Risks of Benzodiazepines in Chronic Obstructive Pulmonary Disease with Comorbid Posttraumatic Stress Disorder

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Abstract

Rationale: Benzodiazepines are associated with mortality and poor outcomes among patients with chronic obstructive pulmonary disease (COPD), but use of benzodiazepines for dyspnea among patients with end-stage disease may confound this relationship.

Objectives: Assess the mortality risks of long-term benzodiazepine exposure among patients with COPD and comorbid post-traumatic stress disorder (PTSD), patients with chronic nonrespiratory indications for benzodiazepines.

Methods: We identified all patients with COPD and PTSD within the Veteran's Health Administration between 2010 and 2012. We calculated propensity scores for benzodiazepine use and compared overall and cause-specific mortality of patients with long-term (≥ 90 d) benzodiazepine use relative to matched patients without use. Secondary analyses assessed propensity-adjusted survival by characteristics of benzodiazepine exposure.

Results: Among 44,555 eligible patients with COPD and PTSD, 23.6% received benzodiazepines long term. In the matched sample of 19,552 patients, we observed no mortality difference (hazard ratio [HR] for long-term use, 1.06; 95% confidence interval [CI], 0.95–1.18) but greater risk of death by suicide among those with long-term use (HR, 2.33; 95% CI, 1.14–4.79). Among matched and unmatched patients, short-term benzodiazepine use, but not long-term use, was associated with increased mortality (short-term: HR, 1.16; 95% CI, 1.05–1.28; long-term: HR, 1.03; 95% CI, 0.94–1.13).

Conclusions: Risks for respiratory compromise related to long-term benzodiazepine use in COPD may be less than previously estimated, but short-term use of benzodiazepines could still pose a mortality risk. Suicide associated with benzodiazepine use in this population warrants further investigation.

Keywords: benzodiazepine; chronic obstructive pulmonary disease; posttraumatic stress disorder; suicide

(Received in original form February 27, 2018; accepted in final form August 28, 2018)

Supported by National Institutes of Health grants T32HL007287-38, F32HL140685-01, and K23HL111116; the Academic Sleep Pulmonary Integrated Research/Clinical Fellowship; and VA Grant 1 I01 HX001270-01A1. The views expressed here are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs. None of the funding sources were involved in the design, conduct or analysis of this project.

Author Contributions: Study design and collection of data: L.M.D., C.A.M., and E.J.H. Analysis of data: L.M.D., C.A.M., and E.J.H. Interpretation of data: L.M.D., C.A.M., L.J.S., M.F.G., L.C.F., R.A.E., D.H.A., and E.J.H. Preparation of manuscript: L.M.D., C.A.M., L.J.S., M.F.G., L.C.F., R.A.E., D.H.A., and E.J.H.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Ann Am Thorac Soc Vol 16, No 1, pp 82–90, Jan 2019

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DOI: 10.1513/AnnalsATS.201802-145OC

Internet address: www.atsjournals.org

Among patients with chronic obstructive pulmonary disease (COPD), chronic symptoms of dyspnea, anxiety, and insomnia are common and detract from quality of life (1, 2). These symptoms often prompt long-term use of benzodiazepine

medications as sedative hypnotics (3), despite concerns for benzodiazepine-related respiratory depression (4, 5). Consistent with these concerns, benzodiazepine use in COPD is associated with a 45% increased risk of exacerbations, greater risk of

respiratory failure, accidental overdose, and increased mortality (6–8). Benzodiazepines also disinhibit self-injurious behavior, and are linked with increased risk of suicide (9–11). This is a major concern for patients with COPD who already have a nearly

twofold increased risk of suicidal ideation relative to the general population (12).

Despite a wealth of existing literature, several areas of uncertainty remain in understanding the risks of benzodiazepines. One area of controversy concerns the risks for individuals already using benzodiazepines long term. Although clinical guidelines discourage prescribing of benzodiazepines beyond several weeks (13), 30% to 40% of individuals with COPD who receive benzodiazepines use them on a long-term basis (14, 15). Among individuals with long-term use, there may be a survival bias; those not having an immediate complication may be less susceptible to future adverse events (16). Discontinuation of benzodiazepines among those with long-term use raises concerns of withdrawal, and discontinuation is likely to be challenging to implement (17). Before resources are devoted to such an endeavor, a more complete understanding of the risks of long-term use is necessary. However, with the exception of one case-control study that found an association between long-term benzodiazepine use and respiratory failure among patients with COPD (6), no studies have examined risks specifically among patients with COPD who receive long-term therapy (18). Furthermore, the risks of accidental overdose and suicide related to long-term benzodiazepine use are also unknown, as prior studies have focused on short-term use or have not distinguished between short- and long-term use (10, 11, 19).

Another area of uncertainty relates to the use of benzodiazepines to treat dyspnea. Although convincing evidence linking benzodiazepines to dyspnea reduction is lacking (20), benzodiazepines are frequently used to palliate symptoms among individuals with severe COPD symptoms (21). As a result, the relationship between use of benzodiazepine medications and poor outcomes in COPD may be confounded by the use of benzodiazepines to treat dyspnea. As dyspnea is associated with mortality, nonfatal respiratory events, and suicidal ideation (22–24), it is important that this confounding is addressed. One strategy to reduce confounding is to examine risks of benzodiazepines in a sample of patients who are likely to be prescribed benzodiazepines to manage nonrespiratory symptoms, and patients with comorbid post-traumatic stress disorder (PTSD) provide one such opportunity. PTSD is present in 6% of the

general population (25), and symptoms of PTSD are found in up to 40% of those with COPD (26). Individuals with PTSD frequently have symptoms of anxiety and insomnia that prompt therapy with benzodiazepines, and almost 25% of patients with PTSD receive benzodiazepines—many long-term (27).

Our main goal is to better understand the risks associated with long-term benzodiazepine use. To assess these risks among a population enriched in nonrespiratory indications for benzodiazepines, the current study used a nationwide cohort of patients with comorbid COPD and PTSD identified from Veteran's Health Administration (VA) administrative data. Specifically, we assessed the risk of all-cause mortality among patients with long-term benzodiazepine exposure compared with propensity-matched patients who did not receive benzodiazepines. Given potential risks of benzodiazepine-related respiratory depression and psychological distress, we included cause-specific mortality due to obstructive lung disease, accidental overdose, and suicide, and the nonfatal outcomes of COPD exacerbations and psychiatric hospitalizations as secondary outcomes. We hypothesized that long-term benzodiazepine exposure would be associated with greater risks of these negative outcomes. To gain a more comprehensive understanding of the risks posed by benzodiazepines, we also evaluated the association of mortality with days' supply of benzodiazepines, days' supply of long-acting agents, dose of benzodiazepines, and concomitant opioid use.

Methods

Using the VA Corporate Data Warehouse, we identified all patients with COPD and comorbid PTSD from 2010 through 2012. The Corporate Data Warehouse includes nationwide medical records, including patient demographics, diagnoses, outpatient visits, hospitalizations, and pharmacy records for patients receiving VA care. The VA Puget Sound Institutional Review Board approved this study (IRB# 00703).

For inclusion, we required two or more encounters with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnoses of COPD (491.xx, 492.xx, 493.2, 496.xx)

during 2010 to 2012. We required two encounters to reduce misclassification (28). The date of the second qualifying COPD diagnosis was defined as the index date. Patients also needed at least one ICD-9-CM diagnosis of PTSD (309.81) in the year before index. We excluded patients enrolled in hospice, aged younger than 40 years, and without full data for propensity scores.

We defined long-term benzodiazepine exposure as filled prescriptions of 90 or more consecutive days' supply of an oral benzodiazepine during the 180 days before index (14). We ascertained exposure before index to avoid immortal person-time bias (29). We quantified benzodiazepine prescribed dose in terms of daily diazepam equivalents (30).

We calculated propensity scores for long-term benzodiazepine exposure using a logistic regression model that incorporated the 44 variables in Table 1. We chose variables hypothesized to influence likelihood of benzodiazepine exposure, mortality, and our secondary outcomes. The variables used included demographics, medical and mental health comorbidities, medications, and healthcare use documented in the year before index. For secondary analyses, we used the same variables to calculate propensity scores for any benzodiazepine use and opioid use.

Our primary outcome was all-cause mortality in the 2 years after index among propensity-matched Veterans with long-term use relative to those without use. We assessed causes of death in secondary analyses. Specifically, we evaluated risk of death related to chronic obstructive respiratory diseases (J40–J47), suicide (U03, X60–X84, Y87.0), and accidental overdose (X40–49). We ascertained vital status and cause of death from the VA Vital Status Files and the VA/Department of Defense Suicide Data Repository, which includes National Death Index data (31). The National Death Index is based on state-mandated death certificates and is considered the “gold standard” for mortality ascertainment (32). Secondary analyses also assessed the risk of medical and psychiatric hospitalizations and COPD exacerbations during the 2 years after index. We captured inpatient COPD exacerbations as hospitalizations with either a primary diagnosis of COPD or respiratory failure with a secondary diagnosis of COPD, and defined outpatient exacerbations as visits with a qualifying ICD-9-CM diagnosis

Table 1. Baseline characteristics of propensity-matched sample

	No Use (n = 9,776)	Long-Term Use (n = 9,776)	% Bias
Demographics			
Age, yr, mean (SD)	62.7 (7.8)	62.4 (7.4)	−3.8
Female	365 (4.2)	420 (4.3)	2.9
White	8,775 (89.8)	8,744 (89.4)	−0.9
Hispanic	260 (2.7)	270 (2.8)	0.6
>50% SC	9,146 (93.6)	9,110 (93.2)	−1.3
Medical and psychiatric history			
BMI, kg/m ² , mean (SD)	29.9 (6.8)	29.9 (6.7)	−0.5
Current smoking	6,719 (68.7)	6,710 (68.6)	−0.2
Generalized anxiety	2,458 (25.1)	2,618 (26.8)	4
Major depression	5,172 (52.9)	5,168 (52.9)	−0.1
Substance use disorder	2,375 (24.3)	2,418 (24.7)	1
Bipolar disorder	861 (8.8)	889 (9.1)	1
Psychotic disorder	778 (8.0)	759 (7.8)	−0.8
Insomnia	830 (8.5)	894 (9.1)	2.4
OSA	2,010 (20.6)	2,032 (20.8)	0.6
Charlson category			−0.7
Charlson 0–1	4,158 (42.5)	4,189 (42.9)	
Charlson 2	2,656 (27.2)	2,655 (27.2)	
Charlson ≥ 3	2,962 (30.3)	2,932 (30.0)	
Coronary disease	440 (4.5)	450 (4.6)	0.5
Congestive heart failure	1,061 (10.9)	1,120 (11.5)	1.9
Cerebrovascular disease	922 (9.4)	910 (9.3)	−0.4
Diabetes mellitus	3,396 (34.7)	3,365 (34.4)	−0.7
Liver disease	634 (6.5)	646 (6.6)	0.5
Malignancy	58 (0.6)	59 (0.6)	0.1
Dementia	133 (1.4)	121 (1.2)	−1.1
Chronic kidney disease	681 (7.0)	673 (6.9)	−0.3
Medication use			
Typical antipsychotic	331 (3.4)	336 (3.4)	0.3
Atypical antipsychotic	3,257 (33.3)	3,232 (33.1)	−0.6
Prazosin	1,090 (11.2)	1,123 (11.5)	1.1
TCA	283 (2.9)	278 (2.8)	−0.3
MAOI	9 (0.1)	8 (0.1)	−0.4
SSRI or SNRI	6,890 (70.5)	6,820 (69.8)	−1.5
LABA	2640 (27.0)	2,682 (27.4)	−1
LAMA	913 (9.3)	878 (9.0)	−1.3
ICS	3,384 (34.6)	3,375 (34.5)	−0.2
Short-acting bronchodilator use			−4.6
None	2,304 (23.6)	2,398 (24.5)	
1–9 canisters/yr	3,980 (40.7)	4,129 (42.2)	
10 canisters/yr	3,492 (35.7)	3,249 (33.2)	
Chronic glucocorticoid	516 (5.3)	524 (5.4)	0.4
Any opioid use	5,849 (59.8)	5,802 (59.4)	−1
Chronic opioid use	5,246 (53.7)	5,177 (53.0)	−1.5
Baseline utilization			
≥1 COPD exacerbations	1,730 (17.7)	1,708 (17.5)	−0.6
Any ED visit in last year	3,781 (38.7)	3,832 (39.2)	1.1
Any medical admission	2,198 (22.5)	2,269 (23.2)	1.7
Any psychiatric admission	529 (5.4)	612 (6.3)	3.5
Primary care utilization			0.3
No primary care visits	66 (0.7)	72 (0.7)	
1–5 primary care visits/yr	5,970 (61.1)	5,942 (60.8)	
≥6 primary care visits/yr	3,740 (38.3)	3,762 (38.5)	
Mental health			0.9
No mental health visits	755 (7.7)	756 (7.7)	
1–9 mental health visits/yr	6,387 (65.3)	6,331 (64.8)	
≥10 mental health visits/yr	2,634 (26.9)	2,689 (27.5)	
Any pulmonary visits	1,993 (20.4)	2,009 (20.6)	0.4
Any sleep visits	463 (4.7)	473 (4.8)	0.5

Definition of abbreviations: % bias = standardized percentage bias; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ED = emergency department; ICS = inhaled corticosteroid; LABA = long-acting β -agonist; LAMA = long-acting muscarinic antagonist; MAOI = monoamine oxidase inhibitors; OSA = obstructive sleep apnea; SC = service connected; SD = standard deviation; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Data presented as n (%) unless otherwise noted. P values obtained from chi-square test and Student's t test for categorical and continuous variables, respectively.

and concomitant respiratory antibiotic or glucocorticoid prescription (33).

Statistical Analysis

To ensure covariate balance (34), we propensity matched patients with long-term benzodiazepine exposure to those with no exposure, and we excluded individuals with short-term exposure (<90 consecutive days' supply) from the propensity-matched analysis. We matched using a caliper width of 0.2 standard deviations (SDs) of propensity score logit without replacement using closest distance within caliper. A histogram of propensity score distribution is included as Figure E1 (see online supplement). We used Cox proportional hazard models clustered by site to assess the overall mortality risk of long-term benzodiazepine use among matched patients. To account for competing risks, cause-specific mortality (chronic obstructive respiratory diseases, suicide, and accidental overdose) was estimated with adjusted subhazard ratios using the Fine and Gray method (35). The incidences of nonfatal events (outpatient COPD exacerbations, inpatient COPD exacerbations, medical hospitalizations, and psychiatric hospitalizations) were compared using negative binomial regression.

In the propensity-matched sample, we also performed secondary analyses to assess overall and cause-specific mortality risks by characteristics of long-term benzodiazepine exposure, including days' supply, dose (in diazepam equivalents), days' supply of long-acting agents of benzodiazepines (diazepam, chlorthalidopexide, and flurazepam), and days' supply of concurrent opioids, using statistical approaches described above (36). To assess outcomes more proximal to the timing of exposure, we also performed a sensitivity analysis where we limited our assessment of mortality to 6 months instead of 2 years.

Finally, given the potential bias of only including propensity-matched individuals in our analyses (37), we performed a secondary nonmatched propensity-adjusted analysis of mortality risk among all patients for whom a propensity score could be calculated. We compared outcomes of those with no benzodiazepine use to those with short-term use (<90 days' supply of benzodiazepines) and long-term use (≥90 d), and we adjusted analyses by propensity score for any benzodiazepine exposure.

For all Cox or Fine-Gray models, the proportional hazards assumption was met (28). All analyses were performed using the STATA statistical package (version 14).

Results

From 2010 to 2012, we identified 46,039 patients with diagnoses of COPD and PTSD who were alive on the index date and were not enrolled in hospice. Of these, 3.2% ($n = 1,484$) were excluded as a result of either age younger than 40 years or the absence of covariate data. Of the remaining 44,555 patients, we then evaluated benzodiazepine use in the 180 days before index and identified 29,237 patients who had no benzodiazepine use, 4,782 patients who had short-term use (<90 days' supply), and 10,536 patients who had long-term use (≥ 90 d). In the propensity-matched sample, 9,776 (33.4%) of eligible patients without use and 9,776 (92.8%) of those with long-term use had sufficient overlap in propensity scores to be matched (Figure 1). Sample characteristics in variables used for propensity matching are included in Table 1. Overall, both groups in our

propensity-matched sample were predominantly male (96%), older (62.5 yr), and white (89%), with a significant burden of medical (57% with Charlson score ≥ 2) and mental health comorbidities. Excellent matching was attained with less than 5% standardized percent bias for all variables. Among individuals with long-term benzodiazepine use in the 180 days before index, patients were prescribed benzodiazepines for an average of 146.0 (SD, 26.9) days (median, 151 d) with a mean daily benzodiazepine prescribed dose of 32.7 (SD, 26.0) mg diazepam equivalents (median, 24.0 mg).

At the end of the 2-year follow-up period in the matched sample, there were 849 deaths among those with long-term benzodiazepine use and 804 deaths among those without such use (Figure 2). Risk of all-cause mortality was not significantly different among those with long-term benzodiazepine use relative to those without use (HR, 1.06; 95% CI, 0.95–1.18; Table 2), and the specific relative risks of death related to obstructive lung disease and accidental overdose were also not different. There was, however, a substantially greater risk for death by suicide among those with long-

term benzodiazepine use (HR, 2.33; 95% CI, 1.14–4.79; Table 2). The incidence of COPD exacerbations and medical hospital admissions did not differ between matched patients with and without exposure to long-term benzodiazepines. Individuals with long-term benzodiazepine use did, however, have a higher rate of psychiatric admissions (incidence rate ratio, 1.37; 95% CI, 1.14–1.65; Table 3).

Among propensity-matched patients with long-term benzodiazepine use, we then assessed fatal outcomes associated with characteristics of benzodiazepines used and the effect of concomitant opioid use. We found the use of long-acting benzodiazepines was positively associated with suicide (HR for every 10 days of exposure, 1.07; 95% CI, 1.01–1.13). We found higher prescribed dose to be associated with increased risk of accidental overdose (HR for every 10 mg of diazepam equivalents, 1.19; 95% CI, 1.07–1.31). We also found that concomitant opioid use was associated with increased risk of overall mortality (HR for every 10 days of exposure, 1.02; 95% CI, 1.01–1.02) and accidental overdose (HR, 1.11; 95% CI, 1.04–1.18; Table 4).

Figure 1. Flow diagram of patients included in propensity matched sample. BMI = body mass index; COPD = chronic obstructive pulmonary disease; PTSD = post-traumatic stress disorder.

Figure 2. Survival in the propensity-matched sample. Kaplan-Meier curves represent survival among those with long-term benzodiazepine use and no benzodiazepine use from propensity-matched sample. *P* value refers to log-rank test assessing risk of death according to group status.

In a sensitivity analysis among the propensity-matched sample, we assessed mortality risks at 6 months. Except for death by accidental overdose, point estimates for risk at 6 months were similar to those at 2 years and were not significant (Table E2).

Finally, we performed a secondary analysis of the risk of overall and cause-specific mortality among all 44,555 patients for whom a propensity score for any benzodiazepine use could be calculated (Table E1). We adjusted all analyses by

propensity score for any benzodiazepine exposure and did not perform matching. In analyses of outcomes over 2 years, individuals with short-term, but not long-term, use had a greater mortality risk relative to those without use (short-term use: HR, 1.16; 95% CI, 1.05–1.28; long-term use: HR, 1.03; 95% CI, 0.94–1.13). Individuals with both short-term and long-term use of benzodiazepines had greater risk of suicides (short-term use: HR, 2.46; 95% CI, 1.16–5.26; long-term use: HR, 2.35; 95% CI, 1.33–4.16; Table 5).

Table 2. Mortality rates and hazard ratios for overall mortality and specific causes of death in the propensity-matched sample

	No Benzodiazepines (n = 9,776)	Long-Term Use (n = 9,776)
Overall		
No. of deaths	804	849
Mortality rate (95% CI)	42.9 (40–46)	45.4 (42.5–48.6)
Hazard ratio (95% CI)		1.06 (0.95–1.18)
Obstructive lung disease*		
No. of deaths	168	192
Mortality rate (95% CI)	9.0 (7.7–10.4)	10.3 (8.9–11.8)
Hazard ratio (95% CI)		1.14 (0.93–1.41)
Suicide*		
No. of deaths	9	21
Mortality rate (95% CI)	0.5 (0.3–0.9)	1.1 (0.7–1.7)
Hazard ratio (95% CI)		2.33 (1.14–4.79)
Accidental overdose*		
No. of deaths	24	23
Mortality rate (95% CI)	1.3 (0.9–1.9)	1.2 (0.8–1.9)
Hazard ratio (95% CI)		0.96 (0.53–1.73)

Definition of abbreviation: CI = confidence interval.

Mortality rate is presented as deaths per 1,000 person-years. Hazard ratio for overall mortality calculated using Cox proportional hazards. Significant hazard ratios in bold typeface.

*Subhazard of each specific cause of death performed using Fine-Gray models incorporating competing risk due to death from other causes.

Discussion

Among patients with COPD and PTSD, we did not find that long-term benzodiazepine use posed a greater risk of all-cause mortality, death due to obstructive lung disease, death due to accidental overdose, or COPD exacerbations relative to no use of benzodiazepines. In contrast, short-term benzodiazepine use was associated with increased mortality risk in analyses with unmatched patients. The most striking and consistent association noted in our analysis was a link between benzodiazepine use and increased risk of suicide. Similar to prior work (38), we also found concomitant opioid exposure to be associated with mortality and accidental overdose among those with long-term benzodiazepine use.

Our findings with respect to the respiratory risks of long-term benzodiazepine use are contrary to those from a prior case-control study that linked long-term benzodiazepine use among patients with COPD with a substantial increase in respiratory failure (6). Given the frequent use of benzodiazepines for dyspnea in end-stage COPD (21, 39), the disparate results may stem from our restriction to individuals with comorbid PTSD, patients who commonly use benzodiazepines for nonrespiratory indications (27). Sample restriction to groups with common indications is an important tool in pharmacoepidemiology to reduce the risk of confounding by indication (40). In addition to restriction, our use of propensity matching may have allowed for better control of measured confounders. It is also possible that underlying susceptibility to benzodiazepine medications may differ between our U.S. Veteran population and the Taiwanese general population sampled in Chen and colleagues (6).

In contrast to the findings related to long-term benzodiazepine use, we found short-term benzodiazepines to be associated with mortality. Our findings related to the risks of short-term use track with prior findings. For instance, among patients with COPD in Ontario, Vozoris and colleagues found newly prescribed benzodiazepines had an increased risk of exacerbations relative to propensity-matched patients without exposure (8). Moreover, among patients with COPD starting oxygen therapy in Sweden, Ekström and colleagues found an increased risk of death (HR, 1.2) with short-term benzodiazepine use relative to nonusers (7). Our findings would suggest a

Table 3. Incidence rate ratios of nonfatal adverse events in patients with long-term benzodiazepine use relative to propensity-matched patients without benzodiazepine use

	No. of Events		IRR (95% CI)
	No Use	Long-Term Use	
COPD exacerbations	7,058	7,258	1.05 (0.98–1.11)
Inpatient COPD exacerbations	958	946	1.01 (0.85–1.20)
Medical hospitalizations	6,869	7,071	1.04 (0.95–1.13)
Psychiatric hospitalizations	1,094	1,487	1.37 (1.14–1.65)

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IRR = incidence rate ratio.

IRRs for each outcome calculated using negative binomial regression. Significant ratios in bold typeface.

greater risk among patients with new or less-frequent exposure, potentially due to a lack of tolerance to benzodiazepines (41). It is worth noting that the associations with short-term use were found in analyses with unmatched patients and may be confounded by the specific episodic reasons for short-term benzodiazepine use, such as acute illnesses not captured in our data. In addition, short-term use could stem from

patient-specific factors, such as frailty, that prompted clinicians to limit benzodiazepine duration. Such possible avenues for unmeasured confounding could be responsible for the observed risks related to short-term use, especially given the relatively small effect sizes of risk (HR for mortality, 1.16; 95% CI, 1.05–1.28) (42).

A strong and robust finding in our results relates to the association of short-

Table 4. Overall and cause-specific mortality associations with benzodiazepine characteristics and concomitant opioid use among propensity-matched patients with benzodiazepine exposure

	Odds Ratio (95% CI)	
	Unadjusted	Adjusted
Days of benzodiazepine exposure, per 10 d*		
Overall mortality	1.01 (0.98–1.03)	1.01 (0.98–1.03)
Death from obstructive lung disease	0.97 (0.92–1.01)	0.96 (0.92–1.00)
Death from suicide	1.08 (0.88–1.32)	1.07 (0.88–1.32)
Death from accidental overdose	1.13 (0.96–1.34)	1.10 (0.93–1.30)
Days of long-acting benzodiazepine exposure, per 10 d*		
Overall mortality	1.00 (0.99–1.02)	1.00 (0.99–1.01)
Death from obstructive lung disease	1.00 (0.98–1.03)	1.00 (0.98–1.02)
Death from suicide	1.07 (1.01–1.13)	1.07 (1.01–1.13)
Death from accidental overdose	1.01 (0.94–1.08)	1.00 (0.94–1.07)
Average prescribed dose of benzodiazepine, per 10 mg of diazepam equivalents*		
Overall mortality	0.97 (0.94–1.00)	0.97 (0.94–1.00)
Death from obstructive lung disease	0.96 (0.89–1.03)	0.95 (0.88–1.02)
Death from suicide	0.96 (0.83–1.11)	0.95 (0.82–1.11)
Death from accidental overdose	1.20 (1.10–1.32)	1.19 (1.07–1.31)
Concomitant opioid use, per 10 d of opioids†		
Overall mortality	1.02 (1.01–1.03)	1.02 (1.01–1.02)
Death from obstructive lung disease	1.00 (0.98–1.02)	1.00 (0.98–1.02)
Death from suicide	1.02 (0.95–1.09)	1.01 (0.93–1.08)
Death from accidental overdose	1.12 (1.06–1.19)	1.11 (1.04–1.18)

Definition of abbreviation: CI = confidence interval.

Significant odds ratios in bold typeface. Odds ratios arise from logistic regression models assessing outcomes at 2 years. Logistic regression was used in lieu of proportional hazard models because the proportional hazards assumption was violated.

*Adjusted models included propensity score for long-term benzodiazepine exposure as a covariate.

†Adjusted models included propensity score for opioid use as a covariate.

and long-term benzodiazepine use with suicide. Similar to other estimates of the suicide rate within the Veteran population (0.3 per 1,000 person-years) (43), the rate of suicide among those without benzodiazepine use (0.4–0.5 per 1,000 person-years; Tables 2 and 5) in our sample was greater than the rate in the civilian population (0.1 per 1,000 person-years) (44). However, the risk of suicide was substantially greater among those with short- and long-term benzodiazepine use (1.1 per 1,000 person-years; Tables 2 and 5). It is worth acknowledging that because of difficulties in assessing intent, death due to suicide as documented in death certificates may be misclassified (45); in particular, there is concern that suicides may be incorrectly documented as accidental overdoses, and vice versa. Some of this concern is attenuated by the observation that a majority of suicides in each group were not related to intentional poisonings ($n = 7$, 78% no use; $n = 14$, 62% long-term use). The association of benzodiazepines with suicide risk has been noted previously among patients with mental health disorders such as major depression and schizophrenia (11, 46–48). Our findings suggest long-acting agents may pose a particular risk for suicide, a finding that may relate to the sustained half-life of medication or the more severe and sustained mental health symptoms that prompt the use of long-acting agents. Benzodiazepines may mediate suicide risk by disinhibiting self-injurious behavior and augmenting self-directed aggression (10, 47, 49–51). Alternatively, the association may be due to confounding by indication; individuals with mental illness are more likely to have insomnia and anxiety-related complaints, and these individuals may be more likely to attempt and commit suicide (19). Although our study does not eliminate this concern, our use of propensity matching and our restriction to a specific population further reduces confounding by indication (40). As mental health comorbidities and suicidal ideation are more common among patients with COPD than the general population (12, 52, 53), caution should be exercised to avoid further increasing suicide risk in this vulnerable population. Among patients with PTSD, additional mental health comorbidities such as depression are also common (35–55%) (54, 55). The overlap and relationships between mental health disorders and COPD, including the overlap

Table 5. Overall mortality and specific causes of death for patients with short- and long-term use of benzodiazepines in the matched and unmatched sample

	No Use (n = 29,237)	Short-Term Use (n = 4,782)	Long-Term Use (n = 10,536)
Overall			
No. of deaths	2,400	459	914
Mortality rate (95% CI)	42.9 (41.2–44.6)	50.6 (46.1–55.4)	45.4 (42.5–48.4)
Hazard ratio (95% CI)		1.16 (1.05–1.28)	1.03 (0.94–1.13)
Obstructive lung disease*			
No. of deaths	462	97	213
Mortality rate (95% CI)	8.2 (7.5–9.1)	10.7 (8.8–13)	10.6 (9.2–12.1)
Hazard ratio (95% CI)		1.21 (0.98–1.49)	1.16 (0.97–1.39)
Suicide*			
No. of deaths	23	10	22
Mortality rate (95% CI)	0.4 (0.3–0.6)	1.1 (0.6–2)	1.1 (0.7–1.7)
Hazard ratio (95% CI)		2.46 (1.16–5.26)	2.35 (1.33–4.16)
Accidental overdose*			
No. of deaths	54	8	24
Mortality rate (95% CI)	1 (0.7–1.3)	0.9 (0.4–1.8)	1.2 (0.8–1.8)
Hazard ratio (95% CI)		0.68 (0.34–1.35)	0.80 (0.47–1.32)

Definition of abbreviation: CI = confidence interval.

Mortality rate is presented as deaths per 1,000 person-years. Hazard ratio for overall mortality calculated using Cox proportional hazards. Models included propensity score for any benzodiazepine exposure as a covariate. Significant hazard ratios in bold typeface.

*Subhazard of each specific cause of death performed using Fine-Gray models incorporating competing risk due to death from other causes.

with PTSD, are emerging topics of interest and are reviewed in detail elsewhere (56, 57).

Our study has several potential limitations. As a study using nationwide administrative data, we did not have access to spirometry and therefore are limited in our ability to confirm the presence and severity of airflow limitation. We are also limited in our ability to capture other measures of COPD severity, such as oxygen use. It is possible that this lack of ascertainment led to residual confounding; however, our use of multiple proxies for COPD risk and severity, such as data related to medication use, exacerbations, and hospitalizations, helps to at least partially address this concern (28). Similarly, it is possible that we incompletely ascertained severity of PTSD and other mental illnesses, which would also lead to residual confounding. However, even if benzodiazepines are simply associated with

suicide because they are used to treat severe symptoms, benzodiazepine use could still be a useful marker for clinicians and health systems to identify patients at greater suicide risk. Our use of propensity matching, although potentially easing interpretation of our findings, excluded a large number of patients, and this may have unnecessarily limited our power. However, when our survival analyses were repeated using the entire sample and propensity score as a covariate, the estimated risks for those with long-term use closely resembled those obtained from the propensity-matched cohort. Given that our sample consisted of patients receiving care in the VA, current results may not generalize to non-Veterans or Veterans who receive non-VA health care. It is also possible that the focus on another mental health comorbidity of COPD, such as generalized anxiety disorder or depression, may have yielded different

results. Finally, prescription data were limited to VA outpatient prescription fills and did not directly measure true medication adherence. Medications and medical care that patients received outside of the VA would not be captured by the current analysis. However, the vast majority of patients were more than 50% service connected and therefore had a strong financial incentive to use VA services exclusively (58). These limitations are offset by substantial strengths, including complete pharmacy records and complete assessment of the outcome of interest, mortality, which together dramatically decrease the risk for bias. Furthermore, our inclusion of all VA patients nationwide with COPD and PTSD allows for full representation of a geographically dispersed and heterogeneous population and a high level of generalizability to Veterans with COPD and PTSD.

Overall, our results identify a strong risk of suicide associated with benzodiazepine use among patients with COPD, and we did not identify an association between long-term benzodiazepine use and overall mortality, death due to lung disease, or COPD exacerbations in a sample enriched in nonrespiratory indications for benzodiazepines. In contrast to the findings with long-term use, short-term benzodiazepine exposure was associated with overall mortality. Our results do not suggest that discontinuation of long-term benzodiazepines would reduce overall mortality or death related to obstructive lung disease or overdose. However, providers should consider discontinuing benzodiazepines among patients already at high suicide risk and should also avoid concomitant opioid use. Furthermore, providers should be aware of the risks that new benzodiazepine prescriptions may present to patients with COPD and PTSD without prior exposure to these medications. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

- Budhiraja R, Parthasarathy S, Budhiraja P, Habib MP, Wendel C, Quan SF. Insomnia in patients with COPD. *Sleep (Basel)* 2012;35:369–375.
- Ohayon MM. Chronic obstructive pulmonary disease and its association with sleep and mental disorders in the general population. *J Psychiatr Res* 2014;54:79–84.
- Kroll DS, Nieva HR, Barsky AJ, Linder JA. Benzodiazepines are prescribed more frequently to patients already at risk for benzodiazepine-related adverse events in primary care. *J Gen Intern Med* 2016;31:1027–1034.
- Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–946.
- Smoller JW, Pollack MH, Otto MW, Rosenbaum JF, Kradin RL. Panic anxiety, dyspnea, and respiratory disease: theoretical and clinical considerations. *Am J Respir Crit Care Med* 1996;154:6–17.

- 6 Chen SJ, Yeh CM, Chao TF, Liu CJ, Wang KL, Chen TJ, *et al.* The use of benzodiazepine receptor agonists and risk of respiratory failure in patients with chronic obstructive pulmonary disease: a nationwide population-based case-control study. *Sleep (Basel)* 2015;38:1045–1050.
- 7 Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014;348:g445.
- 8 Vozoris NT, Fischer HD, Wang X, Stephenson AL, Gershon AS, Gruneir A, *et al.* Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J* 2014;44:332–340.
- 9 Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996–2013. *Am J Public Health* 2016;106:686–688.
- 10 Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ* 2015;350:h2698.
- 11 Dodds TJ. Prescribed benzodiazepines and suicide risk: a review of the literature. *Prim Care Companion CNS Disord* 2017;19:16r02037.
- 12 Goodwin RD. Is COPD associated with suicide behavior? *J Psychiatr Res* 2011;45:1269–1271.
- 13 Olsson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry* 2015;72:136–142.
- 14 Valenstein M, Taylor KK, Austin K, Kales HC, McCarthy JF, Blow FC. Benzodiazepine use among depressed patients treated in mental health settings. *Am J Psychiatry* 2004;161:654–661.
- 15 Vozoris NT, Fischer HD, Wang X, Anderson GM, Bell CM, Gershon AS, *et al.* Benzodiazepine use among older adults with chronic obstructive pulmonary disease: a population-based cohort study. *Drugs Aging* 2013;30:183–192.
- 16 Swallen KC. Hospital use and survival among Veterans Affairs beneficiaries. *N Engl J Med* 2004;350:518–519.
- 17 Fluyau D, Revadigar N, Manobianco BE. Challenges of the pharmacological management of benzodiazepine withdrawal, dependence, and discontinuation. *Ther Adv Psychopharmacol* 2018;8:147–168.
- 18 Lader M. Benzodiazepines revisited—will we ever learn? *Addiction* 2011;106:2086–2109.
- 19 McCall WV, Benca RM, Rosenquist PB, Riley MA, McCloud L, Newman JC, *et al.* Hypnotic medications and suicide: risk, mechanisms, mitigation, and the FDA. *Am J Psychiatry* 2017;174:18–25.
- 20 Simon ST, Higginson IJ, Booth S, Harding R, Weingartner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev* 2016;10:CD007354.
- 21 Godbout K, Tremblay L, Lacasse Y. A distress protocol for respiratory emergencies in terminally ill patients with lung cancer or chronic obstructive pulmonary disease. *Am J Hosp Palliat Care* 2016;33:817–822.
- 22 Casanova C, Marin JM, Martinez-Gonzalez C, de Lucas-Ramos P, Mir-Viladrich I, Cosío B, *et al.* COPD History Assessment in Spain (CHAIN) Cohort. Differential effect of modified medical research council dyspnea, COPD assessment test, and clinical COPD questionnaire for symptoms evaluation within the new GOLD staging and mortality in COPD. *Chest* 2015;148:159–168.
- 23 Motegi T, Jones RC, Ishii T, Hattori K, Kusunoki Y, Furutate R, *et al.* A comparison of three multidimensional indices of COPD severity as predictors of future exacerbations. *Int J Chron Obstruct Pulmon Dis* 2013;8:259–271.
- 24 Fleehtart S, Fan VS, Nguyen HQ, Lee J, Kohen R, Herting JR, *et al.* Prevalence and correlates of suicide ideation in patients with COPD: a mixed methods study. *Int J Chron Obstruct Pulmon Dis* 2014;10:1321–1329.
- 25 Goldstein RB, Smith SM, Chou SP, Saha TD, Jung J, Zhang H, *et al.* The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *Soc Psychiatry Psychiatr Epidemiol* 2016;51:1137–1148.
- 26 Chung MC, Jones RC, Harding SA, Campbell J. Posttraumatic stress disorder among older patients with chronic obstructive pulmonary disease. *Psychiatr Q* 2016;87:605–618.
- 27 Nobles CJ, Valentine SE, Zepeda ED, Ahles EM, Shtasel DL, Marques L. Usual course of treatment and predictors of treatment utilization for patients with posttraumatic stress disorder. *J Clin Psychiatry* 2017;78:e559–e566.
- 28 Cooke CR, Joo MJ, Anderson SM, Lee TA, Udriș EM, Johnson E, *et al.* The validity of using ICD-9 codes and pharmacy records to identify patients with chronic obstructive pulmonary disease. *BMC Health Serv Res* 2011;11:37.
- 29 Suissa S. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. *Am J Respir Crit Care Med* 2003;168:49–53.
- 30 WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2011. Oslo, Norway: WHO. 2010 [updated 2018 Nov 26; accessed 2017 Jul 1]. Available from: <https://www.whocc.no/>.
- 31 Center of Excellence for Suicide Prevention. Joint Department of Veterans Affairs (VA) and Department of Defense (DoD) Suicide Data Repository - National Death Index (NDI). [Accessed 2017 Jun 21]. <http://www.dspo.mil/About-Suicide/Suicide-Data-Repository/>.
- 32 Cowper DC, Kubal JD, Maynard C, Hynes DM. A primer and comparative review of major US mortality databases. *Ann Epidemiol* 2002;12:462–468.
- 33 Melzer AC, Feemster LM, Uman JE, Ramenofsky DH, Au DH. Missing potential opportunities to reduce repeat COPD exacerbations. *J Gen Intern Med* 2013;28:652–659.
- 34 Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol* 2010;172:1092–1097.
- 35 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
- 36 Liu GG, Christensen DB. The continuing challenge of inappropriate prescribing in the elderly: an update of the evidence. *J Am Pharm Assoc (Wash)* 2002;42:847–857.
- 37 Austin PC, Schuster T. The performance of different propensity score methods for estimating absolute effects of treatments on survival outcomes: a simulation study. *Stat Methods Med Res* 2016;25:2214–2237.
- 38 Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. *BMJ* 2017;356:j760.
- 39 Steel A, Goldring J. End-of-life care in patients with chronic obstructive pulmonary disease. *Br J Hosp Med (Lond)* 2015;76:C10–C13.
- 40 Psaty BM, Siscovick DS. Minimizing bias due to confounding by indication in comparative effectiveness research: the importance of restriction. *JAMA* 2010;304:897–898.
- 41 Mora CT, Torjman M, White PF. Effects of diazepam and flumazenil on sedation and hypoxic ventilatory response. *Anesth Analg* 1989;68:473–478.
- 42 VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med* 2017;167:268–274.
- 43 Hudenko W, Homaifar B, Wortzel H. The relationship between PTSD and suicide. National Center for PTSD; 2018 [accessed 2018 Dec 1]. Available from: https://www.ptsd.va.gov/professional/treat/cooccurring/suicide_ptsd.asp.
- 44 Curtin SC, Warner M, Hedegaard H. Increase in suicide in the United States, 1999–2014. NCHS data brief, no 241. Hyattsville, MD: National Center for Health Statistics; 2016.
- 45 Stanistreet D, Taylor S, Jeffrey V, Gabbay M. Accident or suicide? Predictors of coroners' decisions in suicide and accident verdicts. *Med Sci Law* 2001;41:111–115.
- 46 Neutel CI, Patten SB. Risk of suicide attempts after benzodiazepine and/or antidepressant use. *Ann Epidemiol* 1997;7:568–574.
- 47 Tiihonen J, Mittendorf-Rutz E, Torniainen M, Alexanderson K, Tanskanen A. Mortality and cumulative exposure to antipsychotics, antidepressants, and benzodiazepines in patients with schizophrenia: an observational follow-up study. *Am J Psychiatry* 2016;173:600–606.

- 48 Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder: alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. *Arch Gen Psychiatry* 1988;45:111–119.
- 49 Berman ME, Jones GD, McCloskey MS. The effects of diazepam on human self-aggressive behavior. *Psychopharmacology (Berl)* 2005;178:100–106.
- 50 Rothschild AJ, Shindul-Rothschild JA. Benzodiazepines do not cause suicide or suicide attempts. *Prim Care Companion CNS Disord* 2017;19:17lr02171.
- 51 Gardner DL, Cowdry RW. Alprazolam-induced dyscontrol in borderline personality disorder. *Am J Psychiatry* 1985;142:98–100.
- 52 Donovan LM, Rise PJ, Carson SS, Feemster LC, Griffith MF, Kapur VK, et al.; CONCERT Investigators. Sleep disturbance in smokers with preserved pulmonary function and with chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2017;14:1836–1843.
- 53 Iyer AS, Bhatt SP, Garner JJ, Wells JM, Trevor JL, Patel NM, et al. Depression is associated with readmission for acute exacerbation of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2016;13:197–203.
- 54 Husky MM, Mazure CM, Kovess-Masfety V. Gender differences in psychiatric and medical comorbidity with post-traumatic stress disorder. *Compr Psychiatry* 2018;84:75–81.
- 55 Trivedi RB, Post EP, Sun H, Pomerantz A, Saxon AJ, Piette JD, et al. Prevalence, comorbidity, and prognosis of mental health among US veterans. *Am J Public Health* 2015;105:2564–2569.
- 56 Atlantis E, Fahey P, Cochrane B, Smith S. Bidirectional associations between clinically relevant depression or anxiety and COPD: a systematic review and meta-analysis. *Chest* 2013;144:766–777.
- 57 Abrams TE, Blevins A, Weg MW. Chronic obstructive lung disease and posttraumatic stress disorder: current perspectives. *Int J Chron Obstruct Pulmon Dis* 2015;10:2219–2233.
- 58 Hoff RA, Rosenheck RA. Cross-system service use among psychiatric patients: data from the Department of Veterans Affairs. *J Behav Health Serv Res* 2000;27:98–106.