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Association Between Hypnotic Use and All-Cause Mortality in Patients with Chronic Obstructive Pulmonary Disease and Insomnia

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Purpose: Hypnotics are commonly prescribed in patients with COPD to manage insomnia. Given the considerable risks associated with these drugs, the aim of the study was to evaluate the risk of all-cause mortality associated with hypnotics in a cohort of veterans with COPD presenting with insomnia.

Methods: We conducted a retrospective cohort study that used Veterans Health Administration Corporate Data Warehouse with data supplemented by linkage to Medicare, Medicaid, and National Death Index data from 2010 through 2019. The primary outcome was all-cause mortality. Analyses were conducted using propensity score 1:1 matching to balance baseline characteristics.

Results: Of the 5759 veterans with COPD (mean [SD] age, 71.7 [11.2]; 92% men), 3585 newly initiated hypnotic agents during the study period. During a mean follow-up of 7.4 (SD, 2.7) years, a total of 2301 deaths occurred, with 65.2 and 48.7 total deaths per 1000 person-years among hypnotic users and nonusers, respectively. After propensity matching, hypnotic use was associated with a 22% increased risk of mortality compared with hypnotic nonusers (hazard ratio [HR] 1.22; 95% confidence interval [CI],1.11–1.35). The benzodiazepine receptor agonists (BZRAs) group experienced a higher incidence rate of all-cause mortality compared to hypnotic nonusers (Incidence rate ratio [IRR] 1.27; 95% CI, 1.14–1.43). Conversely, the mortality rate of non-BZRA hypnotics decreased after the first 2 years and was not significantly different for hypnotic nonusers (IRR 1.04; 95% CI, 0.82–1.11).

Conclusion: Among patients with COPD and insomnia, treatment with hypnotics was associated with a higher risk of all-cause mortality. The association was observed in patients prescribed BZRAs. The risk of mortality for non-BZRAs moderated after the first 2 years, indicating a class effect.

Keywords: insomnia, chronic obstructive pulmonary disease, mortality, benzodiazepine receptor agonists

Introduction

Chronic obstructive lung disease (COPD) is a chronic debilitating disease characterized by progressive and often irreversible airflow limitation, chronic respiratory symptoms, and systemic manifestations caused by significant exposure to noxious particles or gases.[1] It is the fifth leading cause of morbidity and mortality in the United States affecting millions of individuals.[2] With a death toll expected to exceed 5 million patients per year worldwide by 2060, the economic burden of COPD on healthcare systems is enormous.[3]

Apart from its pulmonary complications, patients with COPD frequently exhibit sleep disturbances emanating from persistent dyspnea, recurrent cough, anxiety, and pain.[4] These sleep disturbances have been associated with increased symptom severity, recurrent exacerbations, and poor quality of life.[5] Sleep quality is further aggravated by the side effects of COPD treatment (ie β-agonists and corticosteroids). Sleep characteristics include prolonged sleep onset latency, frequent arousals, and lower sleep efficiency.[6] According to epidemiologic studies, more than 50% of patients with

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COPD report insomnia.[7] Among those afflicted with cough and wheezes, the rate of those complaining of insomnia rose from 39.0% to 52.8% when both symptoms were present.[8]

Cognitive behavioral therapy is considered the first-line treatment for insomnia in COPD patients and is associated with improvement in fatigue and dyspnea.[9] However, hypnotics are frequently prescribed to improve sleep quality and suppress insomnia. Commonly prescribed drugs include FDA-approved agents for the treatment of insomnia (benzodiazepines, non-benzodiazepine benzodiazepine receptor agonists (Z-drugs), melatonin receptor agonists, doxepin, and dual orexin receptor antagonists (DORAs)) and off-label use medications (trazodone, antipsychotics, and anticonvulsants).[10] The use of these medications comes with associated risks shared with most hypnotics such as next morning residual sleepiness, ataxia, and falls, particularly in elderly COPD patients, and specific to others like benzodiazepine receptor agonists-associated respiratory depression, cognitive impairment, or nocturnal complex behaviors.[11–13] The relationship between hypnotic use and mortality in COPD patients is the subject of increasing scientific investigations given the unremitting global rise in disease burden of COPD. Previous studies have raised concerns about increased mortality risks with hypnotics, however, the available evidence is limited and conflicting.[14,15] Given the substantial impact of COPD on mortality and the widespread use of hypnotics in this population, a better understanding of the effects of hypnotics on mortality in patients with COPD is warranted. In response, we performed this study using electronic records from the large-scale Veterans Health Administration database to test the hypothesis that the use of hypnotics is associated with increased mortality in patients with COPD.

Methods

Ethics

The research protocol was reviewed and approved by the VA Research and Development Committee and was conducted in accordance with all applicable Federal regulations. Informed consent of participants was not needed for this retrospective cohort study. The study is considered to be exempt from the Common Rule per section §46.104 of the Code of Federal Regulations.

Data Sources

Data were obtained from the VA National Corporate Data Warehouse (CDW), a central database repository that aggregates EHR records from the entire US Veterans Health Administration (VHA) medical facilities. The repository encompasses enrolled Veterans and a limited number of non-Veterans such as qualified partners. The VHA electronic health record includes sociodemographic characteristics, outpatient and inpatient clinical encounters, list of prescribed medications, and laboratory reports.[16] Data retrieved from multiple domains were conflated, including inpatient and outpatient diagnosis codes, consults, health factors, and pharmacy data.

Participants

Records of Veterans aged 18 years and older who utilized health services through the VHA system between January 1st, 2010, and May 15th, 2019, were extracted. Regular use of the VHA healthcare system was defined as an encounter at least once a year for 2 consecutive years of utilization prior to entry into the cohort. The cohort encompassed veterans who were newly diagnosed with insomnia which was established when two or more outpatient International Classification of Diseases (ICD)-9 codes (307.42; 327.00, 327.01, 327.02, 327.09; 780.51, 780.5) or ICD-10 codes (F51.01, F51.03, F51.04, F51.05, F51.09; G47.00, G47.01, G47.09) were recorded >30 days apart but within 390 days of each other (the equivalent of 13 30-day months; 30/390 criteria). This approach was instituted to ensure the validity of the diagnosis and to adjust for variability in annual appointment scheduling.[17] Clinic visits that did not involve prescribing medications such as for prosthetics or hearing aids, were not considered for inclusion in the data analysis. Patients with a documented history of post-traumatic stress disorder, sleep apnea (obstructive or central in origin), restless leg syndrome, parasomnia, or circadian rhythm sleep disorder before initiation of hypnotics were excluded. Patients were also excluded if they had alcohol or substance abuse disorders, or if they have received hospice or opioid treatment at any point in the study to reduce potential confounding by indication.

Exposure

Hypnotic medications were identified using outpatient pharmacy records. Hypnotic use outside the VHA was derived from the CMS drug information linked to CDW database. We did not include medications such as off-label sedating antipsychotics or over-the-counter sleeping aids. Hypnotic users were defined as those who received at least two prescriptions for a given drug. This definition is intended to minimize hypnotic misclassification among the patients who received, but did not fill the prescription, or did not adhere to treatment.[18] We sorted hypnotics into two groups: 1) hypnotics whose mechanism of action involves binding to the gamma-aminobutyric acid receptors (benzodiazepines and non-benzodiazepine benzodiazepine receptor agonists) henceforth referred to as BZRAs, and 2) all other hypnotics (trazodone, doxepin, melatonin receptor agonists, and orexin receptor antagonists) henceforth referred to as non-BZRAs. Veterans who used hypnotics prior to the diagnosis of insomnia were excluded. Hypnotic nonusers were included in the cohort after meeting the criteria of VHA utilization for 2 years and were not receiving a hypnotic agent. Patients who subsequently started on a hypnotic agent were assigned to the exposed group on the first date of hypnotic prescription. The exposure interval for hypnotic users was calculated based on the time elapsed between the date of the first hypnotic prescription and 30 days after the date of the last refill. For those patients who were prescribed more than one hypnotic agent during the study, they were considered to be exposed to both or all of these drugs.

Covariates

Baseline variables with known associations with treatment outcome were used as predefined covariates.[19] These covariates included age, sex, race, ethnicity, body mass index, smoking status (active, former, or never smoker), statins, and cardiovascular medications (aspirin, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and beta-blockers). Pre-existing diseases that may act as potential confounders were also retrieved using the International Statistical Classification of Diseases and Related Health Problems, Ninth, and Tenth Revision medical billing category codes (Table S1 in Supplement). The Charlson Comorbidity Index (CCI) was calculated based on these comorbid conditions according to published nomograms.[20] Acute COPD exacerbations (ICD-9 codes 491.21; ICD10 codes J44.1) necessitating emergency department visits were used as a proxy measure of disease severity. Missingness for race (3%), BMI (1.7%), and smoking status (6.4%) were assumed to be missing at random and imputed using a random Forest-based imputation method.[21]

Outcome

The primary outcome was all-cause mortality. Death records were verified by accessing VHA Patient Treatment File, death certificates, VHA National Cemetery Administration, Social Security Administration Death Master File, and VA/CMS Medicare Vital Status File.[22,23] Cardiovascular and respiratory-related deaths were identified by ICD-9 and ICD-10 codes (390–459 for ICD-9 and I00-I99 for ICD-10) and (470–478, 490–496 for ICD-9 and J00-J99 for ICD-10), respectively.

Statistical Analysis

Baseline characteristics were compared using the Student's *t*-test for parametric continuous variables or the Mann–Whitney *U*-test for nonparametric continuous variables as appropriate, and by the Pearson $\chi 2$ test for categorical variables. Median differences with 95% Cis were estimated by the method of Hodges-Lehman. The incidence rate of all-cause mortality was calculated by dividing the number of incident cases by the total follow-up duration in years (person-years).

The primary analysis compared the cause-specific hazard of all-cause mortality between hypnotic and non-hypnotic users. Given the retrospective observational nature of the data, propensity score matching was applied to reduce confounding effects that could account for differences in treatment and control groups.[24,25] A propensity score-matched cohort was created using a greedy 1:1 nearest-neighbor matching without replacement after calculating the propensity scores for the likelihood of receiving a hypnotic agent for chronic insomnia by using logistic regression

models involving all potential confounders. Standardized differences before and after propensity score matching were calculated to examine differences between variables. A threshold of 10% or less was considered acceptable for matching.

Propensity adjusted Cox proportional hazards models with time-dependent interaction term were fit to evaluate the association of hypnotic use with the selected outcome. The exposure variable was treated as a time-varying exposure. Scaled Schoenfeld residual plots were used to verify the proportional hazards assumptions over time.[26] Study participants were censored at the earliest of the follow-up date, death, the latest date of VHA service use, or May 15th, 2019. Kaplan–Meier plots were used to analyze time-to-event for mortality outcomes by receipt of hypnotics.

We performed several sensitivity analyses to test the robustness of our primary outcome. First, we compared risks between those receiving benzodiazepines versus non-benzodiazepine benzodiazepine receptor agonists. Second, we analyzed the risks between the two groups of hypnotics and the nonuser group. Third, we used several different follow-up periods (2, 4, and 6 years) to assess whether the risk of all-cause mortality was consistent across the duration of the study. Fourth, we tested the potential for effect modification of hypnotics on all-cause mortality according to age categories (<65 years and ≥65 years). Tests of interaction were run for all subgroups. All tests were two-sided and a p-value < 0.05 was considered statistically significant. Statistical analyses were performed using Stata/MP version 16 (StataCorp, LLC).

Results

Using data from the CDW, 13,374 veterans with COPD were diagnosed de novo with insomnia during the course of the study. After eliminating cases who had less than one encounter per year for two consecutive years, 12,922 met the eligibility criteria. Of those, 2301 were excluded because of established diagnosis of PTSD, 2161 because of concomitant sleep disorders, and 755 because of alcohol or substance abuse disorders, and opiate use prescribed either for chronic pain or as part of palliative care. In total, 5759 veterans were included into the final cohort (Figure 1). There were 3585 (62.3%) new hypnotic users, and 2174 (37.7%) who never had a hypnotic prescription recorded. Mean age was 71.7 (SD, 11.2) years, 82.1% were white, and 92.3% were men. Trazodone was most prescribed (41.3%), followed by zolpidem (34.4%), and temazepam (8.2%). Table 1 describes the baseline characteristics of the study cohort before and after propensity score matching. In the unweighted cohort, those who were using hypnotics were more likely to be active or former smokers and to have diagnostic codes for hypertension, diabetes mellitus, and congestive heart failure. Compared with hypnotic nonusers, aspirin, statins, angiotensin-converting enzyme inhibitors, and β-blockers were more commonly prescribed to hypnotic users. Hospitalizations from acute COPD exacerbations were also more frequent in the hypnotic users compared with nonusers (p<0.001). After matching, there were no statistically significant differences in baseline characteristics between hypnotic and hypnotic non-users in terms of age, sex, total comorbidities, and acute exacerbations as assessed by absolute standardized differences<0.1.

Primary Outcome

During a mean follow-up of 7.4 (SD, 2.7) years, 1525 (41.4%) patients died from any cause. Before adjustment, there were 65.2 and 48.7 total deaths per 1000 person-years among hypnotic users and nonusers, respectively (incidence rate difference [IRD]/1000 person-years, 16.5 [95% CI, 12.4–20.1], p<0.001). Results from the unadjusted Cox regression analysis indicated that hypnotic users had a 72% increased risk of mortality compared with hypnotic nonusers (hazard ratio [HR] 1.72; 95% CI, 1.40–2.11). After propensity score was applied, there were 60.7 and 52.2 total deaths per 1000 person-years among hypnotic users and nonusers, respectively (IRD/1000 person-years, 8.5 [95% CI, 2.7–14.1], p=0.004). Results from the Cox regression analysis indicated that hypnotic use had a 22% increased risk of all-cause mortality compared with hypnotic nonusers (HR 1.22; 95% CI, 1.11 to 1.35). However, there was n0 difference in the frequency of COPD exacerbations between matched hypnotic users versus nonusers (p=0.23). Propensity-score matched Kaplan-Meier curve comparing the survival probability between hypnotic users and nonusers is shown in Figure 2. Cardiovascular and respiratory diseases accounted for 42% and 40% of all-cause mortality. COPD patients receiving BZRAs had a higher risk of mortality from cardiovascular (HR 1.48; 95% CI, 1.25–1.76) and respiratory complications (HR 1.25; 95% CI, 1.05–1.49) relative to hypnotic nonusers. In contrast, there was no difference in the risk of cardiovascular- or respiratory-related deaths (HR 1.16; 95% CI 0.93–1.45) and (HR 1.05; 95% CI 0.58–1.89) between non-BZRAs and hypnotic nonusers.

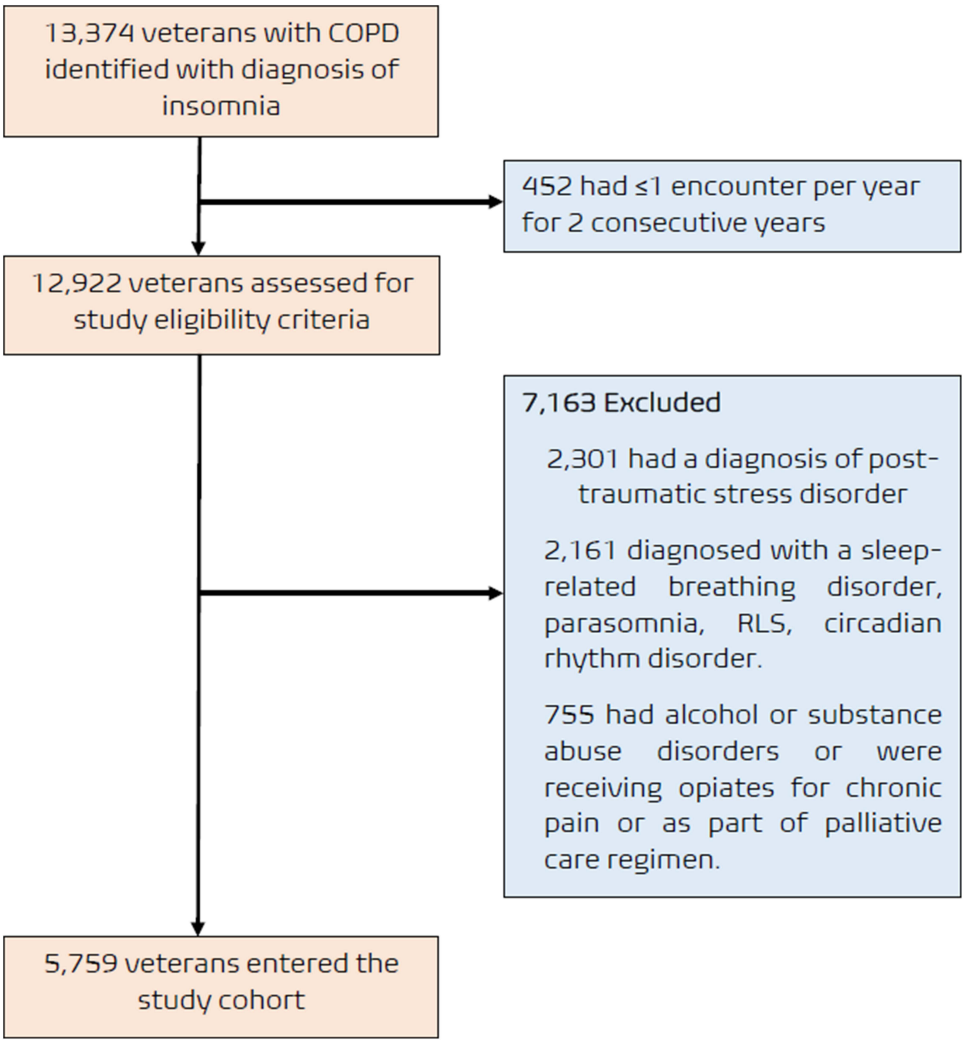

Figure 1 Selection of the study cohort.

Sensitivity Analyses

In the first sensitivity analysis, we compared first the outcomes between those receiving benzodiazepines versus non-benzodiazepine benzodiazepine receptor agonists. Although the benzodiazepine group had a higher incidence of all-cause

Table 1 Baseline Characteristics of the Study Population Before and After Propensity Score Matching

	Full Unweighted Cohort			P value	Propensity Score-Weighted Cohort			P value
	Hypnotic Users (n=3585)	Hypnotic Nonusers (n=2174)	SMD		Hypnotic Users (n=1840)	Hypnotic Nonusers (n=1840)	SMD	
Age, years	71 (13)	73 (16)	0.17	<0.001	72 (15)	72 (15)	0.02	0.56
Age, n (%)								
<50	109 (3)	50 (2)	0.05	0.1	48 (3)	41 (2)	0.02	0.45
50–59	316 (9)	187 (9)	0.007	0.78	176 (10)	160 (9)	0.03	0.36
60–69	1179 (33)	600 (27)	0.12	<0.001	547 (30)	553 (30)	0.007	0.83
70–79	1268 (35)	723 (33)	0.04	0.1	620 (34)	617 (34)	0.003	0.92
≥80	713 (20)	614 (29)	0.19	<0.001	456 (23)	462 (25)	0.007	0.82

(*Continued*)

Table 1 (Continued).

	Full Unweighted Cohort			P value	Propensity Score-Weighted Cohort			P value
	Hypnotic Users (n=3585)	Hypnotic Nonusers (n=2174)	SMD		Hypnotic Users (n=1840)	Hypnotic Nonusers (n=1840)	SMD	
Sex, n (%)			0.21	<0.001			0.03	0.37
Male	3351 (93)	1967 (90)			1734 (94)	1721 (94)		
Female	234 (7)	207 (10)			106 (6)	119 (6)		
Race, n (%)								
Caucasians	2925 (82)	1806 (83)	0.04	0.15	1492 (81)	1510 (82)	0.009	0.44
Black	452 (13)	266 (12)	0.01	0.68	249 (13)	230 (13)	0.02	0.35
Hispanic	85 (2)	41 (2)	0.03	0.22	44 (2)	36 (2)	0.03	0.37
BMI, kg/m^2	27.6 (8.7)	27.1 (8.9)	0.1	0.002	27.1 (8.8)	27.3 (8.8)	0.04	0.57
BMI categories, n (%)								
Underweight	185 (5)	123 (6)	0.02	0.42	110 (6)	105 (6)	0.01	0.73
Normal	1018 (28)	672 (31)	0.06	0.04	545 (29)	543 (29)	0.002	0.94
Overweight	1042 (29)	640 (29)	0.008	0.76	537 (29)	553 (30)	0.02	0.56
Obese	1134 (32)	607 (28)	0.08	0.003	520 (28)	533 (30)	0.02	0.64
Morbidly Obese	206 (6)	132 (6)	0.01	0.61	128 (7)	106 (6)	0.05	0.14
Tobacco use, n (%)			0.1	0.02			0.006	0.81
Active smoker	1537 (43)	865 (40)			797 (43)	781 (42)		
Former smoker	1815 (51)	1134 (52)			954 (52)	973 (53)		
Never smoker	233 (6)	175 (8)			89 (5)	86 (5)		
Comorbidities, n (%)								
Depression	476 (13)	312 (14)	0.03	0.25	254 (14)	261 (14)	0.01	0.74
Hypertension	3156 (88)	1786 (82)	0.17	<0.001	1566 (85)	1560 (85)	0.009	0.78
Cerebrovascular disease	110 (3)	46 (2)	0.06	0.03	47 (3)	42 (2)	0.02	0.59
Diabetes mellitus	1699 (47)	834 (38)	0.18	<0.001	773 (42)	747 (41)	0.03	0.38
MI	478 (13)	261 (12)	0.04	0.14	251 (14)	238 (13)	0.02	0.28
CHF	979 (27)	522 (24)	0.08	0.006	510 (28)	463 (25)	0.06	0.08
CKD	640 (18)	369 (17)	0.02	0.39	342 (19)	332 (18)	0.01	0.67
Cancer	101 (3)	41 (2)	0.06	0.03	38 (2)	39 (2)	0.004	0.91
HIV	41 (1)	21 (1)	0.02	0.52	21 (1)	20 (1)	0.005	0.88
Medications, n (%)								
Aspirin	1681 (47)	716 (33)	0.29	<0.001	710 (39)	692 (38)	0.02	0.54
Statins	2624 (73)	1206 (55)	0.38	<0.001	1156 (63)	1171 (64)	0.01	0.61
Beta-blockers	2057 (57)	941 (43)	0.28	<0.001	897 (49)	911 (50)	0.01	0.64
ACEI/ARB	1814 (51)	784 (36)	0.27	<0.001	774 (42)	773 (42)	0.001	0.97
LABA	2187 (61)	1022 (47)	0.29	<0.001	864 (47)	827 (45)	0.03	0.22
LAMA	1900 (53)	891 (41)	0.24	<0.001	798 (43)	786 (43)	0.01	0.68
ICS	1864 (48)	783 (36)	0.18	<0.001	701 (38)	657 (36)	0.06	0.13
AECOPD	614 (17)	321 (15)	0.06	0.02	327 (18)	300 (16)	0.03	0.23

Abbreviations: ACEI/ARB, Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers; LABA-LAMA, Long acting beta-agonist-long acting; ICS, Inhaled corticosteroid; BMI, Body mass index; CKD, Chronic kidney disease; CHF, Congestive heart failure; MI, Myocardial infarction; HIV, Human immunodeficiency virus; AECOPD, Acute exacerbation of COPD.

mortality (68.4 deaths per 1000 person-years [95% CI, 62.4–74.8]) than the non-benzodiazepine benzodiazepine receptor agonist group (56.8 deaths per 1000 person-years [95% CI, 44.3–72.8)], the difference was not statistically significant (p=0.17). Second, we analyzed the difference in incidence of mortality rates between the two hypnotic groups and the nonuser group of COPD patients with insomnia. The incidence rates of all-cause mortality were 52.2 (95% CI, 48.7–56.1), 52.9 (95% CI, 45.8–58.9), and 66.8 (95% CI, 61.4–72.7) deaths per 1000 person-years for hypnotic nonusers, non-BZRAs, and BZRAs hypnotic users, respectively. The BZRA group experienced a significantly higher incidence rate of all-cause

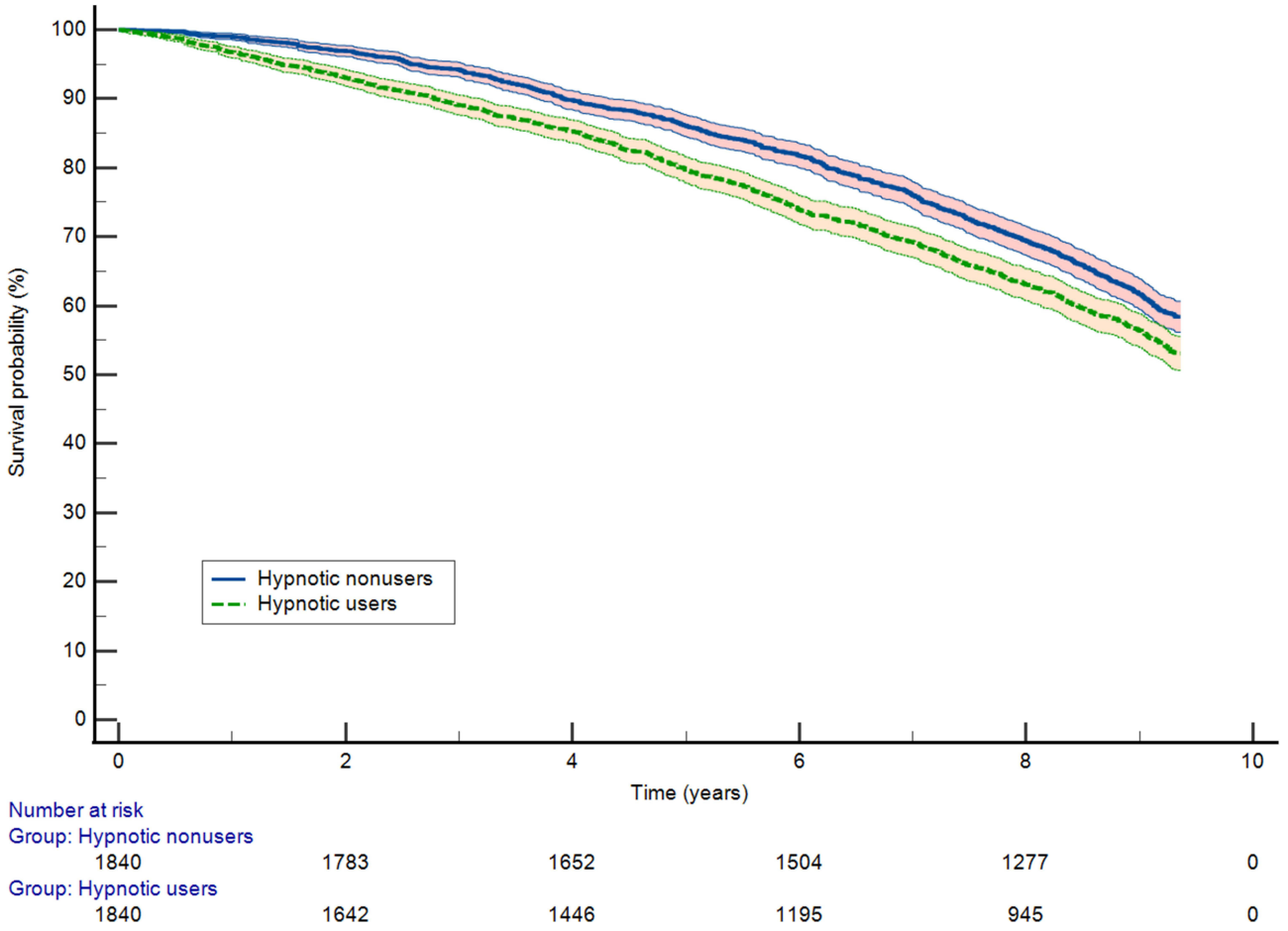

Figure 2 Kaplan–Meier curves for the association between hypnotic use and all-cause mortality in propensity-matched COPD patients with insomnia.

mortality compared to hypnotic nonusers (Incidence rate ratio [IRR] 1.27; 95% CI, 1.14–1.43) (p<0.001). In contrast, there was no difference in the incidence rate of all-cause mortality between the non-BZRA group and hypnotic nonusers (IRR 1.04; 95% CI, 0.82–1.11) (p=0.56). Figure 3 depicts the Kaplan-Meier curve comparing BZRA and non-BZRA groups with hypnotic nonusers. In the third sensitivity analysis, IRRs calculated at 2-year intervals indicated that the use of BZRA hypnotics was associated with significantly higher mortality rates during the 2, 4, and 6 years of follow-ups compared to nonusers. In contrast, the increased mortality rate with the use of non-BZRA hypnotics was limited to the first 2 years after which the mortality rate became no different from the rate observed in nonusers (Table 2). In the fourth sensitivity analysis, stratified grouping by age showed no increased risk of all-cause mortality associated with hypnotic use among patients <65 years old (HR 1.14; 95% CI, 0.91–1.45) (Table 3). However, older COPD patients with insomnia (age ≥ 65 years) had a statistically significant increase in the risk of all-cause mortality compared with those who were hypnotic nonusers (HR 1.25; 95% CI, 1.11–1.39) (p<0.001).

Discussion

In this cohort of US Veterans with COPD and insomnia, the use of hypnotics was independently associated with all-cause mortality, but this association was more pronounced among older patients and in those who were prescribed BZRA hypnotics. The risk of mortality with non-BZRA hypnotics abated after the first 2 years in comparison to BZRA hypnotics and achieved parity with hypnotic nonusers after 4 years of consumption.

Previous studies investigating the association between hypnotic use and mortality have not been consistent in their findings due to heterogeneity in designs, wide array of prescribed hypnotics, and varying lengths of follow-ups.[27–30] The

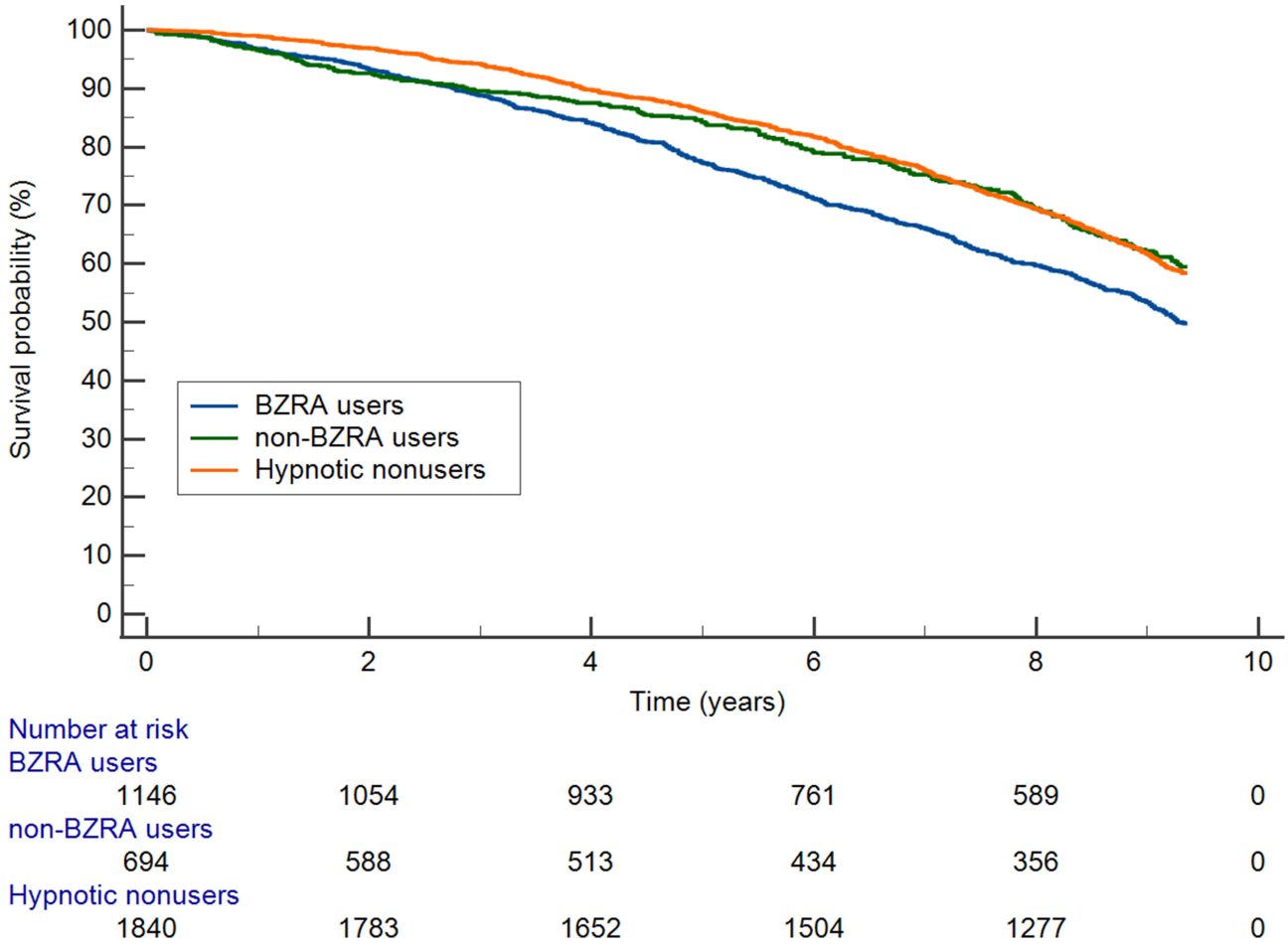

Figure 3 Kaplan–Meier curves for the association between hypnotic categories and all-cause mortality in propensity-matched COPD patients with insomnia.

significance of this association is more abstruse when it comes to a subset of patients with COPD. Based on the results of this study, we have identified a higher risk of mortality with the use of hypnotics in this population. A similar trend was reported from analysis of compiled electronic medical records of a large integrated healthcare system. Kripke and

Table 2 Incidence Rate Ratios of All-Cause Mortality for Propensity-Matched Cohorts with Varying Intervals of Follow-Up

Follow-Up	Person-Years	No of Events	IR (95% CI)*	IRR (95% CI)†	P value
2 years					
Hypnotic nonusers	3635	57	15.7 (12.1–20.3)	-	-
BZRAs	2209	77	34.8 (27.9–43.6)	2.2 (1.5–3.2)	<0.001
Non-BZRAs	1282	49	38.2 (28.9–50.6)	2.4 (1.6–3.6)	<0.001
4 years					
Hypnotic nonusers	3451	131	37.9 (31.9–45.0)	-	-
BZRAs	1990	102	51.2 (42.2–62.2)	1.35 (1.1–1.7)	0.02
Non-BZRAs	1095	31	28.3 (19.9–40.2)	0.7 (0.5–1.1)	0.14
6 years					
Hypnotic nonusers	3165	148	46.7 (39.8–54.9)	-	-
BZRAs	1695	141	83.2 (70.5–98.1)	1.8 (1.4–2.3)	<0.001
Non-BZRAs	952	48	50.4 (38.0–66.9)	1.1 (0.7–1.5)	0.64

Notes: *IR, Incidence rate per 1000 person-years; †IRR, Incidence rate ratio.
Abbreviation: BZRA, Benzodiazepines and non-benzodiazepine benzodiazepine receptor agonists.

Table 3 Stratified Analysis of the Risk of All-Cause Mortality for Propensity-Matched Cohort Associated with Hypnotic Use

Patient Age (Years)	Hypnotic Users			Hypnotic Nonusers			HR (95% CI)†
	Person-Years	No of Events	IR (95% CI) *	Person-Years	No of Events	IR (95% CI) *	
<65	3205	143	44.6 (37.9–52.6)	3499	141	40.3 (34.2–47.5)	1.14 (0.91–1.45)
≥65	9318	617	66.2 (61.2–71.6)	11,145	624	55.9 (51.8–60.6)	1.25 (1.12–1.39)

Notes: *IR, Incidence rate per 1000 person-years; †HR, Hazard ratio.

coworkers[31] found that patients prescribed hypnotics had a significantly increased risk of death compared with those who did not receive hypnotics. A dose-response relationship was ascertained, with calculated hazard ratios ranging between 3.6 (95% CI, 2.9–4.4) for those receiving less than 18 pills/year to 5.3 (95% CI, 4.5–6.3) for those exceeding 132 pills per year. A subsequent retrospective study encompassing 273 primary care practices in the United Kingdom found a two-fold increase in the risk of mortality (HR 2.1, 95% CI, 2.0–2.2) following the prescription of anxiolytic and hypnotic drugs.[32] These estimates are considerably but not surprisingly higher than the hazard ratios observed in our cohort given the more restricted inclusion criteria used to construct our sample. In addition, we would argue that the selection of cases by indication (ie, insomnia) rather than by drug classes would generate more accurate estimates of mortality hazards compared with existing epidemiologic studies.

The pathophysiology by which these drugs may lead to increased mortality has been detailed elsewhere.[33,34] In short, while hypnotic agents produce significant improvements in total sleep time, subjective sleep latency, and frequency of arousals during sleep, they are responsible for myriad of respiratory and non-respiratory side effects, including worsening apneas, severe nocturnal desaturations, frequent exacerbations, respiratory failure, memory impairment, and serious injuries from falls.[33,34] Yet, not all studies involving COPD patients identified detrimental risks and higher mortality rates with hypnotic use.[14,35] The respiratory adverse effects attributed to the use of hypnotics were recently challenged by Lu et al[33] while studying the impact of hypnotics on COPD patients with insomnia. In a meta-analysis of five studies out of 233 published records, benzodiazepines had minimal impact on respiratory parameters apart from maximum transcutaneous carbon dioxide pressure increase during sleep. Notwithstanding, all the enrolled COPD subjects in the selected studies were in stable condition, normocapnic, and without exacerbation for the previous 6 weeks. Moreover, most hypnotics used had short or medium half-life, and were administered for a very short time (one week or less). Interestingly, Donovan and colleagues[14] examined the mortality risks of benzodiazepine exposure among a large group of veterans with COPD and comorbid post-traumatic stress disorder (PTSD) between 2010 and 2012. The study found that short-term users of benzodiazepines (<90 days' supply) had a greater mortality risk relative to nonusers while long-term users (≥90 days) did not. Only the mortality risk from suicide was higher for both short-term and long-term users of benzodiazepines. We have not examined suicide fatalities in our sample because the predominant causes of death among hypnotic users were related to respiratory and heart diseases. We attribute this disparity in causes of mortality to the exclusion of subjects with PTSD from our cohort as well as those prescribed opioids. There is considerable evidence to suggest that concomitant treatment with both opioids and benzodiazepines was associated with greater suicide attempts and intentional self-harm risk relative to either drug alone or neither drug in veterans with PTSD.[36,37]

Our analysis showed that hypnotic use was associated with increased mortality for the first 2 years for all classes of drugs after which the risk of death was concentrated in COPD patients who were prescribed benzodiazepines and non-benzodiazepine benzodiazepine-receptor agonists in comparison to other hypnotics. A similar observation was described in a prospective Swedish National March Cohort, a study comprising 41,695 participants with a mean follow-up of 18.9 years.[38] Within the first 2 years of filling a prescription for hypnotics, all-cause mortality increased by 2.38-fold among hypnotic users with cancer and cardiovascular diseases accounting for 59% of all deaths. An argument can be made that the association between all categories of hypnotics and 2-year mortality is non-causal and is ascribed to confounding by indication. Available evidence suggests that prescriptions for hypnotics are increased in the few months preceding death

for patients possibly manifesting advanced illnesses.[39] While this may be partially true, it is the combination of opioids and benzodiazepines rather than benzodiazepines alone that is more effective in relieving dyspnea in end-stage COPD.[40] By restricting patients with opiate prescriptions from being included into the database, we managed to minimize the bias of confounding by indication.[41] Additionally, we have leveled out the distribution of propensity scores across the two study groups-hypnotic users and nonusers-to compensate for the lack of randomization. Nevertheless, we cannot exclude the possibility that hypnotics have been prescribed for amnesic and anxiolytic effects in COPD patients inflicted with debilitating diseases shortly before death. More relevant to this discussion are the harmful effects of long-term use of BZRA hypnotics compared to non-BZRA hypnotics. Risks from respiratory depression, cognitive impairment, and complex nocturnal behaviors associated with BZRAs do not lessen with time.[31,32] Unfortunately, there are no randomized clinical trials of head-to-head comparison between BZRAs and non-BZRAs hypnotics in COPD patients large enough or long enough to assess mortality risk between these two categories of hypnotics. Until such data is available, the use of trazodone, orexin receptor antagonists, doxepin, or melatonin-based medications may represent a more desirable approach for the treatment of insomnia in COPD patients should the response to behavioral therapy be incomplete or ineffective.

Strengths and Limitations

This study has several strengths, including a large data set encompassing more than 1298 healthcare facilities with both electronic health records and claims data to capture episodes of care, and the use of robust statistical tools to reduce the risk of confounding by indication including propensity score matching. Our study also includes some limitations. First, although we used rigorous approaches to control confounding variables, certain relevant variables might not have been accounted for because it was not directly recorded in our constructed database, thus leading to residual confounding. In this study, we have adjusted for age, gender, smoking, body mass index, ethnicity, depression, and cardiovascular medications. However, residual confounding cannot be ruled out. One potential residual confounder that was not directly measured in our study is socioeconomic status, which is positively associated with hypnotic usage.[42] Second, incomplete coding and coding errors are inherent features of medical claims. It is unlikely that these errors would have significantly altered the results of the study given that that these errors would have occurred at a similar rate in both study groups. Third, there were proportionally fewer women and Hispanics in our study cohort compared to the general population. Veterans comprise a disproportionately larger representation of white males and hence these results may not generalize to other healthcare settings. Fourth, we were not able to have access to the pulmonary function indices, however, we relied on a surrogate measure "acute exacerbation" as a proxy measure of disease severity.[43] Fifth, the utilization of hypnotics is presumed from prescription order entries and hence may not reflect adherence which may overestimate the effect of hypnotics on death rates.

Conclusion

In summary, the findings of this study suggest that there is a significant association between the use of hypnotics for insomnia and an increased risk of all-cause mortality in patients with COPD. The risk of death diverges with prolonged use depending on the hypnotic mechanism of action. Although further research is necessary to establish a causal relationship, these results raise important concerns regarding the safety and long-term effects of hypnotic medications.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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