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Zolpidem and the risk of Parkinson's disease: A nationwide population-based study

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ABSTRACT

Background: This nationwide population-based study investigated the risk of Parkinson's disease (PD) after zolpidem use in patients with sleep disturbance using the National Health Insurance Research Database (NHIRD) in Taiwan.
Material and methods: In total, 59,548 adult patients newly diagnosed with sleep disturbance and who used zolpidem were recruited as the study cohort, along with 42,171 subjects who did not use zolpidem as a comparison cohort from 2002 to 2009. Each patient was monitored for 5 years, and those who subsequently had PD were identified. A Cox proportional hazards model was used to compare the risk of PD between the study and comparison cohorts after adjusting for possible confounding risk factors.
Results: The patients who received zolpidem had a higher cumulative rate of PD than those who did not receive zolpidem during the 5-year follow-up period (1.2% vs. 0.5%, $P < 0.001$). The adjusted hazard ratios were 1.10 (95% CI, 0.88–1.37), 1.41 (95% CI, 1.17–1.72), and 1.27 (95% CI, 1.05–1.55) for zolpidem use with 28–90, 91–365, and more than 365 cumulative defined daily doses (cDDDs), respectively, compared to those who did not use zolpidem.
Conclusions: Among the patients with sleep disturbance, zolpidem use increased the risk of PD after 5 years of follow-up. Further mechanistic research of zolpidem effect in PD is needed.

1. Introduction

Zolpidem is an imidazopyridine that acts on the GABA (γ aminobutyric acid) receptor and is often prescribed in primary care for insomnia (Siriwardena et al., 2006, 2010). However, zolpidem is not without risks, including adverse cognitive effects, psychomotor effects, daytime fatigue, tolerance, addiction, and excess mortality (Chung et al., 2013; Glass et al., 2005; Lai et al., 2014). When prescribing zolpidem, these established risk factors have to be weighed against the benefits.

Zolpidem has been reported to have unexpected effects on neuropsychiatric symptoms and motor dysfunction in patients with Parkinson disease (PD) (Chen et al., 2008; Daniele et al., 1997; Evidente, 2002; Huang et al., 2012). However, the mechanism underlying this phenomenon is unknown. Furthermore, the limited number of subjects and the use of biased populations in these studies were limitations (Lavoisy and Marsac, 1997). In order to include an adequate number of cases and acquire a robust

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estimation of the potential role of insomnia, age, sex, and hypnotics in PD, data from a large representative population followed up for a sufficient length of time are necessary. Therefore, we conducted this population-based study using the National Health Insurance Research Database (NHIRD) in Taiwan to investigate the association between zolpidem and PD in patients with sleep disturbance. Many authors have used the NHIRD to study stroke, dementia, PD and zolpidem (Chen et al., 2012; Lai et al., 2014; Lee et al., 2011; Wahlqvist et al., 2012). The high accuracy of the NHIRD in recording ischemic stroke diagnoses and aspirin prescriptions has been reported, and the NHIRD appears to be a valid resource for population research (Cheng et al., 2011). This nationwide population-based dataset allows researchers to trace the medical service utilization history of all citizens in Taiwan, and provides a unique opportunity to examine the possible association between zolpidem use and the risk of PD in patients with sleep disturbance.

2. Material and methods

2.1. Ethics statements

This study was initiated after being approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi General Hospital, Taiwan. Because the identification numbers and personal information of the individuals included in this study were not included in the secondary files, the review board stated that written consent from the patients was not required.

2.2. Patients and study design

Taiwan implemented a National Health Insurance (NHI) program in 1995 to provide comprehensive health care coverage. Enrollment in this government-run, universal, single-payer insurance system is mandatory, and currently up to 99% of the 23 million residents of Taiwan receive medical care through the NHI program. In addition, over 97% of the hospitals and clinics in Taiwan are contracted to provide health care services (Chiang, 1997), which are reimbursed by the Bureau of NHI, and all data related to these services are collected and input into the NHIRD by the National Health Research Institutes to provide a comprehensive record of medical care. The data consist of ambulatory care records, inpatient care records, and the registration files of the insured, and the database includes all claims data from the NHI program. The NHI Bureau of Taiwan randomly reviews the charts of one out of every 100 ambulatory cases, and one out of every 20 inpatient cases, as well as performing patient interviews to verify the accuracy of the diagnosis (Tseng, 2004).

This study used the 2002–2009 NHIRD. Because the data consisted of de-identified secondary data released to the public for research, this study was exempt from full review by the Institutional Review Board.

The study design featured a study cohort and a comparison cohort. We selected all patients who had been newly diagnosed with sleep disturbance (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 307.41, 307.42, 780.50, 780.51, 780.52, 780.55 and 780.56) from inpatient or outpatient files and who were followed up between 2002 and 2009 (Huang et al., 2013b; Liang et al., 2012). Patients with PD were defined as those with a diagnostic code of PD (ICD-9-CM 332.0) with at least three or more consistent diagnoses in outpatient care (Chen et al., 2012; Wahlqvist et al., 2012).

We selected the patients who received zolpidem as the study cohort and used the date of initiation of zolpidem therapy as the patient's index date. The control cohort included all the other patients with sleep disturbance who did not receive zolpidem. The independent variables were gender, comorbid disorders, schizophrenia, bipolar disorder, geographical area of residence, and socioeconomic status (SES). Other medications were included for analysis including anti-psychotic medication rather than zolpidem (Huang et al., 2014) and other well-known drugs causing parkinsonism (i.e. metoclopramide and flunarizine).

The defined daily dose (DDD) recommended by the WHO is a unit for measuring a prescribed amount of drug; it is the assumed average maintenance dose per day of a drug consumed for its main indication in adults (Lu et al., 2005). The cumulative DDD (cDDD), which indicates the duration of exposure, was estimated as the sum of dispensed DDD of zolpidem to compare its use with the risk of PD. To examine the dose–effect relationship, we categorized the use of zolpidem into four groups in each cohort (less than 28, 28–90, 91–365, and more than 365 cDDDs). The patients who used zolpidem for less than 28 cDDDs were defined as nonusers of zolpidem.

2.3. Other variables

The subjects were classified into three groups: (1) low SES: lower than US$528 per month (New Taiwan Dollar (NT$) 15,840); (2) moderate SES: between US$528 and 832 per month (NT$15,841–25,000); and (3) high SES: US$833 per month (NT$25,001) or more (Lin et al., 2008). We selected NT$15,840 as the low income level cutoff point because this was the government-stipulated minimum wage for full-time employees in Taiwan in 2006. The geographic regions where the individuals resided were recorded as northern, central, southern, and eastern Taiwan.

2.4. Statistical analysis

SPSS version 15 software (SPSS Inc., Chicago, IL, USA) was used for all data analyses. Pearson's chi-square test was used for categorical variables such as gender, SES, geographic region of residence, and comorbidities. Continuous variables were analyzed using a one-way ANOVA test. The cumulative risk of PD for those who did and did not receive zolpidem was estimated with Kaplan–Meier survival curves. A Cox proportional hazards regression model adjusted for patient characteristics (age, gender, diabetes, hypertension, hyperlipidemia, anxiety, depression, alcoholism, obesity, bipolar disorder, schizophrenia, flurazepam, estazolam, triazolam, drugs causing parkinsonism, anti-psychotic medications, socioeconomic status, and geographic regions) was used to analyze the association of zolpidem use with subsequent PD during the 5-year follow-up period. We calculated hazard ratios (HRs) along with 95% confidence intervals (CIs) using a significance level of 0.05. A two-sided P value ($P < 0.05$) was used to determine statistical significance.

3. Results

A total of 101,719 patients with sleep disturbance was included in our study cohort, of whom 59,548 patients used zolpidem and 42,171 did not. The demographic characteristics and selected morbidities for the two cohorts are shown in Table 1. The patients who received zolpidem were more likely to be older, reside in northern Taiwan, have more comorbidities, more use of hypnotics, and lower SES than the controls.

At the end of the follow-up period, 809 patients had PD, including 522 (1.2%) in the zolpidem group and 287 (0.5%) in the control group (Table 2; $P < 0.001$). The 5-year PD incidence rates were 0.8%, 1.3% and 1.7% for the patients who used zolpidem with 28–90, 91–365, and more than 365 cDDDs, respectively (Table 2;