

Association of sedative–hypnotic medications with suicidality

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Evaluation of: 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* DOI: 10.4088/JCP.09m05484gry (2010) (Epub ahead of print).

Several studies have investigated the association between sedative–hypnotics and suicidality, as such medications not only serve as a method for suicide, but are also involved in the usual options for treating psychiatric and medico–surgical disorders. According to population-based studies in Europe, Asia and the USA, sedative–hypnotic medications were significantly associated with suicide. However, these studies failed to address psychiatric comorbidities, new hypnotic medications, such as zolpidem, and the specific times at which such medications were used. Recently, Brower and colleagues have investigated the association of the prescription of sedative–hypnotic drugs with suicidality, to determine whether such medications were associated with suicidal ideation, suicide plans and suicide attempts in a large-cohort sample. They found that the use of sedative–hypnotic medications was significantly associated with suicidal ideation, suicide plans and suicide attempts. In addition, the use of sedative–hypnotic medications was a stronger predictor than insomnia of both suicidal ideation and suicide attempts. This article will discuss the relationship between prescription of sedative–hypnotic medications and suicide in the context of the potential limitations and significance of this recent research.

KEYWORDS: comorbidity • predictor • risk • sedative–hypnotics • suicide

Suicide is the act of deliberately killing one's self. Although other clinical factors have also been involved in attempted and completed suicides, major risk factors for suicide include mental disorders, such as major depressive disorder [1–3], bipolar disorder [3–5], personality disorders [6], alcohol dependence [3,7] and schizophrenia [8–10], as well as certain physical illnesses, such as neurological disorders, cancer and HIV infection [11–14].

Based on current trends across the world, the WHO has estimated that worldwide approximately 1.5 million people will complete suicide, and that 10–20-times more people will attempt suicide [10]. This observation corresponds to data demonstrating that one completed suicide may occur every 20 s, and that one suicide attempt may occur every 1–2 s. Of the various methods of suicide, overdosing on medications is one of the most popular. According to the WHO/EURO Multicenter Study on Suicidal Behavior, the most frequent suicide method was overdosing, whereas cutting and hanging occurred more rarely, and

alcohol consumption was associated with 15% of attempts [15]. This trend was also replicated in a large cohort study in Sweden [16]. In the study of 48,649 people admitted to the hospital from 1973 to 1982 following a suicide attempt, 5740 (11.8%) subsequently completed suicide during the 20–30 years of follow-up. The most common method of attempted suicide was poisoning (84% of those who attempted suicide) [16]. In both this and the WHO/EURO Multicenter Study, sedative–hypnotic medications (SHMs) represented almost two-thirds of all the drugs taken, followed by meprobamate, carbamazepine and antidepressants [15]. According to previous suicide studies, SHMs accounted for approximately 20% of the medications taken by patients who attempted suicide [17]. In addition, patients receiving SHMs were more likely to complete suicide than other patients and were more likely to repeat suicide attempts [18]. Interestingly, a systematic review found that the question of whether the use of sedative–hypnotics prevented or provoked

suicide in anxious depressed patients could not be answered definitively with the clinical data currently available [19,20]. However, the potential risks of prescribing SHMs for depressed patients who may be suicidal are serious. The researchers suggested that alternatives to SHMs should be used if early adjunctive treatment for anxiety in depressed patients is thought to be indicated in routine clinical practice [19].

Recently, Brower *et al.* investigated the independent contribution of prescription SHM use, particularly the nonbenzodiazepine benzodiazepine receptor agonists, to suicidal ideation, plans and attempts in the general US population after adjusting for insomnia and other confounding variables [21]. The results demonstrated that the use of SHMs during the previous 12 months may have been associated with increased suicidal ideation and attempts [21]. This article will discuss the relationship between the prescription of SHMs and suicide-related behaviors, and also address the potential limitations and significance of this research.

Summary of methods & results

The study was a secondary analysis of the National Comorbidity Survey Replication data involving 5692 household respondents interviewed between 2001 and 2003. The authors investigated cross-sectional relationships between the use of SHMs and suicidality during the previous 12 months among these individuals.

Insomnia, experiencing mental disorders during the previous year, lifetime chronic physical illnesses and demographic variables were also controlled for by multivariate and hierarchical regression analyses. According to the results, those who used SHMs during the past 12 months were more likely than nonusers to report suicidal ideation, suicide plans and suicide attempts, although the odds ratios (ORs) were substantially decreased for SHMs users after adjustment of covariates, as presented in FIGURE 1. In addition, SHM use was a stronger predictor of both suicidal thoughts and suicide attempts than insomnia.

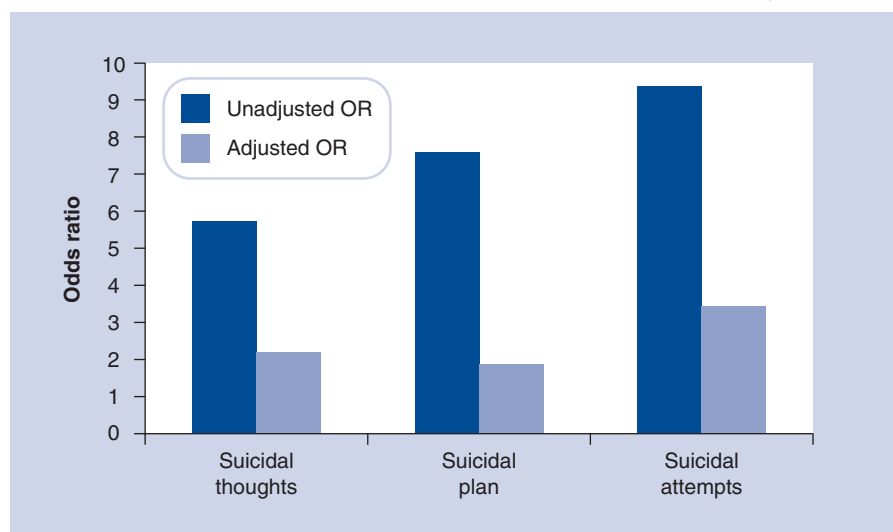


Figure 1. The odds ratios for suicidality in the past 12 months in relation to the use of sedative-hypnotic medication in the past 12 months.

OR: Odds ratio.

Data taken from [8].

Discussion

The study conducted by Brower and colleagues [21] has clear strengths and limitations. Most of the previous similar studies had methodological problems, including lack of data on newly available hypnotics and lifetime use of SHMs, as well as not controlling for comorbid medical/psychiatric disorders, which may be one of the factors confounding the association of SHMs with suicide. However, the study by Brower and colleagues substantially overcame these shortcomings by including nonbenzodiazepine benzodiazepine receptor agonists (not only including benzodiazepines, as in most previous studies) and new hypnotics, such as zolpidem, which was launched in the US market in 1992, controlling for comorbid mental/medical disorders (including insomnia), and analyzing a relatively large patient population. Controlling for insomnia and psychiatric disorders in the data analysis is of particular importance given that the prescription of SHMs may be a clinical marker of the existence of certain psychopathologies. In addition, this study found that SHM use was a stronger predictor than insomnia of suicidal thought and attempts, and that the inclusion of SHM use increased the fitness of the model predicting suicidal actions. Indeed, insomnia was significantly related to suicidality, including suicidal ideation, plans and attempts, by an approximately twofold increase when this variable was included in the model [22]. In particular, patients with two or more types of symptoms of sleep disturbances were approximately three-times more likely to report suicide attempts than those with no sleep-disturbance complaints, underscoring the important role of insomnia in suicide-related actions [22]. Moreover, insomnia was found to increase the risk for suicide-related actions, regardless of the presence of major psychiatric disorders such as mood disorders. Another favorable aspect of this study was its extensive control of major psychiatric disorders, such as mood disorders and substance-related disorders. As interactions among major psychotropics, such as antidepressants, SHMs and

alcohol, may trigger impulsive behavior, the combined use of these medications could potentially be associated with an increased risk for suicidal actions. Thus, controlling for insomnia, psychotropics and psychiatric disorders is crucial for evaluations of the association of SHM use with suicide.

Limitations of this study included the focus on SHM use during the previous 12 months without collecting specific information regarding the exact temporal relationship between suicidality and the use of SHMs. Indeed, the precise causal relationship between SHM use and suicide-related actions could not be determined from the study (i.e., no conclusions regarding the direct relationship between current use and suicide-related actions could be drawn). Although the authors controlled for a substantial number of clinical variables that may have affected the outcome, such as

psychiatric disorders (i.e., severity and duration), the inclusion of all confounding factors was not possible. No particular information regarding the use of SHMs (i.e., clarification of the definition of SHMs) was provided in the study; the authors only presented the question used to gather these data: “did you take SHMs, such as zolpidem or zaleplon?”. In addition, patients suffering from primary insomnia in the absence of emotional problems, nervousness or alcohol-induced problems may have been underrepresented because the question about sleeping pills related their use to ‘reasons of emotion, nervousness or alcohol-induced problems’. A recent case-controlled study of suicide among elderly individuals (aged ≥ 65 years) involved the collection of detailed information on 85 cases via interviews by a psychiatrist [23]. A population-based comparison group ($n = 153$) was also created and interviewed personally. Primary care and psychiatric records were reviewed for both target and comparison individuals. All available information was used to determine past-month mental disorders, in accordance with the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders [23]. According to the crude analysis in this study, antidepressants, antipsychotics, sedatives and hypnotics were associated with increased suicide risk [23]. After adjustment for mood and anxiety disorders, neither antidepressants nor antipsychotics were associated with suicide [23]. However, sedative treatment was associated with an almost 14-fold increase in suicide risk according to the crude analyses, and remained an independent risk factor for suicide even after adjustment for all psychiatric disorders [23]. Having a current prescription for a hypnotic was associated with a four-fold increase in suicide risk in the adjusted model [23]. Thus, information about the individual prescription of SHMs may also improve study design over that used in the current study. Finally, recall bias should also be considered.

Expert commentary & five-year view

Similarly, several studies investigated the types of psychotropic drugs associated with increased morbidity in patients who enacted an intentional drug overdose (IDO) [17,18]. Recently, a cohort study analyzed a data set of 1974 patients consecutively hospitalized for IDO [24]. According to this study, nearly all of the patients had ingested psychotropic medications during the IDO (88.4%); the most frequently ingested drugs were benzodiazepines (71.6%), whereas serious events were more strongly associated with tricyclic antidepressants and lithium. A Virginia Suicide Study conducted from 2003 to 2006 identified 17,897 nonfatal suicide attempts and 3351 completed suicides and found more than 12 nonfatal poison-related suicide attempts and more than two poison-related

completed suicides per day [25]. Poisoning was the most common method used in nonfatal attempts (82.3%) and the third most common method in completed suicides (17.4%). The rate (per 100,000 persons) of attempted suicide via poisoning (49.0) was nearly 26-times greater than the rate of completed suicides via poisoning (1.9).

These results also replicated the finding that a particular class of SHMs may increase the risk of engaging in suicide-related actions. Given that the most common method of attempted suicide was drug poisoning, and given that SHMs have been the most frequently used means of overdosing, restricting accessibility to such medications may be a possible solution to increased suicide rates.

Interestingly, several previous studies have validated the potential effectiveness of this approach. Restriction of access to lethal methods, including legislation regulating pharmaceuticals and gun ownership, has significantly reduced the suicide rate in Japan and the USA, respectively. According to a study on prescription monitoring and an information campaign in Sweden [26], anxiolytic–hypnotic drug abuse and suicide were greatly reduced by restricting the prescription of anxiolytic–hypnotic drugs. However, this strategy may or may not be accompanied by an increase in suicide by other means.

Targeted drug-information campaigns may assist in changing the prescription patterns for SHMs, which may eventually lead to decreases in suicide-related actions. However, suicide methods vary widely in different cultural settings. It would be of interest to determine whether SHMs were associated with increased suicide risk, even in settings in which other suicide methods, such as hanging or shooting, are more common [23]. It should also be noted that the identification of the prevalent religious domination in different countries may illuminate the role of cultural differences in suicide-related actions.

A recent study of suicide in elderly individuals associated sedatives and hypnotics to increased risk of suicide later in life [23]. According to the WHO report, the rapid growth in the oldest groups of the older population is of special relevance to public policy. In most parts of the world, the 80-and-over age group is growing faster than any other and is expected to continue as the fastest-growing segment of the population for at least the next 50 years. A careful evaluation of suicide risk should be performed when an elderly person presents with an apparent need for medications that control anxiety and insomnia.

Finally, a recent primary-care-setting observational study involved the prescription of zolpidem for 2690 patients experiencing chronic insomnia and included an ‘as-needed’ treatment

Key issues

- Brower and colleagues have found that the use of sedative–hypnotic medications was significantly associated with suicidal ideation, suicidal plan and suicidal attempt.
- In addition, the use of sedative–hypnotics was a stronger predictor than insomnia for both suicidal thoughts and suicide attempts.
- Control of insomnia and psychiatric disorders is important since prescription of sedative–hypnotics may be one of the clinical markers for the existence of certain psychopathologies.
- Advanced methodology will be needed to achieve better understanding of the exact role of sedative–hypnotics in association with suicide-related actions.

option. The average number of zolpidem tablets taken decreased by 28%, without any significant impact on treatment efficacy [27]. Other studies have also replicated that patients with chronic insomnia are capable of limiting their hypnotic intake, demonstrating no tendency to increase intake over time, and even demonstrating a trend toward a decreased use of medication [28]. These results convey important information to clinicians in that appropriate assessment for the use of such medications is crucial in identifying patients with a potential risk for suicide-related actions.

Based on currently available data, we have identified several intriguing and important clinical factors related to the increased risk of suicide-related actions. Although they require more specific elaboration, understanding such clinical factors and the mechanisms associated with the use of SHMs and suicidal ideation,

plans and attempts is important for the development of future treatment options and the prevention of suicide. The preparation of evidence-based treatment guidelines, practical strategies and public policies could contribute to the more prudent use of these medications in clinical practice.

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Website

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