Association Between Benzodiazepine or Z-Drug Prescriptions and Drug-Related Poisonings Among Patients Receiving Buprenorphine Maintenance: A Case-Crossover Analysis

Kevin Y. Xu, M.D., M.P.H., Jacob T. Borodovsky, Ph.D., Ned Presnall, M.S.W., Carrie M. Mintz, M.D., Sarah M. Hartz, M.D., Ph.D., Laura J. Bierut, M.D., Richard A. Grucza, Ph.D.

Objective: Persons with opioid use disorder who take benzodiazepines are at high risk for overdose. The objective of this study was to evaluate the association of benzodiazepine and Z-drug use with drug-related poisonings among patients receiving buprenorphine maintenance treatment.

Methods: A case-crossover study design was used to analyze prescription claims among persons ages 12–64 with opioid use disorder who had buprenorphine prescriptions and had claims data in the IBM MarketScan databases (2006–2016), encompassing 14,213,075 person-days of observation time for 23,036 individuals who experienced drug-related poisoning. The exposures were buprenorphine prescriptions and benzodiazepine or Z-drug prescriptions, standardized as daily diazepam-equivalent milligram doses and separated by pharmacologic properties (short-acting or long-acting benzodiazepines, Z-drugs). The outcome of interest was nonfatal drug-related poisoning. Conditional logistic regression was used to evaluate variation in benzodiazepine or Z-drug and buprenorphine use between poisoning and nonpoisoning days.

Results: Buprenorphine treatment days were associated with a nearly 40% reduction in the risk of poisoning events (odds ratio=0.63, 95% CI=0.60, 0.66) compared with nontreatment days, whereas benzodiazepine or Z-drug treatment days were associated with an 88% increase in the risk of such events (95% CI=1.78, 1.98). In stratified analyses by dose, we observed a 78% (95% CI=1.67, 1.88) and 122% (95% CI=2.03, 2.43) increase in poisonings associated with low-dose and high-dose benzodiazepine or Z-drug treatment days, respectively. High-dose, but not low-dose, benzodiazepine or Z-drug treatment was associated with increased poisonings in combination with buprenorphine cotreatment (odds ratio=1.64, 95% CI=1.39, 1.93), but this was lower than the odds risk associated with benzodiazepine or Z-drug treatment in the absence of buprenorphine (low-dose: odds ratio=1.69, 95% CI=1.60, 1.79; high-dose: odds ratio=2.23, 95% CI=2.04, 2.45).

Conclusions: Increased risk of nonfatal drug-related poisoning is associated with benzodiazepine or Z-drug treatment in patients with opioid use disorder, but this risk is partially mitigated by buprenorphine treatment. Dose reduction of benzodiazepines or Z-drugs while maintaining buprenorphine treatment may provide the advantage of lowering drug-related poisoning risk.

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Buprenorphine is an effective treatment for opioid use disorder, contributing to significant reductions in all-cause and opioid-associated mortality amid the current U.S. opioid epidemic (1). Among patients with opioid use disorder who are taking buprenorphine, benzodiazepine use is highly prevalent. Some studies have estimated that as many as 30% of patients with opioid use disorder who receive opioid maintenance treatment also receive benzodiazepine prescriptions (2), with more than one-third of these patients endorsing past-month problematic use of benzodiazepines (3). Although benzodiazepines are frequently prescribed for treatment of comorbid mood and anxiety disorders, which are common in this patient population, recent research has shed light on respiratory depression, overdose risk, and addictive potential associated with benzodiazepine use in patients taking opioids chronically, such as buprenorphine (4–7). It is unclear whether the risks associated with benzodiazepine use outweigh the treatment benefits of buprenorphine.

The relationship between benzodiazepine use and buprenorphine treatment outcomes is poorly characterized. Existing observational studies that examined mortality risk associated with benzodiazepine prescriptions among patients with opioid use disorder have produced contradictory

results (8–10). While some findings suggest that benzodiazepines may enhance retention in buprenorphine maintenance treatment (4, 11), benzodiazepines have also been associated with increases in drug-related poisonings (11–14), all-cause mortality (11), nonoverdose deaths (8), decreased retention in treatment (12, 15–17), and accidental injury-related emergency department visits (5). To our knowledge, no studies have specifically examined potential additive or interactive effects between buprenorphine and benzodiazepines.

Another limitation of the current research base for benzodiazepine-related morbidity and mortality is that the different pharmacologic properties of sedative/hypnotics, such as half-life and potency, have seldom been explored (18). This is an important clinical and scientific gap, given that shorter-acting benzodiazepines, such as alprazolam, are thought to have higher addictive potential than longer-acting medications, such as clonazepam (6, 19). In fact, previous studies of populations without opioid use disorder have shown significant intra-benzodiazepine variation in health outcomes; for example, certain benzodiazepines appear to be associated with greater injury risk in the elderly than others (18). Additionally, little research has investigated drug-related poisoning associated with selective benzodiazepine receptor modulators (Z-drugs: zolpidem, zaleplon, and eszopiclone). These medications have increasingly been found to have a spectrum of adverse effects similar to that for benzodiazepines, with similar dose-response effects on all-cause mortality in the general population (20, 21). Because studies to date have relied on relatively small numbers of benzodiazepine users, they have precluded examination of how drug subclasses (e.g., short-acting compared with long-acting benzodiazepines, Z-drugs) or dosing regimens affect opioid use disorder outcomes.

In light of the research gap on opioid use disorder outcomes among patients taking both buprenorphine and benzodiazepines or Z-drugs, we used the IBM MarketScan Research Databases (2006–2016; IBM, Armonk, N.Y.) in the present study to quantify odds of nonfatal drug-related poisoning (including overdoses) associated with benzodiazepine or Z-drug use in patients with opioid use disorder; to determine whether benzodiazepine or Z-drug use improves, nullifies, or reverses the protective effect of buprenorphine in patients with opioid use disorder; and to evaluate whether different sedative/hypnotic subtypes (e.g., long-acting compared with short-acting agents and Z-drugs) correspond to different poisoning risks.

METHODS

Data Set and Study Subjects

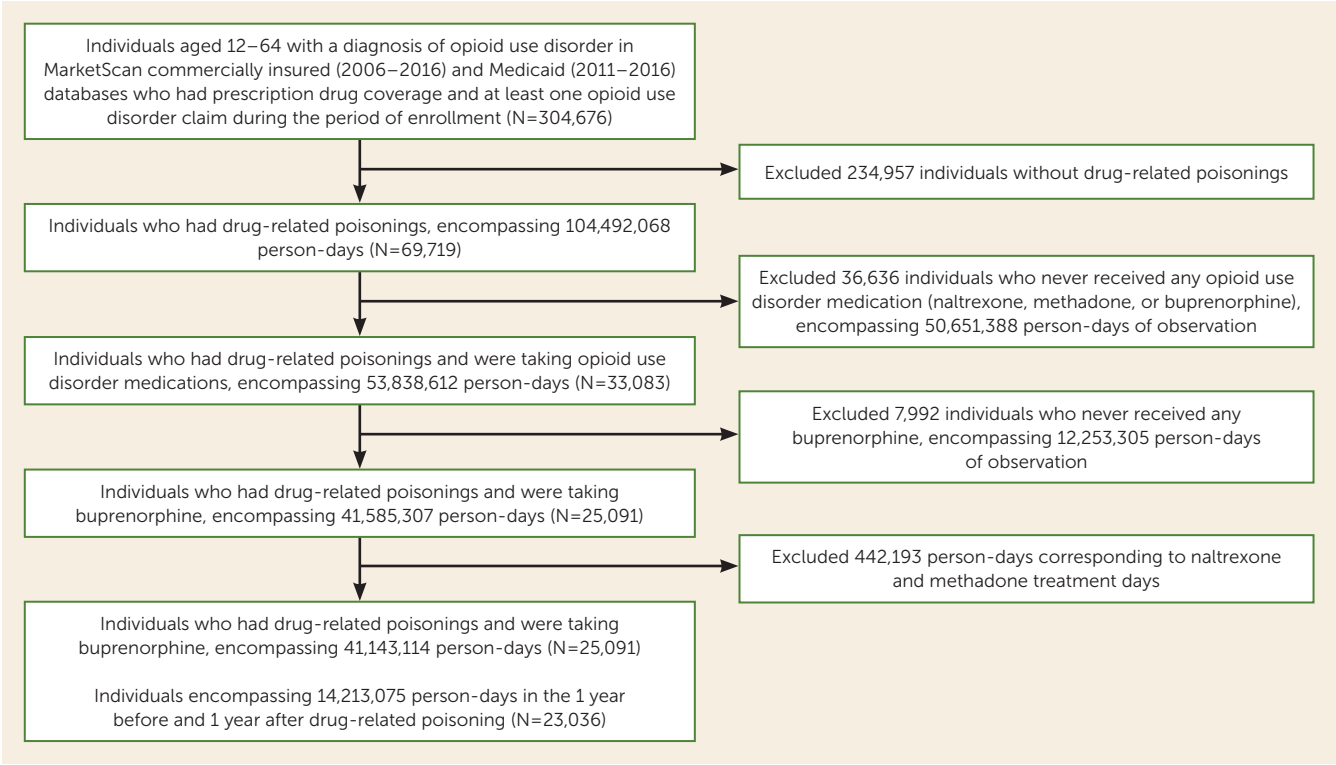
We used pharmaceutical claims data on 304,676 individuals, ages 12–64, in the IBM MarketScan Commercial and Multi-State Medicaid Databases who received buprenorphine treatment for opioid use disorder (Figure 1). The data, spanning from January 1, 2006, to December 31, 2016, represent claims for insured active employees, early (non-Medicare) retirees, and dependents insured by employer-sponsored plans, as well as Medicaid insurance holders, spanning all 50 states (22). Details on data extraction are summarized in the Methods section in the online supplement. Because all data were de-identified, our analysis was exempt from human subjects review by the institutional review board at Washington University, St. Louis.

Individuals ages 12 to 64 with insurance claims indicating an opioid use disorder diagnosis, at least one buprenorphine prescription, and at least one nonfatal drug-related poisoning were included for analysis. Buprenorphine prescriptions were defined by associated diagnostic codes selected using established methods (22) (for the list of codes, see Table S1 in the online supplement). We included persons who had periods of buprenorphine-free treatment as long as they received the medication at another time point. Buprenorphine use was characterized in terms of strength, quantity, and days of supply in order to calculate a daily milligram dose. This was further stratified into daily buprenorphine doses >12 mg and ≤ 12 mg, given previous analyses suggesting differences in treatment retention associated with this dose (23). Because each individual serves as his or her own control in case-crossover designs, all individuals in the sample must experience the outcome at least once. Therefore, we excluded all individuals who did not experience a drug-related poisoning.

Study Design

We used a case-crossover study design that exploited within-subject variation in exposure and outcome, which addresses unobserved time-invariant confounding by allowing each individual to serve as his or her own control. Units of observation were person-days, denoting days during which patients were enrolled in a health insurance plan. Case periods were days when a patient experienced nonfatal drug-related poisonings. Control periods were nearby days without poisoning events (24, 25). We characterized each person-day of observation by the presence or absence of benzodiazepine or Z-drug treatment and the presence or absence of buprenorphine treatment. Each study subject could have multiple poisoning events as long as these events fell within the interval of ≤ 365 days before and after the index poisoning (Figure 2). Individuals with fewer observation days on either side of the index event were included with missing days treated as censored. We evaluated study subjects during a time period up to 1 year before and the year after their first drug-related poisoning (index date), thus limiting subjects to a maximum of 2-year periods of observation to reduce heterogeneity in observation time per person. We included periods both before and after the index poisoning in order to define the poisoning as a repeatable event, allowing for the inclusion of time as a covariate (25, 26). Thus, the unit of analysis was days, stratified within persons, and the comparison of interest was drug exposure status concurrent with drug-related poisoning (case period) compared with exposure status during referent periods when poisoning events did not occur (control period).

FIGURE 1. Derivation of the analytic sample during follow-up of patients with opioid use disorder with a drug-related poisoning



Given their high prevalence in clinical practice and overlapping indications with benzodiazepines, selective serotonin reuptake inhibitors (SSRIs) (sertraline, fluoxetine, escitalopram, and citalopram) were included in our conditional logistic models as an active comparator analysis. This is a validated approach employed by previous investigators (27) to control for unobserved confounding. In other words, the SSRI term assesses whether underlying conditions for which patients were receiving benzodiazepines or Z-drugs contributed to drug-related poisonings.

Ascertainment of Outcomes and Exposures

The primary outcome was nonfatal drug-related poisonings (including overdoses) (Figure 2). Controls were adjacent person-days when a poisoning event did not occur. Poisonings were defined using ICD codes and Healthcare Common Procedure Coding System codes for naloxone reversal. In accordance with guidelines compiled by the Centers for Disease Control and Prevention consensus recommendations for poisoning surveillance (28), the codes we employed encompassed not only opioids but also alcohol, benzodiazepines, psychotropic medication, and overdose with other substances (see Table S1 in the online supplement). This was intended to capture conditions commonly associated with chronic drug misuse, as well as to avoid misclassification bias and underestimation of overdose risks. We searched all emergency department visits, outpatient ambulatory visits, and hospitalizations for relevant diagnostic codes (28).

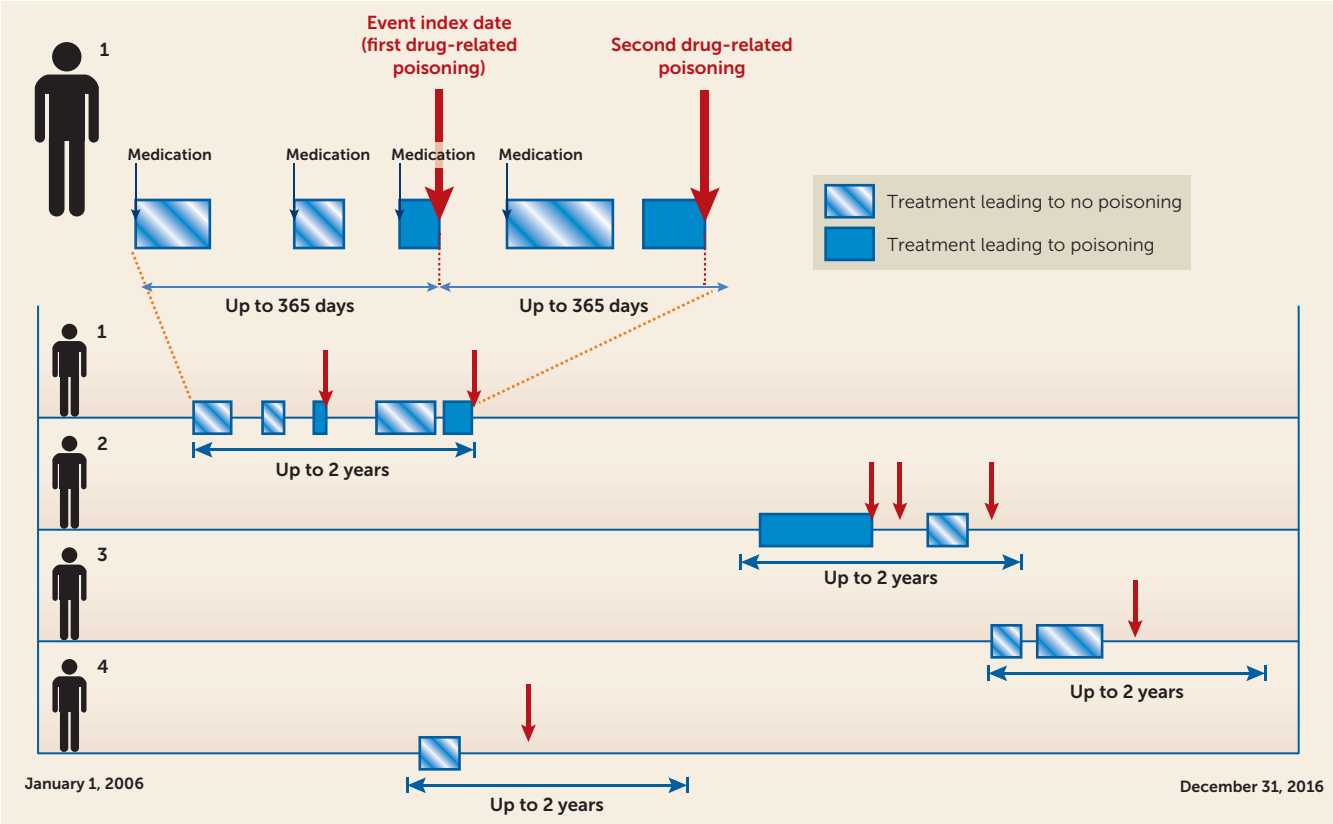
The primary exposure was benzodiazepine or Z-drug prescriptions, ascertained through pharmacy files. A person was assumed to be exposed if he or she was covered by a prescription for a drug on a given day. We characterized initial benzodiazepine, Z-drug, and buprenorphine prescriptions in terms of strength, quantity dispensed, and days of supply. To standardize the daily dose, we calculated the strength of each benzodiazepine or Z-drug in terms of total diazepam-equivalent milligrams (29) using known pharmacologic conversion factors (see Table S2 in the online supplement) (30–32). We calculated a daily diazepam-equivalent dose by multiplying the number supplied by strength (in diazepam-equivalent milligrams) and dividing by days of supply. Benzodiazepine and Z-drug dosage was stratified into high-dose (diazepam-equivalent-mg dose >30 mg) and low-dose (≤30 mg) based on established thresholds (33). Benzodiazepine exposure was categorized by the duration of action, namely, short-acting (half-life ≤24 hours) or long-acting (half-life >24 hours), guided by established classifications (6). Specific classifications of benzodiazepines and Z-drugs, based on previously published definitions, are presented in Table S2 in the online supplement (34, 35).

We also collected data on age, sex, relationship of patient to the primary beneficiary, and insurance status. Because cases were self-matched in a case-crossover design, our models did not warrant adjustment for time-invariant measured confounders (e.g., sex and race).

Statistical Analysis

Analyses were conducted on a day-level data set in which each medication coverage date was identified. All analyses

FIGURE 2. Overview of the case-crossover design analyzing patients with opioid use disorder with a drug-related poisoning[a]



[a] Treatment days during which an individual received a medication, such as a benzodiazepine or buprenorphine, that culminated in drug-related poisoning (hatched boxes) are compared with days that did not coincide with a poisoning event for the same medication (shaded boxes). An observation period spanning up to 1 year (at most) before and after the index poisoning was used. Consequently, each individual could potentially contribute multiple drug-related poisoning events to the final analysis, as long as such events were within a maximum of 1 year before and 1 year after the index poisoning event. For individual 1, five treatment periods are shown, two of which culminated in a drug-related poisoning. This contrasts with individual 2, who had two treatment periods, only one of which culminated in a drug-related poisoning. Individual 2 had three drug-related poisonings, two of which were not preceded by medication treatment. Individuals 3 and 4 notably did not have any treatment periods culminating in drug-related poisoning.

were conducted using SAS, version 9.4 (SAS Institute, Cary N.C.). Before evaluating variation in medication exposure between case and control days, we calculated descriptive statistics for the primary analytical sample (i.e., patients who had nonfatal drug-related poisonings). To compare the characteristics of opioid use disorder treatment between patients with and without poisoning events, we obtained a random sample of persons who never experienced poisonings and compared descriptive statistics between them and those who had poisoning events (see the Methods section and Tables S3 and S4 in the online supplement).

To evaluate the effect of medication exposure, we estimated conditional logistic regression models stratified by subject and modeled the risk of poisoning as a function of drug exposure by days with or without treatment. We first built a crude model containing benzodiazepine or Z-drug prescription status as the only predictor variable. We then built additional models that included predictor variables for both benzodiazepine or Z-drug and buprenorphine prescription status. Simultaneous inclusion of benzodiazepines or Z-drugs and buprenorphine permitted us to model additive or interactive effects of benzodiazepines or Z-drugs and buprenorphine in association with drug-related poisonings. SSRIs were included in our models as an active comparator analysis. Subgroup analyses were conducted to assess the effect of buprenorphine treatment days, compared with days without treatment, on drug-related poisoning among patients who received benzodiazepine or Z-drug prescriptions and those who did not. Controls for both calendar time and time from index poisoning were included using cubic spline methods, described in detail in the Methods section in the online supplement. Several sensitivity analyses were conducted to evaluate the possibility of persistent user bias and to assess the robustness of our findings to alternative time samplings (see Figure S1, the Methods section, and Table S5 in the online supplement).

RESULTS

Study Sample and Treatment Characteristics

Of 304,676 individuals ages 12–64 with an opioid use disorder diagnosis, prescription drug coverage, and at least one opioid

use disorder claim during the period of enrollment, we excluded individuals without drug-related poisonings, individuals who never received medication for opioid use disorder, and individuals without days of naltrexone and methadone treatment and days of observation outside a maximum of a 1-year period before and after the index poisoning (Figure 1). Our final analytic sample comprised 23,036 patients (mean age, 30 years [SD=12.15]; 51% male; mean observation time, 299 days [SD=107.88]), spanning 14,213,075 person-days of insurance coverage (Table 1). A total of 2,210,927 person-days (15.6%) entailed claims for buprenorphine (mean daily dose, 15.4 mg [SD=7.31]). A total of 1,968,944 person-days (13.9%) entailed claims for benzodiazepines or Z-drugs, of which 474,181 person-days entailed concurrent buprenorphine treatment. We calculated the mean daily dose of any benzodiazepine or Z-drug to be 23.4 diazepam-milligram equivalents and the mean daily dose for short-acting benzodiazepines, long-acting benzodiazepines, and Z-drugs to be 25.3, 31.3, and 4.9 diazepam-milligram equivalents, respectively (Table 2).

Benzodiazepines or Z-Drugs and Drug-Related Poisonings

Buprenorphine treatment days were associated with 37% lower odds of drug-related poisoning (95% CI=0.60, 0.66) compared with nontreatment days, whereas odds of poisoning increased 81% on days when patients were treated with benzodiazepines or Z-drugs (95% CI=1.73, 1.91; model 1) (Table 3). When we evaluated benzodiazepines and Z-drugs separately, Z-drug treatment days were associated with increased odds of poisoning events (odds ratio=1.29, 95% CI=1.19, 1.39), but this was notably lower than the odds associated with benzodiazepine treatment days (odds ratio=1.88, 95% CI=1.78, 1.98; model 2). We found no association between SSRI treatment days and drug-related poisonings (odds ratio=0.95, 95% CI=0.90, 1.00; model 3). We observed no difference in the magnitude of protective effect against poisoning conferred by buprenorphine treatment days when conducting stratified analyses of patients who used benzodiazepines or Z-drugs (odds ratio=0.64, 95% CI=0.60, 0.69, model 4) and those who never used benzodiazepines or Z-drugs during the study's observation period (odds ratio=0.64, 95% CI=0.59, 0.69; model 5).

Subgroup and Sensitivity Analyses

We stratified benzodiazepines by mechanism and observed similarly elevated odds of drug-related poisoning for short-acting benzodiazepine treatment days (odds ratio=1.86, 95% CI=1.75, 1.97; model 6) and long-acting benzodiazepine treatment days (odds ratio=1.68, 95% CI=1.54, 1.83; model 6). When we stratified benzodiazepines by low and high doses, we found the increases in the odds of a poisoning event to be 78% (95% CI=1.67, 1.88; model 6) and 122% (95% CI=2.03, 2.43; model 7), respectively. To assess whether this dose-response relationship remained significant across all sedative/hypnotic drugs, we grouped benzodiazepines and Z-drugs

TABLE 1. Prevalence of opioid use disorder treatment with stratification by dose and individual benzodiazepine or Z-drug types at the individual subject level among patients with a drug-related poisoning (N=23,036)[a]

Characteristic		
	N	%
Buprenorphine use	16,451	71.41
Low-dose (≤12 mg daily)	9,469	41.11
High-dose (>12 mg daily)	11,690	50.75
Benzodiazepine or Z-drug use	12,890	55.96
Benzodiazepine use excluding Z-drugs	11,839	51.39
Low-dose (≤30 diazepam-equivalent mg daily)	10,356	44.96
High-dose (>30 diazepam-equivalent mg daily)	5,227	22.69
Short-acting benzodiazepine use	9,292	40.34
Alprazolam	6,210	26.96
Lorazepam	4,433	19.24
Oxazepam	130	0.56
Triazolam	248	1.08
Estazolam	19	0.08
Temazepam	1,127	4.89
Midazolam	47	0.2
Long-acting benzodiazepine use	6,660	28.91
Clonazepam	3,885	16.86
Diazepam	3,612	15.68
Chlordiazepoxide	206	0.89
Clobazam	1	0
Flurazepam	33	0.14
Quazepam	2	0.01
Z-drug use	5,068	22
Zolpidem	4,640	20.14
Eszopiclone	1,025	4.45
Zaleplon	216	0.94
Methadone use	420	1.82
Naltrexone use	1,449	6.29
Naltrexone extended-release use	746	3.24
Selective serotonin reuptake inhibitor use	10,286	44.65
	Mean	SD
Age (years)	30.05	12.15
Year of birth	1980	
Days of observation	298.73	107.88
	N	%
Male	11,713	50.85
Relationship of patient to primary beneficiary		
Employee	4,345	28.30
Spouse	3,746	24.40
Child or other	7,263	47.30
Medicaid	7,682	33.35

[a] The data represent opioid use disorder treatment characteristics at the individual subject level among patients with a history of drug-related poisoning during the study's observation window (up to 1 year before and 1 year after the index poisoning event). While all study subjects had prescriptions for buprenorphine in the IBM MarketScan database (a requirement for inclusion in the final analytic sample), only 71% had buprenorphine claims during the time period up to 1 year before and 1 year after the index poisoning event.

TABLE 2. Opioid use disorder treatment characteristics at the person-days level among individuals with a drug-related poisoning (N=23,036)[a]

Characteristic	N	%
Treatment days marked by drug-related poisoning	26,243	0.18
Days treated with buprenorphine	2,210,927	15.56
Dose (mean±SD)	15.44	7.31
Low-dose (≤12 mg daily)	758,261	5.33
High-dose (>12 mg daily)	1,367,893	9.62
Days treated with selective serotonin reuptake inhibitors	1,715,489	12.07
Days treated with benzodiazepines or Z-drugs	2,493,800	17.55
Dose (diazepam-equivalent mg daily) (mean±SD)	23.39	25.88
Days treated with benzodiazepines excluding Z-drugs	1,968,944	13.85
Dose (diazepam-equivalent mg daily) (mean±SD)	27.58	26.98
Low-dose (≤30 diazepam-equivalent mg daily)	1,453,110	10.22
High-dose (>30 diazepam-equivalent mg daily)	515,834	3.63
Days treated with short-acting benzodiazepines	1,584,424	11.15
Dose (diazepam-equivalent mg daily)	25.33	20.53
Days treated with long-acting benzodiazepines	452,820	3.19
Dose (diazepam-equivalent mg daily)	31.28	38.10
Days treated with Z-drugs	825,610	5.81
Dose (diazepam-equivalent mg daily) (mean±SD)	4.88	1.24
Concurrent use of buprenorphine or benzodiazepines or Z-drugs		
Days without buprenorphine or benzodiazepine or Z-drug treatment	9,982,529	70.23
Days treated with benzodiazepines or Z-drugs only	2,019,619	14.21
Days treated with buprenorphine only	1,736,746	12.22
Days treated with concurrent buprenorphine and benzodiazepines or Z-drugs	474,181	3.34

[a] Data are presented as Ns and percentages except as otherwise noted. Among all individuals with a history of drug-related poisoning during the study's observation window (1 year before and 1 year after the index poisoning event), the number of person-days for which insurance claims were filed for medication treatment was calculated. Because the data in this table do not represent the individual subject level, it was possible for an individual subject to contribute multiple person-days.

together and stratified them into low-dose and high-dose strata, observing a similar pattern of increased poisoning odds associated with dose (low-dose: odds ratio=1.86, 95% CI=1.77, 1.79; high-dose: odds ratio=2.53, 95% CI=2.35, 2.73; model 8). In contrast to benzodiazepines, we found similar protective effects of buprenorphine irrespective of the daily dose threshold (low-dose: odds ratio=0.62, 95% CI=0.57, 0.67; high-dose: odds ratio=0.63, 95% CI=0.59, 0.67; model 9).

Interaction Between Benzodiazepines or Z-Drugs and Buprenorphine

The odds of drug-related poisoning associated with benzodiazepine or Z-drug use, stratified by benzodiazepine or Z-drug dose and buprenorphine course, are presented in Table 3 (model 10). Stratification on these variables allowed for observation of possible interaction effects between benzodiazepine or Z-drug dose and buprenorphine use. For high-dose benzodiazepines or Z-drugs, poisoning odds associated with buprenorphine course were higher than would have been expected based on the assumption of additive risks (Wald χ^2=4.02, p=0.045). Odds ratios associated with low-dose and high-dose benzodiazepine or Z-drug course with buprenorphine use were 1.11 (95% CI=1.00, 1.23) and 1.64 (95% CI=1.39, 1.93), respectively. Notably, these effects were lower than those for low-dose and high-dose benzodiazepines or Z-drugs in the absence of buprenorphine (low-dose: odds ratio=1.69, 95% CI=1.60, 1.79; high-dose: odds ratio=2.23, 95% CI=2.04, 2.45, respectively). In other words, individuals with opioid use disorder taking both buprenorphine and benzodiazepines or Z-drugs had a lower net risk of poisoning than those taking benzodiazepines or Z-drugs without buprenorphine.

DISCUSSION

In this study, we used the IBM MarketScan databases to analyze nonfatal drug-related poisoning (including overdose events) associated with specific benzodiazepines or Z-drugs and dosing regimens in patients with opioid use disorder. Even though buprenorphine treatment days conferred a nearly 40% reduction in poisonings, benzodiazepine or Z-drug treatment days corresponded to a near-doubling in poisoning risk. While individuals taking both buprenorphine and benzodiazepines or Z-drugs were at elevated risk of poisoning, they still had a lower net risk than those taking benzodiazepines or Z-drugs without buprenorphine. We found no association between SSRIs and drug-related poisoning, making it less likely that underlying conditions for which patients were receiving benzodiazepines or Z-drugs contributed to overdoses. Additionally, we found no dose dependence for the association between buprenorphine and poisoning risk.

Our findings may have significant implications for clinical practice. First, our results show a clear dose-dependent pattern of worsened overdose-related outcomes associated with benzodiazepine or Z-drug use, indicating that among patients with opioid use disorder for whom benzodiazepine or Z-drug cessation is risky, lower doses and shorter treatment duration of sedative/hypnotics may reduce risk. Second, we found slightly lower risk with long-acting benzodiazepines compared with short-acting benzodiazepines and substantially lower risk associated with Z-drugs compared with either long- or short-acting benzodiazepines, which may be related to lower mean standardized dosages observed for Z-drugs. Overall, these results suggest that switching benzodiazepine users from short-acting to long-acting agents or to Z-drugs may hold promise in lowering overdose risk.

TABLE 3. Odds of drug-related poisoning associated with benzodiazepine use among individuals with opioid use disorder[a]

Variable	Odds Ratio	95% CI
Model 1		
Buprenorphine	0.63	0.60, 0.66
Any benzodiazepine or Z-drug	1.81	1.73, 1.91
Model 2		
Buprenorphine	0.63	0.60, 0.67
Benzodiazepines, excluding Z-drugs	1.88	1.78, 1.98
Z-drugs	1.29	1.19, 1.39
Model 3		
Buprenorphine	0.63	0.60, 0.67
Benzodiazepines, excluding Z-drugs	1.88	1.79, 1.99
Z-drugs	1.29	1.19, 1.40
Selective serotonin reuptake inhibitors	0.95	0.90, 1.00
Model 4		
Buprenorphine (among benzodiazepine or Z-drug users)	0.64	0.60, 0.69
Model 5		
Buprenorphine (among benzodiazepine or Z-drug nonusers)	0.64	0.59, 0.69
Model 6		
Buprenorphine	0.63	0.60, 0.66
Short-acting benzodiazepines	1.86	1.75, 1.97
Long-acting benzodiazepines	1.68	1.54, 1.83
Z-drugs	1.29	1.19, 1.39
Model 7		
Buprenorphine	0.63	0.60, 0.66
Low-dose benzodiazepines	1.78	1.67, 1.88
High-dose benzodiazepines	2.22	2.03, 2.43
Z-drugs	1.29	1.19, 1.39
Model 8		
Buprenorphine	0.64	0.62, 0.67
Any benzodiazepine or Z-drug, low-dose	1.86	1.77, 1.95
Any benzodiazepine or Z-drug, high-dose	2.53	2.35, 2.73
Model 9		
Low-dose buprenorphine	0.62	0.57, 0.67
High-dose buprenorphine	0.63	0.59, 0.67
Low-dose benzodiazepines	1.78	1.68, 1.88
High-dose benzodiazepines	2.22	2.03, 2.43
Z-drugs	1.29	1.19, 1.39
Model 10		
Buprenorphine only	0.61	0.58, 0.65
Benzodiazepine or Z-drug, low-dose (plus buprenorphine)	1.11	1.00, 1.23
Benzodiazepine or Z-drug, high-dose (plus buprenorphine)	1.64	1.39, 1.93
Benzodiazepine or Z-drug, low-dose (no buprenorphine)	1.69	1.60, 1.79
Benzodiazepine or Z-drug, high-dose (no buprenorphine)	2.23	2.04, 2.45

[a] Low-dose benzodiazepines are ≤30 diazepam-equivalent milligrams daily; high-dose benzodiazepines are >30 diazepam-equivalent milligrams daily; low-dose Z-drugs are ≤30 diazepam-equivalent milligrams daily; high-dose Z-drugs are >30 diazepam-equivalent milligrams daily; low-dose buprenorphine is ≤12 mg/day; and high-dose buprenorphine is >12 mg/day.

Importantly, buprenorphine's beneficial effect was observed among both benzodiazepine or Z-drug users and nonusers. This is an important finding because the safety of benzodiazepine or Z-drug use among buprenorphine users has been a topic of contentious debate in the past, leading to restrictions on buprenorphine treatment among benzodiazepine users that were later reversed by the U.S. Food and Drug Administration (4, 36). Our results demonstrate that even though benzodiazepines and Z-drugs may increase drug-related poisonings, buprenorphine's protective effect is not eliminated by benzodiazepine or Z-drug treatment. Overall, our findings suggest that for patients taking both benzodiazepines or Z-drugs and buprenorphine, dose reduction of benzodiazepines or Z-drugs—while maintaining buprenorphine treatment—may have the advantage of decreasing overdoses associated with both benzodiazepines and the benzodiazepine-buprenorphine interaction. Because previous studies have found benzodiazepines to be associated with improved treatment retention in patients receiving buprenorphine (4, 11), dose reduction of benzodiazepines or Z-drugs may be preferable to abrupt cessation.

There are several limitations of this study. First, despite use of an active comparator and case-crossover design, we cannot exclude the possibility of residual confounding by indication. For example, benzodiazepines may constitute a proxy for underlying anxiety symptoms that lead to sedative/hypnotic prescriptions, substance use, and overdose, as opposed to directly contributing to poisoning. Unmeasured exposures, such as illicit substances and nonprescribed benzodiazepines, have commonly been noted in the opioid user population (37) and warrant further investigation. Second, secular time trends in exposure and outcome may introduce confounding into case-crossover designs (24, 25). We cannot rule out the possibility of unmeasured time-varying factors associated with drug-related poisoning and benzodiazepine or Z-drug exposure. Mitigating this, we made efforts to control for temporal variation and reduce heterogeneity in observation time per person using calendar time and time from event as a covariate and restricting study subjects to a maximum of 2-year periods of observation

bracketing the index event. In addition to an active comparator analysis, we used bidirectional sampling (before and after index poisoning), which has been found to reduce overlap bias resulting from control period selection as a function of event times (25).

In addition, our study is limited by its focus on nonfatal drug-related poisonings as opposed to poisoning deaths. While our reliance on nonfatal poisoning allows for the creation of a more robust clinical risk profile that can be used to prevent fatal cases, further research evaluating the effect of benzodiazepine or Z-drug use on overdose deaths is warranted in light of our findings. Additionally, although the MarketScan data comprise a large, nationally representative sample with strong longitudinal follow-up at the patient level, the database is limited by measurement error, insofar as medication coverage does not always reflect the actual dose consumed. The generalizability of the MarketScan data is also limited to insured patients with observed drug-related poisonings. Our findings may not be generalizable to lower-risk patients who did not experience poisoning events within the study observation period.

A key strength of our study was its use of a case-crossover approach to harness within-person variation (i.e., individuals serving as their own controls) and to estimate the degree to which poisonings were reduced on days when patients were taking benzodiazepines or Z-drugs, as opposed to nontreatment days. Because each patient acted as his or her own control, we reduced the selection and sampling bias that would result from recruitment of different case and control subjects in conventional observational study designs. This also allowed us to examine the relationship between common exposures and less common acute outcomes, such as overdoses (18, 38, 39). Furthermore, this strategy allowed us to investigate subtle changes in exposure (i.e., variation by benzodiazepine or Z-drug dose and subtype) that may result in poisoning (18). We also used SSRIs as an active comparator to control for unobserved confounders and to serve as a proxy for underlying conditions leading to benzodiazepine prescriptions, given their overlapping indications with benzodiazepines and no known association with drug-related poisoning or mortality in adults. The lack of association between SSRI prescriptions and poisoning is notable, suggesting that increased odds of poisoning following receipt of a benzodiazepine prescription is more attributable to benzodiazepines than to underlying conditions leading to a prescription for a benzodiazepine or an SSRI. Finally, our findings are pharmacologically informed, because we used the high statistical power of the MarketScan database to identify subgroups of patients receiving buprenorphine who may have been at elevated risk of treatment failure, such as those taking short-acting or higher-potency benzodiazepines.

CONCLUSIONS

Patients with opioid use disorder who are treated with buprenorphine have double the odds of a drug-related poisoning when benzodiazepines or Z-drugs are coprescribed, with short-acting and high-dose benzodiazepines conferring additional risk. Buprenorphine remains protective against overdose in this high-risk population. Our findings contribute to emerging evidence that patients with opioid use disorder who receive buprenorphine may benefit from cessation or dose reduction of benzodiazepines or Z-drugs while remaining on buprenorphine.

AUTHOR AND ARTICLE INFORMATION

Department of Psychiatry, Health and Behavior Research Center, Washington University School of Medicine, St. Louis (Xu, Presnall, Mintz, Hartz, Bierut, Grucza); Department of Biomedical Data Science, Center for Technology and Behavioral Health, Geisel School of Medicine, Dartmouth, Hanover, N.H. (Borodovsky); Alvin J. Siteman Cancer Center, Barnes Jewish Hospital and Washington University School of Medicine, St. Louis (Bierut); and Departments of Family and Community Medicine and Health and Outcomes Research, St. Louis University, St. Louis (Grucza).

Send correspondence to Dr. Xu (xukeviny@wustl.edu).

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