Prescription Medications for the Treatment of Insomnia and Risk of Suicide Attempt: a Comparative Safety Study

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IMPORTANCE: Guidelines for the pharmacological treatment of chronic insomnia in adults recognize that trazodone and other off-label medications are commonly prescribed despite poor evidence. The Department of Veterans Health Affairs (VA) fills high volumes of inexpensive, over-the-counter sedating antihistamines and older antidepressants in addition to benzodiazepines and zolpidem. Yet little is known about the comparative safety of these agents with regard to suicidal behavior.

OBJECTIVES: To assess the comparative effectiveness of the safety of medications routinely used to treat insomnia in VA.

DESIGN: Comparative effectiveness using propensity score-matched samples.

SETTING: VA.

PARTICIPANTS: VA patients without any history of suicidal ideation or behavior 12 months prior to first exposure.

EXPOSURES: VA formularies and data were used to identify prescriptions for insomnia. Agents accounting for at least 1% of total insomnia fill volume were < 200 mg trazodone, hydroxyzine, diphenhydramine, zolpidem, lorazepam, diazepam, and temazepam. Exposure was defined as an incident monotherapy exposure preceded by 12 months without any insomnia medications. Subjects with insomnia polypharmacy or cross-overs in the 12 months following first exposure were excluded.

MAIN OUTCOMES AND MEASURES: Suicide attempts within 12 months of first exposure.

RESULTS: Three hundred forty-eight thousand four hundred forty-nine subjects met criteria and three well-balanced cohorts by drug class matched to zolpidem were created. After adjusting for days' supply, mental health history, and pain and central nervous system medication history, hazard ratios (compared to zolpidem) were as follows: (< 200 mg) trazodone (HR = 1.61, 95% CI 1.07–2.43); sedating antihistamines (HR = 1.37, 95% CI 0.90–2.07); and benzodiazepines (HR = 1.31, 95% CI 0.85–2.08).

CONCLUSIONS AND RELEVANCE: Compared to zolpidem, hazard of suicide attempt was 61% higher with trazodone (< 200 mg). No significant differences in suicide attempt risk were identified between benzodiazepines or sedating antihistamines and zolpidem, respectively. These findings provide the first comparative effectiveness evidence against the use of trazodone for insomnia.

KEY WORDS: suicide; suicide attempt; suicidal behavior; insomnia; comparative safety; pharmacotherapy; medication; drug; antihistamines; benzodiazepines; zolpidem; hypnotics; trazodone; Veteran.

J Gen Intern Med
DOI: 10.1007/s11606-019-05030-6

Key Points *Questions: What is the comparative safety of medications routinely used to treat insomnia after controlling for history, comorbidities, central nervous system medications, and other factors in patients seen in the VA healthcare system?*

Findings: Among Veterans taking new prescriptions of any one medication routinely used to treat insomnia, incidence of suicide attempt was significantly higher among those who started trazodone compared to zolpidem. Benzodiazepines and sedating antihistamines prescribed for sleep were associated with similar risk of suicide attempt as zolpidem

Meaning: These findings provide empirical support for the American Academy of Sleep Medicine 2017 clinical practice guidelines discouraging the use of trazodone as a first-line therapy for insomnia

Received August 17, 2018
Revised February 5, 2019
Accepted March 28, 2019

Published online: 03 June 2019

INTRODUCTION

As many as 10% of US adults meet diagnostic criteria for insomnia[1–3] and about one-third have difficulty falling or staying asleep.[4,5] Persistent insomnia is associated with increased suicide risk and is a modifiable risk factor.[6–8] Agents approved by the Food and Drug Administration (FDA) for the treatment of insomnia include benzodiazepines, benzodiazepine receptor agonists, ramelteon, and suvorexant. Off-label medications include antihistamines and trazodone, a serotonin reuptake inhibitor/agonist. The 2017 American Academy of Sleep Medicine (AASM) guidelines for the pharmacological treatment of chronic insomnia in adults recognized that trazodone and other off-label medications are commonly prescribed despite poor evidence. Similarly, in the Department of Veterans Health Affairs (VA), the national formulary identifies zolpidem as the preferred agent for insomnia, yet high fill volumes of inexpensive sedating antihistamines and older antidepressants at sub-therapeutic doses for depression (i.e., trazodone = < 200 mg) suggest routine off-label use for insomnia.[9]

Table 1 Medications with ≥1% of Total VA Insomnia Medication Utilization in VA in 2011–2012

Class and agent	FDA-approved for insomnia	Suicidal ideation/behavior warning on the label	Utilization, 2011–2012	
			Unique patients (*n*, %)	Fills (mean, SD)
Hypnotics, miscellaneous				
Zolpidem	Yes	Yes	354,413 (20)	7.88
Benzodiazepines				
Lorazepam	No	Yes	225,057 (13)	8.12
Temazepam	Yes	No	131,296 (8)	8.95
Diazepam	No	No	118,067 (7)	8.52
Antidepressant, serotonin reuptake inhibitor/agonist				
Trazodone	No	Yes	507,370 (29)	6.56
Antihistamine, first generation[10]				
Diphenhydramine	No	No	142,574 (8)	3.58
Hydroxyzine	No	No	264,083 (15)	4.49

Some insomnia agents carry warning labels for risk of adverse events of suicide risk (Table 1).[9] Yet, little is known about the comparative safety of these agents. The literature suggests a possible association between insomnia medications and suicidal ideation and behavior. Among 2245 elderly suicide decedents in Europe, toxicology panels identified benzodiazepines as the means of suicide in about half of poisoning deaths.[11] In the National Comorbidity Survey Replication ($N = 5692$), sedative-hypnotic use was significantly associated with self-reported suicide attempt[12] after adjusting for insomnia, mood and anxiety disorders, general health, and demographics. In a smaller ($N = 525$), cross-sectional community study, self-reported hypnotic use was associated with suicidal ideation after controlling for depression and insomnia.[13] In prospective studies with different follow-up periods, medications for the treatment of insomnia were associated with suicide and/or suicide attempts.[14–16] Sedating antidepressants and antihistamines are used to induce or maintain sleep, although they are not recommended in current clinical practice guidelines.[17–19] Finally, a 2017 review of the studies of hypnotic medication exposures and suicide found that none of the studies had adequately controlled for depression or other psychiatric conditions associated with suicide.[20]

The purpose of this study is to compare the risk of suicide attempt associated with medications commonly prescribed to treat insomnia in the VA over a 2-year period, controlling for days' supply of medication exposure, and history of psychiatric disorders, comorbidities including pain and substance or alcohol abuse, and use of analgesics and central nervous system (CNS) medications.

METHODS

Study Population

Subjects and Data Sources. This cohort consists of patients aged 18 and older receiving care in the Veterans Health Administration (VHA) who filled a first prescription for an insomnia medication in 2011 or 2012. Subjects were defined as active patients if they received at least one prescription medication for an indication other than insomnia or had an inpatient or outpatient visit in the 12 months prior to the index insomnia prescription. Subjects were excluded if they had a possible or confirmed suicide attempt in the 12 months prior to their first insomnia medication prescription. Also excluded were subjects in hospice or skilled nursing facility care or with more than 30 inpatient days at any time during the study period. The observation period was the 12 months after the first insomnia prescription fill date (index date) or until death or suicide attempt, whichever came first. Data were drawn from the VA Corporate Data Warehouse (CDW).[21] The CDW includes prescription fill data and electronic medical records linked by unique patient ID numbers.

Measures

Study Endpoint. The endpoint was suicide attempt as recorded in emergency department encounter records or inpatient discharge summaries in the 12 months of first use of any monotherapy for sleep (ICD-9 external cause of injury codes (E950-E959, E980.6, E980.8, E981-E984, E-988)).[22]

Insomnia Medication Exposure. We reviewed medication labelling, clinical guidelines, and VA formularies (2011–2012) to identify medications used for insomnia, dosing and administration instructions, and any labeled warning for suicidal ideation or behavior risk (Table 1). To ensure adequate sample size to detect the rare event of suicide attempt, we included only agents comprising at least 1% of the fills for sleep medications in 2011 or 2012. These included low-dose (< 200 mg) trazodone, zolpidem, two first-generation antihistamines (hydroxyzine, diphenhydramine), and three benzodiazepines (lorazepam, diazepam, temazepam) (Table 1). Antihistamine fills were included only if administration instructions specified use at bedtime or for sleep or insomnia. The index date for insomnia monotherapy was defined as the date of first fill in 2011 or 2012 following 12 months of no fills for any insomnia medications. Days' supply for the 12-month period following the first fill were categorized as follows: 2–30 days, 31–120 days, and more than 120 days. Fills of 1-day supplies were excluded as these are indicated for procedures (e.g., colonoscopy). We excluded subjects with polypharmacy regimens for insomnia and those who changed sleep monotherapies (i.e., cross-over regimens) during the study period. Only medications filled by VA pharmacies and received by patients were included.

Covariates. The 12-month period before the index prescription date was used to identify potential confounding variables including Gagne comorbidity score, inpatient days, and comorbidities including major depression, post-traumatic stress disorder (PTSD), bipolar disorder, schizophrenia, other psychoses, other anxiety, alcohol or substance use disorder (SUD), personality disorders, sleep disorder, chronic pain, and headache. The presence of a comorbidity was defined by any of the following: two or more outpatient service dates for the same diagnosis or one inpatient diagnosis. To control for differential risks of suicide in the 12-month observation period based on subject history, we included comorbid psychiatric conditions in our propensity score models: major depressive disorder, bipolar affective disorder, schizophrenia, other psychosis, PTSD, anxiety disorders, and personality disorders. We also included history of fills for analgesic and CNS drug classes (opioids, non-opioid analgesics, antidepressants, antipsychotics, anticonvulsants, anti-Parkinson's and other CNS agents). Additional covariates included demographics (age, sex, race, Hispanic ethnicity). Age was categorized as follows: 18–49, 50–60, and over 60 because insomnia treatment selection is confounded with age. Benzodiazepines and sedating antihistamines are contraindicated in older adults.[10] Risk of suicide also varies by age and is non-linear. To account for the degree of exposure to insomnia monotherapy, we categorized days' supply as follows: 2–30 or 31–120 or 121–365 days based on the distribution of days' supply and guidelines for treatment.

Data Analysis

Propensity score matching (with a greedy matching algorithm with a caliper width set at 0.2 of the standard deviation of the logit of the propensity score) was used to control for potential confounding.[23] We estimated the same model to determine the propensity scores for each drug-drug comparison. Only one set of population baseline characteristics was used for all comparisons (Tables 3,4, and 5). Logistic regression was used to estimate the propensity score (i.e., the probability of receiving zolpidem), conditional on the aforementioned covariates. Comparison subjects for trazodone, the benzodiazepines, and the antihistamines were identified by performing a 1:1 match separately with zolpidem on propensity score and age category. The standardized difference of less than 10% was used to examine the balance of the baseline covariates between subjects who filled zolpidem prescriptions and comparator groups in the matched samples.[24] Cox proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals (CI) on the matched data. Covariates included categorical variables for days' supply: 31–120 days and 121–365 days.

Sensitivity Analyses. To ensure that our models were unaffected by somewhat different populations in each model, we repeated the Cox proportional hazard models using only subjects who filled index prescriptions for zolpidem and also matched to every comparator (antihistamines, benzodiazepines, trazodone) ($n = 70,525$). We then included only the antihistamine, benzodiazepine, and trazodone patients who matched those 70,525 zolpidem patients for a total sample of 141,050 for each of the three models. This approximates the multinomial propensity score model. Covariates were those used in the original models and were identical across all three models. The hazard ratios and confidence intervals were similar to those reported in our primary analyses.

This study was approved by the Syracuse VA Institutional Review Board.

RESULTS

A total of 1,742,860 subjects filled at least one prescription for an agent routinely used to treat insomnia in VHA in 2011 and 2012. Of those, 348,449 met the study criteria. The most common insomnia medication fills were for the antidepressant trazodone, followed by benzodiazepines, antihistamines, and zolpidem (Table 1). Subjects were typically white men in their late 50s or early 60s (Table 2). About 1 in 4 had a VA disability rating of 50% or more. Hypertension was the most common comorbidity (35.6–39.8%) followed by arthritis (20.6–22.8%), back pain (16.5–19.4%), depression (14.8–23.5%), and PTSD (11.4–20.2%).

Propensity score modeling matched 76,247 patients with trazodone (< 200 mg), 72,641 patients with benzodiazepines, and 74,229 patients with antihistamines prescribed for insomnia (Table 3). The matched cohorts were well-balanced by demographics, disability rating, inpatient days, comorbidity burden, history of psychiatric, cardiovascular, oncologic and pain conditions, and prescription fills for pain and CNS medications in the 12 months prior to the first insomnia prescription (Tables 3, 4, and 5). Standardized differences were all below 0.10. Cox proportional hazards regressions on the propensity score-matched samples with days' supply as covariates identified the risk of suicide attempt as 61% higher for trazodone than for zolpidem (HR = 1.61, 95% CI 1.07–2.43) (Table 6). Interaction terms (days' supply by trazodone) were insignificant. The risk of suicide attempt for any insomnia medication days' supply beyond 120 days (compared to 30 days or less) was 70% lower than for days' supplies of 30 days or less (HR = 0.30, 95% CI 0.17–0.52). The model was robust to the assumption that suicide attempt risk was constant over time.

The same Cox regression models for benzodiazepines (HR = 1.31, 95% CI 0.85–2.08) and sedating antihistamines (HR = 1.37, 95% CI 0.90–2.07), respectively, identified no difference in suicide attempt risk associated with either class compared to zolpidem (Table 6). In both models, days' supply beyond 120 days compared to days' supply of 30 days or less was associated with lower risk of suicide attempt (benzodiazepines or zolpidem days' supply > 121 days HR = 0.42, 95% CI 0.23–0.78; and sedating antihistamines or zolpidem days' supply > 121 days, HR = 0.53, 95% CI 0.29–0.94). Yet, in both models,

Table 2 Characteristics of Veterans in VHA Who Filled a New Insomnia Medication Prescription in 2011–2012

	Medication			
	Zolpidem	Trazodone	Benzodiazepine	Antihistamine
	N = 77,573	*N* = 104,212	*N* = 83,795	*N* = 82,869
	N (%)	*N* (%)	*N* (%)	*N* (%)
Demographics				
Male	70,663 (91.1)	95,428 (91.6)	76,305 (91.1)	74,332 (89.7)
Female	6910 (8.9)	8784 (8.4)	7490 (8.9)	8537 (10.3)
Age (mean, Std.)	58.3 (16.6)	56.0 (16.2)	61.7 (15.6)	57.9 (15.0)
Age 18–49	21,742 (28.0)	32,476 (31.2)	16,915 (20.2)	22,030 (26.6)
Age 50–60	15,130 (19.5)	24,005 (23.0)	16,857 (20.1)	20,196 (24.4)
Age 61 and older	40,701 (52.5)	47,731 (45.8)	50,023 (59.7)	40,643 (49.0)
White	57,726 (74.4)	69,579 (66.8)	64,705 (77.2)	55,892 (67.4)
African American	10,997 (14.2)	24,125 (23.1)	10,046 (12.0)	18,747 (22.6)
Race not reported	6201 (8.0)	7131 (6.8)	6768 (8.1)	5227 (6.3)
Other race	2649 (3.4)	3377 (3.2)	2276 (2.7)	3003 (3.6)
Disabled > 50%	21,831 (28.1)	28,758 (27.6)	22,796 (27.2)	22,043 (26.6)
Disabled 30–40%	7119 (9.2)	10,307 (9.9)	6731 (8.0)	7027 (8.5)
Disabled 10–20%	9274 (12.0)	12,261 (11.8)	9442 (11.3)	9522 (11.5)
Diagnoses, 12 months prior to index date				
Inpatient days	0.9 (3.7)	1.1 (4.3)	1.1 (4.1)	1.1 (4.1)
Gagne index (mean, SD)	0.3 (1.2)	0.3 (1.1)	0.4 (1.2)	0.3 (1.2)
Major depression	4094 (5.3)	7555 (7.2)	3913 (4.7)	4306 (5.2)
Bipolar disorder	2026 (2.6)	3032 (2.9)	2342 (2.8)	2905 (3.5)
Schizophrenia	820 (1.1)	1972 (1.9)	1629 (1.9)	2330 (2.8)
Other psychosis	386 (0.5)	1012 (1.0)	654 (0.8)	903 (1.1)
PTSD	11,257 (14.5)	21,030 (20.2)	9550 (11.4)	10,566 (12.8)
Other anxiety	4448 (5.7)	8122 (7.8)	6731 (8.0)	6266 (7.6)
Alcohol use disorder	3084 (4.0)	9468 (9.1)	3759 (4.5)	6525 (7.9)
Substance use disorder	1662 (2.1)	5911 (5.7)	1889 (2.3)	4720 (5.7)
Personality disorder	437 (0.6)	920 (0.9)	513 (0.6)	924 (1.1)
Sleep disorder	2312 (3.0)	2335 (2.2)	1216 (1.5)	818 (1.0)
Arthritis	15,949 (20.6)	21,731 (20.9)	18,451 (22.0)	18,884 (22.8)
Back pain	12,787 (16.5)	17,647 (16.9)	16,230 (19.4)	13,821 (16.7)
Migraine	1244 (1.6)	1353 (1.3)	1167 (1.4)	1092 (1.3)
Metastatic cancer	437 (0.6)	241 (0.2)	823 (1.0)	279 (0.3)
Other cancer or tumor	4979 (6.4)	4722 (4.5)	7232 (8.6)	4844 (5.8)
Dementia	293 (0.4)	981 (0.9)	1003 (1.2)	324 (0.4)
Renal disease	3059 (3.9)	3194 (3.1)	3459 (4.1)	3460 (4.2)
Arrhythmias	4344 (5.6)	4513 (4.3)	5490 (6.6)	4250 (5.1)
Congestive heart failure	2843 (3.7)	2995 (2.9)	3387 (4.0)	2791 (3.4)
Coagulopathy	676 (0.9)	797 (0.8)	804 (1.0)	788 (1.0)
Psychosis	7414 (9.6)	13,855 (13.3)	8431 (10.1)	10,330 (12.5)
Hypertension	28,196 (36.3)	37,114 (35.6)	33,342 (39.8)	32,195 (38.9)
Myocardial infarction	904 (1.2)	930 (0.9)	1081 (1.3)	776 (0.9)
Rheumatoid arthritis	649 (0.8)	721 (0.7)	709 (0.8)	721 (0.9)
Non-alcohol drug abuse per Gagne definition	1216 (1.6)	4354 (4.2)	1371 (1.6)	3523 (4.3)
Depression	12,613 (16.3)	24,479 (23.5)	12,439 (14.8)	13,624 (16.4)
Cerebrovascular disease	1999 (2.6)	2792 (2.7)	2904 (3.5)	2237 (2.7)
Ischemic heart disease	8149 (10.5)	8763 (8.4)	9903 (11.8)	7711 (9.3)
Valvular disease	1081 (1.4)	1097 (1.1)	1321 (1.6)	1015 (1.2)
Thyroid disease	2982 (3.8)	3358 (3.2)	3575 (4.3)	3016 (3.6)
Other neurological disorders	2284 (2.9)	3509 (3.4)	4019 (4.8)	2365 (2.9)
Central nervous system medications				
Opioid	28,696 (37.0)	36,706 (35.2)	34,148 (40.8)	31,383 (37.9)
Non-opioid pain relievers	14,330 (18.5)	20,992 (20.1)	16,762 (20.0)	18,390 (22.2)
Anticonvulsants	12,555 (16.2)	17,759 (17.0)	15,763 (18.8)	14,145 (17.1)
Anti-Parkinson's	1643 (2.1)	1817 (1.7)	2040 (2.4)	1153 (1.4)
Antidepressants	23,804 (30.7)	41,024 (39.4)	25,549 (30.5)	25,326 (30.6)
Antipsychotics	5144 (6.6)	8733 (8.4)	6605 (7.9)	7322 (8.8)
Lithium	519 (0.7)	712 (0.7)	722 (0.9)	757 (0.9)
Other CNS medications	1757 (2.3)	3092 (3.0)	3461 (4.1)	1634 (2.3)

interaction terms for days' supply and medication (benzodiazepines or zolpidem, sedating antihistamines for sleep or zolpidem) were insignificant, indicating that risk of suicide attempt was significantly lower for subjects with insomnia monotherapy days' supply of more than 120 days compared to 30 or fewer days' supply, regardless of the specific monotherapy. The Cox regression model assumption of constant suicide rates over time was robust in both models.

DISCUSSION

Compared to zolpidem, trazodone (< 200 mg) was associated with clinically and statistically significant increased risk of suicide attempt on average in propensity-matched samples over time while controlling for history of inpatient days, psychiatric and substance or alcohol use history, comorbidities, pain, central nervous system

Table 3 Selected Patient Characteristics of Propensity Score-Matched Samples of Zolpidem and Trazodone

	Trazodone	Zolpidem	Std.
	N = 76,247	*N* = 76,247	Diff.
	n (%)	*n* (%)	
Demographics			
Male	70,336 (92.2)	69,363 (91.0)	0.046
Female	5911 (7.8)	6884 (9.0)	−0.046
Age (mean, Std.)	57.9 (16.5)	57.9 (16.5)	−0.001
Age 18–49	21,700 (28.5)	21,695 (28.5)	0.000
Age 50–60	15,118 (19.8)	15,119 (19.8)	0.000
Age 61 and older	39,429 (51.7)	39,433 (51.7)	0.000
White	55,374 (72.6)	56,595 (74.2)	−0.036
African American	12,225 (16.0)	10,993 (14.4)	0.045
Race not reported	6058 (7.9)	6030 (7.9)	0.001
Other race	2590 (3.4)	2629 (3.4)	−0.003
Percent disabled > 50%	22,054 (28.9)	21,654 (28.4)	0.012
Percent disabled 30–40%	7824 (10.1)	7097 (9.2)	0.032
Percent disabled 10–20%	9478 (12.3)	9242 (11.9)	0.009
Comorbidities in 12 months prior to index date			
N of inpatient days (mean, Std.)	0.8 (3.7)	0.9 (3.8)	−0.007
Gagne index (mean, Std.)	0.2 (1.1)	0.3 (1.2)	−0.031
Major depression	4869 (6.4)	4075 (5.3)	0.044
Bipolar disorder	1850 (2.4)	2021 (2.7)	−0.014
Schizophrenia	661 (0.9)	820 (1.1)	−0.021
Other psychosis	394 (0.5)	386 (0.5)	0.001
PTSD	14,104 (18.5)	11,226 (14.7)	0.102
Other anxiety	4237 (5.6)	4440 (5.8)	−0.011
Alcohol use disorder	3502 (4.6)	3084 (4.0)	0.027
Substance use disorder	1742 (2.3)	1662 (2.2)	0.007
Sleep disorder	2213 (2.9)	2126 (2.8)	0.007
Arthritis	15,131 (19.8)	15,745 (20.6)	−0.020
Back pain	11,927 (15.6)	12,678 (16.6)	−0.027
Migraine	1059 (1.4)	1236 (1.6)	−0.019
Metastatic cancer	216 (0.3)	429 (0.6)	−0.043
Other cancer/any tumor	3914 (5.1)	4816 (6.3)	−0.051
Dementia	344 (0.5)	293 (0.4)	0.010
Renal	2667 (3.5)	2942 (3.9)	−0.019
Arrhythmias	3832 (5.0)	4167 (5.5)	−0.020
Congestive heart failure	2514 (3.3)	2754 (3.6)	−0.017
Coagulopathy	618 (0.8)	660 (0.9)	−0.006
Psychosis	7962 (10.4)	7389 (9.7)	0.025
Hypertension	27,252 (35.7)	27,604 (36.2)	−0.010
Myocardial infarction	774 (1.0)	885 (1.2)	−0.014
Rheumatoid arthritis	583 (0.8)	630 (0.8)	−0.007
Non-alcohol drug abuse	1285 (1.7)	1216 (1.6)	0.007
Depression, Gagne def.	15,091 (19.8)	12,549 (16.5)	0.087
Cerebrovascular disease	1987 (2.6)	1962 (2.6)	0.002
Ischemic heart disease	7496 (9.8)	7864 (10.3)	−0.016
Valve disease	934 (1.2)	1031 (1.4)	−0.011
Thyroid disease	2731 (3.6)	2893 (3.8)	−0.011
Other neurological	2208 (2.9)	2265 (3.0)	−0.0044
CNS medications			
Opioid	26,401 (34.6)	28,297 (37.1)	−0.052
Non-opioid pain relievers	13,965 (18.3)	14,174 (18.6)	−0.007
Anticonvulsants	12,018 (15.8)	12,406 (16.3)	−0.014
Anti-Parkinson's	1615 (2.1)	1580 (2.1)	0.003
Antidepressants	27,042 (35.5)	23,672 (31.1)	0.094
Antipsychotics	5054 (6.6)	5128 (6.7)	−0.004
Lithium	408 (0.5)	516 (0.7)	−0.018
Other CNS medications	2109 (2.8)	1735 (2.3)	0.031

medications, and demographics. We found no differences in risk of suicide attempt for benzodiazepines or sedating antihistamines prescribed for insomnia compared to zolpidem, respectively. For each insomnia monotherapy, days' supply of 30 days or less was associated with significantly higher risk of suicide attempt than days' supply of 120 days or more. This effect was independent of the specific insomnia monotherapy.

To the best of our knowledge, this study provides the first comparative safety evidence to support the 2017 clinical practice guideline[17] for the pharmacologic treatment of insomnia from the AASM which reject the use of trazodone for insomnia treatment. These findings extend the results of the meta-analysis on which the guideline was based through the inclusion of frail, complex patients routinely excluded from the randomized trials that comprised the meta-analysis.

Table 4 Selected Characteristics of Matched Sample of Zolpidem and Benzodiazepines

	Benzodiazepine	Zolpidem	Std.
	N = 72,641	*N* = 72,641	Diff.
	N (%)	*N* (%)	
Demographics			
Male	65,760 (90.5)	66,625 (91.7)	−0.042
Female	6881 (9.5)	6016 (8.3)	0.042
Age (mean, Std.)	59.9 (15.5)	59.9 (15.6)	0.005
Age 18–49	16,915 (23.3)	17,178 (23.6)	−0.009
Age 50–60	15,272 (21.0)	15,026 (20.7)	0.008
Age 61 and older	40,454 (55.7)	40,437 (55.7)	0.000
White	56,395 (77.6)	54,034 (74.4)	0.076
African American	8431 (11.6)	10,347 (14.2)	−0.079
Race not reported	5852 (8.1)	5835 (8.0)	0.001
Other race	1963 (2.7)	2425 (3.3)	−0.037
Percent disabled > 50%	20,040 (27.6)	20,290 (27.9)	−0.008
Percent disabled 30–40%	6149 (8.5)	6455 (8.9)	−0.015
Percent disabled 10–20%	8440 (11.6)	8548 (11.8)	−0.005
Comorbidities in 12 months prior to index date			
N of inpatient days (mean, Std.)	1.0 (3.9)	0.9 (3.8)	0.0254
Gagne index (mean, Std.)	0.3 (1.2)	0.3 (1.2)	0.0237
Major depression	3417 (4.7)	3803 (5.2)	−0.0245
Bipolar disorder	2078 (2.9)	1877 (2.6)	0.0170
Schizophrenia	1225 (1.7)	791 (1.1)	0.0511
Other psychosis	488 (0.7)	369 (0.5)	0.0214
PTSD	8538 (11.8)	10,131 (13.9)	−0.0656
Other anxiety	5493 (7.6)	4145 (5.7)	0.0746
Alcohol use disorder	3017 (4.2)	2934 (4.0)	0.0058
Substance use disorder	1550 (2.1)	1571 (2.2)	−0.0020
Sleep disorder	1186 (1.6)	1588 (2.2)	−0.0404
Arthritis	15,423 (21.2)	15,074 (20.8)	0.0118
Back pain	13,931 (19.2)	11,947 (16.4)	0.0714
Migraine	1133 (1.6)	1071 (1.5)	0.0070
Metastatic cancer	721 (1.0)	433 (0.6)	0.0447
Other cancer/any tumor	5934 (8.2)	4925 (6.8)	0.0528
Dementia	372 (0.5)	293 (0.4)	0.0161
Renal	2785 (3.8)	3029 (4.2)	−0.0171
Arrhythmias	4417 (6.1)	4286 (5.9)	0.0076
Congestive heart failure	2760 (3.8)	2819 (3.9)	−0.0042
Coagulopathy	659 (0.9)	663 (0.9)	−0.0006
Psychosis	7118 (9.8)	6925 (9.5)	0.0090
Hypertension	27,437 (37.8)	27,702 (38.1)	−0.0075
Myocardial infarction	920 (1.3)	893 (1.2)	0.0033
Rheumatoid arthritis	598 (0.8)	630 (0.9)	−0.0048
Non-alcohol drug abuse	1110 (1.5)	1151 (1.6)	−0.0046
Depression	10,552 (14.5)	11,722 (16.1)	−0.0447
Cerebrovascular disease	2127 (2.9)	1980 (2.7)	0.0122
Ischemic heart disease	8199 (11.3)	8074 (11.1)	0.0055
Valve disease	1070 (1.5)	1061 (1.5)	0.0010
Thyroid disease	2942 (4.1)	2903 (4.0)	0.0027
Other neurological	2854 (3.9)	2204 (3.0)	0.0488
CNS medications			
Opioid	29,718 (40.9)	27,311 (37.6)	0.0679
Non-opioid pain relievers	13,520 (18.6)	13,782 (19.0)	−0.0092
Anticonvulsants	13,272 (18.3)	11,956 (16.4)	0.0478
Anti-Parkinson's	1724 (2.4)	1609 (2.2)	0.0106
Antidepressants	21,593 (29.7)	22,250 (30.6)	−0.0197
Antipsychotics	5479 (7.5)	4794 (6.6)	0.0368
Lithium	639 (0.9)	487 (0.7)	0.0239
Other CNS medications	1976 (2.7)	1731 (2.4)	0.0214

The finding that suicide risk was significantly lower for days' supply of greater than 120 of 365 days across all monotherapies may be due to several reasons. Refills of insomnia medications typically require follow-up and continued low risk of misuse. A typical prescription of zolpidem and benzodiazepines for sleep are both for 30 days or less. Response to treatment may lag by several days or weeks. Similarly, extended days' supply of newly prescribed monotherapies for insomnia are likely associated with frequent follow-up and treatment response. That is, insomnia monotherapy days' supply beyond 120 of 365 days is likely associated with treatment adherence, which is associated with improved outcomes.

The findings of this study are an important contribution because of the widespread use of both off-label trazodone for the management of insomnia and the chronic use of insomnia medications indicated for only short-term use.[17,25,26]

Table 5 Selected Characteristics of Matched Sample of Zolpidem and Antihistamines

	Antihistamine	Zolpidem	Std.
	N = 74,229	*N* = 74,229	Diff.
	N (%)	*N* (%)	
Demographics			
Male	66,568 (89.7)	67,541 (91.0)	−0.044
Female	7661 (10.3)	6688 (9.0)	0.044
Age	58.1 (16.3)	58.2 (16.4)	−0.001
Age 18–49	20,517 (27.6)	20,608 (27.8)	−0.003
Age 50–60	15,357 (20.7)	14,990 (20.2)	0.012
Age 61 and older	38,355 (51.7)	38,631 (52.0)	−0.007
White	52,640 (70.9)	54,934 (74.0)	−0.069
african_american	13,753 (18.5)	10,924 (14.7)	0.103
race_NR	5018 (6.8)	5831 (7.9)	−0.042
race_OTHER	2818 (3.8)	2540 (3.4)	0.020
Percent disabled > 50%	20,468 (7.6)	20,926 (28.2)	−0.014
Percent disabled 30–40%	6541 (8.8)	6809 (9.2)	−0.013
Percent disabled 10–20%	8753 (11.8)	8821 (11.9)	−0.003
Comorbidity in 12 months prior to index date			
N of inpatient days (mean, Std.)	0.9 (3.5)	0.9 (3.8)	−0.0070
Gagne index (mean, Std.)	0.3 (1.2)	0.3 (1.2)	0.0089
Major depression	3590 (4.8)	3977 (5.4)	−0.0237
Bipolar disorder	2250 (3.0)	1982 (2.7)	0.0217
Schizophrenia	1028 (1.4)	820 (1.1)	0.0253
Other psychosis	456 (0.6)	386 (0.5)	0.0126
PTSD	9190 (12.4)	10,881 (14.7)	−0.0667
Other anxiety	4715 (6.4)	4411 (5.9)	0.0171
Alcohol use disorder	3349 (4.5)	3076 (4.1)	0.0181
Substance use disorder	2037 (2.7)	1662 (2.2)	0.0324
Sleep disorder	789 (1.1)	1217 (1.6)	−0.0500
Arthritis	16,559 (22.3)	15,388 (20.7)	0.0384
Back pain	11,862 (16.0)	12,369 (16.7)	−0.0185
Migraine	1036 (1.4)	1141 (1.5)	−0.0118
Metastatic cancer	268 (0.4)	419 (0.6)	−0.0300
Other cancer/any tumor	4496 (6.1)	4721 (6.4)	−0.0126
Dementia	194 (0.3)	293 (0.4)	−0.0233
Renal	3221 (4.3)	2876 (3.9)	0.0234
Arrhythmias	4005 (5.4)	4071 (5.5)	−0.0039
Congestive heart failure	2604 (3.5)	2685 (3.6)	−0.0059
Coagulopathy	682 (0.9)	643 (0.9)	0.0056
Psychosis	7382 (9.9)	7257 (9.8)	0.0057
Hypertension	28,270 (38.1)	27,047 (36.4)	0.0341
Myocardial infarction	728 (1.0)	855 (1.2)	−0.0167
Rheumatoid arthritis	675 (0.9)	614 (0.8)	0.0089
Non-alcohol drug abuse	1494 (2.0)	1216 (1.6)	0.0280
Depression	11,029 (14.9)	12,297 (16.6)	−0.0470
Cerebrovascular disease	1951 (2.6)	1949 (2.6)	0.0002
Ischemic heart disease	7277 (9.8)	7683 (10.4)	−0.0182
Valve disease	957 (1.3)	1012 (1.4)	−0.0065
Thyroid disease	2777 (3.7)	2816 (3.8)	−0.0028
Other neurological	1931 (2.6)	2235 (3.0)	−0.0248
CNS medications			
Opioid	27,629 (37.2)	27,733 (37.3)	−0.0029
Non-opioid pain relievers	15,561 (20.9)	13,974 (18.8)	0.0535
Anticonvulsants	11,931 (16.1)	12,203 (16.4)	−0.0099
Anti-Parkinson's	1110 (1.5)	1540 (2.1)	−0.0437
Antidepressants	21,483 (28.9)	23,257 (31.3)	−0.0521
Antipsychotics	5222 (7.0)	5036 (6.8)	0.0099
Lithium	574 (0.8)	513 (0.7)	0.0096
Other	1358 (1.8)	1728 (2.3)	−0.0349

Trazodone is the most commonly prescribed medication for insomnia[27]; its use for insomnia eclipses its use as an antidepressant. In our sample, the typical patient prescribed low-dose (< 200 mg) trazodone picked up more than six 30-day supplies during the 12-month observation period. Similarly, guidance for the use of zolpidem is that any sleep disturbance not resolved within 7 or 10 days be reevaluated for medical or psychiatric illness.[17,26] Yet, the typical patient with newly prescribed zolpidem picked up more than seven 30-day supplies over 12 months. Addressing questions of the appropriateness of extended prescribing are beyond the scope of this study, yet our findings suggest that suicide attempt risk is comparatively lower for patients who are successfully maintained on insomnia monotherapies beyond 120 days compared to those with supplies of 30 days or less, regardless of the specific medication.

Table 6 Adjusted Incidence of Suicide Attempts by Index Prescription: Zolpidem Versus Trazodone or Benzodiazepines or Antihistamines

Agents (drug class)	Subjects (*N*)	Events (*N*)	Person-years	Suicide attempts per 100,000 person-years	Adjusted HR suicide attempt (95% CI)
Cox proportional hazard model 1					
Trazodone	76,215	57	74,742	76.3	1.61 (1.07–2.43)
Zolpidem	76,215	38	74,625	50.9	
Cox proportional hazard model 2					
Benzodiazepines (temazepam, diazepam, or lorazepam)	72,691	49	70,254	69.7	1.33 (0.85–2.08)
Zolpidem	72,691	34	71,049	47.9	
Cox proportional hazard model 3					
Antihistamines (diphenhydramine, hydroxyzine)	74,311	57	73,138	77.9	1.37 (0.90–2.07)
Zolpidem	74,311	38	72,740	52.2	

Suicide attempt is a strong predictor of suicide[28] suggesting that avoiding use of low-dose trazodone for the treatment of insomnia might delay or deter progression to suicide. It is not clear, however, whether untreated insomnia presents a greater risk of suicidal thought and behavior than treatment with medications on a short- or long-term basis. Although not significantly associated with suicide attempt risk compared to zolpidem, benzodiazepines and sedating antihistamines are contraindicated in older adults.[10] The study subjects' older ages resemble that of the typical VA patient as well as 65% of Veterans who are suicide decedents (ages 50 and over).

The most recent clinical guidelines and evidence reviews strongly support non-pharmacologic interventions as first-line treatments for insomnia.[17,29,30] A recent clinical practice guideline by the American College of Physicians has unequivocally made cognitive-behavioral therapy for insomnia (CBT-I) the only first-line treatment for insomnia; pharmacotherapy is a suggested second-line treatment after failure or inadequate response to behavioral treatment.[30] That recommendation supports an earlier consensus statement from the British Association for Psychopharmacology in 2010.[29] Direct comparisons between pharmacotherapy and non-pharmacologic interventions were beyond the scope of this study.

Limitations

The diagnosis of PTSD was well-balanced in our propensity score models. Yet, the cohorts could not be balanced by nightmares and trazodone is first-line therapy for nightmares associated with PTSD. There is the possibility that the PTSD patients taking trazodone were more likely to be experiencing nightmares before the first prescription than those taking zolpidem. Similarly, healthcare that is supportive for suicidal patients but unmeasured in electronic medical records may include social support, active listening, and motivational interviewing. Yet, these limitations apply to any secondary data analysis.

Sedating antihistamines may be purchased without a prescription; however, all of the fills observed in this study were provided by VA pharmacies and received by patients. It is possible that some patients may have been using non-prescription insomnia medications at the same time as their VA-provided monotherapy against provider recommendations. Yet, this limitation is true of all secondary data analyses using VA prescription fill data.

At least one VA regional guideline recommended low-dose trazodone for the treatment of insomnia during the study period.[31] Yet, it is possible that these low doses represent suboptimal prescribing for depression. This is unlikely because trazodone is not a first-line therapy or depression and the VA pharmacy has access to the electronic medical record and is charged with checking prescriptions and addressing suboptimal doses prior to filling prescriptions.

After the period of observation of this study, zolpidem underwent a dose form change. The maximum dose was reduced from 10 to 5 mg for women after evidence emerged of auto crashes and other adverse events related to extended sedation. Yet, the effect of dosing on the comparative safety of zolpidem and suicide attempts is beyond the scope of this study.

Lapses in medication exposure are difficult to characterize as insomnia medications are typically prescribed "PRN" (as needed) such that 30 doses may cover more than 30 days. (For example, a 30-day supply of zolpidem in VA may contain only 20 doses.) Identifying the unique administration instructions for each fill was beyond the scope of our study. Yet, a strength of our data are that they include only medications filled by VA pharmacy and received by the patient.

Only subjects with a new fill of only one insomnia monotherapy (with no additional agents or cross-overs) were included. This approach isolates the comparative effects of monotherapies and is consistent with the drug safety literature, but a necessary limitation is that it does not allow comparisons of polypharmacy combinations or medication switching.

Finally, as with most observational studies of drug safety, a variety of other exposures and therapies may affect suicide attempt risk that are not controlled in this study such as loss of a job or relationship, cognitive behavioral therapy for insomnia, and exposure to any number of other pharmacotherapies possibly associated with suicide risk.

CONCLUSIONS

Nearly 350,000 Veterans started insomnia monotherapy in VA in 2011–2012, with suicide attempt rates reported at VA emergency departments and hospitals in excess of 50 attempts per 100,000 person-years within 12 months of the first fill. Compared to zolpidem, the incidence of suicide attempts was significantly higher among those with first fills of trazodone at doses indicated off-label for insomnia. These findings are among the first in support of the 2017 AASM clinical guidelines discouraging the use of trazodone for insomnia. To the best of our knowledge, this study is the first to describe the comparative safety of insomnia monotherapies and suicide attempts.

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Authors' Contributions *Jill E. Lavigne, Ph.D.,[1,9] drafted the manuscript and led the study, including identification of monotherapies and concomitant medications, interpretation of results, and drafting of the manuscript. Kwan Hur, Ph.D.,[2] designed the statistical analysis, guided the interpretation of results, and participated in the writing of the manuscript. Cathleen Kane, M.S.,[9] led the data management and implementation of the analyses and contributed to the interpretation of results. Anthony Au, Pharm.D.,[2] advised on the use of medications commonly used in VA to treat insomnia and central nervous system medications. Todd M. Bishop, Ph.D.,[3,9] contributed to the literature review and discussion. Wilfred R. Pigeon, Ph.D.,[3,9] contributed to the discussion section of the manuscript, participated in manuscript preparation, and supported acquisition of funding and other resources.*

Funding/Support *This work was supported by the Department of Veterans Affairs Office of Mental Health and Suicide Prevention with in-kind support provided by the Center of Excellence for Suicide Prevention at the VISN 2 Canandaigua VAMC.*

Compliance with Ethical Standards:

This study was approved by the VA VISN2 (Syracuse VA) Institutional Review Board.

Conflict of Interest: *Dr. Pigeon received speaker fees from Merck in 2015. All other authors have no conflicts of interest to report.*

Disclaimer: *The authors' views or opinions do not necessarily represent those of the Department of Veterans Affairs or the United States Government.*

REFERENCES

1. **Jansson-Frojmark M, Linton SJ.** The course of insomnia over one year: a longitudinal study in the general population of Sweden. Sleep. 2008;31(6):881–886.
2. **Ohayon MM, Reynolds CF.** Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification Sleep Disorders (ICSD). Sleep Med. 2009;10(9):952–960.
3. **Morin CM, Jarrin DC.** Insomnia and healthcare-seeking behaviors: impact of case definitions, comorbidity, sociodemographic, and cultural factors. Sleep Med. 2013;14(9):808–809.
4. **Fernandez-Mendoza J, Vgontzas AN, Bixler EO, et al.** Clinical and polysomnographic predictors of the natural history of poor sleep in the general population. Sleep. 2012;35(5):689–697.
5. **Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS.** Insomnia, depression, and physical disorder in late life: a 2-year longitudinal community study in Koreans. Sleep. 2009;32(0):1221–1228.
6. **Malik S, Kanwar A, Sim LA, et al.** The association between sleep disturbances and suicidal behaviors in patients with psychiatric diagnoses: a systematic review and meta-analysis. Syst Rev. 2014;3(1):18.
7. **Pigeon WR, Pinquart M, Conner K.** Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. J Clin Psychiatry. 2012;73(9):1160–1167.
8. **Pigeon WR, Bishop TM, Titus, CE.** The relationship of sleep disturbance to suicidal ideation, suicide attempts and suicide among adults: a systematic review. Psychiatr Ann. 2016;46(3):177–186.
9. **Lavigne JE, Au A, Jiang R, et al.** Utilization of prescription drugs with warnings of suicidal thoughts and behaviours in the USA and the US Department of Veterans Affairs, 2009. J Pharm HSR. 2012;3(3):157–163.
10. The American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2015;63(11):2227–2246.
11. **Carlsten A, Waern M, Holmgren P, Allebeck P.** The role of benzodiazepines in elderly suicides. Scand J Public Health. 2003;31(3):224–228.
12. **Brower KJ, McCammon RJ, Wojnar M, Ilgen MA, Wojnar J, Valenstein M.** Prescription sleeping pills, insomnia, and suicidality in the National Comorbidity Survey Replication. J Clin Psychiatry. 2011;72(4):515–521.
13. **Pigeon WR, Woosley JA, Lichstein KL.** Insomnia and hypnotic medications are associated with suicidal ideation in a community population. Arch Suicide Res. 2014;18(2):170–180.
14. **Kripke DF, Klauber MR, Wingard DL, et al.** Mortality hazard associated with prescription hypnotics. Biol Psychiatry. 1998;43:687–693.
15. **Allgulander C, Näsman P.** Regular hypnotic drug treatment in a sample of 32,679 Swedes: associations with somatic and mental health, inpatient psychiatric diagnoses, and suicide, derived with automated record-linkage. Psychosom Med. 1991;53:101–108
16. **Mallon L, Broman J-E, Hetta J.** Is usage of hypnotics associated with mortality? Sleep Med. 2009; 10:279–286
17. **Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL.** Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017, 13(2):307–49.
18. **Bertisch SM, Herzig SJ, Winkelman JW, Buettner C.** National use of prescription medications for insomnia: NHANES 1999-2010. Sleep. 2014;37(2):343–349.
19. **Greenbaum MA, Neylan TC, Rosen CS.** Symptom presentation and prescription of sleep medication for veterans with Posttraumatic Stress Disorder. J Nerv Ment Dis. 2017;205(2):112–118.
20. **McCall WV, Benca RM, Rosenquist PB, et al.** Hypnotic medications and suicide: risk, mechanism, mitigation, and the FDA. Am J Psychiatry. 2017;174(1):18–25.
21. **Hoffmire C, Stephens B, Morley S, Thompson C, Kemp J, Bossarte R.** VA Suicide Prevention Applications Network: a national health care system-based suicide event tracking system. Public Health Rep. 2016;131(6):816–821.
22. **Im JJ, Schachter, Schacter RD, Oliva EM, Henderson PT, Paik MC, Trafton JA**, for the PROGRES Team. Association of care practices with suicide attempts in US Veterans prescribed opioid medications for chronic pain management. J Gen Intern Med. (2015) 30: 979. https://doi.org/10.1007/s11606-015-3220-y.
23. **Austin PC.** Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011;10(2):150–61.
24. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res. 2011;46(3):399–424.
25. **Mendelson WB.** A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry. 2005;66(4):469–476.
26. **James SP, Mendelson WB.** The use of trazodone as a hypnotic: a critical review. J Clin Psychiatry. 2004;65(6):752–755.
27. **Greenblatt DJ, Harmatz JS, Shader RI.** Update on psychotropic drug prescribing in the United States: 2014–2015. J Clin Psychopharmacol. 2018;38(1):1–4
28. **Bostwick JM, Pabbati C, Geske JR, McKean AJ.** Suicide attempt as a risk factor for completed suicide: even more lethal than we knew. Am J Psychiatry. 2016;173(11):1094–100.
29. **Wilson SJ, Nutt DJ, Alford C, et al.** British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia,

parasomnias and circadian rhythm disorders. J Psychopharmacol. 2010;24(11):1577–1601.

30. **Quaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD.** Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016;165(2):125–133.

31. VISN 22 Insomnia Guidance. [Last updated 12/14/12]. Last accessed 3/8/19 from: http://vaww.gla.med.va.gov/Pharmacy/Guidelines/insomnia.htm