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ORIGINAL ARTICLE

Long-Term Use of Zolpidem Increases the Risk of Major Injury: A Population-Based Cohort Study

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Abstract

Objective: To estimate the risk of head injury or fracture requiring hospitalization in patients treated with zolpidem.

Patients and Methods: We identified 8188 patients 18 years and older who had received a first prescription for zolpidem between January 1, 2000, and December 31, 2009, and compared them with 32,752 age- and sex-matched patients who had not used sedative-hypnotic agents. Both cohorts were followed up for at least 1 year or until hospitalization for head injury or fracture (major injury). Hazard ratios (HRs) and 95% CIs were calculated by comparing the incidence of major injury requiring hospitalization between the zolpidem user and comparison cohorts, including age groups 18 to 54 and 55 years or more, using a Cox proportional hazards regression analysis.

Results: The adjusted HR for major injury in zolpidem users was 1.67 (95% CI, 1.19-2.34). The adjusted HR for major injury in zolpidem users in the younger cohort (aged 18-54 years) was 1.70 (95% CI, 1.15-2.51) and in the older cohort (aged ≥55 years) was 1.57 (95% CI, 0.78-3.13). The adjusted HR for major injury in zolpidem users increased when the zolpidem dosage increased (HR, 2.04; 95% CI, 1.32-3.13 for 71-800 mg/y; HR, 4.37; 95% CI, 2.12-9.01 for 801-1600 mg/y; and HR, 4.74; 95% CI, 2.38-9.42 for >1600 mg/y).

Conclusion: The long-term use of zolpidem is associated with a significantly greater risk of head injury or fracture requiring hospitalization than in patients who do not use sedative-hypnotic agents ($P<.001$), particularly in the younger (aged 18-54 years) patients.

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Insomnia is the most common sleep-related symptom. Approximately 9% to 15% of the general population exhibits the symptoms and daytime consequences of insomnia worldwide.[1] The short-acting nonbenzodiazepine, zolpidem, is a benzodiazepine receptor agonist that acts at the γ-aminobutyric acid-A receptor complex.[2,3] Zolpidem is the most commonly prescribed hypnotic agent in the United States.[2,3] It is also commonly used in Taiwan.[4] According to Sanofi-Synthélabo, Paris, 1,338,774,000 zolpidem tablets were prescribed in Europe, Japan, and the United States from June 2001 to June 2002.[5] Thus, the potential adverse effects of zolpidem use warrant a thorough examination.

Because zolpidem produced clinically substantial balance and cognitive impairments on awakening from sleep, previous studies have found that zolpidem could increase the risk of fractures in elderly patients.[6,7] However, studies have typically focused on the fracture risk in elderly people who use zolpidem. Studies on the risk of major injury in nonelderly patients (aged 18-54 years in our study) taking zolpidem are scant.[8] Moreover, although zolpidem is licensed only for the short-term treatment of insomnia, it is often prescribed as a long-term treatment of chronic insomnia, despite the lack of information on the safety of long-term use. Therefore, we examined the risk of major injury requiring hospitalization in patients receiving zolpidem in a population-based retrospective cohort study in Taiwan.

PATIENTS AND METHODS

National Health Insurance Research Database

Details of the National Health Insurance (NHI) population-based cohort database for

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Taiwan—the National Health Insurance Research Database (NHIRD)—have been published previously.[9] The NHI program began in March 1995 and incorporated 13 insurance programs that provided health care to 99% of the residents of Taiwan. The program contracts with 97% of the hospitals and clinics in Taiwan, and it provides comprehensive medical services, including outpatient and inpatient care, dental care, physical therapy, preventive care, and prescriptions. The National Health Research Institute (NHRI) administrates the NHIRD. The NHRI released the claims data of 1 million patients (~5% of Taiwan's entire population) that were randomly selected from all beneficiaries who submitted NHI reimbursement claims between 1996 and 2009. The NHRI has reported that no statistically significant differences were found in the distributions of age, sex, or health care expenditures between the subset of the NHIRD and all enrollees. The diagnoses recorded in the NHI claim records were coded by using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*).

Study Sample

We excluded patients using zolpidem before January 1, 2000, and identified patients who had received a first prescription for zolpidem between January 1, 2000, and December 31, 2009. We used the date on which zolpidem treatment was initiated as the index date. We excluded patients taking sedative-hypnotic agents (benzodiazepines and nonbenzodiazepines, including zopiclone) other than zolpidem. We also excluded patients with a history of seizure, parkinsonism, stroke, or dementia. Patients with no history of the use of zolpidem were assigned to the comparison cohort. For each zolpidem user, 4 comparison patients were randomly selected and frequency matched for sex and age. Comparison patients were assigned the same index date as that of zolpidem users. To determine whether zolpidem is associated with the risk of major injury in both younger and older patients, patients in each cohort were grouped by age (18-54 and ≥55 years). The number of patients in the younger zolpidem user cohort (aged 18-54 years) was 6902 and in the corresponding younger comparison cohort was 27,608. The number of patients in the older zolpidem user cohort (aged ≥55 years) was 1286 (age range, 55-98 years) and in the corresponding older comparison cohort was 5144 (age range, 55-101 years). For study purposes, *major injury* was defined as a head injury (*ICD-9-CM* codes 959.01, 432.1, 852.2, and 852.3) or a fracture (*ICD-9-CM* codes 800-829) requiring hospitalization, and patients in both cohorts were followed up for at least 1 year or until the date of major injury. Data were censored for patients who withdrew from the NHI during the study period. The NHIRD encrypts the patients' personal information for privacy protection and provides researchers with anonymous identification numbers associated with the relevant claim information, which includes the patient's sex, date of birth, registry of medical services, and medication prescriptions. Patient consent is not required for accessing the NHIRD. This study was approved by the Institutional Review Board of the China Medical University (CMU-REC-101-012). Our Institutional Review Board specifically waived the requirement for consent.

Because the US Food and Drug Administration directed manufacturers to include labeling for zolpidem that advises health care professionals to consider prescribing lower doses (<5 mg) of immediate-release products, we divided zolpidem users into 4 groups on the basis of annual dosage: infrequent users (≤70 mg/y), occasional users (71-800 mg/y), frequent users (801-1600 mg/y), and regular users (>1600 mg/y). Patient comorbidities identified at baseline included diabetes mellitus (*ICD-9-CM* code 250), sleep disorder (*ICD-9-CM* code 307.4), alcohol-related disorders (*ICD-9-CM* codes 571.0-571.3 and 303), urinary incontinence (*ICD-9-CM* code 788.3), chronic arthritis (*ICD-9-CM* code 712, 714, and 715), antihypertensive drugs, antidepressant drugs, and antipsychotic drugs.

Statistical Analyses

We compared the distributions of sex, age, and comorbidities between the zolpidem user and comparison cohorts by using the χ^2 test for categorical variables and *t* tests for continuous variables. The incidence of major injury in each of the cohorts was calculated per 10,000 person-years. A Cox proportional hazards regression analysis was used to estimate the crude and adjusted hazard ratios (HRs) and 95% CIs on the basis of a comparison of the incidence of major injury in the zolpidem user and comparison

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