Prescription Sleeping Pills, Insomnia, and Suicidality in the National Comorbidity Survey Replication

Kirk J. Brower, MD; Ryan J. McCammon, AB; Marcin Wojnar, MD, PhD; Mark A. Ilgen, PhD; Julita Wojnar, MD, PhD; and Marcia Valenstein, MD

Background: Sedative-hypnotics have been associated with suicide attempts and completed suicides in a number of toxicologic, epidemiologic, and clinical studies. Most studies, however, inadequately address confounding by insomnia, which not only is a component of many mental health disorders that increase suicidal risk, but also is independently associated with suicidality. Moreover, the association of nonbenzodiazepine benzodiazepine receptor agonists (NBRAs) with suicidality has not been specifically studied in the US general population.

Objective: The purpose of this study was to assess the independent contribution of prescription sedative-hypnotic use, particularly the NBRAs, to suicidal ideas, plans, and suicide attempts in the general US population, after adjusting for insomnia and other confounding variables.

Method: Secondary analyses of National Comorbidity Survey Replication data for 5,692 household respondents interviewed between 2001 and 2003 assessed the cross-sectional relationships between prescription sedative-hypnotic use and suicidality in the previous 12 months. Multivariate, hierarchical logistic regression analyses controlled for symptoms of insomnia, past-year mental disorders, lifetime chronic physical illnesses, and demographic variables.

Results: Prescription sedative-hypnotic use in the past year was significantly associated with suicidal thoughts (adjusted odds ratio [AOR] = 2.2; $P < .001$), suicide plans (AOR = 1.9; $P < .01$), and suicide attempts (AOR = 3.4; $P < .01$). It was a stronger predictor than insomnia for both suicidal thoughts and suicide attempts and significantly improved the fit of these regression models (suicidal thoughts, $P < .01$; suicide attempts, $P < .05$).

Conclusions: Prescription sleeping pills, as exemplified by zolpidem and zaleplon, are associated with suicidal thoughts and suicide attempts during the past 12 months, but no evidence of causality was provided by this study. Clinical practitioners should recognize that patients taking similar types of sedative-hypnotics have a marker of increased risk for suicidality.

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Corresponding author: *Kirk J. Brower, MD, University of Michigan Department of Psychiatry, 4250 Plymouth Rd, SPC 5740, Ann Arbor, MI 48109 (kbrower@umich.edu).*

Sedative-hypnotics are commonly used as a means for both attempted and completed suicide as evidenced by emergency department statistics[1,2] and toxicologic analyses.[3–5] Apart from using sedative-hypnotics as a means for suicide, sedative-hypnotic users are also more likely to complete suicide by other methods.[6] This is not surprising given that sedative-hypnotics, especially those with high abuse potential, are disproportionately prescribed to patients with mental disorders,[7,8] a population that has a well-established increased risk for suicide.[9,10] Patients with chronic medical conditions or pain also have an increased risk for suicide[6] as well as for comorbid insomnia.[11] Finally, insomnia alone has been linked to suicide attempts and completed suicides independently of comorbid mental and physical illness.[12–15] Thus, the relationship between sedative-hypnotics and suicidality is complex and very likely reflects multiple causal pathways.

Several population-based studies have attempted to adjust in varying degrees for demographic variables, the presence of mental and physical disorders, and symptoms of insomnia using regression analyses and found that some forms of sedative-hypnotic medication were significantly associated with suicide. Allgulander and Näsman[7] analyzed data from 26,592 Swedes interviewed from 1975 to 1981 and reported that women who had used "hypnotic medication" regularly in the preceding 2 weeks were more likely to die by suicide by 1985 than women who had not. Kripke et al[16] in a population study of 1,099,830 Americans reported a relationship between the use of "prescription sleeping pills" in the 1 month prior to a 1982 baseline interview and suicide in the next 6 years for male users only. Depression, however, was not a covariate in this study, and the new-generation nonbenzodiazepine benzodiazepine receptor agonists (NBRAs) had not yet been introduced to the US market. A Canadian study[6] of older adults compared 602 cases of suicide between 1993 and 2002 to age- and sex-matched controls and found that adults who died of suicide were 4.5 times more likely to have used prescription benzodiazepines in the 30 days prior to suicide than were the controls in the same 30 days. Sedatives, barbiturates, and tranquilizers, however, were not significantly related to suicide in multivariate analyses. Finally, Mallon et al[17] investigated a sample of 3,523 Swedes in 1983 and reported that both male and female regular users of "sleep medication" were more likely than infrequent or nonusers to have committed suicide over a 20-year follow-up period; however, they did not control for alcohol consumption or abuse, nor did they distinguish between different types of sleeping pills.

In contrast to research on completed suicides, Liu[14] investigated suicidal thoughts and suicide attempts in a sample of Chinese adolescent students, but found no correlation between having taken hypnotic medication and suicidality. Neutel and Patten[18] compared the frequency of suicide attempts in Canadians who either were or were not prescribed benzodiazepines. In age-adjusted analyses, benzodiazepine use was significantly associated with suicide attempts that resulted in hospitalization. After multivariate adjustment, the strength of the association was strongest for men, respondents under 40 years of age, and those who were not taking antidepressants. Nevertheless, the investigators did not control for psychiatric diagnoses, and they concluded that their results were confounded by the indications for which the medications were prescribed. Finally, Goodwin and Hasin,[19] analyzing data from the first National Comorbidity Study of the US population in 1990–1992, compared prescription sedative users to nonusers and found significantly increased rates of both suicidal ideation and suicide attempts among the sedative users after adjusting for age, gender, race, marital status, education, and income. Some limitations of this study were (1) lifetime rates of sedative use and suicidality were analyzed, so they may not have necessarily overlapped in time; (2) comparisons between these 2 groups were not adjusted for psychiatric comorbidity or insomnia symptoms; and (3) the new-generation NBRA, zolpidem, was only introduced into the US market in 1992.

In summary, the existing literature of population-based studies suggests that sedative-hypnotic use is associated—albeit not necessarily causally—with completed suicides or suicide attempts among adults after controlling for other variables, but definitions of sedative-hypnotics vary from study to study, and the new-generation NBRAs were not included. NBRAs are worthy of investigation because they are increasingly being prescribed, are generally shorter-acting, may have less potential for rebound insomnia, and may have less impact on cognitive functioning than the older hypnotic sedatives.[20,21] The National Comorbidity Survey Replication (NCS-R) was conducted in the United States between 2001 and 2003 when new-generation sedative-hypnotics were available. Although previously published studies have employed this dataset to analyze separately the correlates of suicidal behaviors[22,23] or insomnia,[24] and we previously published a related study that found a relationship between suicidality and insomnia,[12] none of these prior studies examined the association between sedative-hypnotic use and suicidality. The purpose of this study, therefore, was to assess the possible independent contribution of sedative-hypnotic use to suicidal thoughts, plans, and attempts in the general US population, after adjusting for insomnia and other confounding variables.

METHOD

The NCS-R involved face-to-face interviews with 9,282 respondents, aged 18 years and over, from US households. Details of its methodology have been previously published.[25] The survey was administered in 2 parts, with Part II administered only to 5,692 of the 9,282 Part I respondents, including all Part I respondents with a lifetime mental disorder plus a probability subsample of other respondents. Through the use of survey weighting, both Parts I and II remain representative samples. The use of sedative-hypnotics was assessed by the question, "In the past 12 months, did you take any of the following types of prescription medications under the supervision of a doctor, for your emotions or nerves or your use of alcohol or drugs?" Following this lead-in question were several categories of medications, including "sleeping pills or other sedatives, (such as Ambien or Sonata)?" Possible responses were coded as yes/no, and 5.8% of respondents answered yes. This question was distinguished from the category of "tranquilizers (such as Xanax or Ativan)?" By contrast, only 3.9% answered yes to tranquilizer use. Only the question about "sleeping pills or other sedatives," which focused specifically on the new generation of NBRAs,[20,21] was used for this study.

The Composite International Diagnostic Interview[26] was used in the NCS-R to obtain information about psychiatric symptoms and determine *DSM-IV* psychiatric diagnoses. Three items that addressed suicidal thoughts, plans, and attempts within the past 12 months were "Have you ever seriously thought about committing suicide?" "Have you ever made a plan for committing suicide?" and "Have you ever attempted suicide?" Respondents who endorsed the ideation item were then asked to respond to the items regarding a suicide plan and attempt. Borges et al[22] previously used the NCS-R database to estimate 12-month prevalence rates of suicidal thoughts (2.6%), plans (0.7%), and attempts (0.4%) in the US population. Questions concerning insomnia were asked in Part II of the survey by asking the following 3 yes/no questions: "Did you have a period lasting two weeks or longer in the past 12 months when you had: (1) problems getting to sleep, when nearly every night it took you two hours or longer before you could fall asleep? (2) problems staying asleep, when you woke up nearly every night and took an hour or more to get back to sleep? and (3) problems waking too early, when you woke up nearly every morning at least two hours earlier than you wanted to?" If any 1 of these 3 sleep questions was answered affirmatively, then the respondent was classified as having insomnia for the purposes of these analyses. At least 1 of the insomnia symptoms was endorsed by 29.0% of the sample.

Our data analyses began by examining the unadjusted odds ratios (ORs) for suicidal thoughts, plans, and attempts in those with versus without sedative-hypnotic use. Next, multivariate logistic regression models were used to assess the relationship between sedative-hypnotic use in the past 12 months and suicidality, while controlling for demographic characteristics and other risk factors including 12-month diagnoses of mood, anxiety, and substance use disorders; lifetime chronic health conditions; and insomnia. Demographic variables included gender, age (18–44 vs > 44), race/ethnicity (non-Hispanic white vs other), marital status (never married vs previously married vs married/cohabitating), completed

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education (less than high school vs other), and poverty status (impoverished vs other). The following groups of mental disorders in the past 12 months were also included in the models: mood disorders (major depressive disorder, dysthymic disorder, and bipolar disorder, types I and II); anxiety disorders (panic disorder, agoraphobia, generalized anxiety disorder, social phobia, specific phobia, posttraumatic stress disorder, adult separation anxiety disorder); and substance use disorders (abuse or dependence on alcohol, amphetamines and similarly acting drugs, cannabis, cocaine, hallucinogens, inhalants, opioids, phencyclidine/ketamine, and sedative-hypnotics or anxiolytics). Finally, analyses were controlled for 11 lifetime physical health conditions—seasonal allergies, stroke, heart attack, heart disease, high blood pressure, asthma, lung disease, diabetes, ulcer, seizure disorders, and cancer—which were counted and scored from 0 to 4, with 4 = 4 or more conditions.

Three separate multivariate regression analyses were conducted, 1 for each suicidality variable: ideation, plans, and attempts. Regression analyses were conducted in hierarchical fashion, such that the use of sedative-hypnotics in the past 12 months (yes/no) was entered as the last variable by itself in the second block while all other variables were entered in the first block. This allowed us to test not only the independent significance of sedative-hypnotic use, but also its contribution to the overall model. Results are presented as adjusted ORs with 95% confidence intervals (CIs). The Taylor expansion method was used to estimate the standard errors of estimators based on the complex sample design with the SURVEYLOGISTIC and SURVEYFREQ procedures in SAS 9.1 (SAS Institute Inc; Cary, North Carolina). This study was reviewed and approved by the Institutional Review Board at the University of Michigan.

RESULTS

Table 1 compares prescription sedative-hypnotic users to nonusers in terms of unadjusted and adjusted ORs (95% CIs) for the 3 suicidality variables. Prior to adjusting for other predictors of suicidality, sedative-hypnotic users were 5.7, 7.6, and 9.3 times more likely than nonusers to have endorsed suicidal thoughts, plans, and attempts, respectively, in the past 12 months. After adjusting for all other variables, the ORs for sedative-hypnotic users decreased between 2- and 4-fold while remaining significant predictors of suicidality.

Table 2 shows the 3 sets of hierarchical logistic regression analyses predicting suicidal ideation, plans, and attempts and provides the adjusted ORs for all significant variables before and after entering sedative-hypnotic use in the past 12 months. For suicidal ideation and suicide attempts, adding sedative-hypnotic use significantly improved the fit of the models as indicated by the values for $\Delta \chi^2$. Although sedative-hypnotic users were nearly twice as likely as nonusers to have a plan for suicide, adding sedative-hypnotic use did not improve that model's fit. After sedative-hypnotic use was added to the final models, the strongest predictors for both suicidal ideation and suicide plans were mood disorders and anxiety disorders. By contrast, the strongest predictor for suicide attempts was age (18–44 > 45+ years), followed by mood and anxiety disorders and then sedative-hypnotic use (OR = 3.4 [1.6–7.2]). Insomnia predicted suicidal ideation and plans, but not suicide attempts, after sedative-hypnotic use was added to the final logistic regression models.

Table 1. Unadjusted and Adjusted Odds Ratios (95% CIs)[a] for Suicidality in the Past 12 Months as a Function of Prescription Sedative-Hypnotic Use in the Past 12 Months

	Sedative-Hypnotic Use[a]	
	Unadjusted OR	Adjusted OR[b]
Suicidal thoughts	5.7 (4.1–7.8)***	2.2 (1.5–3.3)***
Suicide plan	7.6 (4.8–11.9)***	1.9 (1.1–3.3)**
Suicide attempt	9.3 (5.9–14.8)***	3.4 (1.6–7.4)**

[a]Reference value for no use = 1.
[b]Odds ratios adjusted for sex, age, race-ethnicity, marital status, education, poverty status, 11 lifetime physical health conditions, mental disorders in the past 12 months (substance use disorders, anxiety disorders, and mood disorders), and insomnia.
**$P < .01$.
***$P < .001$.

Supplementary Analyses

Finally, a set of unplanned supplementary analyses was conducted to determine the approximate sample size needed to detect the association between sedative-hypnotics and suicide attempts in a randomized controlled trial for a population with insomnia. On the basis of the parameters derived from the logistic regression models presented in Table 2, we estimated that a required sample size of 1,068 participants (534 per group) would be necessary to detect a significant difference in suicide attempts between the sedative-hypnotic and placebo groups with 80% power and a 2-sided α value of .05.

DISCUSSION

The major finding of this study is that prescription sedative-hypnotic use in the past year was significantly associated with suicidal thoughts, plans, and suicide attempts in that year after adjusting for demographic characteristics, chronic health conditions, past-year psychiatric illness including depression and substance use disorders, and sleep disturbances for which the sedative-hypnotics may have been prescribed. Controlling for co-occurring insomnia and psychopathology is particularly important because of the possibility that a prescription for sedative-hypnotics may primarily serve as a marker for these problems and may not make its own contribution to the risk of suicidality. Our findings are not consistent with this hypothesis.

Whereas previously we have shown that symptoms of insomnia are associated with suicidal ideation, plans, and attempts,[12] the current study shows that sedative-hypnotic use was a stronger predictor than insomnia for suicidal ideation and suicide attempts and increased significantly the explanatory value of these models. When considered with previously published medical literature, the evidence suggests that sedative-hypnotic use is associated with suicidality,

Table 2. Multivariate Logistic Regression Models of Insomnia, Sedative-Hypnotic Use, and Suicidality in the National Comorbidity Survey Replication (n = 5,692)[a]

	Suicidal Ideation		Suicide Plan		Suicide Attempt	
Predictor	(1)[b]	(2)[b]	(1)[b]	(2)[b]	(1)[b]	(2)[b]
Age						
18–44 y	1.4 (1.0–1.9)	1.4 (1.0–2.0)*	3.4 (1.5–7.6)**	3.5 (1.6–8.0)**	6.4 (2.4–16.9)***	6.7 (2.5–18.2)***
45+ y	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)
Marital status						
Previously married	1.1 (0.8–1.6)	1.1 (0.7–1.6)	1.6 (0.8–3.0)	1.5 (0.7–2.8)	1.8 (0.8–4.1)	1.5 (0.6–3.6)
Never married	2.5 (1.7–3.6)***	2.6 (1.7–3.9)***	2.2 (1.0–5.3)	2.3 (1.0–5.5)	2.2 (1.1–4.4)*	2.4 (1.2–4.8)*
Married/cohabiting	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)
No. of chronic health conditions (0–4+)	1.1 (1.0–1.3)	1.1 (0.9–1.3)	1.3 (1.1–1.6)**	1.3 (1.1–1.6)**	1.4 (1.1–1.9)*	1.4 (1.0–1.9)*
Substance use disorders (12 mo)						
Substance use disorder	2.6 (1.5–4.4)***	2.5 (1.5–4.2)***	1.8 (0.7–4.5)	1.8 (0.7–4.4)	3.1 (1.2–8.3)*	3.0 (1.1–7.7)*
No substance use disorder	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)
Anxiety disorders (12 mo)						
Anxiety disorder	3.5 (2.5–4.8)***	3.4 (2.4–4.7)***	5.8 (2.6–12.9)***	5.6 (2.5–12.5)***	4.6 (2.1–9.9)***	4.3 (1.9–9.6)***
No anxiety disorder	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)
Mood disorders (12 mo)						
Mood disorder	5.8 (4.3–7.7)***	5.3 (4.0–7.2)***	9.5 (4.8–18.9)***	9.0 (4.4–18.2)***	6.7 (3.1–14.6)***	6.1 (2.7–13.4)***
No mood disorder	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)
Any insomnia symptom (12 mo)						
Any insomnia symptom	2.1 (1.6–2.8)***	1.9 (1.4–2.6)***	2.6 (1.4–4.9)**	2.4 (1.3–4.5)**	2.5 (1.2–5.2)*	2.1 (1.0–4.6)
No insomnia symptom	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)	1.0 (…)
Sleeping pills/sedatives (12 mo)						
Sleeping pill use		2.2 (1.5–3.3)***		1.9 (1.1–3.3)*		3.4 (1.6–7.2)**
No sleeping pill use		1.0 (…)		1.0 (…)		1.0 (…)
$\Delta \chi^2$		10.4**		2.4		5.9*

[a]Only significant variables are shown. Odds ratios were also adjusted for sex, race-ethnicity, education, and poverty status.
[b](1) and (2) designate models before and after adding sedative-hypnotic use, respectively.
*$P < .05$.
**$P < .01$.
***$P < .001$.

especially suicide attempts.[7,18,27] In contrast to the previous literature, the NCS-R is a population-based study of adults that was conducted recently enough to focus on the new-generation NBRAs (eg, zolpidem, zaleplon, eszopiclone). To our knowledge, all other published population-based studies that examined a relationship between sedative-hypnotics and suicidality focused specifically on benzodiazepines,[6,18] involved data collection when benzodiazepines were the primary sedative-hypnotics,[7,16,17,19] or did not study adults.[14]

There are several mechanisms by which sedative-hypnotics may be associated with suicidal thoughts, suicide attempts, and completed suicides. First, patients receiving prescriptions for either benzodiazepines or NBRAs have increased access to a method for making a suicide attempt.[3,28,29] Sedative-hypnotics, for example, were mentioned in 37% of visits to US emergency departments in 2006 for drug-related suicide attempts,[1] indicating a relative preference for this method. Accordingly, preferred methods of deliberate self-poisoning require consideration when deciding to prescribe sedative-hypnotics to potentially suicidal patients.[30] This is especially true among alcohol- or other drug-dependent patients who are likely to coingest sedative-hypnotics with other substances, thereby increasing the lethality of attempts.

Second, and very likely, an increased risk for suicidality may be attributable primarily to a premorbid psychiatric or chronic physical illness that is associated with insomnia, which then prompts a prescription for sedative-hypnotics. Even though this study controlled for some psychiatric disorders and chronic physical illnesses, it did not control for all disorders (eg, borderline personality disorder) or for the severity and duration of illnesses. In the present study, it is possible that, even in individuals with psychiatric conditions, sedative-hypnotics were prescribed to those with more severe symptoms or impairment. In one publication[27] involving a clinical sample, for example, the significant difference in suicide attempts between high-dose benzodiazepine users and nonusers disappeared when the analyses were adjusted for borderline personality disorder. Furthermore, our study did not control for adequate treatment of premorbid or comorbid disorders. Thus, alcoholism or depression that was never clinically diagnosed or misdiagnosed, and/or treated inappropriately with sedative-hypnotics for symptomatic insomnia without treating the underlying disorder,[31,32] is a strong possibility.

Third, insomnia symptoms in the absence of comorbid illness have been linked not only to suicidal thoughts, plans, and attempts,[12,14,33–37] but also to completed suicides.[13,15,38,39] These relationships have been reported from adolescence[14,15,37] to elderly status[13] and in both general[12–14,37,40] and clinical[33–36,38,39,41,42] populations. This study, however, found that prescription sleeping pills added significantly to the models for suicidal thoughts and suicide attempts, even after controlling for symptoms of insomnia.

Fourth, it is well accepted that sedative-hypnotics depress the central nervous system physiologically, which explains their therapeutic action. Whether they can also depress patients psychiatrically, however, is controversial. Using benzodiazepines as an example, evidence-based arguments

have been made in favor of depressogenic, antidepressant, and mood-neutral effects. It is beyond the scope of this article to cover this entire literature, and the reader is referred to several reviews.[43–45] Overall, there is general agreement that benzodiazepines alone are ineffective treatment for depression,[46] especially severe depression,[47] although solid evidence that their acute use by depressed individuals increases the risk for suicide is lacking.[44,48] Nevertheless, it is quite likely the case that some patients have emergent or exacerbated depression while taking sedative-hypnotics. Thus, the full spectrum of risks and benefits of sedative-hypnotics must always be taken into account when evaluating potentially suicidal patients,[49–51] and all patients receiving sedative-hypnotics should be periodically screened for suicidality.

Fifth, sedative-hypnotics (similar to alcohol) may lower the threshold for taking action on suicidal thoughts. In severe instances, both case reports and controlled studies indicate the potential for so-called paradoxical reactions to sedative-hypnotics, in which patients become disinhibited, impulsive, and aggressive,[52–54] although the rate appears to be low (1%–5%)[44,55] and some diagnostic groups may have a higher risk.[56,57] Nevertheless, such reactions might include suicide attempts.

Sixth, anxiety and agitation are diagnostic criteria for sedative-hypnotic withdrawal,[58] and a previous analysis of NCS-R data found that disorders characterized by severe anxiety/agitation predicted suicide attempts among individuals with suicidal ideation.[23] Interestingly, a case-control study[59] comparing psychiatric inpatients that either did or did not commit suicide during hospitalization found that reduction or withdrawal from benzodiazepines was more likely during the hospitalization for suicide victims. Although the NBRAs may have less potential for abuse than benzodiazepines,[60] dependence and withdrawal do occur.[61–63]

Study Limitations and Strengths

A number of limitations are noted. Importantly, this is a study of association, not causation. This study provides no evidence that sedative-hypnotics increase the risk of suicidality by causing either depression or paradoxical disinhibition, or via some other physiologic mechanism. Moreover, the study provides no evidence that decreasing prescription use of sedative-hypnotics would have any favorable effect on reducing suicidality. By adjusting for mood disorders, an attempt was made to estimate the unique contribution of sedative-hypnotics to suicidal risk, but if depression mediates the relationship between sedative-hypnotic use and suicidality, then adjusting for depression could lead to an underestimate of their contribution. Conversely, conducting the analysis without adjusting for depression would very likely overestimate the contribution of sedative-hypnotics to suicidal risk. Only a study design that allows causal inferences to be made, however, can determine the extent to which suicidal risk is underestimated or overestimated by these data.

A randomized controlled trial would be needed to establish causality between the use of sedative-hypnotics to treat insomnia and suicide attempts. However, this might not be feasible because a sample size of 1,068 participants would be required. Given this large sample size, it is understandable that prior randomized controlled trials of these medications, which were not designed to detect differences in suicide attempts, did not detect this association.

As with all studies that rely on interviews, the data obtained from respondents may be limited by accuracy of recall or their interpretation of the questions. For example, as part of answering the question on sleeping pills, respondents were asked if they took any types of medications for "your emotions or nerves or your use of alcohol or drugs." They did not respond directly to that question. Rather, a list of different types of prescription medications followed, to which they could answer yes or no. It is possible that respondents who were prescribed sleeping pills in the absence of emotional, nervous, or substance-induced problems might answer no to the question about sleeping pills. Consequently, those with primary insomnia may be underrepresented among those endorsing use of sleeping pills.

As a cross-sectional study, it is known that sedative-hypnotic use and suicidality occurred in the same 12-month period, but the temporal relationship between them during those 12 months is unknown. An argument might more strongly be made for a direct effect if the data showed that suicidality emerged de novo during sedative-hypnotic use, but this was not known. It is likely that, in some individuals, use of sedative-hypnotics followed suicidal thoughts or attempts. In addition, apart from the examples of zolpidem and zaleplon, which were cited by their brand names in the interview, no information about particular prescription sedative-hypnotics was obtained. Thus, respondents who took structural benzodiazepines such as temazepam or flurazepam for sleep problems would very likely be included in this sample of sedative users, making it impossible to know what proportions were taking NBRAs versus other sleeping pills. Similarly, no information about dose and duration of use was obtained. Indeed, answering "yes" or "no" to a question about medication use in the past 12 months is a crude measure.

Finally, as mentioned above, it was not possible to control for all variables that may have confounded the results such as severity or duration of co-occurring mental disorders. Nevertheless, a number of same-year psychiatric diagnoses and lifetime chronic physical illnesses were included as control variables in addition to demographic ones, and confounding by indication[18] was controlled by including insomnia in the multivariate analyses. Although the study cannot shed any light on possible mechanisms for the association found, it makes a unique contribution by extending a known association with suicidality for other sedative-hypnotics[6,7,16–19] to include the new-generation NBRAs[20,21] in a sample representative of the general US population.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Prescription sleeping pills, as exemplified by zolpidem and zaleplon, are associated with suicidal thoughts,

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plans, and suicide attempts during a 1-year period, but no evidence of causality was provided by this study. Clinical practitioners who care for patients taking similar types of sedative-hypnotics should recognize that such patients have a marker of increased risk and, therefore, should be assessed further for suicidality using evidence-based guidelines.[64] While the prescription of benzodiazepine and benzodiazepine-like sedative-hypnotics to patients already at risk for suicide should be cause for some concern, it does not mean that such prescribing is always contraindicated. Risks and benefits as applied to individual patients, not merely populations, must be weighed. Moreover, proper assessment and treatment of disorders that co-occur with insomnia, such as mood disorders and substance use disorders, are critical. Patients with such disorders may be more likely to communicate insomnia than other mental health symptoms and consequently be treated with sedative-hypnotics. Appropriate assessment is key in ensuring that opportunities to identify and appropriately treat underlying mental health disorders and to reduce suicide risks are not missed.

Drug names: alprazolam (Xanax and others), eszopiclone (Lunesta), flurazepam (Dalmane and others), lorazepam (Ativan and others), temazepam (Restoril), zaleplon (Sonata and others), zolpidem (Ambien, Edluar, and others).

Author affiliations: Department of Psychiatry, University of Michigan, Ann Arbor (all authors); VA Serious Mental Illness Treatment Research and Evaluation Center, Ann Arbor, Michigan (Mr McCammon and Drs Ilgen and Valenstein); and Department of Psychiatry, Medical University of Warsaw, Poland (Dr M. Wojnar).

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REFERENCES

1. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *Drug Abuse Warning Network, 2006: National Estimates of Drug-Related Emergency Department Visits*. Rockville, MD: DHHS Publication No. (SMA) 08-4339; 2008.
2. Weir P, Ardagh M. The epidemiology of deliberate self poisoning presenting to Christchurch Hospital Emergency Department. *N Z Med J*. 1998;111(1063):127–129.
3. Buckley NA, McManus PR. Changes in fatalities due to overdose of anxiolytic and sedative drugs in the UK (1983–1999). *Drug Saf*. 2004; 27(2):135–141.
4. Carlsten A, Waern M, Holmgren P, et al. The role of benzodiazepines in elderly suicides. *Scand J Public Health*. 2003;31(3):224–228.
5. Mendelson WB, Rich CL. Sedatives and suicide: the San Diego study. *Acta Psychiatr Scand*. 1993;88(5):337–341.
6. Voaklander DC, Rowe BH, Dryden DM, et al. Medical illness, medication use and suicide in seniors: a population-based case-control study. *J Epidemiol Community Health*. 2008;62(2):138–146.
7. 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(1):101–108.
8. Rasu RS, Shenolikar RA, Nahata MC, et al. Physician and patient factors associated with the prescribing of medications for sleep difficulties that are associated with high abuse potential or are expensive: an analysis of data from the National Ambulatory Medical Care Survey for 1996–2001. *Clin Ther*. 2005;27(12):1970–1979.
9. Bertolote JM, Fleischmann A, De Leo D, et al. Psychiatric diagnoses and suicide: revisiting the evidence. *Crisis*. 2004;25(4):147–155.
10. Harris EC, Barraclough B. Suicide as an outcome for mental disorders: a meta-analysis. *Br J Psychiatry*. 1997;170(3):205–228.
11. Stepanski EJ, Rybarczyk B. Emerging research on the treatment and etiology of secondary or comorbid insomnia. *Sleep Med Rev*. 2006;10(1):7–18.
12. Wojnar M, Ilgen MA, Wojnar J, et al. Sleep problems and suicidality in the National Comorbidity Survey Replication. *J Psychiatr Res*. 2009;43(5): 526–531.
13. Turvey CL, Conwell Y, Jones MP, et al. Risk factors for late-life suicide: a prospective, community-based study. *Am J Geriatr Psychiatry*. 2002;10(4): 398–406.
14. Liu X. Sleep and adolescent suicidal behavior. *Sleep*. 2004;27(7): 1351–1358.
15. Goldstein TR, Bridge JA, Brent DA. Sleep disturbance preceding completed suicide in adolescents. *J Consult Clin Psychol*. 2008;76(1):84–91.
16. Kripke DF, Klauber MR, Wingard DL, et al. Mortality hazard associated with prescription hypnotics. *Biol Psychiatry*. 1998;43(9):687–693.
17. Mallon L, Broman JE, Hetta J. Is usage of hypnotics associated with mortality? *Sleep Med*. 2009;10(3):279–286.
18. Neutel CI, Patten SB. Risk of suicide attempts after benzodiazepine and/or antidepressant use. *Ann Epidemiol*. 1997;7(8):568–574.
19. Goodwin RD, Hasin DS. Sedative use and misuse in the United States. *Addiction*. 2002;97(5):555–562.
20. Sanger DJ. The pharmacology and mechanisms of action of new generation, non-benzodiazepine hypnotic agents. *CNS Drugs*. 2004; 18(suppl 1):9–15, discussion 41, 43–45.
21. Siriwardena AN, Qureshi MZ, Dyas JV, et al. Magic bullets for insomnia? patients' use and experiences of newer (Z drugs) versus older (benzodiazepine) hypnotics for sleep problems in primary care. *Br J Gen Pract*. 2008;58(551):417–422.
22. Borges G, Angst J, Nock MK, et al. A risk index for 12-month suicide attempts in the National Comorbidity Survey Replication (NCS-R). *Psychol Med*. 2006;36(12):1747–1757.
23. Nock MK, Hwang I, Sampson NA, et al. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication [published online ahead of print March 31, 2009]. *Mol Psychiatry*.
24. Roth T, Jaeger S, Jin R, et al. Sleep problems, comorbid mental disorders, and role functioning in the national comorbidity survey replication. *Biol Psychiatry*. 2006;60(12):1364–1371.
25. Kessler RC, Berglund P, Chiu WT, et al. The US National Comorbidity Survey Replication (NCS-R): design and field procedures. *Int J Methods Psychiatr Res*. 2004;13(2):69–92.
26. Kessler RC, Ustün TB. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res*. 2004;13(2):93–121.
27. Lekka NP, Paschalis C, Beratis S. Suicide attempts in high-dose benzodiazepine users. *Compr Psychiatry*. 2002;43(6):438–442.
28. Marzuk PM, Leon AC, Tardiff K, et al. The effect of access to lethal methods of injury on suicide rates. *Arch Gen Psychiatry*. 1992;49(6):451–458.
29. Cantor CH, Baume PJ. Access to methods of suicide: what impact? *Aust N Z J Psychiatry*. 1998;32(1):8–14.
30. Forrester MB. Eszopiclone ingestions reported to Texas poison control centers, 2005 2006. *Hum Exp Toxicol*. 2007;26(10):795–800.
31. Isacsson G, Holmgren P, Druid H, et al. Psychotropics and suicide prevention. Implications from toxicological screening of 5281 suicides in Sweden 1992–1994. *Br J Psychiatry*. 1999;174(3):259–265.
32. Lecrubier Y. Widespread underrecognition and undertreatment of anxiety and mood disorders: results from 3 European studies. *J Clin Psychiatry*. 2007;68(suppl 2):36–41.
33. Hall RC, Platt DE, Hall RC. Suicide risk assessment: a review of risk factors for suicide in 100 patients who made severe suicide attempts: evaluation of suicide risk in a time of managed care. *Psychosomatics*. 1999;40(1):18–27.
34. Chellappa SL, Araújo JF. Sleep disorders and suicidal ideation in patients with depressive disorder. *Psychiatry Res*. 2007;153(2):131–136.
35. Ağargün MY, Kara H, Solmaz M. Sleep disturbances and suicidal behavior in patients with major depression. *J Clin Psychiatry*. 1997;58(6):249–251.
36. Agargun MY, Besiroglu L, Cilli AS, et al. Nightmares, suicide attempts, and melancholic features in patients with unipolar major depression. *J Affect Disord*. 2007;98(3):267–270.
37. Nrugham L, Larsson B, Sund AM. Specific depressive symptoms and disorders as associates and predictors of suicidal acts across adolescence. *J Affect Disord*. 2008;111(1):83–93.

38. Fawcett J, Scheftner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. *Am J Psychiatry*. 1990;147(9):1189–1194.
39. McGirr A, Renaud J, Seguin M, et al. An examination of DSM-IV depressive symptoms and risk for suicide completion in major depressive disorder: a psychological autopsy study. *J Affect Disord*. 2007;97(1-3): 203–209.
40. Tanskanen A, Tuomilehto J, Viinamäki H, et al. Nightmares as predictors of suicide. *Sleep*. 2001;24(7):844–847.
41. Bernert RA, Joiner TEJ Jr, Cukrowicz KC, et al. Suicidality and sleep disturbances. *Sleep*. 2005;28(9):1135–1141.
42. Sjöström N, Waern M, Hetta J. Nightmares and sleep disturbances in relation to suicidality in suicide attempters. *Sleep*. 2007;30(1):91–95.
43. Kripke DF. Greater incidence of depression with hypnotic use than with placebo. *BMC Psychiatry*. 2007;7(1):42.
44. Youssef NA, Rich CL. Does acute treatment with sedatives/hypnotics for anxiety in depressed patients affect suicide risk? a literature review. *Ann Clin Psychiatry*. 2008;20(3):157–169.
45. Smith BD, Salzman C. Do benzodiazepines cause depression? *Hosp Community Psychiatry*. 1991;42(11):1101–1102.
46. Johnson DA. The use of benzodiazepines in depression. *Br J Clin Pharmacol*. 1985;19(suppl 1):31S–35S.
47. Birkenhäger TK, Moleman P, Nolen WA. Benzodiazepines for depression? a review of the literature. *Int Clin Psychopharmacol*. 1995;10(3):181–195.
48. Jonas JM, Hearron AE Jr. Alprazolam and suicidal ideation: a meta-analysis of controlled trials in the treatment of depression. *J Clin Psychopharmacol*. 1996;16(3):208–211.
49. Kripke DF. Chronic hypnotic use: deadly risks, doubtful benefit. *Sleep Med Rev*. 2000;4(1):5–20.
50. Posternak MA, Mueller TI. Assessing the risks and benefits of benzodiazepines for anxiety disorders in patients with a history of substance abuse or dependence. *Am J Addict*. 2001;10(1):48–68.
51. Glass J, Lanctôt KL, Herrmann N, et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ*. 2005; 331(7526):1169.
52. Berman ME, Jones GD, McCloskey MS. The effects of diazepam on human self-aggressive behavior. *Psychopharmacology (Berl)*. 2005; 178(1):100–106.
53. Bramness JG, Skurtveit S, Mørland J. Flunitrazepam: psychomotor impairment, agitation and paradoxical reactions. *Forensic Sci Int*. 2006; 159(2–3):83–91.
54. Rothschild AJ, Shindul-Rothschild, Viguera A, et al. Comparison of the frequency of behavioral disinhibition on alprazolam, clonazepam, or no benzodiazepine in hospitalized psychiatric patients. *J Clin Psychopharmacol*. 2000;20(1):7–11.
55. Dietch JT, Jennings RK. Aggressive dyscontrol in patients treated with benzodiazepines. *J Clin Psychiatry*. 1988;49(5):184–188.
56. Bond AJ, Curran HV, Bruce MS, et al. Behavioural aggression in panic disorder after 8 weeks' treatment with alprazolam. *J Affect Disord*. 1995; 35(3):117–123.
57. Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder: alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. *Arch Gen Psychiatry*. 1988;45(2):111–119.
58. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
59. Gaertner I, Gilot C, Heidrich P, et al. A case control study on psychopharmacotherapy before suicide committed by 61 psychiatric inpatients. *Pharmacopsychiatry*. 2002;35(2):37–43.
60. Hajak G, Müller WE, Wittchen HU, et al. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addiction*. 2003;98(10):1371–1378.
61. Victorri-Vigneau C, Dailly E, Veyrac G, et al. Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *Br J Clin Pharmacol*. 2007;64(2):198–209.
62. Griffiths RR, Johnson MW. Relative abuse liability of hypnotic drugs: a conceptual framework and algorithm for differentiating among compounds. *J Clin Psychiatry*. 2005;66(suppl 9):31–41.
63. Neale G, Smith AJ. Self-harm and suicide associated with benzodiazepine usage. *Br J Gen Pract*. 2007;57(538):407–408.
64. American Psychiatric Association. *Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors*. *Am J Psychiatry*. 2003; 160(suppl 11):1–60.