Predictors of Long-Term and High-Dose Use of Zolpidem in Veterans

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ABSTRACT

Objective: Prescriptions for sedative hypnotics are routinely initiated and renewed to treat insomnia, despite evidence supporting nonpharmacologic treatments as comparable and more favorable over time. We used national Veterans Health Administration data to assess patient characteristics associated with high-dose and long-term zolpidem use.

Method: The study included outpatients with new zolpidem prescriptions (January 1, 2013, to June 3, 2014). We defined high-dose use as use of doses above those recommended in the 2013 FDA safety warning (> 5 mg for women, > 10 mg for men) and defined long-term use as at least 180 days of continued supply. We fit separate logistic regression models by sex to evaluate how patient factors, adjusting for facilities, predicted high-dose and long-term use.

Results: Of 139,525 new zolpidem users, < 1% of men and 41% of women used high doses within 180 days of initiation, and 20% continued to use zolpidem long-term. Prior-year use of other sleep medications was associated with both high-dose and long-term use. Substance abuse/dependence was associated with high-dose use in women (odds ratio = 1.20, $P < .001$). Although long-term use was less likely in those over the age of 85 years, about 1 in 5 users aged 65 to 85 continued long-term. In both sexes, individuals of Hispanic ethnicity and nonwhite races were less likely to use long-term, whereas those with *ICD-9-CM*–defined psychiatric and sleep disorder diagnoses were more likely to use long-term.

Conclusions: Zolpidem use at a higher-than-recommended dose was common in women who were new zolpidem users. In both sexes, 1 in 5 users continued to use zolpidem for at least 180 days. Efforts to improve access to effective nonpharmacologic treatment alternatives may benefit from attention to subpopulations with higher risk of high-dose and long-term use.

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Sleep disturbance is common, with up to 30% of adults experiencing difficulty sleeping.[1] Insomnia is often treated with sedative hypnotic medications,[2] despite well-documented adverse reactions to these medications, including risks of falls, fractures, headache, gastrointestinal disturbances, and morning or daytime fatigue.[3,4] In spite of evidence for adverse effects, within the United States, roughly 4% of adults used sleep medication in the past month.[5] A recent national poll of older adults found that 1 in 12 people over age 65 years take prescription sleep medications, and 1 in 3 older adults use some sort of sleep aid, which includes over-the-counter products and supplements.[6]

Non-benzodiazepine receptor agonists (NBRAs), including zolpidem, are among the most commonly prescribed sedative hypnotics for treatment of insomnia and can improve both sleep onset and sleep duration.[7,8] Although providers may consider use of NBRAs as a safer alternative to benzodiazepines, studies demonstrate a similarly concerning side effect profile including risk of falls, fracture, impaired cognition, and motor vehicle accidents.[9,10] A variety of studies have established nonpharmacologic strategies such as cognitive behavioral therapy for insomnia (CBT-I) as an effective and durable treatment for insomnia.[11–14] Numerous professional organizations[15,16] recommend behavioral interventions as first line for insomnia, with NBRAs reserved for short-term treatment.[17]

With growing zolpidem use and evidence of substantial risk of patient harm associated with high-dose use, in 2013, the US Food and Drug Administration (FDA) released 2 warnings regarding zolpidem, noting its potential to have a negative impact on next-day alertness and driving acuity.[18–20] The warnings recommended different daily doses for men (≤ 10 mg) and women (≤ 5 mg), noting that women eliminate zolpidem from their bodies more slowly than men. The second warning in May 2013 approved a labeling change.

The Veterans Health Administration (VHA) is the largest integrated health care system in the United States, providing care at over 1,000 health care facilities, including outpatient sites of care of varying complexity.[21] In the VHA, a bulletin released by the Pharmacy Benefits Management Service recommended that zolpidem be used at doses no greater than 10 mg/d as early as May 2007. However, despite this warning, overall zolpidem use quadrupled between 2007 and 2013,[22] quite likely because zolpidem was placed on the VHA prescription formulary in August 2007. On the other hand, high-dose zolpidem use decreased significantly in both sexes after the 2007 warning and declined again following the 2013 FDA warning.[22] Nonetheless, nearly half of women veterans remained on high doses in 2014.[20]

Clinical Points

- In 2013, the FDA issued a drug safety warning recommending against high-dose zolpidem use; however, the extent of use of higher-than-recommended doses and long-term use is unknown.
- Roughly 40% of women veterans who use zolpidem are taking a higher-than-recommended dose, and about 1 in 5 veterans have long-term zolpidem use.
- Patients and providers should have access to effective nonpharmacologic treatment alternatives such as cognitive behavioral therapy for insomnia, especially for populations at particularly high risk of medication-related harm, such as older adults, those with substance abuse disorders, and those with other concurrent sedative or sleep medication use.

Veterans may experience multiple comorbidities and exposures that can adversely impact sleep and place them at increased risk for sleep disturbance.[23] A cross-sectional study describing trends in diagnosed sleep disorders among veterans from 2000 to 2010 reported a 6-fold increase in total sleep disorder prevalence—with posttraumatic stress disorder being associated with the highest prevalence.[21] While studies have shown improvements in sleep outcomes with up to 24 weeks of zolpidem use,[7,8] chronic use exposes patients to increased time at risk for medication-related harms. Given the high prevalence of sleep disorder in veterans and the 2013 FDA safety warnings for high-dose zolpidem use, our goal was to use national VHA health system data to assess the extent of above recommended dose (high-dose) zolpidem use and of continuous (long-term) zolpidem use in veterans newly prescribed zolpidem. We also evaluated patient-level factors associated with high-dose and with long-term zolpidem use.

METHODS

Study Cohort and Data

We used the VHA Pharmacy Benefits Management Services (Hines, Illinois) data from July 1, 2012, to November 30, 2014, to create the study cohort of new zolpidem users for the period from January 1, 2013, to June 3, 2014. For every user, we defined new zolpidem use as no zolpidem use during the past 180 days. For predictors, inpatient discharge datasets and outpatient encounter datasets were obtained from the VHA Corporate Data Warehouse. The VA Ann Arbor Health System Institutional Review Board approved this study.

Study Outcomes

The May 2013 FDA zolpidem warning recommended initial daily doses of 5 mg (6.25 mg for extended-release) for women and either 5 mg or 10 mg (6.25 or 12.5 mg for extended-release) for men.[19,20] We therefore defined high-dose zolpidem separately by sex: for men, as daily dose above 10 mg, and for women, above 5 mg. We used the medication data and defined high-dose use as receiving a high dose at any time in the 180 days following the new zolpidem initiation. We defined long-term zolpidem use as at least 180 continuous days of supply, allowing less than 30 days of gap(s) in use.

Predictors

We included patient demographic characteristics, physical comorbidities, presence of psychiatric diagnoses, substance abuse or dependence diagnoses, and other sleep medication use as potential predictors of high-dose and long-term zolpidem use. Demographic variables included patient age, sex, race and ethnicity. Physical comorbidities included all 19 comorbid medical conditions listed in the Charlson Comorbidity Index[24] and were defined based on the data during 1 year prior to zolpidem initiation. We also created a comorbidity index using 17 updated[25] Charlson comorbidities based on the *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)*. Psychiatric diagnoses included posttraumatic stress disorder (PTSD), schizophrenia, bipolar I and II disorders, major depressive disorder, other anxiety diagnosis, other psychosis, depression, dysthymia, personality disorder, and dementia. Sleep disorder included all insomnia diagnoses (primary, persistent, and unspecified). Data on substance abuse or dependence were collected separately for alcohol, cannabis, cocaine, opioid, and other substances. For medication use, zolpidem use during the period 181 to 365 days prior to the new start and other non-zolpidem sleep medication use during the prior year were collected separately by sedative antidepressants, quetiapine, benzodiazepines, and other sedatives (see Table 1 footnote for lists of specific agents). We also included facility characteristics of 4 US regions and rurality.

Statistical Analysis

The recommended dose differed by sex, and thus potential predictors of high-dose and long-term use may differ by sex. We therefore conducted all analyses separately by sex. We evaluated bivariate relationships between each patient characteristic and each study outcome, expressing unadjusted relationships using odds ratios (ORs). We obtained adjusted ORs using logistic regression models with generalized estimating equation to account for potential within-facility correlation. For more meaningful interpretations, we reduced the number of predictors in the logistic regression model in the following way. For physical comorbidities, comorbidity index was grouped into 3 levels of 0, 1, and greater than 1. For psychiatric diagnoses, we created a binary indicator for presence of 1 or more of the following diagnoses: PTSD, schizophrenia, bipolar disorders, major depressive disorder, other anxiety, other psychosis, depression, dysthymia, or personality disorder. We included an indicator of a sleep disorder diagnosis that included insomnia. For substance use, we created an indicator for dependence on or abuse of alcohol, cannabis, cocaine, or opioid or other substance use. Age was included as categories indicating 10-year age interval groups. For prior use of sleep medications, we included various prior medication use by

Table 1. High-Dose Zolpidem Use in Those With vs Without Specific Characteristics at Baseline (N = 139,525), Stratified by Sex, n (%)[a]

	Women (N = 16,866)			Men (N = 122,659)		
	High-Dose: 41.11% (n = 6,934)			High-Dose: 0.40% (n = 495)		
Characteristic	Characteristic Present	Characteristic Absent	OR	Characteristic Present	Characteristic Absent	OR
Age						
< 35 y	1,911 (42.50)	5,023 (40.61)	1.08**	86 (0.45)	409 (0.40)	1.13**
35 to < 45 y	1,640 (43.97)	5,294 (40.30)	1.16**	74 (0.55)	421 (0.39)	1.44**
45 to < 55 y	1,890 (43.17)	5,044 (40.39)	1.12**	95 (0.52)	400 (0.38)	1.36**
55 to < 65 y	1,248 (36.81)	5,686 (42.19)	0.8**	126 (0.41)	369 (0.40)	1.01**
65 to < 75 y	188 (32.03)	6,746 (41.44)	0.67**	92 (0.34)	403 (0.42)	0.79**
75 to < 85 y	38 (23.46)	6,896 (41.28)	0.44**	17 (0.18)	478 (0.42)	0.42**
85–100 y	19 (15.57)	6,915 (41.30)	0.26**	5 (0.13)	490 (0.41)	0.31**
Ethnicity						
Non-Hispanic	6,136 (41.34)	798 (39.41)	1.08	450 (0.42)	45 (0.30)	1.42*
Hispanic	514 (39.69)	6,420 (41.23)	0.94	28 (0.27)	467 (0.42)	0.65*
Unknown	284 (38.90)	6,650 (41.21)	0.91	17 (0.35)	478 (0.41)	0.86*
Race						
White	3,963 (39.78)	2,971 (43.04)	0.87**	387 (0.42)	108 (0.35)	1.21
Black	2,199 (44.78)	4,735 (39.61)	1.24**	61 (0.34)	434 (0.41)	0.83
Other	225 (37.07)	6,709 (41.26)	0.84**	14 (0.43)	481 (0.40)	1.06
Unknown	547 (39.49)	6,387 (41.26)	0.93**	33 (0.34)	462 (0.41)	0.82
Charlson[b] Comorbidity Index weighted						
0	4,847 (42.26)	2,087 (38.68)	1.16**	258 (0.41)	237 (0.39)	1.06*
1	1,278 (39.59)	5,656 (41.47)	0.92**	117 (0.47)	378 (0.39)	1.23*
> 1	809 (37.32)	6,125 (41.67)	0.83**	120 (0.34)	375 (0.43)	0.78*
Any psychiatric diagnosis[c]	5,616 (42.45)	1,318 (36.24)	1.30**	389 (0.49)	106 (0.25)	2.00**
PTSD	2,630 (44.50)	4,304 (39.28)	1.24**	242 (0.59)	253 (0.31)	1.93**
Schizophrenia	191 (51.76)	6,743 (40.87)	1.55**	14 (0.48)	481 (0.40)	1.19
Bipolar I	608 (46.63)	6,326 (40.65)	1.28**	35 (0.71)	460 (0.39)	1.84**
Bipolar II	540 (47.08)	6,394 (40.68)	1.3**	35 (0.84)	460 (0.39)	2.16**
Major depressive disorder	2,170 (43.97)	4,764 (39.93)	1.18**	129 (0.62)	366 (0.36)	1.73**
Other anxiety diagnosis	2,543 (43.39)	4,391 (39.90)	1.15**	139 (0.49)	356 (0.38)	1.32*
Other psychosis	154 (51.16)	6,780 (40.93)	1.51**	18 (0.68)	477 (0.40)	1.72*
Depression	4,406 (42.32)	2,528 (39.16)	1.14**	288 (0.52)	207 (0.31)	1.71**
Dysthymia	387 (42.48)	6,547 (41.03)	1.06	29 (0.61)	466 (0.40)	1.55*
Personality disorder	459 (47.71)	6,475 (40.71)	1.33**	21 (0.72)	474 (0.40)	1.82*
Sleep disorder[d]	1,937 (40.18)	4,997 (41.49)	0.95	121 (0.34)	374 (0.43)	0.8*
Any substance abuse or dependence[b]	972 (47.30)	5,962 (40.25)	1.33**	139 (0.60)	356 (0.36)	1.68**
Substance use remission in prior year	358 (48.97)	6,576 (40.76)	1.40**	64 (0.82)	431 (0.38)	2.21**
Zolpidem use in the period 181–365 days prior to initiation	1,138 (47.16)	5,796 (40.10)	1.33**	73 (0.43)	422 (0.40)	1.09
Any non-zolpidem sleep medication use	3,752 (45.53)	3,182 (36.89)	1.43**	264 (0.49)	231 (0.34)	1.45**
Sedative antidepressants[e]	2,185 (43.96)	4,749 (39.92)	1.18**	183 (0.54)	312 (0.35)	1.53**
Quetiapine	509 (51.47)	6,425 (40.47)	1.56**	49 (0.70)	446 (0.39)	1.83**
Benzodiazepines[e]	2,380 (48.53)	4,554 (38.07)	1.53**	125 (0.44)	370 (0.39)	1.13
Other sedatives[e]	63 (65.63)	6,871 (40.97)	2.75**	6 (1.32)	489 (0.40)	3.34*

[a]High-dose use is defined for women as titrating up to daily dose > 5 mg immediate release or > 6.25 mg extended release and for men, > 10 mg immediate release, 12.5 mg extended release. OR is unadjusted odds ratio of high-dose use associated with the factor.
[b]See Supplementary Table 1 for a complete list of included physical comorbidities and substance abuse or dependence diagnoses.
[c]Includes all psychiatric disorder diagnoses, excluding sleep disorder; substance abuse, dependence, or remission; and dementia.
[d]Includes all insomnia diagnoses (primary, persistent, and unspecified). The following *ICD-9-CM* codes were used: 307.41, 307.42, 780.49, 780.51, and 780.52.
[e]Sedative antidepressants include doxepin, trazodone, amitriptyline, nortriptyline, and mirtazapine. Benzodiazepines include alprazolam, clonazepam, diazepam, lorazepam, and temazepam. Other sedatives include eszopiclone, ramelteon, and zaleplon.
*$P < .05$.
**$P < .001$.
Abbreviations: OR = odds ratio, PTSD = posttraumatic stress disorder.

individual medication categories. We included time in the model to account for possible increase or decrease in time in high-dose and long-term use.

We conducted several alternate sensitivity analyses for high-dose use. To determine if the results are driven by the 4-month period prior to the labeling change, we repeated the analyses after excluding those who initiated zolpidem prior to the May 2013 warning. To explore if there was a delayed transition to lower doses for patients already taking zolpidem, we tested for a significant interaction of prior zolpidem use by time of the new start of zolpidem. To see if patient characteristics associated with high-dose use differed between the newly recommended dose vs the recommended dose prior to the warning in women, we repeated the analysis of women using 10 mg/d as the threshold. Recognizing an interpretation of the FDA warning as not to *initiate* above

Table 2. Predictors of High-Dose Zolpidem Use Within 180 Days of Initiation

	Women (N = 16,865[a])				Men (N = 122,647[a])			
	AOR	*Z*	*P* Value	95% CL	AOR	*Z*	*P* Value	95% CL
Age								
<35 y	Ref				Ref			
35 to <45 y	1.03	0.79	.43	0.96, 1.11	1.17	2.17	.03	1.02, 1.36
45 to <55 y	1.00	0.00	1.00	0.92, 1.09	1.06	0.70	.48	0.91, 1.23
55 to <65 y	0.82	−3.73	.00	0.73, 0.91	0.88	−1.06	.29	0.69, 1.12
65 to <75 y	0.72	−3.42	.00	0.59, 0.87	0.76	−1.51	.13	0.53, 1.08
75 to <85 y	0.45	−4.04	<.0001	0.30, 0.66	0.62	−2.67	.01	0.43, 0.88
85–100 y	0.34	−3.77	<.01	0.19, 0.59	0.48	−2.66	.01	0.28, 0.83
Ethnicity								
Non-Hispanic	Ref				Ref			
Hispanic	0.89	−1.91	.06	0.79, 1.00	0.75	−2.66	.01	0.61, 0.93
Unknown	1.05	0.46	.65	0.86, 1.28	1.13	0.85	.39	0.86, 1.47
Race								
White	Ref				Ref			
Black	0.98	−0.56	.58	0.91, 1.05	0.94	−0.82	.41	0.82, 1.08
Other	0.94	−0.73	.46	0.79, 1.11	0.94	−0.61	.54	0.76, 1.16
Unknown	1.06	0.90	.37	0.93, 1.20	0.98	−0.29	.77	0.83, 1.15
Comorbidity								
No. of comorbidities								
0 (index)	Ref				Ref			
1	0.90	−2.67	.01	0.83, 0.97	1.21	2.38	.02	1.03, 1.41
>1	0.88	−2.78	.01	0.80, 0.96	1.05	0.87	.39	0.94, 1.16
Any psychiatric diagnosis	1.03	0.54	.59	0.93, 1.14	1.35	2.06	.04	1.01, 1.79
Any substance abuse/dependence	1.20	4.18	<.001	1.10, 1.31	1.06	0.63	.53	0.89, 1.26
Sleep disorder	1.03	0.74	.46	0.96, 1.11	0.88	−1.69	.09	0.77, 1.02
Other prior-year sleep medication use								
Sedative antidepressant	1.06	1.54	.12	0.98, 1.14	1.14	1.20	.23	0.92, 1.43
Quetiapine	1.30	4.17	<.0001	1.15, 1.47	1.35	3.06	<.01	1.11, 1.64
Benzodiazepine	1.44	9.71	<.0001	1.34, 1.55	1.04	0.33	.74	0.82, 1.31
Other sedative hypnotics	2.15	3.46	<.01	1.39, 3.32	1.57	0.77	.44	0.49, 4.99
Zolpidem use in the period 181–365 days prior to initiation	1.33	5.79	<.0001	1.21, 1.47	1.19	1.29	.20	0.91, 1.54
Facility characteristics								
Rural vs urban	0.80	−1.51	.13	0.60, 1.07	0.37	−1.90	.06	0.13, 1.03
Region	Ref				Ref			
Northeast								
South	1.04	0.23	.82	0.76, 1.41	0.40	−1.71	.09	0.14, 1.14
Upper Midwest	0.95	−0.37	.71	0.71, 1.26	1.01	0.02	.99	0.31, 3.34
West	0.76	−1.65	.10	0.55, 1.05	1.76	0.69	.49	0.35, 8.90
Time of zolpidem initiation in 30-day increments	0.98	−4.02	<.0001	0.98, 0.99	0.98	−3.62	<.001	0.97, 0.99

[a]One woman and 12 men with missing age are excluded.
Abbreviations: AOR = adjusted odds ratio, ref = reference group.

5 mg/d rather than not to *escalate* to above 5 mg/d, we also evaluated predictors of high-dose initiation. Finally, we used continuous dose as the dependent variable to see if patient characteristics associated with high-dose use were also predictive of higher levels of dosage at initiation and of maximum dose in 180 days.

RESULTS

High-Dose Zolpidem Use

Of 139,525 new zolpidem users, we found that 41.1% of 16,866 women and 0.40% of 122,659 men were prescribed high-dose zolpidem. For women for whom the recommended dose was lowered, 0.44% initiated a dose above 10 mg/d, the previous recommended dose. Unadjusted analyses showed high-dose users to be younger than low-dose users, with mean ± SD ages of 44.5 ± 12.3 years vs 46.2 ± 13.6 years in women and 52.4 ± 15.0 years vs 56.2 ± 16.4 years in men. Black women had higher odds of high-dose use than other races. Comorbidity index was significantly lower in high-dose users than in low-dose users: 0.56 ± 0.22 vs 0.62 ± 1.26 in women and 1.12 ± 1.80 vs 1.30 ± 2.03 in men. In contrast, those with psychiatric diagnoses and substance abuse or dependence diagnoses were more likely to be high-dose users than those without. Lastly, prior use of zolpidem or of non-zolpidem sleep medications was significantly associated with high-dose zolpidem use (Table 1, Supplementary Table 1).

After adjusting for other covariates, age remained independently associated with high-dose use in both sexes; increasing age was associated with decreasing odds of high-dose use (Table 2). Race was no longer associated with high-dose use in either sex. Women with various prior-year sleep medication use, except sedative antidepressant use, had 1.3 times or higher odds of high-dose use compared to women without prior-year sleep medication use. In women, having a comorbid condition was associated with lower odds of high-dose use (OR = 0.90), while substance abuse or dependence was associated with higher odds of high-dose use (OR = 1.20). Presence of a psychiatric diagnosis or sleep disorder diagnosis was not associated with high-dose use.

Table 3. Long-Term Zolpidem Use in Those With vs Without Specific Characteristics at Baseline (N = 139,525), Stratified by Sex, n (%)[a]

	Women (N = 16,866)			Men (N = 122,659)		
	Long-Term Use: 19.65% (n = 3,315)			Long-Term Use: 20.12% (n = 24,685)		
Characteristic	Characteristic Present	Characteristic Absent	OR	Characteristic Present	Characteristic Absent	OR
Age						
< 35 y	716 (15.93)	2,599 (21.01)	0.71**	2,836 (14.78)	21,849 (21.12)	0.65**
35 to < 45 y	752 (20.16)	2,563 (19.51)	1.04**	2,633 (19.73)	22,052 (20.17)	0.97**
45 to < 55 y	931 (21.27)	2,384 (19.09)	1.14**	3,924 (21.51)	20,761 (19.88)	1.10**
55 to < 65 y	748 (22.06)	2,567 (19.05)	1.20**	7,198 (23.23)	17,487 (19.07)	1.28**
65 to < 75 y	115 (19.59)	3,200 (19.66)	1.00**	5,733 (20.93)	18,952 (19.89)	1.07**
75 to < 85 y	34 (20.99)	3,281 (19.64)	1.09**	1,749 (18.33)	22,936 (20.28)	0.88**
85–100 y	19 (15.57)	3,296 (19.68)	0.75**	609 (15.38)	24,076 (20.28)	0.71**
Ethnicity						
Non-Hispanic	2,984 (20.11)	331 (16.35)	1.29	21,941 (20.43)	2,744 (17.99)	1.17
Hispanic	210 (16.22)	3,105 (19.94)	0.78	1,819 (17.56)	22,866 (20.36)	0.83
Unknown	121 (16.58)	3,194 (19.79)	0.81**	925 (18.90)	23,760 (20.18)	0.92**
Race						
White	2,207 (22.15)	1,108 (16.05)	1.49	19,669 (21.43)	5,016 (16.25)	1.41
Black	777 (15.82)	2,538 (21.23)	0.70	2,709 (15.22)	21,976 (20.96)	0.68
Other	104 (17.13)	3,211 (19.75)	0.84**	525 (16.08)	24,160 (20.24)	0.76**
Unknown	227 (16.39)	3,088 (19.95)	0.79	1,782 (18.16)	22,903 (20.30)	0.87
Charlson[b] Comorbidity Index weighted						
0	2,165 (18.88)	1,150 (21.31)	0.86**	11,789 (18.93)	12,896 (21.35)	0.86**
1	657 (20.35)	2,658 (19.49)	1.06	5,472 (22.19)	19,213 (19.60)	1.17
> 1	493 (22.74)	2,822 (19.20)	1.24	7,424 (20.77)	17,261 (19.86)	1.06
Any psychiatric diagnosis[c]	2,731 (20.64)	584 (16.06)	1.36**	17,099 (21.52)	7,586 (17.56)	1.29**
PTSD	1,222 (20.68)	2,093 (19.10)	1.10*	8,498 (20.84)	16,187 (19.77)	1.07**
Schizophrenia	85 (23.04)	3,230 (19.58)	1.23	731 (24.85)	23,954 (20.01)	1.32**
Bipolar I	324 (24.85)	2,991 (19.22)	1.39**	1,242 (25.36)	23,443 (19.91)	1.37**
Bipolar II	284 (24.76)	3,031 (19.28)	1.38**	1,003 (23.96)	23,682 (19.99)	1.26**
Major depressive disorder	1,048 (21.24)	2,267 (19.00)	1.15**	4,743 (22.83)	19,942 (19.57)	1.22**
Other anxiety diagnosis	1,320 (22.52)	1,995 (18.13)	1.31**	6,285 (22.36)	18,400 (19.46)	1.19**
Other psychosis	66 (21.93)	3,249 (19.61)	1.15	572 (21.64)	24,113 (20.09)	1.10*
Depression	2,178 (20.92)	1,137 (17.61)	1.24**	12,209 (22.17)	12,476 (18.46)	1.26**
Dysthymia	216 (23.71)	3,099 (19.42)	1.29*	1,110 (23.46)	23,575 (19.99)	1.23**
Personality disorder	227 (23.60)	3,088 (19.42)	1.28*	670 (22.93)	24,015 (20.06)	1.19**
Sleep disorder[d]	1,042 (21.61)	2,273 (18.87)	1.19**	7,388 (20.99)	17,297 (19.78)	1.08**
Any substance abuse or dependence[b]	485 (23.60)	2,830 (19.11)	1.31	5,045 (21.76)	19,640 (19.74)	1.13**
Substance use remission in prior year	188 (25.72)	3,127 (19.38)	1.44	1.889 (24.35)	22,796 (19.84)	1.30**
Zolpidem use in the period 181–365 days prior to initiation	446 (18.48)	2,869 (19.85)	0.92	2.812 (16.70)	21,873 (20.67)	0.77**
Any non-zolpidem sleep medication use	2,029 (24.62)	1,286 (14.91)	1.86	13.921 (25.72)	10,764 (15.71)	1.86**
Sedative antidepressants[e]	1,275 (25.65)	2,040 (17.15)	1.67	8.785 (25.80)	15,900 (17.94)	1.59**
Quetiapine	285 (28.82)	3,030 (19.08)	1.72	1.994 (28.61)	22,691 (19.61)	1.64**
Benzodiazepines[e]	1,272 (25.94)	2,043 (17.08)	1.70	7.819 (27.63)	16,866 (17.87)	1.75**
Other sedatives[e]	37 (38.54)	3,278 (19.55)	2.58	158 (34.88)	24,527 (20.07)	2.13**

[a]Long-term zolpidem use is defined as use for 6 months with gap(s) of less than 30 days. OR is unadjusted odds ratio of long-term use associated with the factor.
[b]See Supplementary Table 1 for a complete list of included physical comorbidities and substance abuse or dependence diagnoses.
[c]Includes all psychiatric disorder diagnoses, excluding sleep disorder; substance abuse, dependence, or remission; and dementia.
[d]Includes all insomnia diagnoses (primary, persistent, and unspecified). The following *ICD-9-CM* codes were used: 307.41, 307.42, 780.49, 780.51, and 780.52.
[e]Sedative antidepressants include doxepin, trazodone, amitriptyline, nortriptyline, and mirtazapine. Benzodiazepines include alprazolam, clonazepam, diazepam, lorazepam, and temazepam. Other sedatives include eszopiclone, ramelteon, and zaleplon.
*$P < .05$.
**$P < .001$.
Abbreviations: OR = odds ratio, PTSD = posttraumatic stress disorder.

In men, despite low prevalence of high-dose zolpidem use, Hispanic men were less likely to use high doses (OR = 0.75), and those with prior use of quetiapine were more likely to use high doses (OR = 1.35). In both women and men, high-dose use decreased in time ($P < .001$), although in women who started zolpidem in the last 2 months of the study period, high-dose use remained at 38%.

We found consistent results from various alternate analyses of high-dose use. After excluding the dates prior to the FDA approval of the labeling change, despite the smaller sample size, all statistically significant predictors remained significant. One exception was that having a comorbid condition was no longer associated with lower odds of high-dose use in women. We did not find evidence for a delayed transition to lower doses for those already on zolpidem as indicated by no significant interaction between prior zolpidem use and time in either sex. In women, when a high dose was defined as above 10 mg/d, adjusted ORs were 2.65 ($P = .0001$) for prior benzodiazepine use, 12.06 ($P < .0001$) for prior other sedative hypnotics use, and 1.78

Table 4. Predictors of Long-Term Zolpidem Use

	Women (N = 16,865[a])				Men (N = 122,647[a])			
	AOR	*Z*	*P* Value	95% CL	AOR	*Z*	*P* Value	95% CL
Age								
< 35 y	Ref				Ref			
35 to < 45 y	1.34	4.79	< .0001	1.19, 1.52	1.45	10.47	< .0001	1.35, 1.55
45 to < 55 y	1.43	6.52	< .0001	1.28, 1.58	1.65	13.85	< .0001	1.54, 1.77
55 to < 65 y	1.45	6.53	< .0001	1.30, 1.62	1.79	15.96	< .0001	1.67, 1.92
65 to < 75 y	1.21	1.73	.08	0.97, 1.51	1.57	13.46	< .0001	1.48, 1.68
75 to < 85 y	1.48	1.79	.07	0.96, 2.27	1.42	8.33	< .0001	1.31, 1.54
85–100 y	1.08	0.3	.77	0.64, 1.82	1.16	2.47	.01	1.03, 1.31
Ethnicity								
Non-Hispanic	Ref				Ref			
Hispanic	0.74	−3.21	.001	0.61, 0.89	0.77	−6.97	< .0001	0.72, 0.84
Unknown	0.96	−0.29	.77	0.71, 1.3	0.99	−0.21	.83	0.91, 1.08
Race								
White	Ref				Ref			
Black	0.62	−9.05	< .0001	0.56, 0.69	0.61	−15.9	< .0001	0.57, 0.64
Other	0.81	−1.96	.05	0.66, 1.00	0.79	−4.58	< .0001	0.7, 0.87
Unknown	0.76	−2.68	.007	0.63, 0.93	0.88	−4.42	< .0001	0.83, 0.93
Comorbidity								
No. of comorbidities								
0 (index)	Ref				Ref			
1	0.99	−0.26	.79	0.90, 1.09	1.08	3.49	.0005	1.03, 1.13
> 1	1.07	1.13	.26	0.95, 1.20	0.98	−0.84	.40	0.94, 1.02
Any psychiatric diagnosis	1.14	2.11	.03	1.01, 1.28	1.12	4.98	< .0001	1.06, 1.16
Any substance abuse/dependence	1.05	0.7	.48	0.92, 1.19	0.98	−1.00	.32	0.93, 1.02
Sleep disorder	1.22	4.3	< .0001	1.12, 1.34	1.09	5.03	< .0001	1.05, 1.13
Other prior-year sleep medication use								
Sedative antidepressant	1.49	10.43	< .0001	1.39, 1.62	1.43	22.69	< .0001	1.39, 1.48
Quetiapine	1.40	4.57	< .0001	1.21, 1.62	1.36	10.12	< .0001	1.28, 1.45
Benzodiazapine	1.46	9.36	< .0001	1.35, 1.58	1.54	23.53	< .0001	1.48, 1.58
Other sedative hypnotics	1.90	3.02	.002	1.26, 2.89	1.75	6.12	< .0001	1.46, 2.08
Zolpidem use in the period 181–365 days prior to initiation	0.90	−1.9	.06	0.79, 1.00	0.78	−10.13	< .0001	0.75, 0.82
Facility characteristics								
Rural vs urban	0.96	−0.59	.56	0.84, 1.11	1.03	0.76	.45	0.95, 1.13
Region								
Northeast	Ref				Ref			
South	1.25	2.72	.006	1.06, 1.46	1.23	4.31	< .0001	1.12, 1.36
Upper Midwest	1.17	2.01	.04	1.00, 1.38	1.08	1.58	.11	0.98, 1.20
West	0.97		.71	0.83, 1.14	0.96	−0.91	.36	0.87, 1.05

[a]One woman and 12 men with missing age are excluded.
Abbreviations: AOR = adjusted odds ratio, ref = reference group.

(*P* = .04) for prior zolpidem use, all higher in magnitude than the ORs found for above 5 mg/d zolpidem use. We also found that compared with women younger than 35 years old, those aged 35 to < 45 (OR = 2.61; *P* = .009) and 45 to < 55 (OR = 2.23; *P* = .03) were more likely to use a dose above 10 mg/d, while no difference in these age groups was found in the analysis of use of doses above 5 mg/d. Patient characteristics associated with high-dose use in 180 days were similarly predictive of high-dose initiation and of both maximum dose and initial dose. For example, in women, both initial and maximum doses significantly decreased in time, decreased with increasing age in those 55 or older, were higher in those with prior use of sleep medications except sedative antidepressants, and were higher in those with substance abuse or dependence diagnoses (Supplementary Figure 1).

Long-Term Zolpidem Use

Of 139,525 new zolpidem users, 20.1% of men and 19.7% of women continued to use zolpidem for at least 180 days. Long-term users were older than short-term zolpidem users; age means were 46.8 ± 12.5 vs 45.2 ± 13.2 in women and 57.2 ± 14.9 vs 55.9 ± 16.8 in men. Long-term use prevalence was lower in the youngest (age < 35) and the oldest (≥ 85) age cohort in both sexes. However, about 20% of those aged 65 to < 85 years used zolpidem long-term. Hispanic and nonwhite zolpidem users were less likely to use zolpidem long-term. In women, comorbidity index was higher in long-term users than in short-term users, with mean values of 0.66 ± 1.29 vs 0.58 ± 1.23, but there was no difference in men: 1.31 ± 1.92 vs 1.30 ± 2.05. In both sexes, those with psychiatric disorder diagnoses, substance abuse or dependence diagnoses, and prior use of other sleep medication were generally more likely to use zolpidem long-term (Table 3, Supplementary Table 2).

Controlling for other covariates, we found the pattern of associations between patient factors and long-term use to be generally similar between sexes (Table 4). Time was not a significant predictor of long-term use. Hispanic and nonwhite veterans were less likely to use zolpidem

long-term. Those aged 35 to 85 had higher odds of long-term use compared with both the youngest and the oldest age group. Odds of long-term use were significantly higher in those with prior use of various other sleep medications. Of note, unlike other sleep medication use, zolpidem use in the 6 months prior to the clean period was associated with lower odds of long-term zolpidem use in both men (OR = 0.78; $P < .001$) and women (OR = 0.90, only marginally significant). Both presence of a psychiatric disorder (OR = 1.14 for women and 1.12 for men) and sleep disorder diagnosis (OR = 1.22 for women and 1.09 for men) remained associated with long-term use. Any substance abuse or dependence disorder was not an independent predictor of long-term use. Lastly, in both sexes, patients who live in the southern United States were more likely to use zolpidem long-term.

DISCUSSION

Despite the FDA safety warning and label changes specifying new dosing recommendations for zolpidem due to concerns for next-morning impairment, 41% of new female zolpidem users used a daily dose above the recommended dose. The high prevalence of high-dose use in women is due in part to the change in the recommended dose for women. We also found that about 1 in 5 veteran new zolpidem users continued the medication for at least 6 months. This finding is concerning given that multiple professional organizations have recommended short-term use of sedative hypnotics and that chronic use can potentially expose patients to increased time at risk for medication-related harms.[16,17,26,27] While high-dose and long-term zolpidem can be an effective treatment option for some patients, the benefits of this medication—as with all medications—have to be weighed with the potential known risks to patients.

We found that after controlling for prior use of other sleep medications and covariates, older patients in both sexes and women with more comorbid conditions had lower odds of high-dose zolpidem use. This is reassuring as these patients are more vulnerable to potential harms associated with high-dose zolpidem. In women, in whom prevalence of high-dose use is about 40%, we also found substance abuse or dependence to be associated with high-dose zolpidem use. These findings were consistent across the alternative analyses based on continuous dose and on high-dose initiation. Bivariate associations between different substance abuse or dependence and high-dose zolpidem use were consistent across each individual type of substance. This is alarming since the potential harmful effects of high-dose zolpidem can be compounded when taken in combination with other substances including alcohol.[23]

In terms of long-term use, patients of Hispanic ethnicity and nonwhite race were less likely to use zolpidem long-term. Additionally, among patients 65–85 years old, roughly 20% were prescribed long-term zolpidem. Given concerns for increased negative side effects related to zolpidem use in the elderly due to increased risks of falls and fracture,[28] the high prevalence of use among this age group is concerning. We found psychiatric or sleep disorder diagnoses to be associated with long-term zolpidem use. On the other hand, although most substance abuse or dependence were associated with long-term use in unadjusted analyses, after adjusting for other covariates, we did not find a substance abuse or dependence disorder diagnosis to be independently associated with long-term zolpidem use. It is important to note that long-term use showed significant variation by region.

We found the use of various other sleep medications in the prior year to be significantly predictive of both high-dose and long-term zolpidem use across sexes. This is perhaps expected, as patients may experience tolerance to the sedating effects of some sleep aids over time. A large proportion of patients may continue to have insomnia despite trying various other sleep medications. We found prior zolpidem use to be significantly associated with high-dose use, but negatively associated with long-term zolpidem use, particularly in men. This suggests that those patients who are continuing to have difficulty sleeping and have tried zolpidem before might be more likely to either repeat or try a high dose but less likely to use zolpidem long-term.

This study has multiple strengths including the use of a large national database. Some limitations, however, should be noted. Because the study is based on administrative data, the diagnoses and medication data in terms of dosing or actual long-term use by patients are not perfectly accurate. We defined long-term use as continued supply for 6 months or longer. Various studies have used different cutoffs for defining long-term use, such as 120 days.[29] Prevalence of long-term use is quite likely higher if a shorter cutoff for defining long-term use is used. Dosing and long-term use may be highly dependent on providers, and our study did not include any provider-level variables. We also did not examine outcomes such as motor vehicle accidents or fractures. Future work should examine the strength of evidence for the safety warnings or the effect of long-term use. The increased high-dose zolpidem use in women with substance abuse or dependence and in women with prior use of other sleep medication may support tolerability of high doses in this subpopulation of women or suggest abuse of yet another drug and should be further examined carefully.

We are aware of only 1 large-scale study[30] reporting trends in prevalence and in long-term use of Non-benzodiazepine hypnotics. They showed increases in use over 1999–2014 that may be attributable to growth in long-term use based on nationally representative National Health and Nutrition Examination Survey data. A recent study of urban community-based adults with insomnia disorder found 69.4% of those who used prescription sleep aids to have continued use 1 year later.[31] Our findings of about 40% high-dose use in women and about 20% long-term use in both male and female new zolpidem users call for a need to reduce long-term use in general and continue efforts to reduce high-dose use in women.

Our study implies the need for an available alternate treatment option for patients with sleep disorders. Despite the strong evidence supporting the efficacy of CBT-I, there is a substantial shortage of providers of CBT-I to implement this treatment.[11] However, within the VHA, there have been several systematic efforts to broaden the reach of CBT-I. By 2013, CBT-I was available to patients with insomnia in the VHA, and various efforts to disseminate CBT-I have been ongoing, including group-based CBT-I, training of nonspecialists to provide CBT-I,[32–34] and a CBT-I app named CBT-I Coach.[35] Other efforts could include education for patients and physicians about potential dangers of high-dose and long-term use, as well as the availability of CBT-I as an effective treatment option. Other strategies could include providing step-by-step guidelines on how to safely deprescribe, increasing referral by primary care providers to CBT-I, and expanding CBT-I programs with a shorter number of sessions or internet-based platforms to increase access. Our study also suggests specific subpopulations for whom efforts to improve access to effective nonpharmacologic treatment alternatives may need to be considered.

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Additional information: For more information regarding the VHA Pharmacy Benefits Management Services database, please see https://www.data.va.gov/dataset/drug-accountability; for information on the Corporate Data Warehouse, please see https://www.data.va.gov/dataset/corporate-data-warehouse-cdw.

Supplementary material: Available at PSYCHIATRIST.COM.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

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Supplementary Material

Article Title: Predictors of Long-Term and High-Dose Use of Zolpidem in Veterans

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List of Supplementary Material for the article

1. **Table 1** High-Dose Zolpidem Use, N (%), in Those With vs Without the Baseline Characteristics, Stratified by Sex; High-Dose Use Is Defined for Women as Titrating Up to Daily Dose >5 mg Immediate Release or >6.25 mg Extended Release, and for Men, >10 mg Immediate Release, 12.5 mg Extended Release

2. **Table 2** Long-Term Zolpidem Use, N (%), in Those With vs Without the Baseline Characteristics, Stratified by Sex; Long-Term Zolpidem Use Is Defined as Use for 6 Months or Longer With Less Than 30 Days Gap(s)

3. **Figure 1** Coefficients From Three Different Models Are Graphed to Show Consistency in the Direction and Strength of the Associations Between Various Patient Characteristics and High-Dose Zolpidem Use

Disclaimer

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Supplementary Table 1: High-dose zolpidem use (N (%)) in those with vs. without the baseline characteristics, stratified by sex; High-dose use is defined for women as titrating up to daily dose>5mg immediate release or >6.25mg extended release, and for men, >10mg immediate release, 12.5mg extended release. N = 139,525

	Females (N = 16,866) High-dose: 41.11% (N=6,934)				**Males (N = 122,659)** High-dose: 0.40% (N=495)			
	Characteristics				Characteristics			
Characteristics	Present	Absent	OR		Present	Absent	OR	
Physical Comorbidities								
Myocardial infarction	41 (41.84)	6893 (41.11)	1.03		13 (0.43)	482 (0.4)	1.06	
Congestive heart failure	83 (35.32)	6851 (41.19)	0.78		18 (0.26)	477 (0.41)	0.63	
Peripheral vascular disease	76 (34.7)	6858 (41.2)	0.76		21 (0.31)	474 (0.41)	0.75	
Cerebrovascular disease/stroke	116 (34.02)	6818 (41.26)	0.73	*	20 (0.31)	475 (0.41)	0.76	
Dementia	4 (12.9)	6930 (41.16)	0.21	*	1 (0.11)	494 (0.41)	0.28	
COPD	1056 (40.05)	5878 (41.31)	0.95		81 (0.39)	414 (0.41)	0.95	
Rheumatoid disease	166 (39.15)	6768 (41.16)	0.92		4 (0.28)	491 (0.4)	0.7	
Peptic ulcer disease	52 (43.33)	6882 (41.1)	1.1		7 (0.47)	488 (0.4)	1.16	
Mild liver disease	160 (37.04)	6774 (41.22)	0.84		28 (0.44)	467 (0.4)	1.09	
Diabetes without chronic complication	688 (37.99)	6246 (41.49)	0.86	*	122 (0.43)	373 (0.4)	1.07	
Diabetes with chronic complication	116 (36.25)	6818 (41.21)	0.81		35 (0.46)	460 (0.4)	1.16	
Hemiplegia or paraplegia	40 (40)	6894 (41.12)	0.95		3 (0.22)	492 (0.41)	0.54	
Renal disease	83 (32.81)	6851 (41.24)	0.7	*	26 (0.34)	469 (0.41)	0.83	
Any malignancy[1]	274 (36.48)	6660 (41.33)	0.82	*	24 (0.2)	471 (0.43)	0.47	^
Moderate or severe liver disease	8 (38.1)	6926 (41.12)	0.88		5 (0.61)	490 (0.4)	1.53	
Metastatic solid tumor	44 (47.83)	6890 (41.08)	1.31		4 (0.21)	491 (0.41)	0.52	
HIV	17 (41.46)	6917 (41.11)	1.01		4 (0.44)	491 (0.4)	1.1	
Arrhythmia	249 (38.07)	6685 (41.23)	0.88		38 (0.33)	457 (0.41)	0.81	
Angina	38 (39.58)	6896 (41.12)	0.94		7 (0.32)	488 (0.4)	0.8	
Substance abuse or dependence diagnoses								
Alcohol abuse	409 (46.32)	6525 (40.82)	1.25	*	71 (0.69)	424 (0.38)	1.82	^
Alcohol dependence	403 (48.73)	6531 (40.72)	1.38	^	77 (0.68)	418 (0.38)	1.81	^
Alcohol abuse or dependence	640 (46.14)	6294 (40.66)	1.25	^	112 (0.64)	383 (0.36)	1.76	^
Cannabis abuse	192 (52.32)	6742 (40.86)	1.59	^	23 (0.63)	472 (0.4)	1.59	*
Cannabis dependence	99 (48.53)	6835 (41.02)	1.36	*	19 (0.83)	476 (0.4)	2.11	*
Cannabis abuse or dependence	247 (50.72)	6687 (40.83)	1.49	^	37 (0.74)	458 (0.39)	1.9	^

Cocaine abuse	114 (55.61)	6820 (40.93)	1.81	^	13 (0.6)	482 (0.4)	1.5	
Cocaine dependence	132 (59.46)	6802 (40.87)	2.12	^	21 (0.77)	474 (0.4)	1.95	*
Cocaine abuse or dependence	187 (56.16)	6747 (40.81)	1.86	^	27 (0.69)	468 (0.39)	1.76	*
Opioid abuse	63 (56.25)	6871 (41.01)	1.85	*	6 (0.54)	489 (0.4)	1.36	
Opioid dependence	145 (47.7)	6789 (40.99)	1.31	*	24 (0.72)	471 (0.39)	1.83	*
Opioid abuse or dependence	169 (48.01)	6765 (40.97)	1.33	*	24 (0.64)	471 (0.4)	1.62	*
Other abuse	304 (49.84)	6630 (40.78)	1.44	^	58 (0.85)	437 (0.38)	2.26	^
Other dependence	205 (53.25)	6729 (40.83)	1.65	^	51 (1.23)	444 (0.37)	3.31	^
Other abuse of dependence	396 (51.1)	6538 (40.63)	1.53	^	75 (0.88)	420 (0.37)	2.4	^

Cell values are N (%) unless otherwise specified. OR is unadjusted odds ratio of high-dose use associated with the factor.

* for $p<0.05$, and ^ for $p<0.001$.

[1]Including lymphoma and leukemia, except malignant neoplasm of skin

Supplementary Table 2: Long-term zolpidem use (N (%)) in those with vs. without the baseline characteristics, stratified by sex; long-term zolpidem use is defined as use for 6 months or longer with less than 30 days gap(s). N = 139,525.

	Females (N = 16,866) **Long-term use: 19.65 %** **(N=3,315)**				**Male (N = 122,659)** **Long-term use: 20.12%** **(N=24,685)**			
	Characteristics				**Characteristics**			
Characteristics	Present	Absent	OR		Present	Absent	OR	
Physical comorbidities								
Myocardial infarction	27 (27.55)	3288 (19.61)	1.56	*	620 (20.39)	24065 (20.12)	1.02	
Congestive heart failure	63 (26.81)	3252 (19.55)	1.51	*	1310 (19.04)	23375 (20.19)	0.93	*
Peripheral vascular disease	47 (21.46)	3268 (19.63)	1.12		1399 (20.54)	23286 (20.1)	1.03	
Cerebrovascular disease/stroke	74 (21.7)	3241 (19.61)	1.14		1364 (21.33)	23321 (20.06)	1.08	*
Dementia	9 (29.03)	3306 (19.64)	1.67		186 (21.14)	24499 (20.12)	1.06	
COPD	563 (21.35)	2752 (19.34)	1.13	*	4588 (21.91)	20097 (19.76)	1.14	^
Rheumatoid disease	106 (25)	3209 (19.52)	1.37	*	293 (20.68)	24392 (20.12)	1.04	
Peptic ulcer disease	32 (26.67)	3283 (19.6)	1.49		318 (21.24)	24367 (20.11)	1.07	
Mild liver disease	91 (21.06)	3224 (19.62)	1.09		1421 (22.18)	23264 (20.01)	1.14	^
Diabetes without chronic complication	417 (23.03)	2898 (19.25)	1.25	^	6321 (22.06)	18364 (19.54)	1.17	^
Diabetes with chronic complication	72 (22.5)	3243 (19.6)	1.19		1666 (22)	23019 (20)	1.13	^
Hemiplegia or paraplegia	22 (22)	3293 (19.64)	1.15		303 (22.05)	24382 (20.1)	1.12	
Renal disease	61 (24.11)	3254 (19.59)	1.30		1524 (19.79)	23161 (20.15)	0.98	
Any malignancy[1]	146 (19.44)	3169 (19.66)	0.99		2238 (18.71)	22447 (20.28)	0.90	^
Moderate or severe liver disease	7 (33.33)	3308 (19.64)	2.05		178 (21.81)	24507 (20.11)	1.11	
Metastatic solid tumor	14 (15.22)	3301 (19.68)	0.73		239 (12.71)	24446 (20.24)	0.57	^
HIV	11 (26.83)	3304 (19.64)	1.50		173 (19.18)	24512 (20.13)	0.94	

Arrhythmia	145 (22.17)	3170 (19.55)	1.17		2256 (19.84)	22429 (20.15)	0.98	
Angina	24 (25)	3291 (19.62)	1.37		453 (20.92)	24232 (20.11)	1.05	
Substance abuse or dependence								
Alcohol abuse	194 (21.97)	3121 (19.53)	1.16		2082 (20.12)	22603 (20.13)	1.00	
Alcohol dependence	210 (25.39)	3105 (19.36)	1.42	^	2485 (21.88)	22200 (19.95)	1.12	^
Alcohol abuse or dependence	318 (22.93)	2997 (19.36)	1.24	*	3707 (21.18)	20978 (19.95)	1.08	^
Cannabis abuse	82 (22.34)	3233 (19.6)	1.18		752 (20.56)	23933 (20.11)	1.03	
Cannabis dependence	39 (19.12)	3276 (19.66)	0.97		445 (19.42)	24240 (20.14)	0.96	
Cannabis abuse or dependence	103 (21.15)	3212 (19.61)	1.10		1016 (20.22)	23669 (20.12)	1.01	
Cocaine abuse	49 (23.9)	3266 (19.6)	1.29		435 (20.06)	24250 (20.13)	1.00	
Cocaine dependence	66 (29.73)	3249 (19.52)	1.74	^	563 (20.58)	24122 (20.11)	1.03	
Cocaine abuse or dependence	84 (25.23)	3231 (19.54)	1.39	*	811 (20.79)	23874 (20.1)	1.04	
Opioid abuse	24 (21.43)	3291 (19.64)	1.12		247 (22.41)	24438 (20.1)	1.15	
Opioid dependence	88 (28.95)	3227 (19.48)	1.68	^	837 (25.06)	23848 (19.99)	1.34	^
Opioid abuse or dependence	99 (28.13)	3216 (19.47)	1.62	^	936 (24.94)	23749 (19.97)	1.33	^
Other abuse	156 (25.57)	3159 (19.43)	1.42	^	1454 (21.25)	23231 (20.06)	1.08	*
Other dependence	106 (27.53)	3209 (19.47)	1.57	^	969 (23.37)	23716 (20.01)	1.22	^
Other abuse of dependence	207 (26.71)	3108 (19.32)	1.52	^	1909 (22.34)	22776 (19.96)	1.15	^

Supplementary Figure 1: Coefficients from three different models are graphed to show consistency in the direction and strength of the associations between various patient characteristics and high-dose zolpidem use: Left panel is for high-dose use in 180 days (Table 2), middle panel is for maximum dose in 180 days, and right panel is for initial dose. All three graphs plotted coefficients for consistency across panels. Coefficient for time in the graph is for time is in days.