Patterns of zolpidem use among Iraq and Afghanistan veterans: A retrospective cohort analysis

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Abstract

Background

Although concern exists regarding the adverse effects and rate of zolpidem use, especially long-term use, limited information is available concerning patterns of zolpidem use.

Objective

To examine the prevalence and correlates of zolpidem exposure in Iraq and Afghanistan Veterans (IAVs).

Methods

A retrospective cohort study of zolpidem prescriptions was performed with National Veterans Health Administration (VHA) data. We gathered national VA inpatient, outpatient, and pharmacy data files for IAV’s who received VA care between fiscal years (FY) 2013 and 2014. The VA pharmacy database was used to identify the prevalence of long term (>30 days), high-dose zolpidem exposure (>10mg immediate-release; >12.5mg extended-release) and other medications received in FY14. Baseline characteristics (demographics, diagnoses) were identified in FY13. Bivariate and multivariable analyses were used to examine the demographic, clinical, and medication correlates of zolpidem use.

Results

Of 493,683 IAVs who received VHA care in FY 2013 and 2014, 7.6% (n = 37,422) were prescribed zolpidem in FY 2014. Women had lower odds of high-dose zolpidem exposure than men. The majority (77.3%) of IAVs who received zolpidem prescriptions had long-term use

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provided detailed results of the analyses in the paper. These restrictions are in place to maintain patient privacy and confidentiality. Access to these data can be granted to persons who are not employees of the VA; however, there is an official protocol that must be followed for doing so. Those wishing to access the raw data that were used for this analysis may contact Mary Jo Pugh (pughm@uthscsa.edu) to discuss the details of the VA data access approval process. The authors also confirm that an interested researcher would be able to obtain a de-identified, raw dataset upon request pending ethical approval.

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with an average days’ supply of 189.3 days and a minority (0.9%) had high-dose exposure. In multivariable analyses, factors associated with long-term zolpidem exposure included age greater than 29 years old, PTSD, insomnia, Selim Index, physical 2–3 conditions, opioids, antidepressants, benzodiazepines, atypical antipsychotics, and stimulants. High dose exposure was associated with PTSD, depression, substance use disorder, insomnia, benzodiazepines, atypical antipsychotics, and stimulant prescriptions.

Conclusion
The current practices of insomnia pharmacotherapy in IAVs fall short of the clinical guidelines and may reflect high-risk zolpidem prescribing practices that put Iraq and Afghanistan Veterans at risk for adverse effects of zolpidem and poor health outcomes.

Introduction
Once the mainstay of insomnia treatment, benzodiazepine prescription rates have fallen as a result of clinical practice guidelines discouraging their use [1–4]. Subsequently, a steady increase in the use of non-benzodiazepine hypnotics, specifically zolpidem, has been observed within the U.S. Department of Veterans Affairs (VA) healthcare system and non-VA settings [2,5]. Although zolpidem is marketed as a safe alternative for treatment of insomnia, emerging data suggests that its use is associated with safety concerns resembling those seen with benzodiazepines [6].

In addition to causing cognitive impairment and dizziness along with adverse events such as complex sleep related behaviors, falls, head injuries, fractures and traffic accidents [7–11], data now shows that zolpidem is the leading psychiatric medication linked to emergency department (ED) visits with 25% requiring hospital admissions [12], in part due to co-ingestion of another CNS depressant (e.g., benzodiazepine, opioid, alcohol) [13,14]. Data from the national Drug Abuse Warning Network (DAWN) showed that the estimated number of ED visits involving zolpidem-related suicide attempts tripled from 2004 to 2011, reaching over 14,000 visits in the latter year [15]. The rates of abuse and dependency for zolpidem are comparable to benzodiazepines and are especially concerning in patients with mental health conditions and substance use disorders (SUD) [16]. On this basis, zolpidem is classified as a Schedule IV controlled substance in the U.S. along with benzodiazepines [17].

As with any sedative hypnotic agent, the risk for adverse health outcomes is especially concerning with higher doses and long-term use. In January 2003, the U.S. Food and Drug Administration (FDA) issued a drug safety communication to lower the recommended dose for zolpidem products partly because of the lingering next-day psychomotor and cognitive effects for women and older adults who physiologically eliminate zolpidem more slowly due to the increased half-life [18,19]. Although some studies have demonstrated repeated nightly use to be safe and effective for up to one year [20–22], zolpidem is recommended for short-term use to temporarily relieve symptoms of insomnia [23]. However, the specific period of short-term use has not been delineated. Nevertheless, there is growing anecdotal evidence that zolpidem is routinely used contrary to FDA and manufacturer recommendations despite the greater awareness of its potential risks of harm [24–26].

Iraq and Afghanistan war veterans (IAVs) may be particularly vulnerable to zolpidem exposure given their behavioral and medical risk factors for adverse health outcomes, including:
suicide, accidental overdose from prescription medications, and motor vehicle accidents [27–30]. However, no prior work to our knowledge has examined the extent to which zolpidem is used contrary to FDA and manufacturer recommendations in the IAV population. Thus, we aimed to describe the prevalence, duration, and mean daily dose of zolpidem prescriptions among a national cohort of IAVs, in addition to identifying key patient sociodemographic and clinical factors associated with these prescription patterns.

**Methods**

**Design**

This retrospective cohort study was approved by the Institutional Review Boards at the University of Texas Health Science Center at San Antonio and the Edith Nourse Rogers Memorial Veterans Hospital; a waiver of informed consent was granted prior to initiation.

**Population**

We first identified IAVs using the national Operations Enduring and Iraqi Freedom and New Dawn (OEF/OIF/OND) roster file, which is provided by the VA Office of Public Health. This roster identifies individuals who were deployed in support of combat operations in Iraq and Afghanistan or provided direct support from outside the designated combat zones and who were discharged from military service (active duty) or who returned from deployments (Reserve and National Guard) prior to the end of 2011. Those IAVs that accessed VA inpatient or outpatient care at least once annually in fiscal year (FY) 2013 and 2014 (October 1, 2012 to September 30, 2014) were selected for inclusion.

**Data sources**

We obtained VA inpatient and outpatient administrative data using the national VA data repository in Austin, Texas, and pharmacy records from the VA Pharmacy Benefits Management Strategic Health Group. These national data sources were then linked to the OEF/OIF/OND roster using an encrypted identifier, consistent for each individual across all databases. Prescriptions for zolpidem and other medications were identified in FY 2014 and baseline demographic characteristics and comorbid conditions were identified in FY 2013.

**Measures**

**Study outcome definitions**

The main study outcomes were related to zolpidem prescriptions in FY 2014. We first identified all individuals who were dispensed any zolpidem prescriptions based on the generic drug name. Duration of treatment was calculated by adding the days’ supply of zolpidem dispensed during FY 2014. The average daily dose was computed using the following formula:

\[
\text{Average daily dose} = \frac{\text{zolpidem dose per pill} \times \text{quantity of pills dispensed}}{\text{total prescription days' supply}}
\]

Because there is no consensus in the literature on what constitutes long-term zolpidem treatment, we considered zolpidem exposure as long-term if prescriptions were dispensed for more than 30 days because clinical trials found zolpidem treatment to be clinically significant for only four weeks and the FDA approval is for short-term use [23]. High-dose exposure was defined by an average daily dose exceeding 12.5mg for extended-release formulations and 10 mg for immediate-release formulations based on the latest FDA warning [18].
Sociodemographic covariates
We obtained date of birth, sex, race/ethnicity, and educational attainment using the OEF/OIF/OND roster and supplemented with VA data when missing. Age was based on the first day of FY 2013 (October 1st, 2012) and was classified as follows: 18 to 29 years, 30 to 39 years, 40 to 49 years, and 50 years and older. Race/ethnicity was categorized as African American, Asian, Hispanic, Native American/Pacific Islander, non-Hispanic White, and unknown. Education at the time of discharge included less than high school, high school graduate, some college, college or higher degree graduate, and unknown. We obtained marital status (married vs not married) using VA inpatient and outpatient data in FY 2013.

Comorbid condition covariates
We used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes from national VA inpatient and outpatient data to characterize baseline psychiatric and medical comorbidities in FY 2013 as dichotomous variables (yes/no). We used a validated approach to identify chronic conditions (except for TBI- see below) that required ICD-9-CM diagnosis codes based on a minimum of one inpatient clinical encounter or two outpatient clinical encounters at least seven days apart [31]. Based on guidance recommending clinicians code TBI only on the first visit [32], TBI was based on a single inpatient or outpatient diagnosis. Conditions that are prevalent in IAVs and may be associated with zolpidem prescriptions were identified, including: TBI, PTSD, depression, SUD, anxiety, headache, pain other than headache, insomnia, chronic pulmonary disease, and sleep apnea. Finally, the Selim physical comorbidity index (excluding back pain and chronic pulmonary disease) was calculated to measure the burden of medical conditions [33]. Due to non-normal distribution, we classified comorbidity count as zero, one, two to three, and four or more.

Because Central Nervous System (CNS) polypharmacy is common among IAVs, with zolpidem as a common contributor [34], the following VA medication classes prescribed in FY 2014 were identified: antidepressants, benzodiazepines, stimulants, opioid analgesics, atypical antipsychotics, and sedating antihistamines. We classified each medication by days’ supply (e.g., 0, 1–30, 31–60, 61–90, 91–180, and more than 180 days); however, this did not result in any significant differences. Therefore, the CNS acting medications were summed up as any or no use.

Statistical analysis
Bivariate analyses using the $\chi^2$ statistic were performed to describe characteristics of individuals with and without zolpidem prescriptions, and those with and without long-term and high-dose zolpidem exposure. Multivariable logistic regression analyses were used to identify demographic characteristics, comorbidities, and medications associated with receipt of: 1) any zolpidem prescriptions, 2) long-term, and 3) high-dose exposures. Results are reported as adjusted odds ratios (AORs) with 95% confidence intervals (CI). All statistical analyses were conducted using SAS version 9.3 software (SAS Institute, Inc., Cary, North Carolina); $P < 0.05$ was used as the level of statistical significance.

Results
Of the 493,683 individuals who received VA care in FY 2013 and FY 2014, 37,422 (7.6%) received zolpidem. Of those who received zolpidem, 28,937 (77.3%) had long-term exposure and 351 (0.9%) received high-dose zolpidem (Fig 1).
Any zolpidem exposure

Table 1 shows sociodemographic and clinical characteristics for those with and without zolpidem prescriptions, and adjusted odds ratios (AOR) from logistic regression predicting zolpidem exposure in FY14. For those with zolpidem prescriptions dispensed, the mean daily dose was 8.2 ±2.4mg for immediate-release (IR) zolpidem and 11.4 ±2.4mg for extended-release (ER) zolpidem.

Sociodemographic characteristics

Blacks and unknown races had significantly lower odds than whites for receiving zolpidem while Hispanics and Asians had higher odds. Zolpidem exposure increased with education above the high school level and in unmarried individuals.

Comorbid and medication characteristics. Logistic regression analysis indicated that IAVs with PTSD, headache, other pain, and insomnia had higher odds of zolpidem exposure than individuals without these comorbidities. Decreased odds of zolpidem exposure was associated with SUD. Finally, IAVs who were prescribed opioids, antidepressants, benzodiazepines, atypical antipsychotics, sedating antihistamines, or stimulants in FY14 also had higher odds of receiving any outpatient zolpidem prescription.

Long-term zolpidem exposure

Individuals with long-term zolpidem exposure had a mean daily dose of 8.4 ±2.3mg IR zolpidem and 11.4 ±2.3mg ER zolpidem while those with short-term zolpidem exposure had a mean daily dose of 7.6 ±2.6mg IR zolpidem and 10.6 ±2.9mg ER zolpidem. Table 2 shows the socio-demographic and clinical characteristics for individuals with long-term zolpidem use and AORs from logistic regression analysis predicting long-term zolpidem exposure. IAVs 30 years and older had higher odds of long-term zolpidem exposure. On the contrary, those with Black, Asian, or Native American/Pacific Islander racial backgrounds had lower odds of long-term zolpidem exposure. Individuals with PTSD, insomnia, and two to three physical comorbidities had significantly higher odds of long-term zolpidem exposure while IAVs with SUD...
### Table 1. Adjusted odds ratios (AOR) of correlates of zolpidem use among Iraq and Afghanistan veterans in fiscal year 2014.

| Characteristics               | Zolpidem | No zolpidem | AOR   | 95% CI    |
|-------------------------------|----------|-------------|-------|-----------|
|                               | n = 37,422 | 7.6% | n = 455,027 | 92.4%    |
| Zolpidem daily dose, mg       |          |             |       |           |
| Immediate release, mean ±SD   | 8.2 ±2.4 | –           | –     | –         |
| Extended release, mean ±SD    | 11.4 ±2.4| –           | –     | –         |
| Age, years                    |          |             |       |           |
| Mean ±SD                      | 38.1 ±9.6| 37.4 ±9.9   | –     | –         |
| Under 29                      | 7,309    | 19.5       | 107,286 | 23.6     | **0.96** | **0.92–0.99** |
| 30–39                         | 15,612   | 41.7       | 184,917 | 40.6     | 1.06     | 1.01–1.11     |
| 40–49                         | 9,050    | 24.2       | 96,082  | 21.1     | 1.00     | 0.95–1.06     |
| 50+                           | 5,451    | 14.6       | 66,742  | 14.7     | 0.97     | 0.93–1.01     |
| Sex                           |          |             |       |           |
| Men                            | 32,180   | 86.0       | 393,109 | 86.4     | 0.97     | 0.93–1.01     |
| Race/ethnicity                |          |             |       |           |
| White                          | 24,503   | 65.5       | 290,733 | 63.9     | Reference group |
| Black                          | 5,880    | 15.7       | 87,706  | 19.3     | **0.92** | **0.88–0.95** |
| Asian                          | 932      | 2.5        | 11,835  | 2.6      | 1.13     | 1.04–1.24     |
| Hispanic                       | 5,228    | 14.0       | 53,317  | 11.7     | **1.12** | **1.07–1.17** |
| Native American/Pacific Islander | 649     | 1.7        | 6,856   | 1.5      | 1.10     | 0.99–1.23     |
| Unknown                        | 230      | 0.6        | 4,580   | 1.0      | **0.82** | **0.70–0.98** |
| Level of education             |          |             |       |           |
| Less than high school          | 436      | 1.2        | 5,482   | 1.2      | 1.00     | 0.85–1.10     |
| High school graduate           | 29,259   | 77.9       | 354,772 | 78.0     | Reference group |
| Some college                   | 3,775    | 10.1       | 44,850  | 9.9      | 1.07     | 1.02–1.12     |
| College or higher degree       | 3,519    | 9.4        | 44,002  | 9.7      | 1.23     | 1.17–1.29     |
| Unknown                        | 533      | 1.4        | 5,921   | 1.3      | 1.19     | 1.06–1.34     |
| Marital status                 |          |             |       |           |
| Married                        | 19,119   | 51.1       | 208,348 | 45.8     | **0.94** | **0.92–0.97** |
| Comorbidities                  |          |             |       |           |
| Traumatic brain injury         | 10,744   | 28.7       | 74,329  | 16.4     | 0.99     | 0.95–1.02     |
| Posttraumatic stress disorder  | 26,331   | 70.4       | 177,876 | 39.1     | **1.30** | **1.26–1.35** |
| Depression                     | 22,507   | 60.1       | 151,622 | 33.3     | 1.03     | 1.00–1.07     |
| Substance use disorder         | 9,466    | 25.3       | 80,500  | 17.7     | **0.81** | **0.78–0.84** |
| Anxiety                        | 14,259   | 38.1       | 99,347  | 21.8     | 1.01     | 0.97–1.04     |
| Headache                       | 12,629   | 33.8       | 87,930  | 19.3     | **1.06** | **1.02–1.09** |
| Other pain                     | 27,745   | 74.1       | 259,959 | 57.1     | **1.09** | **1.06–1.13** |
| Chronic pulmonary disease      | 2,821    | 7.5        | 25,116  | 5.5      | 0.97     | 0.92–1.03     |
| Sleep apnea                    | 4,081    | 10.9       | 29,946  | 6.6      | 1.00     | 0.96–1.05     |
| Insomnia                       | 12,888   | 34.4       | 46,793  | 10.3     | **1.89** | **1.83–1.95** |
| Selim index, physical          |          |             |       |           |
| None                           | 19,089   | 51.0       | 281,503 | 61.9     | Reference group |
| 1 Condition                    | 10,296   | 27.5       | 106,192 | 23.3     | **1.04** | **1.01–1.08** |
| 2–3 Conditions                 | 6,627    | 17.7       | 57,862  | 12.7     | 1.00     | 0.96–1.05     |
| 4+ Conditions                  | 1,410    | 3.8        | 9,467   | 2.1      | 0.97     | 0.89–1.05     |
| Zolpidem use                   |          |             |       |           |
| FY13 + FY14                    | 24,869   | 66.5       | 15,277  | 3.4      | **1.33** | **1.29–1.38** |
| Medications in FY14            |          |             |       |           |
| Antidepressants                | 28,667   | 76.6       | 163,393 | 35.9     | **2.90** | **2.80–3.00** |
| Benzodiazepines                | 11,535   | 30.8       | 45,869  | 10.1     | **1.56** | **1.51–1.62** |
| Stimulants                     | 2,642    | 7.1        | 12,931  | 2.8      | **1.50** | **1.41–1.59** |
| Opioids                        | 12,250   | 32.7       | 75,975  | 16.7     | **1.33** | **1.29–1.38** |
| Atypical antipsychotics        | 6,266    | 16.7       | 29,843  | 6.6      | **1.06** | **1.01–1.10** |
| Sedating antihistamines        | 5,192    | 13.9       | 28,096  | 6.2      | **1.22** | **1.17–1.28** |

FY: Fiscal Year; SD: Standard Deviation; TBI: Traumatic Brain Injury; SCI Spinal Cord Injury

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Table 2. Adjusted odds ratios (AOR) of correlates of long-term zolpidem use among Iraq and Afghanistan veterans in fiscal year 2014.

| Characteristics           | Long-term | Short-term | AOR  | 95% CI |
|---------------------------|-----------|------------|------|--------|
|                           | n = 28,937 | n = 8,485  |      |        |
| Zolpidem daily dose, mg    | 8.4 ± 2.3  | 7.6 ± 2.6  | –    | –      |
| Immediate release, mean ±SD|           |            |      |        |
| Extended release, mean ±SD| 11.4 ± 2.3 | 10.6 ± 2.9 | –    | –      |
| Age, years                 | 38.6 ± 9.6 | 36.6 ± 9.1 | –    | –      |
| Under 29                   | 5,185 17.9 | 2,124 25.0 | 1.11 | 1.03–1.19 |
| 30–39                      | 11,889 41.1 | 3,723 43.9 | 1.44 | 1.32–1.57 |
| 40–49                      | 7,326 25.3 | 1,724 20.3 | 1.44 | 1.32–1.57 |
| 50+                        | 4,537 15.7 | 914 10.8  | 1.57 | 1.40–1.76 |
| Sex                        | 24,918 86.1 | 7,262 85.6 | 0.99 | 0.91–1.07 |
| Race/ethnicity             | 19,137 66.1 | 5,366 62.2 | 0.80 | 0.74–0.86 |
| White                      | 4,317 14.9 | 1,563 18.4 | 0.77 | 0.66–0.90 |
| Black                      | 675 2.3    | 257 3.0   | 0.79 | 0.65–0.96 |
| Hispanic                   | 4,154 14.4 | 1,074 12.7 | 0.96 | 0.91–1.00 |
| Native American/Pacific Islander | 480 1.7 | 169 2.0  | 0.96 | 0.91–1.00 |
| Unknown                    | 174 0.6   | 56 0.7    | 0.98 | 0.79–1.22 |
| Level of education         | 334 1.2    | 102 1.2   | 1.02 | 0.80–1.29 |
| Less than high school      | 22,366 77.3 | 67,930 80.1 | 0.80 | 0.74–0.86 |
| High school graduate       | 3,006 10.4 | 769 9.1   | 1.00 | 0.91–1.10 |
| Some college               | 2,818 9.7  | 701 8.3   | 1.03 | 0.93–1.13 |
| College or higher degree   | 413 1.4    | 120 1.4   | 0.98 | 0.79–1.22 |
| Marital status             | 15,251 52.7 | 3,868 45.6 | 0.91 | 0.86–0.96 |
| Married                    | 8,495 29.4 | 2,249 26.5 | 1.00 | 0.93–1.06 |
| Comorbidities              | 20,849 72.1 | 5,482 64.6 | 1.07 | 1.01–1.14 |
| Traumatic brain injury     | 17,952 62.0 | 4,555 53.7 | 1.04 | 0.99–1.11 |
| Posttraumatic stress disorder | 7,301 25.2 | 2,165 25.5 | 0.86 | 0.81–0.91 |
| Substance use disorder     | 11,368 39.3 | 2,891 34.1 | 1.04 | 0.99–1.10 |
| Depression                 | 10,018 34.6 | 2,611 30.8 | 1.00 | 0.94–1.06 |
| Anxiety                    | 21,923 75.8 | 5,822 68.6 | 1.04 | 0.98–1.11 |
| Headache                   | 2,234 7.7  | 587 6.9   | 0.92 | 0.83–1.02 |
| Other pain                 | 3,339 11.5 | 742 8.8   | 1.03 | 0.94–1.13 |
| Chronic pulmonary disease  | 10,336 35.7 | 2,552 30.1 | 1.12 | 1.06–1.19 |
| Sleep apnea                | 31,311 83.7 | 34,778 92.9 | 1.60 | 1.50–1.71 |
| Posttraumatic stress disorder | 18,162 48.5 | 30,795 82.3 | 1.47 | 1.38–1.57 |
| Substance use disorder     | 10,690 28.6 | 28,374 75.8 | 1.49 | 1.33–1.67 |
| Depression                 | 18,560 49.6 | 31,112 83.1 | 1.34 | 1.27–1.43 |
| Anxiety                    | 13,568 36.3 | 30,120 80.5 | 1.12 | 1.04–1.21 |
| Headache                   | 12,556 33.6 | 30,058 80.3 | 1.04 | 0.96–1.12 |

FY: Fiscal Year; SD: Standard Deviation; TBI: Traumatic Brain Injury; SCI Spinal Cord Injury

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had lower odds. Regarding medications, individuals who also received opioids, antidepressants, benzodiazepines, atypical antipsychotics, or stimulants had significantly higher odds of long-term zolpidem exposure. Also, Veterans with zolpidem use in FY13 and FY14, and individuals with high dose zolpidem in FY14 had significantly higher odds of long-term zolpidem use in FY14.

**High-dose zolpidem exposure**

Individuals with high-dose zolpidem exposure had a mean daily dose of 15.7 ±3.4mg IR zolpidem and 17.4 ±6.7mg ER zolpidem while those with low-dose zolpidem exposure had a mean daily dose of 8.2 ±2.3mg IR zolpidem and 11.3 ±2.2mg ER zolpidem. Table 3 shows descriptive statistics and AOR for logistic regression analyses predicting high-dose zolpidem exposure. Women had lower odds of high-dose zolpidem prescriptions (AOR = 0.57; 95% CI = 0.37, 0.86) compared to men. Individuals with PTSD, depression, SUD, and insomnia had significantly higher odds of receiving high-dose zolpidem. Furthermore, those Veterans who were prescribed benzodiazepines, atypical antipsychotics, and stimulants also had significantly higher odds of high-dose zolpidem exposure than individuals without these medications. Individuals with zolpidem use in FY13 had increased odds of high-dose zolpidem exposure in FY14.

**Discussion**

We found that approximately 7.6% of IAVs were dispensed one or more zolpidem prescriptions in FY 2014 and more than three-quarters of those individuals (77.3%) had long-term exposure. A Danish study reported similar findings that approximately 94% of individuals who were prescribed Z-drugs (zaleplon, zolpidem, and zopiclone) had longer treatment exposure than the recommended four weeks [35]. Nonetheless, our finding that women were less likely to receive higher dosages is promising. This observation is consistent with a previous study that demonstrated FDA’s January 2013 Drug Safety Communication release has been effective [26], or that prescribing for women largely met the FDA criteria prior to the recommendation.

Suboptimal zolpidem prescribing practices may lead to high-risk drug interactions with serious adverse health outcomes, namely due to potentiation of CNS depressant effects [14,36–41]. We found that individuals prescribed zolpidem long-term were significantly more likely to also receive antidepressants (83.7%), benzodiazepines (48.5%), opioids (49.6%), stimulants (28.6%), or atypical antipsychotics (36.3%) prescriptions. Veterans on high-doses of zolpidem received benzodiazepine (99.5%), opioid (99.5%), and atypical antipsychotics (99.3%) prescriptions. The prescription of additional CNS acting medications is concerning given the potential for drug interactions because CNS polypharmacy is independently associated with overdose and suicide-related behaviors [34]. It is not known whether specific combinations of medications or total number of medications lead to adverse events, but this topic deserves further study.

We found that approximately 7% of the zolpidem cohort also received prescriptions for neuro-stimulants. Stimulant pharmacotherapy is commonly used for the treatment of ADHD and was recommended for the treatment of fatigue and cognitive symptoms by the 2009 VA TBI clinical practice guidelines which were in effect at the time of this study [42,43]. However, stimulants can further exacerbate sleep disturbance symptoms due to their wake-promoting effects [43]. It is not clear whether zolpidem is prescribed for insomnia secondary to ADHD and TBI or as part of a “prescribing cascade,” treating the undesired effects of stimulant medications [44].
Table 3. Adjusted odds ratios (AOR) of correlates of high-dose zolpidem use among Iraq and Afghanistan veterans in fiscal year 2014.

| Characteristics                  | High-dose | Low-dose | AOR       | 95% CI   |
|----------------------------------|-----------|----------|-----------|----------|
|                                  | n = 351  | 0.9%     | n = 37,071 | 99.1%    |          |
| Zolpidem daily dose, mg          |           |          |           |          |          |
| Immediate release, mean ±SD      | 15.7 ±3.4 | 8.2 ±2.3 | –         | –        |          |
| Extended release, mean ±SD       | 17.4 ±6.7 | 11.3 ±2.2 | –         | –        |          |
| Age, years                       |           |          |           |          |          |
| Mean ±SD                         | 38.6 ±8.9 | 38.1 ±9.6 | –         | –        |          |
| Under 29                         | 48 ±13.7  | 7,261 ±19.6 | Reference group |          |          |
| 30–39                            | 162 ±46.2 | 15,450 ±41.7 | 1.31       | 0.94–1.83 |          |
| 40–49                            | 95 ±27.1  | 8,955 ±24.2 | 1.46       | 0.98–2.16 |          |
| 50+                              | 46 ±13.1  | 5,405 ±14.6 | 1.17       | 0.72–1.89 |          |
| Sex                              |           |          |           |          |          |
| Men                              | 325 ±92.6 | 31,855 ±85.9 | 0.57       | 0.37–0.86 |          |
| Race/ethnicity                   |           |          |           |          |          |
| White                            | 250 ±71.2 | 24,253 ±65.4 | Reference group |          |          |
| Black                            | 37 ±10.5  | 5,843 ±15.8 | 0.76       | 0.53–1.09 |          |
| Asian                            | <1 ±0.0   | 929 ±2.5  | 0.38       | 0.12–1.20 |          |
| Hispanic                         | 55 ±15.7  | 5,173 ±14.0 | 1.05       | 0.77–1.41 |          |
| Native American/Pacific Islander | <1 ±0.0   | 645 ±1.7  | 0.58       | 0.21–1.57 |          |
| Unknown                          | <1 ±0.0   | 228 ±0.6  | 1.00       | 0.24–4.06 |          |
| Level of education               |           |          |           |          |          |
| Less than high school            | <2 ±0.0   | 429 ±1.2  | 1.58       | 0.74–3.40 |          |
| High school graduate             | 284 ±80.9 | 28,875 ±77.9 | Reference group |          |          |
| Some college                     | 33 ±9.4   | 3,742 ±10.1 | 0.94       | 0.65–1.36 |          |
| College or higher degree         | 24 ±6.8   | 3,495 ±9.4  | 0.80       | 0.52–1.24 |          |
| Unknown                          | <1 ±0.0   | 530 ±1.4  | 0.59       | 0.19–1.86 |          |
| Marital status                   |           |          |           |          |          |
| Married                          | 179 ±51.0 | 18,940 ±51.1 | 1.13       | 0.90–1.43 |          |
| Comorbidities                    |           |          |           |          |          |
| Traumatic brain injury           | 136 ±38.8 | 10,608 ±28.6 | 1.04       | 0.82–1.32 |          |
| Posttraumatic stress disorder    | 315 ±89.7 | 26,016 ±70.2 | 2.49       | 1.73–3.58 |          |
| Depression                       | 270 ±76.9 | 22,237 ±60.0 | 1.57       | 1.20–2.05 |          |
| Substance use disorder           | 134 ±38.2 | 9,332 ±25.2 | 1.31       | 1.04–1.65 |          |
| Anxiety                          | 149 ±42.5 | 14,110 ±38.1 | 0.89       | 0.71–1.12 |          |
| Headache                         | 142 ±40.5 | 12,847 ±33.7 | 1.02       | 0.80–1.29 |          |
| Other pain                       | 282 ±80.3 | 27,463 ±74.1 | 0.92       | 0.69–1.22 |          |
| Chronic pulmonary disease        | 24 ±6.8   | 2,797 ±7.5  | 0.77       | 0.51–1.18 |          |
| Sleep apnea                      | 57 ±16.2  | 4,024 ±10.9 | 1.28       | 0.95–1.73 |          |
| Insomnia                         | 148 ±42.2 | 12,740 ±34.4 | 1.29       | 1.03–1.60 |          |
| Selim index, physical            |           |          |           |          |          |
| None                             | 149 ±42.5 | 18,940 ±51.1 | Reference group |          |          |
| 1 Condition                      | 107 ±30.5 | 10,189 ±27.5 | 1.12       | 0.86–1.45 |          |
| 2–3 Conditions                   | 80 ±22.8  | 6,547 ±17.7 | 1.20       | 0.88–1.62 |          |
| 4+ Conditions                    | 15 ±4.3   | 1,395 ±3.8  | 1.03       | 0.58–1.84 |          |
| Zolpidem use                     |           |          |           |          |          |
| FY13 + FY14                      | 45 ±12.8  | 12,508 ±33.7 | 2.36       | 1.71–3.25 |          |
| High dose in FY14                | 331 ±94.3 | 28,606 ±77.2 | 3.14       | 1.98–4.98 |          |
| Medications in FY14              |           |          |           |          |          |
| Antidepressants                  | 37,363 ±99.8 | 287 ±76.8 | 0.93       | 0.69–1.25 |          |
| Benzodiazepines                  | 37,236 ±99.5 | 11,721 ±31.3 | 1.44      | 1.15–1.81 |          |
| Stimulants                       | 37,118 ±99.2 | 2,946 ±7.9  | 1.74       | 1.27–2.40 |          |
| Opioids                          | 37,222 ±99.5 | 12,450 ±33.3 | 1.21       | 0.97–1.52 |          |
| Atypical antipsychotics          | 37,169 ±99.3 | 6,519 ±17.4 | 1.39       | 1.08–1.78 |          |
| Sedating antihistamines          | 37,125 ±99.2 | 5,489 ±14.7 | 0.93       | 0.69–1.25 |          |

FY: Fiscal Year; SD: Standard Deviation; TBI: Traumatic Brain Injury; SCI Spinal Cord Injury

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Adverse reactions with zolpidem include abnormal thinking and behavioral changes which could complicate the diagnostic picture regarding depression and PTSD [45]. In this study, depression and PTSD were consistently associated with all aspects of zolpidem exposure. Surprisingly, we found that the likelihood of high-dose zolpidem exposure was significantly greater for individuals with PTSD than those with insomnia. This reflects the fact that zolpidem is recommended as a second-line treatment option for management of sleep disturbances in patients with PTSD [46]. However, since psychiatric disorders such as PTSD and depression carry an inherent risk for overdose death on their own [47,48], the FDA warning for zolpidem regarding an increased risk of worsening depression or suicidality should be considered [23]. This risk can be further potentiated with the addition of high-dose or long duration zolpidem treatment to existing regimens of antidepressants and benzodiazepines [49].

Sedative-hypnotic abuse is commonly seen in individuals with substance use disorders [50,51]. Although initial zolpidem clinical trials reported a lack of abuse and dependence potential, the emerging evidence from epidemiological studies and post-marketing surveillance show that individuals with mental health conditions and substance use disorders are at higher risk for misuse of prescribed zolpidem [52–54]. In this study, it is reassuring that the zolpidem exposure was less likely for those with substance use disorder (SUD). However, among those who had zolpidem exposure, SUD was associated with high-dose zolpidem use. This may suggest suboptimal prescribing practices, tolerance (i.e., physical dependence) to the sedating effects, or drug seeking behavior to alleviate withdrawal effects or enhance the effects of other drugs in this cohort. This finding has clinical implications as individuals with SUDs may be using high-doses of zolpidem with other CNS depressing drugs.

We hope that clinicians consider a broad assessment of insomnia symptoms and optimize the management of the underlying conditions (e.g., sleep apnea, pain, ADHD, SUD) and substance use (e.g., stimulants, illicit drugs, alcohol) prior to initiating pharmacotherapy [55]. If a hypnotic such as zolpidem is initiated, it should be offered short-term for intermittent use and only as an adjunct to cognitive behavioral therapy for insomnia (CBT-I). CBT-I is now considered an important treatment approach for chronic insomnia and recommended as the initial treatment in current treatment practice guidelines [55–58]. Because of the limited number of CBT therapists, new models of delivering CBT for insomnia have been developed to meet the high demand [59–62]. It is important for providers to incorporate CBT to sustain improved sleep and to limit the use of hypnotics [63–65].

Strengths and limitations

The present study had several strengths. To our knowledge, it is the first national-level study investigating the prevalence of zolpidem use and its prescribing patterns among IAVs. However, several limitations should be noted. Our data represents only IAVs enrolled in the VA healthcare system; thus, our results may not be generalized to all OEF/OIF/OND veterans, other veteran groups, or the U.S. general population. Because the current study used VA administrative data obtained from veterans’ medical records in a retrospective manner, our estimates of medications and diagnoses may be conservative as outside care was not included. Additionally, medication adherence and the use of “as needed” therapy cannot be confirmed. Although our models adjusted for important demographic and clinical covariates, our results may be confounded by other variables not captured in the analysis such as disease severity and the use of non-pharmacological approaches (e.g., psychotherapy). Lastly, given that patients with consistent utilization of VA services (at least one annual visit in FY 2013–2014) were included, we may have inadvertently selected for veterans with poorer health status compared to that of the OEF/OIF/OND general population. However, our cohort included about 80% of...
those who had VA care in FY 2014. Despite these limitations, our results elucidate that the prevalent use of zolpidem is associated with higher-risk prescribing patterns in IAV population, particularly those veterans with PTSD or on CNS activating medications. Future studies with trajectory-based models are needed to assess the potential adverse clinical outcomes associated with these prescribing patterns.

Conclusions

As benzodiazepines have fallen out of favor due to safety concerns, an apparent trend towards zolpidem prescribing for treatment of insomnia has become increasingly widespread. The current study found that zolpidem use is common and approximately 80% of IAVs who were prescribed zolpidem had long-term exposure. Additionally, both high-dose and long-term zolpidem exposure were consistently associated with PTSD and CNS polypharmacy (e.g., benzodiazepines and opioids) which may suggest high-risk prescribing practices and subsequent increased risk of adverse health outcomes in this population. We believe our findings can inform the development of future clinical resources and treatment algorithms to guide providers in the optimal dosing and monitoring of zolpidem treatment.

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Patterns of zolpidem use among Iraq and Afghanistan veterans

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