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ORIGINAL ARTICLE

Association Between Zolpidem and Suicide: A Nationwide Population-Based Case-Control Study

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Abstract

Objective: To evaluate the association between zolpidem and the risk of suicide.

Patients and Methods: In this nationwide case-control study, the case group comprised 2199 people who committed suicide or were hospitalized due to suicide attempt between January 1, 2002, and December 31, 2011. To create a control group, we randomly selected 10 people matched to each case according to age, sex, urbanization, and occupation. We measured the risk of suicide/suicide attempt in association with zolpidem exposure by using adjusted odds ratios (ORs) and assessed the dose-response effect of zolpidem.

Results: After adjustment for potential confounders such as the comorbidities of schizophrenia, major depression, bipolar disorder, anxiety, insomnia, substance use, and other mental disorders, the Charlson comorbidity index, and use of benzodiazepine or antidepressants, zolpidem exposure was found to be significantly associated with the risk of suicide/suicide attempt with an OR of 2.08 (95% CIs, 1.83-2.36). The risk increased with the level of zolpidem use. The ORs (95% CIs) for cumulative defined daily doses of less than 90, 90 to 179, and 180 mg or more were 1.90 (1.65-2.18), 2.07 (1.59-2.67), and 2.81 (2.33-3.38), respectively (for trend, $P<.001$). Subgroup analyses showed that the exposure to zolpidem consistently increased the OR in different age groups, sex, urbanization level, occupation, mental disorders, and Charlson comorbidity index levels and in groups of people with or without the presence of insomnia.

Conclusion: This study demonstrated a significant association between using zolpidem and suicide or suicide attempt in people with or without comorbid psychiatric illnesses (all $P<.05$).

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Zolpidem is a nonbenzodiazepine hypnotic agent for initiating and maintaining sleep and is as effective as benzodiazepine (BZD) class drugs. Because of zolpidem's good effect and relatively milder next-day hangover effect than that of traditional BZD hypnotics,[1] it is increasingly prescribed, becoming one of the most commonly prescribed agents for insomnia worldwide and in Taiwan.[2-4] However, some zolpidem-related adverse events have been reported. Tolerance and dependence on zolpidem have caused some patients to become addicted.[5,6] The misuse of zolpidem occurs even among adolescents.[7] Furthermore, a study found that receiving zolpidem prescriptions was associated with a greater than 3-fold increased hazard of death.[8] The US Food and Drug Administration (FDA) stated that patients with depression who use zolpidem may develop suicidal tendencies and intentional overdosage is more common in this patient group. Nevertheless, patients with no known mood disorder have also been reported to commit suicide upon taking zolpidem.[9,10] A recent study reported approximately 24,450 people who have side effects while taking zolpidem from FDA and social media. Among them, 1282 have completed suicide.[11] Whether the suicide is due to zolpidem use per se or due to chronic insomnia or depression has not been confirmed.

By conducting a large nationwide population-based case-control study in Taiwan, we aimed to investigate the association between taking zolpidem and suicide or suicide attempt in people with or without mood or mental disorders.

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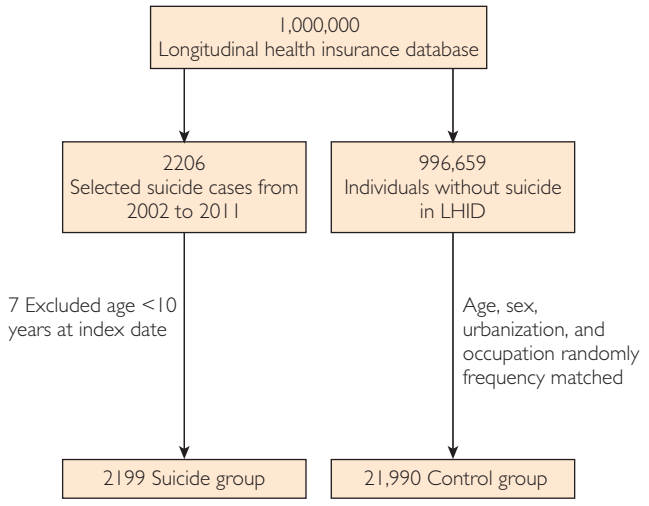

FIGURE. Flowchart for selection of study population.

PATIENTS AND METHODS

Data Source and Identification of Study Subjects

The data analyzed in this study were the claims of 1 million beneficiaries who were randomly selected from the National Health Insurance Research Database (NHIRD) provided by the National Health Insurance Administration (NHIA) in 2000 and have age and sex distributions nearly identical to those of the entire insured population of Taiwan.[12] The NHIRD provides all inpatient and ambulatory medical claims for approximately 99% of the residents of Taiwan.[13] To ensure the accuracy of claims files, the NHIA performs quarterly expert reviews of a random sample of 50 to 100 ambulatory and inpatient claims in each hospital and clinic and false diagnostic reports yield a severe penalty.[14] Therefore, information obtained from the NHIRD is believed to be complete and accurate. Disease diagnoses, based on outpatient and inpatient files, were made according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). For privacy protection, the patient identification numbers necessary to link files with identities were scrambled by the NHIA to ensure patient confidentiality. This study was approved to fulfill the condition for exemption by the Institutional Review Board of China Medical University (CMUH-104-REC2-115). The Institutional Review Board also specifically waived the consent requirement.

Study Population

This was a population-based case-control study. Our hypothesis was that zolpidem might be associated with the action of killing oneself, no matter whether the action leads to death or survival with injury. Thus, cases of suicide defined in this study include those who committed suicide or were hospitalized due to suicide attempt. All cases were identified from January 1, 2002, to December 31, 2011. The types of suicide (*ICD-9-CM* codes E950-E959) were liquid or solid poisoning (*ICD-9-CM* code E950), charcoal burning and poisoning by gases (*ICD-9-CM* code E952), hanging (*ICD-9-CM* code E953), cutting/piercing (*ICD-9-CM* code E956), jumping from high places (*ICD-9-CM* code E957), and others (*ICD-9-CM* codes E951, E954, E955, E958, and E959). For each case, 10 controls with no history of suicide or suicide attempt events were randomly selected and individually matched according to age (per 5 years), sex, urbanization level of residence, and occupation. The date of newly diagnosed suicide, either suicide or suicide attempt, was defined as the *index date*. Patients with a suicide attempt history before 2002, younger than 10 years, or with a date of first zolpidem exposure on or later than the index date were excluded. Figure shows a flow chart of the selection of the study population. We identified 2199 patients who had been diagnosed as suicide attempt or completed suicide and 21,990 controls.

Risk Factors and Covariates

Zolpidem exposure was the major risk factor investigated in this study. We collected patients' zolpidem medication histories from before their index dates and recorded the exposure dose as defined daily dose based on the Anatomical Therapeutic Chemical classification system. The Anatomical Therapeutic Chemical code for zolpidem is N05CF02. To evaluate the dose-response relation between zolpidem use and suicide risk, we calculated the average zolpidem exposure dosage as the total amount of zolpidem exposure before the index date divided by the duration from the initial zolpidem use to the index date (years).[15]

The urbanization level of residence was evaluated by incorporating population density (people/km^2), and population ratio of

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