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SCIENTIFIC INVESTIGATIONS

Prescription medications for insomnia are associated with suicidal thoughts and behaviors in two nationally representative samples

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Study Objectives: Z-drugs (eszopiclone, zolpidem, and zaleplon) are commonly used for insomnia but are also associated with suicide risk. However, it is unclear if this association is unique to Z-drugs. Therefore, the present study estimated the associations between multiple prescription insomnia medications and suicidal thoughts and behaviors.

Methods: Data were acquired from the National Survey on Drug Use and Health for 2015–2018 and the National Health and Nutrition Examination Survey for 2005–2018. Samples were balanced on sociodemographic and mental health covariates using inverse probability of treatment weighting. Associations of Z-drugs, trazodone, and sedative benzodiazepines (temazepam, triazolam, flurazepam) with suicidal ideation, planning, and attempts were estimated using binomial logistic regression.

Results: In the National Survey on Drug Use and Health, Z-drugs were associated with suicidal ideation (odds ratio [OR], 1.32; 95% confidence interval [CI], 1.14–1.54]), suicide planning (OR, 1.44; 95% CI, 1.19–1.75), and suicide attempts (OR, 1.45; 95% CI, 1.13–1.86) after adjusting for age, sex, race/ethnicity, income, depression, illicit substance use, and the 6-item Kessler Psychological Distress Scale and World Health Organization Disability Assessment Schedule II scores. When analyses accounted for the same factors, sedative benzodiazepines were associated with suicide attempts (OR, 1.76; 95% CI, 1.06–2.87) but not suicidal ideation (OR, 1.37; 95% CI, 0.99–1.88) or suicide planning (OR, 1.39; 95% CI, 0.97–2.00). In the National Health and Nutrition Examination Survey, Z-drugs were associated with suicidal ideation (OR, 2.44; 95% CI, 1.41–4.22), as was trazodone (OR, 2.33; 95% CI, 1.45–3.75), after analyses adjusted for age, sex, race/ethnicity, and exposure to various psychotropic medications.

Conclusions: Multiple classes of prescription insomnia medications are associated with suicidal thinking and behaviors, even after analyses adjusted for measures of mental health.

Keywords: suicide, sleep, insomnia, NSDUH, NHANES, sedative hypnotics

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Z-drugs (eszopiclone, zolpidem, and zaleplon) are commonly used for insomnia but are also associated with suicide risk. However, it is unclear if this association is unique to Z-drugs, so the present study estimated the associations between multiple prescription insomnia medications and suicidal thoughts and behaviors.

Study Impact: In analyzing US epidemiological data, Z-drugs (eszopiclone, zaleplon, zolpidem), trazodone, and sedative benzodiazepines (triazolam, temazepam, flurazepam) were associated with suicidal ideation, planning, and attempts. This shows that the associations between prescription insomnia medications and suicidal thoughts and behaviors are not specific to a particular medication class.

INTRODUCTION

Sleep disorders increase the risk for suicide 2- to 3-fold[1,2] apart from depression and other psychiatric illnesses.[2,3] Insomnia in particular is linked to suicidal thoughts and behaviors (STBs) in university students,[4,5] active military and veterans,[6–8] and community-dwelling adults[9] in clinical and nationally representative population data.[10,11] Consequently, treating insomnia may reduce suicide risk. In the United States, insomnia is often treated pharmacologically; an estimated 3% of adults received a prescription medication for insomnia in the past month,[12] and the prevalence of such prescriptions has consistently increased since 1999.[13–17]

Nonbenzodiazepine sedative hypnotics ("Z-drugs": zolpidem, eszopiclone, and zaleplon) are among the most commonly prescribed medications for insomnia.[12] However, there is evidence that Z-drugs may also increase suicide risk. Data from the US National Comorbidity Survey Replication[18] demonstrate that Z-drug users are 2- to 3-fold more likely to report STBs after adjustment for insomnia, mental disorders, and chronic physical illness. Similarly, adverse event reports from the US Food & Drug Administration[19] show that zolpidem use was associated with suicide after analyses controlled for use of other prescription medications. Furthermore, a case-control study of Taiwanese adults[20] established a dose-response relationship

between Z-drug use and suicide risk, a finding that was later replicated in South Korea.[21] Based on this evidence, use of Z-drugs for insomnia may be ill-advised among high-risk individuals.[22]

It is unclear if the association between Z-drugs and suicide is based on a direct pharmacological effect or because Z-drug use is a proxy for insomnia. If the latter is true, then other hypnotic medications should also be associated with STBs. Unfortunately, the evidence on this point is minimal. Lavigne and colleagues[23] reported that patients were more likely to attempt suicide within 12 months of exposure to trazodone compared to Z-drugs but not when exposed to sedating antihistamines or benzodiazepines. However, there was no comparison with individuals not using a prescription sleep aid, so the general risk from using any sleep medication remains undefined.

Therefore, the present study used data from 2 nationally representative survey samples to determine how Z-drugs compared to other prescription sleep medications in relation with STBs. The hypothesis was that all prescription sleep aids investigated would be associated with STBs, and that the magnitude of these associations would be similar across medications. Where possible, analyses were adjusted for potential confounding factors, such as psychiatric illness, illicit substance use, or exposure to other psychotropic medications.

METHODS

Data sources

National Survey on Drug Use and Health

The US National Survey on Drug Use and Health (NSDUH)[24] is an annual survey conducted in all 50 states and the District of Columbia. Recruitment uses census data to divide each state into subregions of equal population size and selects random addresses from within these subregions. Up to 2 respondents from each address are selected to complete the survey via computer-assisted interviews. Survey responses are weighted to be representative of the civilian, noninstitutionalized population of the US aged 12 years and older.

Responses were compiled from 170,538 individuals surveyed between 2015 and 2018 who were 18 years or older and had complete data on the outcomes and treatments of interest. The outcome variables were suicidal thoughts and behaviors measured as yes/no responses to questions about suicidal ideation ("Have you seriously thought about killing yourself in the past year?"), suicide planning ("Have you made plans to kill yourself in the past year?"), and suicide attempts ("Have you attempted to kill yourself in the past year?"). Individuals without suicidal ideation were imputed as having no suicide planning or attempts, and those without suicide planning were imputed as having no attempts. The treatment variables were past-year use of a Z-drug (eszopiclone, zaleplon, zolpidem) or a sedative benzodiazepine (defined as triazolam, temazepam, and flurazepam). Data on use of other sedative medications (eg, trazodone, ramelteon, hydroxyzine) were not available. Age, sex, race, income, past-year occurrence of a depressive episode, past-year illicit substance use (use of an illegal substance or misuse of a prescription medication), past-year maximum score on the 6-item Kessler Psychological Distress Scale[25] (range, 0–24), and past-year maximum score on the World Health Organization Disability Assessment Schedule II[26] (range, 0–24) were extracted for use as covariates.

National Health and Nutrition Examination Survey

The US National Health and Nutrition Examination Survey (NHANES)[27] is also conducted annually in all 50 states and the District of Columbia. As with the NSDUH, the NHANES uses census data to select random addresses from within equally sized regions and then selects individuals at random from each address to be interviewed. Survey responses are weighted to be representative of the civilian, noninstitutionalized population of the US of all ages.

Responses were compiled from 36,308 individuals surveyed between 2005 and 2018 who were aged 18 years or older and had complete data on the outcome and treatments of interest. The primary outcome was suicidal ideation assessed using item 9 of the Patient Health Questionnaire-9,[28] which asks about the frequency of "thoughts that you would be better off dead or hurting yourself in some way" over the past 2 weeks. Responses include "not at all," "several days," "more than half the days," or "nearly every day," and were recoded as either "no suicidal ideation" for "not at all" and "suicidal ideation" for all other responses. The primary treatment was use of a Z-drug or trazodone in the past 30 days. Treatment was determined by participants listing all prescription medications taken in the last 30 days. Sleep duration (< 7 hours, 7–9 hours, > 9 hours) and use of selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, atypical antipsychotics, and mood stabilizers in the past 30 days were extracted for use as covariates.

Statistical analyses

Inverse probability of treatment weighting (IPTW) based on propensity scores was used to balance users vs nonusers for each treatment.[29] Under IPTW, treatment is modeled as a function of relevant covariates, and then each observation is weighted by the inverse probability of receiving the treatment actually received. The weighted sample then provides an unbiased estimate of the association between the treatment and the outcome of interest. For each medication, IPTW was applied twice: once to balance across a limited set of sociodemographic variables (model 1), and again to balance across a more comprehensive set of variables (model 2). These weights were then used in binomial logistic regression to estimate the association between the treatment and the relevant STB. The same variables used in IPTW were also included as covariates in regression models to adjust for any residual differences between treatment groups.

For the NSDUH, model 1 balanced and adjusted for age, sex, race/ethnicity, and income, while model 2 further balanced and adjusted for past-year depressive episodes, illicit substance use, maximum Kessler Psychological Distress Scale score, and maximum World Health Organization Disability Assessment Schedule II score. Each model then estimated the association between treatment with Z-drugs or sedative benzodiazepines and suicidal ideation, planning, and attempts. For the NHANES, model 1 balanced and adjusted for age, sex, and race/ethnicity, while model 2 further balanced and adjusted for sleep duration and use of selective serotonin reuptake inhibitors, serotonin and

Table 1—Diagnostics of the IPTW weighting process for the NSDUH and NHANES data.

			Weights			Max Standardized Difference*	
Dataset	**Model**	**Treatment**	**Mean**	**SD**	**Range**	**Unadjusted**	**Adjusted**
NSDUH	1	Z-drugs	1.0005	0.15	0.13–10.53	0.15	0.01
NSDUH	2	Z-drugs	0.9988	0.22	0.04–14.44	0.45	0.02
NSDUH	1	Sedative benzodiazepines	1.0002	0.07	0.09–12.98	0.14	0.02
NSDUH	2	Sedative benzodiazepines	0.9996	0.09	0.01–8.07	0.58	0.04
Dataset	**Model**	**Treatment**	**Mean**	**SD**	**Range**	**Unadjusted**	**Adjusted**
NHANES	1	Z-drugs	0.9991	0.12	0.36–10.29	0.17	0.04
NHANES	2	Z-drugs	0.9989	0.16	0.02–15.51	0.21	0.05
NHANES	1	Trazodone	0.9995	0.1	0.33–8.06	0.17	0.03
NHANES	2	Trazodone	0.9992	0.18	0.02–18.92	0.27	0.06

*For each IPTW iteration, the standardized differences between treatments for each covariate were reported before (unadjusted) and after (adjusted) IPTW weighting. These differences were converted to absolute values and the maximum difference is reported here. IPTW = inverse probability of treatment weighting, NHANES = National Health and Nutrition Examination Survey, NSDUH = National Survey on Drug Use and Health, SD = standard deviation.

Table 2—Prevalence of STBs among Z-drug and sedative benzodiazepine users in the NSDUH.

Past Year	**Suicidal Ideation**		**Suicidal Planning**		**Suicide Attempt**	
Z-Drug Use	**Mean (%)**	**95% CI**	**Mean (%)**	**95% CI**	**Mean (%)**	**95% CI**
No	3.95	3.82–4.08	1.12	1.06–1.17	0.43	0.40–0.47
Yes	8.98	8.16–9.80	3.29	2.83–3.74	1.31	0.98–1.64
Sedative Benzodiazepine Use	**Mean (%)**	**95% CI**	**Mean (%)**	**95% CI**	**Mean (%)**	**95% CI**
No	4.13	3.99–4.26	1.20	1.13–1.26	0.46	0.42–0.50
Yes	10.09	8.1–12.08	3.47	2.33–4.62	1.69	0.98–2.41

CI = confidence interval, NSDUH = National Survey on Drug Use and Health, STBs = suicidal thoughts and behaviors, Z-drugs = eszopiclone, zaleplon, and zolpidem.

norepinephrine reuptake inhibitors, atypical antipsychotics, and mood stabilizers. Each model then estimated the association between treatment with Z-drugs or trazodone and suicidal ideation. **Table 1** presents the diagnostic measures of the IPTW processing and shows an acceptable distribution of the weights (means close to 1, limited range of weights) and minimization of the covariate differences between treatment groups (standardized differences were less than 10%).

Data processing and statistical analyses were conducted in R (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria). IPTW was implemented using gradient-boosted modeling[30] in the WeightIt package[31] with the original survey sampling weights included. The final weights were then stabilized to reduce the influence of extreme observations. Diagnostics of the IPTW weights and covariate balance were generated using the "cobalt" package.[32] Associations estimated by logistic regression are reported as odds ratios (OR) and 95% confidence intervals (95% CI).

RESULTS

NSDUH

Within the past year, 4.5% of respondents used a Z-drug, 0.89% percent of individuals used a sedative benzodiazepine, and 0.2% used both. The 12-month prevalence of suicidal ideation, planning, and attempts was 4.18%, 1.22%, and 0.47%, respectively. However, STBs were 2- to 3-fold more common among individuals using Z-drugs or sedative benzodiazepines compared to nonusers (**Table 2**).

The associations of Z-drugs and sedative benzodiazepines with STBs are presented in **Table 3.** In model 1, Z-drug use was significantly associated with suicidal ideation (OR, 3.25; 95% CI, 2.94–3.59), planning (OR, 4.16; 95% CI, 3.54–4.89), and attempts (OR, 4.66; 95% CI, 3.73–5.81). These associations were attenuated but still significant in model 2. Sedative benzodiazepines were also associated with suicidal ideation (OR, 3.84; 95% CI, 3.18–4.65), planning (OR, 4.63; 95% CI, 3.54–5.04), and suicide attempts (OR, 6.22; 95% CI, 4.19–9.24) in model 1. However, in model 2 only the association with suicide attempts remained significant (OR, 1.75; 95% CI, 1.06–2.87).

NHANES

In the past 30 days, 1.65% of NHANES respondents used a Z-drug and 1.3% used trazodone. Unfortunately, no one in the sample used a sedative benzodiazepine (triazolam, temazepam, flurazepam), and the number of individuals who used other sedative agents (eg, hydroxyzine, doxepin, melatonin, ramelteon) was too small for analysis. Across respondents, the 2-week prevalence of suicidal ideation was 3.3% (95% CI, 3.0–3.5).

Table 3—Associations between Z-drug use, benzodiazepine use, and STBs in the NSDUH.

Past Year	Suicidal Ideation		Suicide Planning		Suicide Attempt	
Z-Drug Use	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Model 1*	3.25	2.94–3.59	4.16	3.54–4.89	4.66	3.73–5.81
Model 2†	1.32	1.14–1.54	1.44	1.19–1.75	1.45	1.13–1.86
Sedative Benzodiazepine Use	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Model 1	3.84	3.18–4.65	4.63	3.54–6.04	6.22	4.19–9.24
Model 2	1.37	0.99–1.88	1.39	0.97–2.00	1.75	1.06–2.87

*Model 1 weighted and adjusted for age, sex, race/ethnicity, and income. †Model 2 weighted and adjusted for age, sex, race/ethnicity, income, past-year depressive episode, past-year illicit substance use, past-year maximum Kessler Psychological Distress Scale score, and past-year maximum WHODAS score. CI = confidence interval, NSDUH = National Survey on Drug Use and Health, STBs = suicidal thoughts and behaviors, WHODAS = World Health Organization Disability Assessment Schedule II, Z-drugs = eszopiclone, zaleplon, and zolpidem.

Table 4—Associations between Z-drugs, trazodone, and suicidal ideation in the NHANES.

Past Year	Suicidal Ideation	
Z-Drug Use	**OR**	**95% CI**
Model 1*	3.87	2.40–6.25
Model 2†	2.44	1.41–4.22
Trazodone Use	**OR**	**95% CI**
Model 1	4.75	3.47–6.51
Model 2	2.33	1.45–3.75

*Model 1 adjusted for age, sex, and race/ethnicity. †Model 2 adjusted for age, sex, race/ethnicity, and exposure to SSRIs, SNRIs, atypical antipsychotics, and mood stabilizers. CI = confidence interval, NHANES = National Health and Nutrition Examination Survey, SNRI = serotonin and norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, Z-drugs = eszopiclone, zaleplon, and zolpidem.

However, suicidal ideation was more prevalent among those who used a Z-drug (users: 7.46% [95% CI, 4.58–10.33] vs nonusers: 3.19% [95% CI, 2.92–3.45]) or trazodone (users: 10.8% [95% CI, 7.23–14.38] vs nonusers: 3.16 [95% CI, 2.9–3.41]). The relationships between Z-drugs, trazodone, and suicidal ideation are presented in **Table 4.** Both medications were associated with suicidal ideation in model 1 (Z-drugs: OR, 3.87; 95% CI, 2.4–6.25; trazodone: OR, 4.75; 95% CI, 3.47–6.51), and these associations remained significant in model 2.

DISCUSSION

Based on data from 2 nationally representative samples, the present analyses show that individuals who were prescribed Z-drugs, trazodone, or sedative benzodiazepines were more likely to report STBs than nonusers. Moreover, these associations remained significant after the analyses accounted for sociodemographic factors and mental health confounders. Finally, the strength of these associations was similar across the medications studied. While these results support prior work linking Z-drugs to STBs, they expand this association to other prescription sleep medications, which indicates that insomnia may be an underlying factor in this relationship.

Suicide is a complex phenomenon characterized by interactions between remote and proximal risk factors that can promote suicidal thoughts and behaviors. Consequently, analyses of risk factors must account for other confounding variables, particularly mental health and personality traits that are strongly associated with suicide.[22] In the present study, adjusting for mental illness and personality disorders directly was impossible, as neither dataset included formal psychiatric diagnoses. However, the use of several proxy variables effectively accounted for these confounders. In the NSDUH, the data were balanced and adjusted on past-year depression, past-year illicit substance use, and the maximum Kessler Psychological Distress Scale and World Health Organization Disability Assessment Schedule II scores experienced in the prior year. These last 2 factors are worth discussing. The Kessler Psychological Distress Scale measured the severity of a respondent's mental distress by assessing 6 symptoms common to both anxiety and depression, while the World Health Organization Disability Assessment Schedule II measured how each respondent's mental distress interfered with life activities. Although these measures do not address specific mental illnesses, they capture the distress and impairment caused by these illnesses and are arguably more related to suicide risk than diagnostic classifications. However, even when these variables were accounted for, Z-drugs remained associated with STBs, which indicates that this relationship was not due to comorbid psychiatric illness. While accounting for mental health confounders eliminated the associations between sedative benzodiazepines and suicidal ideation/planning, the CIs suggest that this was likely a sample size limitation from accounting for so many variables on a rare outcome in a small number of people (0.89% of respondents). Ultimately, the similar magnitude of associations between sedative benzodiazepines and Z-drugs with STBs highlights a potential common effect underlying both treatments. In the case of the NHANES, the data were balanced on sleep duration and exposure to a range of psychotropic medications, including atypical antipsychotics, mood stabilizers, and antidepressants. Although these variables were a reasonable proxy for mental health outcomes given the limitations of the dataset, they were probably less comprehensive than the covariates used in the NSDUH and may explain the larger ORs reported for Z-drugs.

This study does not prove that the link between Z-drugs (or other sleep aids) and STBs is driven by underlying insomnia. However, it replicates other studies in support of this hypothesis. Kim and colleagues[33] reported that suicide attempts in individuals with depression peaked *just prior to initiation* of a zolpidem prescription and decreased thereafter. This timing implies that suicide risk peaks when insomnia is severe enough for an individual to seek pharmacological treatment and improves only when the medication alleviates their symptoms. Indeed, a randomized controlled trial[34] of zolpidem in suicidal depression showed improvement in suicidal ideation over placebo, indicating that effective treatment with a Z-drug may reduce suicide risk. Conversely, suicide risk may increase if the Z-drug fails to resolve the insomnia. In a 12-year retrospective study of > 1 million people, Cho and colleagues[35] concluded that prolonged zolpidem exposure (80 months or more) was associated with a 2-fold greater hazard of suicide. While sedative hypnotics often become maintenance medications for many individuals with chronic insomnia, such prolonged use may also reflect a failure to resolve the insomnia, which then exacerbates suicide risk. Again, these findings underscore that the association between Z-drugs and STBs is rooted in sleep distress: Effective resolution of sleep distress reduces suicidal ideation while prolonged sleep distress increases risk.

Three percent of American adults received a prescription sleep medication in the past month,[12] meaning nearly 10 million individuals experienced sleep distress sufficient to warrant a prescription and may be at increased risk for suicide. While concerning, this also highlights the role that physicians, behavioral sleep psychologists, and other clinicians can play in reducing suicide risk. As already mentioned, effective treatment of sleep distress using zolpidem can reduce suicidal ideation in at-risk populations,[34] so primary care and mental health providers should assess and treat sleep disorders to remission. Similarly, specialists in sleep medicine should screen for STBs and refer patients for appropriate mental health treatment.[36]

This study has several strengths. First, the use of 2 separate nationally representative samples adds to the strength and generalizability of the findings. Second, the use of IPTW to balance the data across treatment groups further enhances the strength and rigor of the results. In addition, the evaluation of multiple sleep medications allowed for more nuanced findings than previously reported. However, these findings also have limitations. First, the data are cross-sectional, and so causal inferences cannot be established. In addition, analyses were unable to adjust for specific sleep disorders, such as sleep apnea, nightmares, or other parasomnias. Further, STBs were assessed using either 3 self-report questions (NSDUH) or only 1 question (NHANES), none of which were drawn from validated suicide risk assessments. However, such questions have been used in prior studies of suicidality[37–39] and likely provide a reasonable estimate of STBs in the population.

CONCLUSIONS

Prior reports indicate that use of sleep medications, specifically Z-drugs, may increase the risk for suicide. However, underlying sleep distress may be the true driver of suicide risk, and effective treatment of this sleep distress may reduce risk. The present study analyzed data from 2 large, nationally representative samples to determine if the use of 3 classes of sleep medications was associated with STBs, as this would support an underlying common effect of sleep distress. Indeed, Z-drugs, trazodone, and sedative benzodiazepines were all associated with suicidal ideation, planning, and attempts, even when analyses accounted for multiple confounding factors. These results indicate that sleep distress, rather than a particular pharmacological agent, drives suicide risk and highlight the treatment of this distress to reduce risk.

ABBREVIATIONS

CI, confidence interval
IPTW, inverse probability of treatment weighting
NHANES, National Health and Nutrition Examination Survey
NSDUH, National Survey on Drug Use and Health
OR, odds ratio
STBs, suicidal thoughts and behaviors
Z-drugs, eszopiclone, zaleplon, and zolpidem

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