THE CONTRIBUTION OF OPIOID ANALGESIC USE TO THE INITIATION OF ANTIDEPRESSANT MEDICATION IN THE OLDER ADULT POPULATION

by

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Abstract

The purpose of this thesis was to examine the incidence of antidepressant use following opioid initiation. This study relied on the exclusive use of outpatient community dispensations for all prescriptions. The cohort was restricted to Alberta residents aged 55 to 80, enrolled in the Alberta Health Insurance plan for at least one calendar year, and excluded cancer-related pain treatment. Patients were included if their first opioid dispensation occurred between January 1st, 2010, and December 31st, 2014, and the first antidepressant dispensation occurred within one year after the first opioid dispensation. A three-month washout period was applied as a conservative time frame to remove prevalent cases of opioid analgesic use. The end of the follow-up was a new antidepressant dispensation in a previously (12-month) antidepressant-naïve patient, up until one year from the first opioid dispensation or the end of the study. These criteria set up the temporal relationship so that incident opioid analgesic use occurred in patients without current antidepressant use and preceded any new-onset psychiatric comorbidity or exacerbation of an existing morbidity.

The cohort consisted of a population of 408,862. The total number of people between 2010 and 2014 who were dispensed an antidepressant within one year of starting an opioid was 39,650, or 9.7% of the cohort population. Overall, the incidence proportion of antidepressants after the first opioid dispensation decreased by 42.8% across the study period from 2010 to 2014. Compared to men, women had a consistently higher incidence proportion of antidepressants dispensed each year. Out of all the people prescribed an antidepressant after first opioid dispensation having no recent history of antidepressant use or psychiatric diagnosis, 24.43% were being treated for new-onset depression and 19.15% for new-onset anxiety. The declining incidence proportion of antidepressants suggests the possibility of a saturation effect: as prevalent dispensation of opioids increases, fewer unexposed patients are available for incident opioid dispensations and subsequent incident antidepressant dispensations. The results demonstrate that in those people free of opioid and antidepressant use in the year prior to initiation of opioid treatment, subsequent

antidepressant use is most likely attributable to treatment of depression or anxiety as compared to other psychiatric comorbidities.

A risk factor analysis was conducted to enable a better understanding of those individuals who are at a higher risk than others for antidepressant initiation after first opioid dispensation. The risk of incident antidepressant dispensation within one year of opioid initiation increases with high dose opioids (>90 MEQ). Female sex and prior history of depression are also found to predict subsequent antidepressant initiation. Rural residence was not found to have a statistically significant association with antidepressant initiation after opioid dispensation.

The information presented in this study adds to the accumulating evidence regarding a link between opioid analgesic use and the risk of depression. However, this research is unique in that it demonstrates an association between opioid analgesic use and subsequent initiation of antidepressants in general among older adults. Rather than restricting the study to focus on specific indications of opioid analgesic use such as chronic pain, this study approached the data from a wider lens by investigating the correlation between opioid and antidepressant medication use. There is substantial likelihood that opioid therapy will continue to present clinical challenges given Canada's aging population. Opioid prescribing should be coupled with careful screening and treatment of emerging mental health disorders. Screening tools for depression (Patient Health Questionnaire (PHQ)-2 and PHQ-9) and anxiety (Generalized Anxiety Disorder Questionnaire (GAD-Q-IV) and GAD-7) can be programmed into electronic medical record systems to prompt screening prior to opioid initiation. Additionally, understanding the risks associated with antidepressant initiation following first opioid dispensation will enable prescribers to target early intervention efforts and screening tools to mitigate harm and prevent mental health issues from arising in the future. Screening of psychiatric disorders for all patients should take place prior to an opioid trial. For those patients beginning ongoing opioid treatment, antidepressant prophylaxis or treatment of depression should be considered. Future research should explore whether the coadministration of antidepressants and opioids serves to prevent incident psychiatric disorders in those patients initiated on opioids.

Preface

This thesis is an original work by Marla Palakkamanil. No part of this thesis has been previously published.

It should be noted that this thesis is presented in the paper-format. This means that each chapter is presented with its own introduction, discussion, and list of references.

For this thesis, Chapters 2 and 3 are written with the intention that they will be subsequently submitted for publication.

Dedication

This thesis is dedicated to my parents, Thomas and Miriam Palakkamanil, without whom none of my success would be possible.

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CHAPTER 1

INTRODUCTION

1.1 Introduction

The role of opioids in North American society has grown in significance over the years. Opioids have been considered the standard of care in acute and chronic pain relief, but they have also been associated with abuse, addiction and diversion (Rosenblum, Marsch, Joseph, & Portenoy, 2008). Despite limited evidence of their long-term efficacy, "Canada has the second highest rate of opioid prescribing in the world when measured using defined daily doses, and the highest rate overall when considering morphine equivalents dispensed" (McMaster University, 2017, p. 9). This increase in opioid analgesic use is directly related to increases in the rates of opioid use disorder and opioid-related deaths (Frenk, Lukacs, & Gu, 2018). The opioid epidemic has impacted every region of Canada (Belzak & Halverson, 2018). In 2017, there were 1473 opioid-related deaths in British Columbia and a total of 3996 in all of Canada, an increase of more than 400% from 1993 (Fischer, Pang, & Tyndall, 2019). According to Frenk, Lukacs, & Gu (2018), 6.9% of adults aged 20 years and older in the United States reported using a prescription opioid analgesic in the past 30 days (Frenk et al., 2018; Frenk, Porter, & Paulozzi, 2015).

Despite efforts to approach pain care from an integrated biopsychosocial, integrated behavioral, and physical health perspective (Simon, 2012), prescription opioid analgesic use in relation to mental health remains poorly understood (Brooks, Petersen, Kelly, & Reid, 2019). The association between pain and poorer mental health has been established in the literature; however,

relatively little is known about the impact that prescription opioid analgesic use has on the initiation of antidepressants and the onset of psychiatric comorbidities.

1.2 Brief Overview of Opioids: Mechanism of Action

Extracted from the opium poppy plant, *Papaver somniferum*, opioids have been used for centuries to control pain (Salani, Crenshaw, Owusu, & Gonzalez, 2018). All compounds that bind to opiate receptors are referred to as opioids, and include synthetic opiates as well as semisynthetic opiates (Rosenblum et al., 2008). Opioids bind to mu, kappa, and delta opiate receptors distributed throughout the central and peripheral nervous system to effect complex changes at the cellular and molecular level (Rachinger-Adam, Conzen, & Azad, 2011). Depending on which receptors are activated, analgesia may be accompanied by a diverse range of side effects (Rosenblum et al., 2008).

The mu and kappa receptors are associated with pain physiology and inhibition. In addition to decreasing pain perception and increasing tolerance to pain stimuli, other opioid actions such as euphoria (Schulteis & Koob, 1996), endocrine dysregulation, and changes in sleep regulation have been described (Vuong, Van Uum, O'Dell, Lutfy, & Friedman, 2010). Opioids are associated with poor sleep quality, insomnia, respiratory depression, sleep apnea, and sleep-disordered breathing (Zutler & Holty, 2011). The feelings of euphoria produced are due to the high density of mu receptors in the brain and spinal cord (Salani et al., 2018). Kappa receptors are located predominantly in the limbic system, diencephalic area, and spinal cord (Salani et al., 2018). Delta receptors are most closely associated with the emotional and affective aspects of the pain experience (Adams, 2016; Salani et al., 2018). Located mainly in the brain, delta receptors may play a role in psychologic dependency (Grossman & Porth, 2009). An opioid is considered a full

opioid agonist, a partial agonist, or a mixed agonist-antagonist depending on the effect it has on these three receptors (Salani et al., 2018).

1.3 Role of Opioids in Acute and Chronic Pain

While Health Canada has approved indications of opioids for the treatment of non-productive cough (codeine, hydrocodone, normethadone), and treatment of opioid use disorder (methadone and buprenorphine), opioids are most commonly prescribed for the treatment of pain (*Opioids (CPhA Monograph)*, 2019). According to the International Association for the Study of Pain, "pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP Task Force on Taxonomy, 1994). Influenced by factors such as psychological conditions, health status, and sociological factors, the pain mechanism is triggered by a multitude of pain modulating systems (Marchand, 2012; Pati, Gupta, Mayasa, Velivela, & Hussain, 2017).

Pain is classified as either acute pain or chronic pain. Acute pain is defined as pain that persists for less than a month (Pati et al., 2017). Chronic pain has been described as "pain that recurs frequently over a period of months, pain that occurs in association with a non-healing lesion, or pain that persists for at least one month beyond the normal healing time of an acute injury" (Rosenblum et al., 2008, p. 407). Chronic pain is frequently divided into four different categories: 1) neuropathic pain, i.e. pain originating in nerves; 2) non-neuropathic or nociceptive pain, which is often musculoskeletal in origin and arises, for example, in muscles, bones, or ligaments; 3) headaches; and 4) other (Dobkin & Boothroyd, 2008; Els et al., 2018). Pain can be managed using pharmacological options (non-opioid and opioid pharmacotherapy) and non-pharmacological

options, such as electrical stimulation, physical therapy, psychological interventions, or exercise (Thornton et al., 2017).

Since the assessment of pain is subjective and based on individual reporting, objective measurement of pain is impossible to ascertain (Breivik et al., 2008). An individual's experience of pain can be influenced by genetics, society, gender, expectations, situations, psychological state and individual personality (Coghill, 2010). However, a number of self-reporting instruments aid in measuring pain and determining its impact on the physical, social, emotional, and spiritual aspects of an individual's life (Els et al., 2018).

Pain can have a substantially negative impact on quality of life, including the activities of daily living, the ability to work, and the efficiency of that work (Andrew, Derry, Taylor, Straube, & Phillips, 2014). In particular, chronic pain can cause increased incidence of psychological problems, such as anxiety and depression, as well as withdrawal from social situations (Andrew et al., 2014).

1.4 Role of Opioids in Persistent Cough

Chronic, non-productive cough is one of the most common respiratory complaints for which medical attention is sought (Morice et al., 2007). Both physically and mentally debilitating, chronic cough is often associated with inflammatory airway diseases such as asthma, chronic obstructive pulmonary disease, post-viral infections, pulmonary fibrosis, and bronchiectasis (Belvisi & Geppetti, 2004). A questionnaire conducted by Ford, Forman, Moayyedi, & Morice (2006) indicated that 7% of the sampled population experienced coughing bouts on a weekly basis. The intensity and frequency of these coughing bouts interfered with activities of daily living (Morice et al., 2007).

Opioids have long been advocated as the most effective antitussive agents, despite adverse events including physical dependence, respiratory depression, and gastrointestinal symptoms (Belvisi & Geppetti, 2004). However, there is limited evidence to support the recommendation of opioids for chronic cough. A recent trial of codeine for the treatment of chronic bronchitis suggested a similar effect to that of a placebo (J. Smith, Owen, Earis, & Woodcock, 2006). On the contrary, low dose oral morphine has been shown to significantly suppress chronic cough, although its side effect profile may discourage widespread use (Bolser, 2010).

1.5 Opioids and Older Adults

While acute pain and persistent cough occur in the older population, chronic pain and its subsequent treatment with opioids presents a clinical challenge given the myriad of physiological, pharmacological, and psychological aspects of caring for an elderly patient (Chau, Walker, Pai, & Cho, 2008). Chronic pain is associated with substantial disability, increased risk of falls or reinjuries, and psychosocial morbidity, including depression, anxiety, and social isolation.

Among Canada's aging population, pain is a major concern due to its high prevalence. In Canada, the prevalence of pain among older adults living in the community is estimated to be as high as 65%, and up to 80% for those living in long-term care facilities (Lynch, 2011). Within an Albertan sample population, Schopflocher, Taenzer, & Jovey (2011) found that the prevalence of chronic pain increases with age, from less than 6% at age 18 to 18% at age 65 in males and 24% in females. At every age over 18 years, females are more likely to suffer from chronic pain than males (Schopflocher et al., 2011). According to the 2017 Canadian Guideline for Opioids for Chronic Pain, cost estimates associated with managing chronic pain, including direct and indirect expenses, total $43 billion annually. Statistics Canada estimates that by 2036, one in four

Canadians will be over the age of 65, further complicating the issue of pain management in the elderly (Bohnert, Chagnon, & Dion, 2015; Lynch, 2011)

Pain relief constitutes one of the most commonly endorsed goals of older adults. Possibly in response to this finding, health care providers are prescribing opioids to older adults in record numbers. In 2016, opioids were used by 19.3% of Canadian seniors, with increasing use as seniors aged; they were also the "third most common cause of adverse drug reaction-related hospitalizations, accounting for 8.1% of hospitalizations among seniors in 2016" (Canadian Institute for Health Information, 2018). Steinman, Komaiko, Fung, & Ritchie (2015) examined prescribing patterns from 1999 to 2010 in the United States and found that almost one in ten older patients received an opioid prescription. This study observed a wide range of patient characteristics and clinical settings and found that opioid analgesic use by older adults visiting clinics more than doubled during that time period. In the nursing home setting, opioid analgesic use is increasingly common; a study by Hunnicutt et al. (2018) found that one in seven residents were prescribed opioids on an ongoing basis, and 32% of residents were prescribed opioids during 120 days of follow-up.

Long-term opioid therapy can exacerbate existing symptoms and lead to the development of new chronic physical and mental health conditions, as well as other opioid-related adverse effects including "serious fractures, breathing problems during sleep, hyperalgesia, immunosuppression, chronic constipation, bowel obstruction, myocardial infarction, and tooth decay secondary to xerostomia" (Von Korff, Kolodny, Deyo, & Chou, 2011, p. 3). There is also evidence that long-term opioid analgesic use alters pain modulatory systems, with the unintended consequences of increasing pain sensitivity and aggravating the underlying pain condition (Kidner, Mayer, & Gatchel, 2009). In an effort to control pain, increased prescribing of opioid analgesics

has been accompanied by an epidemic of opioid abuse and overdose. The development of opioid use disorder as a result of long-term opioid analgesic use has resulted in a significant public health problem in Canada and the United States. The negative consequences associated with long-term opioid analgesic use also lead to high economic burdens through increased emergency room visits, inpatient visits, other healthcare utilization and healthcare expenditures (Kern et al., 2015).

1.6 Opioids and Psychiatric Comorbidities

An emerging line of inquiry is the use of opioid analgesics and their relationship to the development of psychiatric disorders (Bortolotto & Grilli, 2017; Scherrer, Salas, Copeland, Stock, Schneider, et al., 2016; Scherrer, Salas, Lustman, Burge, & Schneider, 2015; Scherrer et al., 2014; Smith et al., 2015). Cross sectional studies have demonstrated an association between opioid analgesic use and symptoms of depression among patients with noncancer pain (Scherrer et al., 2014). The research by Semenkovich et al. (2014) elucidated a relationship between prescription opioid analgesic use in non-cancer, non-HIV pain with an increased risk for major depressive disorder in opioid-naïve individuals with no prior history of depression and substance use disorders. Furthermore, in a study by Scherrer et al. (2014) using a sample of 49,770 veterans with no recent history of depression or opioid analgesic use, the risk of new-onset depression increased as the duration of opioid analgesic use increased. Despite all patients being at low risk of depression at baseline, those receiving opioids for 90 to 180 days had a 25% increased risk of depression, and those receiving opioids for more than 180 days had a greater than 50% increased risk (Lembke, Humphreys, & Newmark, 2016; Scherrer et al., 2014). The study factored in the progression of pain symptoms and its contribution to the development of depressive symptoms by adjusting for certain chronic pain related states (Lembke et al., 2016). Among veterans, males had a lower magnitude of this risk compared to females (Salas et al., 2018). However, within the

civilian population, the risks for new-onset depression were equivalent between males and females (Salas et al., 2018). In another study involving three different patient populations, results also demonstrated that the risk of new depressive episodes increased with duration of opioid analgesic use (Scherrer, Salas, Copeland, Stock, Ahmedani, et al., 2016). This same association was not found with higher maximum morphine equivalent doses. According to Scherrer, Salas, Sullivan, et al. (2016), long-term use of opioids is associated with 35-100% increased risk of depression, and opioid exposure is related to 100% increased risk of depression. To compound this issue, Scherrer, Salas, Sullivan, et al. (2016) found that the risk of developing treatment resistant depression increases as time spent on opioid analgesics increases.

In a study that classified level of opioid analgesic use as regular/high-dose, intermittent/lower-use, and minimal/low/-dose, patients with regular/higher-dose use and intermittent/lower-dose use had higher depression scores than those with minimal/no opioid analgesic use at 12 months (Von Korff et al., 2016). However, depressive symptoms were similar between regular/higher-dose and intermittent/lower-dose users (Von Korff et al., 2016). In a study by Scherrer, Salas, Schneider, et al. (2017), patients with opioid-related new-onset depression reported significantly higher Patient Health Questionnaire (PHQ) scores, greater treatment adherence, and different psychiatric comorbidities compared to non-opioid patients with new-onset depression. In a sample of patients with long-term opioid analgesic use, Salas et al. (2017) found a significant association between rate of opioid dose escalation and new-onset depression, independent of maximum dose, pain and total opioid duration. Scherrer, Salas, Bucholz, Schneider, Burroughs, et al. (2016) studied the risk of depression as a function of the type of opioid prescribed and demonstrated that long-term use of codeine results in a nearly 30% greater risk of

new-onset depression compared to long-term use of hydrocodone, despite codeine being a less potent opioid.

Several studies have explored the relationship between chronic pain and co-occurring psychiatric disorders, especially depression. For example, Bair , Robinson , Katon , & Kroenke (2003) examined the co-prevalence of chronic pain and depression, finding that the rates of both conditions were higher in the presence of the other condition than when analyzed independently (Sellinger, Sofuoglu, Kerns, & Rosenheck, 2016). According to Cazet et al. (2018), depression is associated with higher levels of pain intensity and disability, and has been shown to be a risk factor for greater impairment and poorer prognosis in those experiencing pain. Sellinger et al. (2016) has suggested that there may be a reciprocal relationship between chronic pain and depression, with each condition having moderating effects on the other.

Fiske, Wetherell, & Gatz (2012) assessed predictors that distinguished those individuals who developed mental illness in old age, compared to those who experienced it earlier in life. These predictors are related to differences in etiology and prognosis, as well as to the lived experience of having a mental illness. Risk factors that contribute to the onset of depression later in life are likely compounded by interactions between genetic vulnerabilities, "cognitive diathesis, age-associated neurobiological changes," and stressful events (Fiske et al., 2012, p. 5). Protective factors offsetting late life depression include psychological resilience, higher education and socioeconomic status (Mojtabai & Olfson, 2004), engagement in valued activities, and religious or spiritual involvement (Fiske et al., 2012; George, Ellison, & Larson, 2002). Studies have shown that roughly more than half of the onset of mental illness occurs in old age, with less than half being experienced during the early phases of life. Brodaty et al. (2001) found that among patients in a geriatric mental health unit, 52% of first onset depression occurred at age 60 and above. In

another study of older home care patients, 71% experienced first onset depression (Bruce et al., 2002). However, the defining age for late life onset varies considerably between studies. According to Fiske et al. (2012), there is general agreement on the distinctive risk factors and presentations for late onset mental illness in older adults. Compared to late onset mental illness, those with early onset are more likely to have a family history of the illness (Heun, Papassotiropoulos, Jessen, Maier, & Breitner, 2001), as well as a higher prevalence of personality disorder or elevated scores on personality traits such as neuroticism (Brodaty et al., 2001). On the contrary, those with late onset mental illness are more likely to have vascular risk factors (Hickie et al., 2001), or concomitant cognitive deficits lending to the development of dementia (Schweitzer, Tuckwell, O'Brien, & Ames, 2002). Among late (but not early) onset depression, white matter hyperintensities or leukoencephalopathy in neurological findings are commonly found (Krishnan, 2002).

Prescription opioid analgesics are more widely consumed in North America than in any other continent (Fischer, Murphy, Kurdyak, & Goldner, 2016). Over the past decade in Canada and the United States, there has been a multifold increase in the utilization of opioid analgesics (Fischer et al., 2016). Consequently, these rising volumes of opioid analgesic use are accompanied by increasing levels of opioid-related morbidity and mortality (Fischer et al., 2016). Emerging literature indicating that new-onset and recurrent depression are unintended consequences of opioid analgesic use is especially concerning (Scherrer, Salas, Sullivan, Schneider, Bucholz, et al., 2016). According to Scherrer, Salas, Sullivan, Schneider, Bucholz, et al. (2016), short term improvements in depression and pain following opioid therapy may lead to increased duration of opioid analgesic use or dosage increases, which in turn increase the risk of undesirable outcomes, such as depression. The possibility that opioid analgesic use has a negative effect on patients'

mental health creates a significant public health problem in North America. Widespread exposure to opioid analgesic therapy may result in the increased prevalence of an otherwise avoidable depression (Scherrer, Salas, Sullivan, et al., 2016).

While the existing literature has focused on the association of opioid analgesic use and the development of depression, there is a paucity of literature that focuses on the role that opioid analgesics play, regardless of indication, on the initiation of antidepressant therapy to treat a psychiatric illness, not limited to depression. The clinical significance of this proposed investigation would provide healthcare professionals with a deeper understanding of the association between opioid analgesic use and psychiatric illness, as well as raise clinician awareness of baseline risk factors. This information may help to inform prescribing and monitoring guidelines in the medication management of the elderly.

1.7 Reasons Why Research on the Role of Opioids in Antidepressant Initiation is Important

In summary, past studies of opioid analgesic use have focused on its role in the development of depression, and the management of chronic pain. There are several reasons why taking a step back and focusing on the medications themselves, rather than on the diagnosis, is important:

1) The vast majority of research on long-term opioid analgesic use is restricted to the population diagnosed with chronic pain and does not consider the other Health Canada-approved indications for opioid-analgesic use. The studies focus primarily on the diagnoses rather than on the potential effects of the medications themselves.

2) The incidence of antidepressant dispensation after first starting an opioid has not yet been established. Although certain antidepressants can be used adjunctively for pain relief, this study will determine the psychiatric diagnosis for which these antidepressants were prescribed.
3) The identification of predictors of antidepressant use following first opioid analgesic use has not been determined. Existing risk profiles are based on opioid analgesic use in general, or on risks of chronic pain.
4) The data from this study is based on the Albertan population from 2008 to 2016. Previous research has not had access to such an extensive database.

Accordingly, the research objectives of this thesis are: 1) to examine the incidence of antidepressant use after the first opioid analgesic dispensation; 2) to determine the diagnosis for which the antidepressant was prescribed; and 3) to explore the factors that influence the risk of antidepressant initiation after first opioid dispensation.

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CHAPTER 2

INCIDENCE OF ANTIDEPRESSANT USE AFTER FIRST OPIOID DISPENSATION AND DIAGNOSIS DETERMINATION

2.1 Introduction

Older adults prescribed opioid analgesics have increased susceptibility to "opioid-induced neurotoxicity (Dowell, Haegerich, & Chou, 2016), higher risks for falls and fractures (Rolita, Spegman, Tang, & Cronstein, 2013), cognitive and psychomotor impairment (Clegg & Young, 2011), and intentional overdose, hospitalization, or mortality" (Brooks et al., 2019, p. 2; West, Severtson, Green, & Dart, 2015). Despite these risks and the lack of robust evidence on the efficacy and effectiveness of long-term use of opioids, there has been a fourfold increase in opioid prescriptions among all adult age groups, including seniors, in the past two decades (Brooks et al., 2019). In 2016, opioids were used by 19.3% of Canadian seniors, with increasing use as seniors aged; they were also the "third most common cause of adverse drug reaction-related hospitalizations, accounting for 8.1% of hospitalizations among seniors in 2016" (Canadian Institute for Health Information, 2018).

According to demographic projections, Canada's seniors population is estimated to increase by 65% over the next 20 years (Canadian Institute for Health Information, 2019). This trend is primarily driven by an increased life expectancy, lower fertility rates, and the aging of the baby boom generation (Statistics Canada, 2019). Therefore, it is imperative that research focus on paramount public health and pharmaceutical concerns as they relate to the needs of older adults, age 55 and over (Baker, 2014).

Of particular concern regarding the older demographic is the recent cohort study finding that individuals receiving opioid treatment are more likely to report high levels of psychological distress compared with those unexposed to opioids (Rogers, Kemp, McLachlan, & Blyth, 2013). Additionally, opioid-naïve patients experiencing chronic pain without a recent history of depression have been found to be at greater risk of developing depression the longer the duration of opioid therapy (Semenkovich et al., 2014). Although the link between pain and poorer mental health has been well established in literature (Fishbain, 2000; Kroenke et al., 2011), the mental health factors associated specifically with opioid analgesic use remain poorly understood (Brooks et al., 2019). With rapidly ageing populations and increasing opioid prescribing rates in Western countries, it is timely to assess the possible association between pharmaceutical opioids and subsequent antidepressant use to understand the risk of developing depression or other psychiatric comorbidities (Smith et al., 2015).

The objectives of this study were two-fold. The first objective was to examine the incidence of antidepressant use after the first opioid analgesic dispensation in the Albertan study population. The second objective was to determine the diagnosis for which the antidepressant was prescribed.

2.2 Method

The data for this study was obtained from five electronic datasets that are maintained by Alberta Health (AH), Alberta Ministry of Health. A description of these datasets is shown in Table 2-1. Within Alberta Health Services, all health services provided, and prescriptions dispensed were linked to the respective patient's personal health number (PHN), or a unique lifetime identifier (ULI) which was then linked to their PHN. To preserve confidentiality, a fictional study identification number was created that uniquely identified each recipient across all datasets. Using

a deterministic record linkage system, this identifier was compared across databases, and a link was created if they were all in agreement. To increase the validity of the created links, combinations of different pieces of identifying information may have been employed.

Data included *International Classification of Diseases, 9th Revision*, and *International Classification of Diseases, 10th Revision, (Canadian Modification)* diagnoses codes, prescription records, and demographic information. All analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC, 2017)

Table 2.1
Alberta Health Datasets

#	Health Datasets	From	To
1	Ambulatory Care *Description:* This file contained information on all ambulatory care visits such as Emergency Department (ED) visits, clinic visits, and same-day surgery. ED data included all services, start and end time of services, ICD-10-CA codes (from 2003) associated with the service, and procedure interventions while in the emergency department. This database has the unique ability to reliably distinguish ED visits from other types of physician visits.	April 1, 2005	March 31, 2016
2	Inpatient *Description:* This file contains all hospital care visits, length of stay, diagnosis (up to 25 ICD-10-CA diagnoses), and procedure interventions while in hospital. Data and coding accuracy were routinely validated both provincially and centrally (via the Canadian Institute for Health Information (CIHI)).	April 1, 2005	March 31, 2016
3	Pharmaceutical Information Network (PIN) *Description:* The PIN dataset contains all prescription drug records including drug class, generic and brand names, strength and dosage, days' supply, dates and quantities dispensed, prescriber, and the dispensing pharmacy.	April 1, 2008	March 31, 2016
4	Practitioner Claims *Description:* This file contains all insured services provided on a fee-for-service basis. Each claim contains age, ICD-9 diagnostic codes, and the date on which the service event ended.	April 1, 2005	March 31, 2016
5	Population Registry *Description:* This file contains information on recipient data, including sex, date of birth, first three digits of postal code, as well as immigration and emigration data. The province of Alberta has a population of approximately 4.3 million (about 12% of Canada's total population).	April 1, 2005	March 31, 2016

Cohort Eligibility

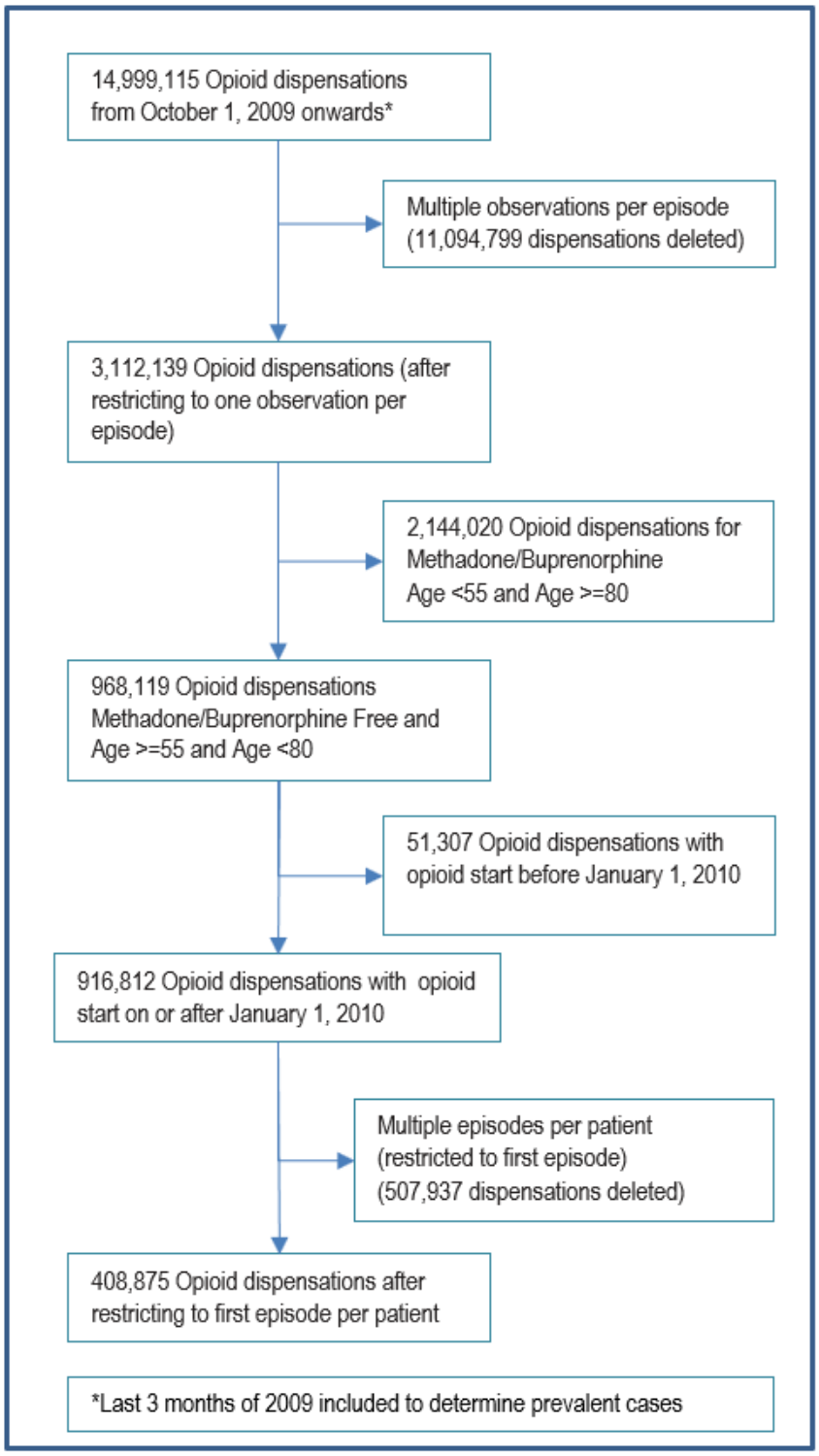
This study relied on the exclusive use of outpatient community dispensations for all prescriptions. The cohort was restricted to Alberta residents aged 55 to 80, enrolled in the Alberta Health Insurance Plan for at least one calendar year, and excluded cancer-related pain treatment.

Opioids included codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, butorphanol, dextropropoxyphene, meperidine, oxycodone, oxymorphone, morphine, nalbuphine, opium, tapentadol, tramadol, and pentazocine. Patients under treatment for opioid use disorder or opioid addiction with methadone or buprenorphine were excluded from the cohort because antidepressants are commonly used therapeutically for comorbid depression, and have a potential effect on the underlying mechanisms of addiction (Lima, Soares, Reisser, & Farrell, 2002; Torrens, Fonseca, Mateu, & Farré, 2005). Treatment of co-occurring mood disorders such depression and bipolar disorders with antidepressants may reduce their opioid cravings and consumption, thus improving patient outcomes (Quello, Brady, & Sonne, 2005). Therefore, antidepressant initiation within this unique subset may be considered a positive outcome and would differ from the cohort population in this study where antidepressant initiation is perceived as a negative outcome.

Patients were included if their first opioid dispensation occurred between January 1st, 2010 and December 31st, 2014, and their first antidepressant dispensation occurred within one year after the first opioid dispensation. A three-month washout period was applied as a conservative time frame to remove prevalent cases of opioid analgesic use. The end of the follow-up was a new antidepressant dispensation in a previously antidepressant-naïve (based on a 12-month history) patient, up until one year from the first opioid dispensation, or the end of the study. These criteria set up the temporal relationship so that incident opioid analgesic use occurred in patients without

current antidepressant use and preceded any new-onset psychiatric comorbidity or exacerbation of an existing morbidity. The steps involved in determining the cohort population are outlined in Figure 2.1.

Figure 2.1
Eligibility Criteria for Inclusion in the Cohort



Outcome

Using the prescription records to identify antidepressant dispensations, patients who had a subsequent antidepressant medication dispensed within one year after the index date of the first opioid dispensation were selected. Where there were multiple opioid dispensations per patient, only the first dispensation was used. The first incidence of antidepressant use after the first opioid dispensation was counted for each year for every individual. As a result, an individual was counted only once per year (incidence proportion). Individuals may have been counted more than once in different years if they had multiple distinct episodes with start dates in different years. If an individual had an episode overlapping two or more years, only the first year was counted. The total crude rates were determined by dividing the number of incident cases by the population in Alberta. Age standardized and age-sex standardized incidence proportions were calculated for each year using the population of Canada from Statistics Canada's 2011 Canadian population as the reference population (Milan, 2011).

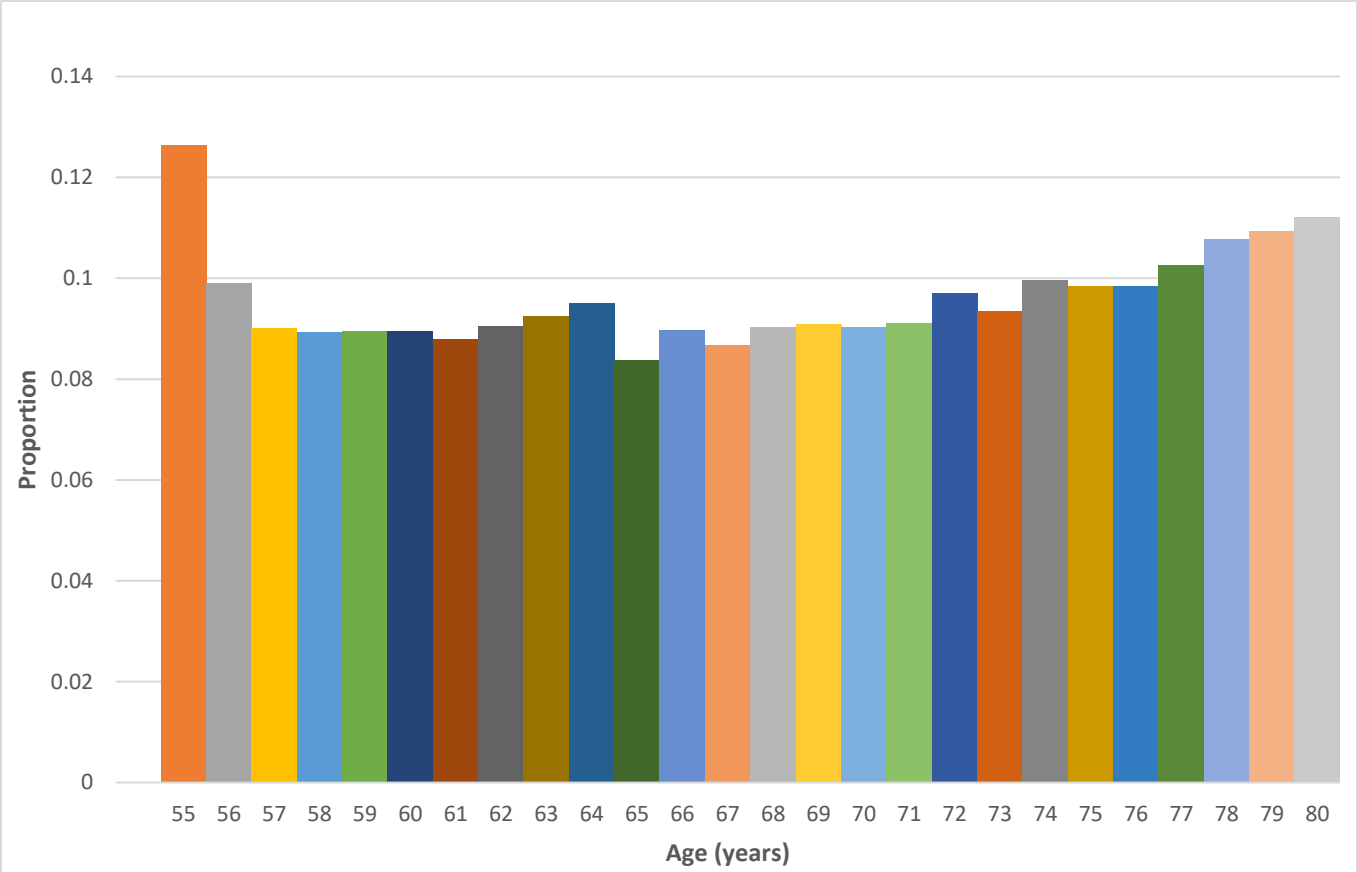
The diagnosis for which the antidepressant was prescribed was determined using the practitioner claims data and inpatient data. ICD-9 and ICD-10-CA codes were used to define depression, anxiety disorder (including generalized anxiety disorder, panic disorder, social phobia, obsessive compulsive disorder, or anxiety disorder not otherwise specified), personality disorder, psychotic disorder, alcohol use disorder, and substance use disorder in the practitioner claims data and inpatient data respectively. These codes were verified against study designs and methods in the data repository for the Manitoba Centre for Health Policy (University of Manitoba, 2019). Those patients who had an antidepressant dispensed in the year prior to the index date of opioid dispensation were excluded. In addition, those with a prior diagnosis of a psychiatric comorbidity within one year from the index date of opioid dispensation were also excluded. These restrictions

ensured that the secondary outcome (diagnosis determination) was an accurate estimate of a new-onset psychiatric comorbidity.

2.3 Results

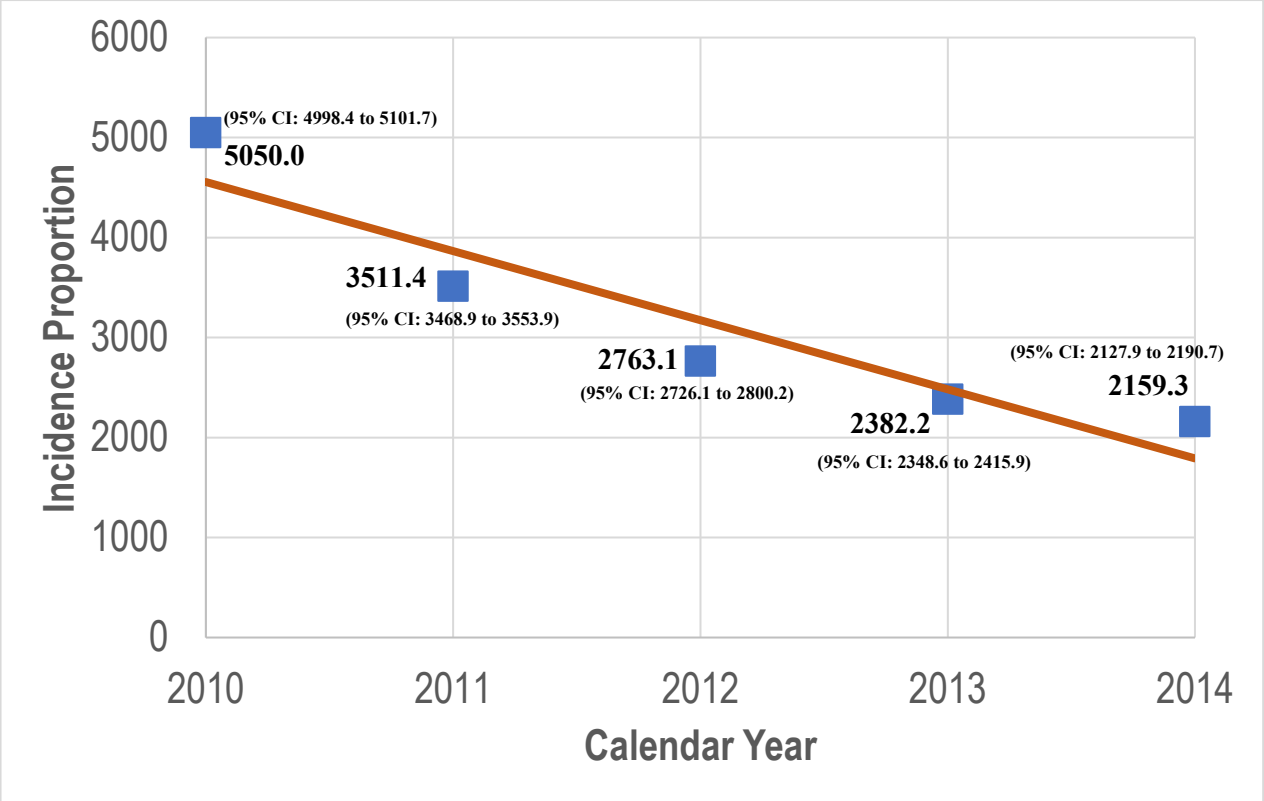
The mean age for reporting an antidepressant dispensation was 63.9 ± 7.2 years. The age distribution of persons reporting an antidepressant dispensation is shown in Figure 2.2.

Figure 2.2
Age distribution of persons with antidepressant initiation after opioid start



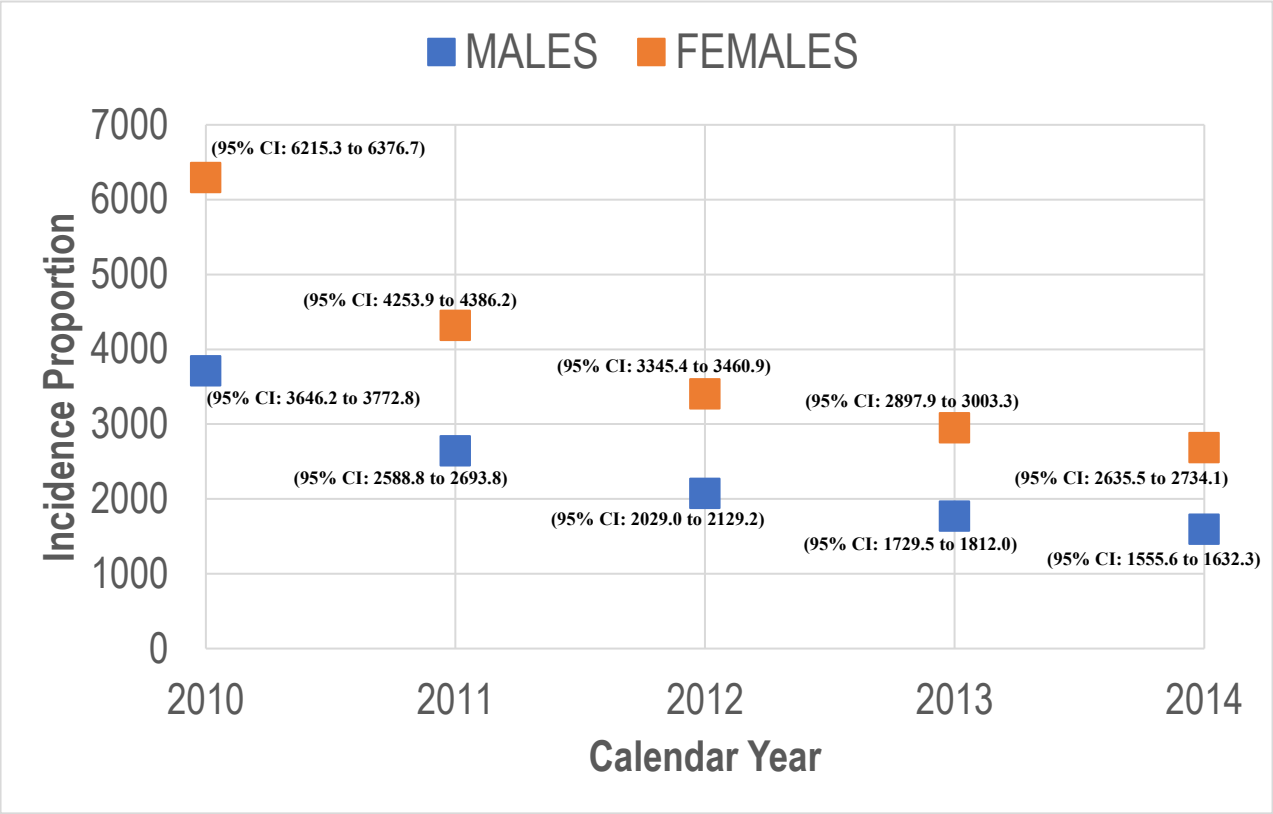
The cohort consisted of a population of 408,862. The total number of people dispensed an antidepressant within one year after starting an opioid was 39,650, or 9.7% of the cohort population between 2010 and 2014.

Figure 2.3
Age-Sex Standardized Antidepressant Incidence Proportion (per 100,000)



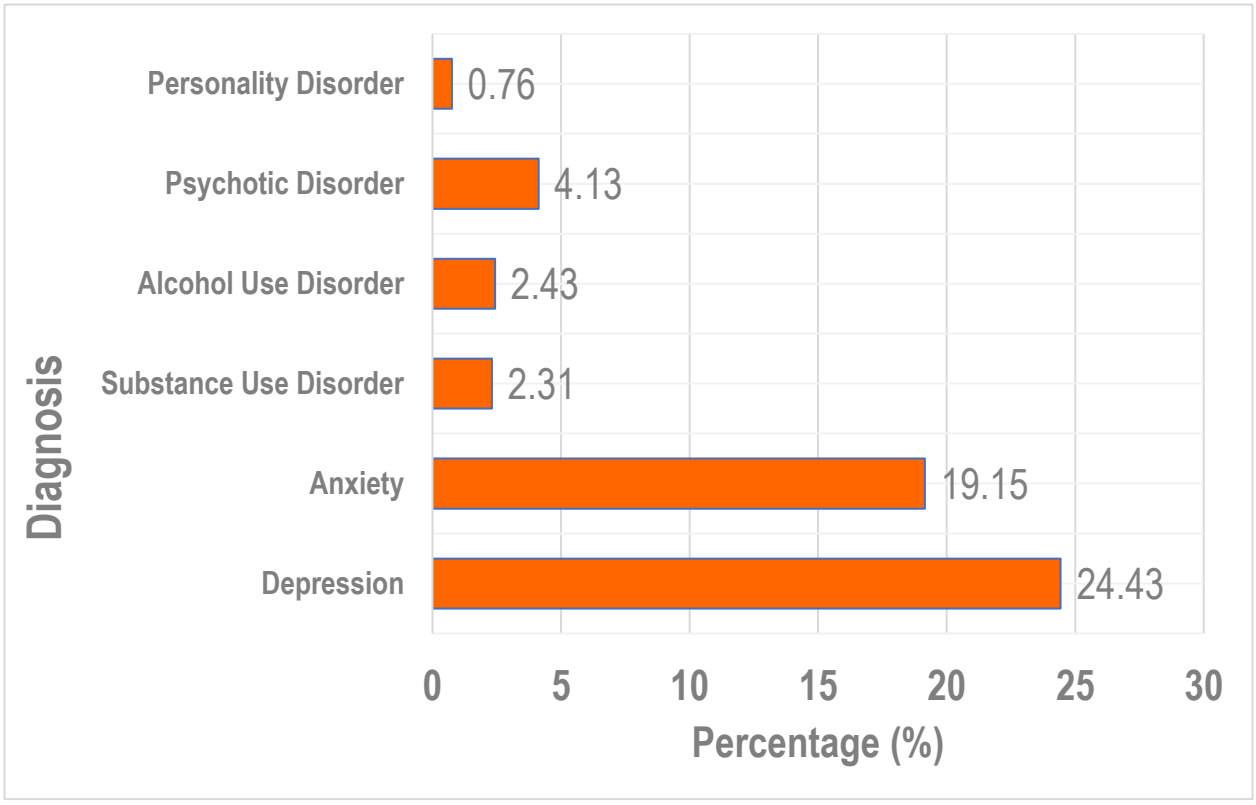
The age-sex standardized incidence proportion of antidepressant dispensation following opioid start is shown in Figure 2.3.

Figure 2.4
Age Standardized Antidepressant Incidence Proportion by Sex (per 100,000)



The age standardized incidence proportion of antidepressant dispensation following opioid start is shown in Figure 2.4.

Figure 2. 5
Diagnosis for which antidepressant was prescribed after opioid start



Out of all the people prescribed an antidepressant after first opioid dispensation having no recent history of antidepressant use or psychiatric diagnosis, 24.43% were being treated for new-onset depression and 19.15% for new-onset anxiety. Figure 2.5 details this distribution of new-onset psychiatric diagnoses.

2.4 Discussion

Between 2010 and 2014, 9.7% of the cohort population was initiated an antidepressant within one year after starting an opioid. According to Patten et al. (2014), about 5.5% of the general Canadian population took antidepressants in 2012. When comparing the use of antidepressants in the general population with the findings of the present study, there is a slightly greater incidence

of antidepressant use after opioid initiation compared to overall antidepressant use in the Canadian population.

The incidence proportion of antidepressants after first opioid dispensation decreased by 42.8% across the study period from 2010 to 2014. Women had a consistently higher incidence proportion of antidepressants dispensed compared to men each year. In a comparable observational cohort study in the United States using the Veterans Health Administration database, Mosher et al. (2015) found that the overall prevalence of opioid dispensation increased substantially from 18.9% in fiscal year 2004 to 33.4% in fiscal year 2012. A comparatively stable pattern of incident opioid prescribing was detected over the study period. Among facilities with the highest prevalence of opioid prescribing rates in fiscal year 2004, declining rates of incident prescribing were detected until the end of the study, fiscal year 2012 (Mosher et al., 2015). Over the time period measured, it is interesting to note that women were also consistently dispensed opioids at higher rates than men (Mosher et al., 2015).

Within Canada, the Alberta Triplicate Prescription Program (TPP) Atlas reported increasing utilization of prescription opioids from 2012 to 2016 (Ellehoj, Oreopoulos, & McDermott, 2018). The first decline in prescription opioid utilization occurred between 2016 and 2017 with 1.81 million opioids utilized in 2016 compared to 1.70 million in 2017 and decreased further in 2018 with 1.55 million opioids utilized (Ellehoj, Eurich, & McDermott, 2019).

With prescribers commonly using prescription opioids as one of several approaches to treating pain as well as chronic cough, a decrease in the incidence of opioid prescribing/opioid utilization as demonstrated by Mosher et al. (2015) and the Alberta TPP Atlas (2015, 2016, 2017, 2018) may reflect current prescribing attitudes for opioids. The implementation of prescription

monitoring programs has assisted in the safe use of opioid medications by monitoring prescribing patterns and dispensing information, which in turn has helped reduce the harm resulting from their use. Similarly, the declining incidence of antidepressants after first opioid dispensation may be occurring as a result of changes in attitudes and willingness to prescribe opioids, or due to changes in the population receiving opioids as physicians tighten up access. A 2014 study by Patten et al. (2014) has shown that while antidepressant use rapidly increased in the 1990s and early 2000s, examination of the 2012 Canadian Community Health Survey – Mental Health (CCHS-MH) revealed that these increases have slowed or stopped in recent years. The frequency of antidepressant use did not increase to an appreciable extent from the national survey conducted in 2002 – only 0.5% outside of Quebec and 1.1% in Quebec (Patten et al., 2014). Further research should examine more recent data to determine whether this frequency has continued to level off or decrease.

The declining incidence proportion of antidepressants suggests the possibility of a saturation effect: as prevalent dispensation of opioids increases, fewer unexposed patients are available for incident opioid dispensations and subsequent incident antidepressant dispensations (Mosher et al., 2015). It may be easier to reduce rates of new prescription opioids than to modify existing opioid regimens and potentially disrupt efficacious treatments (Mosher et al., 2015). Although it is difficult to ascertain the proportion of prevalent opioid prescribing that constitutes long-term use, Edlund, Austen, et al. (2014) found that 57% of veterans receiving opioids had at least a 90 days' supply dispensed each year.

The present study demonstrates that in those people free of opioid and antidepressant use in the year prior to initiation of opioid treatment, subsequent antidepressant use is most likely attributable to treatment of depression or anxiety as compared to other psychiatric comorbidities.

The clinical implication is that opioid analgesic use should be minimized to possibly prevent the development of psychiatric morbidity. Conversely, in accordance with Canadian guidelines for pain management, the addition of adjuvant medications can allow for a reduction in dose or duration of opioid treatments. Specifically, use of selective serotonin reuptake inhibitors (SSRIs) as adjuvants can reduce pain severity and interference in those opioid-dependent patients predisposed to mental health disorders (Fishbain, 2000). Alternatively, non-opioid analgesics for the treatment of acute pain may decrease the frequency and duration of opioid trials, thereby reducing the risk of mental health disorders (Semenkovich et al., 2014).

The results of this study indicate that depression and anxiety were the most common psychiatric diagnoses for which antidepressants were prescribed following first opioid dispensation. These findings are consistent with a study conducted by Wang et al. (2012) in which persistent heroin use during methadone treatment predicted more severe symptoms of depression (Scherrer et al., 2017). While the present study excluded those patients receiving methadone for opioid use disorder, the study by Wang et al. (2012) demonstrates the effect that opioids, regardless of whether they are short-acting (heroin) or long-acting (methadone), have on the development of depressive symptoms. Furthermore, Campbell et al. (2016) determined that suicidality in chronic pain treatment with opioids is likely explained by psychiatric comorbidities. Therefore, opioid prescribing should be coupled with careful screening and treatment of emerging mental health disorders (Scherrer et al., 2017). Screening tools for depression such as PHQ-2 and PHQ-9 can be programmed into electronic medical record systems to prompt screening prior to opioid initiation (Scherrer et al., 2017).

The main strengths of this study are the large population-based sample, the generalizability to patients in Alberta and the completeness of follow-up. The usage of pre-existing administrative

data allowed for time-efficient and cost-effective analysis. In addition, the prescription records provided detailed information for each dispensation including dose, type, and duration.

However, the findings in this study are subject to at least two limitations. First, the existing data was collected for administrative rather than research purposes, suggesting that there may be a lack of control over the quality of the data and the details it provides. Second, although the data includes all patients with an opioid prescription, it does not include life-time medical records or medication histories for each patient. It also does not include other characteristics of each prescription, including indication (e.g. chronic versus acute pain) and whether prescriptions were filled and taken as prescribed. It is important to note that not all drugs prescribed are dispensed, and not all drugs dispensed are consumed. Currently, it is not possible to determine the proportion of prescription medications that remain unfilled, nor the quantity of prescribed medication that is unconsumed (*Pan-Canadian Trends in the Prescribing of Opioids and Benzodiazepines, 2012 to 2017*, 2018).

2.5 Conclusions

The information presented in this study adds to the accumulating evidence regarding a link between opioid analgesic use and the risk of depression. However, this research is unique in that it demonstrates links between opioid analgesic use and subsequent initiation of antidepressants in general among older adults. Rather than restricting the study to focus on specific indications of opioid analgesic use such as chronic pain, this study has approached the data from a wider lens by investigating the correlation between opioid and antidepressant medication use. There is substantial likelihood that opioid therapy will continue to present clinical challenges for Canada's aging population. Future research should investigate the patterns between symptoms of psychiatric

comorbidities and use of opioid medications in older adults. It is also imperative that collaboration be encouraged between prescribing providers, geriatric psychiatry professionals, and behavioral health specialists in order to ensure that both the mental health and physical health symptoms of older adults are addressed.

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CHAPTER 3

BASELINE RISK FACTORS FOR INITIATION OF ANTIDEPRESSANT USE AMONG OPIOID USERS

3.1 Introduction

The prescription of opioids is a foundational approach for pain treatment among all age groups; however, due to declines in organ function, metabolism, and excretion, careful consideration of the safety and efficacy of opioids is essential when prescribing to seniors (Chau, Walker, Pai, & Cho, 2008). In 2016, opioids were used by 19.3% of Canadian seniors, with increasing use as seniors aged; they were also the "third most common cause of adverse drug reaction-related hospitalizations, accounting for 8.1% of hospitalizations among seniors in 2016" (Canadian Institute for Health Information, 2018). To compound these issues, Statistics Canada projects that by 2030, seniors will number over 9.5 million and comprise 23% of the Canadian population (Statistics Canada, 2014). With rapidly ageing populations and increasing opioid prescribing rates in Western countries, it is timely to explore the factors that influence the risk of antidepressant initiation after first opioid dispensation in adults aged 55 and above (Smith et al., 2015).

Currently, there is little insight into the risks of starting antidepressant medications to treat a psychiatric morbidity following opioid initiation. Moreover, prior studies of the link between opioid analgesics and psychiatric morbidity have several limitations, including unknown generalizability to other health care populations, and uncertainty surrounding factors associated with psychiatric morbidity (e.g. dose of opioid, demographic factors). Existing risk profiles have focused primarily on the development of depression after a chronic pain diagnosis and subsequent

long-term use of opioids; however, there is a lack of literature focusing on the specific medications that are prescribed and dispensed, which may have more than one indication.

The objective of this study is to explore the factors that influence the risk of antidepressant initiation after first opioid dispensation. The results of this study will enable a better understanding of those individuals who are at a higher risk for antidepressant initiation and would allow for optimal tailoring of interventions to prevent or reduce associated adverse effects in the older adult population.

3.2 Methods

The data for this study was obtained from five electronic datasets that are maintained by Alberta Health (AH), Alberta Ministry of Health. A description of these datasets is shown in Table 2-1. Within Alberta Health Services, all health services provided, and prescriptions dispensed were linked to the respective patient's personal health number (PHN), or a unique lifetime identifier (ULI) which was then linked to their PHN. To preserve confidentiality, a fictional study identification number was created that uniquely identified each recipient across all datasets. Using a deterministic record linkage system, this identifier was compared across databases, and a link was created if they were all in agreement. To increase the validity of the created links, combinations of different pieces of identifying information may have been employed.

Data included *International Classification of Diseases, 9th Revision*, and *International Classification of Diseases, 10th Revision, (Canadian Modification)* diagnoses codes, prescription records, and demographic information. All analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC, 2017).

Cohort Eligibility

This study relied on the exclusive use of outpatient community dispensations for all prescriptions. The cohort was restricted to Alberta residents aged 55 to 80 enrolled in the Alberta Health Insurance plan for at least one calendar year and excluded cancer-related pain treatment.

Opioids included codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, butorphanol, dextropropoxyphene, meperidine, oxycodone, oxymorphone, morphine, nalbuphine, opium, tapentadol, tramadol, and pentazocine. Patients under treatment for opioid use disorder or opioid addiction with methadone or buprenorphine were excluded from the cohort because antidepressants are commonly used therapeutically for comorbid depression, and have a potential effect on the underlying mechanisms of addiction (Lima et al., 2002; Torrens et al., 2005). Treatment of co-occurring mood disorders such depression and bipolar disorders with antidepressants may reduce their opioid cravings and consumption, thus improving patient outcomes (Quello et al., 2005). Therefore, antidepressant initiation within this unique subset may be considered a positive outcome and would differ from the cohort population in this study where antidepressant initiation is perceived as a negative outcome.

Patients were included if their first opioid dispensation occurred between January 1st, 2010 and December 31st, 2014, and the first antidepressant dispensation occurred within one year after the first opioid dispensation. The end of the follow-up was a new antidepressant dispensation in a previously antidepressant-naïve patient (for past 12 months), up until one year from the first opioid dispensation or the end of the study. These criteria set up the temporal relationship so that incident opioid analgesic use occurred in patients without current antidepressant use and preceded any new-onset psychiatric comorbidity.

Episode Construction

Where there were multiple opioid dispensations per patient, the drug date of dispensation and days supplied were extracted from the prescription records to construct episodes of consecutive dispensations. The beginning of an episode was defined by the first opioid dispensation. Supply days were used to predict the end date of the prescription. Consecutive prescriptions were combined if a new prescription was received within 60 days after the predicted end of the episode. The time between episodes (60 days) was determined through exploratory analysis and confirmed through similar approaches used by both Von Korff et al. (2008) and Katz et al. (2010). For the purposes of this study, only the first episode was considered. If there were multiple dispensations in the first episode of opioid analgesic use for a patient, only the last dispensation in this episode was included.

A morphine equivalent dose was calculated using standard equianalgesic conversion tables that provided the amount of morphine equivalent to the opioid in each given medication (e.g. oxycodone). A daily dose was computed from the number of days' supply and the total dispensed, assuming patients took the maximum dose prescribed per day.

Calculation of Opioid Dose

The total dose of opioid for each prescription was calculated by multiplying the total number of medications dispensed by the strength of the medications (in milligrams). The daily dose for each dispensation was calculated by dividing the dose of opioids (in milligrams) by the number of days supplied. The daily dose was converted to oral morphine equivalents (MEQ), a basic unit of measurement, using published conversion factors defined by the National Opioid Use Guideline Group (McMaster University, 2017). If an individual had two or more opioid

dispensations with a day's supply covering the same dates (overlapping dates), the daily dose was considered as the sum of the daily doses from the various prescriptions for the same day.

Covariates

Baseline sociodemographic factors (age, sex, residence, and income) were determined using the cohort population. Patients were divided into their respective age groups based on their age at baseline (opioid start). Age was calculated from the subject's reported date of birth. Using the first three digits of the patients' postal codes, residence in a rural area or urban area was determined. The Canadian Census Analyzer provided the median household incomes for each postal code (University of Toronto, 2014). Since the population registry data had the postal codes for each patient at fiscal year-end, census year 2016 was used. The opioid at the initial dispensing was categorized as high dose if the total MEQ was greater than 90, a threshold identified as high dose by the Centers for Disease Control and Prevention guidelines, published in 2016 (CDC, 2016).

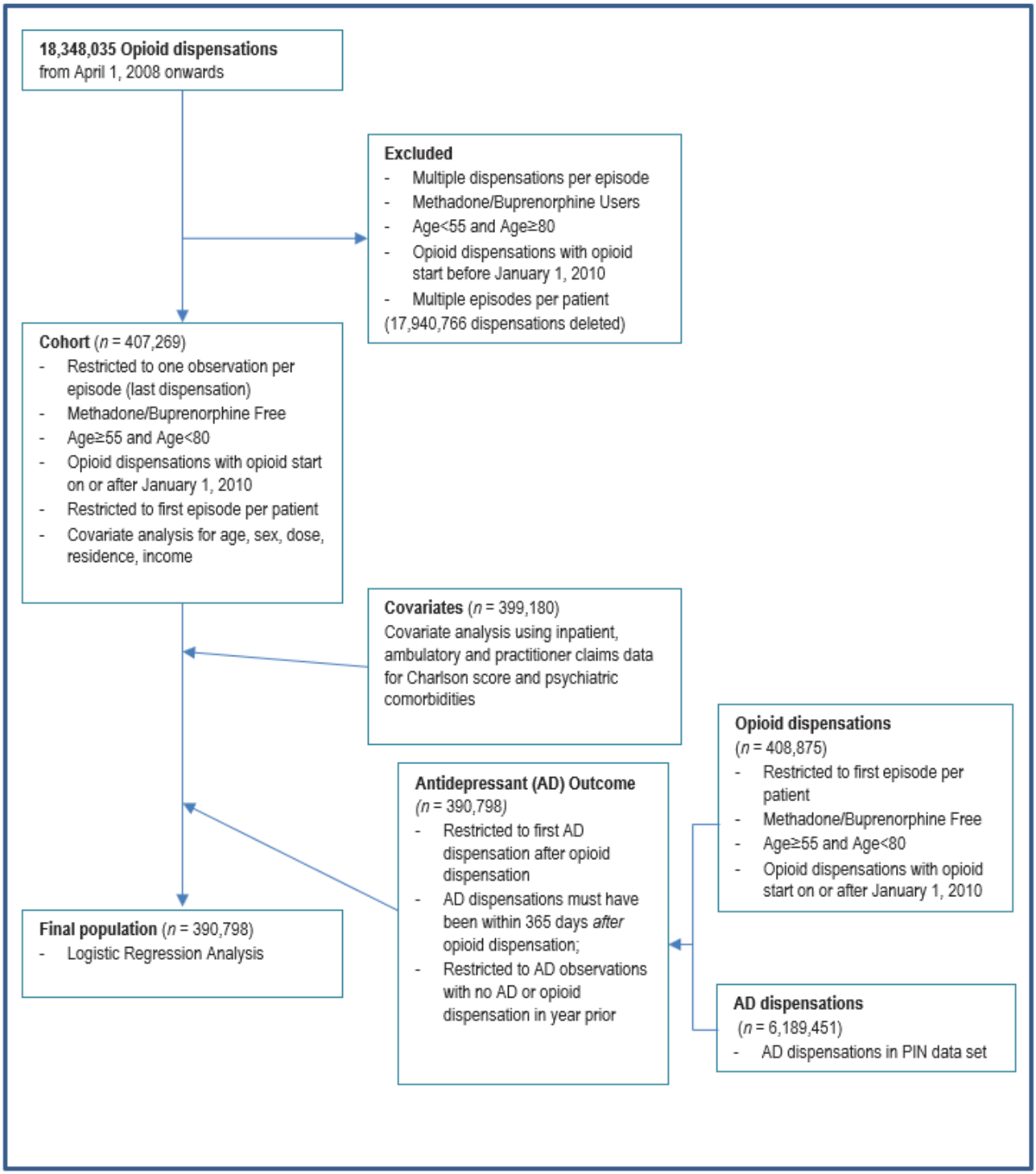
The inpatient, ambulatory care, and practitioner claims datasets were analyzed from January 1, 2008 to provide patients' histories of medical conditions and psychiatric comorbidities. The Charlson Comorbidity Index (CCI) (University of Manitoba, 2019a, 2019b) was used to provide a measure of comorbidity for each person. Psychiatric comorbidities of interest were depression, anxiety, psychotic disorder, alcohol use disorder, substance use disorder, and personality disorder. The diagnostic codes for the CCI and psychiatric comorbidities were verified against study designs and methods in the data repository for the Manitoba Centre for Health Policy (University of Manitoba, 2019c). Combination variables were created which accounted for a diagnosis in the inpatient/ambulatory care data or a diagnosis in the practitioner claims data. The

data was then restricted to the first observation per patient, and if their opioid start was on or after January 1, 2010.

Data Analysis

A logistic regression analysis was performed on the final dataset outlined in Figure 3.1. Baseline characteristics of the cohort are presented as percentages or means and standard deviations in Table 3.1. Simple logistic regression was used to identify predictors for antidepressant initiation after first opioid dispensation compared to non-initiation, and to calculate crude and adjusted odds ratios as well as 95% confidence intervals. Predictors included age, sex, residence, income, initial opioid dose, Charlson Comorbidity Index, and psychiatric comorbidities (depression, anxiety, substance use disorder, alcohol use disorder, psychotic disorder, and personality disorder).

Figure 3. 1
Sample considered for logistic regression analysis



3.3 Results

The final population consisted of 390,798 patients who initiated opioids between January 2010 and December 2014. The mean (SD) age of the population was 63.9 years (6.97) and 49.98% were female. Subject demographics are presented in Table 3-1.

Table 3. 1
Distribution of demographic characteristics by antidepressant initiation

Variable	Total sample (n=390,798) mean±SD/%	Antidepressant Initiation (n=34,592) mean±SD/%	No Antidepressant Initiation (n=356,206) mean±SD/%
Age (years)	63.9±7.0	64.1±7.1	63.9±7.0
Sex			
Females	50.0	60.9	48.9
Males	50.0	39.1	51.1
Residence			
Rural	18.7	19.3	18.7
Urban	81.3	80.7	81.3
Median Household Income (CAD$)	92753.9±23676.7	90846±22482.2	92939±23781.3
Dose			
High-dose (>90 MEQ)	29.52	55.7	27.0
Low-Dose (≤90 MEQ)	70.48	44.3	73.0
Charlson Comorbidity Index	0.394±1.17	0.568±1.373	0.377±1.147
Depression	16.7	35.5	14.8
Anxiety	18.5	29.6	17.4
Substance Use Disorder	1.63	3.64	1.44
Alcohol Use Disorder	2.54	5.08	2.29
Psychotic Disorder	3.21	8.34	2.71
Personality Disorder	0.58	1.54	0.49

Table 3. 2
Risk factors for antidepressant initiation after opioid start: results from logistic regression

Factor	Crude Odds Ratio	95% Confidence Interval	P-value	Adjusted Odds Ratio	95% Confidence Interval	P-value
Age (at opioid start)						
55-59	Reference			Reference		
60-64	1.04	1.01-1.08	0.0049	1.03	1.00-1.07	0.04
65-69	1.06	1.03-1.09	0.0005	1.05	1.02-1.09	0.005
70-74	1.07	1.03-1.11	0.0001	1.05	1.01-1.09	0.009
75-79	1.13	1.09-1.17	<0.0001	1.08	1.04-1.13	0.002
Sex						
Female vs Male	1.63	1.59-1.67	<0.0001	1.45	1.42-1.49	<0.0001
Residence						
Rural vs Urban	1.04	1.01-1.07	0.0067	1.00	0.97-1.03	0.87
Median Household Income (Year 2016)	0.996	0.996-0.997	<0.0001	0.998	0.997-0.998	<0.0001
Dose						
High-dose vs Low-dose	3.40	3.33-3.48	<0.0001	3.24	3.16-3.32	<0.0001
Charlson Comorbidity Index	1.12	1.11-1.13	<0.0001	1.09	1.08-1.10	<0.0001
Depression*	3.16	3.09-3.24	<0.0001	2.55	2.48-2.62	<0.0001
Anxiety	1.99	1.94-2.04	<0.0001	1.43	1.39-1.47	<0.0001
Substance Use Disorder	2.59	2.44-2.76	<0.0001	1.18	1.10-1.26	<0.0001
Alcohol Use Disorder	2.28	2.16-2.40	<0.0001	1.56	1.47-1.65	<0.0001
Psychotic Disorder	3.27	3.13-3.41	<0.0001	1.18	1.12-1.24	<0.0001
Personality Disorder	3.18	2.88-3.50	<0.0001	1.26	1.14-1.40	<0.0001

***Subjects with depression diagnosis had no prior or simultaneous antidepressant dispensation in the past 12 months.

Table 3-2 outlines the baseline risk factors for antidepressant dispensation after opioid analgesic start. The 95% confidence intervals for the odds ratios comparing each of the age groups to the youngest age group (55-59) indicate that older patients are slightly more likely to receive an antidepressant following their first opioid dispensation; however, these results are not clinically meaningful given that the odds ratios differ by only 2-3% between subsequent age groups. Females with higher doses of opioids and having a history of depression were significantly associated with antidepressant initiation. The odds ratio for the Charlson score indicates that a patient with one point higher on the CCI is 8.6% more likely to be initiated an antidepressant medication after first

opioid dispensation. Rural residence was not found to have a statistically significant association with antidepressant initiation after opioid dispensation.

3.4 Discussion

The risk of incident antidepressant dispensation within one year of opioid initiation increases with high dose opioids (>90 MEQ). This finding is consistent with the results of a 2015 study that demonstrated an increased probability of depression with use of opioids at a dose equal to or greater than 50 mg morphine equivalent dose (MED) per day (Scherrer, Salas, Lustman, Burge, & Schneider, 2015). According to Scherrer et al. (2015), both the development and the worsening of depression increase the likelihood of higher MED. This bi-directional association may be mitigated if clinicians focus on treating depression or decreasing MED (Scherrer et al., 2015). When patients on opioid analgesics present with depression, clinicians should consider current opioid dose. Furthermore, when opioids analgesics are considered for patients, it is important that the clinician discuss the risk of depression with the patient.

In a more recent study by Scherrer, Salas, Copeland, Stock, Ahmedani, et al. (2016), the findings were not consistent with the current study and the researchers' previous study. In models controlling for pain and opioid analgesic use duration, higher MED (greater than 100mg/d) compared with lower daily MED (1 to 50mg/d) was not associated with new-onset depression (Scherrer, Salas, Copeland, Stock, Ahmedani, et al., 2016). As suggested by Scherrer, Salas, Copeland, Stock, Ahmedani, et al. (2016), it is possible that in the current and previous studies, increasing the MED was a proxy for duration of opioid analgesic use. Future studies using this Albertan population warrant an investigation into duration of opioid analgesic use as well as dosage of opioid analgesic to determine if the results remain consistent with the present study.

Prior history of depression is also found to predict subsequent antidepressant initiation. It is important to note that due to the limited timescale, the measure of psychiatric comorbidity reflects only the past 12 months and does not indicate life-time prevalence. The findings from this study may be useful in guiding policymakers and clinicians to better mitigate harm by identifying individuals at risk of exacerbation of an existing depression at the time of opioid treatment. Of particular significance is the association between depression and the use of psychotropic medication with an increased risk of opioid misuse (Boscarino et al., 2010). Two Australian studies have found that a history of mental health disorders is a common denominator for mortality due to prescription opioid overdose (Pilgrim, Yafistham, Gaya, Saar, & Drummer, 2015; Roxburgh et al., 2013). Furthermore, Scherrer et al. (2016) observed that people who were in a period of depression remission had an approximately two-fold increased risk of depression recurrence if an opioid analgesic was initiated compared to those not taking opioids. Therefore, a multi-faceted management plan should be established for people with depression being considered for a trial course of opioids (Lalic, Gisev, Bell, Korhonen, & Ilomäki, 2018). In addition to monitoring for new-onset psychiatric comorbidities, clinicians should review the possibility of depression recurrence in conjunction with opioid effectiveness, dose, and duration (Lalic et al., 2018).

It is crucial to develop effective strategies for psychiatric comorbidity prevention based upon an understanding of the risk factors of antidepressant initiation after opioid start. Modifiable risk factors provide targets for psychosocial interventions, which are likely to be preferred over medications for the prevention of psychiatric comorbidities, particularly depression. According to Cuijpers, Smit, & Van Straten (2007), psychosocial interventions have proven effective in reducing the incidence of major depressive disorder. For those risk factors that are non-modifiable such as female sex, opioid prescribing should be coupled with careful screening and treatment of

emerging mental health disorders. The main argument in favor of screening is that it can identify mental health problems earlier, while they are less severe (Bull et al., 2015). PHQ-2 and PHQ-9 are effective screening tools for depression and are shown to be sensitive to age-related physiological changes in the elderly (Amoran, Ogunsemi, & Lasebikan, 2012). Generalized Anxiety Disorder Questionnaire (GAD)-IV and GAD-7 are useful screening tools that identifies whether a complete assessment for anxiety is indicated (Spitzer, Kroenke, Williams, & Löwe, 2006). While the Minnesota Multiphasic Personality Inventory (MMPI) carries higher diagnostic reliability in the diagnosis of psychiatric disorders, it is a considerably longer process (Jahangirian, Akbari, & Dadgostar, 2019). Adherence to screening tool protocols is more likely with the free and less time-consuming PHQ or other validated tool, which can be programmed directly into electronic medical records to prompt screening prior to opioid initiation (Scherrer et al., 2017). Importantly, while these tools can be used for screening and monitoring symptom severity, they cannot replace a clinical assessment and diagnosis.

The main strengths of this study are the large population-based sample, the generalizability to patients in Alberta, and the completeness of follow-up. The usage of pre-existing administrative data allowed for time-efficient and cost-effective analysis. In addition, the prescription records provided detailed information for each dispensation, including dose, type, and duration.

There are several limitations of the analysis reported here. First, the existing data was collected for administrative purposes rather than for research, suggesting that there may be a lack of control over the quality of the data and the details it provides. Second, although the data includes all patients with an opioid prescription, it does not include other characteristics of each prescription, including indication (e.g. chronic versus acute pain) and whether prescriptions were filled and taken as prescribed. It is important to note that not all drugs prescribed are dispensed

and not all drugs dispensed are consumed. Currently, it is not possible to determine the proportion of prescription medications that remain unfilled, nor the quantity of prescribed medication that is unconsumed (*Pan-Canadian Trends in the Prescribing of Opioids and Benzodiazepines, 2012 to 2017*, 2018). Third, it is possible that some individuals may have serious conditions not captured by the Charlson Comorbidity Index (CCI), and therefore, all comorbidities may not have been identified. Nevertheless, the CCI has been extensively studied and has been shown to predict mortality in both Canadian and international studies (Charlson, Pompei, Ales, & MacKenzie, 1987; De Groot, Beckerman, Lankhorst, & Bouter, 2003). Fourth, since the data was only available from 2008, it was not possible to determine patient-specific life-time prevalence of psychiatric comorbidities, or usage of medications prior to this date. Lastly, opioid analgesic duration was not measured as a baseline risk factor for antidepressant initiation following first opioid dispensation. Future research with this dataset should investigate whether duration of opioid analgesic use is a predictor by introducing a time interaction or by capturing the underlying hazard and assessing how it changes over time.

3.5 Conclusion

Mental health comorbidities, older age, high dose of opioid, lower income, higher Charlson scores, and being female, all strongly predict antidepressant initiation following first opioid dispensation. This study highlights the range of characteristics that predict antidepressant initiation leading to new-onset psychiatric disorders. Understanding these risks will enable prescribers to target early intervention efforts and screening tools to mitigate harms and prevent mental health issues from arising in the future. Screening of psychiatric disorders for all patients should take place prior to an opioid trial. For those patients beginning ongoing opioid treatment, antidepressant prophylaxis or treatment of depression should be considered. Future research should explore

whether the coadministration of antidepressants and opioids serve to prevent incident psychiatric disorders in those patients initiated on opioids.

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CHAPTER 4

OVERVIEW AND FUTURE DIRECTIONS

4.1 Overview

The preceding chapters have examined the incidence of antidepressant medication use following opioid initiation due to new-onset psychiatric disorders. The predictors influencing the risk of antidepressant initiation after first opioid dispensation were also determined. Chapter 1 provided a review of previous research on opioid analgesics, examining their mechanism of action, treatment indications, use in older populations, and relationship to psychiatric disorders. Chapter 2 presented an analysis of opioid dispensations and their relation to subsequent antidepressant initiation. Chapter 3 examined the baseline risk factors for antidepressant initiation following opioid commencement.

At the conclusion of Chapter 1, several research questions were posed regarding the role of opioid dispensation on the incidence of antidepressant use and the onset of psychiatric disorders. The high prevalence of opioid analgesic use in society mandates specific research that explores this relationship. The results presented in Chapters 2 and 3 provide support for this hypothesis.

Using a retrospective design, Chapter 2 supplied information demonstrating a greater incidence of antidepressant use after opioid initiation compared to overall antidepressant use in the Canadian population. Across the study period, there was a declining incidence proportion of antidepressants after first opioid dispensation. This decline may be attributed to changes in physicians' practices and attitudes towards opioid prescribing, new guidelines and criteria restricting access to opioids, and the possibility of a saturation effect. Chapter 2 also concluded that in those free of opioid and antidepressant use in the year prior to initiation of opioid treatment,

subsequent antidepressant use is most likely attributed to treatment of depression or anxiety as compared to other psychiatric comorbidities.

Chapter 3 presented an investigation of baseline risk factors for antidepressant dispensation after opioid initiation. It was concluded that the risk of incident antidepressant dispensation within one year of opioid initiation increases with high dose opioids (>90 MEQ), female sex, and prior history of depression. Further risk factor investigation would be beneficial to determine if the predictors here are robust across different cultural groups, and among all age groups.

The main contribution of the present research to the body of knowledge regarding opioid analgesics lies in its examination of the relationship between opioid analgesic use and subsequent antidepressant use to treat psychiatric illness. While Bair et al. (2003) explored the relationship between chronic pain and depression, their analysis focused primarily on the diagnosis of chronic pain and did not account for the specific role that opioid analgesic use has on the development of depression. Both Scherrer et al. (2014) and Semenkovich et al. (2014) described a relationship between opioid analgesic use and the development of major depressive disorder but did not investigate the specific use of antidepressants to treat depression or other psychiatric illnesses. Other studies have determined the predictors of persistent opioid analgesic use and the risk factors contributing to the onset of depression later in life (Fiske et al., 2012; Lalic et al., 2018); however, this study is the first to examine the risks of initiating an antidepressant after first opioid dispensation.

4.2 Future Directions

The existing data used in Chapters 2 and 3 was collected for administrative rather than for research purposes. If additional information could be retrieved for each patient, perhaps a more

extensive understanding of incidence and risk factors would be possible. For example, gathering information on organ functions, dietary habits, smoking habits, alcohol consumption, physical activity, working status, drug interactions, and inherent pharmacogenetic differences may provide useful insights (Solhaug & Molden, 2017). These factors may account for pharmacokinetic (concentration) or pharmacodynamic (receptor/target responsiveness) differences among therapeutics (Solhaug & Molden, 2017). According to Solhaug & Molden (2017), drug interactions and pharmacogenetic differences influence the efficacy and safety of opioids on an individual level, which may, in turn, influence the subsequent use of antidepressants to treat psychiatric disorders. In order to individualize long-term treatment with opioids and other classes of therapeutics, Solhaug & Molden (2017) recommended the routine use of cost-effective blood-based genotyping of CYP enzymes.

The organization of provincial/territorial and federal population-based data collection systems would add greatly to the ability of epidemiologists to identify opioid trends in relation to antidepressant use for treating a psychiatric illness. Comparisons of such analyses between provinces and territories in Canada would aid in the development and assessment of public health policies and preventative strategies. This information may also serve to guide future allocation of health care resources. A major benefit of having access to these large population databases is that when conducting risk factor analyses, true causal connections would not be falsely rejected.

Considering that there is a greater incidence of antidepressant use after opioid initiation compared to overall antidepressant use in the Canadian population, practical strategies must be developed to deal with iatrogenic psychiatric illness caused by using opioid analgesics. Investigating the patterns between symptoms of psychiatric illnesses and the use of opioid analgesics in older adults may reveal important clinical pearls when providing treatment.

Semenkovich et al. (2014) have recommended screening for depression and substance use disorder during opioid trials; however, this screening may be extended to other psychiatric illnesses as well. Antidepressant prophylaxis in patients entering chronic opioid treatment should be considered by practitioners (Semenkovich et al., 2014). Future research should explore the pharmacological consequences of combining opioids and antidepressants to prevent incident psychiatric disorders in those patients initiated on opioids. Combinations with benzodiazepines should also be further researched. Despite the associated risks of using benzodiazepines, these medications are often prescribed for short periods to patients with depression who are beginning antidepressant therapy to more rapidly improve symptoms, diminish associated anxiety, and improve antidepressant continuation therapy (Bushnell, Stürmer, Gaynes, Pate, & Miller, 2017). A detailed analysis exploring the effects of coadministration of antidepressants and short-term benzodiazepines with opioid analgesics to prevent new-onset psychiatric illness should be undertaken.

The complex mechanisms by which opioid analgesic use contributes to new-onset psychiatric illnesses are not fully understood. Semenkovich et al. (2014) have identified several plausible mechanisms for the depressogenic effects of opioids that might account for both early-onset and delayed-onset depression occurring during opioid analgesic use. Further research into the intricacies of these biological mechanisms would help to inform clinical practice guidelines for treating incident psychiatric illnesses attributed to opioid analgesic use.

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