Gender Differences in Prescribing of Zolpidem in the Veterans Health Administration

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Zolpidem, a nonbenzodiazepine sedative hypnotic, is extensively prescribed in the United States[1,2] for short-term treatment of insomnia. However, there have been growing concerns associated with its use, including higher risks of falls and fractures,[3,4] motor vehicle collisions,[5] central nervous system–associated adverse drug reactions,[6] dependence,[7] and mortality.[8] In fact, it has been shown that the mortality implications of taking zolpidem are equivalent to those associated with a benzodiazepine.[9] Clinically significant drug interactions of zolpidem with benzodiazepines are associated with increased hospitalizations.[10] To add to the complexity, gender differences have been noted, with women reporting greater sensitivity than men to the sedative effects of zolpidem.[11]

These safety concerns prompted the FDA in 2013 to recommend cutting doses prescribed to women in half, specifically from 10 mg immediate release (IR) daily to a maximum of 5 mg/day and from 12.5 mg controlled release (CR) daily to 6.25 mg/day.[12] Usually prescribed for a 30-day period, the IR formulation dissolves much more rapidly than the CR formulation to cause sedation facilitating the induction of sleep.[13] Although there was also a recommendation to extend this dose reduction to men, the guidelines remained unchanged for men (5 mg or 10 mg IR and 6.25 mg or 12.5 mg CR). This mandate of a gender-specific guideline for zolpidem was due to the fact that women metabolize the same dose of zolpidem more slowly than men, resulting in 50% higher serum levels.[14] Previous studies have found increased compliance among providers, specifically midlevel and physician providers, with reduced-dose zolpidem in women after the FDA-mandated labeling changes.[15,16] Although adherence to guidelines was attributed to change in prescribing habits of the providers, it could not be ascertained whether it was driven by the drug safety communication from the FDA or individual patient factors. However, these studies included relatively small sample sizes; they did not evaluate the proportion of women who were still being prescribed an inappropriate dosage after the FDA guidance, nor did they examine predictors of this inappropriate outcome.

In line with this FDA recommendation, the national Veterans Health Administration (VHA) Pharmacy Benefits Management (PBM)

ABSTRACT

OBJECTIVES: Use of nonbenzodiazepine sedative hypnotics, especially zolpidem, has grown substantially, raising concerns about safety. Here, we evaluated prescribing patterns of zolpidem in the Veterans Health Administration.

STUDY DESIGN: A cross-sectional study of veterans receiving zolpidem in the outpatient setting from October 1, 2011, to September 30, 2016.

METHODS: The study population consisted of 500,332 zolpidem users (58,598 women and 441,734 men) and a random 10% sample (n = 631,449) of nonusers. We examined 2 outcomes related to inappropriate prescribing: high-dose zolpidem prescribing and overlap with benzodiazepines. We generated interrupted time series and logistic regression models to analyze these outcomes in men and women separately.

RESULTS: In 2016, 29.7% of female veterans received an inappropriately high guideline-discordant dosage compared with 0.1% of male veterans (*P* <.001 for all reported comparisons). Furthermore, more women than men had overlapping benzodiazepine and zolpidem prescriptions (18.8% vs 14.3%). In fully adjusted models, inappropriately high doses were more commonly received by younger women (adjusted odds ratios [AORs]: 2.75 for 21-39 years and 2.97 for 40-49 years compared with ≥80 years) and women with substance use disorder (AOR, 1.48). In the second inappropriateness outcome models, women with anxiety (AOR, 2.28) or schizophrenia (AOR, 2.05) and men with cancer (AOR, 1.42), anxiety (AOR, 2.66), or schizophrenia (AOR, 2.46) were more likely to receive an overlapping prescription of zolpidem and benzodiazepines.

CONCLUSIONS: We found evidence of inappropriate zolpidem prescribing among veterans, particularly women. Greater understanding of the drivers of this inappropriate prescribing is necessary to develop interventions to promote safer, more guideline-concordant prescribing.

Am J Manag Care. 2019;25(3):e58-e65

Service issued a similar directive to lower the doses of zolpidem in women in 2013.[17] However, little is known about zolpidem prescribing patterns in the VHA. Therefore, the goal of this study was to examine utilization trends and inappropriate prescribing of zolpidem in accordance with PBM guidelines in male and female veterans in the VHA. We expected significant differences in inappropriate zolpidem prescribing in male and female veterans by age, with women potentially being more likely to receive zolpidem inappropriately.

TAKEAWAY POINTS

Gender-specific guidelines have been recommended for appropriate zolpidem prescribing to address patient safety concerns.

▸ The present study suggests that a higher proportion of female veterans received an inappropriately high zolpidem dosage and had overlapping zolpidem and benzodiazepine prescriptions compared with male veterans.

▸ Findings have implications both for patient safety and promoting guideline-concordant prescribing in female zolpidem users.

▸ Managed care decision makers may wish to query adherence to guidelines and raise awareness to drive practice changes and reduce morbidity and mortality related to preventable adverse events in their systems of care.

METHODS

The study was approved by the Institutional Review Board of the Bedford Veterans Affairs Medical Center. We examined demographic, diagnostic, and prescription data of patients receiving outpatient prescriptions for zolpidem at any VHA site between October 1, 2011, and September 30, 2016.

Study Population

We examined all patients who received zolpidem (n = 500,332; 441,734 men and 58,598 women) between fiscal year (FY) 2012 and FY 2016. We defined a zolpidem user as a patient who received 3 or more days of continuous zolpidem prescription during the study period. Additionally, we examined a random 10% sample of patients who did not receive zolpidem (n = 631,449). We also used the full study population (N = 1,131,781) as a basis for calculating prevalence rates. The index date for zolpidem users was the earliest prescription of zolpidem they received in the entire study period.

Independent Variables

We examined the sociodemographic factors gender, age, race, Hispanic ethnicity, marital status, VHA co-payment for prescription drugs based on VHA eligibility status, FY of zolpidem prescription, US region where the patient received care, and the urban versus rural status of the facility where the index prescription was written. These variables, and in particular gender and age, have been previously linked to healthcare utilization.[18] We also evaluated a number of physical and mental health conditions that have been shown to be associated with zolpidem use.[19-22] The presence of these conditions was determined from inpatient and outpatient diagnoses using *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *Tenth Revision* (*ICD-10*) codes, using a 1-year look-back period prior to the date of the index prescription (**eAppendix** [available at **ajmc.com**]). We considered a condition to be present when there were at least 2 diagnostic codes for the condition separated by 7 or more days.

Outcome Variables

In this study, we evaluated 2 outcomes relating to appropriateness of zolpidem prescribing. The first measure was whether the daily dose prescribed to male and female veterans exceeded the 2013 PBM recommended dosage (men: IR ≤10 mg or CR ≤12.5 mg; women: IR ≤5 mg or CR ≤6.25 mg). In our study, we calculated the daily dose by multiplying the inferred tablets per day (quantity divided by days' supply) by the tablet strength given in the full description of the medication. We also examined a second measure of inappropriate prescribing in both men and women: the overlap in prescribing of zolpidem with the prescribing of a benzodiazepine. We defined overlapping prescribing as a benzodiazepine prescription for more than 3 days written within 30 days before or after the index zolpidem prescription.

Statistical Analysis

As a first step, we generated descriptive characteristics stratified by gender. We used Pearson's χ^2 test to perform statistical comparisons between men and women. We grouped age and race variables into categories to yield a reasonable frequency distribution. Physical and mental health conditions were binary (yes/no) variables. We applied a sampling weight of 10 to the nonzolpidem cases when computing prevalence and initiation. We imputed missing data on all variables except race, marital status, and comorbidities to allow inclusion of all observations in multivariate analyses. Second, we conducted an interrupted time series analysis before and after the 2013 PBM guidelines (which recommended lower zolpidem doses for women) to determine whether these guidelines led to significant improvement in appropriate zolpidem dosing. For this analysis, we excluded 1849 men and 193 women because they had incomplete dose data on the index date of their zolpidem prescription. We calculated the unadjusted proportion of male and female veterans receiving high-dose zolpidem prescriptions from 2011 to 2016. Finally, we generated multivariate logistic regression models to analyze the determinants of the 2 inappropriate prescribing outcomes, specifically dose exceeding guideline recommendations and overlap with benzodiazepines, in separate models for men and women. We used SAS version 9.4 (SAS Institute Inc; Cary, North Carolina) for all analyses. We used *P* <.001 as the threshold for statistical significance for all analyses.

TABLE 1. Characteristics of Zolpidem Users by Gender (n = 500,332)[a]

Characteristic	Men (n = 6,235,349)[b]	Women (n = 587,910)[b]	P
Zolpidem users, n (%)	441,734 (7.1)	58,598 (10.0)	<.001
Long-term zolpidem use, n (%)			
>30 days	322,478 (73.1)	42,845 (73.2)	.623
>90 days	199,461 (45.2)	25,522 (43.6)	<.001
Age in years, n (%)			<.001
21-39	78,687 (17.8)	20,197 (34.5)	
40-49	54,428 (12.3)	14,263 (24.3)	
50-59	82,676 (18.7)	16,199 (27.6)	
60-69	148,571 (33.6)	6295 (10.7)	
≥70	77,372 (17.5)	1644 (2.8)	
Race, n (%)			<.001
White	336,390 (76.2)	35,773 (61.0)	
Black	61,639 (14.0)	16,566 (28.3)	
Other or unknown	43,705 (9.9)	6259 (10.7)	
Co-payment required, n (%)	215,752 (48.8)	22,488 (38.4)	<.001
Physical condition, n (%)			<.001
Cancer	22,213 (5.0)	1788 (3.1)	
Chronic kidney disease	17,514 (4.0)	567 (1.0)	
Chronic lung disease	43,327 (9.8)	4562 (7.8)	
Coronary artery disease	49,090 (11.1)	1054 (1.8)	
Diabetes	92,981 (21.0)	5363 (9.2)	
Heart failure	15,899 (3.6)	454 (0.8)	
Hypertension	170,195 (38.5)	11,911 (20.3)	
Stroke	8046 (1.8)	375 (0.6)	
Mental condition, n (%)			<.001
Alcohol abuse	39,618 (9.0)	3063 (5.2)	
Anxiety	57,688 (13.1)	12,377 (21.1)	
Bipolar disorder	26,846 (6.1)	6654 (11.4)	
Dementia	3830 (0.9)	161 (0.3)	
Major depression	131,791 (29.8)	25,786 (44.0)	
PTSD	117,677 (26.6)	16,174 (27.6)	
Substance use disorder	20,675 (4.7)	1963 (3.3)	
Region of care, n (%)			<.001
Northeast	54,358 (12.3)	5907 (10.1)	
South	194,680 (44.1)	29,015 (49.5)	
Midwest	83,130 (18.8)	9248 (15.8)	
West	109,566 (24.8)	14,428 (24.6)	
Location of facility (rural), n (%)	67,676 (15.3)	7198 (12.3)	<.001

PTSD indicates posttraumatic stress disorder; VHA, Veterans Health Administration.

[a]Study population of all zolpidem users in VHA, fiscal years 2012-2016.

[b]Patients receiving any outpatient medication in the VHA, fiscal years 2012-2016.

RESULTS

Characteristics of Zolpidem Users

Table 1 reports descriptive characteristics of zolpidem users stratified by gender. Across the VHA, 7.1% of men and 10.0% of women received zolpidem at least once during the study period. Compared with male zolpidem users, female users were younger (45.7 years vs 56.6 years) and were more likely to have anxiety disorders (21.1% vs 13.1%), bipolar disorder (11.4% vs 6.1%), and major depression (44.0% vs 29.8%); $P <.001$ for all. Men receiving zolpidem had higher proportions of coronary artery disease (11.1% vs 1.8%), diabetes (21.0% vs 9.2%), and hypertension (38.5% vs 20.3%) compared with women; $P <.001$ for all.

Trends in High-Dose Zolpidem Prescribing for Men Versus Women

Unadjusted trends in high-dose zolpidem prescriptions by gender before and after the PBM 2013 recommendations for suggested lower dose in women are shown in the **Figure** (A and B). The observed proportion of women receiving the higher dose decreased considerably from 75.9% in 2011 to 29.1% in 2016 ($P <.001$), and the 2013 PBM recommendations had a significant effect after adjustment for secular trends and covariates ($P <.001$). For men, there was a decline in observed receipt of high-dose zolpidem from 1.7% in 2011 to 0.1% in 2016 ($P <.001$), but the recommendations did not have a significant effect ($P = .126$).

Patient Characteristics Associated With Inappropriate Zolpidem Prescribing Stratified by Gender

For our first outcome, inappropriate dose, the analysis was limited to men and women with an index prescription in January 2013 or later, resulting in a sample of 194,355 men and 28,181 women. As reported in **Table 2**, compared with 0.1% of men who received more than 10 mg of IR or 12.5 mg of CR, approximately 29.7% of women zolpidem users were receiving an inappropriate dosage, defined as exceeding 5 mg/day for IR or 6.25 mg/day for CR. Men with substance use disorder (adjusted odds ratio [AOR], 3.34; $P <.001$ for this and all other findings) and men living in the Midwest (AOR, 1.42) were more likely to receive an inappropriate zolpidem dose after adjusting for covariates. In fully adjusted models, younger women were more likely to receive an inappropriately high dose compared with women 80 years or older (AORs: 21-39 years, 2.75; 40-49 years, 2.97). Further, women with certain conditions, including major depression (AOR, 0.91), were less likely to receive an inappropriate dosage. Women in the West were less likely to receive an inappropriate dose (AOR, 0.80) compared with women residing in the Northeast. Similar to the men, women with substance use disorder were more likely to receive an inappropriately high dose of zolpidem (AOR, 1.48).

Of the 500,332 zolpidem users, 193,355 were also prescribed benzodiazepines at some point in the study period. **Table 3** presents the results on the concomitant prescribing of zolpidem and benzodiazepines by gender. A higher proportion of female veterans

had an overlapping benzodiazepine prescription along with their zolpidem prescription within a 30-day period (18.8% of women vs 14.3% of men). For men, there was a significant age effect with coprescribing of zolpidem and benzodiazepines, with men aged 40 to 79 years at an increased risk of this coprescribing compared with men 80 years or older (AORs: 40-49 years, 1.12; 50-59 years, 1.33; 60-69 years, 1.23; 70-79 years, 1.14) for all age categories (*P* < .001 for all comparisons). Conditions including cancer (AOR, 1.42), anxiety (AOR, 2.66), posttraumatic stress disorder (PTSD) (AOR, 1.47), and schizophrenia (AOR, 2.46) were also associated with overlapping prescribing for male veterans. Further, in fully adjusted models for men, sites in the South (AOR, 0.96) and West (AOR, 0.87) were less likely to prescribe overlapping doses compared with sites in the Northeast. Similarly, for women, mental health conditions such as anxiety (AOR, 2.28), bipolar disorder (AOR, 1.73), PTSD (AOR, 1.44), and schizophrenia (AOR, 2.05) were associated with overlapping prescribing of zolpidem and benzodiazepines. Regions other than the Northeast tended to be associated with less overlapping prescribing.

DISCUSSION

In this study, we found that inappropriate prescribing of zolpidem is not uncommon in the VHA, particularly among female veterans. Although there was a drastic decrease in prescribing of an inappropriate zolpidem dose in women from before to after the PBM guideline was issued, 30% of female zolpidem users in the VHA continued to be prescribed an inappropriate dose in 2016, contrary to the 2013 PBM guidance.[17] Further, these decreasing rates of inappropriate prescribing over time potentially suggest that the guidelines may have had some impact, although they might be slow to fully disseminate into practice. Patient characteristics associated with higher odds of receiving an inappropriate dose among women included younger age and requirement of a co-payment. For both male and female veterans, having a substance use disorder was associated with inappropriate high dose.

We also found that a higher proportion of female compared with male veterans were being coprescribed benzodiazepines along with zolpidem, another form of inappropriate prescribing. Because zolpidem has similar hypnotic effects to benzodiazepines and affects the same receptor,[23] this coadministration of the 2 medications may potentially increase harm and incur a higher risk of drug interactions and adverse events; however, to our knowledge, this has not been studied directly. The significant association between mental health conditions, including anxiety, bipolar disorder, PTSD, and schizophrenia, and this inappropriate outcome measure for both men and women suggests the already highlighted risk of dependence on benzodiazepines[24] and zolpidem[25] in patients with psychiatric illnesses, as described in the literature.

Although some observers may assume that providers always follow dosing recommendations closely, the findings of this study suggest that they may not. A recent study conducted in the University of Colorado health system compared zolpidem prescribing practices

FIGURE. Interrupted Time Series: Trend in High-Dose Zolpidem Prescribing, October 2011–September 2016[a,b]

A. Among Men (n = 441,734)

B. Among Women (n = 58,598)
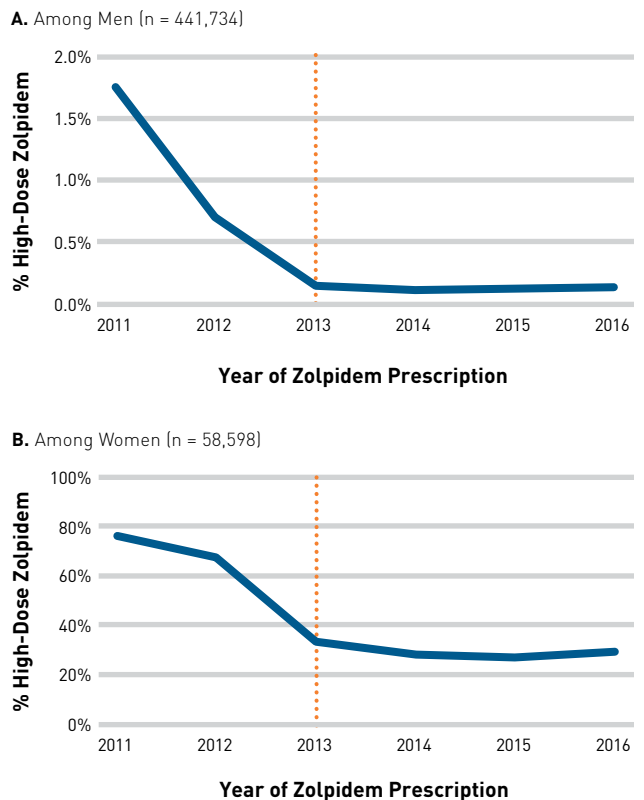
[a]The dotted orange vertical lines represent the year 2013, when the Veterans Health Administration Pharmacy Benefits Management Criteria for Use on lower zolpidem dosage were issued.
[b]Trends are not adjusted for covariates.

before and after the FDA labeling change in 2013.[15] The Colorado study found that providers changed their prescribing habits in response to FDA guidance, reflected by a significant increase in the overall percentage of young women (<65 years) receiving an appropriately low dose of zolpidem after the labeling change. This increase in appropriate prescribing, from 42% before the label change to 70% after the label change, nonetheless implies that 30% of women were still receiving the inappropriate higher dose of zolpidem. Findings from the Colorado study are very similar to those of our study, which also found that 30% of female veterans—88% of them younger than 60 years—continued to receive an inappropriately high dose of zolpidem after the PBM guidance in 2013.[17] Compliance among midlevel providers and physicians with FDA-mandated dosing guidelines was also noted in a retrospective cohort study, but only 16% of the prescriptions in that study were in accordance with the FDA recommendation.[16] Taken together, these findings potentially suggest a quality of care issue that needs to be addressed both within and outside the VHA. Contrary to our study finding of a higher proportion of women receiving an inappropriately high

TABLE 2. Patient Characteristics Associated With Inappropriate Zolpidem Dose by Gender (n = 222,536)[a]

	n (%)		Models Adjusted for All Factors[b] OR (99% CI)	
Variable	**Men (n = 194,355)**	**Women (n = 28,181)**	**Men (C statistic = 0.627)**	**Women (C statistic = 0.584)**
Inappropriate dose[c]	241 (0.1)	8364 (29.7)		
Age in years				
21-39	42,363 (21.8)	10,965 (38.9)	1.81 (0.75-4.37)	2.75 (1.82-4.15)[d]
40-49	25,752 (13.3)	6765 (24.0)	1.69 (0.69-4.14)	2.97 (1.97-4.49)[d]
50-59	34,816 (17.9)	6974 (24.7)	2.00 (0.84-4.76)	2.80 (1.86-4.22)[d]
60-69	58,377 (30.0)	2822 (10.0)	1.45 (0.62-3.41)	2.18 (1.44-3.29)[d]
70-79	20,633 (10.6)	414 (1.5)	1.40 (0.54-3.63)	1.66 (1.03-2.67)
≥80	12,414 (6.4)	241 (0.9)	Ref	Ref
Race				
White	145,698 (75.0)	16,482 (58.5)	Ref	Ref
Black	29,516 (15.2)	8598 (30.5)	1.11 (0.78-1.58)	1.05 (0.99-1.12)
Other or unknown	19,141 (9.8)	3101 (11.0)	0.68 (0.41-1.14)	1.00 (0.92-1.09)
Co-payment required[e]	95,741 (49.3)	10,757 (38.2)	1.23 (0.92-1.65)	1.15 (1.09-1.22)[d]
Index date				
FY 2012	N/A	N/A	N/A	N/A
FY 2013	53,876 (27.7)	7145 (25.4)	1.24 (0.85-1.80)	1.28 (1.19-1.38)[d]
FY 2014	56,006 (28.8)	7846 (27.8)	0.87 (0.58-1.29)	1.06 (0.99-1.15)
FY 2015	46,912 (24.1)	6967 (24.7)	1.20 (0.82-1.77)	0.87 (0.81-0.94)[d]
FY 2016	37,561 (19.3)	6223 (22.1)	Ref	Ref
Physical conditions[e]				
Cancer	10,385 (5.3)	759 (2.7)	0.40 (0.15-1.07)	0.82 (0.69-0.98)
Chronic lung disease	17,776 (9.1)	1868 (6.6)	0.98 (0.61-1.56)	0.92 (0.82-1.02)
Coronary artery disease	18,879 (9.7)	361 (1.3)	0.60 (0.32-1.13)	0.82 (0.62-1.08)
Diabetes	37,046 (19.1)	2241 (8.0)	1.19 (0.82-1.72)	0.93 (0.83-1.03)
Hypertension	67,109 (34.5)	4865 (17.3)	0.84 (0.61-1.15)	0.91 (0.85-0.99)
Mental health conditions[e]				
Alcohol abuse	17,036 (8.8)	1432 (5.1)	1.54 (1.06-2.24)	1.00 (0.88-1.14)
Anxiety	27,546 (14.2)	6286 (22.3)	1.09 (0.79-1.51)	0.97 (0.91-1.04)
Bipolar disorder	10,973 (5.6)	2840 (10.1)	1.28 (0.85-1.93)	0.98 (0.89-1.07)
Major depression	55,594 (28.6)	11,925 (42.3)	1.42 (1.07-1.89)	0.91 (0.86-0.96)[d]
PTSD	48,725 (25.1)	7732 (27.4)	1.14 (0.84-1.54)	0.96 (0.90-1.02)
Schizophrenia	3659 (1.9)	446 (1.6)	0.79 (0.35-1.81)	1.18 (0.97-1.45)
Substance use disorder	9162 (4.7)	835 (3.0)	3.34 (2.24-4.99)[d]	1.48 (1.26-1.74)[d]
Region				
Northeast	22,115 (11.4)	2744 (9.7)	Ref	Ref
South	87,846 (45.2)	14,506 (51.5)	0.50 (0.33-0.77)[d]	1.11 (1.02-1.22)
Midwest	36,497 (18.8)	4233 (15.0)	1.42 (0.94-2.15)[d]	0.95 (0.85-1.05)
West	47,897 (24.6)	6698 (23.8)	1.09 (0.72-1.67)	0.80 (0.72-0.88)[d]
Location of facility (rural)	30,413 (15.6)	3717 (13.2)	0.73 (0.54-0.99)	0.74 (0.69-0.80)[d]

FY indicates fiscal year; N/A, not applicable; OR, odds ratio; PTSD, posttraumatic stress disorder; ref, reference.

[a]Sample of patients with index prescription issued January 2013 to September 2016, as analysis pertains to the period after lower zolpidem dosages for women were mandated by guidelines.

[b]The fully adjusted model controls for all characteristics specified in the table.

[c]Men: greater than 12.5 mg/day continuous release or greater than 10 mg/day immediate release; women: greater than 6.25 mg/day continuous release or greater than 5 mg/day immediate release.

[d]OR differs from the reference group at the P <.001 level.

[e]Reference group consists of patients who do not have the indicated condition.

TABLE 3. Patient Characteristics Associated With Overlapping Prescribing of Zolpidem and Benzodiazepines by Gender (n = 500,332)[a]

Variable	n (%)		Models Adjusted for All Factors[b] OR (99% CI)	
	Men (n = 441,734)	Women (n = 58,598)	Men (C statistic = 0.672)	Women (C statistic = 0.672)
Overlapping prescription[c]	63,011 (14.3)	11,037 (18.8)		
Age in years				
21-39	78,687 (17.8)	20,197 (34.5)	1.06 (0.99-1.12)	1.23 (0.90-1.69)
40-49	54,428 (12.3)	14,263 (24.3)	1.12 (1.05-1.19)[d]	1.44 (1.05-1.97)
50-59	82,676 (18.7)	16,199 (27.6)	1.33 (1.26-1.41)[d]	1.34 (0.98-1.84)
60-69	148,571 (33.6)	6295 (10.7)	1.23 (1.17-1.30)[d]	1.29 (0.93-1.77)
70-79	46,211 (10.5)	967 (1.7)	1.14 (1.07-1.22)[d]	1.13 (0.77-1.66)
≥80	31,161 (7.1)	677 (1.2)	Ref	Ref
Race				
White	336,390 (76.2)	35,773 (61.0)	Ref	Ref
Black	61,639 (14.0)	16,566 (28.3)	0.49 (0.48-0.52)[d]	0.59 (0.55-0.63)[d]
Other or unknown	43,705 (9.9)	6259 (10.7)	0.92 (0.88-0.95)[d]	0.84 (0.77-0.92)[d]
Co-payment required[e]	215,752 (48.8)	22,488 (38.4)	0.81 (0.79-0.83)[d]	0.83 (0.78-0.88)[d]
Index date				
FY 2012	222,781 (50.4)	27,157 (46.3)	1.68 (1.60-1.76)[d]	1.72 (1.55-1.91)[d]
FY 2013	77,120 (17.5)	10,252 (17.5)	1.48 (1.41-1.56)[d]	1.50 (1.33-1.69)[d]
FY 2014	56,627 (12.8)	7897 (13.5)	1.37 (1.29-1.44)[d]	1.25 (1.11-1.42)[d]
FY 2015	47,345 (10.7)	7021 (12.0)	1.17 (1.10-1.24)[d]	1.08 (0.95-1.23)
FY 2016	37,861 (8.6)	6271 (10.7)	Ref	Ref
Physical conditions[e]				
Cancer	22,213 (5.0)	1788 (3.1)	1.42 (1.35-1.49)[d]	1.16 (0.99-1.36)
Chronic lung disease	43,327 (9.8)	4562 (7.8)	1.15 (1.11-1.19)[d]	1.12 (1.02-1.24)
Coronary artery disease	49,090 (11.1)	1054 (1.8)	1.00 (0.97-1.05)	1.14 (0.92-1.41)
Diabetes	92,981 (21.0)	5363 (9.2)	0.89 (0.87-0.92)[d]	0.97 (0.88-1.08)
Hypertension	170,195 (38.5)	11,911 (20.3)	0.99 (0.97-1.02)	0.97 (0.89-1.05)
Mental health conditions[e]				
Alcohol abuse	39,618 (9.0)	3063 (5.2)	0.75 (0.72-0.79)[d]	0.73 (0.64-0.84)[d]
Anxiety	57,688 (13.1)	12,377 (21.1)	2.66 (2.59-2.74)[d]	2.28 (2.14-2.43)[d]
Bipolar disorder	26,846 (6.1)	6654 (11.4)	1.63 (1.57-1.70)[d]	1.73 (1.60-1.88)[d]
Major depression	131,791 (29.8)	25,786 (44.0)	1.28 (1.25-1.32)[d]	1.19 (1.12-1.26)[d]
PTSD	117,677 (26.6)	16,174 (27.6)	1.47 (1.43-1.51)[d]	1.44 (1.35-1.53)[d]
Schizophrenia	8877 (2.0)	1090 (1.9)	2.46 (2.30-2.63)[d]	2.05 (1.72-2.46)[d]
Substance use disorder	20,675 (4.7)	1963 (3.3)	0.92 (0.87-0.98)[d]	0.92 (0.78-1.07)
Region				
Northeast	54,358 (12.3)	5907 (10.1)	Ref	Ref
South	194,680 (44.1)	29,015 (49.5)	0.96 (0.93-1.00)[d]	0.81 (0.74-0.89)[d]
Midwest	83,130 (18.8)	9248 (15.8)	0.97 (0.93-1.01)	0.88 (0.79-0.98)
West	109,566 (24.8)	14,428 (24.6)	0.87 (0.83-0.90)[d]	0.81 (0.73-0.90)[d]
Location of facility (rural)[e]	67,676 (15.3)	7198 (12.3)	0.93 (0.90-0.96)[d]	0.92 (0.85-1.01)

FY indicates fiscal year; OR, odds ratio; PTSD, posttraumatic stress disorder; ref, reference.

[a]Study population of all zolpidem users, FYs 2012-2016.

[b]The fully adjusted model controls for all characteristics specified in the table.

[c]Within 30 days before or after index zolpidem prescription.

[d]OR differs from the reference group at the P <.001 level.

[e]Reference group consists of patients who do not have the indicated condition.

dose in the post–PBM recommendation period, women reported lower odds of high-dose zolpidem exposure (>10 mg IR; >12.5 mg extended release) compared with men in a recent study conducted among veterans of the Iraq and Afghanistan wars.[21] This discrepancy in findings could be due to the focus of the study on a special veteran population characteristically different from the general veteran population.

Potential contributors to this inappropriate prescribing of zolpidem in women could include the fact that the majority of patients served by the VHA are men. Because VHA providers see such a preponderance of male veterans, they may be less familiar with issues specific to treating women, such as the PBM guidance for zolpidem dose reduction for women.[17] Similar differential prescribing patterns and adherence to guidelines in male versus female veterans have been reported in previous studies.[26-28] Additionally, clinician failure to adhere to recommended guidelines, either due to lack of awareness or unfamiliarity with the guidelines or due to other factors that render it difficult to follow the guidelines,[29] could also explain this trend of inappropriate zolpidem prescribing in female veterans.

Our study finding of female veterans, specifically women with existing mental health conditions, as a high-risk group in both the receipt of a guideline-discordant high dose and overlapping prescribing of zolpidem and benzodiazepines compared with male veterans will potentially alert and motivate providers to follow clinical recommendations in their zolpidem prescribing practices with respect to this population. Further, findings may help guide and inform intervention efforts targeted toward female veterans with mental comorbidities to optimize zolpidem prescribing in the VHA. Efforts to reduce inappropriate prescribing among zolpidem users could include targeted dissemination and implementation strategies, including educational outreach, continuing medical education, and audit and feedback.[30,31] The objectives of these activities would be to increase clinician awareness of the existing guidelines for prescribing zolpidem and to compare their prescribing practice with that of their peers and with guideline recommendations. Previous studies have suggested that such an approach may contribute to improved prescribing, especially if delivered in a targeted and personalized manner.[32] The use of clinical decision support systems may also help guide providers to improve practice over time.[33] Even further gains could potentially be made using a more proactive (if more invasive) approach, such as requiring pharmacy approval or a nonformulary consult for inappropriately high doses of zolpidem.

Strengths and Limitations

Our study has important strengths, specifically the detailed nature and large size of the database, which included medication dispensing records, ICD-9/ICD-10 codes, and sociodemographic factors. However, we also acknowledge limitations. First, our study shares the limitations inherent in any analysis of electronic health record data. One such limitation is that diagnosis codes may

not always be applied accurately by clinicians. We addressed this concern in part by requiring 2 ICD-9/ICD-10 codes to confirm the conditions. Second, VHA patients and the VHA system may not be typical of the general population or of other healthcare systems due to the disproportionately large population of men served. Hence, results from this study might not be generalizable to the population outside of the VHA. Third, although we used national VHA pharmacy data to account for zolpidem prescriptions, we did not include prescriptions obtained from Medicare Part D in veterans with dual VHA and Medicare Part D pharmacy use. We plan to focus on these dual zolpidem users in a future study. Finally, in this study, we focused only on patient-level predictors of inappropriate prescribing. We recognize the importance of provider- and system-level factors in the prescribing process and plan to focus on these factors in a separate study.

CONCLUSIONS

We found that after the VHA PBM formally recommended a lower maximum dose of zolpidem for women in 2013,[17] a considerable number of female veterans continued to receive the higher dose or were coprescribed zolpidem and a benzodiazepine. This implies a quality of care problem with implications for patient safety, which may well be amenable to targeted interventions. ■

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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.

Authorship Information: Concept and design (GKJ, RSW, MLC, AJR); acquisition of data (GKJ, JIR); analysis and interpretation of data (GKJ, JIR, AJR); drafting of the manuscript (GKJ, JIR, MLC); critical revision of the manuscript for important intellectual content (GKJ, RSW, MLC, AJR); statistical analysis (JIR); and supervision (GKJ, RSW, AJR).

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eAppendix. Definitions of Comorbid Conditions

Condition	ICD-9 codes	ICD-10 codes
Physical Conditions		
Cancer	140-165, 170-172, 174-176, 179-184, 186-208, 209.1, 209.2, 209.3, 239	C00-C43, C45-C49, C51-C96
Chronic Kidney Disease	403, 405.01, 405.11, 405.91, 581-583, 585-587, 588.8, 588.9	I12, I13, N03, N18
Chronic Liver Disease	456.0, 456.1, 456.2, 571.2, 571.4, 571.5, 571.6, 571.8, 571.9, 572.2, 572.3, 572.4, 572.8, 789.5, V42.7	B15.0, B16.0, B16.2, B17.11, B19.0, B19.11, B19.21, I85, K72.10, K72.11, K73.2, K73.8, K73.9, K74.3, K74.4, K74.5, K76.7
Chronic Lung Disease	490-494, 496, 500-505, 506.4	J44
Coronary Artery Disease	410-414, 429.2	I20-I25
Diabetes	250, 357.2, 362.0, 366.41	E08, E10, E11, E13
Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425, 428	I09.81, I11.0, I13.0, I13.2, I42.0, I42.1, I42.5, I42.8, I42.9, I50
Hypertension	401-405	I10-I13, I15
Peripheral Arterial Disease	440-442, 443.89, 443.9, V43.4	I71.1-I71.9, I73
Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 438	G46.3, G46.4, I63, I69.3, Z86.73
Mental Health Conditions		
Alcohol Abuse	291, 303.00-303.92, 305.0, 357.5, 425.5, 535.3, 571.0, 571.1, 571.2, 571.3, 790.3, 980, E86.0, V11.3	F10 except F10.11 and F10.21 (remission)
Anxiety	300.0x, 300.10, 300.2x	F06.4, F40.8, F40.9, F41.1, F41.3, F41.8, F41.9, F43.22, F43.23
Bipolar Disorder	296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8	F25.0, F31

Dementia	290.0, 29010, 290.4x, 294.10, 294.11, 331.0, 331.19, 331.2, 331.7, 331.82, 331.83, 331.89, 331.9, 797	F01.50, F01.51, F02.80, F02.81, F03.90, F03.91, G31.01, G31.09, G31.1, G31.83
Major Depression	296.2, 296.3, 296.82, 300.4, 311	F32, F33, F43.21, F43.23
PTSD	309.81	F43.1
Schizophrenia	295	F20, F25.1, F25.8, F25.9
Substance Abuse	292, 304.2, 304.4, 304.5, 304.6, 304.7, 304.8, 304.9, 305.3, 305.4, 305.5, 305.6, 305.7, 305.9	F11-F16, F18, F19 except *.11 and *.21 (remission)