Population-based signals of benzodiazepine drug interactions associated with unintentional traumatic injury

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Abstract

Benzodiazepine receptor agonists and related medications, such as Z-drugs and dual orexin receptor antagonists (BZDs), have been associated with unintentional traumatic injury due to their central nervous system (CNS)-depressant effects. Drug-drug interactions (DDIs) may contribute to the known relationship between BZD use and unintentional traumatic injury, yet evidence is still lacking. We conducted high-throughput pharmacoepidemiologic screening using the self-controlled case series design in a large US commercial health insurance database to identify potentially clinically relevant DDI signals among new users of BZDs. We used conditional Poisson regression to estimate rate ratios (RRs) between each co-exposure (vs. not) and unintentional traumatic injury (primary outcome), typical hip fracture (secondary outcome), and motor vehicle crash (secondary outcome). We identified 48 potential DDI signals (1.1%, involving 39 unique co-dispensed drugs), i.e., with statistically significant elevated adjusted RRs for injury. Signals were strongest for DDI pairs involving zolpidem, lorazepam, temazepam, alprazolam, eszopiclone, triazolam, and clonazepam. We also identified four potential DDI signals for typical hip fracture, but none for motor vehicle crash. Many signals have biologically plausible explanations through additive or synergistic pharmacodynamic effects of co-dispensed antidepressants, opioids, or muscle relaxants on CNS depression, impaired psychomotor and cognitive function, and/or somnolence. While other signals that lack an obvious mechanism may represent true associations that place patients at risk of injury, it is also prudent to consider the roles of chance, reverse causation, and/or confounding by indication, which merit further exploration. Given the high-throughput nature of our investigation, findings should be interpreted as hypothesis generating.

Keywords

Benzodiazepines; drug interactions; injury; pharmacoepidemiology; population health; self-controlled case series

INTRODUCTION

More than one in eight US adults used a benzodiazepine (BZD) in the last year, with use most prevalent in persons aged 50–64 years followed by older adults.(Maust et al., 2019) BZD receptor agonists' central nervous system (CNS)-depressant effects have been associated with unintentional traumatic injury, which is among the leading causes of mortality in all age groups.(Haagsma et al., 2016; National Center for Injury Prevention and Control, 2020) Medications with similar clinical effects such as Z-drugs (eszopiclone, zaleplon, zolpidem) and dual orexin receptor antagonists (i.e., suvorexant, lemborexant) may also increase injury risk.(Brandt and Leong, 2017; Haagsma et al., 2016) Among older adults, injuries resulting from motor vehicle crashes and falls are associated with increased mortality.(Hannan et al., 2004; National Center for Injury Prevention and Control, 2018) Drug-drug interactions (DDIs) may contribute to the known relationship between BZD use and unintentional traumatic injury, yet the underlying evidence base is severely lacking. The vast majority of DDI evidence comes from case reports or pharmacokinetic studies. The former provide a very low level of evidence; the latter provide data on surrogate measures that may lack clinical relevance. Prior population based DDI screening studies of unintentional traumatic injury among users of other CNS active drugs (e.g., opioids, antidepressants) have generated some signals among persons co-treated with BZDs.(7,8)

To generate robust real-world evidence on the role of BZD and related drug DDIs on hospital presentation for unintentional traumatic injury, either via an emergency department visit or inpatient hospitalization, we conducted high-throughput pharmacoepidemiologic screening of administrative healthcare data using an observational study design that eliminates confounding by static factors. Our hypothesis generating work aimed to provide an evidence-based list of BZD DDIs of potential clinical relevance to be confirmed or refuted in future etiologic studies.

METHODS

Overview.

We used the self-controlled case series (SCCS) study design to conduct high-throughput screening of claims data from a large, commercial US health insurer. We sought to identify potentially clinically relevant DDI signals with BZD receptor agonists and related drugs (e.g., Z-drugs, dual orexin receptor antagonists; hereafter considered collectively as BZDs) resulting in emergency department presentation or inpatient hospitalization for unintentional traumatic injury. We defined unintentional traumatic injury as a fracture, dislocation, sprain, strain, intracranial injury, internal injury of thorax, abdomen, or pelvis, open wound, injury to blood vessels, crushing injury, injury to nerves or spinal cord, or certain traumatic complications and unspecified injuries—adapted from a diagnosis based definition used by

the American College of Surgeons. We identified separate new-user cohorts of individuals dispensed distinct BZDs, within which we dichotomized observation time as co-exposed (vs. not, i.e., BZD alone) to each among hundreds of commonly dispensed oral medications; to avoid statistically unstable estimates, we excluded as study drugs those used in fewer than five BZD-treated patients. After adjusting for time-varying confounders that were assessed during each day of observation time (i.e., average daily benzodiazepine dose of categorized as quartiles (when feasible); follow-up month categorized as 1, 2, 3, 4, 5, 6, or ≥7; and ever having a prior traumatic injury of interest [binary]), we examined associations between each co-exposure (vs. not) and hospital presentation for: unintentional traumatic injury (primary outcome, hereafter considered injury); typical hip fracture (secondary outcome); and motor vehicle crash while the individual was driving (secondary outcome).(Leonard et al., 2021; Leonard et al., 2020)

We utilized an SCCS design because: its within-person nature (i.e., persons serves as their own 'controls') answers the question of why an outcome occurred when it did in a given individual; it is well suited to studying transient exposures in relation to an abrupt outcome; it eliminates static confounding factors within individual, a critical feature given the lack of randomization; it can adjust for time-varying confounders; it is computationally efficient, since analyses are limited to persons with an outcome; and there is substantial precedent for its use in DDI screening. Methodologic detail was adapted from our prior DDI screening work on opioids, antidepressants, muscle relaxants, antihyperglycemics, and hematological agents.(Leonard et al., 2021; Leonard et al., 2020; Leonard et al., 2019; Zhou et al., 2020)

Data Source.

We utilized enrollment information and healthcare claims (May 1, 2000–June 30, 2019) from Optum's de-identified Clinformatics® Data Mart, a dataset with >71 million commercially insured and Medicare Advantage beneficiaries.

Statistical Analysis.

For each BZD for each outcome, we created an analytic file in which the person-day during an active BZD prescription was the unit of observation. The dependent variable was whether an injury occurred on the given observation day. Independent dichotomous variables were co-exposure to other medications and time-varying covariate status on the given observation day. The contrast of primary interest was the injury occurrence rate ratio (RR, i.e., $rate_{co-exposed}$ / $rate_{BZDalone}$). We used conditional Poisson regression (*xtpoisson* with *fe* option, Stata v16) to estimate RRs and 95% confidence intervals (CIs). We used semi-Bayes shrinkage(Greenland and Poole, 1994; Steenland et al., 2000) to address multiple estimation and minimize false positive signals by increasing the validity of effect estimates and preserving nominal type-1 error; we avoided the traditional Bonferroni correction for multiple estimation as it may be overly conservative and result in high rates of false negatives. We considered findings as DDI signals if the semi-Bayes shrunk confounder adjusted RR exceeded 1.00 and 95% CI excluded 1.00. We compared our results with documentation in two drug interaction knowledgebases (IBM Micromedex, Wolters Kluwer Facts and Comparison eAnswers).

Institutional Review Board (IRB) Approval and Role of Funding.

RESULTS

Among 19 BZDs, we identified 97,564 new users (ranging from 3 [quazepam] to 24,406 [zolpidem]) who experienced an injury, contributing >18 million observation days. Users were predominantly white females, with median ages ranging from 49.5 years for clobazam to 71.5 years for lorazepam. Supplemental Table 1 summarizes data on confounder adjusted RRs for injury. Among 4,263 drug pairs examined, 48 (1.1%, consisting of BZD + one of 39 unique co-dispensed drugs) had statistically significant elevated adjusted RRs for injury after semi-Bayes shrinkage, and were therefore deemed potential DDI signals (Table 1, Figure 1). Signals included co-dispensed drugs in the following therapeutic classes: CNS (N = 21/48 signals), anti-infective (N = 7), endocrine and metabolic (N = 5), renal and genitourinary (N = 4), cardiovascular (N = 4), gastrointestinal (N = 3), respiratory (N = 2), hematological (N = 1), and antineoplastic (N = 1). Signals were strongest for the following pairs: *zolpidem + minoxidil* (RR 2.51, 95% CI 1.09–5.80); *lorazepam + sulindac* (2.50, 1.17–5.33); *temazepam + phenobarbital* (2.29, 1.11–4.73); *alprazolam + eletriptan* (2.27, 1.18–4.37); *eszopiclone + megestrol* (2.15, 1.11–4.19); *temazepam + methadone* (2.14, 1.16–3.94); *triazolam + promethazine* (2.09, 1.07–4.08); *alprazolam + propranolol* (2.08, 1.60–2.71); *clonazepam + tegaserod* (2.06, 1.04–4.11); and *temazepam + rizatriptan* (2.00, 1.07–3.73). Five (10.4%), two (4.1%), and four (8.3%) of the 48 signals are currently flagged as DDIs of concern by Micromedex only, Facts and Comparisons eAnswers only, and both knowledgebases, respectively.

In analyses of secondary outcomes, 17 and 16 BZDs under study provided >800,000 and >300,000 observation days for typical hip fracture and motor vehicle crash, respectively. Among 1,308 drug pairs examined, we identified the following four DDI signals for typical hip fracture, each with *clonazepam*: *trimethoprim* (RR 2.11, 1.07–4.16); *cephalexin* (2.10, 1.05–4.19); *mirtazapine* (2.10, 1.07–4.15); and *sulfamethoxazole* (2.03, 1.01–4.09). We identified no DDI signals among 564 drug pairs examined for motor vehicle crash.

DISCUSSION

In this pharmacoepidemiologic screening study using commercial health insurance data, we identified 48 potential BZD DDI signals associated with injury. The plurality (44%) of signals involved co-dispensed CNS-active drugs, an expected finding given their pharmacodynamic effects. Given the high-throughput nature of our investigation, findings should be interpreted as hypothesis generating and serve to focus limited resources for the conduct of future etiologic studies.

Many identified signals have biologically plausible underpinnings. Synergistic pharmacodynamic effects of co-dispensed antidepressants, opioids, muscle relaxants, and anticonvulsants/gabapentinoids on CNS depression, impaired psychomotor and cognitive function, and/or somnolence (as examples) may result in increased injury rates.(Bolton et

al., 2008; Emeny et al., 2019; Gales and Menard, 1995; Granek et al., 1987; Kanner and Gidal, 2008; Leonard et al., 2021; Leonard et al., 2020; Leveille et al., 1994; Orriols et al., 2012; Rapoport et al., 2011; Ray et al., 1992; Ray et al., 1987; Spina and Leon, 2017; Zint et al., 2010) This potential mechanism supports our findings for *alprazolam + vortioxetine*, *temazepam + methadone*, *alprazolam + tizanidine*, and *clonazepam + gabapentin* (as examples) with injury, and *clonazepam + mirtazapine* with hip fracture. It is also noteworthy that these CNS-active co-dispensed drugs could have a direct pharmacodynamic effect on injury by themselves, leading to elevated RRs for their corresponding drug pairs. Additionally, hypotensive effects of co-dispensed antihypertensives (e.g., propranolol) and diuretics (e.g., furosemide) may also result in increased injury rates. Other plausible signals are supported by potential pharmacokinetic mechanisms. For example, our injury finding for *alprazolam + clarithromycin* may be explained by inhibition of alprazolam's hepatic metabolism. Clarithromycin, a strong cytochrome P450 3A4 inhibitor,(Fohner et al., 2017) can increase alprazolam's concentration and consequently its pharmacologic effect and result in excessive sedation.(Dresser et al., 2000; Whirl-Carrillo et al., 2021) Of note, future etiologic work that confirms or refutes these signals may provide evidence to refine the Beers Criteria from the American Geriatrics Society, given their current recommendation against the use of some but not all of these medications when used alone or in combination in older adults.(The 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019) Our lack of signaling for other expected pairs (e.g., *temazepam + ziprasidone*, RR_{injury} 1.84, 0.95–3.58) may be due to limited statistical precision and suggests that the semi-Bayes shrinkage method was appropriately conservative for use in this hypothesis generating context.

We also identified signals that lack an obvious pharmacokinetic or pharmacodynamic mechanism (e.g., *eszopiclone + megestrol*). While these findings may represent true associations that place patients at risk of injury, it remains prudent to consider the roles of chance, reverse causation, and/or within-person confounding by indication. Confounding could partially explain signals for co-dispensed drugs that are indicated for the treatment of infection or pain, as these indications may be risk factors for injury. Reverse causation would occur if the co-dispensed drug was prescribed in response to an injury event. For example, anti-infectives may be prescribed for prophylaxis of infection after an injury.(Bratzler et al., 2013; Stevens et al., 2014) Therefore, it is unclear if our signals for *lorazepam + sulindac* and *alprazolam + trimethoprim/sulfamethoxazole* (as examples) are true associations or the influence of confounding by indication or reverse causation. An additional limitation is information bias, as prescription dispensings in an administrative claims database may not reflect drug actual periods of drug availability or consumption. Follow-up etiologic studies should consider bias analyses to quantify the impact of misclassification among other biases. (Funk and Landi, 2014)

Randomized trials are very rarely conducted to study clinical outcomes of potential DDIs; most of the existing evidence arises from case reports and/or pharmacokinetic studies assessing changes in drug concentrations. Given the theoretical likelihood of co-dispensed drugs affecting injury rates in BZD users, we conducted a population-based pharmacoepidemiologic screening study to identify potential BZD DDI signals. Our findings serve as an evidence-based list of potential BZD interactions resulting in hospital

presentation for injury. Future etiologic studies should seek to confirm or refute these signals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Funding

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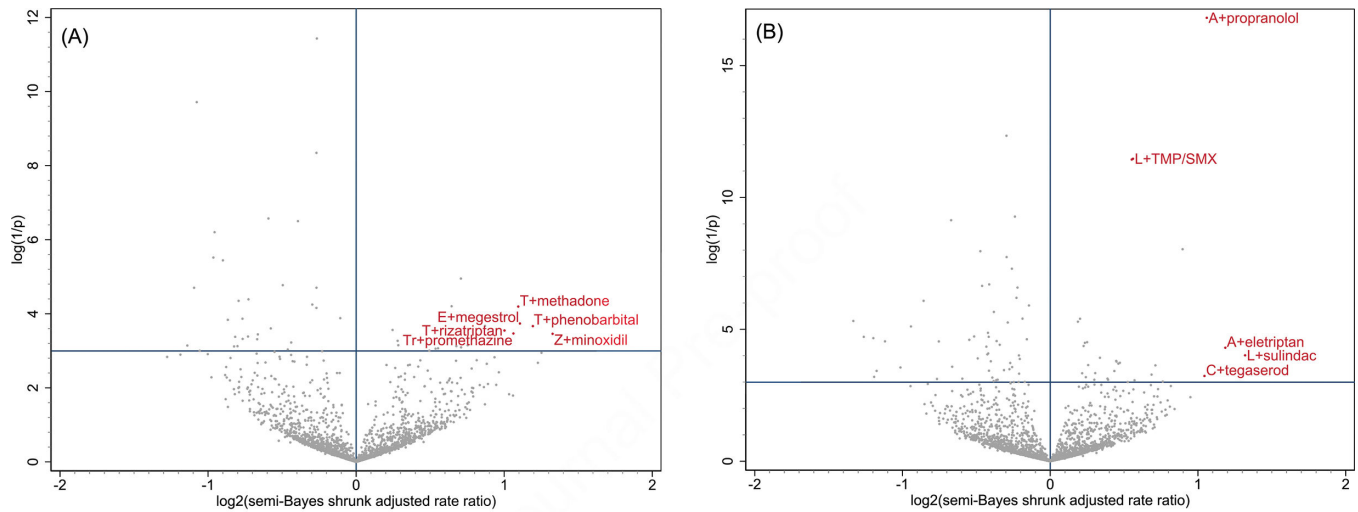
Figure 1. Benzodiazepine + co-administered drug pairs and associations with unintentional traumatic injury

Panel (A) depicts associations for benzodiazepine and nonbenzodiazepine hypnotics: estazolam, eszopiclone [E], flurazepam, quazepam, ramelteon, suvorexant, tasimelteon, temazepam [T], triazolam [Tr], zaleplon, and zolpidem [Z]

Panel (B) depicts associations for benzodiazepine anxiolytics: alprazolam [A], chlordiazepoxide, clobazam, clonazepam [C], clorazepate, diazepam, lorazepam [L], and oxazepam

X-axes, representing the magnitude of association, are the log base 2 semi-Bayes shrunk adjusted rate ratio (RR) for benzodiazepine + co-administered drug vs. benzodiazepine alone. Y-axes, representing statistical significance, are the log (1/p-value) for the semi-Bayes shrunk adjusted RRs.

Data points in each upper right quadrant represent statistically significant elevated semi-Bayes shrunk adjusted RRs for the association between benzodiazepine + co-administered drug vs. benzodiazepine alone and unintentional traumatic injury (i.e., potential drug interaction signals). For ease of reading, we limited labeling to upper right quadrant data points with log base 2 semi-Bayes shrunk adjusted RR ≥ 1 or log (1/p value), for the semi-Bayes shrunk adjusted RR, ≥ 10. TMP/SMX: trimethoprim/sulfamethoxazole

Table 1.

Benzodiazepine drug interaction signals, given statistically significantly increased rates of hospital presentation for unintentional traumatic injury, by pharmacologic category of benzodiazepine, and by magnitude of association within therapeutic class of the co-administered drug

Benzodiazepine	Co-administered drug	Co-administered drug therapeutic class	RR*, semi-Bayes shrunk	Lower bound of 95% CI**	Upper bound of 95% CI
Benzodiazepine receptor agonist, anxiolytic					
Alprazolam	Eletriptan	CNS	**2.27**	1.18	4.37
	Vortioxetine[a]		1.61	1.03	2.52
	Baclofen[c]		1.24	1.01	1.50
	Tizanidine[c]		1.19	1.04	1.36
	Bupropion		1.16	1.01	1.34
	Gabapentin[b]		1.14	1.04	1.25
	Propranolol	Cardiovascular	**2.08**	1.60	2.71
	Metolazone	Renal & Genitourinary	1.86	1.33	2.61
	Clarithromycin[a,b,c]	Anti-infective	1.49	1.01	2.19
	Trimethoprim[c]		1.19	1.02	1.40
	Sulfamethoxazole[c]		1.18	1.01	1.39
	Apixaban	Hematological	1.36	1.04	1.78
Clonazepam	Tegaserod	Gastrointestinal	**2.06**	1.04	4.11
	Gemfibrozil	Cardiovascular	1.64	1.06	2.53
	Methylphenidate	CNS	1.44	1.00	2.07
	Amphetamine		1.39	1.04	1.84
	Sumatriptan		1.36	1.04	1.78
	Dextroamphetamine		1.35	1.03	1.78
	Butalbital[b,c,d]		1.31	1.01	1.71
	Gabapentin[b]		1.15	1.04	1.27
	Levothyroxine	Endocrine & Metabolic	1.18	1.04	1.33
	Furosemide	Renal & Genitourinary	1.17	1.03	1.32

Benzodiazepine	Co-administered drug	Co-administered drug therapeutic class	RR*, semi-Bayes shrunk	Lower bound of 95% CI**	Upper bound of 95% CI
Diazepam	Benzonatate	Respiratory	1.70	1.00	2.87
	Pregabalin [b]	CNS	1.38	1.04	1.82
	Bupropion [a]		1.31	1.01	1.70
Lorazepam	Sulindac [c]	CNS	**2.50**	1.17	5.33
	Bupropion		1.26	1.04	1.54
	Divalproex sodium [a,b]		1.23	1.00	1.51
	Sulfamethoxazole [c]	Anti-infective	1.47	1.24	1.75
	Trimethoprim [c]		1.47	1.24	1.74
Benzodiazepine receptor agonist, hypnotic					
Temazepam	Phenobarbital [b,d]	CNS	**2.29**	1.11	4.73
	Methadone [a-e]		**2.14**	1.16	3.94
	Rizatriptan		**2.00**	1.07	3.73
	Buspirone		1.56	1.09	2.24
	Lovastatin	Cardiovascular	1.47	1.01	2.14
Triazolam	Promethazine	Gastrointestinal	**2.09**	1.07	4.08
Nonbenzodiazepine GABA agonist hypnotic (Z-drug)					
Eszopiclone	Megestrol	Endocrine & Metabolic	**2.15**	1.11	4.19
	Alendronate		1.69	1.02	2.79
Zaleplon	Metformin	Endocrine & Metabolic	1.83	1.08	3.10
Zolpidem	Minoxidil	Cardiovascular	**2.51**	1.09	5.80
	Clarithromycin [a,b,c]	Anti-infective	1.63	1.14	2.33
	Trimethoprim [c]		1.19	1.02	1.38
	Methotrexate	Antineoplastic	1.45	1.00	2.09
	Rabeprazole	Gastrointestinal	1.41	1.00	1.98
	Spironolactone	Renal & Genitourinary	1.22	1.01	1.47
	Montelukast	Respiratory	1.21	1.01	1.46

Benzodiazepine	Co-administered drug	Co-administered drug therapeutic class	RR[*], semi-Bayes shrunk	Lower bound of 95% CI[**]	Upper bound of 95% CI
Nonbenzodiazepine hypnotic, miscellaneous					
Ramelteon	Furosemide	Renal & Genitourinary	1.60	1.01	2.52
Suvorexant	Metformin	Endocrine & Metabolic	1.63	1.01	2.64

RR: rate ratio; CI: confidence interval; CNS: central nervous system; GABA: gamma-aminobutyric acid

RRs >2.00 are bolded to highlight 10 potential signals that may warrant particular attention in future etiologic work.

[*] Causal contrast is concomitant use of benzodiazepine + co-administered drug vs. use of benzodiazepine alone.

[**] p-values <0.05 for lower bounds equal to 1.00 after rounding

[a] Drug interaction with impact on benzodiazepine documented in Facts & Comparisons eAnswers.

[b] Drug interaction with impact on benzodiazepine documented in Micromedex.

[c] Finding may be particularly affected by protopathic bias.

[d] Drug interaction with impact on co-administered drug documented in Micromedex.

[e] Drug interaction with impact on co-administered drug documented in Facts & Comparisons eAnswers.