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

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ABSTRACT

Objectives Coprescribing 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 hospitalisations/emergency department (ED) visits and deaths among opioid users.

Design, setting and participants We conducted a population-based case cross-over 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 hospitalised 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 hospitalisation/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 hospitalisation/ED visit (OR 1.13, p<0.001) and all cause death (OR 1.90; p<0.001). The estimated risk of hospitalisation/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 hospitalisation/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 coprescribing.

Strengths and limitations of this study

- 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 cross-over methodology is a good fit for studies in pharmacoepidemiology like ours since the effect of many confounders can be substantially controlled.
- We considered patient subgroups 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 benzodiazepines/Z–drugs (BZDs) represents a drug use pattern that is of substantial concern because of the increased risk of mortality.[1–3] In Canada and the USA, 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 coprescribed at alarming rates, as shown in our previous work using Alberta data.[7] Data from the USA also show an increasing trend in coprescribing of opioids and BZDs[2 8 9] and 50% of opioid-related deaths in Ontario and Manitoba, Canada involved BZDs.[10 11] Furthermore, two large studies in the USA 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 generalisable 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 hospitalisations and mortality using the characteristics that we and others have identified as relevant.[2 3 7] A knowledge gap exists on the risks of coprescribing of these agents, especially when looking at opioid dose, duration of concurrent use and healthcare utilisation. Using a case cross-over study design, we aimed to examine the association between concurrent use of opioids and BZDs and adverse health outcomes and hypothesised 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 hospitalisations and emergency department (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 anonymised patient-level identifiers, these databases were linked together to establish a complete description of drug exposures and health outcomes.

Identification of patients and outcomes

Two distinct analysis cohorts were generated corresponding to two different study periods. For the hospitalisation and ED analyses, all subjects in Alberta, Canada who received a dispensation for an opioid between 1 January 2016 and 31 December 2018, 18 years of age and over were included. For mortality analyses, all subjects who received a dispensation for an opioid between 1 January 2016 and 31 December 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 hospitalisations or ED visits during 1 January 2016–31 December 2018 (n=1 056 773) and all cause mortality during 1 January 2016–31 December 2017 (n=31 998). The secondary outcome was incident hospitalisation or ED visit due to ICD-10 (International Classification of Diseases, Tenth Revision) diagnoses related to opioid toxicity (ICD10 F04–F99, T400–T404, T406) between 1 January 2016 and 31 December 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 (see online supplemental 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 categorised 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 categorised 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 cross-over 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] (see online supplemental etable 1) and included all Health Canada approved[14] opioid and BZD 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 one dispensation for an opioid and concurrent use was defined as at least 1 day of overlap between an opioid and BZD. Healthcare utilisation[16] was defined by number of unique providers visited and number of opioid prescriptions dispensed. Opioid doses were standardised 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 χ^2 tests of independence using data from 2016 to 2018 (see online supplemental efigure 1). Then, we used the case cross-over design to estimate if concurrent use increased the risk of our defined outcomes. In a case cross-over 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 used 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 7-day risk period immediately before the event with the 7-day control period 1 month earlier. We chose the 1-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 hospitalisation/ED visits and mortality using ORs and their associated 95% CIs. 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 subgroups using data within the year prior to the outcome (see online supplemental efigure 1): sex, age at admission or death, total

Table 1 Characteristics and summary statistics of opioid users with incident hospitalisations/emergency department visits using data from 2016 to 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)
No of dispensations for opioids	11 240 195(-)	5 855 666 (-)	5 384 529 (-)
No of dispensations for BZDs	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)	2276 (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)
No 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)
No 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 no 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)
No of people that received a dispensation for specified opioid molecule and daily OME**			
Buprenorphine/naloxone	7995 (0.76)	3005 (1.7)	7451 (0.85)

Continued

Table 1 Continued

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§
Methadone	7394 (0.70)	3218 (1.8)	7043 (0.80)
Buprenorphine (transdermal patch)	8238 (0.78)	3447 (1.9)	7158 (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	1163 (0.11)	485 (0.27)	1007 (0.12)
Hydromorphone	70 181 (6.6)	22 376 (12.4)	62 205 (7.1)
Fentanyl	8888 (0.84)	6279 (3.5)	8067 (0.92)
Tramadol	316 662 (30.0)	50 891 (28.3)	292 965 (33.4)
Tapentadol	1570 (0.15)	696 (0.39)	1387 (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	N/A	92 757 (51.6)	N/A
31–60		17 327 (9.6)	
61–90		9006 (5.0)	
91–180		14 713 (8.2)	
181–270		8468 (4.7)	
271–360		6270 (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)

All pairwise comparisons between concurrent and opioid only users had p<0.001.
*Unless otherwise indicated.
†n=990 098 for OME analyses.
‡n=171 457 for OME analyses.
§n=818 641 for OME analyses.
¶If patients had BZD use outside of the study windows, then this was captured in our summary statistics.
**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 to 2016.
BZD, benzodiazepines/Z-drug; N/A, not available; OME, oral morphine equivalent.

days of cumulative concurrency prior to event, total days of previous opioid use, healthcare utilisation, OME. All analyses were performed using STATA/MP V.15.1 (StataCorp)

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 hospitalised or visited the ED during 2016–2018 (table 1). Among this cohort, 17%

Table 2 Risk of all cause hospitalisation 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 to 0.21	1	0.46 (<0.001)	0.45 to 0.48	1.13 (<0.001)	1.10 to 1.17
Sex							
Female	0.24 (<0.001)	0.23 to 0.25	1	0.51 (<0.001)	0.49 to 0.52	1.19 (<0.001)	1.14 to 1.23
Male	0.18 (<0.001)	0.18 to 0.19	1	0.43 (<0.001)	0.41 to 0.45	1.10 (<0.001)	1.05 to 1.16
Age at admission							
20–40	0.16 (<0.001)	0.15 to 0.16	1	0.33 (<0.001)	0.31 to 0.35	0.96 (0.33)	0.88 to 1.04
40–65	0.23 (<0.001)	0.22 to 0.23	1	0.48 (<0.001)	0.46 to 0.50	1.12 (<0.001)	1.07 to 1.18
>65	0.30 (<0.001)	0.29 to 0.31	1	0.73 (<0.001)	0.69 to 0.77	1.50 (<0.001)	1.39 to 1.61
Total days of cumulative concurrency							
1–30	0.33 (<0.001)	0.31 to 0.35	1	0.72 (<0.001)	0.67 to 0.78	2.47 (<0.001)	2.26 to 2.70
31–90	0.45 (<0.001)	0.41 to 0.49	1	1.05 (0.36)	0.95 to 1.17	1.50 (<0.001)	1.34 to 1.67
91–180	0.44 (<0.001)	0.39 to 0.49	1	1.09 (0.24)	0.95 to 1.24	1.45 (<0.001)	1.28 to 1.64
181–365	0.42 (<0.001)	0.37 to 0.48	1	1.11 (<0.11)	0.97 to 1.3	1.57 (<0.001)	1.40 to 1.76
>365	0.26 (<0.001)	0.23 to 0.29	1	1.26 (<0.001)	1.11 to 1.41	1.82 (<0.001)	1.67 to 1.99
>900	0.13 (<0.001)	0.09 to 0.21	1	1.64 (0.01)	1.12 to 2.38	3.15 (<0.001)	2.41 to 4.11
Total days of opioid use							
1–7	0.04 (<0.001)	0.03 to 0.05	1	0.08 (<0.001)	0.07 to 0.09	0.90 (0.40)	0.72 to 1.14
8–30	0.15 (<0.001)	0.14 to 0.16	1	0.30 (<0.001)	0.28 to 0.32	1.21 (0.002)	1.07 to 1.38
31–90	0.34 (<0.001)	0.33 to 0.35	1	0.71 (<0.001)	0.66 to 0.76	1.36 (<0.001)	1.22 to 1.51
91–180	0.48 (<0.001)	0.46 to 0.51	1	1.05 (0.35)	0.95 to 1.15	1.54 (<0.001)	1.37 to 1.73
181–365	0.54 (<0.001)	0.52 to 0.57	1	1.27 (<0.001)	1.15 to 1.40	1.73 (<0.001)	1.56 to 1.92
>365	0.41 (<0.001)	0.39 to 0.42	1	1.21 (<0.001)	1.12 to 1.32	1.76 (<0.001)	1.66 to 1.86
No of opioid dispensations							
1–10	0.16 (<0.001)	0.16 to 0.17	1	0.34 (<0.001)	0.33 to 0.35	0.93 (0.01)	0.87 to 0.98
9–30	0.49 (<0.001)	0.47 to 0.51	1	1.20 (<0.001)	1.11 to 1.30	1.62 (<0.001)	1.50 to 1.74
>30	0.35 (<0.001)	0.33 to 0.37	1	1.09 (0.10)	0.98 to 1.21	1.77 (<0.001)	1.65 to 1.89
No of unique prescribers							
1	0.14 (<0.001)	0.13 to 0.14	1	0.30 (<0.001)	0.28 to 0.32	0.73 (<0.001)	0.65 to 0.81
2	0.20 (<0.001)	0.19 to 0.20	1	0.41 (<0.001)	0.39 to 0.43	1.02 (0.64)	0.94 to 1.11
3	0.26 (<0.001)	0.25 to 0.27	1	0.51 (<0.001)	0.48 to 0.54	1.30 (<0.001)	1.19 to 1.42
4	0.32 (<0.001)	0.31 to 0.34	1	0.68 (<0.001)	0.63 to 0.73	1.54 (<0.001)	1.39 to 1.70
>5	0.38 (<0.001)	0.37 to 0.40	1	0.91 (<0.001)	0.86 to 0.96	1.67 (<0.001)	1.57 to 1.77
No of unique pharmacies							
1	0.14 (<0.001)	0.13 to 0.15	1	0.32 (<0.001)	0.31 to 0.35	0.95 (0.25)	0.86 to 1.04
2	0.20 (<0.001)	0.19 to 0.21	1	0.45 (<0.001)	0.43 to 0.48	1.12 (0.007)	1.03 to 1.21
3	0.27 (<0.001)	0.26 to 0.28	1	0.56 (<0.001)	0.52 to 0.59	1.24 (<0.001)	1.14 to 1.35
4	0.31 (<0.001)	0.29 to 0.33	1	0.66 (<0.001)	0.61 to 0.71	1.47 (<0.001)	1.33 to 1.64
>5	0.39 (<0.001)	0.38 to 0.41	1	0.78 (<0.001)	0.73 to 0.83	1.47 (<0.001)	1.38 to 1.57

*Risk interval=7 days before hospitalisation/emergency visit; control interval=7-day period 1 month before hospitalisation/emergency department visit.
†Includes all benzodiazepine receptor modulators.

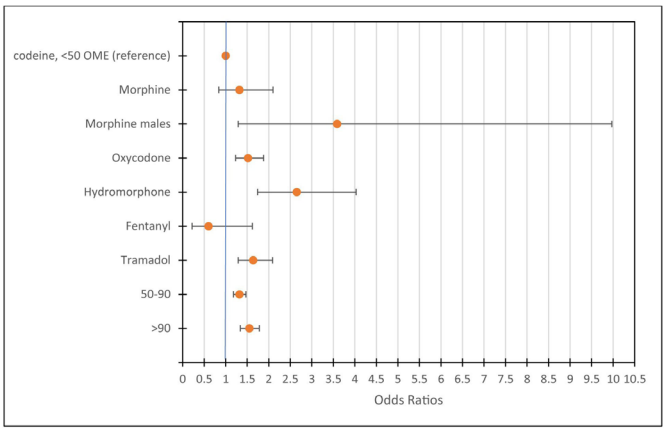

Figure 1 Risk of all cause hospitalisation or emergency department visits among concurrent users of opioids and benzodiazepines by molecule and opioid dose using codeine and <50 OME as reference groups. Bars represent 95% CIs. Dose is OME and <50 OME is the reference. Buprenorphine and methadone have been excluded. OME, oral morphine equivalent.

(n=1 79 805) had at least 1 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 1 day of concurrent use.

Hospitalisations or ED visits

Compared with opioid only use, concurrent use of opioids and BZDs was associated with an elevated risk of hospitalisation 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)

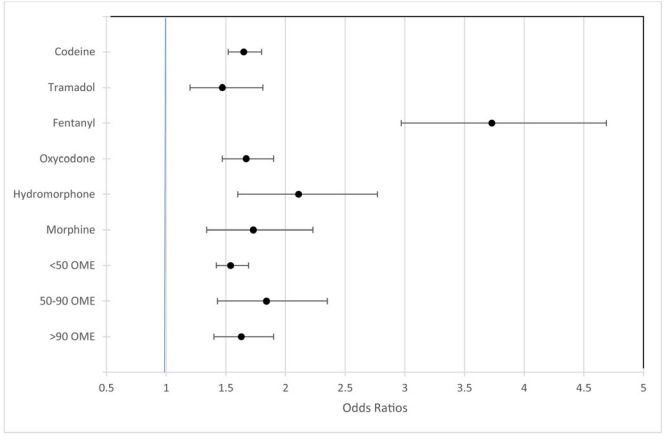

Figure 2 Risk of hospitalisation or emergency department visit comparing specific opioid molecules and opioid doses* used concurrently with BZDs† to their respective monotherapy counterparts‡. Bars represent 95% CIs. *Opioid dose is OME; buprenorphine and methadone have been excluded. †Benzodiazepine receptor modulator (includes Z-drugs). ‡For example, the ORs plotted for codeine represents the risk of codeine + BZD compared with codeine alone and that of <50 OME represents the risk of <50 OME + BZD compared with <50 OME alone. BZD, benzodiazepines/Z-drug; OME, oral morphine equivalent.

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 hospitalised or visited an ED, morphine, oxycodone, hydromorphone and tramadol carried the highest risks when compared with 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 with<50 OME among concurrent patients (figure 1). When specific opioid molecules and OME dose ranges were examined, an increased risk of hospitalisation 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 hospitalisation or ED visit was also higher in concurrent patients when compared with opioid only patients for admissions related to opioid toxicity (OR 1.8; p<0.001).

Mortality

We identified 31 998 deaths between 2016 and 2017 in our cohort of opioid users. Estimated risk of death was substantially higher with concurrent use when compared with 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 with<50 OME group (table 4). Similar to the trends in hospitalisations 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 hospitalisation or ED visits and mortality when compared with 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 twofold increased risk of mortality associated with concurrent BZD and opioid use compared with opioid only use. In particular, those age >65 years, those visiting multiple health providers, and higher OME's were at

Table 3 Risk of all cause death in 2016–2017 among opioid users and subgroups of patients, (n=31 998)

	Analysis group based on exposure category						
	None		Opioid only (reference group)	Benzodiazepine* only		Concurrent	
Patient category	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 to 0.71	1	0.76 (<0.001)	0.69 to 0.83	1.90 (<0.001)	1.76 to 2.05
Female	0.64 (<0.001)	0.60 to 0.70	1	0.68 (<0.001)	0.60 to 0.78	1.73 (<0.001)	1.56 to 1.92
Male	0.70 (<0.001)	0.62 to 0.76	1	0.85 (0.02)	0.75 to 0.97	2.09 (<0.001)	1.87 to 2.33
Age at death							
18–45	1.20 (0.13)	0.94 to 1.54	1	1.98 (<0.001)	1.38 to 2.86	2.26 (<0.001)	1.63 to 3.13
46–65	1.13 (0.03)	1.01 to 1.28	1	1.24 (0.03)	1.02 to 1.51	2.20 (<0.001)	1.90 to 2.55
>65	0.56 (<0.001)	0.52 to 0.60	1	0.61 (<0.001)	0.54 to 0.68	1.79 (<0.001)	1.63 to 1.97
Total days of cumulative concurrency							
1–30	0.82 (0.007)	0.71 to 0.95	1	0.88 (0.17)	0.74 to 1.05	4.93 (<0.001)	4.29 to 5.66
31–90	2.4 (<0.001)	1.84 to 3.15	1	1.18 (0.21)	0.91 to 1.56	1.41 (<0.001)	1.14 to 1.74
91–180	2.39 (<0.001)	1.58 to 3.60	1	1.74 (0.01)	1.12 to 2.68	0.80 (0.20)	0.56 to 1.12
181–365	4.27 (<0.001)	2.58 to 7.07	1	1.54 (0.08)	0.94 to 2.51	0.92 (0.66)	0.63 to 1.33
>365	1.53 (0.26)	0.73 to 3.24	1	1.17 (0.71)	0.51 to 2.72	0.39 (0.003)	0.21 to 0.72
Total days of opioid use							
1–7	0.14 (<0.001)	0.11 to 0.17	1	0.17 (<0.001)	0.12 to 0.23	2.78 (<0.001)	1.79 to 4.32
8–30	0.38 (<0.001)	0.34 to 0.42	1	0.48 (<0.001)	0.40 to 0.59	2.29 (<0.001)	1.89 to 2.78
31–90	1.03 (0.56)	0.92 to 1.16	1	1.46 (<0.001)	1.19 to 1.78	2.58 (<0.001)	2.22 to 3.00
91–180	2.08 (<0.001)	1.75 to 2.48	1	2.62 (<0.001)	1.96 to 3.51	2.16 (<0.001)	1.80 to 2.60
181–365	2.66 (<0.001)	2.18 to 3.24	1	3.13 (<0.001)	2.24 to 4.38	1.83 (<0.001)	1.50 to 2.23
>365	2.83 (<0.001)	2.16 to 3.71	1	2.41 (<0.001)	1.51 to 3.87	1.20 (0.15)	0.93 to 1.53
No of opioid dispensations							
1–10	0.41 (<0.001)	0.38 to 0.44	1	0.45 (<0.001)	0.39 to 0.51	2.23 (<0.001)	1.96 to 2.54
11–30	1.36 (<0.001)	1.20 to 1.54	1	1.72 (<0.001)	1.41 to 2.11	2.70 (<0.001)	2.34 to 3.12
>30	2.11 (<0.001)	1.83 to 2.44	1	1.82 (<0.001)	1.46 to 2.28	1.40 (<0.001)	1.21 to 1.62
No of unique prescribers							
1	0.31 (<0.001)	0.27 to 0.36	1	0.49 (<0.001)	0.32 to 0.74	2.50 (<0.001)	1.76 to 3.56
2	0.51 (<0.001)	0.44 to 0.58	1	0.63 (<0.001)	0.48 to 0.81	2.29 (<0.001)	1.81 to 2.90
3	0.60 (<0.001)	0.52 to 0.69	1	0.71 (0.004)	0.56 to 0.90	2.03 (<0.001)	1.64 to 2.52
4	0.75 (<0.001)	0.64 to 0.87	1	0.82 (0.12)	0.64 to 1.05	2.49 (<0.001)	2.01 to 3.08
>5	1.36 (<0.001)	1.23 to 1.50	1	1.10 (0.15)	0.96 to 1.26	2.01 (<0.001)	1.82 to 2.24
No of unique pharmacies							
1	0.54 (<0.001)	0.50 to 0.60	1	0.72 (<0.001)	0.60 to 0.87	1.41 (<0.001)	1.20 to 1.66
2	0.65 (<0.001)	0.59 to 0.71	1	0.74 (<0.001)	0.62 to 0.87	2.09 (<0.001)	1.82 to 2.40
3	0.73 (<0.001)	0.64 to 0.84	1	0.78 (0.018)	0.63 to 0.96	2.48 (<0.001)	2.09 to 2.93
4	0.99 (0.96)	0.81 to 1.21	1	0.82 (0.18)	0.61 to 1.10	2.20 (<0.001)	1.76 to 2.76
>5	1.30 (0.01)	1.06 to 1.59	1	1.14 (0.33)	0.88 to 1.48	1.81 (<0.001)	1.47 to 2.24

*Benzodiazepine receptor modulator (includes Z-drugs).
control interval, seven-day period one month before death; risk interval, seven days before death.

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 hospitalisations 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 USA. Sun *et al*[2] reported that 17% of opioid patients concurrently used a BZD and that higher durations of

Table 4 Risk of all cause death in 2016–2017 among patients coprescribed BZDs and opioids stratified by OME (n=31 998)

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

Buprenorphine and methadone were excluded.
BZD, benzodiazepines/Z-drugs; OME, oral morphine equivalent.

opioid use also carried higher risks of hospitalisation or ED visit with respect to concurrent users, findings that we also shared. However, compared with 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 USA 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 with 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 hospitalisation or ED visit or death.

Our finding that hospitalisation or ED visit and mortality risks were higher during the initial periods of concurrent use are also similar to another study done in the USA.[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 signalling 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, hospitalisations and ED visits, and mortality from Alberta Health and Vital Statistics were also used to identify our outcomes. Since we used a case cross-over design, many confounding variables would have been completely controlled for in our analysis (eg, age, sex, comorbidities) 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.

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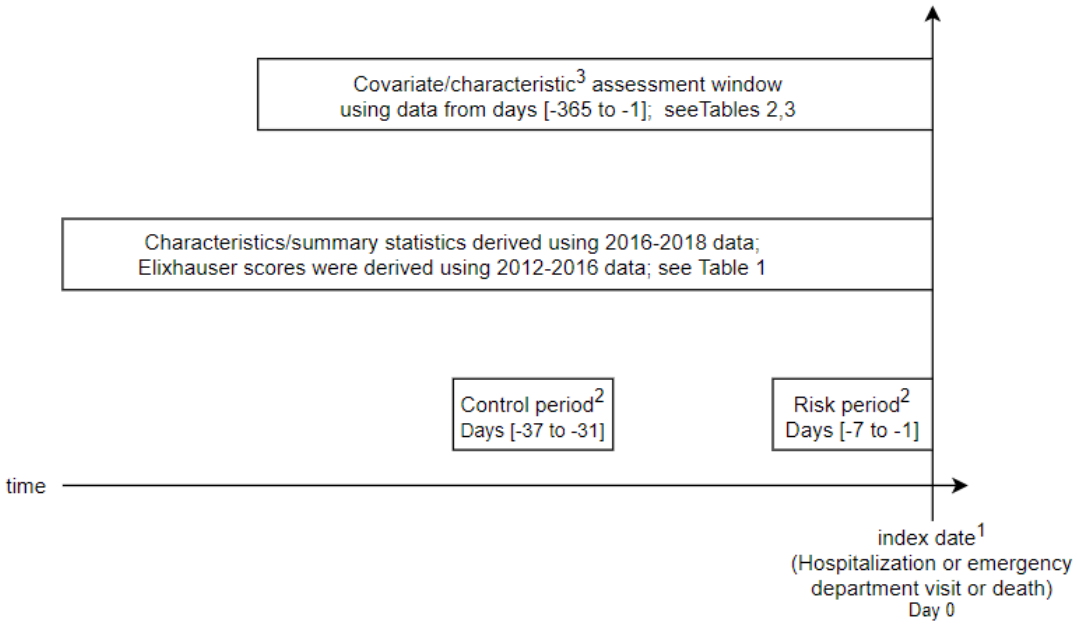
eAppendix

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