HHS Public Access

Author manuscript

Am J Manag Care. Author manuscript; available in PMC 2020 August 01.

Published in final edited form as:

Am J Manag Care. ; 25(12): e358–e365.

Benzodiazepine and Unhealthy Alcohol Use Among Adult Outpatients

Matthew E. Hirschtritt, MD, MPH,
Department of Psychiatry and the UCSF Weill Institute for Neurosciences, University of California, San Francisco (MEH), San Francisco, CA;

Vanessa A. Palzes, MPH,
The Permanente Medical Group, Department of Psychiatry (MEH), Oakland, CA;

Andrea H. Kline-Simon, MS,
Division of Research, Kaiser Permanente of Northern California (MEH, VAP, AHK-S, CIC, SAS), Oakland, CA;

Kurt Kroenke, MD,
Indiana University School of Medicine (KK), Indianapolis, IN;

Cynthia I. Campbell, PhD, MPH,
Regenstrief Institute, Inc (KK), Indianapolis, IN;

Stacy A. Sterling, DrPH, MSW
VA Health Services Research and Development, Center for Health Information and Communication (KK), Indianapolis, IN.

Abstract

OBJECTIVES: Concomitant excessive alcohol consumption and benzodiazepine use is associated with adverse health outcomes. We examined associations of unhealthy alcohol use and other patient characteristics with benzodiazepine use.

STUDY DESIGN: A cross-sectional analysis of 2,089,525 Kaiser Permanente of Northern California outpatients screened for unhealthy alcohol use in primary care between November 1, 2014, and December 31, 2016.

METHODS: We fit multivariable generalized linear models to estimate the associations between unhealthy alcohol use and benzodiazepine dispensation and, among patients who were dispensed a benzodiazepine, mean doses (in mean lorazepam-equivalent daily doses [LEDDs]) and

Address Correspondence to: Matthew E. Hirschtritt, MD, MPH, Department of Psychiatry and the UCSF Weill Institute for Neurosciences, University of California, San Francisco, 401 Parnassus Ave, Box 0984, San Francisco, CA 94143., matthew.hirschtritt@ucsf.edu.

Authorship Information:
Concept and design (MEH, VAP, KK, SAS); acquisition of data (VAP); analysis and interpretation of data (MEH, VAP, KK, CIC, AHK-S, SAS); drafting of the manuscript (MEH, VAP, CIC); critical revision of the manuscript for important intellectual content (MEH, VAP, AHK-S, KK, CIC, SAS); statistical analysis (VAP, AHK-S); provision of patients or study materials (SAS); obtaining funding (SAS); administrative, technical, or logistic support (SAS); and supervision (SAS).

Author Disclosures:
The authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

prescription durations. We controlled for patient sex, age, race/ethnicity, estimated household income, Charlson Comorbidity Index (CCI) score, anxiety disorder, alcohol use disorder, insomnia, musculoskeletal pain, and epilepsy.

RESULTS: In the 12 months centered around (6 months before and 6 months after) the first alcohol-screening visit, 7.5% of patients used benzodiazepines. The following characteristics were independently associated with higher rates of benzodiazepine use, higher LEDD, and longer prescription duration: older age, white race/ethnicity, lower estimated household income, higher CCI score, and the presence of an anxiety disorder, insomnia, musculoskeletal pain, or epilepsy. Women and patients with an alcohol use disorder or unhealthy alcohol use, compared with men and patients with low-risk drinking or abstinence, were more likely to use a benzodiazepine; however, their LEDDs were lower and their prescription durations were shorter.

CONCLUSIONS: Benzodiazepine use in primary care was associated with older age, female sex, white race/ethnicity, lower socioeconomic status, and unhealthy alcohol use. These findings may be applied to develop policies and interventions to promote judicious benzodiazepine use.

Benzodiazepines have been increasingly used in the United States, leading to increases in overdose mortality and healthcare utilization due to their potent sedative properties. Between 1996 and 2013, the percentage of US adults who filled a benzodiazepine prescription increased from 4.1% to 5.6%, and overdose mortality involving benzodiazepines increased from 0.58 to 3.07 per 100,000 adults.[1] In a large primary care sample, 15% of patients were prescribed a benzodiazepine, one-third of whom received high-dose benzodiazepines (ie, a daily dose equivalent of ≥30 mg/day of diazepam); high-dose recipients were more likely than low-dose recipients to have multiple medical comorbidities and high healthcare utilization.[2] Furthermore, between 2003 and 2015, the percentage of outpatient medical visits including a benzodiazepine prescription doubled, and more than half of these visits were to primary care physicians.[3]

Between 7.5% and 20% of primary care patients acknowledge unhealthy alcohol use,[4,5] defined as use exceeding recommended weekly or daily limits.[6] Excessive alcohol use is associated with numerous individual and societal consequences, such as development or exacerbation of medical and mental health comorbidities, decreased medication adherence, increased HIV risk behaviors, motor vehicle crashes, and interpersonal violence.[7] Unhealthy alcohol use may precede development of an alcohol use disorder[8] and frequently goes undetected in routine clinical care.[9,10] In this context, the US Preventive Services Task Force recommends screening all adult primary care patients for unhealthy alcohol use and offering patients with unhealthy alcohol use brief behavioral counseling.[11]

When benzodiazepines and alcohol are used concurrently, their sedative effects significantly increase the risk of adverse events, including fatal overdose.[12] In 2010, alcohol was involved in 27.2% of benzodiazepine-related visits and 21.4% of benzodiazepine-related deaths in US emergency departments.[13] Long-term consequences of combined benzodiazepine and alcohol use include cardiovascular, gastrointestinal, hepatic, kidney, and neurologic injury and exacerbation of psychiatric conditions.[14,15]

Nationally representative survey data from 2015–2016 suggest that past-year alcohol use or an alcohol use disorder is associated with an increased risk of concurrent benzodiazepine use, misuse, and use disorder.[16,17] Similarly, among Medicare beneficiaries in 2002, presence of drug or alcohol use or dependence was associated with higher odds of benzodiazepine use.[18] However, to our knowledge, no health system, primary care–based studies have examined patient characteristics associated with benzodiazepine dispensation, mean dose, and prescription duration. This information may inform the development of tailored interventions to reduce exposure to benzodiazepines among patients with unhealthy alcohol use.

In this study, we examined the prevalence of benzodiazepine use and its associations with patient demographic and clinical characteristics, including unhealthy alcohol use, among Kaiser Permanente of Northern California (KPNC) adult outpatients who were screened for alcohol use in primary care clinics. We hypothesized that people drinking at unhealthy levels, compared with low-risk drinkers and abstainers, would be less likely to receive benzodiazepines and would receive prescriptions of lower doses and shorter durations. Although this contrasts with previous national trends, we postulated that the combination of recent warnings about rising benzodiazepine use in the United States, concerns about concurrent use with other substances, and a primary care initiative in our healthcare system to detect and reduce unhealthy alcohol use would sensitize clinicians to reconsider benzodiazepine prescribing in this patient subgroup.

METHODS

Design, Setting, and Participants

We conducted a retrospective, cross-sectional study using electronic health record (EHR)–derived data among adult outpatients screened for alcohol use in KPNC primary care clinics. KPNC is an integrated healthcare delivery system with more than 4 million members that covers approximately 30% of the population in the served geographic areas. For these analyses, we identified KPNC members 18 years or older who were screened for unhealthy alcohol use with 1 or more completed alcohol screenings as part of an ongoing primary care–based alcohol screening and brief intervention protocol (Alcohol as a Vital Sign [AVS])[19] between November 1, 2014, and December 31, 2016. We defined the study period as the 12-month period centered around (6 months before and 6 months after) each patient's clinic visit in which the first AVS screening occurred. We excluded patients with noncontinuous KPNC coverage during the study period (eAppendix Methods [eAppendix available at ajmc.com]). Use of these data was approved by the institutional review boards of KPNC and the University of California, San Francisco.

Outcome: Benzodiazepine Use

We included outpatient dispensations for benzodiazepines filled at KPNC pharmacies in the 12 months centered around a patient's first AVS screening visit in a primary care clinic. We extracted data for oral formulations of all benzodiazepine-containing medications (ie, alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, and triazolam) dispensed during

the study period. For each patient, we assessed the following prescription attributes: (1) whether a benzodiazepine had been dispensed; (2) the duration of the benzodiazepine prescriptions (calculated by summing the total number of days supplied in the study period[20]); and (3) the mean daily benzodiazepine dose, expressed in mean lorazepam-equivalent daily dose (LEDD), which is an average over the 12-month study period (eAppendix Methods and eAppendix Table 1).

Covariates

Patient sex, age, and race/ethnicity (Asian, black/African American, Hispanic, white, and other/unknown) were extracted from the EHR at the time of the first AVS screening. We estimated household income from the United States Census 2010 median household income data by geocoding patients' residential addresses to Census blocks.[21,22] Using *International Classification of Diseases, Ninth Edition* and *International Classification of Diseases, Tenth Edition, Clinical Modification* codes, we assessed for the presence of the following encounter-associated codes in the study period: anxiety disorders, insomnia, musculoskeletal pain, alcohol use disorders (including alcohol-related psychoses, dependence, and abuse; excluding conditions in remission), and epilepsy (eAppendix Table 2). In addition, we estimated patients' medical comorbidity burden using the Charlson Comorbidity Index score, which estimates 1-year mortality risk based on a weighted score of 17 conditions.[23–25]

To determine whether a patient engaged in unhealthy alcohol use, we used EHR-documented alcohol screening data collected as part of the AVS protocol during the study period. During the primary care visit "rooming" process, medical assistants asked all patients to estimate within the past 90 days (1) the mean number of days per week they consumed alcohol and (2) how many alcoholic drinks they consumed "on a typical drinking day." Using these variables, the EHR calculates the mean number of alcoholic drinks consumed weekly (ie, mean number of drinking days per week multiplied by the number of drinks consumed on a typical drinking day).[26] Based on guidelines established by the National Institute on Alcohol Abuse and Alcoholism,[6] we defined drinking severity as "low-risk alcohol use" (0–14 drinks per week for men ≤65 years or 0–7 drinks per week for all women and for men >65 years) or "unhealthy alcohol use" (>14 drinks per week for men ≤65 years or >7 drinks per week for all women and for men >65 years).

Analytic Approach

We applied χ^2 and Wilcoxon rank-sum tests to examine differences in categorical and continuous patient demographic and clinical characteristic variables (including presence of unhealthy alcohol use) by whether the patient filled a prescription for a benzodiazepine in the 12 months centered around their first AVS screening visit. We fit multivariable logistic regression models to estimate the adjusted odds ratios (AORs) and corresponding 95% CIs of being dispensed a benzodiazepine by patient characteristics. Among patients who were dispensed a benzodiazepine during the study period, we fit log-linear and negative binomial regression models (accounting for positive skew and overdispersion of the data) to estimate the adjusted rate ratios (ARRs) of mean LEDD and duration of their prescriptions,

respectively, by patient characteristics. All analyses were performed using SAS version 9.4 (SAS Institute Inc; Cary, North Carolina). Significance was assessed at 2-sided $P<.05$.

RESULTS

Cohort Characteristics

Approximately 87% of eligible KPNC members during the defined study period completed 1 or more AVS screenings, and 70% of the benzodiazepine prescriptions were ordered by a primary care provider (ie, internal, family, preventive, or adolescent medicine or pediatrics). Among KPNC members included in these analyses, approximately 97% had a continuous prescription benefit for KPNC pharmacies during the 12-month study period. The analytic cohort consisted of 2,089,525 patients (median [interquartile range] age = 49.0 [29.0] years; 53.7% female; 50.0% white; 4.0% unhealthy alcohol users) after excluding patients without continuous KPNC coverage in the 12 months centered around the first AVS screening (n = 803,991) and patients with missing Census-derived estimated household income data (n = 1390) (Table 1).

Benzodiazepine Use

In the study period, 157,449 patients (7.5% of the study sample) filled a prescription for a benzodiazepine (Table 1). Patients with unhealthy alcohol use had slightly higher odds of using benzodiazepines compared with patients with low-risk alcohol use (AOR, 1.15; 95% CI, 1.12–1.19) (Table 2). From the same multivariable analysis, women had 64% higher odds of using a benzodiazepine compared with men (AOR, 1.64; 95% CI, 1.62–1.66). Conversely, nonwhite patients had significantly lower odds of using benzodiazepines compared with white patients. Among racial/ethnic groups, Asian patients were the least likely to use benzodiazepines, with an AOR of 0.38 (95% CI, 0.37–0.38), representing 62% lower odds of using benzodiazepines compared with white patients. Older patients had significantly higher odds of using benzodiazepines compared with younger patients aged 18 to 39 years, with AORs of 1.82 (95% CI, 1.79–1.84) and 1.77 (95% CI, 1.73–1.80) for patients aged 40 to 65 and older than 65 years, respectively. Anxiety disorders, insomnia, musculoskeletal pain, epilepsy, and alcohol use disorder were all significantly associated with benzodiazepine use.

Mean Daily Dose and Duration of Benzodiazepine Prescriptions

Among patients with benzodiazepine prescriptions during the study period, the mean (SD) LEDD was 0.58 (1.51) mg/day and mean (SD) duration was 87.9 (114.0) days. Patients with unhealthy alcohol use had 40% lower LEDDs (ARR, 0.60; 95% CI, 0.55–0.66) and 18% shorter durations (ARR, 0.82; 95% CI, 0.80–0.84) compared with patients with safe alcohol use (Table 3). Women had ARRs of 0.85 (95% CI, 0.83–0.87) and 0.92 (95% CI, 0.90–0.93), representing a 15% lower LEDD and an 8% shorter duration of benzodiazepine prescriptions, respectively, compared with men. Asian patients had the lowest LEDD and shortest prescription durations of any racial/ethnic group compared with white patients. Whereas LEDD was highest among patients aged 40 to 65 years compared with patients aged 18 to 39 years (ARR, 1.49; 95% CI, 1.43–1.55), prescription durations were the longest among patients 65 years or older compared with patients aged 18 to 39 years (ARR, 2.04;

95% CI, 2.00–2.08). Higher LEDD and longer prescription durations were also significantly associated with low (compared with high) Census-derived estimated household income and the presence of an anxiety disorder, insomnia, musculoskeletal pain, and epilepsy.

DISCUSSION

This study is the first to our knowledge to examine the association of unhealthy alcohol use with benzodiazepine use, dosage, and prescription duration in a large primary care sample. Notably, 7.5% of patients in this cohort were dispensed a benzodiazepine in a 12-month period.[1,27] In addition, women, older adults, and white patients were more likely to use benzodiazepines.

The rate of unhealthy alcohol use of 4.0% in our sample is lower than estimates from other health maintenance organization–based primary care samples (7.5%−20%)[4,5] but is within the range estimated in population-based survey samples (0.3%−20%).[27] This discrepancy may be attributable to different populations, years of data collection, and definitions of unhealthy alcohol use. Similarly, the prevalence of filled benzodiazepine prescriptions in our sample (7.5%) is consistent with a cross-sectional analysis of US retail pharmacies (5.2% of adults filled a prescription for a benzodiazepine in 2008)[28] and with data from the Medical Expenditure Panel Survey (the prevalence of filled benzodiazepine prescriptions between 1996 and 2013 among noninstitutionalized adults increased from 4.1% to 5.6%).[1] However, among adults in a primary care practice–based research network in 2011 and 2012, 15% of patients were prescribed a benzodiazepine.[2] This larger percentage may reflect ordered prescriptions instead of filled prescriptions; the number of ordered prescriptions is likely to be greater than the corresponding number of filled prescriptions.[29]

Comparing our results regarding the concomitant use of benzodiazepines and alcohol with other samples is challenging given the methodologic heterogeneity among previous studies. For instance, among psychiatric outpatients (n = 93), roughly 40% used a benzodiazepine and simultaneously consumed alcohol; furthermore, alcohol use severity was associated with higher odds of benzodiazepine use (OR, 2.4; 95% CI, 1.3–4.2).[30] In a study examining nationally representative survey data from 1999 to 2002, Jalbert and colleagues[31] found that 8% to 10% of adult respondents reported both benzodiazepine and unhealthy alcohol use. Consistent with our findings, Kroll and colleagues[2] examined data from a large primary care sample and found that patients with a diagnosis of alcohol abuse (compared with those without) had higher odds of benzodiazepine use (OR, 1.5; 95% CI, 1.3–1.7). In the emergency department setting, Jones and colleagues[32] found that 27.2% of benzodiazepine-related visits involved alcohol. However, in smaller studies involving older patients[33] and college students,[34] the prevalence of concomitant benzodiazepine and unhealthy alcohol use (approximately 3% in these 2 samples) was significantly lower than what we found in this sample.

Clearly, previous analyses of concomitant alcohol and benzodiazepine use vary widely in their study populations, periods, and definitions of unhealthy alcohol consumption and benzodiazepine use. However, in general, the existing literature supports our conclusion that

unhealthy alcohol use is associated with a greater likelihood of concomitant benzodiazepine use.

Our study adds to the literature by examining not only benzodiazepine use but also mean doses and prescription durations among subpopulations of primary care patients. Interestingly, we found that although patients with unhealthy alcohol consumption were more likely to use benzodiazepines, the benzodiazepines were prescribed to them at lower doses and for shorter durations. This pattern persisted even when accounting for the presence of an alcohol use disorder, for which benzodiazepines may be prescribed to manage alcohol withdrawal. These findings fail to confirm the first part of our hypothesis (ie, patients with unhealthy alcohol use are less likely to use benzodiazepines) but do confirm the second part of our hypothesis (ie, that these patients would use benzodiazepines for shorter periods and at lower doses). One possible explanation for this pattern of findings is that those drinking at unhealthy levels may be more likely to use multiple abusable substances,[34] but that clinicians, aware of the contraindications of concomitant use, limit the dose and duration of benzodiazepines for these patients. It is also possible that patients with unhealthy alcohol use may voluntarily limit their use of benzodiazepines to avoid functional impairment associated with concurrent alcohol and high-dose benzodiazepine consumption.

We also found, similar to results of surveys[3,17] and of studies based on Medicare[18] and commercial insurance claims,[28,35] that women were more likely, and nonwhite patients less likely, to use benzodiazepines. Furthermore, we found that women and nonwhite patients who used benzodiazepines used them at lower doses and for shorter durations compared with men and white patients who used benzodiazepines.[36,37] Women may be more likely to seek treatment for an anxiety disorder.[38] Therefore, women may be more likely than men to report anxiety relief and to require lower doses of benzodiazepines in part because they are simultaneously receiving nonbenzodiazepine treatments (eg, antidepressants, psychotherapy).[39] Simultaneously, women may use benzodiazepines at lower doses and for shorter amounts of time compared with men in part because clinicians may believe sex moderates benzodiazepine metabolism, despite limited evidence to support this contention.[40] Previous research demonstrates that nonwhite patients receive fewer benzodiazepine prescriptions than white patients; however, white patients were more likely to have a benzodiazepine dependence diagnosis.[41,42] Nonwhite patients may be less trusting of the healthcare system, particularly as it relates to seeking help for mental health problems.[43,44] White patients may be more assertive in requesting symptom relief[45] compared with nonwhite patients, who may be less likely to seek medical help for psychiatric symptoms such as anxiety.[46] Furthermore, some Asian patients may be more likely to seek nonallopathic remedies for mental health concerns in primary care.[47] Symptoms of anxiety in nonwhite patients may also be underrecognized or undertreated by clinicians, resulting in fewer benzodiazepine prescriptions for nonwhite patients. These sex- and ethnicity-associated disparities in benzodiazepine prescribing may also be the result of implicit clinician biases.[48]

Limitations

These results should be interpreted in the context of several limitations. As with all observational studies, causality cannot be determined. Pharmacy data reflect dispensations and we are unable to measure patient medication consumption; nonetheless, dispensations are commonly used in pharmacoepidemiologic studies[49,50] and, in the current sample, approximately 84% of prescribed benzodiazepines were filled in KPNC pharmacies. Additionally, our results may not be generalizable to uninsured populations. However, some of our findings are consistent with other, nationally representative samples (eg, lower benzodiazepine use among nonwhite patients[41,42]), suggesting that other findings in our study may also be applicable to the general US primary care adult population.

We are also unable to determine whether benzodiazepine use was inappropriate or unhealthy; subsequent studies may identify potentially inappropriate benzodiazepine use using algorithms, such as those used in geriatric samples.[51] Likewise, by restricting our analyses to benzodiazepine use, we did not examine concurrent opioid use, especially among patients with chronic pain. Compared with patients who only use opioids, patients who use both opioids and benzodiazepines are at higher risk of overdose[52]; therefore, national guidelines recommend against prescribing benzodiazepines with opioids.[53] Future studies may examine the association among benzodiazepine and opioid use with unhealthy alcohol consumption.

We included conditions frequently associated with benzodiazepine prescriptions; however, benzodiazepines may be prescribed for other disorders, such as anxious depression.[54] Finally, statistically significant associations may be a product of the large sample size of our study; therefore, we have focused our conclusions on associations with larger AORs and ARRs, which are most likely to be clinically meaningful and successfully replicated in other primary care samples. If these associations are replicated in subsequent studies, they may be applied to develop and validate clinical decision support systems, such as a quantitative risk-stratification tool to identify patients at high risk of concomitant benzodiazepine and unhealthy alcohol use.

CONCLUSIONS

In this large primary care cohort, unhealthy drinking was associated with higher rates of benzodiazepine use. However, benzodiazepine mean dose was lower and duration of use was shorter among patients with unhealthy drinking. Nonetheless, these results suggest that concomitant benzodiazepine and excessive alcohol use among primary care patients should receive increased vigilance, and health system–wide efforts to reduce this potentially lethal combination should be considered.

Source of Funding:

This research was supported by a grant from the National Institute on Alcohol Abuse and Alcoholism (grant number R01-AA025902-01).

eAppendix

eAppendix Methods

1. Further Description of the Alcohol as a Vital Sign Initiative Workflow

Alcohol as a Vital Sign (AVS) is a primary care clinic-based alcohol screening, brief intervention and referral to treatment initiative begun in June 2013 and used in all adult primary care clinics in Kaiser Permanente Northern California (KPNC).[1] During the pre-visit evaluation, in addition to recording conventional vital signs, medical assistants asked patients structured evidence-based screening questions, embedded in the electronic health record (EHR), based on the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) guide for clinicians "Helping Patients Who Drink Too Much"[2] including: (1) On average, how many days a week do you have an alcoholic drink?, and (2) On a typical drinking day, how many drinks do you have? For patients who asked what constitutes 1 "drink," medical assistants provided the following examples: 12 ounces of beer or a wine cooler, 5 ounces of table wine, 3–4 ounces of fortified wine, 1 "jigger" (1.5 ounces) of brandy, or 1 shot (1.5 ounces) of 80-proof distilled spirits.[2] Medical assistants could enter any whole integer or select "refused to respond" or "not applicable" for either question. The initial AVS medical assistant trainings were conducted in small groups by nurse managers at each Medical Center. Ongoing medical assistant training also occurs at each Medical Center and is delivered by nurse managers. The initial curricula and training materials were standardized across the Northern California region, and there is an online repository that contains training materials and is available to all Kaiser Permanente employees. Thus, training is consistent across all medical assistants, and any possible variations in delivery and recording of the AVS screening questions are likely to be minimal.

Approximately 87% of all adult, primary care patients completed this screening within the current study period. Patients who exceeded NIAAA's weekly limits (>7 for women and men aged >65 years, >14 for men aged ≤65 years)[2] were offered time-limited, office-based counselling by physicians based on motivational interviewing principles,[3] as well as referral to chemical dependency treatment, if needed.

2. Calculation of Mean Lorazepam-Equivalent Daily Dose (LEDD)

We calculated each patient's mean LEDD of benzodiazepines by:

1. converting the strength of individual medications to lorazepam-equivalents in milligrams (see eAppendix Table 1, below), and then
2. calculating the total lorazepam-equivalents milligrams of all benzodiazepines filled within the 12 months around each patient's first AVS screening encounter in the study period, and then dividing the total number of milligrams by 366.[4]

eAppendix References

1. Mertens JR, Chi FW, Weisner CM, et al. Physician versus non-physician delivery of alcohol screening, brief intervention and referral to treatment in adult primary care: the

ADVISe cluster randomized controlled implementation trial. *Addict Sci Clin Pract.* 2015;10:26.

2. National Institute on Alcohol Abuse and Alcoholism. Helping patients who drink too much: a clinician's guide. https://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/guide.pdf. Updated 2016. Accessed January 29, 2018.

3. Miller WR, Rollnick S. *Motivational Interviewing: Helping People Change.* 3rd ed. New York: The Guilford Press; 2012.

4. Kroenke K, Krebs EE, Wu J, et al. Telecare collaborative management of chronic pain in primary care: a randomized clinical trial. *JAMA.* 2014;312:240–8.

eAppendix Table 1.

Conversion of Individual Benzodiazepines to Lorazepam-Equivalents *

Medication	Lorazepam-equivalent dose (mg)
alprazolam	0.5
chlordiazepoxide	10.0
clobazam	10.0
clonazepam	0.25
clorazepate	7.5
diazepam	5.0
estazolam	1.0
flurazepam	30.0
lorazepam	1.0
midazolam	2.0
oxazepam	15.0
temazepam	30.0
triazolam	0.25

* The medications included in this table are limited to the benzodiazepines that were dispensed to patients in the current study cohort.

eAppendix Table 2.

Diagnostic Codes for Medical and Psychiatric Conditions

Condition	ICD-9	ICD-10-CM
Anxiety disorders, including PTSD	300.0 *, 300.2 *, 300.3, 309.21, 309.24, 309.28, 309.81, 313.0	F40.***,F41.***,F42.***, F43.0, F43.1 *, F43.22, F43.23, F43.8, F43.9
Insomnia	307.4 *, 327.00, 327.01, 327.02, 327.09, 780.50, 780.51, 780.52, 780.55, 780.56, 780.59	G47.0 *, G47.2 *, G47.8, G47.9, F51.0 *, F51.8, F51.9, Z72.82 *
Seizure disorder	345.**	G40.***
Musculoskeletal pain	back pain (721.3 * – 721.9 *, 722.2 *, 722.30, 722.70, 722.80, 722.90, 722.32, 722.72, 722.82, 722.33, 722.73, 722.83, 724.**, 737.1 *, 737.3 *, 738.4, 738.5, 739.2, 739.3, 739.4, 756.10, 756.11, 756.12, 756.13, 756.19, 805.4, 805.8, 839.2 *, 839.42, 846, 846.0, 847.1, 847.3, 847.2, 847.9), neck pain (721.0 *, 721.1 *, 722.0 *, 722.31,	Available upon request in spreadsheet format

Condition	ICD-9	ICD-10-CM
	722.71, 722.81, 722.91, 723.**, 839.0*, 839.1*, 847. 0), arthritis/joint pain (>=710 and <720 or >=725 and <740)	
Alcohol use-related diagnoses, excluding remission	291*, 303* (excluding 303.03, 303.93), 305.0* (excluding 305.03)	F10.1*, F10.9*, F10.2* (excluding F10.11, F10.21), F10.9*

Abbreviations: CM, Clinical Modification; ICD, International Statistical Classification of Diseases and Related Health Problems

* Indicates any integer

REFERENCES

1. 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(4):686–688. doi: 10.2105/AJPH.2016.303061. [PubMed: 26890165]
2. 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(9):1027–1034. doi: 10.1007/s11606-016-3740-0. [PubMed: 27177914]
3. Agarwal SD, Landon BE. Patterns in outpatient benzodiazepine prescribing in the United States [erratum in JAMA Netw Open. 2019;2(3):e191203. doi: 10.1001/jamanetworkopen.2019.1203]. JAMA Netw Open. 2019;2(1):e187399. doi: 10.1001/jamanetworkopen.2018.7399. [PubMed: 30681713]
4. Fleming MF, Manwell LB, Barry KL, Johnson K. At-risk drinking in an HMO primary care sample: prevalence and health policy implications. Am J Public Health. 1998;88(1):90–93. doi: 10.2105/ajph.88.1.90. [PubMed: 9584040]
5. Mertens JR, Weisner C, Ray GT, et al. Hazardous drinkers and drug users in HMO primary care: prevalence, medical conditions, and costs. Alcohol Clin Exp Res. 2005;29(6):989–998. doi: 10.1097/01.alc.0000167958.68586.3d. [PubMed: 15976525]
6. Helping patients who drink too much: a clinician's guide. National Institute on Alcohol Abuse and Alcoholism website. pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/guide.pdf. Updated July 2016. Accessed January 29, 2018.
7. Excessive alcohol use. CDC website. cdc.gov/chronicdisease/resources/publications/aag/alcohol.htm. Updated December 31, 2015. Accessed November 28, 2018.
8. Zucker RA. Alcohol use and the alcohol use disorders: a developmental-biopsychosocial systems formulation covering the life course In: Cicchetti D, Cohen DJ, eds. Developmental Psychopathology: Volume Three: Risk, Disorder, and Adaptation. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc; 2006:620–656.
9. Aertgeerts B, Buntinx F, Ansoms S, Fevery J. Screening properties of questionnaires and laboratory tests for the detection of alcohol abuse or dependence in a general practice population. Br J Gen Pract. 2001;51(464):206–217. [PubMed: 11255902]
10. Vinson DC, Turner BJ, Manning BK, Galliher JM. Clinician suspicion of an alcohol problem: an observational study from the AAFP National Research Network. Ann Fam Med. 2013;11(1):53–59. doi: 10.1370/afm.1464. [PubMed: 23319506]
11. Curry SJ, Krist AH, Owens DK, et al.; US Preventive Services Task Force. Screening and behavioral counseling interventions to reduce unhealthy alcohol use in adolescents and adults: US Preventive Services Task Force recommendation statement. JAMA. 2018;320(18):1899–1909. doi: 10.1001/jama.2018.16789. [PubMed: 30422199]
12. Tanaka E Toxicological interactions between alcohol and benzodiazepines. J Toxicol Clin Toxicol. 2002;40(1):69–75. doi: 10.1081/clt-120002887. [PubMed: 11990206]
13. Jones CM, Paulozzi LJ, Mack KA; CDC. Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse–related emergency department visits and drug-related deaths—United States, 2010. MMWR Morb Mortal Wkly Rep. 2014;63(40):881–885. [PubMed: 25299603]

14. Gudin JA, Mogali S, Jones JD, Comer SD. Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. Postgrad Med. 2013;125(4):115–130. doi: 10.3810/pgm.2013.07.2684.
15. Longo LP, Johnson B. Addiction: part I. benzodiazepines—side effects, abuse risk and alternatives. Am Fam Physician. 2000;61(7):2121–2128. [PubMed: 10779253]
16. Blanco C, Han B, Jones CM, Johnson K, Compton WM. Prevalence and correlates of benzodiazepine use, misuse, and use disorders among adults in the United States. J Clin Psychiatry. 2018;79(6):18m12174. doi: 10.4088/JCP.18m12174.
17. Maust DT, Lin LA, Blow FC. Benzodiazepine use and misuse among adults in the United States. Psychiatr Serv. 2018;70(2):97–106. doi: 10.1176/appi.ps.201800321. [PubMed: 30554562]
18. Yang HW, Simoni-Wastila L, Zuckerman IH, Stuart B. Benzodiazepine use and expenditures for Medicare beneficiaries and the implications of Medicare Part D exclusions. Psychiatr Serv. 2008;59(4):384–391. doi: 10.1176/ps.2008.59.4.384. [PubMed: 18378837]
19. Mertens JR, Chi FW, Weisner CM, et al. Physician versus non-physician delivery of alcohol screening, brief intervention and referral to treatment in adult primary care: the ADVISe cluster randomized controlled implementation trial. Addict Sci Clin Pract. 2015;10:26. doi: 10.1186/s13722-015-0047-0. [PubMed: 26585638]
20. Quinn PD, Hur K, Chang Z, et al. Incident and long-term opioid therapy among patients with psychiatric conditions and medications: a national study of commercial health care claims. Pain. 2017;158(1):140–148. doi: 10.1097/j.pain.0000000000000730. [PubMed: 27984526]
21. Young-Wolff KC, Klebaner D, Campbell CI, Weisner C, Satre DD, Adams AS. Association of the Affordable Care Act with smoking and tobacco treatment utilization among adults newly enrolled in health care. Med Care. 2017;55(5):535–541. doi: 10.1097/MLR.0000000000000712. [PubMed: 28288073]
22. American FactFinder. United States Census Bureau website. factfinder.census.gov/faces/nav/jsf/pages/index.xhtml?. Updated 2018. Accessed November 1, 2018.
23. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. J Clin Epidemiol. 2008;61(12):1234–1240. doi: 10.1016/j.jclinepi.2008.01.006. [PubMed: 18619805]
24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–383. doi: 10.1016/0021-9681(87)90171-8. [PubMed: 3558716]
25. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11):1130–1139. doi: 10.1097/01.mlr.0000182534.19832.83. [PubMed: 16224307]
26. Hirschtritt ME, Kline-Simon AH, Kroenke K, Sterling SA. Depression screening rates and symptom severity by alcohol use among primary care adult patients. J Am Board Fam Med. 2018;31(5):724–732. doi: 10.3122/jabfm.2018.05.180092. [PubMed: 30201668]
27. Reid MC, Fiellin DA, O'Connor PG. Hazardous and harmful alcohol consumption in primary care. Arch Intern Med. 1999;159(15):1681–1689. doi: 10.1001/archinte.159.15.1681. [PubMed: 10448769]
28. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiatry. 2015;72(2):136–142. doi: 10.1001/jamapsychiatry.2014.1763. [PubMed: 25517224]
29. Park Y, Yang H, Das AK, Yuen-Reed G. Prescription fill rates for acute and chronic medications in claims-EMR linked data. Medicine (Baltimore). 2018;97(44):e13110. doi: 10.1097/MD.0000000000013110. [PubMed: 30383700]
30. Uchida T, Hirano J, Sakurai H, Suzuki T, Mimura M, Uchida H. Concomitant use of alcohol and benzodiazepine hypnotics in psychiatric outpatients: a cross-sectional survey [published online April 15, 2019]. Int Clin Psychopharmacol. doi: 10.1097/YIC.0000000000000264.
31. Jalbert JJ, Quilliam BJ, Lapane KL. A profile of concurrent alcohol and alcohol-interactive prescription drug use in the US population. J Gen Intern Med. 2008;23(9):1318–1323. doi: 10.1007/s11606-008-0639-4. [PubMed: 18575940]

32. Jones CM, McAninch JK. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. Am J Prev Med. 2015;49(4):493–501. doi: 10.1016/j.amepre.2015.03.040. [PubMed: 26143953]
33. Simon GE, Ludman EJ. Outcome of new benzodiazepine prescriptions to older adults in primary care. Gen Hosp Psychiatry. 2006;28(5):374–378. doi: 10.1016/j.genhosppsych.2006.05.008. [PubMed: 16950371]
34. McCabe SE, Cranford JA, Morales M, Young A. Simultaneous and concurrent polydrug use of alcohol and prescription drugs: prevalence, correlates, and consequences. J Stud Alcohol. 2006;67(4):529–537. doi: 10.15288/jsa.2006.67.529. [PubMed: 16736072]
35. Pereto A Data: seniors prescribed benzodiazepines most often. AthenaHealth website. athenahealth.com/insight/sites/insight/files/8.6%20Data%20Seniors%20prescribed%20benzodiazepines%20most%20often.pdf. Published August 6, 2018. Accessed December 31, 2018.
36. McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. J Psychiatr Res. 2011;45(8):1027–1035. doi: 10.1016/j.jpsychires.2011.03.006. [PubMed: 21439576]
37. McLean CP, Anderson ER. Brave men and timid women? a review of the gender differences in fear and anxiety. Clin Psychol Rev. 2009;29(6):496–505. doi: 10.1016/j.cpr.2009.05.003. [PubMed: 19541399]
38. Vesga-López O, Schneier FR, Wang S, et al. Gender differences in generalized anxiety disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). J Clin Psychiatry. 2008;69(10):1606–1616. [PubMed: 19192444]
39. Pigott TA. Gender differences in the epidemiology and treatment of anxiety disorders. J Clin Psychiatry. 1999;60(suppl 18):4–15.
40. Franconi F, Brunelleschi S, Steardo L, Cuomo V. Gender differences in drug responses. Pharmacol Res. 2007;55(2):81–95. doi: 10.1016/j.phrs.2006.11.001. [PubMed: 17129734]
41. Cook B, Creedon T, Wang Y, et al. Examining racial/ethnic differences in patterns of benzodiazepine prescription and misuse. Drug Alcohol Depend. 2018;187:29–34. doi: 10.1016/j.drugalcdep.2018.02.011. [PubMed: 29626743]
42. Kaufmann CN, Spira AP, Depp CA, Mojtabai R. Long-term use of benzodiazepines and nonbenzodiazepine hypnotics, 1999–2014. Psychiatr Serv. 2018;69(2):235–238. doi: 10.1176/appi.ps.201700095. [PubMed: 29089011]
43. Ault-Brutus AA. Changes in racial-ethnic disparities in use and adequacy of mental health care in the United States, 1990–2003. Psychiatr Serv. 2012;63(6):531–540. doi: 10.1176/appi.ps.201000397. [PubMed: 22422014]
44. Halbert CH, Armstrong K, Gandy OH Jr, Shaker L. Racial differences in trust in health care providers. Arch Intern Med. 2006;166(8):896–901. doi: 10.1001/archinte.166.8.896. [PubMed: 16636216]
45. Street RL Jr, Gordon HS, Ward MM, Krupat E, Kravitz RL. Patient participation in medical consultations: why some patients are more involved than others. Med Care. 2005;43(10):960–969. doi: 10.1097/01.mlr.0000178172.40344.70. [PubMed: 16166865]
46. Snowden LR. Barriers to effective mental health services for African Americans. Ment Health Serv Res. 2001;3(4):181–187. [PubMed: 11859964]
47. Jimenez DE, Bartels SJ, Cardenas V, Dhaliwal SS, Alegría M. Cultural beliefs and mental health treatment preferences of ethnically diverse older adult consumers in primary care. Am J Geriatr Psychiatry. 2012;20(6):533–542. doi: 10.1097/JGP.0b013e318227f876. [PubMed: 21992942]
48. FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. BMC Med Ethics. 2017;18(1):19. doi: 10.1186/s12910-017-0179-8. [PubMed: 28249596]
49. Sodihardjo-Yuen F, van Dijk L, Wensing M, De Smet PA, Teichert M. Use of pharmacy dispensing data to measure adherence and identify nonadherence with oral hypoglycemic agents. Eur J Clin Pharmacol. 2017;73(2):205–213. doi: 10.1007/s00228-016-2149-3. [PubMed: 27796465]
50. Pratt N, Roughead E. Assessment of medication safety using only dispensing data. Curr Epidemiol Rep. 2018;5(4):357–369. doi: 10.1007/s40471-018-0176-6. [PubMed: 30596002]

51. Préville M, Bossé C, Vasiliadis HM, et al. Correlates of potentially inappropriate prescriptions of benzodiazepines among older adults: results from the ESA study. Can J Aging. 2012;31(3):313–322. doi: 10.1017/S0714980812000232. [PubMed: 22800936]

52. 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. doi: 10.1136/bmj.j760. [PubMed: 28292769]

53. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA. 2016;315(15):1624–1645. doi: 10.1001/jama.2016.1464. [PubMed: 26977696]

54. Benasi G, Guidi J, Offidani E, Balon R, Rickels K, Fava GA. Benzodiazepines as a monotherapy in depressive disorders: a systematic review. Psychother Psychosom. 2018;87(2):65–74. doi: 10.1159/000486696. [PubMed: 29466801]

TAKEAWAY POINTS

Among patients in an integrated healthcare delivery system who were screened in primary care for unhealthy alcohol use, we examined cross-sectional benzodiazepine use patterns.

- Unhealthy alcohol users, patients with an alcohol use disorder, and women were more likely to use benzodiazepines, but at lower doses and for shorter durations, compared with low-risk alcohol users and men.
- Patients who were older, white, and of lower socioeconomic status were more likely to use benzodiazepines and had higher doses and prescription durations.
- These findings may inform the development of systemwide interventions to address disproportionate benzodiazepine use among specific patient groups, especially among unhealthy alcohol users.

TABLE 1.

Demographic and Clinical Characteristics of Overall Study Sample and by Dispensation of a Benzodiazepine

Characteristic	Overall (N = 2,089,525)	Dispensed a Benzodiazepine (n = 157,449)	Not Dispensed a Benzodiazepine (n = 1,932,076)	*P*[a]
Sex, n (%)				<.001
Male	967,348 (46.3)	49,997 (31.8)	917,351 (47.5)	
Female	1,122,177 (53.7)	107,452 (68.2)	1,014,725 (52.5)	
Age in years				<.001
18–39, n (%)	694,764 (33.2)	31,699 (20.1)	663,065 (34.3)	
40–65, n (%)	921,929 (44.1)	77,298 (49.1)	844,631 (43.7)	
>65, n (%)	472,832 (22.7)	48,452 (30.8)	424,380 (22.0)	
Median (IQR)	49.0 (29.0)	56.0 (24.0)	49.0 (29.0)	<.001
Race/ethnicity,[b] n (%)				<.001
White	1,044,613 (50.0)	103,941 (66.0)	940,672 (48.7)	
Asian	378,411 (18.1)	1 1,398 (7.2)	367,013 (19.0)	
Black/African American	144,331 (6.9)	9684 (6.2)	134,647 (7.0)	
Hispanic	386,149 (18.5)	22,765 (14.5)	363,384 (18.8)	
Other/unknown	136,021 (6.5)	9661 (6.1)	126,360 (6.5)	
Household income, n (%)				<.001
High	696,680 (33.4)	50,630 (32.1)	646,050 (33.4)	
Middle	696,487 (33.3)	53,017 (33.7)	643,470 (33.3)	
Low	696,358 (33.3)	53,802 (34.2)	642,556 (33.3)	
CCI score, median (IQR)	0 (0)	0 (1.0)	0 (0)	<.001
Anxiety disorder, n (%)				<.001
No	1,913,956 (91.6)	91,205 (57.9)	1,822,751 (94.3)	
Yes	175,569 (8.4)	66,244 (42.1)	109,325 (5.7)	
Insomnia, n (%)				<.001
No	2,017,560 (96.6)	133,051 (84.5)	1,884,509 (97.5)	
Yes	71,965 (3.4)	24,398 (15.5)	47,567 (2.5)	
Musculoskeletal pain, n (%)				<.001
No	1,205,075 (57.7)	58,267 (37.0)	1,146,808 (59.4)	
Yes	884,450 (42.3)	99,182 (63.0)	785,268 (40.6)	
Alcohol-use disorder, n (%)				<.001
No	2,070,71 1 (99.1)	152,583 (96.9)	1,918,128 (99.3)	
Yes	18,814 (0.9)	4866 (3.1)	13,948 (0.7)	
Epilepsy, n (%)				<.001
No	2,075,836 (99.3)	154,850 (98.3)	1,920,986 (99.4)	
Yes	13,689 (0.7)	2599 (1.7)	1 1,090 (0.6)	
Any associated diagnosis,[c] n (%)				<.001
No	1,100,896 (52.7)	30,066 (19.1)	1,070,830 (55.4)	
Yes	988,629 (47.3)	127,383 (80.9)	861,246 (44.6)	

Characteristic	Overall (N = 2,089,525)	Dispensed a Benzodiazepine (n = 157,449)	Not Dispensed a Benzodiazepine (n = 1,932,076)	P[a]
Unhealthy alcohol use,[d] n (%)				<.001
No	2,005,335 (96.0)	149,509 (95.0)	1,855,826 (96.1)	
Yes	84,190 (4.0)	7940 (5.0)	76,250 (3.9)	

CCI indicates Charlson Comorbidity Index; IQR, interquartile range.

[a]Chi-squared tests were used for categorical variables and Wilcoxon rank-sum tests were used for continuous variables.

[b]Race/ethnicity data were self-reported by patients and recoded administratively into predefined categories.

[c]Includes presence of diagnostic codes for an anxiety disorder, insomnia, musculoskeletal pain, or an alcohol-use disorder.

[d]Patients were asked to estimate alcohol use within the past 90 days. Unhealthy alcohol use was defined as more than 7 drinks per week for all women and men older than 65 years or more than 14 drinks per week for men 65 years or younger. See eAppendix Methods for additional information.

TABLE 2.

Associations of Demographic and Clinical Characteristics With Dispensation of a Benzodiazepine

Characteristic	AOR (95% CI)[a]	*P*
Sex		
Male	1	
Female	1.64 (1.62–1.66)	<.001
Age in years		
18–39	1	
40–65	1.82 (1.79–1.84)	<.001
>65	1.77 (1.73–1.80)	<.001
Race/ethnicity[b]		
White	1	
Asian	0.38 (0.37–0.38)	<.001
Black/African American	0.65 (0.63–0.66)	<.001
Hispanic	0.61 (0.60–0.62)	<.001
Other/unknown	0.74 (0.72–0.76)	<.001
Household income		
High	1	
Middle	1.02 (1.01–1.04)	<.001
Low	1.02 (1.00–1.03)	.02
CCI score, mean (SD)[c]	1.12 (1.12–1.12)	<.001
Anxiety disorder		
No	1	
Yes	9.71 (9.59–9.84)	<.001
Insomnia		
No	1	
Yes	3.65 (3.58–3.72)	<.001
Musculoskeletal pain		
No	1	
Yes	1.63 (1.61–1.65)	<.001
Alcohol-use disorder		
No	1	
Yes	2.30 (2.21–2.39)	<.001
Epilepsy		
No	1	
Yes	1.81 (1.72–1.90)	<.001
Any associated diagnosis[d]		
No	N/A	N/A
Yes	N/A	N/A
Unhealthy alcohol use[e]		
No	1	

Characteristic	AOR (95% CI)[a]	P
Yes	1.15 (1.12–1.19)	<.001

AOR indicates adjusted odds ratio; CCI, Charlson Comorbidity Index; N/A, not applicable.

[a]AORs are derived from a model that includes all variables listed in this table.

[b]Race/ethnicity data were self-reported by patients and recoded administratively into predefined categories.

[c]AOR corresponds to a 1-point increment in the CCI score.

[d]Includes presence of diagnostic codes for an anxiety disorder, insomnia, musculoskeletal pain, or an alcohol-use disorder. This summary variable was excluded from multivariate models because of collinearity with individual diagnostic codes.

[e]Patients were asked to estimate alcohol use within the past 90 days. Unhealthy alcohol use was defined as more than 7 drinks per week for all women and men older than 65 years or more than 14 drinks per week for men 65 years or younger. See eAppendix Methods for additional information.

Am J Manag Care. Author manuscript; available in PMC 2020 August 01.

TABLE 3.

Demographic and Clinical Characteristics by Mean Benzodiazepine LEDD and Prescription Duration Among Primary Care Adult Patients Screened for Unhealthy Alcohol Use (n = 157,449)

	LEDD			Duration		
Characteristic	**Mg/Day, Mean (SD)**	**ARR (95% CI)[a]**	***P***	**Days, Mean (SD)**	**ARR (95% CI)[a]**	***P***
Sex						
Male	0.65 (1.69)	1		90.7 (116.4)	1	
Female	0.55 (1.41)	0.85 (0.83–0.87)	<.001	86.6 (112.9)	0.92 (0.90–0.93)	<.001
Age in years						
18–39	0.40 (1.44)	1		51.7 (85.6)	1	
40–65	0.65 (1.66)	1.49 (1.43–1.55)	<.001	88.1 (115.2)	1.67 (1.65–1.70)	<.001
>65	0.59 (1.27)	1.20 (1.15–1.26)	<.001	111.2 (122.0)	2.04 (2.00–2.08)	<.001
Race/ethnicity[b]						
White	0.62 (1.56)	1		95.1 (118.0)	1	
Asian	0.32 (1.02)	0.54 (0.49–0.58)	<.001	60.0 (92.4)	0.65 (0.63–0.66)	<.001
Black/African American	0.49 (1.29)	0.72 (0.68–0.76)	<.001	72.7 (103.2)	0.75 (0.73–0.77)	<.001
Hispanic	0.50 (1.41)	0.76 (0.73–0.79)	<.001	72.4 (102.5)	0.77 (0.76–0.79)	<.001
Other/unknown	0.70 (1.76)	1.05 (1.01–1.10)	.01	94.2 (119.7)	0.99 (0.96–1.02)	.43
Household income						
High	0.51 (1.33)	1		82.0 (110.0)	1	
Middle	0.57 (1.48)	1.14 (1.10–1.18)	<.001	87.5 (113.8)	1.07 (1.05–1.08)	<.001
Low	0.65 (1.67)	1.28 (1.24–1.32)	<.001	93.7 (118.0)	1.14 (1.13–1.16)	<.001
CCI score, Pearson's r[c]	0.05	1.03 (1.03–1.04)	<.001	0.11	1.04 (1.03–1.04)	<.001
Anxiety disorder						
No	0.47 (1.33)	1		79.5 (107.9)	1	
Yes	0.73 (1.71)	1.57 (1.53–1.60)	<.001	99.3 (121.0)	1.35 (1.33–1.36)	<.001
Insomnia						
No	0.56 (1.50)	1		82.1 (109.9)	1	
Yes	0.68 (1.53)	1.10 (1.07–1.13)	<.001	119.4 (130.0)	1.34 (1.32–1.36)	<.001
Musculoskeletal pain						
No	0.46 (1.22)	1		72.6 (99.8)	1	

Characteristic	LEDD			Duration		
	Mg/Day, Mean (SD)	ARR (95% CI)[a]	*P*	Days, Mean (SD)	ARR (95% CI)[a]	*P*
Yes	0.65 (1.64)	1.31 (1.27–1.35)	<.001	96.8 (120.7)	1.14 (1.13–1.16)	<.001
Alcohol-use disorder						
No	0.58 (1.51)	1		88.5 (114.3)	1	
Yes	0.56 (1.49)	0.83 (0.77–0.89)	<.001	66.5 (102.8)	0.73 (0.71–0.76)	<.001
Epilepsy						
No	0.56 (1.45)	1		87.1 (113.2)	1	
Yes	1.51 (3.40)	2.14 (2.05–2.24)	<.001	132.3 (148.7)	1.76 (1.68–1.85)	<.001
Any associated diagnosis[d]						
No	0.40 (1.09)	N/A	N/A	66.8 (94.0)	N/A	N/A
Yes	0.62 (1.58)	N/A	N/A	92.8 (117.7)	N/A	N/A
Unhealthy alcohol use[e]						
No	0.59 (1.53)	1		88.8 (114.9)	1	
Yes	0.36 (0.84)	0.60 (0.55–0.66)	<.001	71.4 (95.6)	0.82 (0.80–0.84)	<.001

ARR indicates adjusted rate ratio; CCI, Charlson Comorbidity Index; LEDD, lorazepam-equivalent daily dose; N/A, not applicable.

[a]ARRs are derived from a model that includes all variables listed in this table (separately for LEDD and duration).

[b]Race/ethnicity data were self-reported by patients and recoded administratively into predefined categories.

[c]ARRs correspond to a 1-point increment in the CCI score.

[d]Includes presence of diagnostic codes for an anxiety disorder, insomnia, musculoskeletal pain, or an alcohol-use disorder. This summary variable was excluded from multivariate models because of collinearity with individual diagnostic codes.

[e]Patients were asked to estimate alcohol use within the past 90 days. Unhealthy alcohol use was defined as more than 7 drinks per week for all women and men older than 65 years or more than 14 drinks per week for men 65 years or younger. See eAppendix Methods for additional information.