Prevalence of Concurrent Use of Prescribed Opioids and Benzodiazepine/Z-drugs and its Effect on Adverse Outcomes in Alberta

by

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Abstract

The opioid crisis has received much attention over the past few years in which prescribed opioids have been a significant contributor. In fact, Canada has among the highest rates of opioid prescribing in the world despite increasing recognition of the significant risks associated with such prescribing practices, including fatal overdose and dependency. Furthermore, individuals older than 65 years are especially prone to the consequences of prescribed opioids. As a result of this, clinical practice guidelines on the safe use and prescribing of opioids have been developed from a variety of sources and are acknowledged by health provider regulatory bodies across the country. A similar picture exists for benzodiazepines and Z-drugs (zopiclone, zolpidem), collectively known as benzodiazepine receptor modulators (BZDs). BZDs are widely prescribed psychotropic compounds for anxiety disorders and insomnia. Canadian clinical practice guidelines suggest that BZD treatment may be appropriate for short term use only in adults, and in some cases, as second line treatment. Use of BZDs outside of these recommendations is considered inappropriate because of the risk of adverse effects, especially in older adults.

Within the opioid crisis, co-prescribing of opioids and BZDs represents a much less highlighted drug use pattern that is of substantial concern because of the higher risk of mortality. In fact, BZDs are implicated in up to 50% of opioid related deaths. Although there are no specific clinical guidelines on indications for co-prescribing of these medications, there are many recommendations warning against this practice. As such, safe drug use policies cannot target opioids and BZDs in isolation. Despite these warnings, co-prescribing of opioids and BZDs still occurs at alarming levels.

The first objective of this research program was to expand the body of knowledge on co-prescribing by characterizing the prevalence of concurrent use of BZDs among opioid users using administrative data from Alberta in 2017. This was accomplished using a cross sectional approach in which the prevalence of concurrency was estimated among various sub-groups of patients. The results showed that the prevalence of concurrent use/co-prescribing of opioids and BZDs is higher among females, older adults and those with higher opioid doses and longer duration of opioid use. Higher healthcare utilization was also associated with a higher prevalence of concurrent use.

The second objective was to quantify the added risk of concurrent BZD and opioid use compared to opioid only use. In this study, we used a case crossover method to compare the risk of hospitalization or emergency department (ED) visits and death between the concurrent population and opioid only

population (reference group). Our results showed that concurrent use was associated with an increased risk of hospitalization, ED visits and death compared to opioid only use.

In summary, our studies suggest that co-prescribing of opioids and BZDs occurs in Alberta at a substantial level, especially among certain sub-groups of the population and that this drug use pattern is also associated with a higher risk of adverse outcomes above that of opioid only use, an already high-risk group. These results suggest that the clinical warnings around co-prescribing of these agents may not be fully acknowledged by providers and that more education and monitoring may be needed.

Preface

This thesis is an original work by Vishal Sharma. A version of Chapter 2 of this thesis has been published in BMJ Open *BMJ Open*2019;**9:**e030858 and a version of Chapter 3 has been submitted for publication at the time of submission of this thesis.

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1 Chapter 1: Introduction

1.1 Statement of the Problem

The opioid crisis in Canada has raised concerns regarding inappropriate prescribing of opioids, especially since a key driver of this crisis is prescription opioid use. The current opioid epidemic follows on the enormous growth in use of prescription opioids in Canada in the last few decades; over 20 million prescriptions for opioids were dispensed in 2016 making Canada the second largest consumer of prescription opioids in the world, after the USA. [1] The health burden associated with opioid related mortality and disability in Canada is significant and has increased dramatically from 1990 to 2014.[2] This has resulted in an average of 16 hospitalizations a day in Canada due to opioid poisonings with seniors over 65 years having the highest rates of opioid poisoning-related hospitalizations.[3]

A similar picture exists for BZDs and Z drugs (zopiclone and zolpidem), collectively known as BZDs receptor modulators. BZDs are one of the most widely prescribed psychotropic compounds for treating insomnia and anxiety.[4] Canadian clinical practice guidelines for the management of anxiety and insomnia suggest that BZDs treatment is appropriate for short term use in adults (aged 20-64 years) and in some cases as second line treatment.[5,6] However, studies show that BZD use has steadily increased in both number of people using and length of use despite guideline cautions.[7,8]. Use of BZDs outside of these guidelines is considered "potentially inappropriate" given the potential for adverse effects, especially in those over 65 years.[4,5,9] For example, the risk of motor vehicle accidents, falls and hip fractures leading to hospitalization and death can more than double in older adults taking BZDs.[10]

Although less quantified in published literature, polydrug use in the context of the opioid crisis is now receiving attention because of its influence on negative outcomes. Combined use of opioids with non-opioid substances, such as alcohol, BZDs, and cocaine to name a few, is becoming more recognized as a risk factor for opioid related deaths.[1] Concurrent use of opioids and BZDs is of particular concern since a chart review in Manitoba found that BZDs were one of the most frequently prescribed medications 6 months before an opioid related death and studies in the USA report that nearly one-third of fatal opioid overdoses also involved a BZDs.[1,11] Despite these findings and numerous evidence based practice recommendations [12-15] that advise against co-prescribing, concurrent use of opioids and BZDs remains an ongoing issue. There are no studies using Canadian data that have characterized and quantified the effect of concurrent use of opioids and BZDs in any population of opioid users.

1.2 Concurrent Use of Opioids and BZDs

There is a shift in treatment emphasis away from opioids in the setting of chronic pain and mental illness and according to the CDC (Centers for Disease Control), opioids are not first-line or routine therapy for chronic pain because the benefits of long-term opioid therapy are not well supported by evidence.[12,13,16] Furthermore, if opioids are to be used in the chronic setting, current guidelines recommend doing so at daily doses <50mg OME (oral morphine equivalents) and not exceeding 90 mg OME.[5,15] Also described in recent guidelines, use of BZDs is commonly being less emphasized in the treatment of anxiety and insomnia and are a target for de-prescribing initiatives, especially in seniors.[17,18]

No clinical practice guidelines exist regarding indications for concurrent use of opioids and BZDs. To the contrary, there are numerous clinical recommendations based on high grade evidence that warn against concurrent use. In fact, the CDC specifically states that prescribers should avoid concurrent BZDs and opioid prescribing.[12] The recommendations from Canadian guidelines are even stronger, saying that BZDs should be tapered and discontinued when starting opioids and that BZDs use is an indication for opioid tapering.[15] A major driving force for these recommendations is the observation that combined BZDs and opioid use is now considered a risk factor for fatal overdoses.[1,15]

Despite all the recommendations, concurrent prescribing of opioids and BZDs still occurs at alarming rates. Only a few studies have looked at concurrent use, with even fewer using Canadian data. A study done in the USA showed that prevalence of concurrent use has increased over time and that concurrency was more common in patients receiving opioids for >90 days, women and the elderly.[19] No such characterization studies using Canadian data were found. Though long-suspected, the adverse outcomes of concurrent use of opioids and BZDs are now only recently being quantified. Studies in the USA have shown that concurrent use of opioids and BZDs has higher rates of emergency room visits and overdose deaths when compared to opioid only users.[11,20] Outcome data on the effect of concurrent use of BZDs is not available in Canada among prescription opioid users. However, a recent prevalence study in Ontario showed that around 30% of people who died from an opioid related cause also had an active BZDs prescription.[21]

1.3 Characterizing Concurrent Use of Opioids and BZDs

Characterizing concurrent use of opioids and BZDs involves performing a descriptive study that answers the questions of who, what, when, and where and obtaining prevalence of concurrency rates

related to these questions. There is very little published research that characterizes the concurrent use of opioids and BZDs. One study from the USA on trends in concurrent prescribing from 2002-2014 described concurrency in the context of opioid formulation, duration of opioid use, age and sex.[19] In it, the researchers found that prevalence of concurrent use was higher among females, older adults and those with longer duration of opioid use.

A descriptive study using Alberta data would build upon the body of knowledge that previous studies have generated for the Canadian context. Very little is known in Canada with respect to the characteristics of patients using BZDs and opioids concurrently. Beyond common characteristics such as age, sex and geography (rural/urban), a number of additional characteristics may be of relevance when evaluating concurrency of BZDs and opioids. Potential characteristics from previously published literature and guidelines have suggested that opioid dependency and treatment with methadone, prior health care utilization, opioid dose thresholds based on the risk/benefit profile (e.g., <50, 50-90, and >90 OME), duration of opioid use and defined daily doses (DDDs) of BZDs may all be potential characteristics of interest when looking at concurrency of BZDs and opioid use. [14,15,22,23] Whether some or all of these factors are associated with higher or lower rates of BZDs and opioid use is unknown in Canada. This information would be of importance to policy makers and clinicians in term of both monitoring and to minimize any potential risks to patients while maximizing potential benefits if BZDs and opioids are required to be used concurrently.

1.4 Effect of Concurrent Use of Opioids and BZDs on Outcomes

The effect of concurrent use on health outcomes was quantified by 2 large studies in the USA.[11,20] Both of these studies showed that concurrent use increased the risk of ER visits, hospital admissions (adjusted OR 2.14; P<0.001), and mortality (adjusted HR 3.86; P<0.05) when compared to opioid only users. No outcomes studies using Canadian data have been identified. Given differences between the health systems and how opioids and BZDs are financially covered in the USA and Canada, it is unclear if a similar pattern of outcomes exists in Canada. In fact, given the very high use of BZDs and opioids and our universal coverage of most of these drugs on formularies, it is possible Canadian patients may be subjected to worse outcomes associated with concurrent use.

The above-mentioned studies used retrospective cohort and case cohort analyses to study the effect of concurrency on outcomes. The limitations of these approaches are that there will always be residual confounding even after extensive covariate adjustment and furthermore, the study populations in these studies will be different from the Alberta, Canada population. Another method that can be

used to study exposure-outcome relationships and may overcome the previous limitations is the case crossover approach that uses Alberta data, first described by Maclure and summarized as follows.[24] This design is a newer analytical epidemiological approach which is unique because cases (i.e. those with the outcomes of interest) serve as their own controls. Experience with case crossover studies has shown that this design applies best if the exposure is intermittent, the effect on risk is immediate and transient, and the outcome is abrupt [24]. However, this design has been used to study exposure-outcomes that deviate from this definition as well [24]. To estimate relative risk, the exposure frequency during a window just before outcome onset (case window, hazard window) is compared with exposure frequencies during control times rather than in control persons; the control is the same person at a different time. The case and control periods are compared statistically using conditional logistic analysis using discordant exposures to estimate the relative risk. Case crossover studies are a good fit when using administrative databases. A common issue with studies using administrative data is lack of data on confounders. This can largely be addressed when cases are used as their own controls with the caveat that major confounders have not been introduced in the period of time between the control period and case period. With self matching, data on confounders such as co-morbidities is generally not needed, as long as the control period is not too distant from the case window (confounding characteristics remain relatively constant). Since cases serve as their own controls in case crossover studies, cases and controls are comparable in most of their known and unknown confounders except for intermittent exposures and this overcomes the problem of between-person confounding by constant characteristics.[25] However, within-person confounding by transient factors, such as fluctuations in disease severity (confounding by indication), is still possible. Furthermore, time trend bias may occur if the case and control time windows are very long. With a long time period under study, there may be changes in exposure frequencies (changes in prescribing patterns) due to introduction of new medications or changes in practice guidelines which may cause a systematic difference in frequency of exposures between control and case periods.[25] Selecting the number of control periods is also important, since increasing the number of control periods can reduce confidence intervals as more 'data points' are available to improve the precision of the estimates.[24] However, since exposure is determined retrospectively in case crossover studies, there is always a chance of misclassification and measurement error of the exposure and this could be compounded with more controls windows and time periods prior to the case period.[25]

A limitation of this study design is the basic requirement that at least some subjects must have crossed at least once from unexposed to exposed or vice versa.[26] Another question that arises is how

the estimated relative risk from a case crossover design compares to those obtained from a cohort or case control study and how it should be interpreted. A cohort study allows for the estimation of relative incidence and for estimating excess risk of an exposure in a population. In contrast, a case crossover design assesses individual changes in risk relative to periods of exposure and non-exposure in those who are intermittently exposed.[27] The relative risk estimated from cohort and case crossovers will not be directly comparable and different terminology, such as individual relative risk, should be used in reporting the results of case crossover studies.[27]

The attributes of a case crossover approach can be applied when studying the effect of concurrent use of opioids and BZDs on outcomes. The exposure (use of BZDs) is intermittent in many people in the population of opioid users. The effect on the risk of hospitalizations can occur immediately after exposure to BZDs and is transient, depending on the dosing and half lives of the specific medications involved. Also, hospitalizations are an abrupt event that can easily be dated. The biggest challenge, as in any case crossover study, is determining the size of the case window before the event as well as the size, time frame reference and number of control windows. Having the appropriate case and control windows is crucial in estimating the relative risk of concurrent use on hospitalizations, ED visits and deaths because only those subjects that cross from non-concurrent to concurrent use and vice versa are included in the statistical analysis [25]. The conditional analysis will compare exposure (concurrent use) frequencies between control periods and case windows.

Many, if not all, of the potentially confounding characteristics that are stable over the time frame will be effectively controlled. Within person confounding mentioned above, such as confounding by indication or disease severity, should not be an issue since there are no official indications for concurrent use of opioids and BZDs; in almost all clinical scenarios, concurrent use should not occur. However, in the palliative care and cancer treatment settings, concurrent use may be warranted and as disease severity changes, so too can exposure to concurrent use. Confounding with these cases should be limited in numbers since most of the concurrent use is for other health conditions, such as chronic non-cancer pain. The time trend bias will also have minimal impact. BZDs have been around for a long time and use of these agents has been relatively stable over the past decade.[28] Misclassification of exposure to BZDs use in the opioid population is possible. Although administrative databases will be used to accurately classify if a patient received a BZDs or opioid, there is still the possibility that patients were not actively consuming the medications (i.e., potential for misclassification bias). This is a limitation

of all study designs and is not unique to the case crossover design that use administrative health database.

1.5 Summary

The focus of this research program is to characterize the concurrent use of BZDs and opioids and to quantify the effect, if any, of concurrent use on adverse health care outcomes (ER, hospitalizations, or mortality). This research has not previously been done using Canadian data. Despite the numerous practice recommendations and warnings against concurrent use, including the fact that concurrent use is now considered a risk factor for fatal opioid overdose, co-prescribing of BZDs and opioids outside of the palliative and cancer settings still remains an issue. Furthermore, certain segments of the population, namely the elderly and those taking higher doses, may be at especially high risk. This research using Alberta data aims to add to the body of knowledge regarding the use of opioids, especially in the context of poly drug use, and their place in therapy. Ultimately, this research may impact health provider behaviour when it comes to prescribing these medications.

1.6 Objectives

The objectives of this research program were:

1) To characterize the prevalence of concurrency of BZDs and opioids using 2017 Alberta population data
2) To determine in the population of prescription opioid users in Alberta, does co-prescribed BZDs and opioids increase the risk of hospitalizations or emergency visits and mortality when compared to opioid only use.

The first objective was accomplished using administrative health data from Alberta Health for the year 2017. We evaluated the following characteristics with respect to prevalence of concurrency of BZDs and opioids: age, sex, average daily OME, duration of opioid use, opioid dependence treatment, rural/urban status, median household income, number of unique health providers and number of DDDs. Although there was no hypothesis associated with this objective, we would expect relatively low prevalence of concurrency of BZDs and opioids given the numerous warnings against concurrent use, especially in high risk groups like the elderly.

The second objective was realized using a case crossover method using administrative health data from Alberta Health between the years of 2016-2018. We hypothesized that exposure to BZDs

and opioids (concurrent use) would increase the risk of hospitalization or ED visits and mortality relative to opioid use alone.

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Chapter 2: Characterization of concurrent use of prescription opioids and benzodiazepines/Z-drugs in Alberta, Canada: a population-based study

2.1 Introduction

Canada has among the highest rates of opioid prescribing in the world and since 1980, the volume of opioids sold to hospitals and pharmacies has increased by 3000% despite increasing recognition of the significant prescribing risks associated with such practices, including fatal overdoses, dependency, motor vehicle collisions, and falls and fractures among the elderly.[1,14,29] Individuals older than 65 years are especially prone to the consequences of opioids, with this group accounting for 63% of unintentional opioid poisonings and having the highest rate of opioid poisoning hospitalizations.[1,3] A similar picture exists for benzodiazepines and Z-drugs (zopiclone and zolpidem), collectively known as benzodiazepine receptor modulators because of their effects on γ-aminobutyric acid receptors.[30,31] Benzodiazepine receptor modulators are one of the most widely prescribed psychotropic compounds for anxiety disorders and insomnia.[4] Canadian clinical practice guidelines for the management of anxiety disorders and insomnia suggest that benzodiazepine receptor modulator treatment is appropriate for short term use in adults (aged 20-64) and in some cases as second line treatment.[5,6] Use of benzodiazepine receptor modulators outside of these recommendations is considered "potentially inappropriate" given the potential for adverse effects, especially in those over 65.[4,5,9] For example, the risk of motor vehicle accidents, falls and hip fractures leading to hospitalization and death can more than double in older adults taking benzodiazepines.[10] A 2006 study in British Columbia found that 3.5% of the population were considered "long term" users of benzodiazepines and 47% were over the age of 65.[7] Furthermore, a recent study reported that 10% of Albertans in 2015 received a benzodiazepine with the prevalence of use increasing with age.[8]

Given the similar concerns with prescribing and associated adverse outcomes, concurrent use of opioids and benzodiazepine receptor modulators is strongly discouraged for most patients.[12,14,15] Other studies have evaluated the characteristics of concurrent use. One American study found that concurrency was more common in chronic opioid users, women and the elderly.[19] However, this study did not stratify concurrent use by daily oral morphine equivalents. Two other studies using data from the US further described a rising trend in concurrent use of opioids and benzodiazepine receptor modulators.[32,33] No studies were found that used Canadian data. There are no specific clinical guidelines on indications for concurrent use of these medications and in fact, expert perspectives warn that opioids and benzodiazepines should very rarely be prescribed together. [14,15,34] Furthermore, studies and safe medication use guidelines have identified concurrent use of these medications as a risk factor for fatal opioid overdose.[1,15] In Canada, national and provincial initiatives have aimed at reducing inappropriate opioid and benzodiazepine prescribing, as well as decreasing the potential for harm. [12,14,15]

Alberta has implemented procedures around the individual prescribing of opioids and benzodiazepine receptor modulators. Both of these medication classes have been actively monitored in Alberta since 1986 through the Triplicate Prescription Program (TPP), a prescription drug monitoring program in which prescribers must register with in order to prescribe a TPP medication. However, previous literature suggests that benzodiazepine receptor modulators and opioids cannot be targeted by safe use policies in isolation.[35] There is very little published data on concurrent use, and none in Alberta, Canada. Thus, the objective of this study is to expand our understanding of concurrent use of opioids and benzodiazepine receptor modulators by characterizing the prevalence of concurrent use among opioid users using administrative data from the province of Alberta in 2017.

2.2 Methods

Study Population

This study included all individuals in Alberta with at least one dispensation record from community pharmacies for an opioid between January 1, 2017 to December 31, 2017.

Data Sources

Data from Alberta Netcare's Pharmaceutical Information Network (PIN) was used for this study. PIN data includes >95% of all dispensations from community pharmacies in Alberta irrespective of insurance coverage, thus providing comprehensive data on all medication dispensations (from all prescriber types) occurring in the province outside of the hospital setting.[36] Information on dispensed medication (drug identification number, dispense date, days supply, quantity, strength, name, directions), patient (age, sex, unique patient identifier) and prescriber (type and license number) was available. The validity of the days supply variable for each dispensation was evaluated to ensure it fell within a plausible clinical range based on the defined daily dose for a single dispensation; less than 0.01% of the days supply values were deemed to be outside of this range and a new days supply was imputed based on an individual's historical average for a particular ingredient. All unique identifiers (patient, prescriber) were anonymized for the purposes of this analysis which was approved by the health ethics research board at the University of Alberta (#Pro00083807).

Study Measures

All opioid and benzodiazepine receptor modulator dispensations were retrieved from PIN for 2017. An opioid user was defined as anyone who received at least 1 dispensation for an opioid. Patient characteristics considered in other studies [19,32,33], as well as any additional clinically relevant characteristics available in the administrative databases were examined to identify factors associated with concurrent use. Chronic opioid use was defined as total opioid days greater than 90, as others have [14], or more than 10 opioid dispensations in one year. An opioid dependency treatment (ODT) user was anyone that was dispensed a prescription for methadone or buprenorphine/naloxone. Postal codes

(forward sortation index) were used to categorize individuals as rural/urban and into income categories (<50k, 50-75k, 75-100k, 100-125k, >125k). Average daily oral morphine equivalents (OME's) and number of daily defined doses (DDDs) were calculated for all opioids and benzodiazepine receptor modulators, respectively, using the conversion factors specified by the TPP[23]. Methadone and buprenorphine were excluded from OME specific analyses. We used daily OME thresholds of <50, 50-90 and > 90 as categories in our analyses since these are clinically accepted in the guidelines for determining the risk/benefit profile when prescribing opioids for pain.[15]

The key variable of interest was whether an opioid user also used a benzodiazepine receptor modulator concurrently in 2017. Although we were not able to directly observe utilization of these medications by individuals, we considered "use" as any day on which an individual had a supply of medication on hand based on the date and days supply of each dispensation. Using the dispensation information from PIN, we generated binary variables for each day of the year to indicate if it was "covered" by an opioid or benzodiazepine receptor modulator. Beginning on the dispensation day, each day was categorized as covered until the end of the days supplied. For each patient, a day was categorized as concurrent if it was covered by both an opioid and benzodiazepine receptor modulator. We then calculated the number of days, both cumulative and consecutive, that were categorized as concurrent. For example, if a patient received a 30-day opioid dispensation on Jan 1 and a 20-day benzodiazepine receptor modulator dispensation on Jan 20, this would be quantified as 11 days of concurrent use. In our main analyses, concurrency was defined as having 1 or more days categorized as concurrent.

Statistical Analyses

We conducted a descriptive analysis to examine the characteristics of concurrent use of opioids and benzodiazepine receptor modulators. All summary statistics were calculated using the denominator of total population of opioid users in Alberta for 2017.

The measure of interest was prevalence of concurrent use by age, sex, average daily OME thresholds (<50, 50-90, >90), duration of opioid use (chronic (as defined previously) vs intermittent), opioid dependence therapy (ODT), rural vs urban residence , number of unique providers, median annual household income thresholds, and number of DDD's of benzodiazepine receptor modulators. Analyses were also stratified by the total days of cumulative concurrency (1-7, 8-30, 31-90, >90) and consecutive days of concurrency (1-7, 8-30, 31-60, 61-90, >90). We used chi^2 tests of independence to compare prevalence proportions between the different groups in the above-named characteristics. All analyses were performed using STATA/MP 13.1 (StataCorp., College Station, TX).

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. There are no plans to disseminate the results of the research to study participants.

2.3 Results

There were 547,709 Albertans who received at least one dispensation for an opioid and qualified as an opioid user (Figure 1). Females represented 53% (n=292,396) of opioid users, 18% (n=98,083) were over the age of 65 years, and the majority of patients were from urban areas (84%) (Table 1). Overall, 20% (n=108,604) of opioid users were considered chronic users and ODT patients represented 1.7% (n=9139) of opioid users. When methadone and buprenorphine were excluded, 88% (n=468,863), 9.5% (n=51,033) and 2.8% (n=14,933) represented those in the <50, 50-90, and >90 OME categories, respectively. A substantial number of patients received opioids from 3 or more pharmacies (7%) or from 3 or more prescribers (16%).

Among the 547,709 opioid users, 24% (n=132,156) received a benzodiazepine receptor modulator and 17.6% (n=96,581) had at least one day of concurrent use of an opioid and a benzodiazepine receptor modulator during 2017. The mean total days of concurrency over the entire year was 98 (SD=114) days (median of 37 (IQR 10-171)). Among patients with concurrent use, a substantial number had high durations of concurrent use during the year; 53% had over 30 days of concurrency and 36% had over 90 days of concurrency (Table 2). When we examined the duration of consecutive days of concurrency, the mean longest duration was 45 (SD=60) with a median of 24 days (IQR 8-59). Most concurrent patients (64%) had concurrent use for less than 30 consecutive days (Table 2).

Differences in concurrency were noted based on sex, urban/rural status, and median household incomes, with the prevalence of concurrency being highest among the lowest incomes, as well as a strong trend in age (Table 1, Figure 2). Indeed, <2% of all opioid users under the age of 20 years used a benzodiazepine receptor modulator concurrently relative to nearly 30% of those over the age of 65 years. The highest concurrence was observed in the highest age groups, who are also most at risk of severe adverse events (Table 3). Concurrency was more common in chronic opioid users compared to intermittent users (Table 1). Similarly, chronic opioid users had a higher number of concurrent days in the year compared to intermittent users (Table 4).

Characteristics associated with potentially inappropriate use of opioids (e.g., older age, high OME's, multiple providers) had substantially higher concurrent benzodiazepine receptor modulator use (Table 1, Figures 2-4). Although the absolute number of patients using an average daily OME >90 was low (2.8% of opioid users), 46% had concurrent use with a benzodiazepine receptor modulator. Among concurrent users in the > 90 OME category, 58.8% had concurrent use >90 days (Figure 3) and 12.8% of those with > 90 days of concurrent use were also taking > 90 OME per day (Figure 4).

There were also clear trends with respect to providers. As the number of unique providers increased, so too did the prevalence of concurrency. Although the absolute numbers were low (<5%), the opioid users that visited more than 5 pharmacies or prescribers in 2017 both had a prevalence of concurrency of 62% (Table 1). Opioid users who received a benzodiazepine receptor modulator, either concurrently or not, visited more providers compared to those who received only an opioid or benzodiazepine receptor modulator (Figure 5). Interestingly, among concurrent users, 78% (n=74882) received an opioid and benzodiazepine receptor modulator from the same prescriber and 94% (n=90561) from the same pharmacy. Moreover, 58% of concurrent users (n=56098) received an opioid and benzodiazepine receptor modulator on the same day from the same prescriber while 64% (n=61715) received an opioid and benzodiazepine receptor modulator from the same pharmacy on the same day.

The trend between number of DDD's of benzodiazepine receptor modulators and concurrency is similar to that with average daily OME's. Most of the opioid patients concurrently used a benzodiazepine receptor modulator at the lowest number of DDD's (66%). However, around 88% of those using >2-3 times the DDD were concurrent users (Table 1).

2.4 Interpretation

Many reputable clinical resources indicate that benzodiazepine receptor modulators should not be combined with opioids, yet this study showed that nearly 20% of patients using an opioid did so in combination with a benzodiazepine receptor modulator in Alberta [12,14,15]. Those on >90 mg OME had the highest prevalence of concurrency when compared to lower doses. Moreover, among concurrent users, total days of concurrency was high with about half of these patients using opioids and benzodiazepine receptor modulators at the same time for more than 30 days. Perhaps not so surprising is the high prevalence of concurrency in those with a greater number of distinct prescribers. In addition, our observation of a higher prevalence of concurrency in chronic opioid users compared to intermittent users was expected since prolonged opioid use provided more opportunities for concurrent use. These

results should be concerning to clinicians and policy makers because the potential for adverse outcomes associated with opioid use is greatly increased since a significant proportion of opioid fatalities involve benzodiazepine receptor modulators.[1,11]

Our observation that concurrent use of a benzodiazepine receptor modulator occurred in 20-25% of opioid users was similar to the recent Vozoris study using data from the United States.[33] While both studies also found a higher prevalence of concurrency in females than males, this difference was not significant after adjusting for covariates in the Vozoris study. One reason for this discrepancy may be the underlying patterns of benzodiazepine receptor modulator use; in Canada, these drugs are used more frequently in females than males [37]. Our observations that concurrency increased with age and was prevalent in nearly 30% of opioid users > 65 years of age contrasts with previous studies. For example, Vozoris reported a trend towards decreased concurrency among patients 60 years and older [33], and Hwang and colleagues reported concurrency in <20% of elderly patients.[19] Possible reasons for the discrepancy in age related trends include differences in study methodology (survey data versus administrative data), study population (increasing use of benzodiazepine receptor modulators amongst the elderly in Canada and Alberta [37-39]), our inclusion of Z drugs to identify benzodiazepine receptor modulators, and prescriber perception of safety of Z drugs over benzodiazepines [40]. Regardless, the high prevalence of concurrent use among those over 65 years is especially concerning because they are at high-risk for adverse clinical outcomes. Indeed, many clinical guidelines advise against prescribing benzodiazepines in most seniors, let alone in combination with an opioid.[41,42] Furthermore, patients aged 65 years and older consistently have the highest rates of hospitalization due to opioid poisoning.[3]

To date, we are unaware of other studies that have suggested those taking very high daily doses of opioids (>90 OME per day) also have high concurrency rates. Irrespective of the reason for concurrent use (i.e., opioid use disorder and doctor shopping or when used for more appropriate indications) the evidence suggests that high dose opioid users have up to 5x the risk of overdose and those above 100

OME have a much higher risk of fatal over dose.[15,43] Combining opioids and benzodiazepine receptor modulators in these groups could certainly contribute to further adverse outcomes already at high rates.

Although concurrent use of opioids and benzodiazepine receptor modulators is often deemed clinically inappropriate, beyond substance use disorder situations, one has to question why the observed prevalence is so high despite the numerous efforts across the country, and in Alberta, to mitigate this high-risk prescribing. In the groups with the highest concurrent use (females, ODT patients, chronic and high dose opioid users, elderly, etc.), most, if not all, are known to have a higher prevalence of conditions related to pain and mental health.[44-46]. Our results showed that 78% of concurrent users received both medications from the same prescriber and 94% from the same pharmacy with over half receiving these drugs on the same day. There is an opportunity here to educate providers about the risks of concurrent use and to verify if concurrent use is truly appropriate. Furthermore, treatment emphasis in chronic pain and mental health patients is changing where opioids and benzodiazepines are no longer first line treatment options and where integrated and multidisciplinary treatments are preferred.[47] Connecting patients with these preferred treatment modalities is often difficult because of cost and time and often opioids and /or benzodiazepines are used to address the unmet needs of patients.

The strengths of our study included the large population-based sample with near complete capture of all opioid and benzodiazepine receptor modulator dispensations occurring in community pharmacies within the province. Pharmacies in Alberta are mandated by the College of Pharmacy to ensure accurate prescription records such that use of PIN data can accurately capture most, if not all, of the opioid and benzodiazepine receptor modulator dispensations and the information provided with each of these dispensations. Another strength is that our analyses included average daily OME's when characterizing concurrent use, something that we have not seen in other studies. There are, however,

some limitations in our study. First, we are assuming that patients took their medications as dispensed. Medication adherence in opioid users is a challenging issue.[48] We assumed that days supply was entered correctly by pharmacies when calculating our OME and DDD values, however no validation of the PIN days supply field has been completed to date. Second, our study was limited to descriptive analyses and does not provide outcomes data from concurrent use. Clinically, there are instances where concurrent use may be considered appropriate, especially in palliative care and cancer treatment settings. Information on the indications for concurrent prescribing were not available in the PIN database used for this study.

Despite these limitations, Alberta still has an alarming prevalence of concurrent use. The opioid crisis in Alberta and Canada is being driven in part, by prescription opioids.[21] However, due to wide spread attention to the opioid crisis, the number of opioid prescriptions and morphine milligram equivalents prescribed sharply declined in all provinces in 2016 and 2017, including Alberta.[49,50]. It is clear that continued efforts are required to curb the concurrent utilization of opioids and benzodiazepine receptor modulators in the province, and elsewhere as it is unlikely Alberta is unique in this regard. Furthermore, as increasing clinical emphasis is being placed on non-pharmacologic management of chronic pain and not prescribing opioids to patients with mental-health disorders, as well as ongoing monitoring and educational campaigns, we will hopefully see a decrease in concurrent use.[12,13,15,46]

Table 1. Summary statistics of prevalence of concurrency^ among opioid users and possible high -risk markers.

Characteristic (among opioid users)	N (%)	Prevalence of concurrency within characteristic. Percent (n)[#]	Prevalence of concurrency among all opioid users. Percent (n=547709)	Percent of concurrent users (n)
Opioid users	547709 (100)	17.6 (96581)[##]	---	---
Sex:				
Male	255293 (46.6)	14.9 (37955)	6.9	39.3 (37955)
Female	292396 (53.4)	20.0 (58620)	10.7	60.7 (58620)
Average daily OME*:				
<50	468863 (87.7)	15.7 (73411)	13.7	80.2 (73411)
50-90	51033 (9.5)	22.1 (11287)	2.1	12.3 (11287)
>90	14933 (2.8)	46.2 (6899)	1.3	7.5 (6899)
Duration of opioid use**:				
Chronic	108604 (19.8)	47.1 (51214)	9.4	53.0 (51214)
Intermittent	439105 (80.2)	10.3 (45367)	8.3	47.0 (45367)
ODT	9139 (1.7)	37.2 (3401)	0.62	3.5 (3401)
Not on ODT	538570 (98.3)	17.3 (93180)	17.1	96.5 (93180)
Postal code zone:				
Rural	85666 (15.6)	22.0 (18809)	3.4	19.5 (18809)
Urban	462043 (84.4)	16.8 (77772)	14.2	80.5 (77772)
Median Household Income (x 1000)				
<50	107240 (19.6)	23.1 (24781)	4.5	25.7 (24781)
50-75	261354 (47.2)	17.9 (46725)	8.5	48.4 (46725)
75-100	151352 27.6)	14.2 (21496)	3.9	22.3 (21496)
100-125	27314 (5.0)	12.9 (3514)	0.6	3.6 (3514)
>125	448 (0.08)	14.5 (65)	0.01	0.07 (65)
# of unique dispensing pharmacies:				
1	426557 (77.9)	12.0 (51413)	9.4	53.2 (51413)
2	82048 (15.0)	31.1 (25550)	4.7	26.4 (25550)
3	23155 (4.2)	45.3 (10482)	1.9	11.0 (10482)
4	8260 (1.5)	53.1 (4387)	0.80	4.5 (4387)
5+	7689 (1.4)	61.8 (4749)	0.88	4.9 (4749)
# of unique prescribers:				
1	352596 (64.4)	7.1 (25158)	4.6	26.0 (25158)
2	107347 (19.6)	25.9 (27805)	5.1	28.8 (27805)
3	42656 (7.8)	42.2 (17990)	3.3	18.6 (17990)
4	20126 (3.7)	50.5 (10163)	1.9	10.5 (10163)
5+	24984 (4.6)	61.9 (15465)	2.8	16.0 (15465)
Age:				
0-17	20366 (3.7)	1.5 (307)	0.06	0.3 (307)
18-65	429259 (78.4)	16.3 (70000)	12.8	72.5 (70000)
>65	98083 (17.9)	26.8 (26274)	4.8	27.2 (26274)
Number of benzodiazepine DDD's				
0-1	94192 (71.3)	67.4 (63531)	11.6	65.8 (63531)
1-2	30423 (23.0)	86.7 (26370)	4.8	27.3 (26370)
2-3	4761 (3.6)	89.1 (4243)	0.77	4.4 (4243)
>3	2780 (2.1)	87.7 (2437)	0.44	2.5 (2437)

^ Concurrency is defined as 1 or more days of overlap between an opioid and benzodiazepine receptor modulator.

*methadone and buprenorphine patients were excluded.

**chronic opioid users were defined by having at least 90 days of cumulative opioid use or at least 10 opioid prescriptions in the year. This includes ODT patients.

p-value for chi^2 test of independence (difference between prevalence of concurrency between groups within characteristic) <0.001 for all characteristics.

95% confidence interval for prevalence of concurrency=17.5-17.7

Table 2. Characteristics of concurrent use (n=96,581)

Characteristic	%
Total days of cumulative concurrency	
Mean (SD)*	**98 (114)***
1-7	**21**
8-30	**26**
31-90	**17**
>90	**36**
Longest Duration of consecutive concurrency	
Mean (SD)*	**45 (60)***
1-7	**24**
8-30	**40**
31-60	**13**
61-90	**8**
>90	**14**

***Days**

Table 3. Prevalence of Concurrency by Age group and total days of concurrency among opioid users (%)

	Days of Concurrency				
Age Group	**1-7**	**8-30**	**31-90**	**>90**	**Total (n=)**
0-9	0.76	0.06	0.06	0.12	1669
10-19	1.4	0.4	0.1	0.1	30551
20-29	3	2	1	2	68710
30-39	3	3	2	4	92549
40-49	4	4	3	7	93387
50-59	4	6	3	9	107917
60-69	4	6	4	10	83267
70-79	5	7	5	10	43973
80-89	6	9	6	9	21029
>90	8	8	5	9	4656
Total (n=)	20503	25614	15940	34524	547708

Table 4. Prevalence of Concurrency by category of Opioid Use and total days of concurrency. (p-value < 0.001)

Days of cumulative concurrency	% Intermittent users (n=439,105)	% Chronic users (n=108,604)
1-7	4.1 (18,163)	2.2 (2,340)
8-30	4.5 (19,712)	5.4 (5,902)
31-90	1.7 (7,492)	7.8 (8,448)
>90	0 (0)	31.8 (34,524)

Figure 1. Patient flow diagram of denominator used for analyses

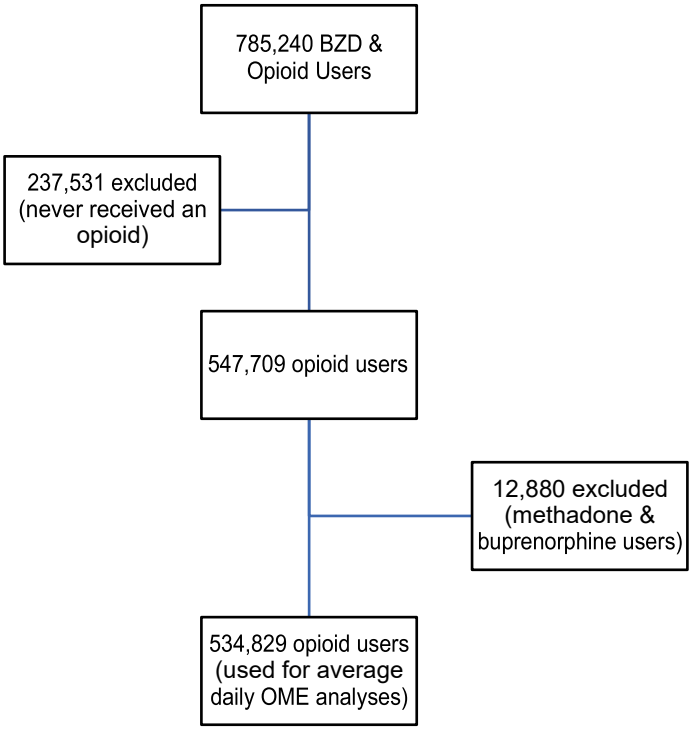


Figure 2. Prevalence of concurrency by age group among all opioid users in 2017 (n=547,708).

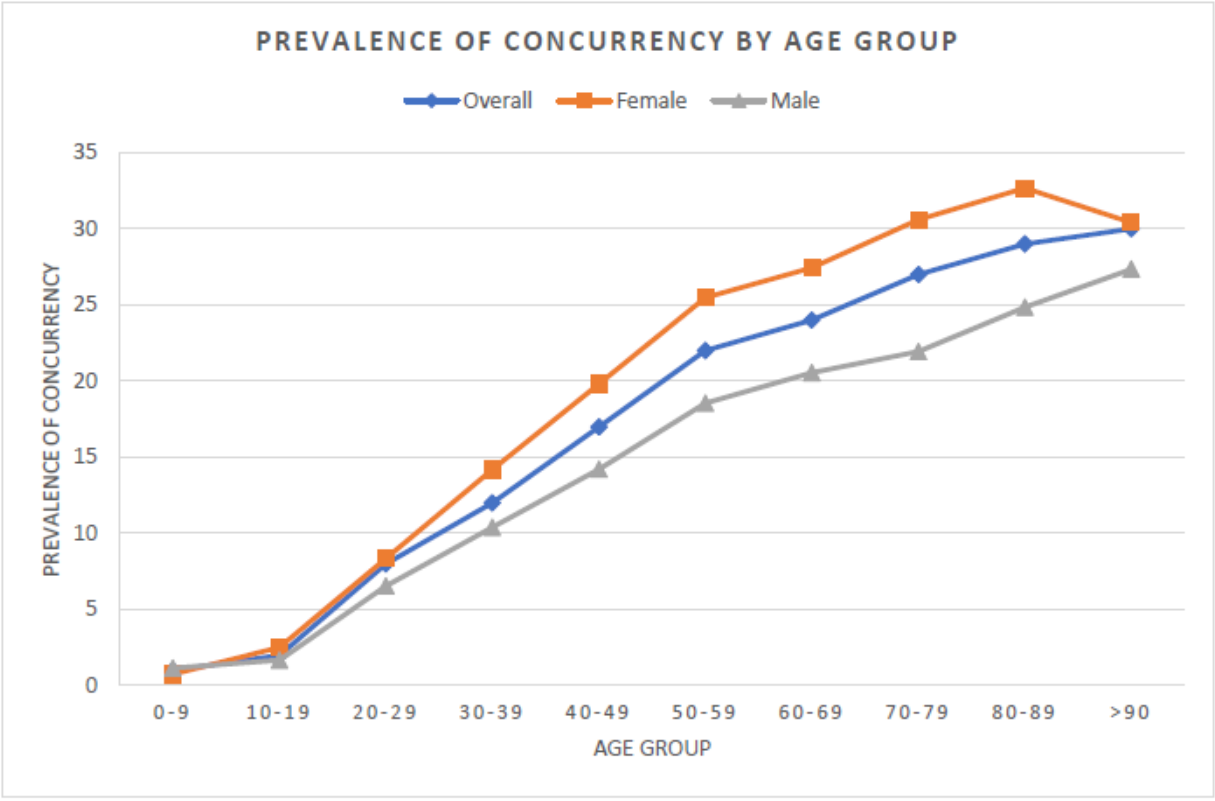
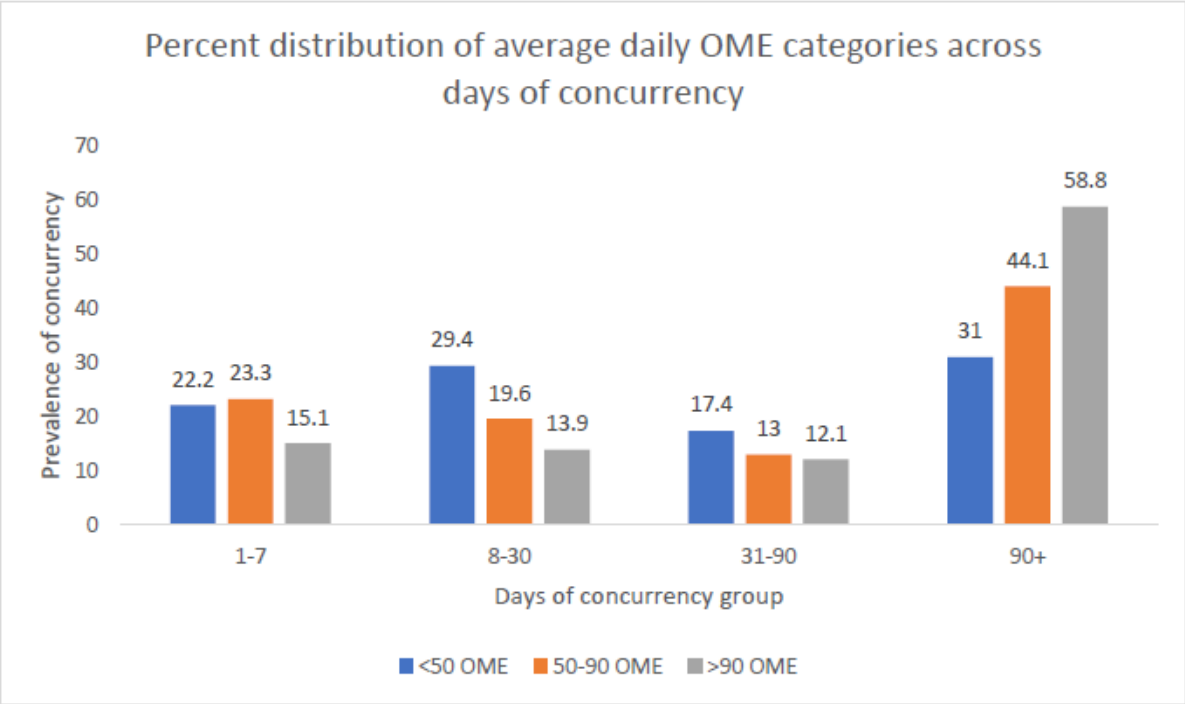
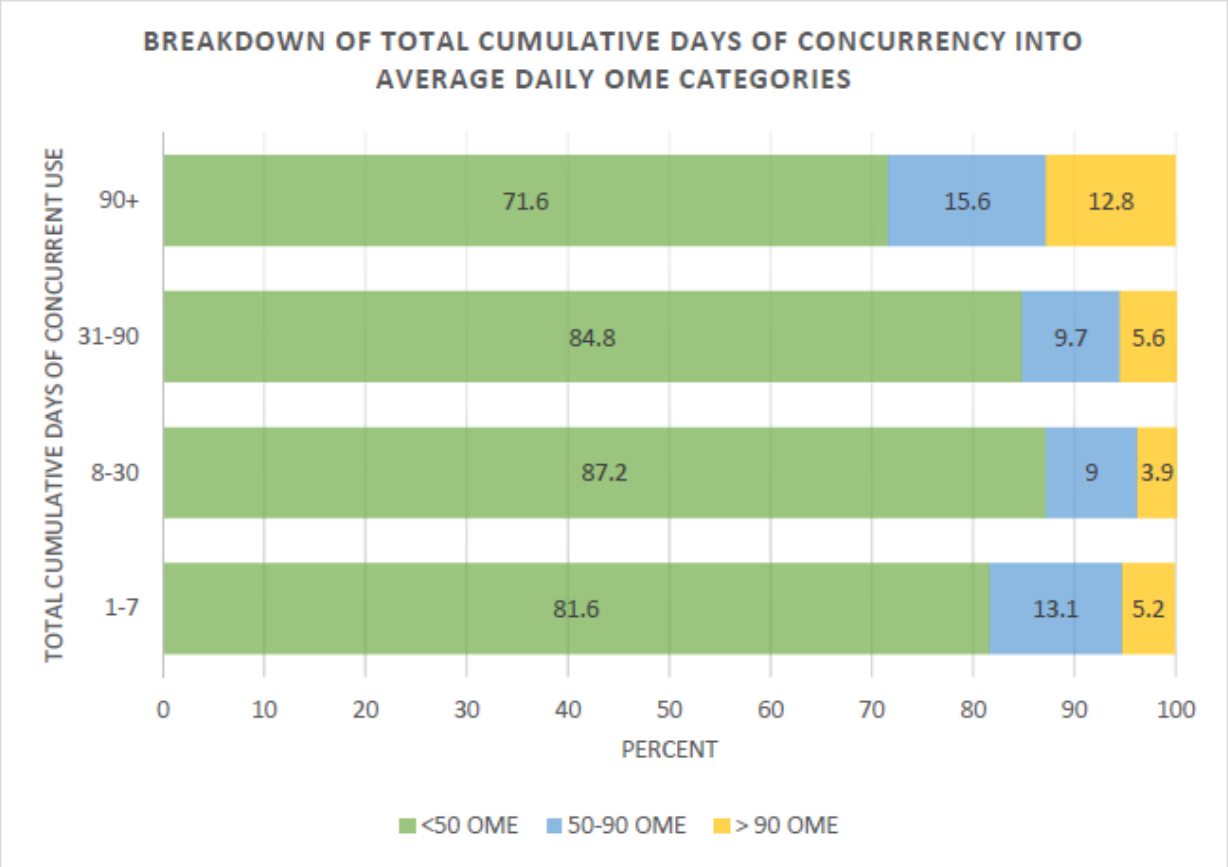


Figure 3. Prevalence of concurrency by total days of concurrency and average daily OME category in 2017 (n=91597)*.



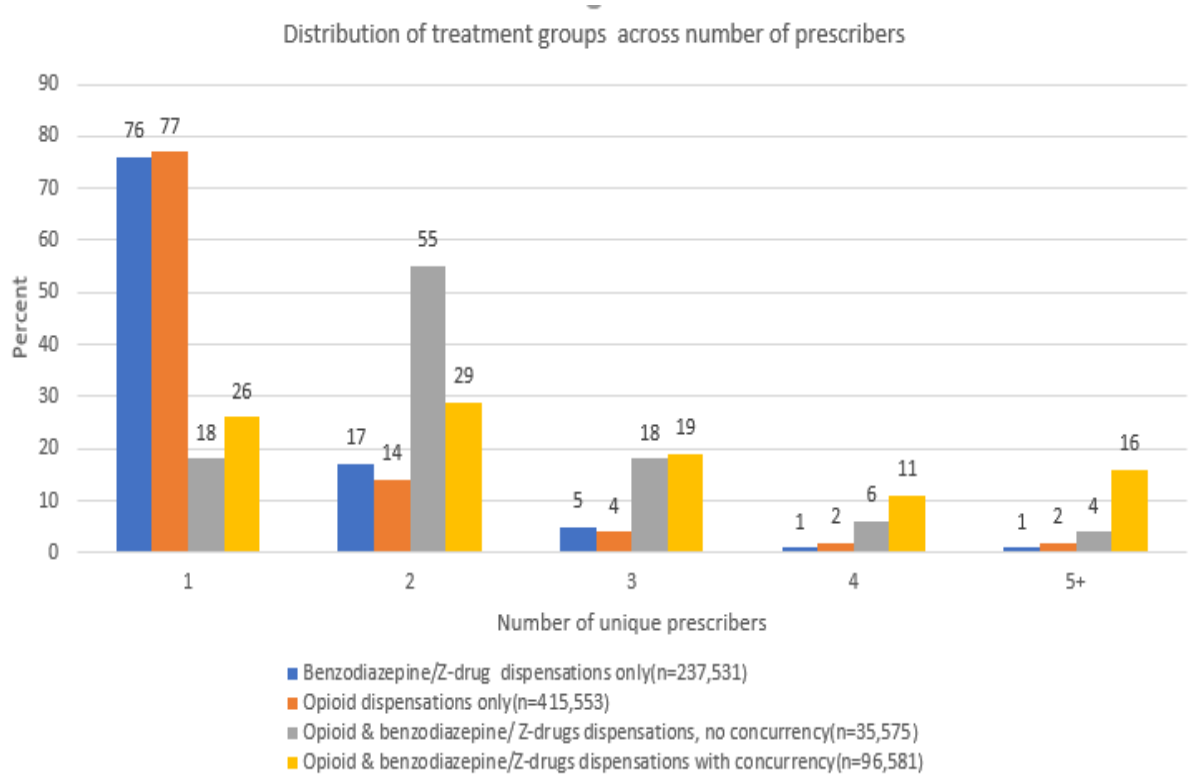
*** Excludes methadone and buprenorphine.**

Figure 4. Percent distribution of average daily OME categories within categories of total cumulative days of concurrent use (n=91597)*



*** Excludes methadone and buprenorphine.**

Figure 5. Distribution (percentage) of patient categories by number of unique prescribers



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Chapter 3 Concurrent use of opioids and benzodiazepines/Z-drugs and risk of hospitalization and death: case crossover study

Introduction

Canada has among the highest rates of opioid prescribing in the world and since 1980, the volume of opioids sold to hospitals and pharmacies has increased by 3000% despite increasing recognition of the significant risk associated with such prescribing practices, including fatal overdoses, dependency, motor vehicle collisions, and falls and fractures among the elderly [1,14,29]. Individuals older than 65 years are especially prone to the consequences of opioids[1,3]. The policy response to the opioid crisis has focused on establishing guidelines for safe and appropriate prescribing of opioids [14,51]. A similar picture exists for benzodiazepines and Z-drugs (zopiclone, zolpidem), collectively known as benzodiazepine receptor modulators (BZDs). BZDs are widely prescribed psychotropic compounds for anxiety disorders and insomnia [17]. Canadian clinical practice suggest that BZD treatment may be appropriate for short term use only in adults [5,6]. Use of BZDs outside of these recommendations is considered potentially inappropriate given the potential for adverse effects, especially in those over 65 [5,9,10,17] years. However, Canadian data have shown high prevalence of BZD use (up to 47%) among the elderly [7,8]. Furthermore, receipt of BZDs could be a marker of mental illness, which carries its own risk of mortality [52,53].

In the context of the opioid crisis, concurrent use of opioids and BZDs represents a lesser known drug use pattern that is of substantial concern because of the increased risk of mortality [11,20,51]. Although there are no specific clinical guidelines on indications for concurrent use of opioids and BZDs, there are numerous evidence based recommendations warning against concurrent prescribing of these medications [14,15,51] and previous literature suggests that opioids and BZDs should not be targeted in isolation by safe use policies [35]. Despite these warnings, opioids and BZDs are still being co-prescribed at alarming rates. Indeed, data from the US show an increasing trend in co-prescribing of opioids and BZDs

[11,19,33] and 50% of opioid related deaths in Ontario and Manitoba, Canada involved BZDs [54,55]. Furthermore, 2 large studies in the US showed that concurrent use of opioids and BZDs carried a higher risk of hospital admission and mortality than opioid use alone [11,20]. However, the Canadian studies did not quantify the risk associated with concurrent use and the two US studies used populations limited to US military veterans and those who were privately insured. Studies in other countries have also reported high prevalence of concurrent use of opioids and BZDs [56-58], but have not explored the risk of hospitalization or mortality associated with this pattern of use. Thus, the risk associated with concurrent opioid and BZD use in a general population remains unknown.

To our knowledge, no broad population-based studies have quantified the effect of concurrent opioids and BZD use on outcomes such as hospitalizations and mortality using the characteristics that we and others have identified as relevant[11,20]. Using a case crossover study design, we aimed to examine the association between concurrent use of opioids and BZDs and adverse health outcomes. We hypothesized that concurrent use would increase the risk of these outcomes. Our results will help fill an evidence gap on the adverse outcomes associated with concurrent prescribing of opioids and BZDs.

Methods

Data Sources

Multiple distinct databases from Alberta Health were linked together to establish a complete description of drug exposures and health outcomes. These unique databases are linkable at the patient level through individual patients' Personal Health Numbers; all information was anonymized. These databases include: ***Pharmaceutical Information Network (PIN):*** PIN data includes all Alberta dispensing records from community pharmacies as per Alberta College of Pharmacy guidelines[59] occurring outside of the hospital setting. PIN collects all dispensations irrespective of age or insurance status in Alberta, ***Population and Vital Statistics Data:*** *contain death dates for Alberta residents,* ***Hospitalizations and Emergency Department Visits: National Ambulatory Care Reporting System (NACRS) and Discharge***

Abstract Database (DAD)[60], and ***Physician Visits (Alberta Health):*** date of service, a single ICD-9 code associated with the claim, procedure and billing information. This study was approved by the health ethics research board at the University of Alberta (#Pro00083807).

Identification of Patients

Using this linked administrative data, we identified all opioid users in Alberta, defined as anyone who received at least 1 dispensation for an opioid during the study periods described below. To maximize use of the data, two distinct analysis cohorts were generated. For the hospitalization and emergency department (ED) analyses, all subjects in Alberta, Canada who received a dispensation for an opioid between Jan 1, 2016 and Dec 31, 2018, 18 years of age and over were included. For mortality analyses, all subjects who received a dispensation for an opioid between Jan 1, 2016 to Dec 31, 2017 were included. This distinction was required as mortality data was not yet available for 2018 as reporting is 12-24 months delayed in the province.

Outcomes

Our primary outcomes were all-cause, incident hospitalization or ED visits and all-cause mortality. The secondary outcomes were incident hospitalization or ED visit attributable to mental health and opioid toxicity (Table 1). The international classification of disease (ICD) 10th revision code from the most responsible diagnosis was used to determine if the admission was related to these conditions. These endpoints maybe more specific to the population using BZD and opioids. Cause of death is not reliably recorded in the province to allow for specific cause of death analyses.

Exposure

For our cohort of opioid users, the exposure of interest was whether an opioid user also used a benzodiazepine/Z-drug (BZD) concurrently during the study period. We considered "use" as any day on which a patient had a supply of medication on hand on the basis of the date and days' supply of each dispensation as others have [11]. Using the dispensation information from PIN, we generated binary variables for each day of follow up to indicate if it was "covered" by an opioid or BZD. Beginning on the dispensation day, each day was categorized as covered until the end of the days supplied. For each patient, a day was categorized as concurrent if it was covered by both an opioid and BZD (Figure 1).

For every patient in our opioid cohort, each day of follow up was categorized into one of four mutually exclusive groups of exposures: **1)** neither opioid nor BZD use (none), **2)** opioid only use, **3)** BZD only use and **4)** concurrent use of opioid and BZD (concurrent).

Study Design and Statistical Analyses

An opioid user was defined as anyone who received at least 1 dispensation for an opioid and concurrent use was defined as at least 1 day of overlap between an opioid and BZD. Health care utilization was defined by number of unique providers visited and number of opioid prescriptions dispensed. The opioid molecules that were considered in all analyses are specified in Table 4.

We first undertook descriptive analyses to determine the prevalence of concurrency with a BZD among opioid users with an incident hospitalization or ED visit. We characterized concurrent users and opioid only users by providing summary statistics using the following characteristics: sex, age at admission, health care utilization, total days of cumulative concurrency and opioid use, level of morbidity defined using the Elixhauser Comorbidity Index[61], opioid molecule, and average daily dose (oral morphine equivalents (OME)). OME's of <50, 50-90 and >90 were used as categories since these are clinically accepted in Canadian guidelines for determining the risk/benefit profile when prescribing opioids for pain [14,15]; buprenorphine and methadone were excluded from all OME analyses.

We then used the case-crossover design to estimate if concurrent use of opioids and BZDs was associated with an increased risk of our defined outcomes when compared to opioid only use. In a case crossover study, each person serves as their own control; consequently, eliminating confounding due to age, sex, and other fixed patient factors [24] that are unlikely to change during the cross-over periods. This methodology is increasingly being utilized to evaluate exposures encountered in pharmacoepidemiology and when using administrative databases [24-26]. All patients who experienced the previously defined outcomes (event) during the study period were identified. Then for each patient, a "case window" was defined as the 7 days immediately preceding the event (Figure 2). As per the case cross over design, we also identified a control window (7-day period one month prior to the event). We chose the one month time period based on other published pharmacoepidemiology studies using this methodology [62]. In essence, this approach allows the comparison of the exposure the patient was receiving immediately prior to the event (one of the four previously defined exposure groups) relative to the control window exposure profile when no event occurred.

Conditional logistic regression[63] was used to contrast the four defined exposure groups in the seven-day risk period immediately before the event with the seven-day control period one month earlier. For each of the defined exposure groups, we estimated the risk of incident hospitalization/ED visits and mortality using odds ratios and their associated 95 percent confidence intervals. The opioid only exposure group was used as the reference group in order to estimate the risk of concurrent use relative to opioid only use. The analyses were stratified into the following sub-groups: sex, age at admission or death (20-40, 40-65, >65; 18-45, 46-65, >65), total days of cumulative concurrency (1-30, 31-90, 91-180, 181-365, >365), total days of opioid use (1-7, 8-30, 31-90, 91-180, 181-365, >365), health care utilization (number of unique pharmacies and prescribers visited; 1,2,3,4,>5), opioid molecule and daily dose (OME). All analyses were performed using STATA/MP 15.1 (StataCorp., College Station, TX)

Sensitivity Analyses

First, we performed the primary statistical analyses on the overall population that excluded cancer and palliative patients like others have [20,64] since all of the opioid use guidelines are in the context of chronic, non-cancer pain. We assumed patients had cancer or were palliative if they had any of the ICD codes for cancer or palliative care (Table 1) at any time between 2012-2017. Second, we changed the length of the exposure assessment windows to 3 and 10 days. Last, we added a second control period that preceded the event by 2 weeks.

Results

There were 1,056,773 patients in Alberta classified as opioid users that were hospitalized or visited the ED during 2016-2018. Among this cohort, 17% (n=179,805) had at least one day of concurrent use with a BZD. Similarly, there were 31,998 patients who died during 2016-2017 and 34.5% (n=11,055) had at least one day of concurrent use.

Differences in concurrency were noted based on sex, age, healthcare utilization, duration of opioid use, opioid molecule and dose (Table 2). Females represented 60% of concurrent patients while those aged 41-65 represented half of all concurrent patients. A strong trend in concurrent use was noted in healthcare utilization; as healthcare utilization increased, so too did the proportion of concurrent patients with 37% and 29% of concurrent patients visiting >5 unique prescribers and >5 pharmacies, respectively (Table 2). This same trend was also noted for duration of opioid use with 52% of concurrent patients having >90 days of cumulative opioid use. Notable differences were also observed when the concurrent patient group was compared to the non-concurrent group with respect to the characteristics. Concurrent patients were older (median age 56 vs 47) with much higher healthcare utilization and higher morbidity scores (Table 2). Furthermore, concurrent patients had double the prevalence of >90 OME opioid prescriptions when compared to non-concurrent patients.

Hospitalizations or Emergency Department visits

With respect to hospitalizations or ED visits, compared to opioid only use, concurrent use of opioids and BZDs was associated with an elevated risk of hospitalization or ED visit ((prevalence of exposure to concurrent use in control and case windows, respectively:2.1% vs. 3.3%); OR 1.13; P<0.001). After stratification, those over 65 years of age (3.6% vs. 4.8%; OR 1.5; P<0.001) and those visiting >5 health providers (13.0% vs. 16.5%; OR 1.67; P<0.001) had the highest risk associated with concurrent use and hospitalizations or ED visits. There was a slight difference in risk when comparing sex with females (2.8% vs. 3.8%; OR 1.19; P<0.001) having a higher risk than males (2.1% vs. 2.9%; OR 1.10; P<0.001). With respect to total days of concurrency, although any duration of concurrency was associated with a substantial increase in risk, one of the highest risks was observed in those that had concurrent use of less than a month (1-30 days) (1.4% vs. 5.8%; OR 2.47; P<0.001) (Table 3). Not unexpectant, increasing duration of use of opioids was also associated with an increasing estimated risk (Table 3).

When specific opioid molecules were examined, an increased risk of hospitalization or ED visits was noted for all opioid molecules when used concurrently with a BZD; however, fentanyl and hydromorphone used concurrently with a BZD was associated with a substantially higher risk of hospitalization or ED visit than the respective opioid molecule used alone (Figure 3). Moreover, among the concurrent patients that were hospitalized or visited an ED, morphine, oxycodone, hydromorphone and tramadol carried the highest risks when compared to codeine and used concurrently with BZDs, with hydromorphone carrying the highest risk (OR 2.65; P<0.001) (Figure 4). Morphine and hydromorphone also posed a much higher risk than codeine in males specifically (OR 3.59; P<0.001) and (OR 4.49; P<0.001), respectively (Figure 4). As expected, there was a dose response effect on estimated risk where higher OME's had higher risk of hospitalization or ED visits compared to <50 OME among concurrent patients (Figure 4).

In the secondary analyses, the estimated risk of hospitalization or ED visit was also substantially higher in concurrent patients when compared to opioid only patients for admissions related to mental health (1.81; P<0.001) or opioid toxicity (OR 1.79; P<0.001) (Table 4).

Mortality

We identified 31,998 deaths between 2016-2017 in our cohort of opioid users. Estimated risk of death was substantially higher with concurrent use when compared to opioid only use when comparing the event and control windows (12.7% vs. 18.6%; OR 1.90; P<0.001). Stratification by sex revealed a higher risk of death with concurrent use in males than in females (Table 5). Among concurrent patients, there was an opioid dose response effect on estimated risk of death with >90 OME associated with up to triple the risk when compared to <50 OME group (Table 5). Those aged 18-45 years had the highest estimated risk of death (14.3% vs. 17.1%; OR 2.26; P<0.001). Similar to the trends in hospitalizations or ED visits, there was an elevated estimated risk of death (12.1% vs. 49.1%; OR 4.93; P<0.001) during the first 30 days of concurrent use (Table 5). Furthermore, healthcare utilization, especially number of unique pharmacies visited, was associated with higher risk (Table 5).

Sensitivity Analyses

In sensitivity analyses, concurrent use and dose response effects of opioids and BZDs were still associated with a higher risk of hospitalization or ED visits and mortality when compared to opioid only users when cancer and palliative patients were excluded (Tables 6 and 7) and when the length of the exposure assessment window was changed or a second control window was added (Table 8).

Discussion

Many clinical resources warn that BZDs should not be combined with opioids [14,15,51], yet our study showed that nearly 20% of patients using an opioid did so in combination with a BZD in Alberta, Canada. Concurrent use was higher in females and nearly a third of concurrent patients were >65 years of age. A

concerning trend in adverse outcomes was observed with a near two-fold increased risk of mortality associated with concurrent BZD and opioid use.

In particular, those age >65 years, those visiting multiple health providers, and those using higher OME's were at highest estimated risks. Importantly, the data also show that one of the highest risks was observed in those who had concurrent use of less than a month with a near 2.5-fold relative increase in hospitalizations or ED visits. Although perceived to be safer, tramadol concurrently used with BZDs had a substantially higher risk than codeine, especially among females.

Our findings are consistent with two large studies done in the United States. Sun et al. reported that 17% of opioid patients concurrently used a BZD, an estimate very similar to ours [11]. Furthermore, Sun et al. showed that higher durations of opioid use also carried higher risk of hospitalization or ED visit with respect to concurrent users, a finding that we also shared. However, compared to Sun et al, our overall cohort risk was lower (OR 2.14 vs 1.13). This could be due to differences in study population and methodology; the Sun study included privately insured patients and used a retrospective analysis whereas we included all Albertans regardless of coverage and used a case-crossover design. The other study, done by Park et al., estimated risk of death among US veterans exposed to concurrent use of opioids and BZDs [20] and noted a much higher prevalence of concurrency than we did (27% vs 17%). Although both of our studies associated concurrent use of opioids and BZDs with increased risk of death, overall and in a dose dependent manner, the Park et al risk estimates were much higher than ours, almost double. Of note, however, Park et al included only veterans, which proportionally represented an older and predominantly male population compared to ours. When our mortality analysis was stratified by age, our risk of death estimates were very similar to the Park et al study. Furthermore, compared with the general population, veterans in the US have a higher prevalence of substance use disorders and mental illness, which carry their own risks [65-67]. As other studies have also observed, the estimated risk of an opioid-related death from taking 50-90 OME was double when compared to lower

OME doses [64] and this risk was amplified with the concurrent use of BZDs. Estimates from our analyses indicate that this risk could increase by a factor of 2-3x from the addition of a BZD, depending on the age of the patient. Indeed, our findings showed that adding a BZD to any opioid molecule and to any opioid dose multiplied the risk of hospitalization or ED visit or death by several fold.

Our finding that hospitalization or ED visit and mortality risks were higher during the initial periods of concurrent use are also similar to another study done in the US [68]. Both of our estimates associate a higher risk during the first few days of concurrent use.

The strengths of our study include the large population-based sample with near complete capture of all opioid and BZD dispensations from community pharmacies using PIN. As well, hospitalizations and ED visits, and mortality from Alberta Health and Vital Statistics were also used to identify our outcomes. Another strength is that our analyses was stratified by healthcare utilization and opioid molecule, something we have not seen in other studies. Since we used a case crossover design, many confounding variables would have been completely controlled for in our analysis (e.g. age, sex, co-morbidities) relative to that of other studies conducted to date, however, there could be residual confounding and bias due to the fact that opioid only users could be different than concurrent users in characteristics which our data may not capture adequately. We conducted a sensitivity analysis that excluded patients diagnosed with a malignancy and palliative status to explore these issues and our original risk estimates were preserved. Importantly, other unknown factors which may have changed between the control and case windows could have affected our results. Another limitation is that we are assuming that patients took their medications as prescribed. Medication adherence in opioid users is a challenging issue [48].

Despite all of the safe opioid prescribing guidelines[14,51], our findings show that Alberta, Canada still experiences troubling trends and risks associated with concurrent use of opioids and BZDs.

Although total prescribed OME's have declined across Canada during the past few years [49], the trend with concurrent use of opioids and BZDs is unknown and may in fact be increasing [11,19]. From a clinical perspective, prescribers should closely follow opioid use guidelines and avoid concurrent prescribing with BZDs for most clinical scenarios [14,51]. Indeed, both the relative and absolute effects are high, with a near doubling of the risk of hospitalization or ED visit or mortality with concurrent use compared to opioid-only use. This scenario presents an opportunity for providers to monitor and potentially avoid use altogether or reassess for dose tapering. Policy makers, professional regulatory bodies and colleges should reinforce safe opioid use prescribing guidelines and educate providers about the additional risks associated with concurrent use of opioids and BZDs.

Table 1. ICD codes and opioid molecules used in this study

Injury diagnoses	ICD-10 codes: S00-T79
Mental health diagnoses	ICD-10 codes: F04-F99
Opioid toxicity diagnoses	ICD-10 codes: T400-T404; T406
Opioid molecule considered in all analyses	Buprenorphine/naloxone, methadone, buprenorphine, codeine, morphine, oxycodone, oxycodone/naloxone, hydromorphone, fentanyl, tramadol, tapentadol
Sensitivity Analyses: Cancer and palliative patients excluded	ICD-10 codes: C00-D49; Z51 ICD-9 codes: 140-239; V66.7

Buprenorphine and methadone were excluded from all OME analyses

Table 2. Characteristics of opioid users with incident hospitalizations/emergency department visits in the period 2016-2018

Characteristic	Total No. (%) of patients~ *n=1,056,773**	No. (%) of concurrent users~ *n=179,805@*	No. (%) of opioid only users~ *n=876,968$*
opioid users	1,056,773 (100)	179,805 (100)	876,968 (100)
Number of dispensations for opioids	11,240,195(--)	5,855,666 (--)	5,384,529 (--)
Number of dispensations for BZRA's	6,050,709(--)	4,767,945 (--)	1,282,764 (--)
Sex:			
Female	581,457 (55)	109,128 (60.7)	472,411 (53.9)
Male	475,316 (45)	70,677 (39.3)	404,557 (46.1)
Age at admission, year,			
median (IQR)	49 (34-62)	56 (43-67)	47 (32-61)
Mean (SD)	48.7 (18.1)	55.2 (17.0)	47.4 (18.1)
10-20	48,721 (4.6)	2,276 (1.3)	46,445 (5.3)
21-40	339,380 (32.1)	36,192 (20.1)	303,188 (34.5)
41-65	464,720 (44.0)	90,626 (50.4)	374,094 (42.7)
>65	203,909 (19.3)	50,708 (28.2)	153,201 (17.5)
Number of unique prescribers visited,			
median (IQR)	2 (1-3)	4 (2-6)	1 (1-2)
Mean (SD)	2.3 (2.2)	4.5 (3.4)	1.9 (1.4)
1	508,745 (48.1)	19,252 (10.7)	489,493 (55.8)
2	246,935 (23.4)	33,594 (18.7)	213,341 (24.3)
3	124,773 (11.8)	33,473 (18.6)	91,300 (10.4)
4	66,825 (6.3)	26,573 (14.8)	40,252 (4.6)
>5	109,495 (10.4)	66,913 (37.2)	42,582 (4.9)

Number of unique pharmacies visited, median (IQR)	2 (1-3)	3 (2-5)	2 (1-2)
Mean (SD)	2.37 (2.18)	4.1 (3.8)	2.02 (1.45)
1	431,651 (40.8)	29,486 (16.4)	402,165 (45.8)
2	301,730 (28.5)	41,064 (22.8)	260,666 (29.7)
3	151,297 (14.3)	33,578 (18.8)	117,710 (13.4)
4	73,698 (7.0)	23,356 (13.0)	50,342 (5.7)
>5	98,406 (9.3)	52,321 (29.1)	46,085 (5.3)
Total number of opioid prescriptions dispensed, median (IQR)	2 (1-4)	8 (2-29)	1 (1-3)
Mean (SD)	9.8 (51.4)	32.6 (101.5)	5.2 (30.9)
1-10	919,059 (87.0)	100,809 (56.0)	818,250 (93.3)
11-20	48,371 (4.6)	22,796 (12.7)	25,575 (2.9)
20-30	23,706 (2.2)	13,163 (7.3)	10,543 (1.2)
>31	65,637 (6.2)	43,037 (23.9)	22,600 (2.6)
Total cumulative days of opioid use, Median (IQR)	11 (5-39)	104 (21-522)	9 (5-23)
mean (SD)	94.5 (224)	297.9 (358.0)	52.8 (154.7)
1-30	744,607 (70.5)	54,670 (30.4)	689,937 (78.7)
31-60	94,659 (9.0)	20,406 (11.4)	74,253 (8.5)
61-90	35,536 (3.4)	10,934 (6.1)	24,602 (2.8)
>90	181,971 (17.2)	93,795 (52.2)	88,176 (10.1)

Table 2. Characteristics of opioid users with incident hospitalizations/emergency department visits in the period 2016-2018 (continued)

Number of people that received a dispensation for specified opioid molecule and daily OME#:			
buprenorphine/naloxone	7,995 (0.76)	3,005 (1.7)	7,451 (0.85)
methadone	7,394 (0.70)	3,218 (1.8)	7,043 (0.80)
buprenorphine (transdermal patch)	8,238 (0.78)	3,447 (1.9)	7,158 (0.82)
codeine	738,601 (69.9)	120,514 (67.0)	701,243 (80.0)
morphine	29,796 (2.8)	12,069 (6.7)	25,828 (3.0)
oxycodone	119,289 (11.3)	37,692 (21.0)	108,036 (12.3)
oxycodone/naloxone	1,163 (0.11)	485 (0.27)	1,007 (0.12)
hydromorphone	70,181 (6.6)	22,376 (12.4)	62,205 (7.1)
fentanyl	8,888 (0.84)	6,279 (3.5)	8,067 (0.92)
tramadol	316,662 (30.0)	50,891 (28.3)	292,965 (33.4)
tapentadol	1,570 (0.15)	696 (0.39)	1,387 (0.16)
50 OME^	854,759 (86.3)	154,742 (90.3)	812,574 (99.2)
50-90 OME^	166,392 (16.8)	48,642 (28.4)	144,629 (17.7)
>90 OME^	101,837 (10.3)	40,265 (23.5)	86,620 (10.6)

Total days of cumulative concurrency among concurrent users **1-30** **31-60** **61-90** **91-180** **181-270** **271-360** **>361**	N/A	92,757 (51.6) 17,327 (9.6) 9,006 (5.0) 14,713 (8.2) 8,468 (4.7) 6,270 (3.5) 31,264 (17.4)	N/A
Elixhauser score: **Mean (SD)** **Median (IQR)**	2.86 (2.45) 2 (1-4)	4.36 (2.8) 4 (2-6)	2.56 (2.25) 2 (1-4)

***n=990,098 for OME analyses**
[@]n=171,457 for OME analyses
[$]n=818,641 for OME analyses
~unless otherwise indicated

 # defined as having at least 1 day at specified dose or molecule

^OME=oral morphine equivalents, buprenorphine and methadone dropped from OME analysis

Table 3. Risk of all cause hospitalization or emergency department visits in people using opioids and benzodiazepine receptor modulators during 2016-2018.

Patient Group	Analysis Group*							
	None		Opioid only (reference)		Benzodiazepine^ only		Concurrent	
	OR (p-value)	95% CI	OR		OR (p-value)	95% CI	OR (p-value)	95% CI
Overall population	0.21 (<0.001)	0.20-0.21	1		0.46 (<0.001)	0.45-0.48	1.13 (<0.001)	1.10-1.17
Sex:								
Female	0.24 (<0.001)	0.23-0.25	1		0.51 (<0.001)	0.49-0.52	1.19 (<0.001)	1.14-1.23
Male	0.18 (<0.001)	0.18-0.19	1		0.43 (<0.001)	0.41-0.45	1.10 (<0.001))	1.05-1.16
Age at admission:								
20-40	0.16 (<0.001)	0.15-0.16	1		0.33 (<0.001)	0.31-0.35	0.96 (0.33)	0.88-1.04
40-65	0.23 (<0.001)	0.22-0.23	1		0.48 (<0.001)	0.46-0.50	1.12 (<0.001)	1.07-1.18
>65	0.30 (<0.001)	0.29-0.31	1		0.73 (<0.001)	0.69-0.77	1.50 (<0.001)	1.39-1.61
Total days of cumulative concurrency:								
1-30	0.33 (<0.001)	0.31-0.35	1		0.72 (<0.001)	0.67-0.78	2.47 (<0.001)	2.26-2.70
31-90	0.45 (<0.001)	0.41-0.49	1		1.05 (0.36)	0.95-1.17	1.50 (<0.001)	1.34-1.67
91-180	0.44 (<0.001)	0.39-0.49	1		1.09 (0.24)	0.95-1.24	1.45 (<0.001)	1.28-1.64
181-365	0.42 (<0.001)	0.37-0.48	1		1.11 (<0.11)	0.97-1.3	1.57 (<0.001)	1.40-1.76
>365	0.26 (<0.001)	0.23-0.29	1		1.26 (<0.001)	1.11-1.41	1.82 (<0.001)	1.67-1.99
>900	0.13 (<0.001)	0.09-0.21	1		1.64 (0.01)	1.12-2.38	3.15 (<0.001)	2.41-4.11

Total days of opioid use:								
1-7	0.04 (<0.001)	0.03-0.05	1		0.08 (<0.001)	0.07-0.09	0.90 (0.40)	0.72-1.14
8-30	0.15 (<0.001)	0.14-0.16	1		0.30 (<0.001)	0.28-0.32	1.21 (0.002)	1.07-1.38
31-90	0.34 (<0.001)	0.33-0.35	1		0.71 (<0.001)	0.66-0.76	1.36 (<0.001)	1.22-1.51
91-180	0.48 (<0.001)	0.46-0.51	1		1.05 (0.35)	0.95-1.15	1.54 (<0.001)	1.37-1.73
181-365	0.54 (<0.001)	0.52-0.57	1		1.27 (<0.001)	1.15-1.40	1.73 (<0.001)	1.56-1.92
>365	0.41 (<0.001)	0.39-0.42	1		1.21 (<0.001)	1.12-1.32	1.76 (<0.001)	1.66-1.86

Table 3. Risk of all cause hospitalization or emergency department visits in people using opioids and benzodiazepine receptor modulators during 2016-2018 (continued)

Number of opioid dispensations:								
1-10	0.16 (<0.001)	0.16-0.17	1		0.34 (<0.001)	0.33-0.35	0.93 (0.01)	0.87-0.98
11-30	0.49 (<0.001)	0.47-0.51	1		1.20 (<0.001)	1.11-1.30	1.62 (<0.001)	1.50-1.74
>30	0.35 (<0.001)	0.33-0.37	1		1.09 (0.10)	0.98-1.21	1.77 (<0.001)	1.65-1.89
Number of unique prescribers:								
1	0.14 (<0.001)	0.13-0.14	1		0.30 (<0.001)	0.28-0.32	0.73 (<0.001)	0.65-0.81
2	0.20 (<0.001)	0.19-0.20	1		0.41 (<0.001)	0.39-0.43	1.02 (0.64)	0.94-1.11
3	0.26 (<0.001)	0.25-0.27	1		0.51 (<0.001)	0.48-0.54	1.30 (<0.001)	1.19-1.42
4	0.32 (<0.001)	0.31-0.34	1		0.68 (<0.001)	0.63-0.73	1.54 (<0.001)	1.39-1.70
>5	0.38 (<0.001)	0.37-0.40	1		0.91 (<0.001)	0.86-0.96	1.67 (<0.001)	1.57-1.77

Number of unique pharmacies:								
1	0.14 (<0.001)	0.13-0.15	1		0.32 (<0.001)	0.31-0.35	0.95 (0.25)	0.86-1.04
2	0.20 (<0.001)	0.19-0.21	1		0.45 (<0.001)	0.43-0.48	1.12 (0.007)	1.03-1.21
3	0.27 (<0.001)	0.26-0.28	1		0.56 (<0.001)	0.52-0.59	1.24 (<0.001)	1.14-1.35
4	0.31 (<0.001)	0.29-0.33	1		0.66 (<0.001)	0.61-0.71	1.47 (<0.001)	1.33-1.64
>5	0.39 (<0.001)	0.38-0.41	1		0.78 (<0.001)	0.73-0.83	1.47 (<0.001)	1.38-1.57

Note: CI = confidence interval, OR=odds ratio

*** Risk interval= seven days before hospitalization/emergency visit; control interval= seven-day period one month before hospitalization/emergency department visit**

^includes all benzodiazepine receptor modulators

Table 4. 2016-2018 cause specific risk of hospitalization or emergency department visit using ICD-10 codes among opioid users.

	Analysis Group			
	None	Opioid only (reference group)	Benzodiazepine` only	Concurrent
Cause	OR (p-value) 95% CI	OR (p-value) 95% CI	OR (p-value) 95% CI	OR (p-value) 95% CI
Mental health^	0.69 (<0.001) 0.65-0.70	1	1.75 (<0.001) 1.67-1.83	1.81 (<0.001) 1.71-1.91
Opioid toxicity~	0.72 (<0.001) 0.63-0.82	1	1.19 (0.09) 0.97-1.46	1.79 (<0.001) 1.49-2.15

Note: OR= odds ratio; 95% CI= 95% confidence interval; Risk interval= seven days before hospitalization/emergency visit; control interval= seven-day period one month before hospitalization/emergency department visit

`benzodiazepine receptor modulators (includes Z-drugs)

^n=176,881

~n=8,404

Table 5. Risk of all cause death in 2016-2017 among opioid users among subgroups of patients and OME˜. *N=31,998*

	Analysis Group				OME~		
	None	Opioid only (reference group)	Benzodiazepine/Z-drug only	Concurrent	<50 (reference group)	50-90	>90
Patient Category	OR (p-value) 95% CI	OR (p-value) 95% CI	OR (p-value) 95% CI	OR (p-value) 95% CI	OR (p-value) 95% CI	OR (p-value) 95% CI	OR (p-value) 95% CI
Overall population	0.67 (<0.001) 0.64-0.71	1	0.76 (<0.001) 0.69-0.83	1.90 (<0.001) 1.76-2.05	1	1.72 (<0.001) 1.35-2.19	3.13 (<0.001) 2.50-3.92
Sex:							
Female	0.64 (<0.001) 0.60-0.70	1	0.68 (<0.001) 0.60-0.78	1.73 (<0.001) 1.56-1.92	1	1.76 (0.001) 1.25-2.48	3.22 (<0.001) 2.35-4.40
Male	0.70 (<0.001) 0.62-0.76	1	0.85 (0.02) 0.75-0.97	2.09 (<0.001) 1.87-2.33	1	1.68 (0.003) 1.19-2.37	3.04 (<0.001) 2.20-4.19
Age at death:							
18-45	1.20 (0.13) 0.94-1.54	1	1.98 (<0.001) 1.38-2.86	2.26 (<0.001) 1.63-3.13	1	0.90 (0.83) 0.35-2.31	2.31 (0.08) 0.92-5.85
46-65	1.13 (0.03) 1.01-1.28	1	1.24 (0.03) 1.02-1.51	2.20 (<0.001) 1.90-2.55	1	2.19 (<0.001) 1.41-3.39	2.78 (<0.001) 1.84-4.18
>65	0.56 (<0.001) 0.52-0.60	1	0.61 (<0.001) 0.54-0.68	1.79 (<0.001) 1.63-1.97	1	1.60 (0.003) 1.18-2.18	3.41 (<0.001) 2.57-4.52

Total days of cumulative concurrency:							
1-30	0.82 (0.007) 0.71-0.95	1	0.88 (0.17) 0.74-1.05	4.93 (<0.001) 4.29-5.66	1	1.94 (0.08) 0.92-4.07	2.96 (<0.001) 1.70-5.15
31-90	2.4 (<0.001) 1.84-3.15	1	1.18 (0.21) 0.91-1.56	1.41 (0.001) 1.14-1.74	1	1.60 (0.03) 1.04-2.46	4.08 (<0.001) 2.79-5.98
91-180	2.39 (<0.001) 1.58-3.60	1	1.74 (0.01) 1.12-2.68	0.80 (0.20) 0.56-1.12	1	2.00 (0.01) 1.19-3.34	3.05 (<0.001) 1.81-5.12
181-365	4.27 (<0.001) 2.58-7.07	1	1.54 (0.08) 0.94-2.51	0.92 (0.66) 0.63-1.33	1	1.27 (<0.34) 0.75-2.13	2.36 (0.001) 1.41-3.97
>365	1.53 (0.26) 0.73-3.24	1	1.17 (0.71) 0.51-2.72	0.39 (0.003) 0.21-0.72	1	2.09 (0.04) 1.04-4.18	2.17 (0.03) 1.07-4.40
Total days of opioid use:							
1-7	0.14 (<0.001) 0.11-0.17	1	0.17 (<0.001) 0.12-0.23	2.78 (<0.001) 1.79-4.32	1	--	--
8-30	0.38 (<0.001) 0.34-0.42	1	0.48 (<0.001) 0.40-0.59	2.29 (<0.001) 1.89-2.78	1	3.09 (<0.08) 0.88-10.9	4.23 (0.002) 1.69-10.62
31-90	1.03 (0.56) 0.92-1.16	1	1.46 (<0.001) 1.19-1.78	2.58 (<0.001) 2.22-3.00	1	1.74 (0.02) 1.10-2.73	3.98 (<0.001) 2.67-5.94
91-180	2.08 (<0.001) 1.75-2.48	1	2.62 (<0.001) 1.96-3.51	2.16 (<0.001) 1.80-2.60	1	1.76 (0.02) 1.10-2.84	2.87 (<0.001) 1.85-4.46
181-365	2.66 (<0.001) 2.18-3.24	1	3.13 (<0.001) 2.24-4.38	1.83 (<0.001) 1.50-2.23	1	1.22 (0.41) 0.75-1.98	2.27 (0.001) 1.41-3.67
>365	2.83 (<0.001) 2.16-3.71	1	2.41 (<0.001) 1.51-3.87	1.20 (0.15) 0.93-1.53	1	2.18 (0.01) 1.18-4.04	2.96 (0.001) 1.60-5.50

Number of opioid dispensations:	0.41 (<0.001)		0.45 (<0.001)	2.23 (<0.001)		2.13 (0.009)	3.48 (<0.001)
1-10	0.38-0.44	1	0.39-0.51	1.96-2.54	1	1.21-3.76	2.18-5.55
	1.36 (<0.001)		1.72 (<0.001)	2.70 (<0.001)		1.34 (0.18)	5.08 (<0.001)
11-30	1.20-1.54	1	1.41-2.11	2.34-3.12	1	0.87-2.08	3.35-7.71
	2.11 (<0.001)		1.82 (<0.001)	1.40 (<0.001)		1.82 (0.001)	1.96 (<0.001)
>30	1.83-2.44	1	1.46-2.28	1.21-1.62	1	1.28-2.59	1.40-2.74
Number of unique prescribers:	0.31 (<0.001)		0.49 (0.001)	2.50 (<0.001)		1.22 (0.81)	1.50 (0.66)
1	0.27-0.36	1	0.32-0.74	1.76-3.56	1	0.23-6.38	0.25-8.86
	0.51 (<0.001)		0.63 (<0.001)	2.29 (<0.001)		1.00 (1.00)	5.00 (0.004)
2	0.44-0.58	1	0.48-0.81	1.81-2.90	1	0.34-2.94	1.66-15.04
	0.60 (<0.001)		0.71 (0.004)	2.03 (<0.001)		1.07 (0.85)	2.13 (0.043)
3	0.52-0.69	1	0.56-0.90	1.64-2.52	1	0.47-2.45	1.03-4.43
	0.75 (<0.001)		0.82 (0.12)	2.49 (<0.001)		1.51 (0.21)	2.13 (0.011)
4	0.64-0.87	1	0.64-1.05	2.01-3.08	1	0.79-2.90	1.19-3.82
	1.36 (<0.001)		1.10 (0.15)	2.01 (<0.001)		2.00 (<0.001)	3.50(<0.001)
>5	1.23-1.50	1	0.96-1.26	1.82-2.24	1	1.49-2.67	2.67-4.60

Number of unique pharmacies:	0.54 (<0.001)		0.72 (<0.001)	1.41 (0.76)		1.45 (0.11)	2.22 (<0.001)
1	0.50-0.60	1	0.60-0.87	1.20-1.66	1	0.92-2.28	1.47-3.34
	0.65 (<0.001)		0.74 (<0.001)	2.09 (0.001)		2.00 (<0.001)	4.11 (<0.001)
2	0.59-0.71	1	0.62-0.87	1.82-2.40	1	1.43-2.78	3.05-5.53
	0.73 (<0.001)		0.78 (0.018)	2.48 (<0.001)		1.68 (0.005)	4.00 (<0.001)
3	0.64-0.84	1	0.63-0.96	2.09-2.93	1	1.17-2.42	2.88-5.56
	0.99 (0.96)		0.82 (0.18)	2.20 (<0.001)		2.06 (0.008)	6.24 (<0.001)
4	0.81-1.21	1	0.61-1.10	1.76-2.76	1	1.20-3.53	3.93-9.90
	1.30 (0.01)		1.14 (0.33)	1.81 (<0.001)		1.99 (0.001)	3.04 (<0.001)
>5	1.06-1.59	1	0.88-1.48	1.47-2.24	1	1.33-2.97	2.10-4.39

Note: OR= odds ratio; 95% CI= 95% confidence interval; Risk interval= seven days before death; control interval= seven-day period one month before death

OME, Oral morphine equivalents. Buprenorphine and methadone were excluded

~This OME analysis is among concurrent users of opioids and benzodiazepine receptor modulators

--No counts

Table 6. Sensitivity Analysis: Risk of all cause hospitalization or emergency department visit and death, excluding malignancies, among those using benzodiazepine receptor modulators and opioids

	Analysis Group			
	None	Opioid only (reference group)	Benzodiazepine only[#]	Concurrent
Event	OR (p-value) 95% CI	OR	OR (p-value) 95% CI	OR (p-value) 95% CI
All cause hospitalization or emergency department visit*	0.25 (<0.001) 0.24-0.25	1	0.54 (<0.001) 0.52-0.56	1.21 (<0.001) 1.16-1.28
All cause death^	0.56 (<0.001) 0.54-0.59	1	0.50 (<0.001) 0.46-0.54	1.15 (<0.001) 1.07-1.24

Note: OR= odds ratio; 95% CI= 95% confidence interval; Risk interval= seven days before death; control interval= seven-day period one month before death

[#]benzodiazepine receptor modulators (includes Z-drugs)

***n=477,991**

^n=44,677

Table 7. Sensitivity Analysis: Risk of death, excluding malignancies, comparing opioid dose^ and concurrency. n=44,677

Opioid Dose (OME)	OR (p-value)	95% CI
<50 (reference)	1	
<50+BZD*	0.91 (0.36)	0.74-1.12
50-90 (reference)	1	
50-90 + BZD	1.08 (0.79)	0.63-1.84
>90 (reference)	1	
>90 + BZD	1.30 (0.03)	1.03-1.62

^oral morphine equivalents

***benzodiazepine receptor modulator (includes Z-drugs)**

Table 8. Sensitivity Analysis: Risk of hospitalization/ED visit and death using different lengths and numbers of study windows.

	Analysis Group			
	None	Opioid only (reference group)	Benzodiazepine only	Concurrent
Event	OR (p-value) 95% CI	OR	OR (p-value) 95% CI	OR (p-value) 95% CI
Hospitalizations/ED visits				
Two control windows (2 weeks and 1-month preceding event)	0.18 (<0.001) 0.18-0.19	1	0.46 (<0.001) 0.45-0.47	1.18 (0.001) 1.14-1.22
3-day study windows	.18 (<0.001) 0.18-0.19	1	0.45 (<0.001) 0.44-0.47	1.09 (<0.001) 1.05-1.13
10-day study windows	0.22 (<0.001) 0.21-0.22	1	0.48 (<0.001) 0.47-0.50	1.15 (<0.001) 1.11-1.19
Deaths				
Two control windows (2 weeks and 1-month preceding event)	0.65 (<0.001) 0.62-0.68	1	0.77 (<0.001) 0.71-0.85	2.12 (<0.001) 1.98-2.28
3-day study windows	0.73 (<0.001) 0.68-0.77	1	0.74 (<0.001) 0.68-0.81	1.72 (<0.001) 1.59-1.85
10-day study windows	0.64 (<0.001) 0.61-0.68	1	0.78 (<0.001) 0.71-0.86	2.02 (<0.001) 1.87-2.17

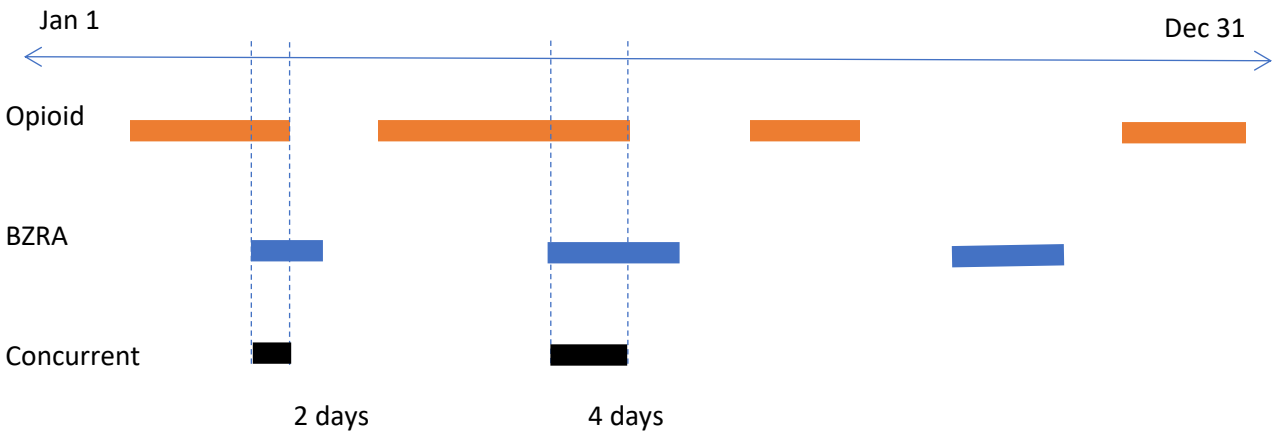
n=1,056,773 for hospitalizations/ED visits; n=31,998 for deaths

Table 9. Risk of all cause death in 2016-2018 comparing opioid doses and concurrency.

Opioid Dose (OME)	OR (p-value)	95% CI
<50	1	
<50+BZD*	1.07 (0.63)	0.81-1.39
50-90	1	
50-90 + BZD	1.73 (0.09)	0.92-3.27
>90	1	
>90 + BZD	2.72 (<0.001)	2.26-3.27

***Benzodiazepine receptor modulator**

Figure 1. Determination of concurrent use of opioid and BZD using a hypothetical patient.



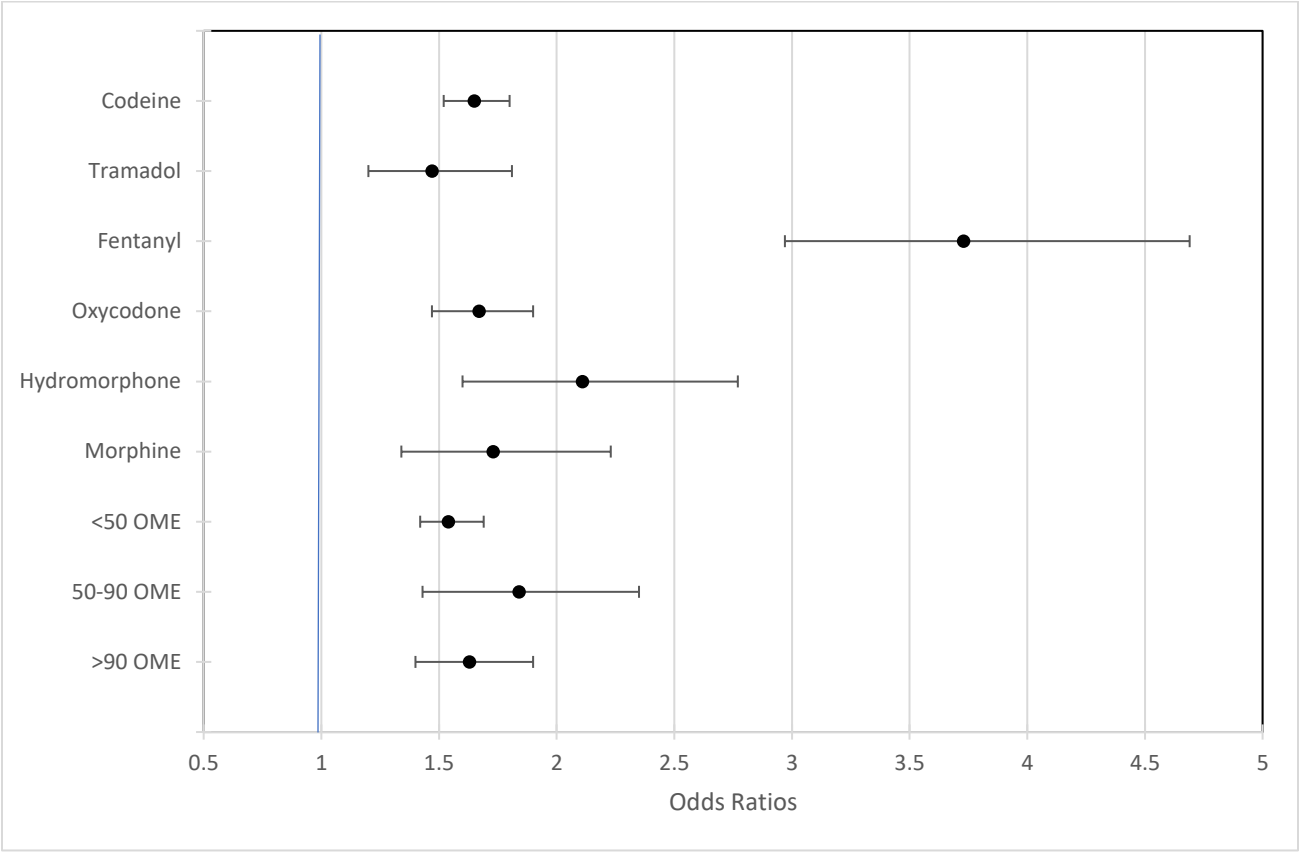
total concurrency=6 days

longest consecutive days of concurrency=4days

Figure 2. Case crossover design and study windows

Exposures are measured in each window and conditional logistic regression is used to contrast the control window(s) and case windows.

Figure 3. Risk of hospitalization or emergency department visit comparing specific opioid molecules and opioid doses* used concurrently with BZDs~ to their respective monotherapy counterparts^



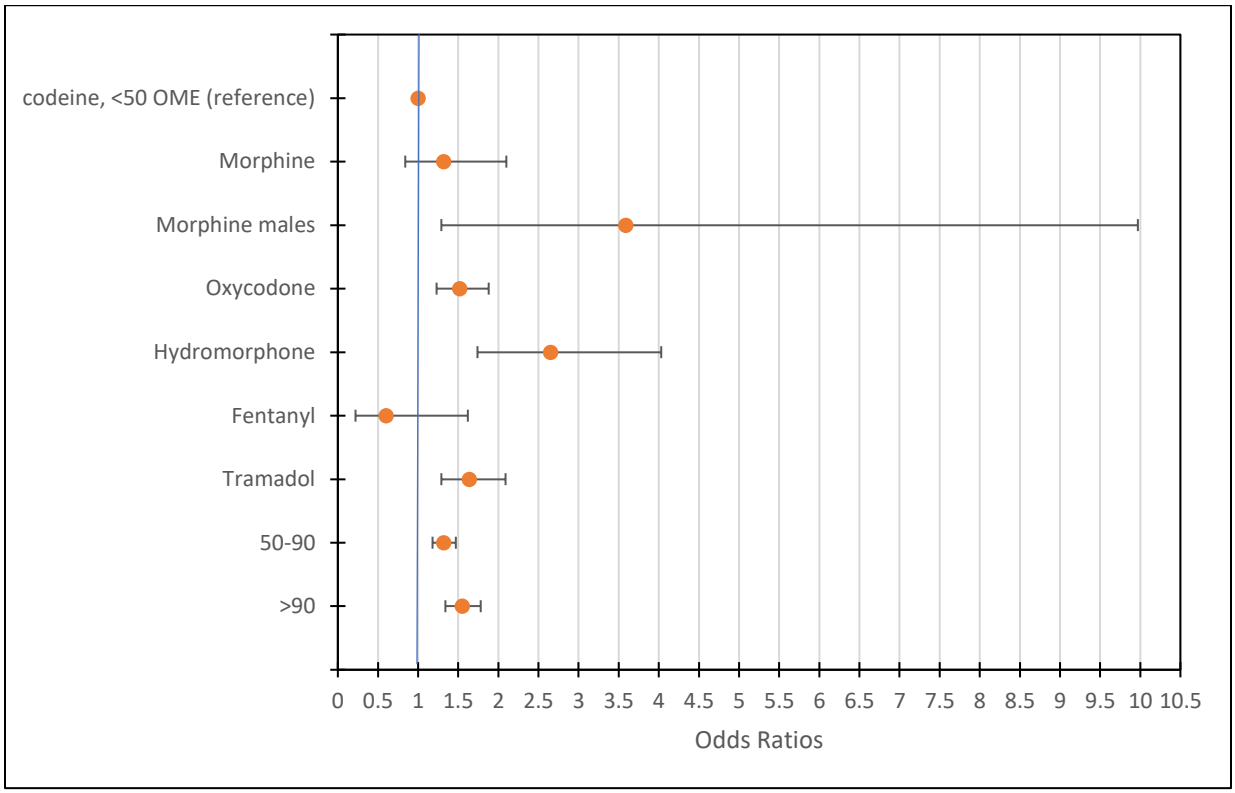
Note: bars represent 95% confidence intervals

***Opioid dose is oral morphine equivalents (OME); buprenorphine and methadone have been excluded**

~Benzodiazepine receptor modulator (includes Z-drugs)

^For example, the odds ratio plotted for codeine represents the risk of codeine + BZD compared to codeine alone and that of <50 OME represents the risk of <50 OME + BZD compared to <50 OME alone

Figure 4. Risk of all cause hospitalization or emergency department visits among concurrent users of opioids and benzodiazepines by molecule and opioid dose* using codeine and <50 OME* as reference groups.



Note: bars represent 95% confidence intervals

***Dose is oral morphine equivalents (OME) and <50 OME is the reference. Buprenorphine and methadone have been excluded.**

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Chapter 4: Summary

Guidelines for appropriate prescribing of opioids in the context of chronic non-cancer pain indicate that BZDs should not be concurrently prescribed with opioids because of the risk of adverse outcomes like overdose and death [14,15,51]. These same guidelines also recommend limiting the dose of opioids in chronic pain scenarios to <50 OME and no higher than 90 OME. This is especially true for seniors and those with mental health illness [47]. Despite these guidelines, our research showed that in Alberta, concurrent use of these medications is widespread with nearly 20% of opioid users having been co-prescribed a BZD for at least 1 day or more. Furthermore, our descriptive analyses showed that seniors, those on high doses of opioids (>90 OME), chronic opioid use and high health care utilization (visiting many providers) had higher estimates of prevalence of concurrent use. These patterns of concurrent use also translated into increased adverse outcomes. Indeed, our outcomes research analyses showed that concurrent use was associated with higher risks of hospitalizations, ED visits and deaths when compared to opioid only use. This was true for our stratified analyses with seniors, those on higher doses of opioids, and in those with prior higher health care utilization having increased risk. Those diagnosed with mental illness were also at higher risk and in fact, our results showed that adding a BZD to any opioid at any dose was associated with higher risks of adverse outcomes. Our findings in terms of characterization and outcomes of concurrent use are consistent with other research done in the US [11,19,20].

Given the opioid crisis and the overuse of BZDs in society, future research should focus on why this drug use pattern is still occurring and should address three levels: the patient level, health provider level and government/policy level. At the patient level, research should investigate whether there are unmet health needs and if patients are able to connect with health care resources that may alleviate pain without the need of opioids. Similarly, at the provider level, research should focus on barriers that providers face in trying to connect patients to appropriate treatments. As well, barriers to uptake of new knowledge (new clinical practice guidelines where opioids are not first line therapies) could also be investigated further. Research at the government/policy level can address what could be done to mitigate this drug use pattern and to determine if enough resources are being allocated to meeting the health needs of patients and to support health providers.

It is clearly evident that co-prescribing of opioids and BZDs in chronic pain scenarios comes with high risks and questionable clinical benefits. Furthermore, there are no clinical indications for concurrent use in chronic pain other than strong warnings against such use. In order to avoid adverse

outcomes, health providers must acknowledge the latest evidence and recommendations against co-prescribing, as well, professional regulatory bodies should also reinforce safe drug use guidelines and perhaps emphasize more continuing education on this topic. Ongoing monitoring and using a prescription drug monitoring program (like Netcare) in order to detect high health care utilization would be warranted since a major issue in concurrent use is patients seeking these agents from multiple providers.

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