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

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Data Sharing: The data used in this study is not available for external analysis. However, administrative health data can be accessed from AH by following defined research protocols and confidentiality agreements.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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Summary box:

Section 1: What is already known on this topic

- Co-prescribing opioids and benzodiazepines is associated with increased risk of hospitalization and death.

- Many clinical guidelines on safe opioid prescribing warn against co-prescribing of opioids and benzodiazepines.
- Although concurrent use of opioids and benzodiazepines has been studied in the USA among US Veterans and the privately insured population, risk of concurrent use has not been estimated in a more general population among various sub-groups of patients in Alberta, Canada.

Section 2: What this study adds

- Risk of hospitalization, emergency visit or death is associated with concurrent use of opioids and benzodiazepines compared to opioid only use in the general population in Alberta, Canada
- This higher estimated risk is associated with older adults, those with mental health issues, chronic opioid users and higher users of the health care system.
- Higher risk of concurrent use on hospitalization, emergency visit or death was observed with any opioid molecule that was prescribed at any dose.

Abstract

Objectives: In Canada, co-prescribing of benzodiazepines/Z-drugs (BZDs) and opioids is a less highlighted drug-use pattern of considerable concern due to risk of adverse events. The objective of this study is to estimate the effect of concurrent use of BZDs on the risk of hospitalizations/emergency department (ED) visits and deaths among opioid users.

Design, Setting and Participants: We conducted a population-based case crossover study during 2016-2018 involving Albertans 18 and over who received opioids. Of these patients, we included those who were hospitalized, visited the ED, or died.

Intervention: Concurrent use of opioids and BZDs.

Outcomes: We estimated the risk of incident all-cause hospitalization/ED visits and all-cause mortality associated with concurrent BZD use by applying a matched-pair analyses comparing concurrent use to opioid only use.

Results: 17% of opioid users (179,805/1,056,773) concurrently used a BZD. Overall, concurrent use was associated with higher risk of hospitalization/ED visit (OR 1.13, P<0.001) and all cause death (OR 1.90; P<0.001). The estimated risk of hospitalization/ED visit was highest in those >65 (OR 1.5; P<0.001), higher health care utilization (OR 1.67; P<0.001) and >365 days of opioid use (OR 1.76; P<0.001). Events due to mental health and opioid toxicity were also associated with concurrent use (OR 1.8; P<0.001). Opioid dose-response effects among concurrent patients who died were also noted (OR 3.13; P<0.001).

Interpretation: Concurrent use of opioids and BZDs further contributes to the risk of hospitalization/ED visits and mortality in Alberta, Canada over opioid use alone, with higher opioid doses, age and healthcare utilization carrying higher risks. Regulatory bodies and health providers should reinforce safe drug-use practices and be vigilant about co-prescribing.

Strengths and Limitations

- The use of a large population-based sample with near complete capture of all opioid and benzodiazepine dispensations from community pharmacies in Alberta,
- The case crossover methodology is a good fit for studies in pharmacoepidemiology like ours since the effect of many confounders can be substantially controlled,
- We considered patient sub-groups that have not previously been studied with respect to concurrent use of opioids and benzodiazepines.
- We assumed that patients took their medications as prescribed and recorded in the administrative data set. This is a limitation for all studies using administrative data,
- There is always residual confounding and importantly, unknown factors which may have changed between the control and case windows could have affected our results.
- Information on the indication for concurrent prescribing was not available from the administrative database.

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 [1-3]. Individuals older than 65 years are especially prone to the consequences of opioids[3,4]. The policy response to the opioid crisis has focused on establishing guidelines for safe and appropriate prescribing of opioids [1,5]. A similar picture exists for benzodiazepines and Z-drugs (zopiclone, zolpidem), collectively known as benzodiazepine receptor modulators (BZDs). BZDs are widely prescribed for anxiety disorders and insomnia [6]. Canadian clinical practice suggest that BZD treatment may be appropriate for short term use only in adults [7,8]. Use of BZDs outside of these recommendations is considered potentially inappropriate given the potential for adverse effects, especially in those over 65 [6,7,9,10] years and Canadian data have shown high prevalence of BZD use among the elderly [11,12]. Furthermore, receipt of BZDs could be a marker of mental illness, which carries its own risk of mortality [13,14].

In the context of the opioid crisis, concurrent use of opioids and BZDs represents a less highlighted drug use pattern that is of substantial concern because of the increased risk of mortality [5,15,16]. 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 [1,5,17] and previous literature suggests that opioids and BZDs cannot be targeted by safe use policies in isolation [18]. Despite these warnings, opioids and BZDs are still being co-prescribed at alarming rates, as shown in our previous work using Alberta data[19]. Data from the US also show an increasing trend in co-prescribing of opioids and

BZDs [15,20,21] and 50% of opioid related deaths in Ontario and Manitoba, Canada involved BZDs [22,23]. 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 [15,16]. 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 that were privately insured, and may not be generalizable to other populations.

To our knowledge, no broad Canadian population-based studies have quantified the effect of concurrent BZD and opioid use on outcomes such as hospitalizations and mortality using the characteristics that we and others have identified as relevant[15,16]. Using a case crossover study design, we aimed to examine the association between concurrent use of opioids and BZDs and adverse health outcomes and hypothesized that concurrent use would further increase 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

Demographic information and dispensation records from community pharmacies were obtained from Alberta Netcare Pharmaceutical Information Network (PIN). Information on hospitalizations and ED visits was collected using the Canadian Institute for Health Information's Discharge Abstract Database and National Ambulatory Care Reporting System. Physician visits/claims and death records were provided by Alberta Health and Population and Vital Statistics, respectively. Using anonymized patient level identifiers, these databases were linked together to establish a complete description of drug exposures and health outcomes. This

study was approved by the health ethics research board at the University of Alberta (#Pro00083807).

Identification of Patients and Outcomes

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 in the province as reporting is 12-24 months delayed in the province.

Our primary outcomes among the cohort of opioid users were all cause, incident hospitalizations or ED visits during Jan 1, 2016-Dec 31, 2018 (n=1,056,773) and all cause mortality during Jan 1, 2016 - Dec 31, 2017 (n=31,998). The secondary outcome was incident hospitalization or ED visit due to ICD-10 diagnoses related to mental health and opioid toxicity (ICD10 F04-F99, T400-T404, T406) between Jan 1, 2016 and Dec 31, 2018 as these endpoints maybe more specific to the population using BZD and opioids. The date of the event served as the index date for all analyses.

Exposure

The exposure of interest was whether an opioid patient also used a 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 [15] As described in our previous work [19], for each patient, a day was categorized as concurrent if it was covered by both an opioid and BZD. 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)** any concurrent use of opioid and BZD (concurrent).

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.

We used the case-crossover design to estimate if concurrent use increased the risk of our defined outcomes. 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]. This methodology is increasingly being utilized to evaluate exposures encountered in pharmacoepidemiology and when using administrative databases [24-26].

Conditional logistic regression 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. We chose the one month time period based on other published pharmacoepidemiology studies using this methodology [27]. 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, total days of cumulative concurrency prior to event, total days of previous opioid use, health care utilization, opioid molecule and dose (oral morphine equivalents, OME). All analyses were performed using STATA/MP 15.1 (StataCorp., College Station, TX)

Sensitivity Analyses

We performed the primary analyses on a subset of the population that excluded cancer and palliative patients like others have [16,28] by removing all patients that had relevant ICD codes (ICD9: 140-239, V66.7; ICD10: C00-D49, Z51) at any time between 2012-2018 identified from the above-mentioned databases. We also performed the analyses after adjusting the length of the study windows to 3 and 10 days and adding a second control period that preceded the event by 2 weeks.

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.

Results

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

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; Table 2). 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. With respect to total days of concurrency prior to the event, 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 2). Not unexpectant, increasing duration of previous use of opioids was also associated with an increasing estimated risk (Table 2).

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 (Figure 1). As expected, there was a dose response effect on estimated risk where higher OME's had higher risk compared to <50 OME among concurrent patients (Figure 1). When specific opioid molecules and OME dose ranges were examined, an increased risk of hospitalization or ED visit was noted for all opioid molecules and doses when used concurrently with a BZD (Figure 2).

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 or opioid toxicity (OR 1.8; P<0.001).

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 control and case windows (12.7% vs. 18.6%; OR 1.90; P<0.001) with males having a higher risk than females (Table 3). 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 4). 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 cumulative concurrent use (Table 3)

In sensitivity analyses, concurrent use was still associated with a higher risk of hospitalization or ED visits and mortality when compared to opioid only use after adjusting the length of study windows, number of control windows, and when cancer and palliative patients were excluded.

Discussion

Many clinical resources warn that BZDs should not be combined with opioids [1,5,17], yet our study showed a substantial proportion of patients using an opioid did so in combination with a BZD in Alberta, Canada. A concerning trend in adverse outcomes was observed with a near two-fold increased risk of mortality associated with concurrent BZD and opioid use compared to opioid only use. In particular, those age >65 years, those visiting multiple health providers, and higher OME's were at highest relative risks. Importantly, the data also show that one of the highest risks was observed in those that 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.[15] reported that 17% of opioid patients concurrently used a BZD and that higher durations of opioid use also carried higher risks of hospitalization or ED visit with respect to concurrent users, findings 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 [16]. 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 population than ours. When our death 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 [29-31]. 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 [28]. 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.

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 [32]. 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. 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 adequately capture. We conducted a sensitivity

analysis that excluded patients diagnosed with a malignancy or 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 [33].

Despite the messages from safe opioid prescribing guidelines[1,5], 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 [34], the trend with concurrent use of opioids and BZDs is unknown and may in fact be increasing [15,20]. From a clinical perspective, prescribers should closely follow opioid use guidelines and avoid concurrent prescribing with BZDs in most clinical scenarios [1,5]. There is an opportunity for providers to monitor and potentially avoid concurrent use altogether or reassess for dose tapering. Future research should focus on why health providers and patients continue to accept and rely on concurrent prescribing of these agents as a form of treatment. Policy makers and professional regulatory bodies should reinforce safe opioid use prescribing guidelines and educate providers about the additional risks associated with concurrent use of opioids and BZDs.

List of Figures:

Figure 1. 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.

Figure 2. Risk of hospitalization or emergency department visit comparing specific opioid molecules and opioid doses used concurrently with BZDs~ to their respective monotherapy counterparts

Table 1. 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 1. 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		92,757 (51.6)	
31-60		17,327 (9.6)	
61-90		9,006 (5.0)	
91-180	N/A	14,713 (8.2)	N/A
181-270		8,468 (4.7)	
271-360		6,270 (3.5)	
>361		31,264 (17.4)	
Elixhauser score:			
Mean (SD)	2.86 (2.45)	4.36 (2.8)	2.56 (2.25)
Median (IQR)	2 (1-4)	4 (2-6)	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 2. Risk of all cause hospitalization or emergency department visits in people using opioids and benzodiazepine receptor modulators during 2016-2018.

	Analysis Group*							
	None		Opioid only (reference)		Benzodiazepine^ only		Concurrent	
Patient Group	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 2. 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 3. Risk of all cause death in 2016-2017 among opioid users and subgroups of patients. *N=31,998*

Patient Category	None OR (p-value) 95% CI	Opioid only (reference group)	Benzodiazepine /Z-drug only OR (p-value) 95% CI	Concurrent 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
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
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
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
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
>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

Table 3. Risk of all cause death in 2016-2017 among opioid users and subgroups of patients. *N=31,998 (continued)*

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
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
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
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
>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

Table 3. Risk of all cause death in 2016-2017 among opioid users and subgroups of patients *N=31,998 (continued)*

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
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
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
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
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
>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

Number of opioid dispensations:				
1-10	0.41 (<0.001) 0.38-0.44	1	0.45 (<0.001) 0.39-0.51	2.23 (<0.001) 1.96-2.54
11-30	1.36 (<0.001) 1.20-1.54	1	1.72 (<0.001) 1.41-2.11	2.70 (<0.001) 2.34-3.12
>30	2.11 (<0.001) 1.83-2.44	1	1.82 (<0.001) 1.46-2.28	1.40 (<0.001) 1.21-1.62

Table 3. Risk of all cause death in 2016-2017 among opioid users and subgroups of patients. ***N=31,998 (continued)***

Number of unique prescribers:				
1	0.31 (<0.001) 0.27-0.36	1	0.49 (0.001) 0.32-0.74	2.50 (<0.001) 1.76-3.56
2	0.51 (<0.001) 0.44-0.58	1	0.63 (<0.001) 0.48-0.81	2.29 (<0.001) 1.81-2.90
3	0.60 (<0.001) 0.52-0.69	1	0.71 (0.004) 0.56-0.90	2.03 (<0.001) 1.64-2.52
4	0.75 (<0.001) 0.64-0.87	1	0.82 (0.12) 0.64-1.05	2.49 (<0.001) 2.01-3.08
>5	1.36 (<0.001) 1.23-1.50	1	1.10 (0.15) 0.96-1.26	2.01 (<0.001) 1.82-2.24

Table 3. Risk of all cause death in 2016-2017 among opioid users and subgroups of patients. ***N=31,998 (continued)***

Number of unique pharmacies:				
1	0.54 (<0.001) 0.50-0.60	1	0.72 (0.001) 0.60-0.87	1.41 (<0.001) 1.20-1.66
2	0.65 (<0.001) 0.59-0.71	1	0.74 (<0.001) 0.62-0.87	2.09 (<0.001) 1.82-2.40
3	0.73 (<0.001) 0.64-0.84	1	0.78 (0.018) 0.63-0.96	2.48 (<0.001) 2.09-2.93
4	0.99 (0.96) 0.81-1.21	1	0.82 (0.18) 0.61-1.10	2.20 (<0.001) 1.76-2.76
>5	1.30 (0.01) 1.06-1.59	1	1.14 (0.33) 0.88-1.48	1.81 (<0.001) 1.47-2.24

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 modulator includes Z-drugs

Table 4. Risk of all cause death in 2016-2017 among patients co-prescribed BZDs and opioids stratified by OME (n=31,998)

Category	OME		
	<50 (reference group)	50-90	>90
	OR (p-value) 95% CI	OR (p-value) 95% CI	OR (p-value) 95% CI
Overall population	1	1.72 (<0.001) 1.35-2.19	3.13 (<0.001) 2.50-3.92
Female	1	1.76 (<0.001) 1.25-2.48	3.22 (<0.001) 2.35-4.40
Male	1	1.68 (0.003) 1.19-2.37	3.04 (<0.001) 2.20-4.19
Age at death:			
18-45	1	0.90 (0.83) 0.35-2.31	2.31 (0.08) 0.92-5.85
46-65	1	2.19 (<0.001) 1.41-3.39	2.78 (<0.001) 1.84-4.18
>65	1	1.60 (0.003) 1.18-2.18	3.41 (<0.001) 2.57-4.52

Note: BZD: benzodiazepines/Z-drugs; OME: Oral morphine equivalents, <50 OME category is the reference group; Buprenorphine and methadone were excluded

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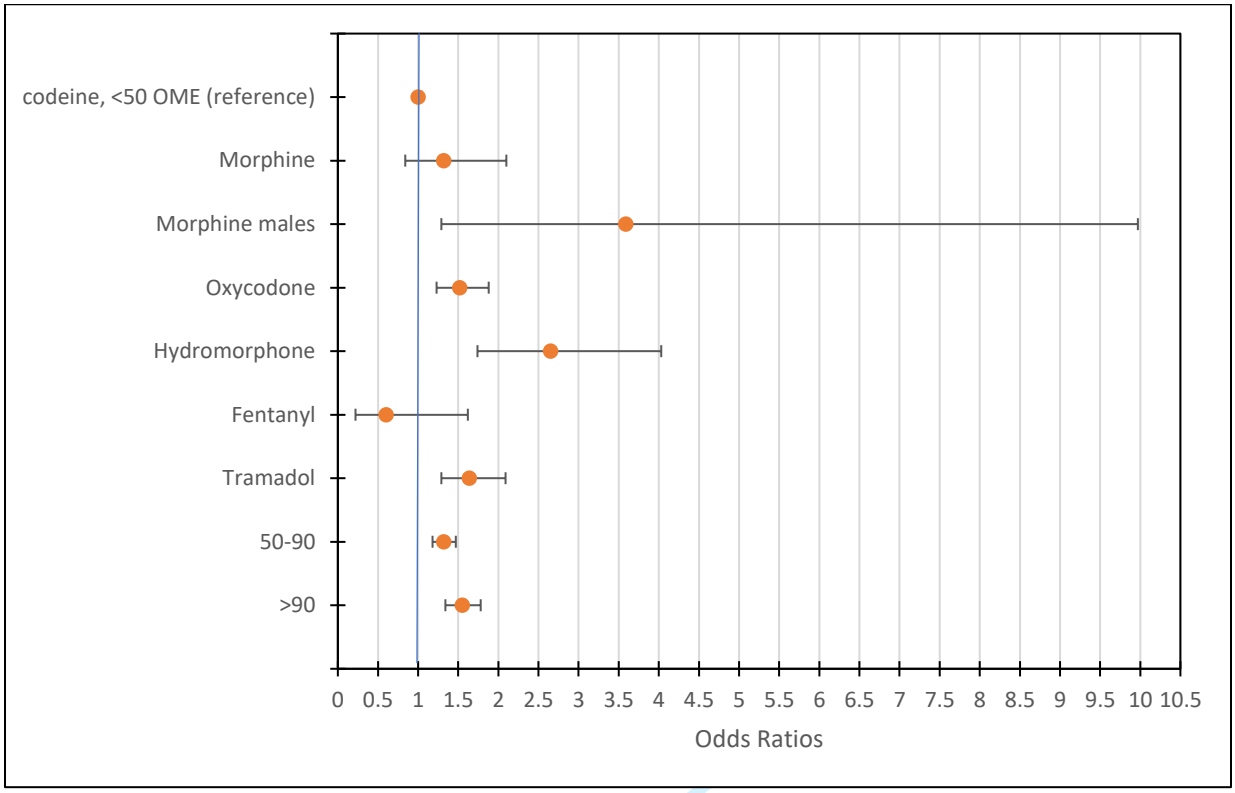
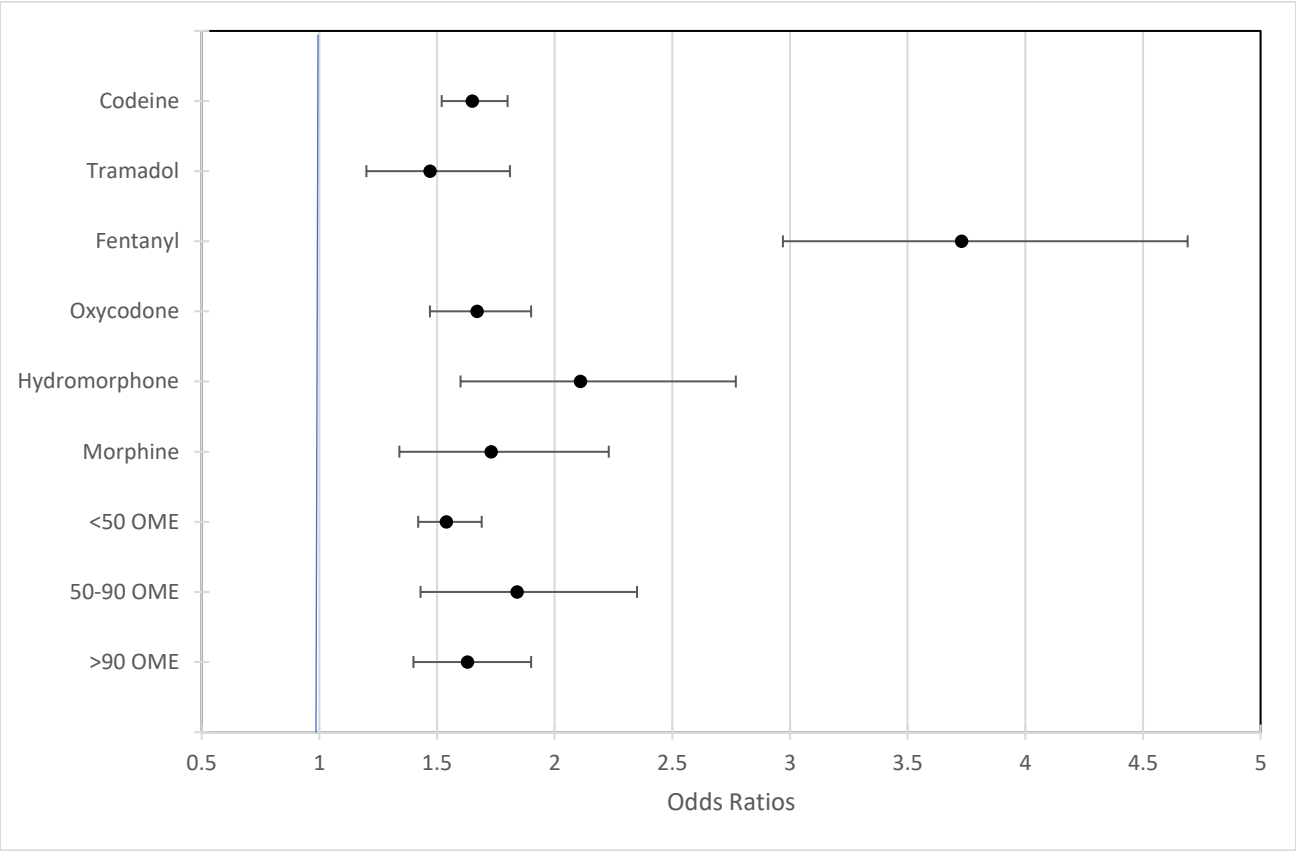
Figure 1. Risk of all cause hospitalization or emergency department visits among concurrent users of opioids and benzodiazepines by molecule and opioid dose* using codeine and <50 OME* as reference groups.



Note: bars represent 95% confidence intervals

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

Figure 2. 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

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	8

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*8-9*
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Concurrent use of opioids and benzodiazepines/Z-drugs in Alberta, Canada and the risk of hospitalization and death: a case crossover study

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Concurrent use of opioids and benzodiazepines/Z-drugs in Alberta, Canada and the risk of hospitalization and death: a case crossover study

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Data Sharing: The data used in this study is not available for external analysis. However, administrative health data can be accessed from Alberta Health by following defined research protocols and confidentiality agreements.

Transparency: The lead author (the manuscript's guarantor, Dean Eurich) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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Abstract

Objectives: Co-prescribing of benzodiazepines/Z-drugs (BZDs) and opioids is a drug-use pattern of considerable concern due to risk of adverse events. The objective of this study is to estimate the effect of concurrent use of BZDs on the risk of hospitalizations/emergency department (ED) visits and deaths among opioid users.

Design, Setting and Participants: We conducted a population-based case crossover study during 2016-2018 involving Albertans 18 years of age and over who received opioids. From this group, we identified 1,056,773 people who were hospitalized or visited the ED, and 31,998 who died.

Intervention: Concurrent use of opioids and BZDs.

Outcomes: We estimated the risk of incident all-cause hospitalization/ED visits and all-cause mortality associated with concurrent BZD use by applying a matched-pair analyses comparing concurrent use to opioid only use.

Results: Concurrent BZD use occurred in 17% of opioid users (179,805/1,056,773). Overall, concurrent use was associated with higher risk of hospitalization/ED visit (OR 1.13, P<0.001) and all cause death (OR 1.90; P<0.001). The estimated risk of hospitalization/ED visit was highest in those >65 (OR 1.5; P<0.001), using multiple health providers (OR 1.67; P<0.001) and >365 days of opioid use (OR 1.76; P<0.001). Events due to opioid toxicity were also associated with concurrent use (OR 1.8; P<0.001). Opioid dose-response effects among concurrent patients who died were also noted (OR 3.13; P<0.001).

Interpretation: Concurrent use of opioids and BZDs further contributes to the risk of hospitalization/ED visits and mortality in Alberta, Canada over opioid use alone, with higher opioid doses, older age and increased number of unique health providers carrying higher risks.

Regulatory bodies and health providers should reinforce safe drug-use practices and be vigilant about co-prescribing.

Strengths and Limitations

- The use of a large population-based sample with near complete capture of all opioid and benzodiazepine dispensations from community pharmacies in Alberta.
- The case crossover methodology is a good fit for studies in pharmacoepidemiology like ours since the effect of many confounders can be substantially controlled,
- We considered patient sub-groups that have not previously been studied with respect to concurrent use of opioids and benzodiazepines.
- We assumed that patients took their medications as prescribed and recorded in the administrative data set.
- There is always residual confounding and importantly, unknown factors which may have changed between the control and case windows could have affected our results.

Introduction

In the context of the opioid crisis, concurrent use of opioids and BZDs represents a drug use pattern that is of substantial concern because of the increased risk of mortality [1-3]. In Canada and the United States, the policy response to the opioid crisis has focused on establishing guidelines for safe and appropriate prescribing of opioids [1,4]. 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 [1,4,5] and previous literature suggests that opioids and BZDs cannot be targeted by safe use policies in isolation [6]. Despite these warnings, opioids and BZDs are still being co-prescribed at alarming rates, as shown in our previous work using Alberta data[7]. Data from the US also show an increasing trend in co-prescribing of opioids and BZDs [2,8,9] and 50% of opioid related deaths in Ontario and Manitoba, Canada involved BZDs [10,11]. 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 [2,3]. 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 that were privately insured which may not be generalizable to the Canadian population.

To our knowledge, no Canadian population-based studies have quantified the effect of concurrent BZD and opioid use on outcomes such as hospitalizations and mortality using the characteristics that we and others have identified as relevant[2,3,7]. A knowledge gap exists on the risks of co-prescribing of these agents, especially when looking at opioid dose, duration of concurrent use, and health care utilization. Using a case crossover study design, we aimed to

examine the association between concurrent use of opioids and BZDs and adverse health outcomes and hypothesized that concurrent use would further increase risk of these outcomes. Our results will help fill the evidence gap on the adverse outcomes associated with concurrent prescribing of opioids and BZDs.

Methods

Data Sources

Demographic information and dispensation records from community pharmacies were obtained from Alberta Netcare Pharmaceutical Information Network (PIN). Information on hospitalizations and ED visits was collected using the Canadian Institute for Health Information's Discharge Abstract Database and National Ambulatory Care Reporting System. Physician visits/claims and death records were provided by Alberta Health and Population and Vital Statistics, respectively. Using anonymized patient level identifiers, these databases were linked together to establish a complete description of drug exposures and health outcomes. This study was approved by the health ethics research board at the University of Alberta (#Pro00083807).

Identification of Patients and Outcomes

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.

Our primary outcomes among the cohort of opioid users were all cause, incident hospitalizations or ED visits during Jan 1, 2016-Dec 31, 2018 (n=1,056,773) and all cause mortality during Jan 1, 2016 - Dec 31, 2017 (n=31,998). The secondary outcome was incident hospitalization or ED visit due to ICD-10 diagnoses related to opioid toxicity (ICD10 F04-F99, T400-T404, T406) between Jan 1, 2016 and Dec 31, 2018 as this endpoint maybe more specific to the population using BZD and opioids[12]. The date of the event served as the index date for all analyses.

Exposure

The exposure of interest was whether an opioid patient also used a 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 [2]. As described in our previous work[7], for each patient, a day was categorized as concurrent if it was covered by both an opioid and BZD. 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)** any concurrent use of opioid and BZD (concurrent). In our case crossover analyses, "none", "opioid only", "BZD only" and "concurrent" refer to drug use during the study windows. We identified opioid and BZD prescriptions using Anatomical Therapeutic Chemical codes[13] (eTable 1) and included all Health Canada approved[14] opioid and benzodiazepine/Z-drug formulations which are monitored in the Alberta Triplicate Prescription Program[15].

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[16] was defined by number of unique providers visited and number of opioid prescriptions dispensed. Opioid doses were standardized into oral morphine equivalents (OME) using conversion factors outlined by the Triplicate Prescription Program[17] in Alberta, Canada.

We first conducted a descriptive analysis of our study population and performed pairwise comparisons between "opioid only users" and "concurrent users" using t-tests and chi^2 tests of independence. Then, we used the case-crossover design to estimate if concurrent use increased the risk of our defined outcomes. In a case crossover study, each person serves as their own control; consequently, eliminating confounding due to age, sex and other fixed patient factors [18]. This methodology is increasingly being utilized to evaluate exposures encountered in pharmacoepidemiology and when using administrative databases [18-20].

Conditional logistic regression 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. We chose the one month time period based on other published pharmacoepidemiology studies using this methodology [21]. 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, total days of cumulative concurrency prior to event, total days of previous opioid use, health care utilization, opioid molecule and dose (OME). All analyses were performed using STATA/MP 15.1 (StataCorp., College Station, TX)

Sensitivity Analyses

We performed the primary analyses on a subset of the population that excluded cancer and palliative patients like others have [3,22] by removing all patients that had relevant ICD codes

(ICD9: 140-239, V66.7; ICD10: C00-D49, Z51) at any time between 2012-2018 identified from the above-mentioned databases. We also performed the analyses after adjusting the length of the study windows to 3 and 10 days and adding a second control period that preceded the event by 2 weeks.

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.

Results

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

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; Table 2). 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. With respect to total days of concurrency prior to the event, although any duration of concurrency was associated with an 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 2). Not unexpectant, increasing duration of previous use of opioids was also associated with an increasing estimated risk (Table 2).

Among the concurrent patients who were hospitalized or visited an ED, morphine, oxycodone, hydromorphone and tramadol carried the highest risks when compared to codeine and used concurrently with BZDs (Figure 1). As expected, there was an opioid dose response effect on estimated risk where higher OME's had higher risk compared to <50 OME among concurrent patients (Figure 1). When specific opioid molecules and OME dose ranges were examined, an increased risk of hospitalization or ED visit was noted for all opioid molecules and doses when used concurrently with a BZD (Figure 2).

In the secondary analysis, the estimated risk of hospitalization or ED visit was also higher in concurrent patients when compared to opioid only patients for admissions related to opioid toxicity (OR 1.8; P<0.001).

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 control and case windows (12.7% vs. 18.6%; OR 1.90; P<0.001) with males having a higher risk than females (Table 3). 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 4). 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 cumulative concurrent use (Table 3)

In sensitivity analyses, concurrent use was still associated with a higher risk of hospitalization or ED visits and mortality when compared to opioid only use after adjusting the

length of study windows, number of control windows, and when cancer and palliative patients were excluded.

Discussion

Many clinical resources warn that BZDs should not be combined with opioids [1,4,5], yet our study showed a substantial proportion of patients using an opioid did so in combination with a BZD in Alberta, Canada. A concerning trend in adverse outcomes was observed with a near two-fold increased risk of mortality associated with concurrent BZD and opioid use compared to opioid only use. In particular, those age >65 years, those visiting multiple health providers, and higher OME's were at highest relative risks. Importantly, the data also show that one of the highest risks was observed in those that 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.[2] reported that 17% of opioid patients concurrently used a BZD and that higher durations of opioid use also carried higher risks of hospitalization or ED visit with respect to concurrent users, findings 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 [3]. Although both of our studies associated concurrent use of opioids and BZDs with increased risk of death, overall and in an opioid-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 population than ours. When our death 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 [23-25]. As other studies have observed, the estimated risk of an opioid-related death from taking 50-90 OME was double when compared to lower OME doses [22]. 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.

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 [26]. Both of our estimates associate a higher risk during the first few days of concurrent use as more susceptible patients may experience adverse outcomes earlier in concurrent use, thus signaling that even short periods of concurrent use carry risks.

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. 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 adequately capture. 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 [27].

Despite the messages from safe opioid prescribing guidelines[1,4], 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 [28], the trend with concurrent use of opioids and BZDs is unknown and may in fact be increasing [2,8]. From a clinical perspective, prescribers should closely follow opioid use guidelines and avoid concurrent prescribing with BZDs in most clinical scenarios [1,4]. There is an opportunity for providers to monitor and potentially avoid concurrent use altogether or reassess for dose tapering. Future research should focus on why health providers and patients continue to accept and rely on concurrent prescribing of these agents as a form of treatment. Policy makers and professional regulatory bodies should reinforce safe opioid use prescribing guidelines and educate providers about the additional risks associated with concurrent use of opioids and BZDs.

List of Figures:

Figure 1. 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.

Figure 2. Risk of hospitalization or emergency department visit comparing specific opioid molecules and opioid doses used concurrently with BZDs~ to their respective monotherapy counterparts

Table 1. 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 1. 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		92,757 (51.6)	
31-60		17,327 (9.6)	
61-90		9,006 (5.0)	
91-180	N/A	14,713 (8.2)	N/A
181-270		8,468 (4.7)	
271-360		6,270 (3.5)	
>361		31,264 (17.4)	
Elixhauser score:**			
Mean (SD)	2.86 (2.45)	4.36 (2.8)	2.56 (2.25)
Median (IQR)	2 (1-4)	4 (2-6)	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
****Determined using Physician Claims data from 2012-2016**
***If patients had BZD use outside of the study windows, then this was captured in our summary statistics.
Note: **All pairwise comparisons between concurrent and opioid only users had p<0.001**

Table 2. Risk of all cause hospitalization or emergency department visits in people using opioids and benzodiazepine receptor modulators during 2016-2018.

	Analysis Group*							
	None		Opioid only (reference)		Benzodiazepine^ only		Concurrent	
Patient Group	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 2. 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 3. Risk of all cause death in 2016-2017 among opioid users and subgroups of patients. *N=31,998*

Patient Category	Analysis Group							
	None		Opioid only (reference group)		Benzodiazepine^ only		Concurrent	
	OR (p-value)	95% CI	OR (p-value)		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
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
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
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
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
>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
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
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
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
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
>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

Table 3. Risk of all cause death in 2016-2017 among opioid users and subgroups of patients. *N=31,998 (continued)*

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
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
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
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
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
>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
Number of opioid dispensations:								
1-10	0.41 (<0.001)	0.38-0.44	1		0.45 (<0.001)	0.39-0.51	2.23 (<0.001)	1.96-2.54
11-30	1.36 (<0.001)	1.20-1.54	1		1.72 (<0.001)	1.41-2.11	2.70 (<0.001)	2.34-3.12
>30	2.11 (<0.001)	1.83-2.44	1		1.82 (<0.001)	1.46-2.28	1.40 (<0.001)	1.21-1.62
Number of unique prescribers:								
1	0.31 (<0.001)	0.27-0.36	1		0.49 (<0.001)	0.32-0.74	2.50 (<0.001)	1.76-3.56
2	0.51 (<0.001)	0.44-0.58	1		0.63 (<0.001)	0.48-0.81	2.29 (<0.001)	1.81-2.90
3	0.60 (<0.001)	0.52-0.69	1		0.71 (0.004)	0.56-0.90	2.03 (<0.001)	1.64-2.52
4	0.75 (<0.001)	0.64-0.87	1		0.82 (0.12)	0.64-1.05	2.49 (<0.001)	2.01-3.08
>5	1.36 (<0.001)	1.23-1.50	1		1.10 (0.15)	0.96-1.26	2.01 (<0.001)	1.82-2.24

Table 3. Risk of all cause death in 2016-2017 among opioid users and subgroups of patients. *N=31,998 (continued)*

Number of unique pharmacies:								
1	0.54 (<0.001)	0.50-0.60	1		0.72 (<0.001)	0.60-0.87	1.41 (<0.001)	1.20-1.66
2	0.65 (<0.001)	0.59-0.71	1		0.74 (<0.001)	0.62-0.87	2.09 (<0.001)	1.82-2.40
3	0.73 (<0.001)	0.64-0.84	1		0.78 (0.018)	0.63-0.96	2.48 (<0.001)	2.09-2.93
4	0.99 (0.96)	0.81-1.21	1		0.82 (0.18)	0.61-1.10	2.20 (<0.001)	1.76-2.76
>5	1.30 (0.01)	1.06-1.59	1		1.14 (0.33)	0.88-1.48	1.81 (<0.001)	1.47-2.24

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 modulator (includes Z-drugs)

Table 4. Risk of all cause death in 2016-2017 among patients co-prescribed BZDs and opioids stratified by OME (n=31,998)

Category	OME		
	<50 (reference group)	50-90	>90
	OR (p-value) 95% CI	OR (p-value) 95% CI	OR (p-value) 95% CI
Overall population	1	1.72 (<0.001) 1.35-2.19	3.13 (<0.001) 2.50-3.92
Female	1	1.76 (<0.001) 1.25-2.48	3.22 (<0.001) 2.35-4.40
Male	1	1.68 (0.003) 1.19-2.37	3.04 (<0.001) 2.20-4.19
Age at death:			
18-45	1	0.90 (0.83) 0.35-2.31	2.31 (0.08) 0.92-5.85
46-65	1	2.19 (<0.001) 1.41-3.39	2.78 (<0.001) 1.84-4.18
>65	1	1.60 (0.003) 1.18-2.18	3.41 (<0.001) 2.57-4.52

Note: BZD: benzodiazepines/Z-drugs; OME: Oral morphine equivalents, <50 OME category is the reference group; Buprenorphine and methadone were excluded

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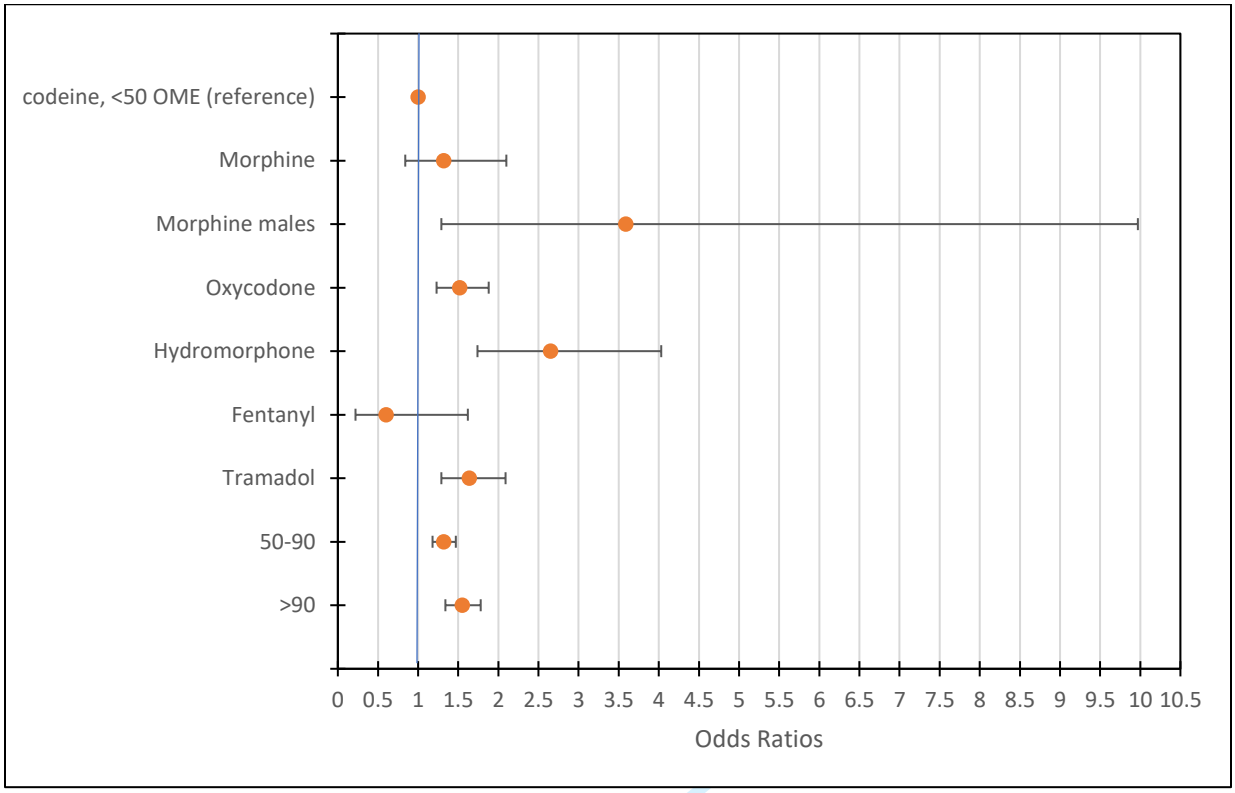
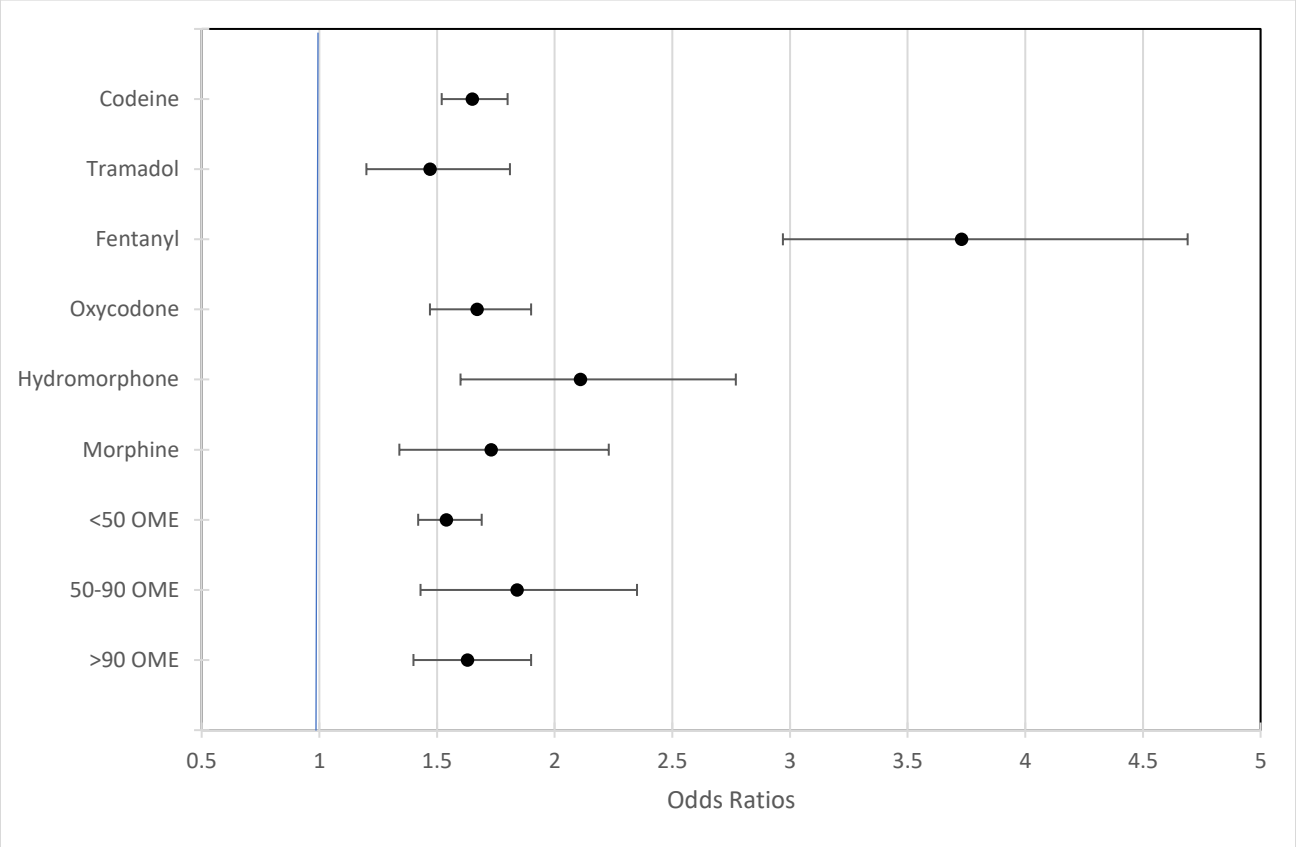
Figure 1. Risk of all cause hospitalization or emergency department visits among concurrent users of opioids and benzodiazepines by molecule and opioid dose* using codeine and <50 OME* as reference groups.



Note: bars represent 95% confidence intervals

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

Figure 2. 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

eAppendix

eTable 1. ATC codes (Anatomical Therapeutic Chemical codes) used to identify opioid and benzodiazepine/Z-drug prescriptions from prescription data (Pharmaceutical Information Network)

ATC Code	4th Level Sub-Group
Opioid	
N02AF	Morphinan derivatives
N02AG	Opioids in combination with antispasmodics
N02AE	Oripavine derivatives
N02AD	Benzomorphan derivatives
N02AC	Diphenylpropylamine derivatives
N02AB	Phenylpiperidine derivatives
N02AA	Natural opium alkaloids
N07BC	Drugs used in opioid dependence
N01AH	Opioid anesthetics
R05DA	Opium alkaloids and derivatives
N02AJ	Opioids in combination with non-opioid analgesics
N02AX	Other opioids
BZRA	
N03AE	Benzodiazepine derivatives
N05BA	Benzodiazepine derivatives
N05CD	Benzodiazepine derivatives
N05CF	Benzodiazepine related drugs

BZRA: benzodiazepine/Z-drug

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	8

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*8-9*
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Concurrent use of opioids and benzodiazepines/Z-drugs in Alberta, Canada and the risk of hospitalization and death: a case crossover study

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Secondary Subject Heading:	Public health, Research methods
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, Substance misuse < PSYCHIATRY, PAIN MANAGEMENT, Adverse events < THERAPEUTICS

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Concurrent use of opioids and benzodiazepines/Z-drugs in Alberta, Canada and the risk of hospitalization and death: a case crossover study

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Transparency: The lead author (the manuscript's guarantor, Dean Eurich) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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Abstract

Objectives: Co-prescribing of benzodiazepines/Z-drugs (BZDs) and opioids is a drug-use pattern of considerable concern due to risk of adverse events. The objective of this study is to estimate the effect of concurrent use of BZDs on the risk of hospitalizations/emergency department (ED) visits and deaths among opioid users.

Design, Setting and Participants: We conducted a population-based case crossover study during 2016-2018 involving Albertans 18 years of age and over who received opioids. From this group, we identified 1,056,773 people who were hospitalized or visited the ED, and 31,998 who died.

Intervention: Concurrent use of opioids and BZDs.

Outcomes: We estimated the risk of incident all-cause hospitalization/ED visits and all-cause mortality associated with concurrent BZD use by applying a matched-pair analyses comparing concurrent use to opioid only use.

Results: Concurrent BZD use occurred in 17% of opioid users (179,805/1,056,773). Overall, concurrent use was associated with higher risk of hospitalization/ED visit (OR 1.13, P<0.001) and all cause death (OR 1.90; P<0.001). The estimated risk of hospitalization/ED visit was highest in those >65 (OR 1.5; P<0.001), using multiple health providers (OR 1.67; P<0.001) and >365 days of opioid use (OR 1.76; P<0.001). Events due to opioid toxicity were also associated with concurrent use (OR 1.8; P<0.001). Opioid dose-response effects among concurrent patients who died were also noted (OR 3.13; P<0.001).

Interpretation: Concurrent use of opioids and BZDs further contributes to the risk of hospitalization/ED visits and mortality in Alberta, Canada over opioid use alone, with higher opioid doses, older age and increased number of unique health providers carrying higher risks.

Regulatory bodies and health providers should reinforce safe drug-use practices and be vigilant about co-prescribing.

Strengths and Limitations

- The use of a large population-based sample with near complete capture of all opioid and benzodiazepine dispensations from community pharmacies in Alberta.
- The case crossover methodology is a good fit for studies in pharmacoepidemiology like ours since the effect of many confounders can be substantially controlled,
- We considered patient sub-groups that have not previously been studied with respect to concurrent use of opioids and benzodiazepines.
- We assumed that patients took their medications as prescribed and recorded in the administrative data set.
- There is always residual confounding and importantly, unknown factors which may have changed between the control and case windows could have affected our results.

Introduction

In the context of the opioid crisis, concurrent use of opioids and BZDs represents a drug use pattern that is of substantial concern because of the increased risk of mortality [1-3]. In Canada and the United States, the policy response to the opioid crisis has focused on establishing guidelines for safe and appropriate prescribing of opioids [1,4]. 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 [1,4,5] and previous literature suggests that opioids and BZDs cannot be targeted by safe use policies in isolation [6]. Despite these warnings, opioids and BZDs are still being co-prescribed at alarming rates, as shown in our previous work using Alberta data[7]. Data from the US also show an increasing trend in co-prescribing of opioids and BZDs [2,8,9] and 50% of opioid related deaths in Ontario and Manitoba, Canada involved BZDs [10,11]. 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 [2,3]. 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 that were privately insured which may not be generalizable to the Canadian population.

To our knowledge, no Canadian population-based studies have quantified the effect of concurrent BZD and opioid use on outcomes such as hospitalizations and mortality using the characteristics that we and others have identified as relevant[2,3,7]. A knowledge gap exists on the risks of co-prescribing of these agents, especially when looking at opioid dose, duration of concurrent use, and health care utilization. Using a case crossover study design, we aimed to

examine the association between concurrent use of opioids and BZDs and adverse health outcomes and hypothesized that concurrent use would further increase risk of these outcomes. Our results will help fill the evidence gap on the adverse outcomes associated with concurrent prescribing of opioids and BZDs.

Methods

Data Sources

Demographic information and dispensation records from community pharmacies were obtained from Alberta Netcare Pharmaceutical Information Network (PIN). Information on hospitalizations and ED visits was collected using the Canadian Institute for Health Information's Discharge Abstract Database and National Ambulatory Care Reporting System. Physician visits/claims and death records were provided by Alberta Health and Population and Vital Statistics, respectively. Using anonymized patient level identifiers, these databases were linked together to establish a complete description of drug exposures and health outcomes. This study was approved by the health ethics research board at the University of Alberta (#Pro00083807).

Identification of Patients and Outcomes

Two distinct analysis cohorts were generated corresponding to two different study periods. 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.

Our primary outcomes among the cohort of opioid users were all cause, incident hospitalizations or ED visits during Jan 1, 2016-Dec 31, 2018 (n=1,056,773) and all cause mortality during Jan 1, 2016 - Dec 31, 2017 (n=31,998). The secondary outcome was incident hospitalization or ED visit due to ICD-10 diagnoses related to opioid toxicity (ICD10 F04-F99, T400-T404, T406) between Jan 1, 2016 and Dec 31, 2018 as this endpoint maybe more specific to the population using BZD and opioids[12]. The date of the event served as the index date for all analyses (eFigure 1).

Exposure

The exposure of interest was whether an opioid patient also used a BZD concurrently during the two study periods. 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 [2]. As described in our previous work[7], for each patient, a day was categorized as concurrent if it was covered by both an opioid and BZD. For every patient in our two previously defined opioid cohorts and study periods, 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)** any concurrent use of opioid and BZD (concurrent). In our case crossover analyses, "none", "opioid only", "BZD only" and "concurrent" refer to drug use during the case crossover study windows. We identified opioid and BZD prescriptions using Anatomical Therapeutic Chemical codes[13] (eTable 1) and included all Health Canada approved[14] opioid and benzodiazepine/Z-drug formulations which are monitored in the Alberta Triplicate Prescription Program[15].

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[16] was defined by number of unique providers visited and number of opioid prescriptions dispensed. Opioid doses were standardized into oral morphine equivalents (OME) using conversion factors outlined by the Triplicate Prescription Program[17] in Alberta, Canada.

We first conducted a descriptive analysis of our study population and performed pairwise comparisons between "opioid only users" and "concurrent users" using t-tests and chi^2 tests of independence using data from 2016-2018 (eFigure 1). Then, we used the case-crossover design to estimate if concurrent use increased the risk of our defined outcomes. In a case crossover study, each person serves as their own control; consequently, eliminating confounding due to age, sex and other fixed patient factors [18]. This methodology is increasingly being utilized to evaluate exposures encountered in pharmacoepidemiology and when using administrative databases [18-20].

Conditional logistic regression was used to contrast the four defined exposure categories in the seven-day risk period immediately before the event with the seven-day control period one month earlier. We chose the one month time period based on other published pharmacoepidemiology studies using this methodology [21]. 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 using data within the year prior to the outcome (eFigure 1): sex, age at admission or death, total days of cumulative concurrency prior to event, total days of previous opioid use, health care utilization, opioid molecule and dose (OME). All analyses were performed using STATA/MP 15.1 (StataCorp., College Station, TX)

Sensitivity Analyses

We performed the primary analyses on a subset of the population that excluded cancer and palliative patients like others have [3,22] by removing all patients that had relevant ICD codes (ICD9: 140-239, V66.7; ICD10: C00-D49, Z51) at any time between 2012-2018 identified from the above-mentioned databases. We also performed the analyses after adjusting the length of both the risk and control periods to 3 and 10 days and adding a second control period that preceded the event by 2 weeks.

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.

Results

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

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; Table 2). 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. With respect to total days of concurrency prior to the event, although any duration of concurrency was associated with an 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 2). Not unexpectant, increasing duration of previous use of opioids was also associated with an increasing estimated risk (Table 2).

Among the concurrent patients who were hospitalized or visited an ED, morphine, oxycodone, hydromorphone and tramadol carried the highest risks when compared to codeine and used concurrently with BZDs (Figure 1). As expected, there was an opioid dose response effect on estimated risk where higher OME's had higher risk compared to <50 OME among concurrent patients (Figure 1). When specific opioid molecules and OME dose ranges were examined, an increased risk of hospitalization or ED visit was noted for all opioid molecules and doses when used concurrently with a BZD (Figure 2).

In the secondary analysis, the estimated risk of hospitalization or ED visit was also higher in concurrent patients when compared to opioid only patients for admissions related to opioid toxicity (OR 1.8; P<0.001).

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 control and case windows (12.7% vs. 18.6%; OR 1.90; P<0.001) with males having a higher risk than females (Table 3). 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 4). 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 cumulative concurrent use (Table 3)

In sensitivity analyses, concurrent use was still associated with a higher risk of hospitalization or ED visits and mortality when compared to opioid only use after adjusting the length of study windows, number of control windows, and when cancer and palliative patients were excluded.

Discussion

Many clinical resources warn that BZDs should not be combined with opioids [1,4,5], yet our study showed a substantial proportion of patients using an opioid did so in combination with a BZD in Alberta, Canada. A concerning trend in adverse outcomes was observed with a near two-fold increased risk of mortality associated with concurrent BZD and opioid use compared to opioid only use. In particular, those age >65 years, those visiting multiple health providers, and higher OME's were at highest relative risks. Importantly, the data also show that one of the highest risks was observed in those that 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.[2] reported that 17% of opioid patients concurrently used a BZD and that higher durations of opioid use also carried higher risks of hospitalization or ED visit with respect to concurrent users, findings 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 [3]. Although both of our studies associated concurrent use of opioids and BZDs with increased risk of death, overall and in an opioid-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 population than ours. When our death 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 [23-25]. As other studies have observed, the estimated risk of an opioid-related death from taking 50-90 OME was double when compared to lower OME doses [22]. 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.

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 [26]. Both of our estimates associate a higher risk during the first few days of concurrent use as more susceptible patients may experience adverse outcomes earlier in concurrent use, thus signaling that even short periods of concurrent use carry risks.

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. 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 adequately capture. 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 [27].

Despite the messages from safe opioid prescribing guidelines[1,4], 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 [28], the trend with concurrent use of opioids and BZDs is unknown and may in fact be increasing [2,8]. From a clinical perspective, prescribers should closely follow opioid use guidelines and avoid concurrent prescribing with BZDs in most clinical scenarios [1,4]. There is an opportunity for providers to monitor and potentially avoid concurrent use altogether or reassess for dose tapering. Future research should focus on why health providers and patients continue to accept and rely on concurrent prescribing of these agents as a form of treatment. Policy makers and professional regulatory bodies should reinforce safe opioid use prescribing guidelines and educate providers about the additional risks associated with concurrent use of opioids and BZDs.

List of Figures:

Figure 1. 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.

Figure 2. Risk of hospitalization or emergency department visit comparing specific opioid molecules and opioid doses used concurrently with BZDs~ to their respective monotherapy counterparts

Table 1. Characteristics and summary statistics of opioid users with incident hospitalizations/emergency department visits using data from 2016-2018.

Characteristic	Total No. (%) of patients~ *n=1,056,773**	No. (%) of concurrent users~ *n=179,805@*	No. (%) of non-concurrent opioid 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 1. 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		92,757 (51.6)	
31-60		17,327 (9.6)	
61-90		9,006 (5.0)	
91-180	N/A	14,713 (8.2)	N/A
181-270		8,468 (4.7)	
271-360		6,270 (3.5)	
>361		31,264 (17.4)	
Elixhauser score:**			
Mean (SD)	2.86 (2.45)	4.36 (2.8)	2.56 (2.25)
Median (IQR)	2 (1-4)	4 (2-6)	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
****Determined using data from 2012-2016**
***If patients had BZD use outside of the study windows, then this was captured in our summary statistics.
Note: **All pairwise comparisons between concurrent and opioid only users had p<0.001**

Table 2. Risk of all cause hospitalization or emergency department visits in people using opioids and benzodiazepine receptor modulators during 2016-2018.

	Analysis group based on exposure category*							
	None		Opioid only (reference)		Benzodiazepine^ only		Concurrent	
Patient Group	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 2. 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 3. Risk of all cause death in 2016-2017 among opioid users and subgroups of patients. *N=31,998*

Patient Category	Analysis group based on exposure category							
	None		Opioid only (reference group)		Benzodiazepine^ only		Concurrent	
	OR (p-value)	95% CI	OR (p-value)		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
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
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
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
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
>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
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
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
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
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
>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

Table 3. Risk of all cause death in 2016-2017 among opioid users and subgroups of patients. *N=31,998 (continued)*

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
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
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
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
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
>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
Number of opioid dispensations:								
1-10	0.41 (<0.001)	0.38-0.44	1		0.45 (<0.001)	0.39-0.51	2.23 (<0.001)	1.96-2.54
11-30	1.36 (<0.001)	1.20-1.54	1		1.72 (<0.001)	1.41-2.11	2.70 (<0.001)	2.34-3.12
>30	2.11 (<0.001)	1.83-2.44	1		1.82 (<0.001)	1.46-2.28	1.40 (<0.001)	1.21-1.62
Number of unique prescribers:								
1	0.31 (<0.001)	0.27-0.36	1		0.49 (<0.001)	0.32-0.74	2.50 (<0.001)	1.76-3.56
2	0.51 (<0.001)	0.44-0.58	1		0.63 (<0.001)	0.48-0.81	2.29 (<0.001)	1.81-2.90
3	0.60 (<0.001)	0.52-0.69	1		0.71 (0.004)	0.56-0.90	2.03 (<0.001)	1.64-2.52
4	0.75 (<0.001)	0.64-0.87	1		0.82 (0.12)	0.64-1.05	2.49 (<0.001)	2.01-3.08
>5	1.36 (<0.001)	1.23-1.50	1		1.10 (0.15)	0.96-1.26	2.01 (<0.001)	1.82-2.24

Table 3. Risk of all cause death in 2016-2017 among opioid users and subgroups of patients. *N=31,998 (continued)*

Number of unique pharmacies:								
1	0.54 (<0.001)	0.50-0.60	1		0.72 (<0.001)	0.60-0.87	1.41 (<0.001)	1.20-1.66
2	0.65 (<0.001)	0.59-0.71	1		0.74 (<0.001)	0.62-0.87	2.09 (<0.001)	1.82-2.40
3	0.73 (<0.001)	0.64-0.84	1		0.78 (0.018)	0.63-0.96	2.48 (<0.001)	2.09-2.93
4	0.99 (0.96)	0.81-1.21	1		0.82 (0.18)	0.61-1.10	2.20 (<0.001)	1.76-2.76
>5	1.30 (0.01)	1.06-1.59	1		1.14 (0.33)	0.88-1.48	1.81 (<0.001)	1.47-2.24

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 modulator (includes Z-drugs)

Table 4. Risk of all cause death in 2016-2017 among patients co-prescribed BZDs and opioids stratified by OME (n=31,998)

Category	OME		
	<50 (reference group)	50-90	>90
	OR (p-value) 95% CI	OR (p-value) 95% CI	OR (p-value) 95% CI
Overall population	1	1.72 (<0.001) 1.35-2.19	3.13 (<0.001) 2.50-3.92
Female	1	1.76 (<0.001) 1.25-2.48	3.22 (<0.001) 2.35-4.40
Male	1	1.68 (0.003) 1.19-2.37	3.04 (<0.001) 2.20-4.19
Age at death:			
18-45	1	0.90 (0.83) 0.35-2.31	2.31 (0.08) 0.92-5.85
46-65	1	2.19 (<0.001) 1.41-3.39	2.78 (<0.001) 1.84-4.18
>65	1	1.60 (0.003) 1.18-2.18	3.41 (<0.001) 2.57-4.52

Note: BZD: benzodiazepines/Z-drugs; OME: Oral morphine equivalents, <50 OME category is the reference group; Buprenorphine and methadone were excluded

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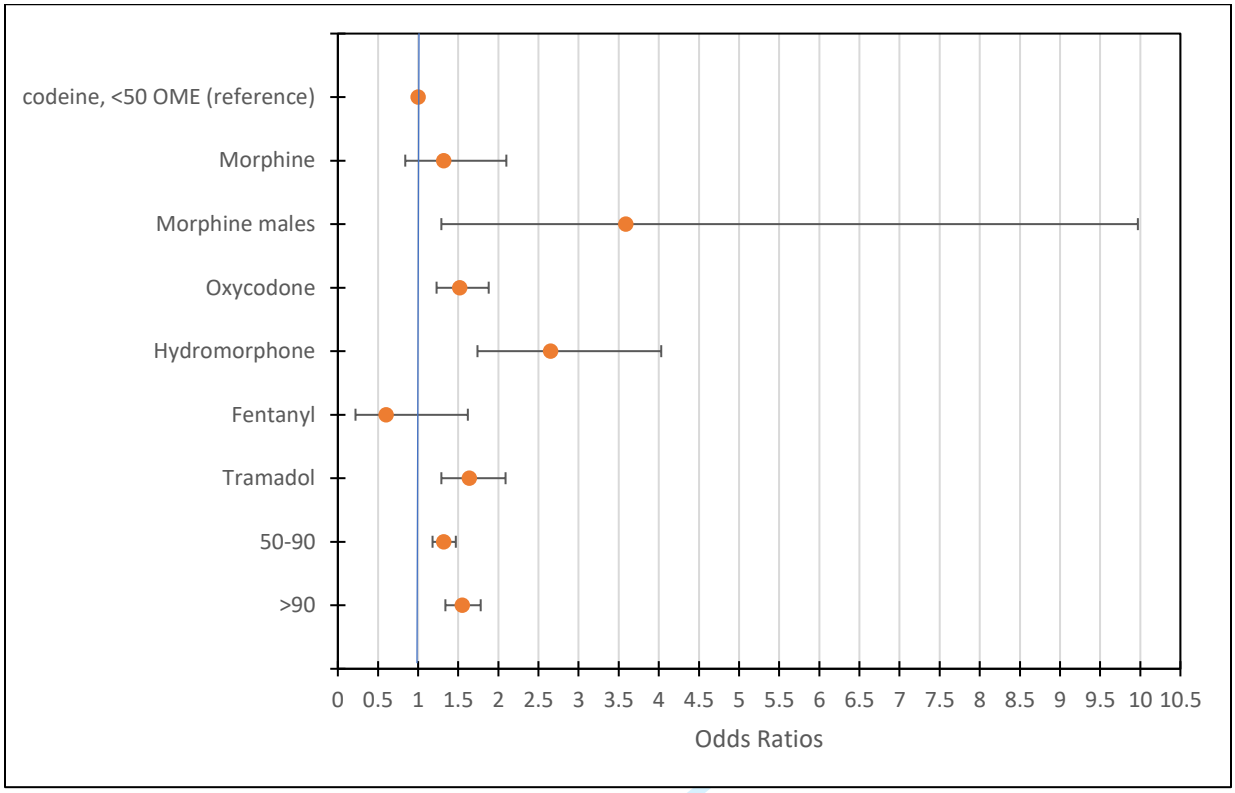
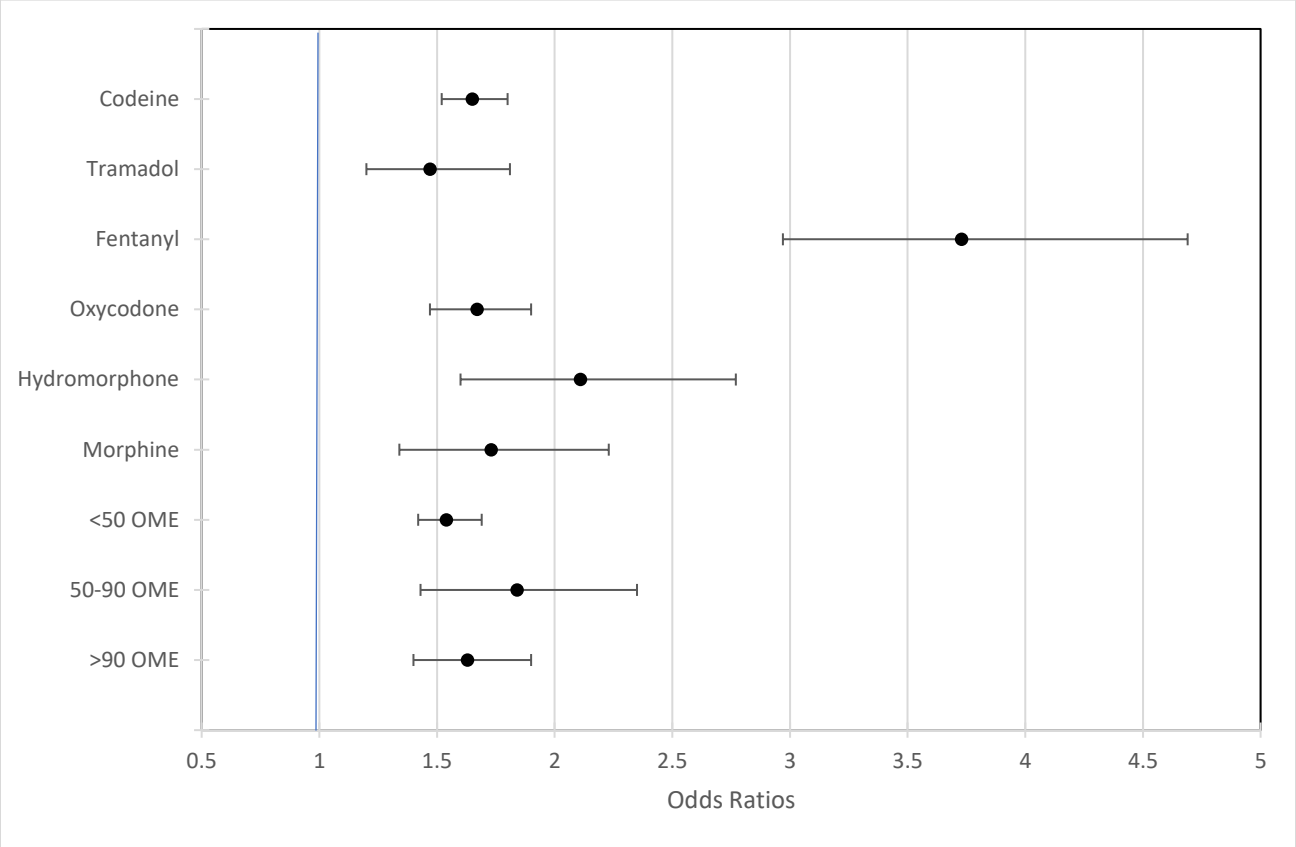
Figure 1. Risk of all cause hospitalization or emergency department visits among concurrent users of opioids and benzodiazepines by molecule and opioid dose* using codeine and <50 OME* as reference groups.



Note: bars represent 95% confidence intervals

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

Figure 2. 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

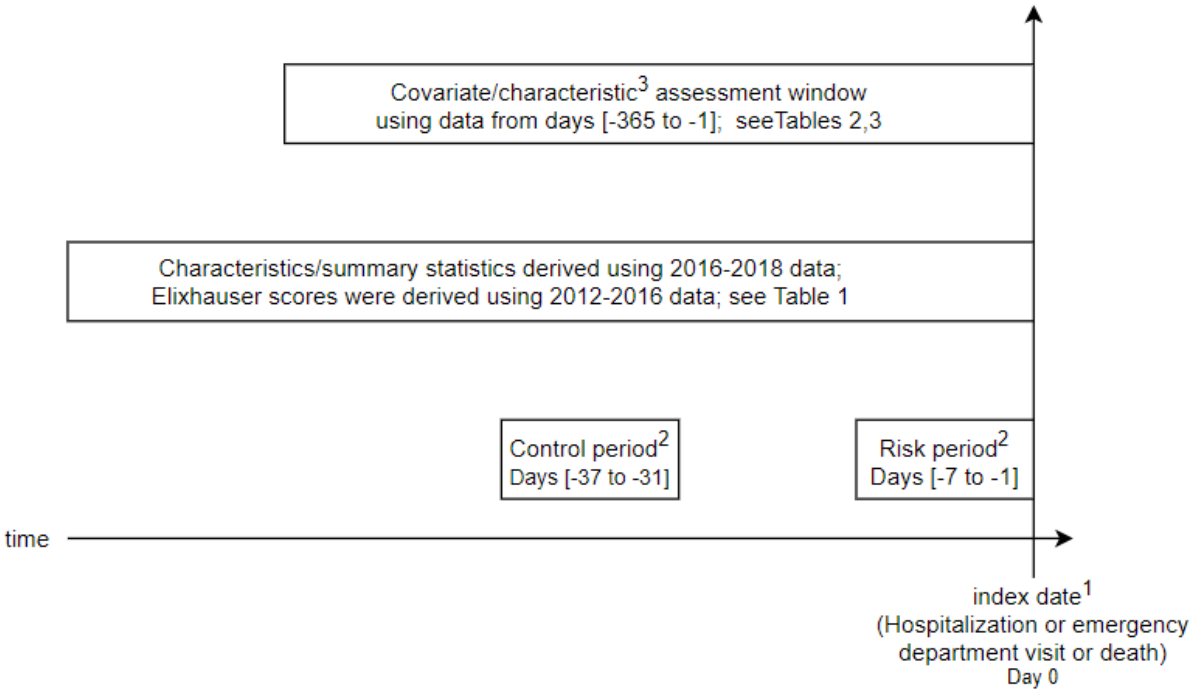
eAppendix

eTable 1. ATC codes (Anatomical Therapeutic Chemical codes) used to identify opioid and benzodiazepine/Z-drug prescriptions from prescription data (Pharmaceutical Information Network)

ATC Code	4th Level Sub-Group
Opioid	
N02AF	Morphinan derivatives
N02AG	Opioids in combination with antispasmodics
N02AE	Oripavine derivatives
N02AD	Benzomorphan derivatives
N02AC	Diphenylpropylamine derivatives
N02AB	Phenylpiperidine derivatives
N02AA	Natural opium alkaloids
N07BC	Drugs used in opioid dependence
N01AH	Opioid anesthetics
R05DA	Opium alkaloids and derivatives
N02AJ	Opioids in combination with non-opioid analgesics
N02AX	Other opioids
BZRA	
N03AE	Benzodiazepine derivatives
N05BA	Benzodiazepine derivatives
N05CD	Benzodiazepine derivatives
N05CF	Benzodiazepine related drugs

BZRA: benzodiazepine/Z-drug

eFigure 1. Schematic of case crossover design. Each patient's exposure category (opioid only, BZD only, concurrent, none) was coded in both the risk and control periods. These exposures were contrasted using conditional logistic regression.



BZD: benzodiazepine

Note:

1. Hospital admission or emergency department visit between Jan 1 2016 to Dec 31, 2018; Death between Jan 1, 2016 and Dec 31, 2017
2. Exposure categories measured in each of risk and control periods: 1) BZD only, 2) opioid only, 3) concurrent BZD and opioid, and 4) none
3. Characteristics include cumulative days of concurrent use, total days of opioid use, number of opioid dispensations, and health care utilization

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	8

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*8-9*
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.