Benzodiazepines are Prescribed More Frequently to Patients Already at Risk for Benzodiazepine-Related Adverse Events in Primary Care

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BACKGROUND: Benzodiazepine use is associated with adverse drug events and higher mortality. Known risk factors for benzodiazepine-related adverse events include lung disease, substance use, and vulnerability to fracture.
OBJECTIVE: To determine whether benzodiazepine prescribing is associated with risk factors for adverse outcomes.
DESIGN: Longitudinal cohort study between July 1, 2011, and June 30, 2012.
PARTICIPANTS: Patients who visited hospital- and community-based practices in a primary care practice-based research network.
MAIN MEASURES: Odds ratio of having a target medical diagnosis for patients who received standard and high-dose benzodiazepine prescriptions; rates per 100 patients for outpatient and emergency department visits and hospitalizations.
KEY RESULTS: Among 65,912 patients, clinicians prescribed at least one benzodiazepine to 15 % (9821). Of benzodiazepine recipients, 5 % received high doses. Compared to non-recipients, benzodiazepine recipients were more likely to have diagnoses of depression (OR, 2.7; 95 % CI, 2.6–2.9), substance abuse (OR, 2.2; 95 % CI, 1.9–2.5), tobacco use (OR, 1.7; 95 % CI, 1.5–1.8), osteoporosis (OR, 1.6; 95 % CI, 1.5–1.7), chronic obstructive pulmonary disease (OR, 1.6; 95 % CI, 1.5–1.7), alcohol abuse (OR, 1.5; 95 % CI, 1.3–1.7), sleep apnea (OR, 1.5; 95 % CI, 1.3–1.6), and asthma (OR, 1.5; 95 % CI, 1.4–1.5). Compared to low-dose benzodiazepine recipients, high-dose benzodiazepine recipients were even more likely to have certain medical diagnoses: substance abuse (OR, 7.5; 95 % CI, 5.5–10.1), alcohol abuse (OR, 3.2; 95 % CI, 2.2–4.5), tobacco use (OR, 2.7; 95 % CI, 2.1–3.5), and chronic obstructive pulmonary disease (OR, 1.5; 95 % CI, 1.2–1.9). Benzodiazepine recipients had more primary care visits per 100 patients (408 vs. 323), specialist outpatient visits (815 vs. 578), emergency department visits (47 vs. 29), and hospitalizations (26 vs. 15; $p < .001$ for all comparisons).
CONCLUSIONS: Clinicians prescribed benzodiazepines and high-dose benzodiazepines more frequently to patients at higher risk for benzodiazepine-related adverse events. Benzodiazepine prescribing was associated with increased healthcare utilization.

KEY WORDS: psychopharmacology; benzodiazepines; anxiety; sleep disorders.
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INTRODUCTION

Benzodiazepines are commonly used to treat anxiety and sleep disorders, as well as a number of primary medical conditions. However, they are often prescribed to patients who either do not have a clear indication[1] or have poor indications such as depression.[2]

The use of benzodiazepines is associated with higher mortality.[3,4] National registries in Europe and the United States have linked benzodiazepines use to elevated rates of respiratory suppression in patients with chronic obstructive pulmonary disease (COPD)[5] and with overdose death in substance use disorders.[6,7] Benzodiazepines may also be linked to cancer risk and to exacerbation of obstructive sleep apnea (OSA) severity.[8,9] In the elderly, benzodiazepines are associated with delirium in the hospital[10,11] and with hip fractures,[12] disability,[13] and dementia[14,15] in the community.

Although benzodiazepines are frequently prescribed by primary care physicians (PCPs),[16] few studies have described in detail which primary care patients receive benzodiazepine prescriptions. Most studies that have explored this question were performed outside of North America.[17–26] These works identified some demographic predictors of benzodiazepine prescription (e.g., increased age and female gender) and an association with higher medical comorbidity in general, but did not focus on specific medical diagnoses. While benzodiazepines have known risks of adverse events in the elderly, including fractures, and in patients with lung disease and

substance use disorders, no prior studies have examined benzodiazepine prescriptions within the distribution of conditions that increase the risk of benzodiazepine-related adverse events in primary care in North America.

We hypothesized that clinicians prescribe benzodiazepines disproportionately to primary care patients with factors or diagnoses that increase the risk of benzodiazepine-related adverse events, and that patients who receive benzodiazepines have higher healthcare utilization rates. If confirmed, such risk factors and utilization rates could explain some of the association between benzodiazepine use and higher mortality. We performed a longitudinal cohort study to identify associations between benzodiazepine prescribing, risk factors for benzodiazepine-related adverse events, and healthcare utilization.

METHODS

Setting

The Brigham and Women's Primary Care Practice-Based Research Network (BWPC PBRN) includes 16 hospital- and community-based practices and community health centers in eastern Massachusetts. The BWPC PBRN practices used a fully functional, Certification Commission for Healthcare Information Technology (CCHIT)-certified electronic health record (EHR), which included problem lists, medication lists, and prescriptions. By policy, all medicines were prescribed through the EHR. Medications not prescribed by affiliated clinicians were listed in the EHR without dosing information.

Sociodemographic information was collected during registration and was updated periodically. Billing codes were recorded in a separate, dedicated billing system. Partners HealthCare—an integrated health delivery system in eastern Massachusetts, of which Brigham and Women's Hospital is a part—had an information system that captured outpatient visits, emergency room visits, and hospitalizations for all Partners HealthCare facilities.

Approval for the conduct of this study was obtained from the Partners HealthCare Institutional Review Board.

Data Extraction

We used the Partners HealthCare Research Patient Data Repository, which aggregates data from throughout Partners HealthCare facilities, to identify all patients who made at least one visit to any of the ten BWPC PBRN practices that were participating in an unrelated clinical trial between July 1, 2011, and June 30, 2012.[27–29] We extracted and combined sociodemographic and clinical information from the EHR with billing codes.

We included all coded benzodiazepine prescriptions and listings. From the EHR we extracted prescription details that included the name of the medication, dose, frequency, total number of units prescribed, number of refills, and prescribing clinician. Our data source included prescriptions; we could not measure prescription fills or actual benzodiazepine use by patients.

We extracted medical diagnoses from the EHR problem list and ICD-9 billing codes associated with individual encounters (*see* online appendix). We extracted medical diagnoses defined by the Healthcare Effectiveness Data and Information Set (HEDIS; asthma, COPD, cardiovascular disease, depression, diabetes, hypertension, obesity, osteoporosis, and tobacco use),[30] psychiatric diagnoses for which benzodiazepines are commonly prescribed (anxiety and insomnia), and diagnoses for which benzodiazepines are contraindicated or controversial (alcohol abuse, sleep apnea, and substance abuse).[6,7,9,31]

We also extracted data about antidepressant medication prescribing from the EHR, because these are commonly considered first-line agents for depression and anxiety. We included the antidepressants fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine, mirtazapine, bupropion, venlafaxine, desvenlafaxine, duloxetine, nefazodone, amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine, phenelzine, tranylcypromine, isocarboxazid, trazodone, and vilazodone.

We extracted medical encounters from encounter-level billing data, including primary care visits (both any visit to the primary care clinic and any visit with the PCP of record), specialist outpatient visits, emergency department (ED) visits, and hospitalizations, and length of stay for patients with one or more hospitalizations. We defined a patient's PCP as the PCP of record from the EHR. Listed PCPs are nearly always primary care clinicians.

Data Analysis

We calculated benzodiazepine dosing and days prescribed based on a combination of pill dose/strength, dosing frequency, and number of pills prescribed during the study period. We converted prescriptions of lorazepam, clonazepam, and alprazolam—which, together with diazepam, accounted for 97 % of benzodiazepine prescriptions—to "average daily diazepam-equivalent dosages." Only days for which benzodiazepines were prescribed were included in the calculation of average daily dose.

High-dose benzodiazepine prescribing has been defined in the literature as a daily dose equivalent of ≥30 mg per day of diazepam.[32] Although potency equivalence between benzodiazepine agents is not clearly established, we defined 30 mg diazepam equivalents as 3 mg/d alprazolam, 3 mg/d clonazepam, and 5 mg/d lorazepam.[32,33] For patients with multiple benzodiazepine agents (3 % of patients receiving benzodiazepines) for which diazepam-equivalent dosing could be calculated, we added them together as though they were concurrent or consecutive prescriptions of a single diazepam-equivalent agent. Other benzodiazepine prescriptions and benzodiazepine prescriptions without complete prescribing information were not included in the comparison between high-dose and standard-dose prescriptions.

To determine which patients were most likely to receive benzodiazepine prescriptions, we compared patients who received at least one benzodiazepine prescription with those who did not. We assessed differences in demographic variables, medical diagnoses, and inpatient and outpatient encounters. Among benzodiazepine recipients, we made parallel comparisons between patients who did and did not receive high-dose prescriptions.

Statistical Analysis

We used means, medians, percentages, odds ratios, and rate ratios with 95 % confidence intervals to compare patients who did and did not receive benzodiazepines and those who received high doses versus standard doses. We compared categorical variables using the chi-square test and continuous variables using Student's *t* test. We performed the Mann–Whitney–Wilcoxon test to compare days dosed among categorical variables with two groups and the Kruskal-Wallis test for the same comparison among categorical variables with three or more groups. We calculated odds ratios using logistic regression, and we used Poisson regression to calculate rate ratios. We used SAS software (version 9.3; Cary, NC) for all analyses and considered p values < 0.05 statistically significant.

RESULTS

Cohort Characteristics

Among 65,912 patients who visited one of the ten included primary care practices during the study year, at least one benzodiazepine prescription was issued to 15 % (9821); of these patients, 44 % received at least one benzodiazepine prescription from their PCPs of record as opposed to other providers within or outside their primary care practices. Among the 9821 patients who received a benzodiazepine prescription, the mean age was 55 years, 77 % were white, 7 % were black, and 59 % had private insurance. Patients received a median of 30 (IQR = 10–60) days of benzodiazepines at a mean daily diazepam dose equivalent of 11 mg. There were 9532 (97 %) patients who received only one type of benzodiazepine agent during the study period, 280 (3 %) who received two, eight (<1 %) who received three, and one (<1 %) who received more than three. The most commonly prescribed benzodiazepines were lorazepam ($n = 5057$; 51 %;), clonazepam ($n = 2007$; 20 %), diazepam ($n = 1372$; 14 %), and alprazolam ($n = 1371$; 14 %). The mean daily dose prescribed, by benzodiazepine, was 1.7 mg for lorazepam (10.0 mg diazepam-equivalent), 1.5 mg for clonazepam (14.5 mg diazepam-equivalent), 10.8 mg for diazepam, and 1.0 mg for alprazolam (10.1 mg diazepam-equivalent).

Benzodiazepine Prescribing

Clinicians prescribed benzodiazepines more commonly to patients who were older, were women, had Medicare or Medicaid insurance, and were divorced, widowed, or separated (Table 1). Clinicians prescribed to white patients at a higher rate than to non-white patients. Medical diagnoses associated with a higher likelihood of being prescribed a benzodiazepine included substance abuse, depression, tobacco use, alcohol abuse, osteoporosis, chronic obstructive pulmonary disease (COPD), sleep apnea, and asthma. Clinicians prescribed a higher median days dosed to Medicare recipients and a lower median days dosed to black patients. Only 43 % of patients who were prescribed a benzodiazepine had a diagnosis of anxiety or insomnia noted on a problem list or coded in billing data, and 44 % were concurrently prescribed antidepressants.

Patients to whom benzodiazepines were prescribed were higher users of medical care. On average, they made more primary care, specialist outpatient, and emergency department visits, were hospitalized more frequently, and when hospitalized, had a slightly longer length of stay (Table 2).

High-Dose Benzodiazepine Prescribing

Among patients with benzodiazepine prescriptions, the PCPs of record prescribed high doses to 5 %, including to 3 % of lorazepam recipients, 9 % of clonazepam recipients, 2 % of diazepam recipients, and 6 % of alprazolam recipients. Other clinicians prescribed high doses to 5 % of lorazepam recipients, 10 % of clonazepam recipients, 3 % of diazepam recipients, and 6 % of alprazolam recipients.

Demographic characteristics associated with a higher likelihood of being prescribed a high-dose benzodiazepine included younger age, male gender, Medicaid insurance, non-married status, and lower education level (Table 3). Medical diagnoses associated with a higher likelihood of receiving a high-dose benzodiazepine prescription included alcohol abuse, anxiety, asthma, COPD, depression, diabetes, obesity, substance abuse, and tobacco use. Among patients with high-dose prescriptions, 52 % were concurrently prescribed antidepressants.

On average, patients who received high-dose benzodiazepine prescriptions had a greater number of emergency visits and hospitalizations compared to patients who received standard-dose prescriptions (Table 2).

DISCUSSION

Benzodiazepine prescriptions come from multiple sources within the healthcare system, including PCPs, specialists, and ED and inpatient clinicians. In our sample, close to half of the patients who received benzodiazepine prescriptions received at least one from their PCPs, reflecting the relevance of benzodiazepine prescribing among clinicians who work in primary care. Benzodiazepines have a well-established role in the treatment of several conditions commonly seen in primary care, including anxiety and insomnia, and it is likely that benzodiazepine prescribing is safe for many patients,

Table 1 Patient Characteristics by Benzodiazepine Prescription and Days Dosed

Characteristic	Benzodiazepine prescription ($n=9821$)	No benzodiazepine prescription ($n=56,091$)	Odds ratio (95 % CI)	*P* value	Days dosed	*P* value
	Mean (± SD)					
Patient age, years	55 (15)	52 (17)	1.12 (1.10–1.13)*	<0.001	n/a	
Number of medications	1.83 (1.48)	1.06 (1.33)	1.39 (1.37–1.41)	<0.001	n/a	
	N (column %)				Median (IQR)	
Patient gender				<0.001		<0.001
Men	2699 (27)	20,732 (37)	Referent		30 (14–90)	
Women	7122 (73)	35,359 (63)	1.55 (1.48–1.62)		30 (10–60)	
Patient race/ethnicity				<0.001		<0.001
White†	7607 (77)	36,110 (64)	Referent		30 (12–75)	
Black	687 (7)	7182 (13)	0.45 (0.42–0.49)		20 (7.5–40)	
Hispanic	715 (7)	5588 (10)	0.61 (0.56–0.66)		30 (10–60)	
Asian	122 (1)	2165 (4)	0.27 (0.22–0.32)		30 (15–90)	
Other	71 (1)	583 (1)	0.58 (0.45–0.74)		30 (10–60)	
Unknown	619 (6)	4463 (8)	0.66 (0.60–0.72)		30 (10–60)	
Language				<0.001		0.009
English	9203 (94)	51,093 (91)	Referent		30 (10–60)	
Spanish	153 (2)	2756 (5)	0.76 (0.68–0.84)		30 (15–90)	
Other	375 (4)	1603 (3)	0.53 (0.45–0.63)		30 (15–90)	
Unknown	90 (1)	639 (1)	0.78 (0.63–0.98)		30 (15–60)	
Insurance				<0.001		<0.001
Private	5842 (59)	38,172 (68)	Referent		30 (10–60)	
Medicare	3041 (31)	12,639 (23)	1.57 (1.50–1.65)		45 (20–90)	
Medicaid	816 (8)	4447 (8)	1.20 (1.11–1.30)		30 (10–60)	
None or other	122 (1)	833 (1)	0.96 (0.79–1.16)		20 (10–35)	
Marital status				<0.001		<0.001
Married	5131 (52)	30,533 (54)	Referent		30 (10–65)	
Single	2954 (30)	17,792 (32)	0.99 (0.94–1.04)		30 (10–60)	
Divorced/separated	948 (10)	3752 (7)	1.50 (1.39–1.62)		30 (15–60)	
Widowed	569 (6)	2579 (5)	1.31 (1.19–1.44)		45 (25–90)	
Unknown	219 (2)	1435 (2)	0.91 (0.79–1.05)		30 (15–90)	
Education				<0.001		<0.001
Completed post-secondary	5378 (55)	29,937 (53)	Referent		30 (10–60)	
Some post-secondary	1769 (18)	9256 (17)	1.06 (1.00–1.13)		30 (10–60)	
Completed high school/GED	1681 (17)	9697 (17)	0.97 (0.91–1.02)		30 (15–75)	
Some high school	291 (3)	1559 (3)	1.04 (0.91–1.18)		30 (15–90)	
8th grade or less	216 (2)	1404 (3)	0.86 (0.74–0.99)		30 (15–90)	
Unknown	486 (5)	4238 (8)	0.64 (0.58–0.70)		30 (10–60)	
Diagnoses and other prescriptions‡						
Alcohol abuse	292 (3)	1128 (2)	1.50 (1.31–1.70)	<0.001	30 (15–90)	0.50
Antidepressant	4345 (44)	9795 (17)	3.75 (3.58–3.92)	<0.001	30 (15–90)	<0.001
Anxiety	3803 (39)	5603 (10)	5.69 (5.42–5.98)	<0.001	30 (15–75)	<0.001
Asthma	1788 (18)	7484 (13)	1.45 (1.37–1.53)	<0.001	30 (15–90)	0.004
COPD	1727 (18)	6720 (12)	1.57 (1.48–1.66)	<0.001	30 (15–90)	<0.001
CVD	2130 (22)	9154 (16)	1.42 (1.35–1.50)	<0.001	30 (15–90)	<0.001
Depression	3077 (31)	8043 (14)	2.73 (2.60–2.86)	<0.001	30 (15–90)	<0.001
Diabetes	1250 (13)	7437 (13)	0.95 (0.89–1.02)	0.15	30 (15–90)	<0.001
Hypertension	4133 (42)	21,113 (38)	1.20 (1.15–1.26)	<0.001	30 (15–90)	<0.001
Insomnia	815 (8)	1588 (3)	3.11 (2.84–3.39)	<0.001	30 (20–90)	<0.001
Obesity	1664 (17)	8707 (16)	1.11 (1.05–1.18)	<0.001	30 (10–60)	0.30
Osteoporosis	1119 (11)	4220 (8)	1.58 (1.47–1.69)	<0.001	30 (20–90)	<0.001
Sleep apnea	730 (7)	2922 (5)	1.46 (1.34–1.59)	<0.001	30 (15–90)	0.002
Substance abuse	252 (3)	668 (1)	2.19 (1.89–2.53)	<0.001	30 (14–75)	0.92
Tobacco use	738 (8)	2611 (5)	1.66 (1.53–1.81)	<0.001	30 (15–90)	0.03

COPD chronic obstructive pulmonary disease; CVD cardiovascular disease
**The OR for patient age is per decade*
†*The OR for whites vs. non-whites receiving benzodiazepines was 2.05 (95 % confidence interval, 1.94–2.17)*
‡*The referent for odds ratios for diagnoses and other prescriptions is patients who did not have that diagnosis or prescription*

particularly when treatment is limited in dose and duration.[34] Our finding that clinicians prescribed benzodiazepines disproportionately to patients with at least some known risk factors for benzodiazepine-related adverse events—including increased age, pulmonary diseases, osteoporosis, and substance use disorders—may help to explain the relationship between benzodiazepine use and poor health outcomes.

Benzodiazepines are associated with adverse effects, including higher mortality.[3,4] Although causality has not been definitively determined, strong associations between benzodiazepine prescribing and mortality have been described in certain patient groups. Higher mortality rates have been found in patients with COPD, presumably due to respiratory suppression.[5] Patients with opioid use disorders have a higher risk of overdose death—both suicide and non-suicide—when taking benzodiazepines.[6,7,35] Senior patients are particularly vulnerable, because benzodiazepines are associated with falls,[36–39] hip fractures,[12] delirium,[10,11] disability,[13] dementia,[14,15] and motor vehicle accidents.[40] Osteoporosis has been linked to fractures alongside benzodiazepine prescriptions in

Table 2 Utilization by Benzodiazepine Prescription and Dose

	Benzodiazepine prescription ($n = 9831$)	No benzodiazepine prescription ($n = 56,091$)	Rate ratio (95 % confidence interval)	*P* value	High dose ($n = 481$)	Standard dose ($n = 9340$)	Rate ratio (95 % confidence interval)	*P* value
Primary care visits*								
Primary care physician visit rate (per 100 patients)	299	242	1.23 (1.22–1.25)	<0.001	324	297	1.12 (1.07–1.18)	<0.001
Primary care clinic visit rate (per 100 patients)	408	323	1.26 (1.25–1.28)	<0.001	440	406	1.12 (1.07–1.17)	<0.001
Specialist outpatient visits								
Patients with specialist visits (%)	9062 (92)	49,404 (88)		<0.001	431 (90)	8631 (92)		0.025
Visit rate (per 100 patients)	815	578	1.41 (1.40–1.42)	<0.001	887	810	1.13 (1.09–1.16)	<0.001
Emergency visits								
Patients with emergency visits (%)	2275 (23)	9433 (17)		<0.001	144 (30)	2131 (23)		<0.001
Visit rate (per 100 patients)	47	29	1.62 (1.56–1.67)	<0.001	73	45	1.66 (1.49–1.85)	<0.001
Hospitalizations								
Patients with hospitalizations (%)	1202 (12)	4631 (8)		<0.001	88 (18)	1114 (12)		<0.001
Hospitalization rate (per 100 patients)	26	15	1.74 (1.67–1.82)	<0.001	44	25	1.81 (1.57–2.08)	<0.001
Mean length of stay	3.5	3.4		<0.001	3.1	3.3		0.0052

**All patients included in the analysis made at least one primary care visit*

patients at risk of falls, although no direct relationship between osteoporosis and benzodiazepine prescriptions has been described.[41,42] Prescribing benzodiazepines disproportionately to patients with COPD, substance use disorders, and osteoporosis, and who are older may contribute to their mortality risk through these mechanisms. Associations between benzodiazepines and tobacco use have been cited as a possible explanation for the association between benzodiazepines and cancer risk;[8] our finding of a similar association supports the hypothesis that tobacco use confounds the relationship between benzodiazepines and the risk of cancer, although we did not measure cancer diagnoses directly, and this relationship remains poorly understood.

Our finding that high-dose prescribing was also associated with diagnoses of COPD and substance use disorders raises special concern. The magnitude of the association between benzodiazepines and mortality in general appears to be dose-dependent,[3,4] and dose-dependent relationships between benzodiazepines and mortality have been described independently for COPD[5] and overdose deaths.[43] Therefore, the disproportionate prescribing of high-dose benzodiazepines to patients with COPD and substance use disorders may amplify the effect of prescribing standard-dose benzodiazepines to patients already at risk of adverse outcomes.

The association between higher days dosed and receipt of Medicare may reflect an association between older age and longer benzodiazepine prescriptions, but we did not measure this directly and therefore cannot conclude that this is true. That clinicians prescribed shorter and fewer benzodiazepine prescriptions to black patients is notable, although we do not draw conclusions about medical risks of prescribing from this. We combined very brief prescriptions (e.g., single doses) with longer prescriptions in our analysis because mortality risk is associated with single benzodiazepine doses in a dose–response fashion.[4,8]

The increased frequency of medical diagnoses and higher rates of healthcare utilization associated with benzodiazepine prescriptions indicate that, in general, patients who receive benzodiazepines have higher levels of medical comorbidity. Prior studies in Brazil, the Netherlands, and Australia have linked benzodiazepine prescriptions—without a dose relationship—to patient self-reporting of poorer health status.[21–23] Benzodiazepine prescriptions were similarly linked to higher frequencies of medical diagnoses in two population-based Canadian studies,[40,41] and with a higher score on the Charlson comorbidity index in an Israeli study.[18] Studies linking benzodiazepines to a higher number of medical visits[21] and increased length of hospital stay[26] have been conducted in Israel and Japan, respectively.

The fact that the use of benzodiazepines was associated with higher rates of inpatient and outpatient utilization in our study is consistent with two hypotheses: that patients with higher medical comorbidity are more likely to receive a benzodiazepine prescription, and that benzodiazepines may increase a patient's risk of adverse health outcomes. Both may be correct; our findings suggest a possible mechanism by which benzodiazepine prescriptions are associated with adverse outcomes for at least some patients.

Limitations

Our findings of an association do not necessarily signify causation. Some high-risk medical diagnoses such as respiratory illnesses[44] and substance use disorders[45] are associated

Table 3 Patient Characteristics by Benzodiazepine Dose

Characteristic	High dose* (*n* = 481)	Standard dose (*n* = 9340)	Odds ratio (95 % CI)	*P* value
	Mean (± SD)			
Patient age, years	51 (13)	55 (15)	0.81 (0.77–0.86)†	<0.001
Number of medications	2.04 (1.64)	1.82 (1.47)	1.09 (1.04–1.15)	<0.001
	N (%)			
Patient gender				<0.001
Men	179 (37)	2520 (27)	Referent	
Women	302 (63)	6820 (73)	0.62 (0.52–0.75)	
Patient race/ethnicity‡				0.28
White	367 (76)	7240 (78)	Referent	
Black	29 (6)	658 (7)	0.87 (0.59–1.28)	
Hispanic	45 (9)	670 (7)	1.33 (0.96–1.82)	
Asian	5 (1)	117 (1)	0.84 (0.34–2.08)	
Other	1 (0)	70 (1)	0.28 (0.04–2.04)	
Unknown	34 (7)	585 (6)	1.15 (0.80–1.65)	
Language				0.39
English	452 (94)	8751 (94)	Referent	
Spanish	22 (5)	353 (4)	1.21 (0.78–1.88)	
Other	5 (1)	148 (2)	0.65 (0.27–1.60)	
Unknown	2 (0)	88 (1)	0.44 (0.11–1.79)	
Insurance				<0.001
Private	220 (46)	5622 (30)	Referent	
Medicare	154 (32)	2887 (31)	1.36 (1.10–1.68)	
Medicaid	100 (21)	716 (8)	3.57 (2.78–4.58)	
None/other	7 (1)	115 (1)	1.56 (0.72–3.38)	
Marital Status				<0.001
Married	260 (43)	4925 (53)	Referent	
Single	191 (40)	2763 (30)	1.65 (1.35–2.02)	
Divorced/separated	55 (11)	893 (10)	1.47 (1.08–2.00)	
Widowed	17 (4)	552 (6)	0.74 (0.45–1.22)	
Unknown	12 (2)	207 (2)	1.39 (0.76–2.52)	
Education				<0.001
Completed post-secondary	192 (40)	5186 (56)	Referent	
Some post-secondary	121 (25)	1648 (18)	1.98 (1.57–2.51)	
Completed high school/GED	96 (20)	1585 (17)	1.64 (1.27–2.10)	
Some high school	36 (7)	255 (3)	3.81 (2.61–5.56)	
8th grade or less	7 (1)	209 (2)	0.91 (0.42–1.95)	
Unknown	29 (6)	457 (5)	1.71 (1.15–2.56)	
Diagnoses and other prescriptions§				
Alcohol abuse	39 (8)	253 (3)	3.17 (2.23–4.50)	<0.001
Antidepressant	251 (52)	4094 (44)	1.40 (1.16–1.68)	<0.001
Anxiety	228 (47)	3575 (38)	1.45 (1.21–1.75)	<0.001
Asthma	110 (23)	1678 (18)	1.35 (1.09–1.69)	0.007
COPD	117 (24)	1610 (17)	1.54 (1.24–1.91)	<0.001
CVD	99 (21)	2031 (22)	0.93 (0.74–1.17)	0.55
Depression	201 (42)	2876 (31)	1.61 (1.34–1.94)	<0.001
Diabetes	70 (15)	1180 (13)	1.18 (0.91–1.53)	0.22
Hypertension	201 (42)	3932 (42)	0.99 (0.82–1.19)	0.89
Insomnia	38 (8)	777 (8)	0.95 (0.67–1.33)	0.75
Obesity	110 (23)	1554 (17)	1.49 (1.19–1.85)	<0.001
Osteoporosis	38 (8)	1081 (12)	0.66 (0.47–0.92)	0.013
Sleep apnea	45 (9)	685 (7)	1.30 (0.95–1.79)	0.099
Substance abuse	64 (13)	188 (2)	7.47 (5.53–10.09)	<0.001
Tobacco use	82 (17)	656 (7)	2.72 (2.12–3.50)	<0.001

COPD chronic obstructive pulmonary disease; CVD cardiovascular disease
**We defined high-dose benzodiazepine prescribing as a dose of ≥30 mg per day of diazepam or equivalent*
†The OR for patient age is per decade
‡The OR for whites vs. non-whites receiving a high benzodiazepine dose was 0.96 (95 % CI, 0.75–1.23)
§The referent for odds ratios for diagnoses and other prescriptions is patients who did not have that diagnosis or prescription

with anxiety, which may be appropriate indications for a benzodiazepine prescription. Benzodiazepines may be employed directly to treat breathlessness, particularly as a palliative intervention at the end of life, although the evidence supporting a favorable risk/benefit ratio for this is limited, [46] and we would expect these numbers to be small. Benzodiazepines also have a role in the treatment of alcohol withdrawal, although their use in alcohol disorders or withdrawal is not typically recommended in ambulatory settings.[31] We did not record other medical indications for benzodiazepines such as muscle spasms. Our study relied on electronic documentation of information, which approximates but may not equal actual benzodiazepine use by patients. Our study could underestimate benzodiazepine use if patients receive care outside of our health system. Conversely, it could overestimate benzodiazepine use because we rely on prescribing data rather than filled prescriptions or claims. Because 56 % of prescriptions came from providers outside primary care, and prescriptions from all

providers were grouped together in our data, our findings may not reflect prescribing patterns for PCPs specifically, although we do not believe this detracts from the relevance of our findings. Our definition of high-dose benzodiazepine prescribing might be considered arbitrary, given the absence of clearly established potency comparisons between benzodiazepine agents; however, the cutoffs we used were close to other measurements of the 90th percentile of mean daily doses.[33]

CONCLUSION

We found that clinicians prescribed benzodiazepines more frequently to patients with known risk factors for benzodiazepine-related adverse events. Prescribers should take into account their patients' risk factors for adverse events when considering a benzodiazepine. For patients with COPD, substance use disorders, osteoporosis, and advanced age—those who appear to be the most likely to receive benzodiazepine prescriptions and, for the two former categories, at the highest doses—the choice of prescribing a benzodiazepine should be made with great caution.

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Compliance with Ethical Standards:

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