New Coprescription of Opioids and Benzodiazepines and Mortality Among Veterans Affairs Patients With Posttraumatic Stress Disorder

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ABSTRACT

Background: Opioids and benzodiazepines are commonly coprescribed medications. The mortality risk associated with their concurrent use is unknown.

Objective: To estimate the all-cause mortality risk for patients newly prescribed opioids and benzodiazepines concurrently relative to patients prescribed benzodiazepines only, opioids only, or neither medication.

Methods: This propensity score–matched, retrospective, cohort study included 17,476 patients receiving Veterans Affairs (VA) health care between October 1, 2009, and September 30, 2011, and diagnosed with posttraumatic stress disorder identified using *ICD-9-CM* code 309.81. One-year total and cause-specific mortality was assessed by hazard ratios and subhazard ratios, adjusted for propensity score, age, baseline psychiatric and medical comorbidity, and daily medication dose.

Results: Concurrent users (n = 4,369) were propensity score matched 1:1 with benzodiazepine-only users, opioid-only users, and nonusers. One year after medication start, the concurrent cohort had higher rates of all-cause mortality (116 deaths) relative to benzodiazepine-only (75 deaths; adjusted hazard ratio = 1.52; 95% CI, 1.14–2.03), opioid-only (67 deaths; 1.76; 95% CI, 1.32–2.35), and nonuser (60 deaths; 1.85; 95% CI, 1.30–2.64) cohorts. Risk of overdose death was greater among patients in the concurrent cohort relative to patients in the benzodiazepine-only (adjusted subhazard ratio = 2.59; 95% CI, 1.00–6.66), opioid-only (2.58; 95% CI, 1.09–6.11), and nonuser (9.16; 95% CI, 2.27–37.02) cohorts. For circulatory disease–related deaths, the adjusted subhazard ratio for concurrent medication users was 1.81 (95% CI, 1.01–3.24) relative to nonusers.

Conclusions: New coprescription of opioids and benzodiazepines was associated with increased all-cause mortality and overdose death compared with new prescription of benzodiazepines only, opioids only, or neither medication and increased circulatory disease–related death relative to neither medication.

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Pharmaceutical overdose deaths involving opioids and benzodiazepines have increased over the last decade,[1] with a 4.3-fold increase in benzodiazepine-related overdose deaths that also involved opioids between 2002 and 2015.[2] However, overdose deaths very likely underestimate the mortality risk of these medications. Opioids and benzodiazepines are associated with increased fall-related injuries and motor vehicle accidents that contribute to premature death and may be associated with increased risk of death caused by circulatory and respiratory disease.[3–10] Despite these potential risks, few studies have examined all- and specific-cause mortality associated with coprescribing opioids and benzodiazepines relative to prescribing benzodiazepines only, opioids only, or neither medication class.[6,11]

Clinical guidelines discourage opioid and benzodiazepine coprescribing due to the aforementioned risks.[12,13] However, dual use is common among those with psychiatric conditions such as posttraumatic stress disorder (PTSD).[14–16] Patients with PTSD present with chronic symptoms, including anxiety and insomnia, frequently treated with benzodiazepines, and chronic pain, frequently treated with opioids.[17,18] Due to their side effects,[19] these medications may pose significant harm to those with PTSD who are at increased risk of circulatory and respiratory diseases.[20,21] Accumulating evidence indicates those with PTSD are at increased risk of incident coronary heart disease events, higher levels of atherosclerosis markers, and myocardial ischemia.[22–24]

This study assessed the safety of opioid and benzodiazepine coprescribing by comparing Veterans Affairs (VA) patients with PTSD who were coprescribed these medications to those prescribed either benzodiazepines alone, opioids alone, or neither medication using appropriate pharmacoepidemiologic approaches (ie, propensity score–matched cohorts, incident-user design)[25] to reduce possible confounding. We compared all-cause mortality risk among patients newly coprescribed opioids and benzodiazepines to propensity score–matched patients newly prescribed opioids only, benzodiazepines only, or neither medication class. Secondarily, we compared risk of overdose-, circulatory-, and respiratory-related death in these 4 medication cohorts.

Clinical Points

- Prior medication studies have established an association between overdose deaths and prescription opioids and benzodiazepines, but little is known about the comparative safety of coprescribing these medication classes in terms of all-cause mortality and other causes of death.
- New coprescription of opioids and benzodiazepines is associated with increased short-term all-cause mortality and overdose death compared with new prescription of benzodiazepines only, opioids only, or neither medication and is associated with increased circulatory disease–related death relative to prescription of neither medication.
- Results suggest that providers should consider these risks and educate patients prior to coprescribing and support efforts to discontinue dual use of these medication classes.

METHODS

Study Cohort and Data Sources

VA patients were eligible if they were aged ≥ 18 years and received a primary or secondary PTSD diagnosis, identified using *International Classification of Diseases*, *Ninth Revision* (*ICD-9*), code 309.81, at at least 1 outpatient visit or inpatient discharge from VA facilities between October 1, 2009, and September 30, 2011. To reduce potential confounding by indication, patients were excluded if they had documented cancer or human immunodeficiency virus (HIV) diagnoses in the year prior to medication starts or received hospice or opioid substitution treatment at any point in the study.

The VA Corporate Data Warehouse (CDW), a national data repository with patient-level medical record information including demographic, diagnostic, utilization, and pharmacy data, was used to identify and characterize the sample and assess medication use. Medicare data supplied race information when missing, and the Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn Roster identified service in these operations. The VA Vital Status File (VSF) was used to ascertain death, and the VA/Department of Defense Suicide Data Repository,[26] which includes National Death Index (NDI) data, was used to identify mortality cause. VA VSF has been validated to identify 98.3% of NDI deaths.[27] The study was approved by the VA Puget Sound Health Care System institutional review board.

We utilized outpatient CDW pharmacy files, which include type and quantity of medication prescribed, dose, number of days supplied, and pharmacy release date, to identify patients with new opioid-only, benzodiazepine-only, and concurrent opioid and benzodiazepine therapies of ≥ 30 consecutive days (breaks of ≤ 15 days between refills allowed). New concurrent therapy was defined as prescriptions for opioid and benzodiazepine medications filled within 30 days of each other, with no more than 15 days of cumulative supply from either medication class in the prior 6 months to allow use for medical procedures. New opioid-only therapy was defined as a filled prescription for an opioid medication, with no more than a 15-day supply of opioids filled and no filled benzodiazepines in the prior 6 months. New benzodiazepine-only therapy was defined similarly. The benzodiazepine-only cohort did not include patients prescribed opioids in the 1 year following entry, nor did the opioid-only cohort include patients prescribed benzodiazepines during that time. Patients were considered nonusers if they filled no prescriptions in either medication class for 6 months before and 12 months after their index date (defined in the Follow-Up section).

Matching

To reduce potential confounding, patients newly coprescribed opioids and benzodiazepines were matched to patients in the opioid-only, benzodiazepine-only, and nonuser cohorts according to propensity score, representing the predicted probability of a patient receiving opioid and benzodiazepine prescriptions and derived from logistic regression models that included 41 covariates (see Table 1). Separate logistic models were run for each comparison cohort (ie, concurrent and benzodiazepine-only, concurrent and opioid-only, and concurrent and nonuser cohorts). Within each of the 3 comparison cohorts, propensity scores were matched 1:1 using a "greedy" matching algorithm.[28] One-to-two matching was considered, but sample sizes for comparison cohorts were insufficient. Covariates entered into propensity score models included demographics; psychiatric and medical diagnoses; modified Charlson Comorbidity Index (CCI) score[29,30]; other medication use; treatment utilization; initial benzodiazepine or opioid dose, as applicable; and facility-level complexity.

Follow-Up

Concurrent medication users entered the cohort on the date opioid and benzodiazepine prescriptions first overlapped, while opioid-only (or benzodiazepine-only) medication users entered the cohort on the release date of first opioid (or benzodiazepine) prescription. To ensure non–medication users were receiving VA care, we identified the first quarter in years 2010–2011 that patients attended ≥ 2 days of VA outpatient care. Day 1 of the qualifying quarter served as the index date for non–medication users. Patients left their respective cohorts 1 year after their entry date or on their date of death, whichever was earlier. Patients in benzodiazepine-only and opioid-only cohorts could stop receiving prescriptions for benzodiazepines and opioids, respectively, and those in the concurrent cohort could stop receiving one or both medication classes during follow-up; however, patients remained in cohorts assigned at index. Follow-up was limited to 1 year to estimate short-term mortality risk.

Endpoint

The study endpoints were death by any cause, circulatory-related disease, respiratory-related disease, and

Table 1. Baseline Characteristics for Concurrent Opioids and Benzodiazepines, Opioids Only, Benzodiazepines Only, and Neither Medication Cohorts of Patients With PTSD After Propensity Score Matching[a]

Variable	Concurrent (n = 4,369)	Benzodiazepine Only (n = 4,369)	Standard Difference (%)	Opioid Only (n = 4,369)	Standard Difference (%)	No Medication (n = 4,369)	Standard Difference (%)
Age, mean (SD), y	47.4 (15.1)	46.9 (16.0)	2.8	47.2 (15.5)	1.2	47.1 (15.5)	2.0
Sex							
Male	3,871 (88.6)	3,888 (89.0)	1.2	3,849 (88.1)	1.6	3,883 (88.9)	0.9
Female	498 (11.4)	481 (11.0)		520 (11.9)		486 (11.1)	
Race							
Black	467 (10.7)	477 (10.9)	2.1	463 (10.6)	4.5	446 (10.2)	2.0
White	3,588 (82.1)	3,569 (81.7)		3,640 (83.3)		3,598 (82.4)	
Other	212 (4.9)	228 (5.2)		179 (4.1)		225 (5.1)	
Unknown	102 (2.3)	95 (2.2)		87 (2.0)		100 (2.3)	
Ethnicity							
Not Hispanic/Latino	3,974 (91.0)	3,958 (90.6)	1.3	3,979 (91.1)	1.6	3,975 (91.0)	2.2
Hispanic/Latino	255 (5.8)	264 (6.0)		242 (5.5)		268 (6.1)	
Unknown	140 (3.2)	147 (3.4)		148 (3.4)		126 (2.9)	
OEF/OIF service era	1,534 (35.1)	1,576 (36.1)	2.0	1,551 (35.5)	0.8	1,559 (35.7)	1.2
Service connection ≥ 50%	3,244 (74.3)	3,259 (74.6)	0.8	3,243 (74.2)	0.1	3,244 (74.3)	0.0
Psychiatric conditions							
Anxiety disorder	1,415 (32.4)	1,422 (32.5)	0.3	1,400 (32.0)	0.7	1,391 (31.8)	1.2
Bipolar disorder	398 (9.1)	415 (9.5)	1.3	428 (9.8)	2.3	397 (9.1)	0.1
Psychotic disorder	194 (4.4)	189 (4.3)	0.6	193 (4.4)	0.1	206 (4.7)	1.3
Depressive disorder	2,154 (49.3)	2,091 (47.9)	2.9	2,237 (51.2)	3.8	2,207 (50.5)	2.4
Substance use conditions							
Alcohol use disorder	740 (16.9)	762 (17.4)	1.3	763 (17.5)	1.4	754 (17.3)	0.9
Opioid use disorder	133 (3.0)	113 (2.6)	2.8	138 (3.2)	0.7	132 (3.0)	0.1
Stimulant use disorder	182 (4.2)	172 (3.9)	1.2	191 (4.4)	1.0	187 (4.3)	0.6
Sedative use disorder	51 (1.2)	39 (0.9)	2.7	55 (1.3)	0.8	51 (1.2)	0.0
Other substance use disorder	290 (6.6)	280 (6.4)	0.9	302 (6.9)	1.1	283 (6.5)	0.6
Medical comorbidity							
Charlson Comorbidity Index score, mean (SD)	0.6484 (1.2)	0.6507 (1.2)	−0.2	0.658 (1.2)	−0.8	0.5985 (1.2)	4.1
Diabetes	662 (15.2)	645 (14.8)	1.1	653 (14.9)	0.6	623 (14.3)	2.5
Chronic obstructive pulmonary disease	665 (15.2)	659 (15.1)	0.4	700 (16.0)	2.2	615 (14.1)	3.2
Congestive heart failure	132 (3.0)	138 (3.2)	0.8	135 (3.1)	0.4	118 (2.7)	1.9
Cerebrovascular disease	142 (3.3)	148 (3.4)	0.8	147 (3.4)	0.6	130 (3.0)	1.6
Dementia	23 (0.5)	19 (0.4)	1.3	22 (0.5)	0.3	20 (0.5)	1.0
Hyperthyroidism	16 (0.4)	19 (0.4)	1.1	9 (0.2)	3.0	15 (0.3)	0.4
Peripheral vascular disease	127 (2.9)	138 (3.2)	1.5	130 (3.0)	0.4	119 (2.7)	1.1
Renal disease	135 (3.1)	138 (3.2)	0.4	132 (3.0)	0.4	121 (2.8)	1.9
Rheumatoid arthritis	28 (0.6)	28 (0.6)	0.0	25 (0.6)	0.9	30 (0.7)	0.6
Liver disease	148 (3.4)	153 (3.5)	0.6	168 (3.8)	2.5	158 (3.6)	1.2
Pain, back/neck/head	3,313 (75.8)	3,332 (76.3)	1.0	3,325 (76.1)	0.6	3,378 (77.3)	3.5
Pain, other	1,886 (43.2)	1,909 (43.7)	1.1	1,898 (43.4)	0.6	1,874 (42.9)	0.6
Traumatic brain injury	356 (8.1)	368 (8.4)	1.0	402 (9.2)	3.7	344 (7.9)	1.0
Weight (first percentile)	53 (1.2)	48 (1.1)	1.1	52 (1.2)	0.2	54 (1.2)	0.2
Fracture	209 (4.8)	203 (4.6)	0.6	227 (5.2)	1.9	215 (4.9)	0.6
Medications							
Antipsychotics	998 (22.8)	1,032 (23.6)	1.8	1,051 (24.1)	2.9	990 (22.7)	0.4
Anticonvulsants	1,337 (30.6)	1,331 (30.5)	0.3	1,412 (32.3)	3.7	1,271 (29.1)	3.3
Corticosteroids	1,081 (24.7)	1,072 (24.5)	0.5	1,101 (25.2)	1.1	1,018 (23.3)	3.4
Z-drugs	818 (18.7)	828 (19.0)	0.6	779 (17.8)	2.3	797 (18.2)	1.2
QT-prolonging drugs[b]	2,755 (63.1)	2,762 (63.2)	0.3	2,787 (63.8)	1.5	2,754 (63.0)	0.0
Inpatient days							
0	3,548 (81.2)	3,549 (81.2)	4.1	3,494 (80.0)	3.2	3,564 (81.6)	1.6
1–3	131 (3.0)	152 (3.5)		136 (3.1)		135 (3.1)	
4–7	186 (4.3)	196 (4.5)		194 (4.4)		184 (4.2)	
8–14	154 (3.5)	157 (3.6)		167 (3.8)		143 (3.3)	
> 14	350 (8.0)	315 (7.2)		378 (8.7)		343 (7.9)	
Emergency department visits							
0–1	3,728 (85.3)	3,716 (85.1)	1.3	3,716 (85.1)	1.1	3,732 (85.4)	1.7
2–5	567 (13.0)	583 (13.3)		573 (13.1)		572 (13.1)	
> 5	74 (1.7)	70 (1.6)		80 (1.8)		65 (1.5)	
Total visit days, mean (SD)	15.5 (25.7)	15.5 (18.2)	0.2	16.2 (19.3)	−3.0	15.1 (19.5)	1.6
Facility complexity level[c]							
1 (High)	2,978 (68.2)	2,942 (67.3)	5.2	2,988 (68.4)	3.1	2,980 (68.2)	2.1
2 (Medium)	738 (16.9)	699 (16.0)		724 (16.6)		748 (17.1)	
3 (Low)	605 (13.8)	666 (15.2)		621 (14.2)		602 (13.8)	
Excluded	48 (1.1)	62 (1.4)		36 (0.8)		39 (0.9)	
Initial daily dose, mean (SD), mg							
Benzodiazepines, diazepam equivalents	21.0 (19.7)	20.5 (20.5)	2.9				
Opioids, morphine equivalents	39.5 (56.0)			37.9 (63.7)	2.7		

[a]Values are shown as n (%) unless otherwise noted. [b]QT-prolonging drugs were identified from CredibleMeds (crediblemeds.org). [c]Facility complexity is a weighted index score based on patient volume, patient risks, clinical programs, research and teaching programs, and risks. The score is calculated by the Veterans Health Administration Office of Productivity, Efficiency, and Staffing.

Abbreviations: OEF/OIF = Operations Enduring or Iraqi Freedom, PTSD = posttraumatic stress disorder, Z-drug = nonbenzodiazepine drug used in the treatment of sleep problems.

Table 2. Selected Baseline Characteristics Among Patients With PTSD (N = 17,476)

Characteristic	Value[a]
Women	1,985 (11.4)
Age, mean (SD), y	47.1 (15.5)
OEF/OIF service era	6,220 (35.6)
Race	
Black	1,853 (10.6)
White	14,395 (82.4)
Other	844 (4.8)
Unknown	384 (2.2)
Psychiatric conditions	
Anxiety disorder	5,628 (32.2)
Bipolar disorder	1,638 (9.4)
Psychotic disorder	782 (4.5)
Depressive disorder	8,689 (49.7)
Substance use conditions	
Alcohol use disorder	3,019 (17.3)
Opioid use disorder	516 (3.0)
Stimulant use disorder	732 (4.2)
Sedative use disorder	196 (1.1)
Cannabis use disorder	977 (5.6)
Use of medications	
Z-drugs	3,222 (18.4)
QT-prolonging drugs[b]	11,058 (63.3)
Medical comorbidity	
Diabetes	2,583 (14.8)
Chronic obstructive pulmonary disease	2,639 (15.1)
Pain condition	14,893 (85.2)
Traumatic brain injury	1,470 (8.4)

[a]Values are shown as n (%) unless otherwise noted.
[b]QT-prolonging drugs were identified from CredibleMeds (crediblemeds.org).
Abbreviations: OEF/OIF = Operations Enduring or Iraqi Freedom, PTSD = posttraumatic stress disorder, Z-drug = nonbenzodiazepine drug used in the treatment of sleep problems.

overdose during 1-year follow-up. Drug overdose deaths were identified using *ICD-10-CM* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14.[31] Circulatory- and respiratory-related deaths were identified by codes I00–I99 and J00–J99, respectively.

Statistical Analysis

Analyses compared adjusted mortality risk during 1-year follow-up among the 4 medication cohorts. All-cause mortality was estimated from hazard ratios using Cox regression models. To account for competing risks, cause-specific mortality (overdose, circulatory-related, respiratory-related) was estimated with adjusted subhazard ratios using the Fine and Gray method.[32] Models were adjusted for baseline propensity score, age, CCI score (0, 1, and ≥ 2), and count of psychiatric diagnoses (0, 1, and ≥ 2) and were clustered on VA facility to control for facility-level correlation. To adjust for medication dose over study course, models included a time-varying covariate for daily dose of the shared medication (ie, concurrent and benzodiazepine-only comparisons adjusted for benzodiazepine dose, concurrent and opioid-only comparisons adjusted for opioid dose). Opioid and benzodiazepine dosages were converted to morphine and diazepam milligram equivalents per day using standard conversions.[12,33,34]

The adjusted risk difference in mortality incidence between patients coprescribed opioids and benzodiazepines and patients in the 3 comparison cohorts was estimated for overall and cause-specific mortality. The risk difference was calculated as $I_0 \times (\text{hazard ratio} - 1)$, with hazard ratio representing the adjusted hazard ratio and I_0 the unadjusted incidence of the 3 comparison cohorts. The 95% CIs were calculated similarly.

To test key study assumptions, we conducted sensitivity analyses limited to patients younger than 50 years, those with low medical and low psychiatric comorbidity, and those receiving a mean opioid dose < 20 mg morphine equivalents per day and a mean benzodiazepine dose < 10 mg diazepam equivalents per day. These cutoff points represent the lowest end of the daily dose range for both medication classes.[11] Low medical comorbidity analyses included patients with CCI scores of zero, and low psychiatric comorbidity analyses included patients with PTSD only (ie, without comorbid psychiatric conditions). Sensitivity analyses were adjusted for baseline propensity score and a time-varying covariate for shared medication dose as applicable. Analyses were performed in Stata version 14.0 (StataCorp; College Station, Texas). All *P* values were 2-sided; $P < .05$ was considered statistically significant.

RESULTS

In total, 4,415 patients started concurrent opioid and benzodiazepine therapy, 36,079 started benzodiazepine-only therapy, 60,627 started opioid-only therapy, and 155,451 started neither medication. Prior to matching, cohorts differed on baseline characteristics, with standardized differences exceeding 10% for most covariates. After propensity score matching, each cohort included 4,369 patients, and cohorts were comparable on demographic, clinical, and utilization variables, with most standard differences less than 3% and no differences exceeding 6% (Table 1). No differences were detected between the original concurrent cohort and matched-sample cohort. The matched sample overall was 47.1 years old (SD = 15.5), and 11.4% were women (Table 2). Pain disorders (85.2%) and chronic obstructive pulmonary disease (15.1%) were the most common medical comorbidities and depressive (49.7%) and anxiety (32.2%) disorders the most common psychiatric comorbidities. Exposure to QT-prolonging medications was common (63.3%). Opioid and benzodiazepine mean initial doses were not different between study cohorts (Table 3); however, the doses and days supplied of these medication classes during follow-up were significantly larger in the concurrent cohort compared to the opioid-only and benzodiazepine-only cohorts. Number of days supplied of benzodiazepines was ≥ 90 days among 73.2% and 61.5% of concurrent and benzodiazepine-only cohorts, respectively; 73.2% and 54.8% of concurrent and opioid-only cohorts, respectively, received ≥ 90 days' worth of opioids.

During 1 year, the concurrent medication cohort had 116 deaths during 4,321 person-years of follow-up (26.8 per 1,000 person-years), relative to 75 during 4,333 person-years of follow-up in the benzodiazepine-only (17.3 per 1,000

Table 3. Mean Dose and Number of Days Supplied of Opioids and Benzodiazepines at Baseline and During Follow-Up Among Cohorts of Patients With PTSD

	Concurrent Opioids and Benzodiazepines (n = 4,369)		Benzodiazepines Only (n = 4,369)			Opioids Only (n = 4,369)		
Variable	Mean	SD	Mean	SD	*P* Value	Mean	SD	*P* Value
Initial daily dose, mg								
Benzodiazepines, diazepam equivalents	21.0	19.7	20.5	20.5	.183			
Opioids, morphine equivalents	39.5	56.0				37.9	63.7	.213
Daily dose during follow-up, mg[a]								
Benzodiazepines, diazepam equivalents	23.4	20.9	21.2	20.8	< .001			
Opioids, morphine equivalents	43.6	58.7				37.9	60.6	< .001
Days supplied during follow-up[a]								
Benzodiazepines	165.7	238.7	92.4	147.6	< .001			
Opioids	169.3	221.7				95.3	154.6	< .001

[a]Includes initial prescription.
Abbreviation: PTSD = posttraumatic stress disorder.

Table 4. All-Cause Mortality by Common Causes of Death Among Cohorts of Patients With PTSD

	Concurrent Medications		Comparison Cohort				
Variable	Deaths, n	Incidence per 1,000 Person-Years	Deaths, n	Incidence per 1,000 Person-Years	Adjusted Hazard/ Subhazard Ratio (95% CI)	Adjusted Risk Difference (95% CI)	*P* Value
Concurrent medications vs benzodiazepines only[a]							
All-cause mortality	116	26.8	75	17.3	1.52 (1.14 to 2.03)	9.03 (2.43 to 17.83)	.004
Circulatory diseases	35	8.1	20	4.6	1.75 (0.94 to 3.28)	3.48 (−0.28 to 10.50)	.078
Respiratory diseases	14	3.2	9	2.1	1.60 (0.77 to 3.34)	1.26 (−0.48 to 4.85)	.206
Overdose	18	4.2	7	1.6	2.59 (1.00 to 6.66)	2.56 (0.01 to 9.15)	.049
Concurrent medications vs opioids only[b]							
All-cause mortality	116	26.8	67	15.4	1.76 (1.32 to 2.35)	11.74 (4.94 to 20.81)	< .001
Circulatory diseases	35	8.1	23	5.3	1.55 (0.89 to 2.70)	2.90 (−0.59 to 8.99)	.123
Respiratory diseases	14	3.2	11	2.5	1.32 (0.65 to 2.65)	0.80 (−0.88 to 4.19)	.443
Overdose	18	4.2	7	1.6	2.58 (1.09 to 6.11)	2.54 (0.14 to 8.23)	.032
Concurrent medications vs neither medication[c]							
All-cause mortality	116	26.8	60	13.8	1.85 (1.30 to 2.64)	11.78 (4.10 to 22.75)	.001
Circulatory diseases	35	8.1	19	4.4	1.81 (1.01 to 3.24)	3.54 (0.04 to 9.80)	.046
Respiratory diseases	14	3.2	5	1.2	2.79 (0.99 to 7.82)	2.06 (−0.01 to 7.87)	.052
Overdose	18	4.2	2	0.5	9.16 (2.27 to 37.02)	3.76 (0.58 to 16.61)	.002

[a]Analyses adjusted for propensity score, baseline age, medical comorbidity, mental health comorbidity, and time-varying covariate for diazepam equivalents per day.
[b]Analyses adjusted for propensity score, baseline age, medical comorbidity, mental health comorbidity, and time-varying covariate for morphine equivalents per day.
[c]Analyses adjusted for propensity score, baseline age, medical comorbidity, and mental health comorbidity.
Abbreviation: PTSD = posttraumatic stress disorder.

Table 5. Sensitivity Analyses Limited to Patients With Age < 50 Years, Low Medical and Mental Health Comorbidity, and Low Opioid and Benzodiazepine Doses Among Cohorts of Patients With PTSD

	Concurrent Medications			Comparison Group				
	Patients,	Deaths		Patients,	Deaths		Adjusted Hazard	*P*
Variable	n	n	%	n	n	%	Ratio (95% CI)	Value
Concurrent medications vs benzodiazepines only[a]								
Age < 50 y	2,346	32	1.4	2,382	18	0.8	1.78 (1.01 to 3.13)	.046
Low medical comorbidity (Charlson Comorbidity Index score = 0)	2,889	36	1.2	2,906	22	0.8	1.57 (0.97 to 2.54)	.068
Low mental health comorbidity (PTSD only)	1,325	35	2.6	1,320	19	1.4	1.81 (1.05 to 3.13)	.033
Low dose (< 10 mg diazepam equivalents, < 20 mg morphine equivalents)	349	13	3.7	1,085	18	1.7	2.30 (1.06 to 4.99)	.035
Concurrent medications vs opioids only[b]								
Age < 50 y	2,346	32	1.4	2,308	13	0.6	2.33 (1.33 to 4.09)	.003
Low medical comorbidity (Charlson Comorbidity Index score = 0)	2,889	36	1.2	2,845	21	0.7	1.65 (0.96 to 2.82)	.070
Low mental health comorbidity (PTSD only)	1,325	35	2.6	1,297	13	1.0	2.56 (1.37 to 4.79)	.003
Low dose (< 10 mg diazepam equivalents, < 20 mg morphine equivalents)	349	13	3.7	1,495	28	1.9	2.05 (0.98 to 4.32)	.058
Concurrent medications vs neither medication[c]								
Age < 50 y	2,346	32	1.4	2,359	3	0.1	10.78 (3.40 to 34.17)	< .001
Low medical comorbidity (Charlson Comorbidity Index score = 0)	2,889	36	1.2	2,974	11	0.4	3.38 (1.76 to 6.49)	< .001
Low mental health comorbidity (PTSD only)	1,325	35	2.6	1,290	13	1.0	2.61 (1.38 to 4.92)	.003

[a]Analyses adjusted for propensity score and time-varying covariate for diazepam equivalents per day.
[b]Analyses adjusted for propensity score and time-varying covariate for morphine equivalents per day.
[c]Analyses adjusted for propensity score.
Abbreviation: PTSD = posttraumatic stress disorder.

person-years), 67 during 4,347 person-years of follow-up in the opioid-only (15.4 per 1,000 person-years), and 60 during 4,338 person-years of follow-up in the neither medication (13.8 per 1,000 person-years) cohort. The adjusted hazard ratio (95% CI) for all-cause mortality in the concurrent cohort was 1.52 (95% CI, 1.14–2.03) relative to the benzodiazepine-only cohort, 1.76 (95% CI, 1.32–2.35) relative to the opioid-only cohort, and 1.85 (95% CI, 1.30–2.64) relative to the nonuser cohort (Table 4). The adjusted risk difference for the concurrent cohort was 9.03 (95% CI, 2.43–17.83), 11.74 (95% CI, 4.94–20.81), and 11.78 (95% CI, 4.10–22.75) excess deaths per 1,000 person-years relative to the benzodiazepine-only, opioids-only, and nonuser cohorts, respectively.

The most common causes of death included circulatory diseases (31.0%) followed by respiratory diseases (12.3%) and overdose (10.7%). Patients in the concurrent cohort were at greater risk of overdose death than patients in the benzodiazepine-only (adjusted subhazard ratio = 2.59; 95% CI, 1.00–6.66), opioid-only (2.58; 95% CI, 1.09–6.11), and nonuser (9.16; 95% CI, 2.27–37.02) cohorts (Table 4). The risk of circulatory disease–related death was greater for the concurrent cohort relative to the nonuser cohort (adjusted subhazard ratio = 1.81; 95% CI, 1.01–3.24). No increased risk of death by respiratory disease was observed in the concurrent cohort relative to any cohorts.

Relative risks of all-cause mortality between cohorts resembled the full sample in sensitivity analyses limited to patients younger than 50 years and having low psychiatric comorbidity (Table 5). The adjusted hazard ratio for all-cause mortality between concurrent and nonuser cohorts among patients younger than 50 increased substantially to 10.78 (95% CI, 3.40–34.17). Concurrent cohort patients with low medical comorbidity had greater mortality risk relative to the nonuser cohort only, and those receiving low medication doses had greater mortality risk relative to the benzodiazepine-only cohort only.

DISCUSSION

Although studies have reported an association between concurrent opioid and benzodiazepine use and increased risk of overdose,[11,16,35] the comparative safety of these medication classes has not been well established. Our results indicate that among patients with PTSD, mortality risk in the year following first prescription was 1.52 times greater among concurrent users relative to benzodiazepine-only users, 1.76 times greater relative to opioid-only users, and 1.85 times greater relative to nonusers. This corresponds to 9.0, 11.7, and 11.8 excess deaths per 1,000 person-years of new concurrent medication use relative to benzodiazepine-only, opioid-only, and neither medication cohorts. Focusing on all-cause rather than overdose-related mortality provides a comprehensive assessment of the risks associated with these medications. Notably, nearly 90% of deaths were due to non-overdose causes. Underscoring the potential risks of this medication combination, increased all-cause mortality was consistently observed even among younger patients (aged < 50 years) and those with lower psychiatric comorbidity.

Surprisingly, all-cause mortality risk among the concurrent medication cohort relative to the nonuser cohort was similar in magnitude to the mortality risk relative to the single medication class cohorts. This finding may reflect the short-term risk of all-cause mortality between cohorts of new medication users evenly matched on demographics and on psychiatric and medical comorbidities. Unfortunately, as patients in each of the 3 comparison cohorts were matched separately to patients in the concurrent medication cohort, comparisons between single medication and neither medication cohorts were not possible.

To decrease potential confounding by indication, cohorts excluded patients with cancer or HIV diagnoses or in hospice or opioid substitution treatment. Cohorts were limited to patients with PTSD and matched according to propensity scores calculated from demographic and clinical characteristics, medications, and utilization variables possibly linked to mortality risk. Further, cohorts were limited to patients initiating medications to address survival bias.[36] These steps mitigate concern for substantial confounding by indication.

Sensitivity analyses tested the robustness of primary findings among younger patients, those with low medical and psychiatric comorbidity, and those receiving low opioid and low benzodiazepine doses. Among patients aged < 50 years and those with low psychiatric comorbidity, differences in mortality risk remained significant and resembled those found in full sample analyses. Except for concurrent and nonuser cohort comparisons, mortality risk differences were not detected among patients with low medical comorbidity, although point estimates were similar to those of full sample analyses. Likewise, among patients receiving low medication doses, higher mortality risk was seen in concurrent users relative to benzodiazepine-only users but not opioid-only users; however, sample sizes were small and point estimates were similar. Overall, sensitivity analyses suggest that significant confounding is unlikely.

New concurrent use appeared to increase risk of circulatory disease–related death relative to nonuse of both medications, which is consistent with the thinking that opioids in combination with benzodiazepines impair cardiac function.[37] However, new concurrent users did not incur additional risk beyond that of patients prescribed either medication alone. This finding may be due to insufficient power or indicate that studies of longer-term medication use or with longer follow-up assessment are needed to adequately assess risk. Regardless, the finding that concurrent use increases short-term risk of circulatory disease–related mortality relative to nonuse suggests that clinicians should consider this risk and educate patients prior to coprescribing.

Our finding that concurrent medication use did not increase risk of respiratory disease–related death relative to nonusers of these medications should be interpreted with caution. The point estimate indicated nearly 3 times the risk,

and respiratory-related deaths were few, possibly limiting the statistical power of these analyses.

Consistent with research highlighting involvement of opioids and benzodiazepines in overdose deaths,[11,16,35] the overdose death rate among patients receiving concurrent medications was nearly 3 times that of patients prescribed opioids or benzodiazepines alone. A recent study by Garg and colleagues,[11] comparing overdose deaths among Washington State Medicaid enrollees receiving opioids and benzodiazepines, reported an overdose rate similar to that in our study (4.2 vs 4.2 per 1,000 person-years), a lower overdose rate among those receiving opioids only (1.3 vs 1.6 per 1,000 person-years), and a larger effect relative to those prescribed opioids only (7.5 [95% CI, 5.5–10.0] vs 2.58 [95% CI, 1.09–6.11]). The larger effect may result from survival bias, as the Garg et al study[11] was not limited to patients receiving new opioid therapy,[36] as well as differences in study design and approaches to confounding.

Our study has several limitations. While restricting our sample to patients with PTSD addressed potential confounding by indication, a focus on PTSD limits the generalizability of results. Further, potential differences on unmeasured variables (eg, PTSD severity, pain severity) may have impacted study results. Our results may not generalize to non-veterans or veterans not receiving VA care. Prescription data reflect VA outpatient fills only and do not account for medications received in the community or capture compliance. We did not account for whether patients were receiving medications at time of death. As baseline psychiatric and medical comorbidity were more severe among patients in the concurrent cohort, and the study design attempted to account for these differences in analyses, study cohorts may inherently differ from typical patients receiving these medications. Further, by focusing on patients who received opioids and benzodiazepines within a month of each other, we very likely excluded patients with more typical treatment courses (ie, second medication class added after first medication class prescribed long-term). Analyses of cause-specific deaths and sensitivity analyses may be underpowered. While analyses adjusted for shared medication dose (ie, opioid dose in the concurrent vs opioid-only comparisons), we did not examine the effect of dose on mortality risk.

This study underscores the risk of benzodiazepine and opioid coprescribing in the short term and supports opioid therapy guideline recommendations to avoid coprescribing and to educate patients and prescribers about mortality risks of coprescribing, even at low doses and among those with low comorbidity. As traditional education approaches such as passive dissemination of educational materials and training alone are minimally effective as risk mitigation strategies,[38] multifaceted interventions such as medication alerts or reminders,[39,40] audits, and feedback[41] may be necessary to reduce coprescribing. Current VA initiatives focus on decreasing opioid prescribing in primary care settings. Given that benzodiazepines are primarily prescribed in mental health clinics and prescribers are wary of addressing medications prescribed by others,[39] it is critical to include mental health prescribers in efforts to discontinue dual use of these medications.

CONCLUSIONS

Patients with PTSD who are newly prescribed both opioids and benzodiazepines are at increased risk of 12-month all-cause mortality, including death by overdose, relative to those newly prescribed opioids only, benzodiazepines only, or neither medication class. Increased mortality risk was observed even among younger patients and those with lower psychiatric comorbidity, highlighting the dangers posed by this medication combination. While this study answers questions about risks associated with incident use of these medications, additional work is needed to determine whether similar results are seen in patients prescribed one or both medication classes long-term and in different populations. Efforts to evaluate strategies to prevent coprescribing from occurring and to promote discontinuation or tapering among those at risk are warranted.

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