sectional study. All four studies examined opioid prescribing in the United States. Consson et al. (2020) examined differences between characteristics of patients and physicians that determined opioid prescribing attributes following total knee arthroplasty surgery, this study utilized electronic health records. The other three studies examined opioid prescription dispensations at a population level utilizing National or State health databases. Lund, Ohl, Hadlandsmyth, & Mosher (2019) utilized the National Veterans Health Database; Zhou, Yu, & Losby (2018) utilized the US Medicare database; and Sears, Edmonds, & Fulton-Kehoe (2020) used the

Washington State Prescription Monitoring Program data. The studies' methods and general findings are in Table 4.

Rural Urban Classification

When examining the differences in how rurality was defined all four studies utilized US Federal rural classification schemes, although this was not consistent. Two studies utilized the National Center for Health Statistics Urban-Rural Classification scheme for counties (Sears et al., 2020; Zhou et al., 2018). Consson et al. (2020) used the US Census rural-urban continuum codes, and Lund et al. (2019) used the Rural-Urban community areas (RUCA) developed by the US Department of Agriculture. All these classification schemes used US Census boundaries, although the criteria used to establish rural urban classifications were different. The RUCA incorporated population density, urbanization, and daily commuting into the US census categories when classifying rural and urban. In contrast, the National Center for Health Statistics Urban-Rural Classification scheme used population size and the US Office of Management and Budget's criteria of metropolitan and nonmetropolitan counties.

Opioid Prescriptions

Each study identified opioid prescriptions differently. Lund et al. (2019) included all non-injectable forms of schedule II opioids that were dispensed in an outpatient setting. Sears et al. (2020) reviewed all opioids dispensed to outpatients that were included in the Washington Tracking network. Zhou et al. (2018) identified prescribed opioids utilizing the Centers for Disease Control and Prevention compilation of opioid formulations, excluding generic drug names, that are commonly prescribed for treating opioid dependence, such as buprenorphine. Consson et al (2020) identified post-discharge opioid prescriptions from patients' electronic health record.

Morphine milligrams equivalent. All the studies used Morphine Milligrams Equivalent (MME) to determine dosage; however, some studies used total prescribed, others used average daily dose. Consson et al. used total prescribed MME per prescription and categorized it as greater or less than 1,350 MME prescribed. Lund et al. calculated total prescribed MME per capita, based on all patients who received at least one prescription from a pharmacy. Sears et al. and Zhou et al. calculated MME per day; however, Sears et al. calculated age and sex standardized rates, and Zhou et al. calculated the average MME per day. These were then classified in non-mutually exclusive categories: Sears et al. had three categories, ≥ 50 MME, ≥ 90 MME, ≥ 120 MME; and Zhou et al. had two categories ≥ 50 MME, ≥ 90 MME.

Days supplied. Days supplied for initial prescription were categorized in all the studies. Consson et al. categorized prescription length greater than 15 days and Sears et al. used greater than 14 days. Lund et al. provided an average number of days per person and greater than 30 days. Two studies examined long term or chronic usage of opioids; Zhou et al. classified individuals as chronic users if they had 6 or more opioid prescriptions in a year. Sears et al. classified someone as a chronic user if they had an opioid prescription for more than 60 days.

Rural and Urban Differences in Opioid Prescribing

The rural and urban differences in the prescription characteristics can be found in Table 5. Overall, rural counties received more prescription opioids compared to urban counties (Lund et al., 2019; Sears et al., 2020; Zhou et al., 2018). However, Sears et al. and Zhou et al. found that there were more significant differences between counties that were classified as large metropolitan and all other counties. They found that compared to large metropolitan counties all other counties had significantly higher rates of opioid prescriptions.

When examining the differences in days supplied, residents of rural or non-metropolitan counties had had significantly longer prescriptions compared to urban/metropolitan county residents. Consson et al. also found a higher proportion rural of patients received a longer duration opioid prescription compared to urban patients however the difference was not significant. Consson et al. also examined prescriber characteristics and found that prescribers located in metropolitan counties prescribed opioids for longer duration than prescribers in non-metropolitan and rural areas. Three studies compared rural and urban differences in chronic or long-term prescription opioid use. All three found a significantly higher proportion of rural or non-metropolitan residents were classified as receiving long term opioid therapy (Lund et al., 2019; Sears et al., 2020; Zhou et al., 2018).

Three of the studies found that rural and non-metropolitan residents were more likely to be prescribed higher MME dosages compared to urban/metropolitan residents (Lund et al., 2019; Sears et al., 2020; Zhou et al., 2018). Consson et al. found a higher proportion rural of patients received a lower total MME prescription following surgery compared to urban patients; however, the difference was not significant. When examining prescriber location, Consson et al. found that prescribers located in non-metropolitan and rural counties prescribed opioids at significantly higher MMEs for a second post discharged prescription compared to metropolitan prescribers.

Discussion

With rural areas experiencing higher rates of both fatal and non-fatal overdoses (Cerda et al., 2017; Green, Grau, Carver, Kinzly, & Heimer, 2011; Wunsch et al., 2009) and higher opioid prescribing when compared to urban areas (Garcia et al., 2019; Lund et al., 2019; Sears et al., 2020; Zhou et al., 2018) this systematic review was conducted to determine if there were specific

prescription characteristics that may help explain why this discrepancy has been observed. The four studies that met the inclusion criteria examined differences in opioid prescriptions between rural and urban counties in the United States.

Our systematic review of these studies indicated that there are differences in opioid prescribing patterns based on geography. There is evidence that suggests that individuals in rural areas receive opioid prescriptions that last longer and have higher MME compared to urban residents (Lund et al., 2019; Sears et al., 2020; Zhou et al., 2018). Although all the studies showed a difference in opioid prescription duration and MME based on rurality, one of the studies found that difference to be where the prescriber was located and not the patient. They found that non-metropolitan/rural prescribers prescribed higher MMEs during recovery after surgery (Consson et al., 2020). In addition, non-metropolitan/rural residents receive prescriptions for a longer duration compared to metropolitan residents. Several of the authors hypothesised that the rural vs. urban differences for opioid prescription duration and MMEs may be due to limited to access to alternative treatments for pain (Consson et al., 2020; Lund et al., 2019; Sears et al., 2020). Sears et al. and Zhou et al. also examined economic disparities between counties and found that they were also related to the variation between opioid prescription duration and MMEs.

Limitations

There are several limitations to this systematic review. Firstly, all the studies were conducted in the US, which limits the generalizability of the findings. Secondly, the prescription opioids that were included in the analysis across the studies varied. Some of the studies excluded those opioids that are commonly used in the treatment of opioid use disorders, while others did not. In addition, the definitions of the prescription characteristics varied across studies

and there were no common categorizations for MMEs and duration. Thirdly, some research may have been missed due to only including articles written in English.

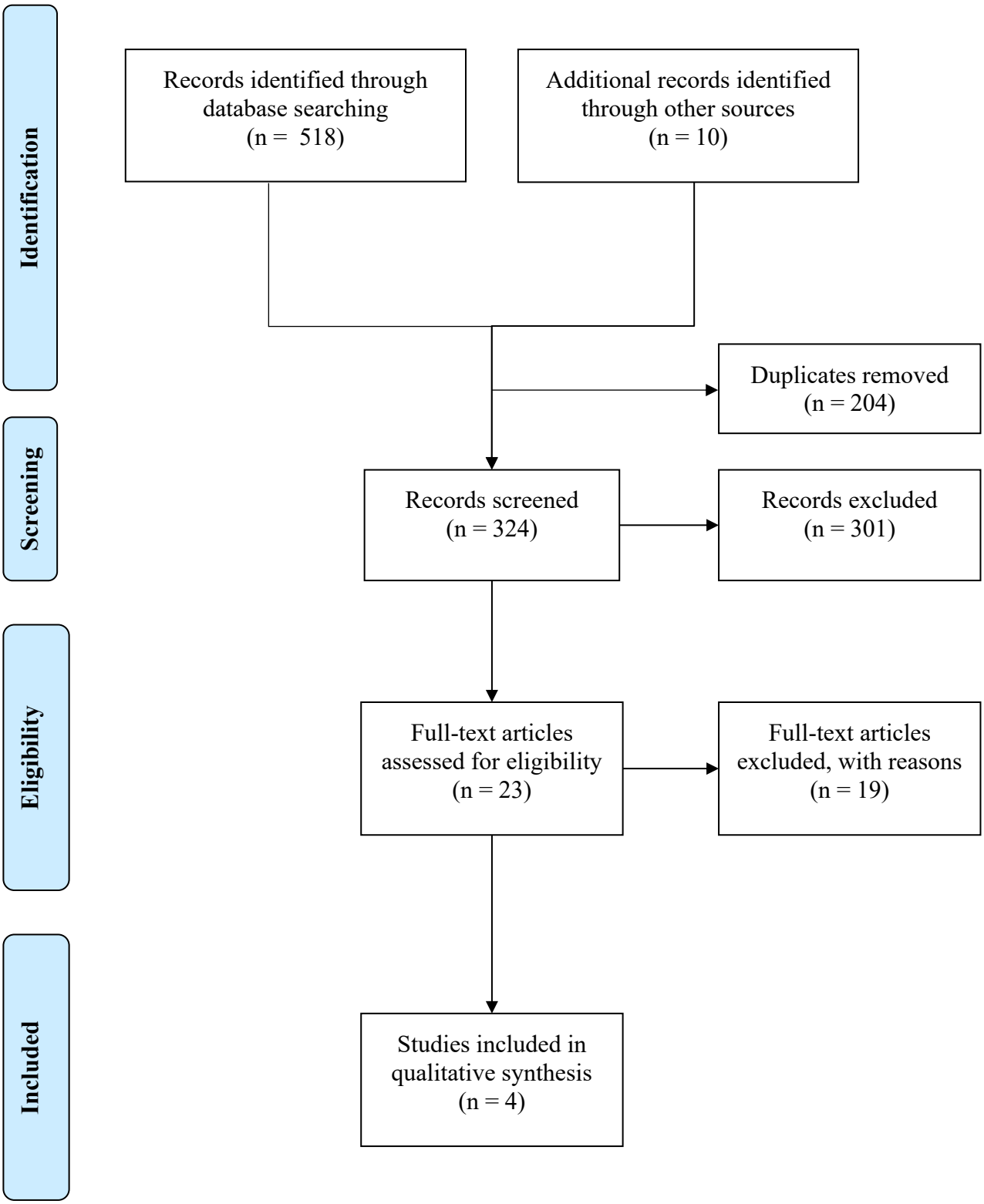
Conclusions

This systematic review illustrates that there is geographical variation in opioid prescription characteristics with rural residents receiving opioid prescriptions for a longer duration and a higher dose compared to urban residents. Further research is needed to determine if this difference is related to the prescriber or the prescription recipient, or both. A better understanding of what may be driving the differences between rural and urban areas might allow for better education for both prescribers and patients to understand what resources may be available to rural patients for the treatment of pain. There is also a need for additional research to understand what opioid prescriptions characteristics may be impacting the difference fatal and non-fatal overdose rates between rural and urban residents; identifying these differences may allow for more nuanced prescribing recommendations.

Table 1. Inclusion and Exclusion Criteria for the Systematic Review

Inclusion Criteria	Exclusion Criteria
• Original research • Geographic comparison between rural and urban • Opioid prescription, including prescription characteristics • English language • Outcome of overdose – fatal or non-fatal	• Systematic Reviews/Meta-analysis • Focused exclusively on opioid use disorder treatment • Evaluation of interventions • Reviews/opinion piece • Qualitative methodology

Figure 1. PRISMA Flow Diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table 2. Excluded Studies Reason for Exclusion

Author	Reason for exclusion
Buda et al. (2020)	Focus on treatment or guidelines adherence
Cerda et al. (2017)	No prescription characteristics
Foo et al. (2017)	No rural breakdown; no prescription characteristics, focus not opioids
Franklin et al. (2013)	No rural breakdown; no prescription characteristics, focus on prescriber opinions
Garcia et al. (2019)	No prescription characteristics
Gladstone et al. (2015)	No rural breakdown; no prescription characteristics
Green et al. (2011)	No rural breakdown; no prescription characteristics
James et al. (2019)	No rural breakdown; no prescription characteristics
Kea et al. (2016)	No rural breakdown; no prescription characteristics
Kuo et al.(2016)	No prescription characteristics
Modarai et al. (2013)	No prescription characteristics
Morden et al. (2014)	No rural breakdown
Romeiser et al. (2019)	No rural breakdown; no prescription characteristics
Shah et al. (2012)	Not primary research
Stopka et al. (2019)	No rural breakdown
Wang et al. (2013)	No prescription characteristics
Wang et al. (2014)	No prescription characteristics
Witt et al. (2018)	Evaluation of an intervention
Wunsch et al. (2009)	No prescription characteristics

Table 3. Study Design and Aim of Included Studies

Authors	Country	Data Source	Years	Study Design	Aim of study
Consson et al. (2020)	Northwest, United States	Electronic health records	2016-2017	Cohort	Determine the predictors of patients who receive opioids for >15 days post-surgery
Lund, Ohl, Hadlandsmyth, & Mosher (2019)	United States	National Veterans Health Database	2016	Cohort	Examination of prescribing intensity and duration to see how it has changed since 2012 and if there is a difference between rural and urban
Sears, Edmonds, & Fulton-Kehoe (2020)	Washington, United States	Washington State Prescription Monitoring Program data	2012-2017	Cross-sectional	Opioid prescribing patterns across urban-rural and economic distress classifications. Rural-Urban distribution of relevant health services, economic factors, and population characteristics

Zhou, Yu, & Losby (2018)	United States	National Medicare	2014	Cohort	Examine the association between county-level socioeconomic factors and opioid prescribing

Table 4. Characteristics and Major Findings of Included Studies

Author	Inclusion Criteria	Exclusion Criteria	Number of Subjects	Rural/Urban Classification	Prescription Characteristics	Major Findings
Consson et al. (2020)	• Patients >18 years old • Who had total knee arthroplasty between January 2016 to December 2017	• Previous chronic opioid prescriptions • Missing data	• 621	• United States Census Bureau Rural-Urban Continuum codes	• MME • Days supplied	• No significant difference for the first post discharge prescription between rural and metropolitan patients • Nonmetropolitan urban and rural providers prescribed significantly more MMEs for the second post discharge prescription • Nonsurgical metropolitan providers prescribed the most MMEs for the third post discharge prescription
Lund, Ohl, Hadlandsmyth,	• Any veteran who received at least one outpatient prescription	• Patients receiving care in	• 4,928,195	• Rural-Urban Commuting Areas - US	• MME • Days supplied	• Opioid prescribing was higher for rural veterans compared to urban

& Mosher (2019)	dispensed through Veterans Health Administration	Puerto Rico and Manila		Dept. of Agriculture		• Rural had more days supplied dispensed and longer term of usage • If facilities had a high proportion of rural veterans, the prescribing of opioids was less compared to facilities with a low proportion of rural veterans • Overtime both rural and urban prescribing rates declined at the same rate
Sears, Edmonds, & Fulton-Kehoe (2020)	• County level data • Licensed pharmacies and practitioners report all dispensed noninpatient prescriptions for more than a 24-hour supply of Schedule II, III, IV, and V controlled substances	• NA	• NA	• National Center for health statistics Urban-Rural Classification scheme for counties	• MME • Days supplied	• There were significant trends between metro and other counties with non-metro seeing higher rates of: o Opioid prescription o Chronic opioids o High dose opioids

						○ Concurrent use with sedative ○ Initial opioid >14 days ○ Transition to chronic opioids • Economic distressed counties saw increase in rates for all metrics except concurrent sedative metric • Prescribing practices have not diverged between rural and urban areas over time
Zhou, Yu, Losby (2018)	• < 65 Years old, disabled individuals • Enrolled in Medicare part D for a minimum 12 months	• Individuals in managed care program or fee-for-service • Individuals on cancer treatment,	• 3,493,551	• National Center for health statistics Urban-Rural Classification	• MME • Days supplied	• More rural counties had a greater proportion of prescriptions • Counties with higher income had a lower total MME

	end stage renal disease, or hospice care	scheme for counties	• Counties with higher unemployment had an increase in total MME • The greater economic disparity in a county there was a corresponding decrease in total MME

Table 5. Rural and Urban Prescription Characteristic Study Findings

Authors	Overall Opioid Prescription	MME	Days Supplied
Consson et al. (2020)	NA	<u>< 1350 MME prescription</u> **Patient** [ns] • Metropolitan: 87% • Nonmetro urban: 83% • Nonmetro rural: 90% **Prescriber of 2nd post discharge prescription***** • Metropolitan prescriber: 54% • Nonmetropolitan urban and rural prescriber: 36%	<u><15 days prescription</u> **Patient** [ns] • Metropolitan: 72% • Nonmetro urban: 76% • Nonmetro rural: 70% **Prescriber of 2nd post discharge prescription***** • Metropolitan prescriber: 40% • Nonmetropolitan urban and rural prescriber: 50%

Lund, Ohl, Hadlandsmyth, & Mosher (2019)	NA	MME per capita*** • Rural: 1,306 MME • Urban: 988 MME	Mean supply dispensed at initiation*** • Rural: 14.8 days • Urban: 12.7 days Proportion of 30-day supply*** • Rural: 23.1% • Urban: 18.8%
Sears, Edmonds, & Fulton-Kehoe (2020)	**Age/Sex Adjusted Rate Per 1,000** Any Opioid *** • Large central metro: 76.4 • Large fringe metro: 94.3 • Medium metro: 105.4 • Small metro: 103.6	**Age/Sex Adjusted Rate Per 1,000** ≥ 50 MME*** • Large central metro: 4.6 • Large fringe metro: 8.2 • Medium metro: 10.4 • Small metro: 9.2	**Age/Sex Adjusted Rate Per 1,000** Initial Day's Supply ≥ 14 days*** • Large central metro: 0.7 • Large fringe metro: 1.2 • Medium metro: 1.6 • Small metro: 1.5

- Micropolitan: 98.0
- Noncore: 100.2

- Micropolitan: 10.0
- Noncore: 9.9

- Micropolitan: 1.4
- Noncore: 1.7

≥ 90 MME***

- Large central metro: 1.8
- Large fringe metro: 3.1
- Medium metro: 3.3
- Small metro: 4.7
- Micropolitan: 5.3
- Noncore: 5.1

Chronic Opioid***

- Large central metro: 12.8
- Large fringe metro: 22.6
- Medium metro: 30.4
- Small metro: 27.7
- Micropolitan: 26.5
- Noncore: 29.5

≥ 120 MME***

- Large central metro: 1.8
- Large fringe metro: 3.1

		• Medium metro: 3.1 • Small metro: 3.2 • Micropolitan: 3.6 • Noncore: 3.4	
Zhou, Yu, & Losby (2018)	Any Opioid** • Large central metro: 43% • Large fringe metro: 47% • Medium metro: 49% • Small metro: 51% • Micropolitan: 53% • Noncore: 56%	≥ 50 MME Daily Dose** • Large central metro: 13% • Large fringe metro: 16% • Medium metro: 16% • Small metro: 15% • Micropolitan: 16% • Noncore: 16% ≥90 MME Daily Dose** • Large central metro: 8% • Large fringe metro: 10% • Medium metro: 10% • Small metro: 9% • Micropolitan: 10% • Noncore: 10%	Long term opioid therapy* • Large central metro: 22% • Large fringe metro: 26% • Medium metro: 27% • Small metro: 29% • Micropolitan: 31% • Noncore: 34%

- Large central metro: 7%
- Large fringe metro: 9%
- Medium metro: 8%
- Small metro: 8%
- Micropolitan: 8%
- Noncore: 8%

Note. ^{ns} Not significant, * $p < 0.05$, ** $p < 0.001$, *** $p < 0.001$

Table 6. Ovid Search Syntax

1.	(exp analgesics, opioid or exp alfentanil or exp butorphanol or exp codeine or exp dextromoramide or exp diphenoxylate or exp fentanyl or exp heroin or exp hydrocodone or exp hydromorphone or exp levorphanol or exp meperidine or exp meptazinol or exp methadone or exp methadyl acetate or exp morphine or exp morphine derivatives or exp nalbuphine or exp narcotics or exp opiate alkaloids or exp oxycodone or exp oxymorphone or exp pentazocine or exp phenazocine or exp piperidines or exp sufentanil or exp tramadol or exp opiates).af.
2.	(acemethadone or acetylmethadol or alfenta$ or bupernorphine or butorphanol or codein$ or dextromoramide or dextropropoxyphene or dezocine or diamorphine or dihydrocodeine or diphenoxylate or dipipanone or fentanyl or heroin or hydrocodone or hydromorphone or hetobemidone or levorphanol or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or narcotic$ or opioid$ or "opioid use" or opiate$ or oxycodone or oxymorphone or papaveretum or pentazocine or pethidine or phenazocine or piperidines or propoxyphene napsylate or remifentanil or sufentanil or tapentadol or tramadol).af.
3.	(abstral or acet codeine or acet* or act buprenorphine or act oxycodone cr or act tramadol or alfenta or alfentanil or alfentanil hcl or alphaprodine* or anadol or anileridine* or apo-fentanyl or apo-hydromorphone or apo-oxycodone or apo-tramadol or auro-tramadol or bar-hydromorphone hcl or belbuca or buprenorphine* or butorphanol or butorphanol tartrate or butrans or co fentanyl or codeine* or codofen or darvon* or demer idine or demerol* or diacetylmorphine* or diamorphine* or dilaudid* or doloral* or duragesic* or durela or empracet or endocet* or endodan* or exdol* or fentanyl* or fentora or fiorinal*

	or hydrocodone or hydromorph* or hydromorphon* or hydromorphone hydrochloride or ibucodone or jamp-acet-tramadol or jurnista or kadian or leritine or levodromoran or levo-dromoran or levorphanol* or mar-tramadol or m-ediat or meperidine* or m-eslon or metadol* or methadone* or methadose or mint-tramadol or morphine* or ms contin* or ms ir* or ms-contin* or ms-ir* or mylan-buprenorphine or mylan-fentanyl* or mylan-tramadol* or nalbuphine* or nisentil or novo-propoxyn or ntp-morphine or nubain or nucynta or numorphan or onsolis or opana* or oramorph* or oxy* or oxycodone* or oxycontin or oxymorphone* or oxyneo or painex or palladone or pat-fentanyl or pat-tramadol or pentazocine* or percocet* or percodan or pethidine* or phl-acet-codeine or pms hydromorphone or pms-butorphanol or pms-codeine or pms-fentanyl or pms-methadone or pms-morphine sulfate or pms-oxycodone or pms-tramadol or priva-tramadol or procet or propoxyphene* or ralivia or ran-fentanyl or ran-oxycodone or ran-tramadol or ratio-codeine or ratio-emtec or ratio-lenoltec or ratio-morphine or ratio-oxycocet or ratio-oxycodan or remifentanil or remifentanil hcl or remifentanil* or rivacocet or riva-oxycodone or riva-tramadol or rounox codeine or routec or roxanol or roxicet or sandoz fentanyl or sandoz morphine or sandoz oxycodone or stadol or statex or sublimaze or suboxone or subutex or sufenta or sufentanil* or supeudol or talwin or tapentadol* or targin or taro-tramadol or teva-buprenorphine or teva-fentanyl or teva-hydromorphone or teva-morphine sr or teva-oxycodone or teva-tramadol or tramacet or tramadol* or tramaphen-odan or trianal* or triatec or tridural or ultiva or ultram or zytram or opioid or opiates).af.
4.	1 or 2 or 3

5.	(chronic pain or pain or chronic pain or chronic disease or pain management or non-cancer chronic pain or arthritis, rheumatoid or fibromyalgia or fatigue syndrome, chronic or fibromyalg* or migraine or migraine disorders or hyperalgesia or neuralgia or neural pain or neoplasms or neuralgia or spinal cord or neuropath* pain or sciatic nerve or arthritis, reactive or arthritis, infectious or arthritis, rheumatoid or "national institute of arthritis and musculoskeletal and skin diseases (u.s.)" or arthritis, gouty or arthritis-encephalitis virus, caprine or arthritis, juvenile or arthritis, experimental or arthritis or arthritis or arthritis, psoriatic or osteo?arthritis or osteoarthritis, hip or osteoarthritis or osteoarthritis, spine or osteoarthritis, knee or pain measurement or hyperalgesia or pain, postoperative or neurologic manifestations or occupational diseases or "wounds and injuries" or musculoskeletal diseases or musculoskeletal pain or musculoskeletal pain or muscular diseases or coccidioidomycosis or pain or headache disorders, secondary or post-traumatic headache or headache disorders, primary or headache or tension-type headache or headache disorders or headache or cluster headache or head ache or acute pain or pain measurement or appendicitis or pain or acute pain or acute disease or pain, postoperative or preoperative period or preoperative care or pre?operative or trauma or accident or accidents or neuralgia).af.
6.	(Rural Health or rural population or hospitals, Rural or rural nursing or rural health services or rural mp or geography, Medical or geography or geography mp or small town mp or remote communities mp or health services, Indigenous or nonurban mp or nonmetropolitan mp or geographic* mp or rural environments).af.

7.	(Inappropriate Prescribing or Electronic Prescribing or Prescribing or Practice Patterns, Physicians' or Prescribe or Drug Prescriptions or Prescription Drugs or Prescrib* or Prescription Drugs or opioid prescribing).af.
8.	4 and 5 and 6 and 7

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Chapter 3: Impact of Chronic Pain on Illicit Substance Overdose. Differences between Rural and Urban Areas in British Columbia

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Disclaimer: All inferences, opinions, and conclusions drawn in this article are those of the authors, and do not necessarily reflect the opinions or policies of the [British Columbia] Ministry of Health, [British Columbia] Ministry of Mental Health and Addictions, British Columbia Centre of Disease Control, British Columbia Coroner's Service, British Columbia Emergency Health Services.

Introduction

Chronic pain is defined as a pain that has continued past what would be considered the normal length of time for proper healing (Dobkin & Boothroyd, 2006). The normal healing time typically used is between three and six months, however this estimate is arbitrary, since people heal at different rates for a variety of reasons (Dobkin & Boothroyd, 2006; Ospina & Harstall, 2002). Chronic pain can cause additional psychological, social, and physiological problems; these can include reduced mobility, loss of strength, eating difficulties, and sleep problems (Brennan, Carr, & Cousins, 2007; Brennan, Carr, & Cousins, 2016; Lohman, Schleifer, & Amon, 2010; Noble et al., 2010; Ramage-Morin & Gilmour, 2010; Zimmer & Rubin, 2016). Psychologically and socially, people suffering with chronic pain have increased incidence of anxiety and depression, withdrawal from social situations, reduced participation in the workforce, lower life expectancy, and increase the risk of suicide (Moore, Derry, Taylor, Straube, & Phillips, 2014; Brennan et al., 2007; Brennan et al., 2016; Lohman et al., 2010; Ramage-Morin & Gilmour, 2010).

Findings from the Canadian Community Health Survey show that 10% of Canadians between the ages 12 and 44 have experienced or are suffering from chronic pain (Ramage-Morin & Gilmour, 2010). Consistently, the available evidence shows that more females suffer from chronic pain compared to males, and chronic pain prevalence increases with age (Ramage-Morin & Gilmour, 2010; Schopflocher, Taenzer, & Jovey, 2011). There is also some evidence that people in rural areas have higher prevalence rates of chronic pain than those individuals living in urban areas (Hoffman, Meier, & Council, 2002; Ramage-Morin & Gilmour, 2010). Differences in prevalence of chronic non-cancer pain[1] and its treatment has been suggested as one potential

[1] Chronic non-cancer pain will be referred to as chronic pain

driver for the geographical variations seen in fatal and non-fatal overdose rates (Bohnert, Logan, Ganoczy, & Dowell, 2016; Cerda et al., 2017; Cheatle, 2011; Todd et al., 2018; Wunsch, Nakamoto, Behonick, & Massello, 2009). The objective of this study is to examine the effect chronic pain has on the risk of experiencing a fatal or non-fatal overdose in rural and urban populations.

Methods

Data Source

The British Columbia Provincial Overdose Cohort (BC Provincial Overdose Cohort, 2017) was used for this analysis. It combines several different administrative datasets to explore the potential drivers of overdose deaths in British Columbia. The British Columbia Provincial Overdose Cohort is a dynamic cohort updated annually. The cohort utilized for this analysis contained individuals living in British Columbia between January 2015 and December 2017 who experienced an overdose event, and a 20% random sample of the British Columbian population (BC Centre for Disease Control, 2018; MacDougall et al., 2019). Once the cohort was established, a five-year history of all British Columbia hospital discharge summaries, emergency department visits, physician billing records and prescription dispensations from community pharmacies were linked to the cohort using a personal health identifier (BC Centre for Disease Control, 2018; MacDougall et al., 2019). Any individuals who did not have a valid British Columbia personal health number were excluded from the cohort (BC Centre for Disease Control, 2018). Table 7 displays the data sources used for this study.

Study Population

The study population included all individuals who were included in the cohort. Individuals' time at risk was excluded if they had one hospitalization for cancer or palliative care

prior to experiencing a fatal or non-fatal overdose, or censoring. Individuals were also excluded if sex was listed as unknown, and if geographical location of individuals could not be established.

Variables

This study included both time-varying and time-constant variables. The variables that could vary with time were chronic and acute pain, geography, age, and health care accessibility. Time-constant variables include sex, substance use disorder, and mental health disorder, excluding substance use disorders.

Exposures. Chronic pain was identified using the same methodology as Tonelli et al. (2015). The DAD, and MSP databases were used to identify those individuals who have the ICD-10 and ICD-9 codes identified by Tonelli et al. to indicate chronic pain (Appendix A). If the individual has two such diagnoses flagged within 30 days or less, they were flagged as having chronic pain. This flag was retained for a minimum of two years but was extended if there were additional episodes with qualifying diagnoses within those two years. The individual would be flagged as having chronic pain each time the above criteria were met.

Geography was determined by utilizing three different datasets: client roster, residence file, and event location. The client roster provided 2011 census dissemination area (DA) for most individuals in the cohort for each year of the study. For those individuals who did not have a residence location in the client registry, additional datasets were available which provided residence location of an additional 327 individuals. If the DA was not available for certain years and if the individuals had health care utilization data for those years, the previous value was used. Once the DA of individuals were established for each year of study, the remoteness and accessibility indices developed by Statistics Canada (Alasia, Bedard, Belanger, Guimond, &

Penney, 2017) were used to quantify remoteness. Dissemination areas were classified as urban if the remoteness index was < 0.30. The BC Ministry of Health rurality designations (Ministry of Health, 2019) provided further direction for urban/rurality groups.

Covariates. Age of the individuals was calculated based on the birth month and year of each individual, and the start date for each follow-up record. Age was then grouped into 6 categories: ≤19, 20-29, 30-39, 40-49, 50-59, 60+.

Mental health status was derived using the DAD and MSP utilizing the ICD9/10 codes used by CIHI (Canadian Institute for Health Information, 2012). If an individual had one mental health ICD9/10 code in the DAD or two within one year in MSP, they were flagged as having a mental health diagnosis; the substance related disorders were flagged separately. Accessibility of health services was derived using the same methodology as geography and was categorized into two categories: accessible and limited accessibility; DA's were classified as accessible if their accessibility index was ≥ 0.80.

Outcome. The primary event of interest was experiencing an overdose event, which is defined as the first fatal or non-fatal overdose event experienced by the individual. Fatal and non-fatal overdose events were combined, as previous research has found that there were minimal differences between the two groups, which is consistent with other analyses using this cohort (Otterstatter et al., 2018; Smolina et al., 2019). A secondary analysis was conducted with the outcome interest being experiencing a fatal overdose to examine if there were distinct factors that impact fatal overdose, such as access to health care. The Provincial Overdose Cohort had overdose events identified utilizing several different sources: DAD, MSP, NACRS, Drug and Poison Information Centre database, the surveillance system in emergency departments, BC Coroners' deaths identified as an illicit drug overdose, and BC EHS patients that were classified

as opioid overdose or required naloxone as part of their treatment (MacDougall et al., 2019; Ministry of Health et al., 2016).

Statistical Analysis

The observation period for this study was from January 1, 2010 to December 31, 2017. To examine the association between chronic pain and covariates, two by two tables and Cramer's V were calculated due to the large sample size (Raouafi, Achiche, & Raison, 2018). Multivariate Cox regression analysis was conducted to examine the impact of chronic pain on non-fatal and fatal overdose events. To determine if covariates should be included in the model, bivariate analyses were conducted and a p value of ≤ 0.1 was used to determine if it would be considered for inclusion. In addition, once an overall model was developed, a secondary analysis of fatal overdoses was conducted to determine if fatal overdoses had distinct contributing factors compared to the overall model. Significant association between covariates and chronic pain will be examined in the multivariate analysis.

The proportional hazard assumptions were tested utilizing the global proportional hazards test and was significant; however, the proportional hazards test is sensitive to small violations due to large sample sizes, and it is recommended to check the proportional hazards utilizing scaled Schoenfeld plots and log-log plots for individual variables (Therneau & Grambsch, 2000). After examining the Scaled Schoenfeld plots and log-log plots it was determined that the proportional hazards assumption was not violated. Likelihood ratio tests were used to test statistical interactions between the exposures of interest and covariates. Dataset construction was conducted in SAS® 9.4 and statistical analyses were conducted in Stata® 16.0.

Results

During the observation period 9% (n = 98,372) of cohort individuals experienced chronic pain. The proportion and measure of association of chronic pain amongst covariates of interest can be found in Table 8. There were weak associations between chronic pain and geography, sex, and health care accessibility. There were moderate associations between chronic pain and mental health disorders, substance use disorder, and age group.

Overdose Events

Table 9 presents the overall cohort characteristics for overdose events. Over the study observation period, a total of 22,677 (2%) of the individuals experienced an overdose event, for an incidence rate of 37.0 overdose events per 100,000 person years (95% CI = 36.5 - 37.5). For the exposures of interest, individuals who experienced chronic pain during the observation period had an incidence rate of 1,033 overdose events per 100,000 person years (95% CI = 997.8 – 1069.4), and individuals living in rural areas during the observation period had an incidence rate of 34.1 overdose events per 100,000 person years (95% CI = 33.0 – 35.3).

Table 10 presents the results of the bivariate and multivariate Cox regression analysis. In the multivariate analysis, the exposures of interest were significantly associated with experiencing an overdose event during the observation period: chronic pain and geography (AHR =1.19; 95% CI = 1.12 – 1.27). Chronic pain had significant interactions with geography (AHR = 1.14; 95% CI = 1.03 – 1.25), sex (AHR = 0.85; 95% CI = 0.78 – 0.92), and substance use (AHR = 0.53; 95% CI = 0.49 – 0.58). Geography had a significant interaction with substance use (AHR = 0.58; 95% CI = 0.54 – 0.63). When examining the covariates people with a substance use disorder diagnosis (AHR = 41.06; 95% CI = 39.60 – 42.56) had the highest risk of experiencing and overdose event during the observation period.

Overdose Deaths

There were 3,493 fatal overdoses during the observation period, which is an incidence rate of 5.7 fatal overdoses per 100,000 person years (95% CI = 5.5 – 5.9). Table 11 presents the characteristics for individuals who experienced a fatal overdose. For the exposures of interest, individuals who experienced chronic pain during the observation period had an incidence rate of 187.1 fatal overdoses per 100,000 person years (95% CI =172.6 – 202.9) and individuals living in rural areas during the observation period had an incidence rate of 5.1 fatal overdoses per 100,000 person years (95% CI = 4.7 – 5.6).

Table 12 presents the results of the bivariate and multivariate Cox regression analysis. In the multivariate analysis, the exposures of interest chronic pain (AHR = 2.83; 95% CI = 2.29 – 3.50) was significantly associated with experiencing a fatal overdose during the observation period; geography (AHR =1.06; 95% CI = 0.1 – 1.24) was not significantly associated with experiencing a fatal overdose. Chronic pain had significant interactions with sex (AHR = 0.80; 95% CI = 0.65 – 0.98), and substance use (AHR = 0.61 95% CI = 0.50 – 0.74). Geography had a significant interaction with substance use (AHR = 0.69; 95% CI = 0.57 – 0.83). When examining the covariates, people with a substance use disorder diagnosis (AHR = 18.73; 95% CI = 17.16 – 20.46) had the highest risk of experiencing and overdose event during the observation period.

Discussion

The present study has a prevalence rate of chronic pain, 9%, which is similar to findings from other chronic pain studies (Ospina & Harstall, 2002; Ramage-Morin & Gilmour, 2010). There was an observed weak association between geography, sex and health care accessibility

and chronic pain and a moderate association between chronic pain and age group, substance use and mental health disorders.

Consistent with other chronic pain studies (Del Giorno, Frumento, Varrassi, Paladini, & Coaccioli, 2017; Ramage-Morin & Gilmour, 2010) we found that individuals who lived in rural areas, at baseline, were 1.4 times more likely to experience chronic pain compared to those living in urban areas and people living in areas with limited access to health care services were 1.3 times more likely to experience chronic pain, compared to those with access to health care services. There was also a sex difference where females were 1.2 times more likely to experience chronic pain compared to males.

We also examined mental health and substance use disorders and chronic pain. The present study found that individuals who had a mental health diagnosis were 2.4 times more likely to experience chronic pain, compared to individuals who did not have a mental health diagnosis. Individuals who had a diagnosis of a substance use disorder were 3.3 times more likely to experience chronic pain, compared to individuals who did not have a substance use disorder diagnosis. With the current study design, we were unable to determine if the mental health and substance use disorders preceded the chronic pain diagnosis or resulted from it; however, there are a number of studies that show a positive correlation between chronic pain and psychological problems (Brennan et al., 2007; Brennan et al., 2016; Lohman et al., 2010; Noble et al., 2010; Ramage-Morin & Gilmour, 2010).

Overdose Events

Overall, the present study demonstrates that the risk of experiencing an overdose event for individuals is influenced by chronic pain and where people live. The risk of suffering an overdose event for people experiencing chronic pain differed with geography, sex, and substance

use disorder. Individuals experiencing chronic pain who live in a rural area have an approximately 1.14 times higher risk of experiencing an overdose event compared to those who live in an urban area. People who live in rural areas have limited access to non-pharmacologic interventions for chronic pain, such as physiotherapy or multidisciplinary pain services, which may increase the reliance on pharmacological interventions, and may increase the risk of experiencing an overdose event (Eaton et al., 2018; Schuchat, Houry, & Guy, 2017). The interaction between chronic pain and rurality was not significant, when considering fatal overdoses.

The interaction between sex and chronic pain showed for chronic pain increased the risk of overdose for both males and female; however, the increase in risk for males was less compared to females. Previous research has found that females are treated differently when seeking treatment for chronic pain, with females reporting their chronic pain being dismissed by health providers more frequently compared to males and receiving less analgesics for pain treatment for the same type of pain compared to males (Hoffman et al., 2002; Igler et al., 2017). If females do not receive adequate treatment for pain, they may seek relief from multiple sources, either by seeking treatment from multiple providers (Campbell et al., 2010) or through seeking illicit drugs to relieve their pain (Cicero, Lynskey, Todorov, Inciardi, & Surratt, 2008), which may increase the likelihood of females experiencing a fatal or non-fatal overdose.

For those individuals experiencing chronic pain, and having a substance use disorder, the risk of an overdose event is reduced by approximately 47%, and the risk of an overdose death is reduced by approximately 39% compared to those who have chronic pain and no substance use disorder. This reduced risk may be due to the increased monitoring that is recommended for individuals who have a substance use disorder and are experiencing chronic pain, who are being

treated with prescription analgesics (Morasco, Duckart, & Dobscha, 2011). It may also be the result of people with substance use disorders gaining access to prescription pharmaceuticals, which helps lessen addiction behaviour as well as treat their chronic pain, thereby reducing their reliance of illicit drugs. Another possibility is that people with substance use disorder may have developed a higher degree of opioid tolerance, or use other safeguards, such as using with others, that may reduce their risk of overdose compared to people without substance used disorders.

There was a significant interaction between living in a rural area and substance use. Individuals who lived in rural areas and had a substance use diagnosis were 42% less likely to experience an overdose event, and 31% less likely to suffer a fatal overdose compared to those individuals living in urban areas and having a substance use diagnosis. This may be the result of how geography and substance use disorder were treated in the analysis; substance use disorder did not vary with time, whereas geography was time varying. This may have attributed too much time at risk for an overdose event to rurality and substance use disorder if people who migrate to urban centres develop substance use disorder; or people with substance use disorders who migrate to more urban centres as the disorder progresses. However, research has found that migration from rural to urban centres does not increase the risk of developing a substance use disorder, and the prevalence of substance use disorders are similar between urban and rural communities (Cronk & Sarvela, 1997; Jirapramukpitak, Prince, & Harpham, 2008; Keyes et al., 2014; Maggi et al., 2010; Mueser, Essock, Drake, Wolfe, & Frisman, 2001).

Another hypothesis of why the risk of experiencing an overdose event is lower for individuals with substance use disorder who live in rural areas is the drug supply they utilize for their addiction. Individuals in rural area report that they use less illicit drugs as their drugs of choice, and primarily use diverted prescription drugs and/or misuse their own prescriptions

(Click, Basden, Bohannon, Anderson, & Tudiver, 2018; Keyes et al., 2014; Monnat & Rigg, 2016). This may mitigate some of the risk of experiencing overdose events from the toxic illicit drug supply that is circulating in British Columbia (Tyndall, 2020).

Other explanations for the difference in risk between people with substance use disorder who live in rural and urban areas is that there may be differences in medical care which leads to an underdiagnosis of substance use disorder. There may also be differences in social support networks, with research showing that people living in rural areas having stronger support networks have reduced morbidity and mortality related to substance use (Hamdan-Mansour, Puskar, & Sereika, 2007). Research has shown however, that attitudes in rural areas towards substance use can negatively affect the development of harm reduction and treatment services (Beachler, Zeller, Heo, Lanzillotta-Rangeley, & Litwin, 2021; Ezell et al., 2021).

Limitations

There are several limitations to this study. Overdose events were primarily identified using administrative data, which would not capture overdose events that had no contact with health care services; therefore, only those individuals who sought care for an overdose from health care services or suffered a fatal overdose are included. Any individual who had an overdose event, who was reversed by a community member, and did not seek care from a health facility, was not included in the study. In addition, the derived variables, substance use disorder, mental health disorders, chronic pain, and acute pain, utilized administrative health data and are subject to the same limitations to overdose events. If individuals do not seek health care services or health care services are unavailable it will not be captured. This may cause those individuals who live in rural areas to be underrepresented as there is limited access to health care services compared to those in urban areas. There may also be inconsistent coding standards between

health care service providers, which may have led to misclassification of overdose events. Nevertheless, this unique dataset combined overdose events from various sources to ensure that all overdoses that resulted in contact with the health system were captured.

Conclusion

Chronic pain and where a person resides appear to have an impact on the risk of experiencing an overdose event; however, the risk depends upon several distinct factors. Chronic pain increases an individual's risk of overdose, but the risk is even greater for people living in rural areas compared to urban areas. In addition, experiencing chronic pain and having substance use disorder diagnosis reduces the risk of experiencing an overdose compared to individuals with a substance use disorder diagnosis that are not experiencing chronic pain; as does living in a rural area and having a substance use disorder diagnosis compared to those individuals who have a substance use disorder diagnosis living in urban areas. These findings suggest that the factors that influence the risk of experiencing an overdose event are complex and may differ based on an individual's location.

Table 7. Data Sources Used for Analysis

BC Provincial Overdose Cohort V1. (2017)
Discharge Abstract Database (DAD). V1 (British Columbia Ministry of Health [BC MOH], 2019)
Medical Services Plan (MSP) Payment Information File. V1 (BC MOH, 2019)
PharmaNet. V2(BC MOH, 2019)
Client Roster. V1(BC MOH, 2019)

Table 8. Proportions and Measures of Association Between Chronic Pain and Covariates Chronic Pain

	No		Yes		
	(961,109)	%	N (98,372)	%	Cramer's V
Geography					
Urban	771,203	80.2%	72,943	74.2%	0.044***
Rural	189,906	19.8%	25,429	25.8%	
Age Group					
< 19	294,326	30.6%	5,988	6.1%	0.187***
20-29	143,963	15.0%	10,129	10.3%	
30-39	127,059	13.2%	14,528	14.8%	
40-49	132,389	13.8%	19,967	20.3%	
50-59	120,926	12.6%	19,816	20.1%	
60+	142,446	14.8%	27,889	28.4%	
Sex					
Male	481,908	50.1%	45,235	46.0%	0.024***
Female	479,201	49.9%	53,137	54.0%	
Health Care Accessibility					
Accessible	894,130	93.0%	89,522	91.0%	0.023***
Limited Accessibility	66,979	7.0%	8,850	9.0%	
Substance Use Disorder					
No	925,613	96.3%	87,344	88.8%	0.107***
Yes	35,496	3.7%	11,028	11.2%	

Mental Health Disorder Excluding Substance Use Disorder					
No	803,546	83.6%	64,421	65.5%	0.137***
Yes	157,563	16.4%	33,951	34.5%	

Note. Chronic pain is experiencing chronic pain at any point during follow up, other variables are at baseline. An individual is considered rural if they lived in a rural area during the study time period.

*** $p \leq 0.001$

Table 9. Cohort Characteristics for Outcome Overdose Events

	N Participants	N Events	Time at Risk	Rate Per 100,000 Person Years	95% CI
Time Varying*					
Chronic Pain					
Yes	97,702	3,194	309,191	1033.02	997.81 - 1069.41
No	1,059,441	19,483	60,955,280	32.96	31.52 - 32.41
Geography					
Rural	215,195	3,623	10,616,117	34.13	33.03 - 35.26
Urban	906,254	19,054	50,648,354	37.62	37.09 - 38.16
Age Group					
<19	300,314	1,840	17,169,052	10.72	10.24 - 11.22
20-29	222,796	6,028	8,886,402	67.83	66.14 - 69.57
30-39	220,292	5,481	8,204,896	66.80	65.06 - 68.59
40-49	227,114	4,148	8,765,963	47.32	45.90 - 48.78
50-59	229,020	3,188	8,178,119	39.98	37.65 - 40.36
60+	249,979	1,992	10,060,038	19.80	19.95 - 20.69
Health Care Accessibility					
Accessible	1,004,282	21,367	56,885,144	37.56	37.06 - 38.07
Limited Accessibility	98,086	1,310	4,379,327	29.91	28.34 - 37.58
Non-time varying Variables					

Sex					
Male	527,143	15,320	30,477,499	50.27	49.48 - 51.07
Female	532,338	7,357	30,786,554	23.90	23.36 - 24.45
Substance Use Disorder					
Yes	46,524	14,699	2,670,401	550.44	541.58 - 559.37
No	1,012,957	7,978	58,593,652	13.62	13.32 - 13.92
Mental Health Disorder Excluding Substance Use Disorder					
Yes	191,514	11,242	11,046,540	101.77	99.90 - 103.67
No	867,967	11,435	50,217,514	22.77	22.36 - 23.19

Note. 1,059,481 total participants

* Summing time varying participants will sum to greater than total participants

Table 10. Results of Bivariate and Multivariate Cox Regression Model for Overdose Events

	Bivariate			Multivariate		
	HR	SE	95% CI	Adjusted HR	SE	95% CI
Time Varying						
Chronic Pain						
Yes	3.08***	0.06	2.96 - 3.19	2.76***	0.13	2.53 - 3.02
No			Baseline			
Geography						
Rural	0.92***	0.02	0.89 - 0.96	1.19***	0.04	1.12 - 1.27
Urban			Baseline			
Age Group						
<19			Baseline			
20-29	5.64***	0.15	5.35 - 5.94	2.05***	0.09	1.89 - 2.23
30-39	5.17***	0.14	4.91 - 5.45	1.54***	0.07	1.41 - 1.68
40-49	4.02***	0.11	3.08 - 4.25	1.16**	0.05	1.06 - 1.27
50-59	2.95***	0.09	2.77 - 3.11	0.83***	0.04	0.75 - 0.91
60+	1.25***	0.04	1.17 - 1.33	0.62***	0.03	0.56 - 0.68
Health Care Accessibility						
Accessible	1.23***	0.04	1.17 - 1.30	1.25***	0.04	1.17 - 1.33
Limited Accessibility			Baseline			
Non-time varying Variables						
Sex						

Male	2.12***	0.03	2.06 - 2.18	1.14**	0.05	1.04 - 1.25
Female			Baseline			
Substance Use Disorder						
Yes	48.75***	0.68	47.44 - 50.10	41.06***	0.75	39.60 - 42.56
No			Baseline			
Mental Health Disorder Excluding Substance Use Disorder						
Yes	4.72***	0.06	4.60 - 4.85	1.22***	0.02	1.18 - 1.25
No			Baseline			
Interactions						
Chronic by Rural				3.14**	0.05	2.53 - 3.77
Chronic by Male				2.34***	0.03	1.98 - 2.78
Chronic by SUD				21.81***	0.02	19.30 - 24.66
Rural by SUD				23.98***	0.02	21.49 - 26.75
Male by 20-29				2.75***	0.07	2.28 - 3.32
Male by 30-39				2.30***	0.08	1.89 - 2.79
Male by 40-49				1.86***	0.09	1.86 - 2.28
Male by 50-59				1.38***	0.01	1.11 - 1.71
Male by 60+				0.73*	0.08	0.58 - 0.91

Note. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

SUD = Substance Use Disorder

Table 11. Cohort Characteristics for Outcome Fatal Overdose

	N Participants	N Deaths	Time at risk	Rate Per 100,000 Person Years	95% CI
Time Varying*					
Chronic Pain					
Yes	98,372	586	313,163	187.12	172.57 - 202.9
No	1,059,441	2,907	60,976,519	4.77	4.60 - 4.94
Geography					
Rural	215,335	546	10,619,931	5.14	4.73 - 5.59
Urban	906,373	2,947	50,670,227	5.82	5.61 - 6.03
Age Group					
<19	300,314	108	17,170,901	0.63	0.52 - 0.76
20-29	223,385	610	8,893,689	6.86	6.34 - 7.43
30-39	221,134	820	8,211,533	9.99	9.33 - 10.69
40-49	227,686	797	8,770,963	9.09	8.48 - 9.74
50-59	229,470	723	8,181,679	8.84	8.22 - 9.51
60+	250,226	435	10,060,918	4.32	3.94 - 4.75
Health Care Accessibility					
Accessible	10,034,335	3,291	56,909,504	5.78	5.59 - 5.98
Limited Accessibility	98,157	202	4,380,654	4.61	4.02 - 5.29
Non-time varying Variables					

Sex					
Male	527,143	2,707	30,494,181	8.88	8.55 - 9.22
Female	532,338	786	30,795,501	2.55	2.38 - 2.74
Substance Use Disorder					
Yes	46,524	1,955	2,688,283	72.72	69.56 - 76.01
No	1,012,957	1,538	58,601,399	2.62	2.50 - 2.76
Mental Health Disorder Excluding Substance Use Disorder					
Yes	191,514	1,578	11,059,871	14.27	13.58 - 14.99
No	867,967	1,915	50,229,811	3.81	3.65 - 3.99

Note. 1,059,481 total participants

* Summing time varying participants will sum to greater than total participants

Table 12. Results of Bivariate and Multivariate Cox Regression Model for Fatal Overdose

	Bivariate			Multivariate		
	HR	SE	95% CI	Adjusted HR	SE	95% CI
Time Varying						
Chronic Pain						
Yes	3.69***	0.17	3.37 - 4.03	2.83***	0.36	2.29 - 3.50
No	Baseline					
Geography						
Rural	0.90*	0.04	0.82 - 0.98	1.06ns	0.08	0.91 - 1.24
Urban	Baseline					
Age Group						
<19	Baseline					
20-29	9.54***	1.00	7.78 - 11.71	2.82***	0.58	1.99 - 4.02
30-39	12.92***	1.32	10.57 - 15.79	3.34***	0.59	2.37 - 4.71
40-49	12.98***	1.33	10.62 - 15.87	3.73***	0.65	2.66 - 5.26
50-59	11.22***	1.16	9.17 - 13.73	3.44***	0.60	2.44 - 4.86
60+	4.60***	0.50	3.73 - 5.68	2.40ns	0.43	0.91 - 2.19
Health Care Accessibility						
Accessible	1.23***	0.09	1.06 - 1.42	1.18ns	0.10	0.06 - 1.41
Limited Accessibility	Baseline					
Non-time varying Variables						
Sex						

Male	3.48***	0.14	3.22 - 3.77	1.48*	0.29	1.00 - 2.17
Female			Baseline			
Substance Use Disorder						
Yes	28.44***	0.97	26.6 - 30.4	18.73***	0.84	17.16 - 20.46
No			Baseline			
Mental Health Disorder Excluding Substance Use Disorder						
Yes	3.88***	0.13	3.63 - 4.15	1.27***	0.05	1.18 - 1.37
No			Baseline			
Interactions						
Chronic by Rural				1.10ns	0.12	0.75 - 1.62
Chronic by Male				2.26*	0.08	1.49 - 3.43
Chronic by SUD				11.43***	0.06	8.58 - 15.14
Rural by SUD				12.92***	0.07	9.78 - 16.98
Male by 20-29				6.12***	0.48	2.19 - 13.47
Male by 30-39				7.52***	0.49	3.48 - 16.25
Male by 40-49				7.65***	0.44	3.65 - 16.46
Male by 50-59				6.78**	0.43	4.39 - 14.68
Male by 60+				3.38ns	0.32	0.82 - 4.80

Note. ns = not significant; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

SUD = Substance Use Disorder

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Chapter 4: Differences in Opioid Prescription Characteristics between Rural and Urban British Columbia

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Disclaimer: All inferences, opinions, and conclusions drawn in this article are those of the authors, and do not necessarily reflect the opinions or policies of the [British Columbia] Ministry of Health, [British Columbia] Ministry of Mental Health and Addictions, British Columbia Centre of Disease Control, British Columbia Coroner's Service, British Columbia Emergency Health Services.

Introduction

Opioid prescribing as a treatment option for chronic pain has been increasing worldwide. By 2016 the United States (US) and Canada had become the two highest consumers of prescription opioids (Fischer, Jones, & Rehm, 2014; Jones, Vojtila, Kurdyak, & Fischer, 2020). This has been followed by an increase in both medical and nonmedical prescription opioid use morbidity and mortality (Fischer & Argento, 2012; Keyes, Cerdá, Brady, Havens, & Galea, 2014). As a result, there has been development of new opioid prescribing guidelines and standards. In 2016, the College of Physicians and Surgeons of British Columbia adopted a new prescribing standard, Safe Prescribing of Opioids and Sedatives and in 2017 the new Canadian Guideline for Opioids for Chronic Non-Cancer Pain was released. These standards and guidelines focused on initiation and dosing, rotation and tapering of opioids, expert guidance on prescribing opioids and risk mitigation (Busse, 2017; College of Physicians and Surgeons of British Columbia, 2016). Even with the adoption of new standard, there was an increase in the morbidity and mortality related to opioids (BC Coroners Service, 2018; Canadian Institute for Health Information, 2018).

There has been geographical variation in opioid prescribing across Canada and within provinces, with Ontario and Alberta seeing some of the highest rates in the country (Gomes, Mamdani, Paterson, Dhalla, & Juurlink, 2014). With the differences in prescribing rates, there is also a geographical difference in opioid related morbidity and mortality. When examining opioid poisoning hospitalizations from 2016-2017, the rate has ranged from a low of 9.4 hospitalizations per 100,000 population in Quebec to a high of 34.5 hospitalizations per 100,000 population in the three Canadian Territories (Canadian Institute for Health Information, 2017). When examining mortality within British Columbia, there have been regional differences in the

in illicit drug death rate, with rural regions in British Columbia experiencing an 171% increase in illicit drug deaths, compared to an urban region experiencing an 77% increase in illicit drug deaths between the same time period (Office of the Chief Coroner, 2021). This study aims to characterize the differences of opioid prescribing between rural and urban regions in British Columbia for those individuals who suffered from chronic or acute pain between 2010 and 2017.

Methods

Data Source

The British Columbia Provincial Overdose Cohort (BC Provincial Overdose Cohort, 2017) was used for this analysis. It combines several different administrative datasets to explore the potential drivers of overdose deaths in British Columbia. The British Columbia Provincial Overdose Cohort is a dynamic cohort, which is updated yearly. The cohort utilized for this analysis included a 20% random sample of the British Columbia population individuals living in British Columbia between January 2015 and December 2017, and those who experienced a fatal or non-fatal overdose during that time period; any individuals who did not have a valid British Columbia personal health number were excluded from the cohort, which was then linked to health records from 2010 onward (BC Centre for Disease Control, 2018; MacDougall et al., 2019). Opioid prescription dispensations were identified utilizing the PharmaNet dataset. Hospital and physician visits were used to identify pain type, and the client roster was used to identify patient characteristics and home dissemination area of residence. The data sources used for the analysis are in Table 15.

Study Population

The analysis cohort included individuals who had a hospital or physician visit that indicated chronic pain, or acute pain between January 2010 and December 2017 and with at least

one outpatient opioid prescription dispensed in British Columbia. Chronic pain was identified utilizing the same methodology as Tonelli et al. (2015) and acute pain was identified using a modified identification hierarchy developed by Pasricha et al. (2018).

Age of the individuals was calculated based on the birth month and year of each individual, and date of dispensation. Rural-Urban classification was determined utilizing 2011 census dissemination area (DA) for each year of the study. These were then classified as Rural or Urban using the remoteness and accessibility indices developed by Statistics Canada (Alasia, Bedard, Belanger, Guimond, & Penney, 2017). The DAs were classified as urban if the remoteness index was less than 0.30. These were then linked to the PharmaNet data based on year of dispensation. Individuals were excluded if sex was listed as unknown, and if geographic location of individuals could not be confirmed.

Opioid Prescriptions

The opioid specific characteristics were identified in dataset by using Drug Identification Number /Product Identification Number assigned by Health Canada; these included milligrams morphine equivalents (MME), and if they were considered short or long acting. The milligrams morphine equivalents (MME) were further classified as ≤ 50 MMEs, ≤ 90 MMEs, > 90 MMEs, based on the Canadian and American CDC guidelines (Busse, 2017; Dowell, Haegerich, & Chou, 2016). The dispensed opioids were also categorized into two groups, strong and weak, using the WHO analgesic ladder (World Health Organization, 1996). Weak opioids include drugs such as codeine, meptazinol, and tramadol. Strong opioids include drugs such as buprenorphine, fentanyl, hydromorphone, methadone, morphine, and oxycodone (Canadian Institute for Health Information, 2018).

Pain Type and Length of Prescription

The opioid prescriptions were identified as being associated with pain if they were dispensed within 14 days following an ICD 9/10 code indicating chronic or acute pain; if no preceding pain diagnosis was found they were classified as "no associated pain diagnosis". If a dispensation occurred within 14 days of an acute pain flag and during a chronic pain episode, it was classified as acute associated with chronic pain.

The duration of initial prescription was the length of the initial prescription from the patient's index acute or chronic pain diagnosis and categorized using the guidelines established for chronic non-cancer pain (Dowell et al., 2016). Prescriptions were identified as within recommended chronic pain guidelines for acute pain if the initial prescription was ≤ 7 days and for chronic pain ≤ 90 days. If the duration of prescription was > 7 days for acute pain, or > 90 days for chronic pain, it was then categorized as longer than recommended guidelines. For those dispensations that were flagged as acute associated with chronic pain the acute pain guidelines were used to classify dispensation length.

Statistical Analysis

Opioid dispensation characteristics were compared between rural and urban residents using Chi-squared test. With large a sample size even minor differences can be statistically significant; thus, Cramer's V were calculated to show the measure of association due to the large sample size (Kotrlik, Williams, & Jabor, 2011; O'Keeffe et al., 2015; Raouafi, Achiche, & Raison, 2018). Dataset was conducted in SAS 9.4 and statistical analyses were conducted in Stata 16.0.

Results

Between 2010 and 2017 there were 827,994 individuals who experienced acute or chronic pain. Of those individuals 45.0% (n = 372,244) received an opioid dispensation, which represents approximately 19.5 opioid dispensations per person between 2010 and 2017.

Rural Urban Differences in Opioid Prescribing Characteristics

Table 14 shows the number and proportion of dispensations by age group and sex, between rural and urban residents, χ^2 (df = 5) = 16,000, $p < 0.001$, $\varphi_{Cramer} = 0.05$. Individuals in the 30-39 and 50-59 age groups who live in rural areas received more dispensations for opioids compared to urban individuals in the same age groups. Rural residents who were female also received more dispensations for an opioid prescription compared to females living in urban areas, χ^2 (df = 1) = 1,200, $p < 0.001$, $\varphi_{Cramer} = .01$.

Table 15 shows the number and proportion of type of provider and opioid category for dispensations between rural and urban residents, χ^2 (df = 1) = 10,000, $p < 0.001$, $\varphi_{Cramer} = 0.03$. A slightly higher proportion of rural residents received prescriptions from physicians compared to urban residents. Type of opioid prescribed varies between rural and urban residents, χ^2 (df = 6) = 12,000, $p < 0.001$, $\varphi_{Cramer} = 0.04$. Rural residents received a higher proportion of opioids with codeine, fentanyl, morphine, and methadone.

Table 16 shows the number and proportion of prescription characteristics between rural and urban residents. Rural residents had a lower proportion of opioid that were prescribed at a lower MME per day compared to urban residents, χ^2 (df = 2) = 2,100, $p < 0.001$, $\varphi_{Cramer} = 0.02$. Rural residents received a higher proportion of short acting opioid than urban residents, χ^2 (df = 2) = 3,300, $p < 0.001$, $\varphi_{Cramer} = 0.02$. Rural residents were more often prescribed opioids that were considered weak compared to urban residents χ^2 (df = 2) = 3,600, $p < 0.001$, $\varphi_{Cramer} = 0.02$.

When examining pain type associated with the prescription, rural residents had a higher proportion of prescriptions associated with chronic pain, or acute pain associated with chronic pain than urban residents χ^2 (df = 3) = 9,700, p < 0.001, φ_{Cramer} = 0.04. When examining length of prescriptions in relation to recommended guidelines, rural residents (13.7%) received prescriptions that were longer than recommended guidelines compared to urban residents (10.6%) χ^2 (df = 2) = 14,000, p < 0.001, φ_{Cramer} = 0.04. However, urban residents (36.3%) were more likely to have no hospital or physician visit associated with pain compared to rural residents (33.2%). There was a small but significant difference in the number of days prescribed between rural and urban residence for chronic pain (χ^2 (df = 1) = 9.71, p < 0.01, φ_{Cramer} = 0.001), with a higher proportion of urban residents (0.23%) receiving prescriptions greater than 90 days compared to rural residents (0.20%). A higher proportion of rural residents received prescriptions that were greater than 7 days for acute pain (50.2%; χ^2 (df = 2) = 35,000, p < 0.001, φ_{Cramer} = 0.13), acute pain associated with chronic pain (53.4%; χ^2 (df = 2) = 21,000, p < 0.001, φ_{Cramer} = 0.12 and when there was no associated pain (54.6%; χ^2 (df = 2) = 62,000, p < 0.001, φ_{Cramer} = 0.15), compared to urban residents.

Rural Urban Differences in Opioid Prescriptions

Overall, individuals who received dispensations while living in rural areas received approximately 19.9 opioid dispensations per person between 2010 and 2017, and urban residents received 18.5 opioid dispensations per person between 2010 and 2017 (z = 78.7, p < 0.001). Figure 2 shows the yearly proportion of prescriptions for rural and urban residence from 2010 – 2017 (χ^2 (df = 7) = 5,700, p < 0.001, φ_{Cramer} = 0.03). Figure 3 shows the proportion of opioid prescriptions by MME per day from 2010 - 2017 for rural and urban residents. For rural residents, the proportion of opioid prescriptions with < 50 MME has increased from 61.9% of all

opioid prescriptions in 2010 to 69.0% in 2017, with proportion of opioid prescriptions with 90+ MME per day decreasing from 22.1% of all opioid prescriptions in 2010 to 14.2% in 2017 (χ^2 (df = 14) = 11,000, $p < 0.001$, $\varphi_{Cramer} = 0.06$). For urban residents, the proportion of opioid prescriptions with < 50 MME has increased from 62.2% of all opioid prescriptions in 2010 to 68.4% in 2017, with proportion of opioid prescriptions with 90+ MME per day decreasing from 21.4% of all opioid prescriptions in 2010 to 17.2% in 2017 (χ^2 (df = 14) = 17,000, $p < 0.001$, $\varphi_{Cramer} = 0.04$).

Discussion

The current study showed rural residents receive a higher number of opioid prescriptions per person compared to urban residents, which is consistent with other research that has examined opioid prescriptions between rural and urban residents (Lund, Ohl, Hadlandsmyth, & Mosher, 2019; Sears, Edmonds, & Fulton-Kehoe, 2020; Zhou, Yu, & Losby, 2018). However, when opioid prescriptions for each year of the study were examined, between 2010 and 2013 a higher proportion of opioid prescriptions were dispensed to rural residents and in 2014, urban residents begin to receive a higher proportion of opioid prescriptions compared to rural residents. In 2017, there was no significant difference between rural and urban residents in the proportion of opioid prescriptions.

There was also a decline in the proportion of opioid prescriptions dispensed to both rural and urban residents in 2016 and of note, the lowest proportion of opioid prescription dispensations in the study period was in 2017. This decline corresponds to the adoption of the new standard, Safe Prescribing of Opioids and Sedatives, established by the College of Physicians and Surgeons of British Columbia (College of Physicians and Surgeons of British Columbia, 2016) and the release of the Canadian Guideline for Opioids for Chronic Non-Cancer

Pain in 2017. Witt et al. (2018) found that the implementation of opioid prescribing guidelines in the U.S. decreased the number of patients using opioid therapy, and Lund et al. (2019), in a study of U.S. veterans that there was a decline in both rural and urban counties from 2012 - 2016 in opioid prescribing.

There were significant differences between rural and urban residents and opioid prescribing characteristics. However, there was a very weak association between where people live and the associated prescribing characteristics, with only duration of an opioid prescription showing a weak association. People who lived in rural areas with acute pain, or no associated pain diagnosis received a higher proportion of opioid prescriptions that were longer than 7 days compared to urban residents. There was little difference between urban and rural residents for duration of opioid prescriptions for chronic pain. Other epidemiological studies have also shown that people in rural areas typically have a more days dispensed compared to urban residents (Lund et al., 2019; Sears et al., 2020).

One finding in the current study that differs from other studies is that MME per day were lower for rural residents in comparison to urban residents, whereas other studies have shown individuals in rural areas had higher MMEs per day (Lund et al., 2019; Sears et al., 2020; Zhou et al., 2018). The differences in findings may be due to how MME per day was classified; Lund et al. used MME per capita, Zhou et al and Sears et al. examined only high dose opioid prescriptions between rural and urban residents and the current study examined low dose and high dose opioid prescriptions.

Limitations

Caution should be used in generalizing to other populations. Although, the sample size was large, it contains a subset, individuals who experienced chronic or acute pain, of the

population and may not be generalizable to other populations. Additionally, only prescriptions dispensed in community pharmacies could be included in the dataset. Prescriptions that were filled or dispensed in hospital were not captured. We cannot determine whether the dispensed prescriptions were taken as prescribed or were diverted for non-medical use. In addition, the days supply in the PharmaNet dataset may not be accurate, as some prescriptions are taken as needed, and the pharmacist will enter how long they think the prescription will last (Canadian Institute for Health Information, 2019).

Conclusion

Opioid prescribing rates in British Columbia are decreasing in both rural and urban areas; by 2017 the prescribing rates for rural and urban residents were the same. Between 2010 and 2017 the proportion of prescriptions with <50 MME per day has increased, and the proportion of individuals receiving > 90 MME per day has decreased for both rural and urban residents. There is little difference between rural and urban areas in the prescriber profession, age, sex, strength of opioid, type, or MMEs per day. There was a difference in the length of prescription with people in rural areas who are experiencing acute pain receiving more prescriptions for greater than seven days.

Table 13. Data Sources Used for Analysis

BC Provincial Overdose Cohort V1. (2017)
Discharge Abstract Database (DAD). V1 (British Columbia Ministry of Health [BC MOH], 2019)
Medical Services Plan (MSP) Payment Information File. V1 (BC MOH, 2019)
PharmaNet. V2(BC MOH, 2019)
Client Roster. V1(BC MOH, 2019)

Table 14. Differences Between Rural and Urban Residents for Opioid Prescription Dispensations: Age Group and Sex

	Urban		Rural		
	5,601,944		1,656,094		
	N	%	N	%	Cramer's V
Age Group					
<19	46,019	0.8%	14,549	0.9%	0.05***
20-29	252,021	4.5%	73,691	4.4%	
30-39	637,671	11.4%	227,728	13.8%	
40-49	1,349,207	24.1%	334,743	20.2%	
50-59	1,503,567	26.8%	474,129	28.6%	
60+	1,813,459	32.4%	531,254	32.1%	
Sex					
Female	2,773,258	49.5%	845,636	51.1%	0.01***
Male	2,828,686	50.5%	810,458	48.9%	

Note. Age group was assigned when prescription dispensation occurred.

*** $p \leq 0.001$

Table 15. Differences Between Rural and Urban Residents for Opioid Prescription Dispensations: Prescriber Profession and Opioid Category

	Urban		Rural		
	5,601,944		1,656,094		
	N	%	N	%	Cramer's V
Prescriber Profession					
Physician	5,215,601	93.1%	1,569,986	94.8%	0.04***
Dentist	243,366	4.3%	65,224	3.9%	
Pharmacist	123,396	2.2%	17,735	1.1%	
Nurse Practitioner	17,226	0.3%	3,011	0.2%	
Other	2,355	0.0%	138	0.0%	
Opioid Category					
Buprenorphine	20,332	0.4%	2,410	0.1%	0.04***
Codeine	1,933,855	34.5%	620,904	37.5%	
Fentanyl	132,501	2.4%	48,232	2.9%	
Hydromorphone	888,569	15.9%	229,261	13.8%	
Methadone	136,816	2.4%	42,421	2.6%	
Morphine	1,108,199	19.8%	329,642	19.9%	
Oxycodone	941,329	16.8%	254,677	15.4%	
Other	440,343	7.9%	128,547	7.8%	

*** $p \leq 0.001$

Table 16. Differences Between Rural and Urban Residents for Opioid Prescription Dispensations: Prescription Characteristics

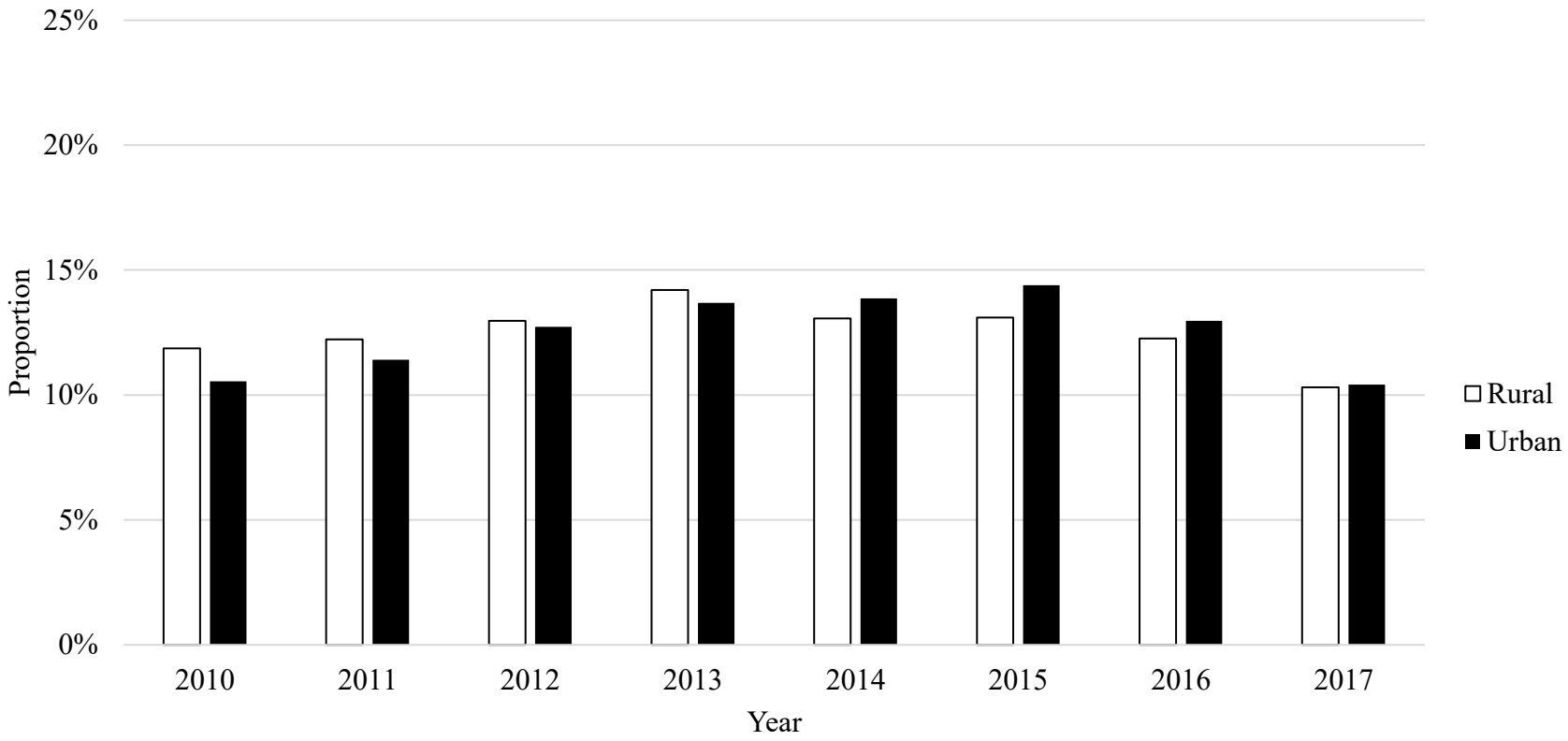
	Urban 5,601,944		Rural 1,656,094		
	N	%	N	%	Cramer's V
MME Per Day					
<50	3,528,335	63.0%	1,060,420	64.0%	0.02***
50-90	866,639	15.5%	265,896	16.1%	
90+	1,206,970	21.5%	329,778	19.9%	
Acting					
Long	1,810,659	32.3%	523,892	31.6%	0.02***
Short	3,770,142	67.3%	1,130,412	68.3%	
Unknown	21,143	0.4%	1,790	0.1%	
Length of Prescription					
Within Guidelines	2,974,506	53.1%	880,552	53.2%	0.04***
Longer than Guidelines	595,446	10.6%	226,134	13.7%	
No Associated Pain Diagnosis	2,031,992	36.3%	549,408	33.2%	
Opioid Strength					
Weak	2,041,060	36.4%	643,404	38.9%	0.02***
Strong	3,560,202	63.6%	1,012,141	61.1%	
Unknown	1,012	0.02%	718	0.04%	
Pain Type Associated with Prescription					
Acute	1,570,613	28.0%	448,660	27.1%	0.04***
Chronic	945,560	16.9%	317,097	19.1%	

Acute associated with Chronic	1,053,779	18.8%	340,929	20.6%	
No Associated Pain Diagnosis	2,031,992	36.3%	549,408	33.2%	
Length of Prescription by Pain Type					
Acute Pain					
<3 days	523,385	33.3%	88,470	19.7%	0.13***
3-7 days	455,955	29.0%	135,173	30.1%	
7+ days	591,273	37.6%	225,017	50.2%	
Chronic Pain					
< 90 days	943,375	99.8%	316,460	99.8%	0.001**
91+ days	2,185	0.23%	637	0.20%	
Acute associated with Chronic					
<3 days	343,382	32.6%	68,660	20.1%	0.12***
3-7 days	263,560	25.0%	90,118	26.4%	
7+ days	446,837	42.4%	182,151	53.4%	
No Associated Pain Diagnosis					
<3 days	690,213	34.0%	99,137	18.0%	0.16***
3-7 days	554,589	27.3%	150,471	27.4%	
7+ days	787,190	38.7%	299,800	54.6%	

Note. Participants pain type and location assigned when prescription was dispensed.

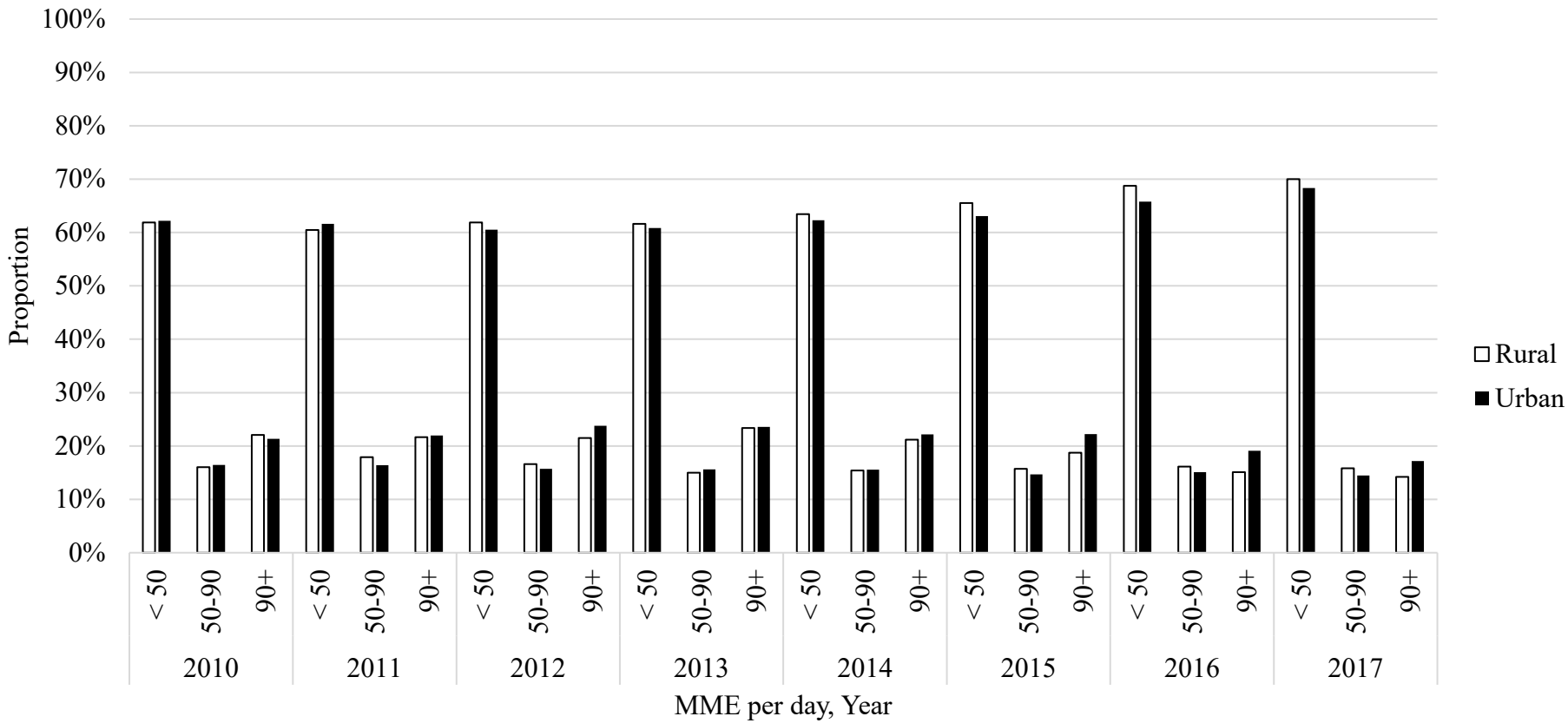
** $p \leq 0.01$; *** $p \leq 0.001$

Figure 2. Proportion of Opioid Prescriptions Per Year by Rural and Urban Residents



χ^2 (df = 7) = 5,700, $p < 0.001$, $\varphi_{Cramer} = 0.03$

Figure 3. Proportion of Opioid Prescriptions by MME per Day, Per Year, by Rural and Urban Residents



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Chapter 5: Rural and Urban Differences: Impact of the Opioid Prescriptions and the Use of Multiple Prescribers on the Risk of Illicit Substance Overdose

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Disclaimer: All inferences, opinions, and conclusions drawn in this article are those of the authors, and do not necessarily reflect the opinions or policies of the [British Columbia] Ministry of Health, [British Columbia] Ministry of Mental Health and Addictions, BC Centre of Disease Control, BC Coroner's Service, BC Emergency Health Services.

Introduction

In North America, there has been an increase in rate of prescription opioid consumption compared to the rest of the world, and with this increase there been an increase in opioid related morbidity and mortality (Canadian Institute for Health Information, 2018; Fischer, Benedikt & Argento, 2012; Fischer, Benedikt, Jones, & Rehm, 2014; Keyes, Cerdá, Brady, Havens, & Galea, 2014). Research examining opioid mortality rates in North America has found regional differences at a variety of geographic levels (Canadian Institute for Health Information, 2017; Fischer, Benedickt, Vojtila, & Rehm, 2018; Kuo, Raji, Chen, Hasan, & Goodwin, 2016; Lund, Ohl, Hadlandsmyth, & Mosher, 2019). In examining why there may be differences in morbidity and mortality between geographic levels, studies have shown that both prescription and illegal drug use occur at comparable rates in rural and urban areas (Cronk & Sarvela, 1997; Keyes, Cerdá, Brady, Havens, & Galea, 2014); however, overdose deaths in rural areas have increased at a greater rate compared to urban areas. In rural Virginia, the drug overdose deaths increased 300% in six years, with the majority of deaths overdose from prescription opioids (Wunsch, Nakamoto, Behonick, & Massello, 2009). When investigating probable causes for why prescription opioid deaths may be higher in rural areas compared to urban areas, prescription and usage patterns need to be examined. Studies which have examined opioid prescriptions and differences between rural and urban populations have reported that rural populations have received greater proportion of opioid prescriptions and at higher doses than urban populations (Garcia et al., 2019; Lund et al., 2019; Palombi, St Hill, Lipsky, Swanoski, & Lutfiyya, 2018; Rigg & Monnat, 2015; Rigg, Monnat, & Chavez, 2018; Wunsch et al., 2009; Zhou, Yu, & Losby, 2018), which may increase the risk of experiencing an adverse event related to prescription opioids.

Another possible explanation for the regional differences in opioid related morbidity and mortality is the non-medical use of prescription opioids. The non-medical use (NMU) of prescription opioids is defined as taking an opioid that was prescribed for someone else (Lynch, 2013) and it is seen as a growing issue, due to the increase in user morbidity and mortality in relation to opioids. This issue is more evident in North America compared to other countries (Fischer, Benedikt, Keates, Bühringer, Reimer, & Jürgen, 2014). Several studies have correlated the NMU of prescription opioids, which has been suggested to increase risk of heroin abuse, lead to mental health issues, and may lead to other substance misuse problems (Becker, Sullivan, Tetrault, Desai, & Fiellin, 2008; Fotta, 2017).

When people who use drugs inappropriately were asked what type of drugs they used, those who lived in rural and remote areas stated that they used prescription drugs more frequently than those individuals who were living in urban areas (Shah, Lathrop, Flores, & Landen, 2012; Wunsch et al., 2009). The researchers asked participants where drugs were acquired and found that people in rural areas used their own prescriptions or obtained them from family and/or friends; they did not use street drugs as often compared to people who live in urban centres (Click, Basden, Bohannon, Anderson, & Tudiver, 2018; Monnat & Rigg, 2016). Keyes et al. (2014) hypothesised that increased availability of prescription opioids, and having larger social networks, increases the likelihood of individuals sharing prescription opioids in rural areas.

Another source for prescription opioids is the utilization of multiple prescribers to fill prescriptions. Research examining rural and urban differences in gaining access to prescription opioid has found that there were minimal differences in where rural and urban residents gain access to prescription opioids; one observed source for such prescriptions was physician's offices

(Wang, Fiellin, & Becker, 2014). Another hypothesised source is emergency departments, with one study finding that between 2005 and 2011, Emergency Department (ED) visits that involved prescription opioids increased 146% (Pletcher, Kertesz, Kohn, & Gonzales, 2008; Simeone, 2017; Skaer & Nwude, 2016). The identification of the potential contribution NMU of prescription opioids to opioid related morbidity and mortality has prompted many regions to implement drug monitoring programs that monitor prescriptions across a geographic area; however, the use of multiple prescribers has continually increased (Broida, Gronowski, Kalnow, Little, & Lloyd, 2017; Huijun, Kass, Wilsey, & Li, 2014; Skaer & Nwude, 2016). The objective of this study is to examine differences between rural and urban populations, opioid prescriptions, prescription characteristics, and the use of multiple prescribers and the risk of a fatal or non-fatal overdose among individuals who have experienced acute and/or chronic pain.

Methods

Data Source

The British Columbia Provincial Overdose Cohort (BC Provincial Overdose Cohort, 2017) was used to establish the study population for this study. It combines several different administrative datasets to explore the potential drivers of overdose deaths in British Columbia. The British Columbia Provincial Overdose Cohort is a dynamic cohort, which is updated yearly. The cohort utilized for this analysis included individuals living in British Columbia between January 2015 and December 2017 who experienced an overdose event and a 20% random sample of the British Columbia population (BC Centre for Disease Control, 2018; MacDougall et al., 2019). Once the cohort was established, a five-year history of all British Columbia hospital discharge summaries, emergency department visits, physician billing records, and prescription dispensations from community pharmacies were linked to the cohort using a personal health

identifier (BC Centre for Disease Control, 2018; MacDougall et al., 2019). Any individuals who did not have a valid British Columbia personal health number were excluded (BC Centre for Disease Control, 2018). Table 15 presents the data sources used to create the British Columbia Provincial Overdose Cohort that was available for study.

Study Population

From the British Columbia Provincial Overdose Cohort, individuals who experienced chronic pain or acute pain at any time between January 2010 and December 2017 were included in the study population. Individuals were excluded if sex was listed as unknown (n = 43), or if geographic location of individuals could not be confirmed (n = 7,532). When examining overdose death, an additional 1,007 individuals met the inclusion criteria prior to their index event.

Variables

This study included both time-varying and time-constant variates. The variables that could vary with time were chronic and acute pain, geography, opioid prescriptions and related characteristics, other pharmaceuticals, age, and health care accessibility. Time-constant variables included sex, substance use disorder, mental health disorder excluding substance use disorders, and having had an opioid prescription prior to the index pain diagnosis.

Chronic and acute pain. Chronic pain was identified utilizing the same methodology as Tonelli et al. (2015). The DAD and MSP databases were used to identify those individuals who had the ICD-10 and ICD-9 codes identified by Tonelli et al. to indicate chronic pain (Appendix A). If the individual had two diagnoses flagged within 30 days or less, they would be flagged as having chronic pain. This flag remained for two years after the last date that indicated

chronic pain. The individual would be flagged as having chronic pain each time the above criteria were met.

Acute pain was identified using a modified identification hierarchy developed by Pasricha et al. (2018). Both the Canadian Classification for Health Intervention (CCI), and ICD-9/10 codes were used to identify individuals suffering with acute pain (Appendix B). Table 18 displays the number and proportion of individuals in each acute care category at index diagnosis. An individual was flagged as experiencing acute pain for each time the criteria were met. The acute pain episode lasted three months and could turn into chronic pain if the chronic pain criteria were met. These exposures are independent of one another; thus, individuals could have both chronic and acute pain episodes occurring at the same time.

Geography. Geography was determined by utilizing the client roster. The client roster provided the 2011 census dissemination area (DA) for most individuals in the cohort for each year of the study. If the DA was not available for some years, and individuals had health care utilization data for those years, the previous value was used. Once the DA of individuals were established, the remoteness and accessibility indices developed by Statistics Canada (Alasia, Bedard, Belanger, Guimond, & Penney, 2017) were used to quantify remoteness. To establish the threshold between rural and urban, the rurality designations developed by the British Columbia Ministry of Health were used (Ministry of Health, 2019). Once the threshold was established, DAs were classified as urban if the remoteness index was < 0.30. Accessibility of health services was derived using the same methodology as geography and was categorized into two categories: accessible and limited accessibility; DAs were classified as accessible if their accessibility index was ≥ 0.80.

Opioid prescriptions and related characteristics. Opioid prescriptions were identified utilizing community pharmacy dispensation data found in PharmaNet, which captures all prescriptions for drugs that are dispensed in a community or outpatient hospital pharmacy. The opioid specific dispensations were identified in dataset for researchers by using Drug Identification Number /Product Identification Number (DIN/PIN) assigned by Health Canada. The dispensations identified as an Opioid Antagonist Therapy (OAT) were treated separately.

Dispensed opioids were categorized into two groups, strong and weak, using the WHO analgesic ladder (World Health Organization, 1996). Weak opioids include drugs such as codeine, meptazinol, and tramadol. Strong opioids include drugs such as buprenorphine, fentanyl, hydromorphone, methadone, morphine, and oxycodone (Canadian Institute for Health Information, 2018). Opioid prescriptions were classified as long or short acting utilizing the identifier developed by the data provider which was developed utilizing the DIN/PIN of the dispensed opioid.

The opioid prescriptions were identified as being associated with pain if they were dispensed within 14 days following an ICD 9/10 code indicating chronic or acute pain; if no preceding pain diagnosis was found they were classified as “no associated pain diagnosis”. The duration of initial prescription was the length of the initial prescription from their index acute or chronic pain diagnosis and categorized using the guidelines established for chronic non-cancer pain (Dowell, Haegerich, & Chou, 2016). Prescriptions were identified as within recommended chronic pain guidelines for acute pain if the initial prescription was ≤ 7 days and for chronic pain ≤ 90 days. If the duration of prescription was > 7 days for acute pain, or > 90 days for chronic pain, it was then categorized as longer than recommended guidelines.

The milligrams morphine equivalents (MME) per day were provided in the Pharmanet data for each dispensation and were classified as ≤ 50 MMEs, ≤ 90 MMEs, > 90 MMEs, based on both the Canadian and American CDC guidelines (Busse, 2017; Dowell et al., 2016). The MME per day were also calculated for each opioid episode. An opioid episode was calculated by combining consecutive dispensations that occurred within 21 days of the estimated time of the end of the previous prescription (Von Korff et al., 2008) and were classified the as above.

Multiple prescribers. The use of multiple prescribers was identified using the PharmaNet database. All opioid dispensations were examined to determine if multiple prescribers were used. The prescriber number and prescription number associated were used to identify unique prescriptions from the dispensation data. There is no consistent definition of multiple prescribers based on a time period (Adewumi et al., 2020). Therefore, once unique prescriptions were identified individuals were flagged as using multiple prescribers if they received a dispensed opioid prescription, for the same opioid type, by two or more prescribers within a 30-day period, which is consistent with the methodology used by Wilsey et al. (2010).

Demographics. The demographic variables were gathered from the British Columbia client roster file that contains all individuals who are registered in the British Columbia Medical Service Plan (MSP); approximately 99.99% of all British Columbia residents participate in MSP (Ministry of Health, 2021). Age of the individuals was calculated based on the birth month and year of each individual, and the start date for each follow-up record. Age was then grouped into 6 categories: ≤19, 20-29, 30-39, 40-49, 50-59, 60+. The sex of individuals was taken from the client registry.

Other prescribed pharmaceuticals. Additional pharmaceutical dispensations for benzodiazepines, gabapentin, and OAT, were identified in the PharmaNet data and included as

time-varying covariates. For each of these pharmaceuticals, dispensation episodes were also created by combining consecutive dispensations that occurred within 21 days of the estimated time of the end of the previous prescription.

During the development of the analytic dataset, it was observed that 16% of individuals in the cohort had received an opioid prescription prior to the index pain diagnosis. These individuals were flagged as having an opioid dispensation prior to their index pain diagnosis, to adjust for any potential bias.

Mental health and substance use disorders. Mental health status was derived using the DAD and MSP utilizing the ICD9/10 codes and methodology used by CIHI (Canadian Institute for Health Information, 2012). A person with a single mental health diagnosis that was recorded during an inpatient hospital stay was flagged as having a mental health condition, while two instances of a mental health diagnoses within community were required to confirm the diagnosis of a mental health condition.

Outcome. The primary event of interest was a record of an individual who experienced an overdose event, which was defined as the first fatal or non-fatal overdose. Fatal and non-fatal overdose events were combined as previous research reported minimal differences between the two groups and is consistent with other analyses using this cohort (Otterstatter et al., 2018; Smolina et al., 2019). A secondary analysis was conducted with the outcome interest being experiencing a fatal overdose. Both fatal and non-fatal overdoses were identified in the Provincial Overdose Cohort (MacDougall et al., 2019; Ministry of Health et al., 2016).

Time at Risk

The index date for each individual was the date of their diagnosis of acute or chronic pain. The individual was then followed until a fatal or non-fatal overdose, or until a censoring

event occurred. Censoring events included end of follow-up for the current study, moving out of province, a hospitalization for cancer or palliative care, or death not related to an overdose.

Statistical Analysis

A multivariate Cox regression analysis was conducted to examine the impact of opioid prescriptions and multiple prescribers have on non-fatal and fatal overdose events. To determine if covariates should be included in the model, bivariate analyses were conducted and a p-value of ≤ 0.1 was used to determine if it would be considered for inclusion. In addition, once an overall model was developed, a secondary analysis of fatal overdoses was conducted to determine if fatal overdoses had distinct contributing factors compared to the overall model.

The opioid prescription and prescription characteristics were highly correlated; thus, multivariate cox models were conducted for each of the opioid prescription variables independently. The proportional hazard assumptions were tested utilizing the global proportional hazards test and was significant; however, the proportional hazards test is sensitive to small violations due to large sample sizes, and comparison for proportional hazards utilizing scaled Schoenfeld plots and log-log plots for individual variables is recommended (Therneau & Grambsch, 2000). After examining the scaled Schoenfeld plots and log-log plots, it was determined that the proportional hazards assumption was not violated. Likelihood ratio tests were used to test statistical interactions between the exposures of interest and covariates. Dataset construction was conducted in SAS 9.4© and statistical analyses were conducted in Stata 16.0©.

Results

The number of individuals who had an acute or chronic pain diagnosis during the observation period was 826,987. When conducting the secondary analysis, examining overdose

death, an additional 1,007 individuals met the inclusion criteria, for a total of 827,994 individuals.

Overdose Events

Table 19 presents the overall cohort characteristics for overdose events. Over the study observation period, a total of 19,321 (2%) of individuals experienced an overdose event, for an incidence rate of 4.39 overdose events per 1,000 person years (95% CI = 4.33 – 4.45). For the exposures of interest, individuals who lived in rural areas had an incidence rate of 3.99 overdose events per 1,000 person years (95% CI = 3.74 – 4.01). Individuals who had an opioid prescription had an incidence rate of 15.83 overdose events per 1,000 person years (95% CI = 15.16 – 16.52). Individuals in the cohort identified as using multiple prescribers had an incidence rate of 22.30 overdose events per 1,000 person years (95% CI = 21.89 – 22.71).

Table 20 presents the results of the bivariate Cox regression analysis examining risk of experiencing an overdose event. In the bivariate analysis all exposure variables and covariates were significantly associated with the experience of an overdose event during the observation period.

Table 21 presents the results of the multivariate Cox regression analysis for opioid prescription and multiple prescribers. In the multivariate analysis, variables that were significantly associated with time to experiencing an overdose event during the study period included: geography (AHR = 0.89; 95% CI = 0.84 – 0.95), chronic pain (AHR = 0.88; 95% CI = 0.85 – 0.92), and acute pain (AHR = 1.21; 95% CI = 1.18 – 1.26). Examining the different opioid variables, there were significant interactions between substance use disorder and (a) opioid prescription (Table 22); (b) MME per day (Table 23); and (c) opioid strength and acting

(Table 24). There was also a significant interaction between multiple prescribers and geography (Table 25).

Overdose Deaths

There were 3,035 fatal overdoses during the observation period, which is an incidence rate of 6.86 fatal overdoses per 10,000 person years (95% CI = 6.62 – 7.10). Table 26 presents the characteristics for individuals who experienced a fatal overdose. For the exposures of interest, individuals who experienced chronic pain during the observation period had an incidence rate of 1.91 fatal overdoses per 1,000 person years (95% CI = 1.76 – 2.07), and individuals who experienced acute pain during the observation period had an incidence rate of 0.86 fatal overdoses per 1,000 person years (95% CI = 0.79 – 0.92). Individuals who lived in rural areas had an incidence rate of 0.58 fatal overdoses per 1,000 person years (95% CI = 0.53 – 0.64). Individuals who had an opioid prescription had an incidence rate of 2.80 fatal overdoses per 1,000 person years (95% CI = 2.53 – 3.10). Individuals in the cohort identified as using multiple prescribers had an incidence rate of 3.26 fatal overdoses per 1,000 person years (95% CI = 3.11 – 3.42).

Table 27 presents the results of the bivariate Cox regression analysis examining the risk of fatal overdoses. In the bivariate analysis all exposure variables and covariates were significantly associated with the experience of an overdose event during the observation period.

Table 28 presents the results of the multivariate Cox regression analysis for opioid prescription and multiple prescribers. In the multivariate analysis, variables that were significantly associated with time to experiencing a fatal overdose during the study period included: geography (AHR = 0.82; 95% CI = 0.70 – 0.98), and acute pain (AHR = 1.13; 95% CI = 1.04 – 1.24). Examining the different opioid variables there were significant interactions

between substance use disorder and (a) opioid prescription (Table 29); (b) MME per day (Table 30); and (c) opioid strength and acting (Table 31). There was also a significant interaction between multiple prescribers and geography (Table 32).

Discussion

The present study observed 41% of the cohort receiving an opioid prescription dispensation during the study's observation period, which is similar to another study that examined analgesic use and chronic pain treatment, where 44% of analgesic prescriptions were opioids (Clark, 2002). The current research indicates that the risk of experiencing an overdose event and opioid prescription depends upon whether or not the individual has a substance use disorder diagnosis. Individuals with a substance use disorder diagnosis who had an opioid prescription had a 51% reduction in the risk of experiencing an overdose event and a 54% reduction of risk in experiencing a fatal overdose compared to individuals with a substance use disorder diagnosis who did not have an opioid prescription. However, for individuals without a substance use disorder diagnosis, those who had an opioid prescription had a risk of experiencing an overdose event or death that was more than two times the risk for those with no opioid prescription. These results may be impacted by opioid medication discontinuation. Recent studies have shown that abrupt discontinuation of long-term, high-dose opioid prescriptions can increase the risk of an adverse opioid-related health event (Mark & Parish, 2019).

Opioid Prescription Characteristics

The findings of this study suggest that individuals with a substance use disorder diagnosis who had an opioid prescription regardless of the MME per day had a reduction in risk of an overdose event, with prescriptions containing 50 – 90 MME per day showing the highest reduction in risk compared to individuals with a substance use disorder diagnosis and without an

opioid prescription. When examining MME per day and the risk of fatal overdose, individuals with a substance use disorder diagnosis who had an opioid prescription regardless of the MME per day had a reduction in risk of a fatal overdose, with prescriptions containing 91+ MME per day showing the highest reduction in risk compared to individuals with a substance use disorder diagnosis and without an opioid prescription. When examining individuals without a substance use disorder diagnosis, the findings are similar to Dasgupta et al. (2016) in that the risk of overdose increases with average daily MME. Our study found that for individuals without a substance use disorder diagnosis there was increase in the risk of experiencing a fatal or non-fatal overdose with an increase in MME per day compared to those with no opioid prescription.

When examining opioid prescription strength and opioid duration of action, individuals without substance use disorder diagnosis who have opioid prescriptions that were longer acting and either considered weak or strong had an increase in the risk of experiencing an overdose event that was three times that of those with no opioid prescription, whereas for a fatal overdose, strong, long-acting opioids had the highest increase in risk. The greatest reduction in risk of experiencing an overdose event for individuals with a substance use disorder diagnosis was for those who had a short acting opioid prescription, compared to individuals with a substance use disorder diagnosis but without an opioid prescription. In individuals with a substance use disorder diagnosis, for both fatal and non-fatal overdoses, strong, short acting opioids showed the greatest reduction in risk compared to individuals with a substance use disorder diagnosis but no opioid prescription.

Geography

The current study found that after adjustment the risk of experiencing an overdose event was 11% lower in people lived in rural areas compared to urban. The difference between rural

and urban areas and the risk of experiencing an overdose event may be the result of opioid diversion or practitioners prescribing opioids for opioid replacement therapy. Research has shown that rural areas experience more prescription drug diversion compared to urban areas (Keyes et al., 2014), and a study by Cheng et al. (2020) found that individuals who exclusively gained access to prescription opioids for non-medical use were less likely to experience an overdose. In addition, recent studies examining opioid tapering for individuals on long-term opioid therapy have found there is an increased risk of terminating opioid therapy and overdose (Glanz, Binswanger, Shetterly, Narwaney, & Xu, 2019; Perez, Buonora, Cunningham, Heo, & Starrels, 2020). Sears, Edmonds, & Fulton-Kehoe (2020) found that physicians practicing in rural areas were slower to adopt the new prescribing guidelines and standards which may allow individuals to gain or retain access to pharmaceutical-grade drugs for a longer period, thereby reducing their risk of experiencing an overdose from the toxic illicit drug supply (Tyndall, 2020). This difference in risk between rural and urban areas may diminish as rural physicians begin to adopt the new prescribing guidelines and standards, as this may cause a reduction of the number of prescription opioids available for diversion for non-medical use.

Multiple Prescribers

Multiple prescriber use was strongly associated with overdose events in the present study, which is consistent with previous research (Peirce, Smith, Abate, & Halverson, 2012; Walker, Weatherby, Cepeda, & Bradford, 2019). This risk also depended upon where individuals lived. The current study also showed that living in rural areas and utilizing multiple prescribers reduced the risk of overdose events by 18% compared to those who live in urban areas. The reduction in risk in rural areas may be related to opioid diversion and access to a clean drug supply. Another explanation of why there is a difference between rural and urban areas may be related to limited

access to health care in rural areas, rather than necessarily being an indicator of drug-seeking behaviour. Although there has been a suspected link between utilizing multiple prescribers and drug-seeking behaviour (Peirce et al., 2012; Walker et al., 2019), there may be other possible explanations for people utilizing multiple prescribers. These can include limited access to primary care providers and a reliance on locums, lack of access to non-pharmacological pain management, or being referred to another prescriber as part of regular treatment (Adewumi et al., 2020). The concept of multiple prescribers needs to be explored further to determine if it more typically represents drug seeking-behaviour or limited access to health care services, and with regard to the impact on health outcomes.

In the current study, having a dispensation of a benzodiazepine or gabapentin was significantly associated with an increased risk of experiencing a fatal or non-fatal overdose. When examining only fatal overdoses it was found that people who had dispensation of OAT had a 77% reduction in their risk of experiencing an overdose death, but no significant difference in experiencing an overdose event. Current research on the effectiveness of OAT reducing risk of overdose events has been mixed. Smolina et al. (2020) found that people with dispensed medications used for opioid use disorders were more likely to experience an overdose, but Pearce et al. (2020) found that when examining overdose deaths OAT significantly reduced risk of death for people with opioid use disorder. The findings suggest further research is needed to determine why the effectiveness of OAT is limited in reducing the risk of overdose. It is important to recognize that individuals who are prescribed OAT are at increased risk of overdose due to their problematic use of opioids, thus confounding the analysis of OAT's effectiveness.

Individuals in this study who had received an opioid dispensation prior to their index pain diagnosis had a significantly increased risk of experiencing an overdose event or an overdose

death. From the current study it cannot be determined if this is due to inappropriate prescribing practices or issues with charting practices. Further research is required to determine the reason for individuals receiving opioid dispensations prior to a pain diagnosis.

Limitations

There are several limitations to this study. The study design is retrospective, thus cannot show causation, only correlation between the outcome of interest and the explanatory variables. Overdose events were primarily identified using administrative data, which would not capture all overdose events that had no contact with health care services; only those individuals who sought care for an overdose from health care services or suffered a fatal overdose were included. Any individual who had an overdose event that was reversed by a community member, and who did not seek care from a health facility were not included in the study. In addition, the derived variables, substance use disorder, mental health disorders, chronic pain, and acute pain, utilized administrative health data and are subject to the same limitations as overdose events. If individuals do not seek health care services or health care services are unavailable it will not be captured. This may cause those individuals who live in rural areas to be underrepresented as there is limited access to health care services compared to urban areas. There may be inconsistent coding standards between health care providers, which may have led to misclassification of overdose events. Nevertheless, this unique dataset combined overdose events from a number of various sources to ensure that all overdoses that resulted in contact with the health system were captured.

Only prescriptions dispensed in community pharmacies could be included in the dataset. Prescriptions that were not filled or dispensed in hospital are not captured. In addition, we

cannot determine whether the dispensed prescriptions were taken as prescribed or were diverted for non-medical use.

Conclusion

In summary, in the current study the impact opioid prescriptions had on the risk of experiencing a fatal or non-fatal overdose was varied. For those individuals who did not have a substance use disorder diagnosis, having an opioid prescription significantly increased the risk of experiencing a fatal or non-fatal overdose. However, for those individuals who did have a substance use disorder diagnosis it reduced the risk of experiencing a fatal or non-fatal overdose. Even with the mitigating effects of having an opioid prescription, the greatest risk factor for experiencing a fatal or non-fatal overdose was having a substance abuse disorder; however further study is needed to determine if this finding has been impacted by opioid prescription discontinuation.

Table 17. Data Sources Used in Creating Cohort for Study

BC Provincial Overdose Cohort V1. (2017)
Discharge Abstract Database (DAD). V1 (British Columbia Ministry of Health [BC MOH], 2019)
Medical Services Plan (MSP) Payment Information File. V1 (BC MOH, 2019)
PharmaNet. V2(BC MOH, 2019)
Client Roster. V1(BC MOH, 2019)

Table 18. Number and Proportion of Participants by Acute Pain Category

Acute Pain Category	Number of Participants	Percentage
Injury Excluding Poisoning	496,284	40.7%
Headache/Migraine	189,677	15.5%
Infectious Disease	122,978	10.1%
Joint/Muscle Pain	100,953	8.3%
Chest Pain	83,219	6.8%
Abdominal and Pelvic Pain	77,883	6.4%
Back Pain	62,886	5.2%
Ear, Nose, Throat Pain	36,508	3.0%
Surgical Treatment/Diagnostic Procedure	26,718	2.2%
Pregnancy and Delivery	8,345	0.7%
Other	14,625	1.2%

Note. Participants can be in more than one group, as the index date for acute pain contained multiple ICD9/10 codes

Table 19. Cohort Characteristics for Outcome Overdose Events

	N Participants	N Events	Time at Risk	Rate Per 1,000 Person Years	95% CI
Time Varying*					
Opioid Prescription					
Yes	344,926	2,070	130,788.28	15.83	15.16 - 16.52
No	824,591	17,251	4,272,953.05	4.04	3.98 - 4.10
Opioid Strength and Acting					
None	824,600	17,251	4,272,953.05	4.04	3.98 - 4.10
Weak*Long Acting	5,931	69	2,870.79	24.04	18.98 - 30.43
Weak*Short Acting	257,520	588	49,803.49	11.81	10.88 - 12.80
Strong*Long Acting	20,536	452	19,810.93	22.82	20.81 - 25.02
Strong*Short Acting	170,290	961	58,303.06	16.48	15.47 - 17.55
MME Per Day Opioid Px Episode					
None	824,609	17,251	4,272,953.05	4.04	3.98 - 4.10
1 - 49	302,658	1,102	88,292.54	12.48	11.76 - 13.23
50 - 90	82,431	297	18,446.89	16.10	14.37 - 18.40
91+	32,394	671	24,048.85	27.90	25.87 - 30.09
Chronic Pain					
Yes	97,692	3,194	302,848.71	10.55	10.19 - 10.92
No	820,066	16,127	4,100,892.62	3.93	3.87-3.99
Acute Pain					

Yes	825,287	4,266	758,665.17	5.62	5.46 - 5.79
No	814,229	15,055	3,645,076.15	4.13	4.06 - 4.20
Geography					
Rural	170,085	3,163	815,993.18	3.88	3.74 - 4.01
Urban	695,499	16,158	3,587,748.15	4.50	4.43-4.57
Opioid Antagonist Therapy					
Yes	10,644	2,396	24,886.81	96.28	92.50 - 100.21
No	825,403	16,925	4,378,854.52	3.87	3.81 - 3.92
Benzodiazepine					
Yes	187,651	2,832	231,359.59	12.24	11.80 - 12.70
No	818,059	16,489	4,172,381.74	3.95	3.89 - 4.01
Gabapentin					
Yes	73,530	1,829	78,323.13	23.35	22.31 - 24.45
No	824,981	17,492	4,172,381.74	4.19	3.98 - 4.10
Age Group					
<19	181,858	1,426	799,292.32	1.78	1.69 - 1.88
20-29	147,595	4,852	545,469.21	8.90	8.65 - 9.15
30-39	158,668	4,620	599,930.31	7.70	7.48 - 7.93
40-49	156,774	3,637	638,979.60	5.69	5.51 - 5.88
50-59	181,413	2,905	714,898.58	4.06	3.92 - 4.21
60+	228,553	1,881	1,105,171.30	1.70	1.63 - 1.78
Health Care Accessibility					
Accessible	777,936	18,190	4,069,913.32	4.47	4.40 - 4.53

Limited Accessibility	75,420	1,131	333,828.00	3.39	3.20 - 3.59
Non-time varying Variables					
Multiple Prescribers					
Yes	86,083	11,407	511,618.18	22.30	21.89 - 22.71
No	740,904	7,914	3,892,123.15	2.03	1.99 - 2.08
Sex					
Male	404,201	12,786	2,114,980.16	6.05	5.94 - 6.15
Female	422,786	6,535	2,288,761.16	2.86	2.79 - 2.93
Substance Use Disorder					
Yes	43,379	13,451	242,655.56	55.43	54.50 - 56.38
No	783,608	5,870	4,161,085.77	1.41	1.38 - 1.45
Mental Health Disorder Excluding Substance Use Disorder					
Yes	177,021	10,419	1,025,401.29	10.16	9.97 - 10.36
No	649,966	8,902	3,378,340.03	2.64	2.58 - 2.69
Opioid Prescription Prior to Index Pain ICD Code					
Yes	133,874	9,886	678,127.85	14.58	14.29 - 14.87
No	693,113	9,435	3,725,613.48	2.53	2.48 - 2.58

Note. 826,987 total participants

* Summing time varying participants will sum to greater than total participants

Table 20. Results of Bivariate Hazard Ratios for Opioid Prescription Characteristics and Risk of Overdose Events

	HR	SE	95% CI
Opioid Prescription			
Yes	3.56***	0.83	3.40 - 3.73
No		Baseline	
Opioid Strength and Acting			
None		Baseline	
Weak*Long Acting	4.67***	0.53	3.69 - 5.91
Weak*Short Acting	2.77***	0.12	2.55 – 3.00
Strong*Long Acting	5.10***	0.25	4.65 - 5.60
Strong*Short Acting	3.63***	0.12	3.41 - 3.88
MME Per Day Episode			
None		Baseline	
1-49	2.75***	0.09	2.59 - 2.93
50-90	3.67***	0.21	3.26 - 4.10
91+	6.57***	0.26	6.08 - 7.09
Multiple Prescribers			
Yes	10.25***	0.15	9.96 - 10.54
No		Baseline	
Opioid Antagonist Therapy			
Yes	23.42***	0.51	22.45 - 24.45
No		Baseline	
Benzodiazepine Prescription			

Yes	2.92***	0.06	2.80 - 3.04
No		Baseline	
Gabapentin Prescription			
Yes	4.73***	0.12	4.51 - 4.96
No		Baseline	
Geography			
Rural	0.85***	0.20	0.82 - 0.88
Urban		Baseline	
Chronic Pain			
Yes	2.17***	0.42	2.09 - 2.53
No		Baseline	
Acute Pain			
Yes	1.64***	0.03	1.58 - 1.69
No		Baseline	
Age Group			
<19		Baseline	
20-29	4.51***	0.14	4.26 - 4.79
30-39	3.77***	0.11	3.55 - 4.00
40-49	2.79***	0.09	2.62 - 2.96
50-59	1.92***	0.06	1.79 - 2.04
60+	0.75***	0.03	0.69 - 0.80
Health Care Accessibility			
Accessible	1.33***	0.04	1.25 - 1.42

Limited Accessibility	Baseline		
Sex			
Male	2.18***	0.03	2.11 - 2.24
Female	Baseline		
Substance Use Disorder			
Yes	39.13***	0.61	37.95 - 40.35
No	Baseline		
Mental Health Disorder Excluding Substance Use Disorder			
Yes	3.65***	0.05	3.55 - 3.76
No	Baseline		
Opioid Prescription Prior to Index Pain ICD Code			
Yes	6.17***	0.09	5.99 - 6.34
No	Baseline		

Note. *** $p \leq 0.001$

Table 21. Results of Multivariate Hazard Ratios for Overall Opioid Prescription and Risk of Overdose Events

	HR	SE	95% CI
Opioid Prescription			
Yes	2.38***	0.10	2.18 – 2.59
No		Baseline	
Multiple Prescribers			
Yes	2.21***	0.04	2.04 - 2.21
No		Baseline	
Opioid Antagonist Therapy			
Yes	1.00ns	0.02	0.96 – 1.30
No		Baseline	
Benzodiazepine Prescription			
Yes	1.24***	0.03	1.19 - 1.30
No		Baseline	
Gabapentin Prescription			
Yes	1.69***	0.04	1.60 - 1.78
No		Baseline	
Geography			
Rural	0.89***	0.03	0.84 - 0.95
Urban		Baseline	
Chronic Pain			
Yes	0.88***	0.02	0.85 - 0.92
No		Baseline	

Acute Pain			
Yes	1.21***	0.02	1.18 - 1.26
No		Baseline	
Age Group			
<19		Baseline	
20-29	1.15**	0.05	1.05 - 1.26
30-39	0.74***	0.04	0.67 - 0.81
40-49	0.52***	0.03	0.47 - 0.57
50-59	0.38***	0.02	0.34 - 0.42
60+	0.28***	0.02	0.25 - 0.31
Health Care Accessibility			
Accessible	1.26***	0.05	1.17 - 1.36
Limited Accessibility		Baseline	
Sex			
Male	1.00 ns	0.05	0.90 - 1.11
Female		Baseline	
Substance Use Disorder			
Yes	20.15***	0.16	19.35 - 20.98
No		Baseline	
Mental Health Disorder Excluding Substance Use Disorder			
Yes	3.65***	0.05	3.55 - 3.76
No		Baseline	
Opioid Prescription Prior to Index Pain ICD Code			

Yes	2.25***	0.04	2.27 - 2.42
No		Baseline	
Interactions			
Opioid Prescription by SUD	9.74***	0.01	9.07 – 10.46
Multiple Prescribers by Rural	1.74***	0.07	1.62 – 1.87
Male by 20-29	1.81***	0.08	1.66 - 2.00
Male by 30-39	1.32***	0.06	1.21 - 1.44
Male by 40-49	0.96ns	0.04	0.88 - 1.05
Male by 50-59	0.71***	0.03	0.65 - 0.78
Male by 60+	0.40***	0.02	0.36 - 0.44

Note. ns = not significant; ** $p \leq 0.01$; *** $p \leq 0.001$

SUD = Substance Use Disorder

Table 22. Adjusted Hazard Ratio for Interaction Term Opioid Prescription and Substance Use Disorder for Risk of Overdose Event

Opioid Prescription	Substance Use Disorder	Adjusted Hazard Ratio (95% CI)
Yes	Yes	9.74 (9.07-10.46)
Yes	No	2.38 (2.18-2.58)
No	Yes	20.15 (19.35-20.98)
No	No	Baseline

Note: Adjusted for OAT, benzodiazepine, gabapentin, geography, chronic pain, acute pain, sex, age group, multiple prescribers, healthcare accessibility, sex, mental health disorder, opioid prescription prior to index pain ICD code

Table 23. Adjusted Hazard Ratio for Interaction Term MME Per Day and Substance Use Disorder for Risk of Overdose Event

MME Per Day	Substance Use Disorder	Adjusted Hazard Ratio (95% CI)
None	No	Baseline
1-49	No	1.98 (1.77-2.20)
50-90	No	2.59 (2.15-3.11)
90+	No	3.72 (3.20-4.32)
None	Yes	20.16 (19.36 – 21.00)
1-49	Yes	9.84 (9.02-10.73)
50-90	Yes	9.39 (8.05-10.95)
90+	Yes	9.93 (8.97-10.99)

Note: Adjusted for OAT, benzodiazepine, gabapentin, geography, chronic pain, acute pain, sex, age group, multiple prescribers, healthcare accessibility, sex, mental health disorder, opioid prescription prior to index pain ICD code

Table 24. Adjusted Hazard Ratio for Interaction Term Opioid Strength and Acting and Substance Use Disorder for Risk of Overdose Event

Opioid Strength and Acting	Substance Use Disorder	Adjusted Hazard Ratio (95% CI)
None	No	Baseline
Weak*Long Acting	No	3.18 (2.12-4.76)
Weak*Short Acting	No	1.67 (1.43-1.95)
Strong*Long Acting	No	3.13 (2.63-3.72)
Strong*Short Acting	No	2.68 (2.39-3.00)
None	Yes	20.17 (19.37-21.01)
Weak*Long Acting	Yes	13.27 (9.87 – 17.84)
Weak*Short Acting	Yes	9.39 (8.43-10.45)
Strong*Long Acting	Yes	11.49 (10.18-12.96)
Strong*Short Acting	Yes	9.20 (8.38-10.09)

Note: Adjusted for OAT, benzodiazepine, gabapentin, geography, chronic pain, acute pain, sex, age group, multiple prescribers, healthcare accessibility, sex, mental health disorder, opioid prescription prior to index pain ICD code

Table 25. Adjusted Hazard Ratio for Interaction Term Multiple Prescribers and Geography for Risk of Overdose Event

Multiple Prescribers	Geography	Adjusted Hazard Ratio (95% CI)
Yes	Rural	1.74 (1.62-1.87)
Yes	Urban	2.12 (2.04-2.21)
No	Rural	0.89 (0.84-0.95)
No	Urban	Baseline

Note: Adjusted for opioid prescription, OAT, benzodiazepine, gabapentin, geography, chronic pain, acute pain, sex, age group, multiple prescribers, healthcare accessibility, sex, mental health disorder, opioid prescription prior to index pain ICD code

Table 26. Cohort Characteristics for Outcome Fatal Overdose

	N Participants	N Events	Time at Risk	Rate Per 1,000 Person Years	95% CI
Multiple Prescribers					
Yes	86,083	1,715	525,980.09	3.26	3.11 - 3.42
No	740,904	1,320	3,900,902.82	0.34	0.32 - 0.36
Opioid Prescription*					
Yes	346,014	371	132,599.57	2.80	2.53 - 3.10
No	825,750	2,664	4,294,283.35	0.62	0.60 - 0.64
Opioid Strength and Acting*					
None	825,759	2,664	4,294,283.35	0.62	0.60 - 0.64
Weak*Long Acting	6,126	12	2,932.30	4.09	2.32 - 7.21
Weak*Short Acting	258,433	112	50,499.78	2.22	1.84 - 2.66
Strong*Long Acting	21,016	79	20,231.70	3.90	3.13 - 4.87
Strong*Short Acting	171,029	168	58,935.79	2.85	2.45 - 3.32
MME Per Day Opioid Px Episode*					
None	825,767	2,664	4,294,283.35	0.62	0.60 - 0.64
1 - 49	303,769	208	88,678.72	2.33	2.03 - 2.67
50 - 90	82,936	60	18,987.58	3.16	2.43 - 4.04
91+	32,814	103	24,933.28	4.13	3.39 - 4.99
Chronic Pain*					
Yes	98,363	586	306,819.80	1.91	1.76 - 2.07

No	821,192	2,449	4,120,063.12	0.59	0.57 - 0.62
Acute Pain*					
Yes	826,313	655	763,698.86	0.86	0.79 - 0.92
No	815,372	2,380	3,663,184.06	0.65	0.62 - 0.68
Geography*					
Rural	696,501	476	819,519.47	0.58	0.53 - 0.64
Urban	170,353	2,559	3,607,363.44	0.71	0.68 - 0.74
OAT*					
Yes	12,960	112	29,579.13	3.79	3.15 - 4.56
No	826,570	2,923	4,397,303.78	0.66	0.64 - 0.69
Benzodiazepine*					
Yes	188,636	496	233,955.89	2.12	1.94 - 2.32
No	819,345	2,539	4,192,927.02	0.61	0.58 - 0.63
Gabapentin*					
Yes	74,661	321	80,445.22	3.99	3.58 - 4.45
No	826,058	2,714	4,346,437.70	0.62	0.60 - 0.65
Age Group*					
<19	181,942	93	800,664.00	0.12	0.09 - 0.14
20-29	148,372	485	551,705.47	0.88	0.80 - 0.96
30-39	159,668	702	605,909.77	1.16	1.08 - 1.25
40-49	166,413	701	643,242.04	1.09	1.01 - 1.17
50-59	181,894	642	718,126.61	0.89	0.83 - 0.97
60+	228,837	412	1,107,235.03	0.37	0.34 - 0.41

Health Care Accessibility*					
Accessible	778,944	2,861	4,091,828.18	0.70	0.27 - 0.3
Limited Accessibility	75,544	174	335,054.74	0.52	0.45 - 0.6
Sex					
Male	404,932	2,298	2,129,820.14	1.08	1.04 - 1.12
Female	423,062	737	2,297,062.77	0.32	0.30 - 0.34
Substance Use Disorder					
Yes	44,039	1,862	259,658.38	7.17	6.85 - 7.5
No	783,955	1,173	4,167,224.53	0.28	0.27 - 0.3
Mental Health Disorder Excluding Substance Use Disorder					
Yes	177,406	1,500	1,038,132.27	1.44	1.37 - 1.52
No	650,588	1,535	3,388,750.64	0.45	0.43 - 0.48
Opioid Prescription Prior to Index Pain ICD Code					
Yes	134,372	1,328	691,367.88	1.92	1.82 - 2.03
No	693,622	1,707	3,735,515.03	0.46	0.44 - 0.48

Note. 827,994 total participants

* Summing time varying participants will sum to greater than total participants

Table 27. Results of Bivariate Cox Regression Model for the Outcome of Fatal Overdose

	HR	SE	95% CI
Opioid Prescription			
Yes	4.01***	0.22	3.60 - 4.48
No		Baseline	
Opioid Strength and Acting			
None		Baseline	
Weak*Long Acting	4.99***	1.45	2.83 - 8.81
Weak*Short Acting	3.36***	0.32	2.77 - 4.06
Strong*Long Acting	5.53***	0.63	4.42 - 6.91
Strong*Short Acting	3.99***	0.32	3.42 - 4.67
MME Per Day Episode		4.99***	1.45
None		Baseline	
1-49	3.32***	0.24	2.88 - 3.82
50-90	4.66***	0.61	3.61 - 6.02
91+	6.21***	0.62	5.10 - 7.56
Multiple Prescribers			
Yes	8.74***	0.32	8.14 - 9.40
No		Baseline	
Opioid Antagonist Therapy			
Yes	4.66***	0.45	2.96 - 3.59
No		Baseline	

Benzodiazepine Prescription			
Yes	3.26***	0.16	2.96 - 3.59
No		Baseline	
Gabapentin Prescription			
Yes	5.05***	0.30	4.49 - 5.67
No		Baseline	
Geography			
Rural	0.81***	0.04	0.73 - 0.89
Urban		Baseline	
Chronic Pain			
Yes	2.53***	0.12	2.31 - 2.77
No		Baseline	
Acute Pain			
Yes	1.60***	0.07	1.46 - 1.75
No		Baseline	
Age Group			
<19		Baseline	
20-29	6.74***	0.76	5.40 - 8.42
30-39	8.57***	0.95	6.90 - 10.63
40-49	8.07***	0.89	6.50 - 10.02
50-59	6.37***	0.77	5.12 - 7.91
60+	2.47***	0.28	1.97 - 3.09
Health Care Accessibility			

Accessible	1.36***	0.11	1.17 - 1.58
Limited Accessibility		Baseline	
Sex			
Male	3.46***	0.15	3.18 - 3.75
Female		Baseline	
Substance Use Disorder			
Yes	23.91***	0.89	22.22 - 25.72
No		Baseline	
Mental Health Disorder Excluding Substance Use Disorder			
Yes	2.98***	0.11	2.77 - 3.19
No		Baseline	
Opioid Prescription Prior to Index Pain ICD Code			
Yes	4.44***	0.16	4.14 - 4.77
No		Baseline	

*** $p \leq 0.001$

Table 28. Results of Multivariate Cox Regression Model for Opioid Prescription, Outcome of Fatal Overdose

	HR	SE	95% CI
Opioid Prescription			
Yes	2.23***	0.10	1.85 - 2.68
No		Baseline	
Multiple Prescribers			
Yes	2.38***	0.12	2.16 - 2.62
No		Baseline	
Opioid Antagonist Therapy			
Yes	0.23***	0.02	0.19 - 0.28
No		Baseline	
Benzodiazepine Prescription			
Yes	1.46***	0.08	1.32 - 1.63
No		Baseline	
Gabapentin Prescription			
Yes	1.81***	0.12	1.59 - 2.05
No		Baseline	
Geography			
Rural	0.82*	0.07	0.70 - 0.98
Urban		Baseline	
Chronic Pain			
Yes	1.01ns	0.05	0.91 - 1.11
No		Baseline	

Acute Pain			
Yes	1.13**	0.05	1.04 - 1.24
No		Baseline	
Age Group			
<19		Baseline	
20-29	1.54*	0.29	1.06 - 2.23
30-39	1.68**	0.31	1.18 - 2.41
40-49	1.74**	0.32	1.22 - 2.49
50-59	1.46*	0.27	1.02 – 2.09
60+	0.97ns	0.18	0.67 - 1.39
Health Care Accessibility			
Accessible	1.21*	0.12	1.01 - 1.46
Limited Accessibility		Baseline	
Sex			
Male	1.21ns	0.25	0.80 - 1.83
Female		Baseline	
Substance Use Disorder			
Yes	13.10***	0.65	11.89 – 14.43
No		Baseline	
Mental Health Disorder Excluding Substance Use Disorder			
Yes	1.03 ns	0.04	0.95 - 1.12
No		Baseline	
Opioid Prescription Prior to Index Pain ICD Code			

Yes	2.25***	0.04	2.27 - 2.42
No		Baseline	
Interactions			
Opioid Prescription by SUD	5.95***	0.01	5.00 - 7.09
Multiple Prescribers by Rural	1.69***	0.14	1.44 - 1.98
Male by 20-29	4.96***	0.84	3.55 - 6.94
Male by 30-39	5.84***	0.98	4.19 - 8.14
Male by 40-49	5.17***	0.87	3.71 - 7.21
Male by 50-59	4.22***	0.72	3.02 - 5.89
Male by 60+	2.17***	0.37	1.54 - 3.06

Note. ns = not significant; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

SUD = Substance Use Disorder

Table 29. Adjusted Hazard Ratio for Interaction Term Opioid Prescription and Substance Use Disorder for Risk of Overdose Death

Opioid Prescription	Substance Use Disorder	Adjusted Hazard Ratio (95% CI)
Yes	Yes	5.95 (5.00-7.09)
Yes	No	2.23 (1.85-2.68)
No	Yes	13.10 (11.89-14.42)
No	No	Baseline

Note: Adjusted for OAT, benzodiazepine, gabapentin, geography, chronic pain, acute pain, sex, age group, multiple prescribers, healthcare accessibility, sex, mental health disorder, opioid prescription prior to index pain ICD code

Table 30. Adjusted Hazard Ratio for Interaction Term MME Per Day and Substance Use Disorder for Risk of Overdose Death

MME Per Day	Substance Use Disorder	Adjusted Hazard Ratio (95% CI)
None	No	Baseline
1-49	No	1.79 (1.41-2.27)
50-90	No	2.81 (1.95-4.06)
90+	No	3.36 (2.44-4.61)
None	Yes	13.11 (11.90-14.44)
1-49	Yes	6.90 (5.61-8.49)
50-90	Yes	6.06 (4.13-8.67)
90+	Yes	4.82 (3.65-6.37)

Note: Adjusted for OAT, benzodiazepine, gabapentin, geography, chronic pain, acute pain, sex, age group, multiple prescribers, healthcare accessibility, sex, mental health disorder, opioid prescription prior to index pain ICD code

Table 31. Adjusted Hazard Ratio for Interaction Term Opioid Strength and Acting and Substance Use Disorder for Risk of Overdose Death

Opioid Strength and Acting	Substance Use Disorder	Adjusted Hazard Ratio (95% CI)
None	No	Baseline
Weak*Long Acting	No	2.16 (0.87-5.80)
Weak*Short Acting	No	1.65 (1.20-2.28)
Strong*Long Acting	No	3.09 (2.17-4.40)
Strong*Short Acting	No	2.42 (1.89-3.09)
None	Yes	13.11 (11.90-14.45)
Weak*Long Acting	Yes	9.16 (4.54-18.49)
Weak*Short Acting	Yes	6.37 (4.93-8.24)
Strong*Long Acting	Yes	6.43 (6.70-8.81)
Strong*Short Acting	Yes	5.41 (4.27-6.85)

Note: Adjusted for OAT, benzodiazepine, gabapentin, geography, chronic pain, acute pain, sex, age group, multiple prescribers, healthcare accessibility, sex, mental health disorder, opioid prescription prior to index pain ICD code

Table 32. Adjusted Hazard Ratio for Interaction Term Multiple Prescribers and Geography for Risk of Overdose Death

Multiple Prescribers	Geography	Adjusted Hazard Ratio (95% CI)
Yes	Rural	1.69 (1.44-1.98)
Yes	Urban	2.38 (2.16-2.62)
No	Rural	0.82 (0.69-0.96)
No	Urban	Baseline

Note: Adjusted for opioid prescription, OAT, benzodiazepine, gabapentin, geography, chronic pain, acute pain, sex, age group, multiple prescribers, healthcare accessibility, sex, mental health disorder, opioid prescription prior to index pain ICD code

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Chapter 6: Conclusion

The preceding chapters reviewed existing literature regarding rural and urban differences in opioid prescriptions. In addition, it presented the results of analysis of the impact of chronic pain, opioid prescriptions, and multiple prescribers on risk of experiencing a fatal or non-fatal overdose. These analyses utilized the BC Provincial Overdose Cohort (BC Centre for Disease Control, 2017), which was established as part of the BC Provincial Health Officer's declaration of a Public Health Emergency for opioid related fatal and non-fatal overdoses.

The systematic review of the literature found four articles that examined differences between rural and urban areas and opioid prescribing characteristics. The findings suggest there is geographical variation in opioid prescription characteristics. Several of the studies showed that individuals who live in rural areas receive opioid prescriptions for longer periods of time and at a higher dose compared to urban residents. However, one study found the difference between rural and urban prescriptions was related to the prescriber and not the patient, with rural physicians prescribing higher doses of opioids for longer periods of time compared to urban physicians. The systematic review highlights the need for further research that examines geographic differences in opioid prescribing practices, and the impact these prescribing practices may have on adverse events.

When exploring the relationship between rurality, chronic pain, and the risk of overdose, it was found that living in a rural area and experiencing chronic pain significantly increased the risk of experiencing an overdose. The risk of experiencing an overdose was even greater for those individuals who both lived in rural areas and experienced chronic pain. A contributing factor for why individuals who live in rural areas and experience chronic pain may have an increased risk in overdose may be related to a reliance on pharmaceutical treatments for chronic

pain, for which previous research has shown that long-term use of opioids may increase the risk of the development of an opioid use disorder (Martell et al., 2007).

When examining the differences in opioid prescribing between rural and urban areas in British Columbia, it was found that opioid prescribing decreased between 2010 and 2017. When examining the prescribing characteristics, people living in rural areas who are experiencing acute pain received prescriptions for greater than seven days more frequently than those who lived in urban areas. There was little difference in opioid prescription characteristics, prescriber's profession, strength of opioid, type, MMEs per day, age, or sex of the individual between rural and urban areas.

Upon review of the association between risk of overdose and receiving an opioid prescription, it was found that having an opioid prescription increases the risk of experiencing an overdose. After adjusting for potential confounders, a significant interaction was identified between opioid prescriptions and substance use disorder diagnosis. For individuals who had an opioid prescription but did not have a substance use disorder diagnosis the opioid prescription increased their risk of experiencing a fatal or non-fatal overdose. However, for those individuals who had an opioid prescription and a substance use disorder diagnosis, the opioid prescription decreased their risk of experiencing a fatal or non-fatal overdose. When examining the prescription characteristics for individuals who had a diagnosis of a substance use disorder, there was a reduction in the risk of overdose regardless of MME per day, with prescriptions containing 50 – 90 MME per day showing the highest reduction in risk for an overdose event, and 91+ MME per day showing the greatest reduction in the risk for a fatal overdose, compared to individuals with a substance use disorder diagnosis and without an opioid prescription. For individuals without a substance use disorder diagnosis there was an increase in the risk of

experiencing a fatal or non-fatal overdose with an increase in MME per day compared to those with no opioid prescription; with lower MME per day categories showing around a one to two times increase in risk and the higher MME per day category showing a greater than threefold increase in the risk of experiencing a fatal or non-fatal overdose compared to those without an opioid prescription. The risk of experiencing an overdose was increased when people utilized multiple prescribers; although this risk was mitigated for those individuals who lived in a rural area. The reduction in risk in rural areas may be related to opioid diversion and access to a clean drug supply.

Across all three quantitative studies in this dissertation, individuals diagnosed with a substance use disorder diagnosis or any other mental health disorder, and access to health care services were associated with an increased risk of a fatal or non-fatal overdose. The increased risk of a fatal or non-fatal overdose associated with access to health care services was an unanticipated finding. One potential explanation is that people who experience overdose have an increased use of health care services compared to those who have not had an overdose (Chang, Kharrazi, Bodycombe, Weiner, & Alexander, 2018; Otterstatter et al., 2018).

There was also a significant interaction between age and sex across all three quantitative studies. The results consistently showed that males had a higher risk of experiencing an overdose across all age groups. There was some variation across the studies with regard to which age group experienced the highest risk of overdose depending upon the covariates included in the multivariate analysis, however, generally there was an inverted U distribution across the age groups with the risk of overdose peaking between 30 and 60 years old and then dropping after 60 years old.

General Conclusions

This thesis explored chronic pain, geography, opioid prescriptions, and the use of multiple prescribers in relation to the risk of overdose in British Columbia. Through the analysis of the data, it was found that chronic pain significantly increased the risk of experiencing an overdose; however, when prescription for opioids was included in the analysis, there was no longer an increase in risk for experiencing a fatal or non-fatal overdose associated with chronic pain. The risk for experiencing a fatal or non-fatal overdose when individuals had a prescription for opioids was influenced by whether they had a substance use disorder diagnosis, with it mitigating the risk of a fatal or non-fatal overdose for those individuals who had a diagnosis of a substance use disorder, but for those individuals who did not have a substance use disorder there was an increase in the risk. When examining geographic differences opioid prescriptions and the prescription characteristics there was minimal variation on opioid prescription characteristics, with the exception of a longer duration of opioid prescriptions for acute pain for individuals who lived in rural areas, which is consistent with the findings of the systematic review. In addition, the overdose risk related to opioid prescriptions and their characteristics did not vary significantly based on geography. The use of multiple prescribers increased people's risk of overdose; however, for an individual living in a rural area the use of multiple prescribers mitigated the risk of experiencing an overdose.

Strengths

The systematic review used valid, replicable methods to evaluate the current literature on rural and urban differences of opioid prescription characteristics and risk of fatal or non-fatal overdoses. Two reviewers were utilized to avoid selection bias in the review process, and inclusion and exclusion criteria were established prior to the start of the review.

The retrospective cohort design with administrative data linkages is a cost-efficient, effective, and valid method to evaluate the association between chronic pain, prescription opioids, and multiple prescribers and an association with the risk of overdose. The cohort utilized contained a large number of people from across British Columbia and their associated health records. Utilizing multivariate analysis was an effective way of controlling for potential confounders in the study (Rothman, Greenland, & Lash, 2008).

This study utilized previously validated methodology to identify the variables of interest allowing for comparability. In addition, using the British Columbia Provincial Overdose Cohort allows for comparable results to other studies using the same data source.

Limitations

As these were retrospective observational research studies, they have a number of limitations that are inherent to the design and data sources. Retrospective investigations cannot show causation, only correlation between the outcome of interest and the explanatory variables. Administrative data sources are not collected for research purposes and therefore the researcher is unable to capture all potentially important confounders of interest, such as socioeconomic status, gender, intergenerational and/or historical trauma (Brave Hart et al. 2011; Sotero, 2009), family history of substance abuse disorders, and other factors that may predispose individuals to a higher risk of substance use disorders and/or overdose.

In addition, overdose events were identified using administrative data, which would not capture overdose events for which individuals did not seek health care intervention. Only those individuals who sought care for an overdose from health care services or suffered a fatal overdose would be included. Any individual who had a non-fatal overdose that was reversed by a community member, and who did not seek care from a health facility, would not be captured in

the study. Nevertheless, this unique dataset combined overdose events from a number of various sources to ensure that all overdoses that resulted in contact with the health system were captured.

In addition, the derived variables such as: substance use disorder, mental health disorders, chronic pain, and acute pain, utilized administrative health data and are subject to the same limitations as overdose events. If individuals do not seek health care services or health care services are unavailable, the derived variables will not be captured in the dataset. This may cause those individuals who live in rural areas to be underrepresented as there is limited access to health care services compared to those in urban areas.

There may be inconsistent coding standards which may have led to misclassification derived variables. The dataset only provided prescriptions dispensed in community pharmacies, and prescriptions that were filled, or dispensed in hospital were not captured. In addition, it cannot be determined if the dispensed prescriptions were taken as prescribed.

Implications

The presented research highlights the complexity in understanding the risk of overdose. The findings from these studies suggest that reducing access to opioid prescriptions to the entire population may have mixed results when overdose endpoints are considered; with those who do not have a substance use disorder potentially benefiting from reduced access to opioid prescriptions, but those individuals with a substance use disorder potentially experiencing harm. A more targeted approach for the different populations should be explored. In the current study, the geographical differences in the rate of overdose based on were not explained by the differences in opioid prescribing practices; thus, further study is needed to understand the potential factors that will help explain the differences in overdose rates between rural and urban areas.

Future Research Directions

The current study has highlighted areas for future research. Some opportunities for future research include:

- Explore other potential factors that may explain the differences in fatal and non-fatal overdose rates between rural and urban areas
- Continue monitoring the change in the risk of fatal and non-fatal overdose related to prescription opioid in rural and urban areas in subsequent updates of the cohort.
- Further explore the difference in risk for fatal and non-fatal overdose in people with and without substance use disorder related to opioid prescriptions.
- Examine the impact of opioid tapering guidelines on the risk of overdose.
- Explore records of opioid prescriptions that are not associated with a corresponding pain diagnosis, to determine if this is evidence of inappropriate prescribing practices or poor data quality.

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Appendix A: Chronic Pain Codes

ICD 9 Codes

307.8	720.9	723.3	724.5
307.89	721	273.4	724.6
338	721.1	723.5	724.7
338.2	721.2	723.6	724.79
338.4	721.3	723.7	724.8
719.41	721.4	723.8	724.9
719.45	721.6	723.9	729
719.46	721.8	724	729.1
719.47	721.9	724.1	729.2
719.49	722	724.2	729.4
720	723	724.3	729.5
720.2	723.1	724.4	

ICD 10 Codes

F45.4	M43.6	M48.1	M53.3
M08.1	M45	M48.8	M53.8
M25.50	M46.1	M48.9	M53.9
M25.51	M46.3	M50.8	M54
M25.55	M46.4	M50.9	M54.8
M25.56	M46.9	M51	M60.8
M25.57	M47	M53.1	M60.9
M43.2	M48.0	M53.2	M63.3

M79.0	M79.6	M96.1	R52.2
M79.2	M79.7	R52.1	R51

Appendix A: Acute Pain Coding

ICD 9 Codes

053	620	784.0
339	625.2	784.1
346	681-682	786.5
379.91	719.4	786.51
413.9	723	786.52
443	724.5	800-999 (Excluding
550-553	729	poisoning)
592	781.0	
594	784	

ICD 10 Codes

B02	L03	R078
G43	M255	R079
G44	M54	R252
H571	M79	R51
I209	N20-22	R52.0
I73	N83	R52.9
I84	N940	S-block
K40-46	R07	T1-T14
K80	R071	T20-35
K87	R072	

Canadian Classification of Health Interventions (CCI) Codes

First Position:

- 1 – Physical Therapeutic interventions
    - All
- 2 – Other Diagnosis Interventions
    - All
- 5 - Obstetrical/Fetal Intervention
    - MD: 40, 45, 47, 50, 51, 53, 54, 55, 56, 60
    - PC: 80, 91
- Excluding anesthesia codes