Long-Term Benzodiazepine Use and Discontinuation Among Patients in the U.S. Veterans Health Administration

Christine Timko, Ph.D., Katherine J. Hoggatt, Ph.D., Aryan Esmaeili, Ph.D., Eleanor Lewis, Ph.D., Mai Chee Lor, M.P.H., Donovan T. Maust, M.D., Andrea L. Nevedal, Ph.D.

Objective: Although long-term benzodiazepine use is not recommended, patients are often prescribed benzodiazepines for >30 days (long-term use). Data from the Veterans Health Administration (VHA) may inform efforts to discontinue such use. This study sought to describe benzodiazepine use and discontinuation among VHA patients and compared patients who continued and discontinued use.

Methods: The study used nationwide electronic health record data for all VHA-enrolled patients (age ≥18) from fiscal year (FY) 2019 (N=6,032,613). The primary outcome, benzodiazepine discontinuation, was defined as no prescription refill for 120 days.

Results: In FY2019, 3.5% of VHA enrollees were prescribed benzodiazepines for >30 days, which was 72.0% of those prescribed benzodiazepines. One-third of veterans prescribed long-term benzodiazepines discontinued use. Continuation was more likely among patients who were older, not Black, taking benzodiazepines longer, and taking higher doses. When demographic factors were controlled, patients who continued long-term use were more likely to have a diagnosis of anxiety, posttraumatic stress disorder (PTSD), bipolar disorder, or psychosis and less likely to have depression or an alcohol or drug use disorder. Continuation was associated with a lower likelihood of sleep and cardiopulmonary disorders and of dementia.

Conclusions: Higher discontinuation prevalence among patients with substance use disorders, dementia, or cardiopulmonary disorders is encouraging. However, the challenge remains of discontinuing long-term use among patients who are White, older, or diagnosed as having anxiety, PTSD, bipolar disorder, or psychosis. There is a need to identify provider, patient, and contextual factors driving long-term benzodiazepine use in these patient groups to effectively apply evidence-based discontinuation strategies.

Psychiatric Services 2022; 73:1217–1224; doi: 10.1176/appi.ps.202100617

Benzodiazepine use among adults in the United States is common and increasing (1, 2). One in 10 U.S. adults reported past-year use of prescribed benzodiazepines (2). The Veterans Health Administration (VHA) may offer lessons to apply in other health care settings for clinical guideline adherence to benzodiazepine-prescribing practices (3). VHA lowered benzodiazepine prescription rates through its Psychotropic Drug Safety Initiative (PDSI) (4), which focused on patient groups at higher risk of contraindications (older patients and patients with posttraumatic stress disorder [PTSD]). Benzodiazepine prescribing declined markedly among older adults receiving VHA care, in contrast to much smaller declines in Medicare and commercial populations (3). In a medical cannabis program, veterans were less likely than nonveterans to use benzodiazepines (5). Yet in the VHA, knowledge gaps remain regarding the overall prevalence of long-term benzodiazepine use and whether some

HIGHLIGHTS

- Of 6,032,613 veterans enrolled in VHA health care in FY2019, 4.9% were prescribed any kind of benzodiazepine as outpatients, and 3.5% were prescribed long-term benzodiazepines (>30 days) as outpatients, which was 72.0% of all VHA patients prescribed benzodiazepines.
- Compared with patients who continued benzodiazepine use, patients who discontinued were younger and more likely to be Black, had been taking benzodiazepines for a shorter time, and were taking a lower dose.
- When the analysis controlled for patients' demographic characteristics, benzodiazepine discontinuation was more likely among those with diagnoses of depression and substance use disorders but less likely among those with diagnoses of anxiety, PTSD, bipolar disorder, and psychosis.

patient groups may be overlooked for discontinuation of potentially harmful benzodiazepine use.

Benzodiazepines are a class of central nervous system depressants with anxiolytic, hypnotic, muscle relaxant, anticonvulsant, and sedative effects and are approved for treating anxiety, insomnia, seizures, alcohol withdrawal, and other conditions (6). They are relatively safe to use for 2–4 weeks or for acute as-needed use, but side effects (e.g., falls, sedation, and confusion) are amplified among older adults, and prolonged use leads to physiological dependence (6). Although clinical guidelines recommend that longer-term (>30 days) use of benzodiazepines should be avoided (7), a systematic review estimated the prevalence of long-term benzodiazepine use (ranging across studies from 1 month to several years) to be 3% in the general population (7). The mean relative proportion of persons using benzodiazepines long term was 24% (7).

Because of persistent long-term benzodiazepine prescribing despite recommendations that use not exceed 30 days, it is important to determine demographic characteristics as well as benzodiazepine history (duration and dose) and other clinical characteristics that distinguish patients who discontinue use from those who do not. Regarding demographic factors, being male and younger and having fewer educational and socioeconomic resources were associated with discontinuation (8–12). Regarding benzodiazepine history, having a prescribed lower dose and shorter length of use were associated with discontinuation (8, 9, 11, 12). Further, absence of depression symptoms or sleep difficulties, fewer chronic medical or mental health conditions, and less pain, stress, and alcohol or other substance use were associated with discontinuation (10, 12, 13). In contrary findings, more severe depression was associated with benzodiazepine discontinuation among older Canadians (14).

The study reported here used data for fiscal year (FY) 2019 (October 2018 to September 2019) from VHA's Corporate Data Warehouse (CDW), a national-level database housing clinical, administrative, and financial information. One aim was to describe benzodiazepine use of all VHA-enrolled patients, by reporting the percentages of patients who were prescribed benzodiazepines and the percentages who were prescribed benzodiazepines long term (>30 days). Then, among all patients prescribed any benzodiazepines, the aim was to report the dose, the percentage of patients prescribed long-term benzodiazepines, the percentage with a benzodiazepine dose reduction, and the percentage switched to long-acting benzodiazepines. Although patients taking higher dosages of benzodiazepines may tolerate larger reductions better than patients taking lower dosages (15), definitions of high dose range from >10 mg to >50 mg diazepam-equivalent daily dose (EDD) (16–19). Dose reduction and switch to long-acting benzodiazepines are important because clinical guidelines recommend that patients discontinue long-term benzodiazepine use by gradual tapering combined with this switch (20). Guidelines recommend longer tapering in which the benzodiazepine dose is reduced by 10%–25% every 4 weeks.

Given recommendations that patients' long-term benzodiazepine use be discontinued, the second aim was to describe benzodiazepine discontinuation of patients prescribed long-term benzodiazepines in FY2019, report the percentage who discontinued them (i.e., had no benzodiazepine prescription fill for at least 120 days after a previous prescription), and compare discontinuation and continuation groups on demographic characteristics, benzodiazepine history, and health conditions. This approach has not been conducted in the VHA and will help identify patient subpopulations that may be overlooked for tapering, as well as whether more tailored discontinuation strategies are needed for high-risk populations.

Discontinuing benzodiazepines can be distressing for patients (21). Identifying differences between patients who discontinue benzodiazepines and those who do not can inform providers as they make decisions with their patients about sustaining or terminating benzodiazepine use. Providers may focus on patient groups already flagged as high risk (e.g., those with a history of PTSD or a substance use disorder) for benzodiazepine contraindications, and this study aimed to identify other subgroups of patients who may be receiving guideline-discordant care. Findings may also inform providers' clinical judgments when assessing risks and benefits of tapering patients' benzodiazepines to discontinuation.

METHODS

Data Source and Study Cohort

Data from the VHA CDW was used to assess and characterize outpatient benzodiazepine use. VHA-enrolled patients (who may or may not have received VHA care during the study period) included were age 18 or older. The study, which complied with guidelines from the Stanford University Institutional Review Board, utilized CDW outpatient pharmacy files, which included type and quantity of medication prescribed, dose, number of days supplied, and pharmacy release date. It did not consider benzodiazepine incidents (providers' medication mistakes).

Benzodiazepine Prescriptions

Benzodiazepines were alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, oxazepam, prazepam, quazepam, temazepam, and triazolam. Included medications were determined by consulting with two VHA physician leaders who prescribe benzodiazepines.

Long-term benzodiazepine use was defined as >30 days of prescribed benzodiapezines (6) during FY2019 (October 1, 2018–September 30, 2019). The number of days a patient was prescribed benzodiazepines was identified on the basis of pharmacy fills beginning from 3 months pre-FY2019 (July through September 2018) to ensure that the study accounted for benzodiazepine prescriptions dispensed before the FY began (22).

Benzodiazepine history was captured by years of benzodiazepine use: total number of years patients had been prescribed benzodiazepines since they had enrolled in the VHA. Also, benzodiazepine dose for FY2019 was calculated by estimating the diazepam EDD for all benzodiazepines (22). Dose was measured with an "as prescribed" approach, which assumed that patients took their benzodiazepines according to prescribers' instructions (23).

Benzodiazepine dose reduction was defined by creating a categorical variable for an EDD reduction of 10%–25% in benzodiazepine refills during FY2019.

Switch to long-acting benzodiazepines was defined as a patient's benzodiazepine prescription changing in FY2019 to a long-acting benzodiazepine (chlordiazepoxide and diazepam, with elimination half-life of >100 hours [24]).

Discontinuation of benzodiazepines was defined as a patient's not having a benzodiazepine prescription for ≥120 days (4 months) after a prescription ended. To ensure that patients were not misclassified as having discontinued, the no-prescription period was extended for 4 months past FY2019 (October 2019 through January 2020). Studies have used a range of 3–12 months of not having a benzodiazepine prescription for patients to be considered as discontinued (11).

Demographic Characteristics

Patients' demographic characteristics, obtained from the VHA CDW, were gender (male or female), age, race and ethnicity (White, Black, Hispanic or Latino, and other), and marital status (married or unmarried).

Health Conditions

Health conditions were determined by *ICD-10* diagnosis codes. Mental health conditions examined were anxiety, depression, PTSD, bipolar disorder, psychosis, alcohol use disorder, and drug use disorder. Sleep conditions were insomnia and sleep apnea. Medical conditions were in the Elixhauser Comorbidity Index (25). Each comorbidity category in the index is dichotomous (present or not present), and the index counts the number of present conditions.

Analysis Plan

Descriptive statistics were computed for patients' benzodiazepine prescriptions, demographic characteristics, and health conditions. Characteristics of the benzodiazepine discontinuation and continuation groups were compared by using chi-square tests for categorical variables. With the large sample size in this study, very small differences can be statistically significant but not clinically meaningful (26). Therefore, we focused on relative differences of 10% or more as clinically meaningful (27, 28).

We used logistic regression to estimate point and interval estimates of the odds ratio (OR) to summarize associations between health conditions and benzodiazepine discontinuation, while controlling for patient demographic characteristics. Analyses conducted used SAS Enterprise Guide and Stata, release 15.1.

RESULTS

Benzodiazepine Use

In FY2019, of 6,032,613 veterans enrolled in VHA health care, 4.9% (N=294,008) were prescribed any kind of benzodiazepine as outpatients, for any length of time. The most common benzodiazepines prescribed were clonazepam (33.1% [N=97,317] of veterans prescribed any benzodiazepine), lorazepam (22.4%, N=65,858), and alprazolam (20.0%, N=58,801). Also, of all VHA-enrolled patients, 211,714 (3.5%) were prescribed benzodiazepines as outpatients long term, which was 72.0% of all VHA patients prescribed benzodiazepines.

Of all veterans prescribed benzodiazepines in FY2019, most were male and about one-half were over age 65 and married (Table 1). Most had been taking benzodiazepines for at least 3 years, and about one-third were taking a diazepam EDD of 10–20 mg. Over one-half of patients prescribed benzodiazepines had a diagnosis of an anxiety disorder, over one-third had a diagnosis of PTSD, about one-quarter had insomnia, and over one-half had one or two medical conditions.

During FY2019, of the 211,714 VHA patients prescribed long-term benzodiazepines, 18.9% (N=39,915) had a dose reduction of 10%, 10.8% (N=22,943) had a dose reduction of 25%, and 0.5% (N=1,042) switched to long-acting benzodiazepines. Of the 211,714 VHA patients prescribed benzodiazepines long term in FY2019, 69,928 (33.0%) discontinued them.

Comparisons

In terms of clinically meaningful differences, patients who discontinued benzodiazepines were younger than those who continued (more likely to be <45 years) and were more likely to be Black (Table 1). Compared with patients who continued, those who discontinued had been taking benzodiazepines for a shorter duration—that is, they were more likely to have been taking them for ≤2 years—and were less likely to have been taking them for ≥3 years. In addition, patients who discontinued had been taking a lower dose—that is, they were more likely to be taking 1–10 mg—and they were less likely to be taking 20–30 mg or ≥30 mg (measured as diazepam EDD).

Patients who discontinued benzodiazepines were less likely than those who continued benzodiazepines to have a diagnosis of PTSD or psychosis but more likely to have a diagnosis of alcohol or drug use disorder, valvular disease, peripheral vascular disease, dementia, renal failure, liver disease, or congestive heart failure. Patients who discontinued were more likely than those who continued to have multiple medical conditions—that is, they were less likely to have one or two conditions and more likely to have three or more conditions.

When the analysis controlled for patients' demographic characteristics (Table 2), benzodiazepine discontinuation was associated with a lower likelihood of mental disorder

TABLE 1. Characteristics of Veterans Health Administration patients prescribed benzodiazepines for >30 days in fiscal year 2019, by those who continued or discontinued benzodiazepine use

	Continued (N=141,786)		Discontinued (N=69,928)			Total (N=211,714)	
Characteristic	N	%	N	%	p	N	%
Demographic							
Age					<.001		
<45[a]	21,352	15.1	14,378	20.6		35,730	16.9
45–65	49,051	34.6	22,261	31.8		71,722	33.9
>65	71,383	50.4	32,879	47.0		104,262	49.2
Male	122,124	86.1	59,015	84.4	<.001	181,139	85.6
Race and ethnicity					<.001		
White	107,019	75.5	50,833	72.7		157,852	74.6
Black[a]	13,816	9.7	8,265	11.8		22,081	10.4
Hispanic or Latino	10,829	7.6	5,610	8.0		16,439	7.8
Other	10,122	7.1	5,220	7.5		15,342	7.2
Married	77,668	54.8	37,696	53.9	<.001	115,364	54.5
Benzodiazepine history							
Years of use					<.001		
≤2[a]	15,304	10.8	17,015	24.3		32,319	15.3
≥3[a]	126,482	89.2	52,913	75.7		179,395	84.7
Estimated diazepam-equivalent daily dose (mg)					<.001		
0–9.99[a]	32,525	22.9	24,158	34.5		56,673	26.8
10.00–19.99	47,316	33.4	25,135	35.9		72,385	34.2
20.00–29.99[a]	28,857	20.4	11,711	16.8		40,632	19.2
30.00 or more[a]	33,088	23.3	8,924	12.8		42,024	19.8
Mental disorder							
Anxiety	86,269	60.8	39,297	56.2	<.001	125,566	59.3
Depression	39,850	28.2	20,446	29.2	<.001	60,296	28.6
PTSD[a]	54,011	38.2	24,082	34.8	<.001	78,093	36.9
Bipolar disorder	11,110	7.9	4,964	7.2	<.001	16,074	7.6
Psychosis[a]	24,524	17.4	10,642	15.2	<.001	35,166	16.7
Alcohol use disorder[a]	4,018	2.8	3,473	5.0	<.001	7,491	3.6
Drug use disorder[a]	3,712	2.6	2,913	4.2	<.001	6,625	3.2
Sleep disorder							
Insomnia	31,327	22.2	16,673	24.1	<.001	48,000	22.8
Sleep apnea	22,875	16.2	11,580	16.7	.002	34,455	16.4
Cardiopulmonary disease							
Valvular disease[a]	2,057	1.5	1,164	1.7	<.001	3,221	1.5
Pulmonary circulation disease	661	0.5	533	0.8	<.001	1,194	0.6
Peripheral vascular disease[a]	4,950	3.5	2,594	3.8	.004	7,544	3.6
Congestive heart failure[a]	4,650	3.3	3,310	4.8	<.001	7,960	3.8
Chronic pulmonary disease	16,839	11.9	8,752	12.6	<.001	25,591	12.2
Other medical condition							
Dementia[a]	2,774	1.9	2,806	4.0	<.001	5,580	2.7
Renal failure[a]	5,246	3.7	3,184	4.6	<.001	8,430	4.0
Liver disease[a]	4,340	3.1	2,397	3.5	<.001	6,737	3.2
N of conditions, as measured by the Elixhauser Comorbidity Index					<.001		
None	30,284	21.4	16,467	23.6		46,751	22.1
1 or 2[a]	78,832	55.6	35,314	50.5		114,146	53.9
≥3[a]	32,670	23.0	18,147	26.0		50,817	24.0

[a] Characteristic with a clinically meaningful difference between the continued and discontinued groups.

diagnoses of anxiety, PTSD, bipolar disorder, and psychosis and a higher likelihood of depression, alcohol use disorder, and drug use disorder. Discontinuation was associated with the sleep disorders of insomnia and sleep apnea, with dementia, and with each type of cardiopulmonary disorder studied.

Table 3 presents results of a sensitivity analysis in which long-term benzodiazepine use was defined as >120 days (N=147,207). The analysis used logistic regression to estimate point and interval estimates of the adjusted OR to summarize associations between health conditions and benzodiazepine discontinuation (N=24,923, 16.9% of those using benzodiazepines for >120 days), controlling for demographic characteristics. Associations of health conditions with discontinuation varied little by how long-term use was defined.

DISCUSSION

Of veterans enrolled in VHA health care in FY2019, 4.9% were prescribed a benzodiazepine, and 3.5% were prescribed benzodiazepines long term (>30 days). In addition, of all VHA patients prescribed benzodiazepines, 72.0% received long-term prescriptions. Further, of VHA patients who were prescribed benzodiazepines long term in FY2019, one-third discontinued them.

In contrast, prescribed benzodiazepine use is higher (10.4%) among the U.S. civilian and noninstitutionalized population (2). The prevalence of long-term prescribing (or of discontinuation) among patients with any benzodiazepine prescription (or with long-term prescriptions) is difficult to compare across samples, because different definitions of long-term prescribing or discontinuation are utilized. For example,

TABLE 2. Analysis of clinical characteristics as predictors of benzodiazepine discontinuation among patients using benzodiazepines for >30 days (N=211,714), with control for demographic characteristics

	AOR[a]	95% CI	p
Mental disorder (reference: absence of specified disorder)			
Anxiety	.79	.77–.80	<.001
Depression	1.04	1.02–1.06	<.001
PTSD	.81	.80–.83	<.001
Bipolar disorder	.89	.86–.92	<.001
Psychosis	.86	.84–.88	<.001
Alcohol use disorder	1.78	1.70–1.87	<.001
Drug use disorder	1.60	1.52–1.68	<.001
Sleep disorder (reference: absence of specified disorder)			
Insomnia	1.12	1.09–1.14	<.001
Sleep apnea	1.05	1.02–1.08	<.001
Cardiopulmonary disease (reference: absence of specified disease)			
Valvular disease	1.22	1.13–1.31	<.001
Pulmonary circulation disease	1.73	1.54–1.94	<.001
Peripheral vascular disease	1.15	1.10–1.21	<.001
Congestive heart failure	1.58	1.51–1.66	<.001
Chronic pulmonary disease	1.15	1.11–1.18	<.001
Other medical condition (reference: absence of specified condition)			
Dementia	2.24	2.12–2.37	<.001
Renal failure	1.33	1.27–1.39	<.001
Liver disease	1.17	1.11–1.23	<.001
N of conditions, as measured by the Elixhauser Comorbidity Index (reference group: none)			
1 or 2	1.12	1.09–1.15	<.001
≥3	.86	.84–.88	<.001

[a] AOR, adjusted odds ratio.

TABLE 3. Analysis of clinical characteristics as predictors of benzodiazepine discontinuation among patients using benzodiazepines for >120 days (N=147,207), with control for demographic characteristics

	AOR[a]	95% CI	p
Mental disorder (reference: absence of specified disorder)			
Anxiety	.97	.94–1.00	.036
Depression	1.22	1.19–1.26	<.001
PTSD	.94	.92–.97	<.001
Bipolar disorder	1.08	1.03–1.14	.003
Psychosis	1.07	1.03–1.11	.001
Alcohol use disorder	2.09	1.95–2.23	<.001
Drug use disorder	2.1	1.96–2.24	<.001
Sleep disorder (reference: absence of specified disorder)			
Insomnia	1.21	1.17–1.24	<.001
Sleep apnea	1.06	1.02–1.1	.001
Cardiopulmonary disease (reference: absence of specified disease)			
Valvular disease	1.25	1.12–1.38	<.001
Pulmonary circulation disease	1.85	1.58–2.16	<.001
Peripheral vascular disease	1.22	1.14–1.31	<.001
Congestive heart failure	1.66	1.56–1.77	<.001
Chronic pulmonary disease	1.25	1.20–1.30	<.001
Other medical condition (reference: absence of specified condition)			
Dementia	2.40	2.23–2.58	<.001
Renal failure	1.41	1.32–1.5	<.001
Liver disease	1.23	1.14–1.32	<.001
N of conditions, as measured by the Elixhauser Comorbidity Index (reference group: none)			
1 or 2	.98	.95–1.02	.409
≥3	1.38	1.33–1.44	<.001

[a] AOR, adjusted odds ratio.

of older, low-income adults with a benzodiazepine prescription between 2008 and 2016, 26.4% had long-term prescriptions, defined as having a prescription 1 year later (29). The lower prevalence of benzodiazepine prescribing among VHA patients, compared with the general population, could reflect responses to VHA's PDSI (4). PDSI provides performance data on prescribing measures and facilitates clinical review of patients who may benefit from improvement in psychotropic medication regimens.

This study identified characteristics of patients for whom long-term benzodiazepine prescribing was more likely. Compared with patients who discontinued benzodiazepines, patients who continued were older (less likely to be <45 years old), despite known risks of benzodiazepine use among older people (30), and less likely to be Black (were White or Hispanic). In addition, patients who continued had been taking benzodiazepines for a longer duration and at a higher dose. Unknown is whether providers have practice inertia with older adults who have been taking benzodiazepines longer or whether providers perceive more compassionate care as supporting older patients' preferences to continue benzodiazepine use.

Similar to our results, the findings of a study of older patients indicated that White race and larger initial prescription were associated with long-term benzodiazepine use (29), raising concerns that these factors are associated with benzodiazepine prescribing. Non-VHA patients from minority groups received fewer benzodiazepine prescriptions, compared with White patients, suggesting that Black, Hispanic, and Asian patients may be discontinuing benzodiazepines before their clinical need is resolved (31). Similarly, tracking of all patients receiving controlled-substance prescriptions in California over 4 years found that benzodiazepines, stimulants, and opioids were more likely to be prescribed in majority-White areas (32). Among VHA patients reporting chronic pain, Black patients were less likely than White patients to be prescribed opioids (33).

These findings fit with literature that identified provider-level processes contributing to racial health care disparities, including conscious and unconscious biases favoring White over Black patients, poorer communication with Black patients, and less empathy and trust toward Black patients (32, 33). This literature includes a study of opioids among Medicare beneficiaries with disability, in which Black patients received 36% fewer morphine milligram equivalents annually, compared with White patients (34). This result probably reflects both overtreatment of White patients and undertreatment of Black patients with controlled substances, stemming from systemic structural racism and providers' biases (34). Research is needed on provider readiness to offer patients from racial and ethnic minority groups benzodiazepines when indicated, patient preferences for benzodiazepines, and whether lower prescription rates among minority groups offer benefits or harms. It is important to better understand how patients' cultural beliefs and values, providers' inertia regarding previous practices and any biases, and contextual factors explain why White patients are less likely to receive guideline-concordant care, such that they continue to take benzodiazepines long term.

This study identified health characteristics of patients for whom long-term benzodiazepine prescribing was more likely. Diagnoses of alcohol use disorder, drug use disorder, depression, and dementia were associated with a higher likelihood of benzodiazepine discontinuation, whereas anxiety, PTSD, bipolar disorder, and psychosis were associated with a lower likelihood of discontinuation. In regard to alcohol use, a recent study found that primary care patients with unhealthy alcohol use had a higher likelihood of using benzodiazepines, compared with moderate drinkers and nondrinkers (35). However, consistent with our findings, when patients with unhealthy alcohol use were prescribed benzodiazepines, their average benzodiazepine dose was lower and the duration of use was shorter, compared with moderate drinkers and abstainers (35). Although the shorter duration is likely beneficial because benzodiazepine use with heavy alcohol use may increase risks of overdoses, accidents, and worsening psychiatric conditions, it is not known whether the impetus for this regimen came from prescribing physicians or patients. In light of well-established knowledge that benzodiazepine use combined with use of other substances is unsafe (23)—and is unsafe for older persons with dementia because of increased harms from potential side effects (36)—the higher prevalence of discontinuation in the study reported here among patients with drug use disorder or dementia is encouraging.

Evidence regarding benzodiazepine use for depression is more complex. A Cochrane review found that a combination of antidepressants and benzodiazepines was more effective than antidepressants alone in improving depression early, but this effect was not sustained (37). Because of the potential for people to become dependent on benzodiazepines, longer-term studies are needed to examine combined benzodiazepine and antidepressant treatment that involves withdrawing the benzodiazepine after a short period, such as 1 month (37).

Even for the main indications of anxiety, for which we found discontinuation less likely, and of insomnia, for which discontinuation was more likely (in concert with VHA's national dissemination of cognitive-behavioral therapy for insomnia [38, 39]), benzodiazepines showed little advantage over placebos after an initial improvement period during the first few weeks of treatment (40). In addition, benzodiazepines have not been shown to reduce PTSD symptoms, and in light of benzodiazepines' serious adverse effects over time, other PTSD treatment options are recommended, such as trauma-focused psychotherapies and some antidepressant medications (41–43). Similarly, findings support restricted prescription of benzodiazepines for individuals with bipolar disorder, because benzodiazepine use may increase the risk for greater neurocognitive impairment and recurrence of a mood episode (44, 45). Further, a meta-analysis found that among patients experiencing psychosis-induced aggression or agitation, adding a benzodiazepine to other medications did not provide clear benefit and potentially caused adverse effects (46).

In addition to the association between benzodiazepine discontinuation and the sleep disorder of insomnia, this study found that sleep apnea was associated with a higher likelihood of discontinuation. This finding is in keeping with clinical recommendations that benzodiazepines should not be prescribed to patients with sleep apnea, because sleep apnea commonly co-occurs with insomnia, and benzodiazepines may increase the risk of acute respiratory failure among patients with apneas (47). Because benzodiazepines may adversely affect respiration through a variety of mechanisms (48), this study's finding that benzodiazepine discontinuation was more likely among patients diagnosed as having various cardiopulmonary disorders or liver or renal disease is also encouraging. Benzodiazepines carry risk of respiratory depression and increased sedation and cognitive impairment among patients with liver impairments, and patients with renal failure or impairment should have benzodiazepine dosages decreased or discontinued (48).

Limitations of the study include that it did not examine patients' benzodiazepine prescriptions or diagnoses provided by non-VHA sources, such as Medicare. The study did not have data on the appropriateness of benzodiazepines that patients were prescribed or indications for benzodiazepine use. It also lacked data on patient characteristics that may be predictors of benzodiazepine use or discontinuation, such as social determinants of health, which merit future study.

CONCLUSIONS

This study's findings suggest that challenges remain in discontinuing long-term benzodiazepine use among patients who are older than 45 years, White, taking higher doses for longer, and diagnosed as having anxiety, PTSD, bipolar disorder, or psychosis. In addition to gradual benzodiazepine tapering (20), behavioral interventions may facilitate

discontinuation. Indeed, psychological factors may be better predictors than benzodiazepine history of discontinuation success (14). Benzodiazepine history (length of use and dose) was a good predictor of short- but not long-term discontinuation, such that discontinuation programs should focus on patients' social support and self-perceived competence in order to improve program effectiveness (14). Although these two factors are important in programs for illicit drug discontinuation, in prescription drug withdrawal programs they are often not considered (14). Most prescription drug withdrawal programs prioritize psychoeducation, brief interventions, relaxation, and techniques to reduce anxiety and increase quality of sleep (14). Future studies of benzodiazepine discontinuation in the VHA and other health care systems may include behavioral interventions to increase efficacy and effectiveness of discontinuation approaches.

AUTHOR AND ARTICLE INFORMATION

Center for Innovation to Implementation (Timko, Lor, Nevedal) and Program Evaluation and Resource Center (Lewis), Department of Veterans Affairs (VA) Palo Alto Health Care System, Menlo Park, California; Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California (Timko); San Francisco VA Medical Center and Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, San Francisco (Hoggatt); VA Health Economics Resource Center, Menlo Park, California (Esmaeili); Department of Psychiatry, University of Michigan, and Center for Clinical Management Research, VA Ann Arbor Healthcare System, Ann Arbor (Maust). Send correspondence to Dr. Timko (christine.timko@va.gov).

This research was supported by Senior Research Career Development Award RCS 00-001 to Dr. Timko and by the VA Health Services Research and Development Service (Locally Initiated Project 20-AN-1 to Dr. Nevedal and IIR 16-210 to Dr. Maust). The authors thank Ilse Wiechers, M.D., M.H.S., and Jannie Xu for guidance on this study. The views expressed are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

The authors report no financial relationships with commercial interests.

Received October 21, 2021; revisions received February 1 and March 8, 2022; accepted March 10, 2022; published online May 3, 2022.

REFERENCES

1. Agarwal SD, Landon BE: Patterns in outpatient benzodiazepine prescribing in the United States. JAMA Netw Open 2019; 2: e187399
2. Maust DT, Lin LA, Blow FC: Benzodiazepine use and misuse among adults in the United States. Psychiatr Serv 2019; 70:97–106
3. Maust DT, Kim HM, Wiechers IR, et al: Benzodiazepine use among Medicare, commercially insured, and veteran older adults, 2013–2017. J Am Geriatr Soc 2021; 69:98–105
4. Wiechers IR: Improving psychopharmacological care for older veterans: implementation of phase 2 of the Psychotropic Drug Safety Initiative. Am J Geriatr Psychiatry 2016; 24:S155–S156
5. Kang H, Hunniecutt J, Quintero Silva L, et al: Biopsychosocial factors and health outcomes associated with cannabis, opioids and benzodiazepines use among older veterans. Am J Drug Alcohol Abuse 2021; 47:497–507
6. Champion C, Kameg BN: Best practices in benzodiazepine prescribing and management in primary care. Nurse Pract 2021; 46: 30–36
7. Kurko TAT, Saastamoinen LK, Tähkäpää S, et al: Long-term use of benzodiazepines: definitions, prevalence and usage patterns—a systematic review of register-based studies. Eur Psychiatry 2015; 30:1037–1047
8. Gorgels WJMJ, Oude Voshaar RC, Mol AJJ, et al: Discontinuation of long-term benzodiazepine use by sending a letter to users in family practice: a prospective controlled intervention study. Drug Alcohol Depend 2005; 78:49–56
9. Stowell KR, Chang CC, Bilt J, et al: Sustained benzodiazepine use in a community sample of older adults. J Am Geriatr Soc 2008; 56: 2285–2291
10. Taipale H, Särkilä H, Tanskanen A, et al: Incidence of and characteristics associated with long-term benzodiazepine use in Finland. JAMA Netw Open 2020; 3:e2019029
11. Takeshima N, Ogawa Y, Hayasaka Y, et al: Continuation and discontinuation of benzodiazepine prescriptions: a cohort study based on a large claims database in Japan. Psychiatry Res 2016; 237:201–207
12. Voshaar RCO, Gorgels WJ, Mol AJ, et al: Predictors of long-term benzodiazepine abstinence in participants of a randomized controlled benzodiazepine withdrawal program. Can J Psychiatry 2006; 51:445–452
13. Takano A, Ono S, Yamana H, et al: Factors associated with long-term prescription of benzodiazepine: a retrospective cohort study using a health insurance database in Japan. BMJ Open 2019; 9: e029641
14. Allary A, Proulx-Tremblay V, Bélanger C, et al: Psychological predictors of benzodiazepine discontinuation among older adults: results from the PASSE 60+. Addict Behav 2020; 102:106195
15. Ogbonna CI, Lembke A: Tapering patients off of benzodiazepines. Am Fam Physician 2017; 96:606–610
16. Liebrenz M, Schneider M, Buadze A, et al: High-dose benzodiazepine users' perceptions and experiences of anterograde amnesia. J Am Acad Psychiatry Law 2016; 44:328–337
17. Tamburin S, Federico A, Faccini M, et al: Determinants of quality of life in high-dose benzodiazepine misusers. Int J Environ Res Public Health 2017; 14:38–59
18. Lugoboni F, Bertoldi A, Casari R, et al: Adult attention-deficit/hyperactivity disorder and quality of life in high-dose benzodiazepine and related z-drug users. Eur Addict Res 2020; 26: 274–282
19. High Dose and Watchful Dosing of Benzodiazepines: A Review of the Safety and Guidelines. Ottawa, Canadian Agency for Drugs and Technology in Health, 2012
20. Re-Evaluating the Use of Benzodiazepines: A VA Clinician's Guide. Washington, DC, Department of Veterans Affairs, Veterans Administration Pharmacy Benefits Management Academic Detailing Service, 2016
21. Guina J, Merrill B: Benzodiazepines II: waking up on sedatives: providing optimal care when inheriting benzodiazepine prescriptions in transfer patients. J Clin Med 2018; 7:20
22. Gerlach LB, Strominger J, Kim HM, et al: Discontinuation of chronic benzodiazepine use among adults in the United States. J Gen Intern Med 2019; 34:1833–1840
23. Park TW, Saitz R, Ganoczy D, et al: Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ 2015; 350: h2698
24. Effective Treatments for PTSD: Helping Patients Taper From Benzodiazepines. Washington, DC, Department of Veterans Affairs, National Center for PTSD, 2013
25. Elixhauser A, Steiner C, Harris DR, et al: Comorbidity measures for use with administrative data. Med Care 1998; 36:8–27
26. Schultz M, Glickman ME, Eisen SV: Predictors of decline in overall mental health, PTSD and alcohol use in OEF/OIF veterans. Compr Psychiatry 2014; 55:1654–1664

27. Page P: Beyond statistical significance: clinical interpretation of rehabilitation research literature. Int J Sports Phys Ther 2014; 9: 726–736
28. Timko C, Hoggatt KJ, Wu FM, et al: Substance use disorder treatment services for women in the Veterans Health Administration. Womens Health Issues 2017; 27:639–645
29. Gerlach LB, Maust DT, Leong SH, et al: Factors associated with long-term benzodiazepine use among older adults. JAMA Intern Med 2018; 178:1560–1562
30. Olfson M, King M, Schoenbaum M: Benzodiazepine use in the United States. JAMA Psychiatry 2015; 72:136–142
31. 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
32. Friedman J, Kim D, Schneberk T, et al: Assessment of racial/ethnic and income disparities in the prescription of opioids and other controlled medications in California. JAMA Intern Med 2019; 179:469–476
33. Burgess DJ, Nelson DB, Gravely AA, et al: Racial differences in prescription of opioid analgesics for chronic noncancer pain in a national sample of veterans. J Pain 2014; 15:447–455
34. Morden NE, Chyn D, Wood A, et al: Racial inequality in prescription opioid receipt—role of individual health systems. N Engl J Med 2021; 385:342–351
35. Hirschtritt ME, Palzes VA, Kline-Simon AH, et al: Benzodiazepine and unhealthy alcohol use among adult outpatients. Am J Manag Care 2019; 25:e358–e365
36. Rochon PA, Vozoris N, Gill SS: The harms of benzodiazepines for patients with dementia. CMAJ 2017; 189:E517–E518
37. Ogawa Y, Takeshima N, Hayasaka Y, et al: Antidepressants plus benzodiazepines for adults with major depression. Cochrane Database Syst Rev 2019; 6:CD001026
38. Karlin BE, Trockel M, Taylor CB, et al: National dissemination of cognitive behavioral therapy for insomnia in veterans: therapist- and patient-level outcomes. J Consult Clin Psychol 2013; 81:912–917
39. Carlson GC, Kelly MR, Mitchell M, et al: Benefits of cognitive behavioral therapy for insomnia for women veterans with and without probable post-traumatic stress disorder. Womens Health Issues 2022; 32:194–202
40. Moore N, Pariente A, Begaud B: Why are benzodiazepines not yet controlled substances? JAMA Psychiatry 2015; 72:110–111
41. Tannenbaum C, Martin P, Tamblyn R, et al: Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial. JAMA Intern Med 2014; 174:890–898
42. Akiki TJ, Abdallah CG: Are there effective psychopharmacologic treatments for PTSD? J Clin Psychiatry 2019; 80:18ac12473
43. Guina J, Rossetter SR, DeRhodes BJ, et al: Benzodiazepines for PTSD: a systematic review and meta-analysis. J Psychiatr Pract 2015; 21:281–303
44. Cañada Y, Sabater A, Sierra P, et al: The effect of concomitant benzodiazepine use on neurocognition in stable, long-term patients with bipolar disorder. Aust N Z J Psychiatry 2021; 55: 1005–1016
45. Perlis RH, Ostacher MJ, Miklowitz DJ, et al: Clinical features associated with poor pharmacologic adherence in bipolar disorder: results from the STEP-BD study. J Clin Psychiatry 2010; 71:296–303
46. Zaman H, Sampson SJ, Beck AL, et al: Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database Syst Rev 2017; 12:CD003079
47. Matheson E, Hainer BL: Insomnia: pharmacologic therapy. Am Fam Physician 2017; 96:29–35
48. Vozoris NT: Do benzodiazepines contribute to respiratory problems? Expert Rev Respir Med 2014; 8:661–663