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ORIGINAL ARTICLE

Zolpidem Increased Cancer Risk in Patients with Sleep Disorder: A 3-year Follow-up Study

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Background: Zolpidem has been increasingly used in patients with sleep disorder due to its minimal respiratory depressor effects and short half-life. **Materials and Methods:** Recent case reports indicate that zolpidem usage may be associated with increased cancer mortality. This study aimed to determine the impact of zolpidem usage on the risk of incident cancer events in sleep disorder patients over a 3-year follow-up. Of the 6924 subjects diagnosed with sleep disorder in 2004, 1728 had used zolpidem. A Cox proportional hazard model was performed to estimate 3-year cancer event-free survival rates for patients using zolpidem and those not using it, after adjusting for confounding and risk factors. **Results:** At the end of follow-up, 56 patients had incident cancers, 26 (1.5%) who used zolpidem, and 30 (0.6%) who did not. After adjustments for gender, age, comorbidities, and other medications, patients using zolpidem had a 1.75 times (95% confidence interval [CI], 1.02–3) greater risk of cancer events than those not using zolpidem during the 3-year follow-up. Greater mean daily dose and longer use were associated with increased risk. Among patients with sleep disorder, mean daily dose >10 mg and length of drug use >2 months was associated with 3.74 times greater risk (95% CI, 1.42–9.83; $P = 0.008$) of incident cancer events. **Conclusions:** In this study, zolpidem use increased cancer events risk in sleep disorder patients. Risks and benefits of chronic zolpidem usage should be explained to sleep disorder patients, and long-term use should be monitored.

Key words: Cancer, hazard ratios, mean daily dose, sleep disorder, zolpidem

INTRODUCTION

The clinical use of sedatives or hypnotics has increased gradually so that a 53% growth in prescriptions over 5 years was reported in 2006.[1] Some 6–10% of US adults have used hypnotics, and the percentage is higher in Europe.[2] The most commonly prescribed medications are benzodiazepines, nonbenzodiazepines, gamma-aminobutyric acid (GABA) agonists, melatonin receptor agonists, sedating antidepressants, antihistamines, and wake-promoting drugs.[3] However, the potential side effects of hypnotics, such as cancer risk, may be overlooked.

Zolpidem, an imidazopyridine in use since 1980, has been increasingly used in patients with sleep disorder due to its very few respiratory depressor effects and short half-life of 2.5 h.[4,5] Of the 8607 patients who reported side effects of zolpidem on the eHealthMe website, which continuously monitor drug adverse effects, 71 (i.e. 0.82%) reported incident cancer.[6] Previous studies reported an association of hypnotics and cancer death.[7-9] However, in these studies, neither the specific hypnotic drug nor the quantity was provided. Furthermore, zolpidem was not included in these series. Recently, Kripke *et al*. conducted a matched cohort study and found that taking

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hypnotics, either zolpidem or temazepam, was associated with increased cancer risk in rural US patients.[10] The main limitation of this study was its stratification of hypnotic drug dosage in three equivalent groups to validate the dose-response relationship; however, such stratification is not practical in terms of clinical use.

The critical dosage and length of use at which zolpidem will affect the development of incident cancer events in patients with sleep disorder have not clearly explored. The goals of the current study are (1) to determine the relative risk of incident cancer events associated with zolpidem use in sleep disorder patients using a population-based dataset and (2) to provide the critical dosage and length of zolpidem usage associated with increased cancer risk.

MATERIALS AND METHODS

Ethics statement

This study was initiated after approval by the Institutional Review Board of Buddhist Dalin Tzu Chi General Hospital, Taiwan. Since all identifying personal information was stripped from the secondary files before analysis, the review board waived the requirement for written informed consent from the patients involved.

Database

The National Health Insurance Program, which provides compulsory universal health insurance, was implemented in Taiwan in 1995. It enrolls up to 99% of the Taiwanese population and contracts with 97% of all medical providers. The resulting database contains comprehensive information on insured subjects including dates of clinical visits, diagnostic codes, details of prescriptions, and expenditure amounts. This study used the Longitudinal Health Insurance Dataset for 2004–2006 released by the Taiwan Nation Health Research Institute. The patients studied did not differ statistically significantly from the general population in age, gender, or health care costs, as reported by the Taiwan National Health Research Institute (www. nhri.org.tw).

Study population

All patient records in the dataset between January 1, 2002, and December 31, 2002, with sleep disorder diagnostic codes (International Classification of Diseases, 9th revision-Clinical Modification [ICD-9-CM] 780.5x) from an urban area were included in the study.[11,12] Excluded were those with any type of cancer (ICD-9-CM codes 140-208) diagnosed before or during the index ambulatory visit.

Identification of study cohort

A total of 6924 sleep disorder patients were identified. Each patient was tracked for 3 years from his or her index ambulatory visit in 2002 to identify outcomes, including any type of incident cancer (ICD-9-CM 140-208). To maximize case ascertainment, only patients verified by also being in cancer and catastrophic illness patient database were included in the study. These patients were then linked to the administrative data for the period 2002–2004 to calculate cancer disease-free survival time, with cases censored for patients who withdrew coverage from the National Health Insurance Program or were still robust without defined events at the end of follow-up.

Definition of exposure and covariate adjustment

The main exposure of interest was zolpidem. The dosage, date of prescription, supply days, and a total number of pills dispensed were obtained from the outpatient pharmacy prescription database. The mean daily dose was estimated by dividing the cumulative number of pills prescribed by the follow-up time from the date of initiating zolpidem treatment to the date of incident cancer, date of stopping medicine, or end of this follow-up study. The defined daily dose (DDD) was 10 mg for zolpidem. Other medications included in analysis were antihypertensives (i.e. propranolol, terazosin, doxazosin, prazosin, atenolol, furosemide, nifedipine, verapamil, diltiazem, isosorbide dinitrate, lisinopril, amitriptyline, chlorpromazine, or prochlorperazine), psychotropic agents (i.e. diazepam, alprazolam, or haloperidol), oral hypoglycemic agents, and insulin. Information on patients' age, gender, comorbidities, and monthly income level as a proxy of socioeconomic status (SES) were collected. The comorbidities for each patient was based on the modified Charlson comorbidity index score, a widely used measure for risk adjustment in administrative claims data sets.[13]

Statistical analysis

The SAS statistical package, version 9.2 (SAS Institute, Inc., Cary, NC), and SPSS version 15 (SPSS Inc., Chicago, IL, USA) were used for data analysis. Pearson's Chi-square test was used for categorical variables, demographic characteristics (age group and gender), comorbidities, and medications.

The 3-year cancer event-free survival rate was estimated using the Kaplan–Meier method. The cumulative risk of incident cancer event was estimated as a function of time from initial treatment. A Cox proportional hazard regression model was used to calculate the risk of cancer event in sleep disorder patients who used zolpidem versus those who did not, after adjustments for age, gender, comorbidities, SES and other medication usage. A $P < 0.05$ was considered statistically significant in the regression models.

RESULTS

The distribution of demographic characteristics for the two cohorts is shown in Table 1. Those taking zolpidem were significantly older and more likely to be female than those who did not take it. They were also more likely to have more comorbidities, low SES, and more frequently used antiglycemic drugs, psychotropic agents, and antihypertensive medications.

At the end of follow-up, 56 patients had incident cancers, 26 (1.5%) in those using zolpidem, and 30 (0.6%) in those not using it. Patients using zolpidem had an increased risk of cancer events. Table 2 shows the types of cancer events for the two cohorts stratified by gender. Increased mean daily dose and longer use were associated with increased cumulative risk of cancer events [Figures 1 and 2]. After adjustments for gender, age, comorbidities, and other medications, patients using zolpidem had a 1.75-times (95% CI, 1.02–3.02) higher risk of cancer events than those who did not use zolpidem during the 3-year follow-up period. Figure 3 shows the combined effect of mean daily dose and length of zolpidem use on increased cancer risk. Table 3 shows the adjusted ratios of cancer incidence with zolpidem usage after adjusting for gender, comorbidities, and other medications. Mean daily dose >1 DDD and usage >2 months was associated with 3.74 times (95% CI, 1.42–9.83; P = 0.008) higher risk of incident cancer events in a Cox regression model.

DISCUSSION

Our data showed that zolpidem usage was associated with increased incident cancer risk in patients with sleep disorder. Zolpidem usage >1 DDD for a period >2 months incurred a 3.7-fold higher risk of cancer events. Although zolpidem, the

Table 1: Baseline characteristics (n=6924)

Variables	Zolpidem use (n=1728) n (%)	Without zolpidem use (n=5196) n (%)	P
Gender			
Male	565 (32.7)	1859 (35.8)	0.02
Female	1163 (67.3)	3337 (64.2)	
Patient age (years)			
18-45	690 (39.9)	3034 (58.4)	<0.001
45-54	433 (25.1)	1141 (22.0)	
55-64	268 (15.5)	525 (10.1)	
65-74	210 (12.2)	336 (6.5)	
75 and more	127 (7.3)	160 (3.1)	
Charlson comorbidity index score			
0	1670 (96.6)	5092 (98.0)	0.005
1-2	50 (2.9)	89 (1.7)	
≥3	8 (0.5)	15 (0.3)	
Medication use			
Antiglycemic drug			
Yes	9 (0.5)	10 (0.2)	0.024
No	1719 (99.5)	5186 (99.8)	
Psychotropic agents			
Yes	460 (26.6)	567 (10.9)	<0.001
No	1268 (73.4)	4629 (89.1)	
Antihypertensives			
Yes	503 (29.1)	655 (12.6)	<0.001
No	1225 (70.9)	4541 (87.4)	
Socioeconomic status			
Low	1221 (70.7)	3255 (62.5)	<0.001
Moderate	315 (18.2)	1175 (22.6)	
High	192 (11.1)	766 (14.7)	

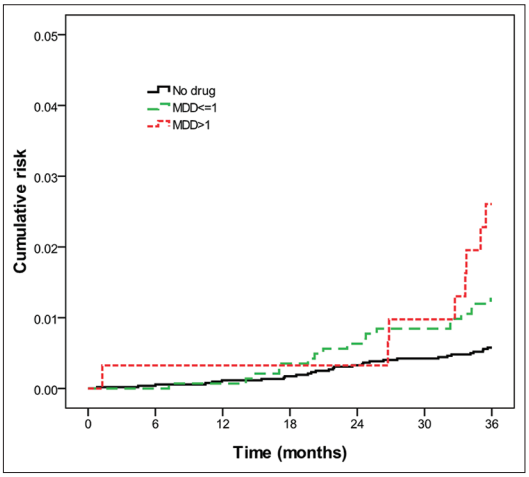

Figure 1: Effect of zolpidem dose on cancer risk

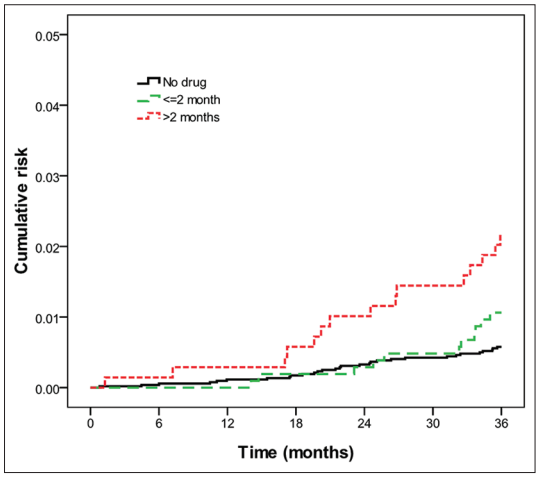

Figure 2: Effect of zolpidem duration on cancer risk

Table 2: Incident tumors in individuals with zolpidem usage and those without by stratification for gender

	Individuals without zolpidem usage (*n*=3337), (%)	Individuals with zolpidem usage (*n*=1163), (%)	*P*
Female individuals			
Breast cancer	8 (0.2)	5 (0.4)	
Cervical cancer	4 (0.1)	0 (0)	
Hepatoma	1 (0.03)	2 (0.2)	
Colorectal cancer	3 (0.1)	2 (0.2)	
Lung cancer	1 (0.03)	0 (0)	
Oral cancer	1 (0.03)	1 (0.1)	
Others	4 (0.1)	7 (0.6)	
Total tumors	22 (0.7)	17 (1.5)	0.011
	Individuals without zolpidem usage (*n*=1859), (%)	Individuals with zolpidem usage (*n*=565), (%)	*P*
Male individuals			
Hepatoma	0 (0)	1 (0.2)	
Colorectal cancer	1 (0.1)	2 (0.4)	
Lung cancer	3 (0.2)	0 (0)	
Oral cancer	0 (0)	3 (0.5)	
Prostate cancer	0 (0)	1 (0.2)	
Skin cancer	1 (0.1)	1 (0.2)	
Others	3 (0.2)	1 (0.2)	
Total tumors	8 (0.4)	9 (1.6)	0.007

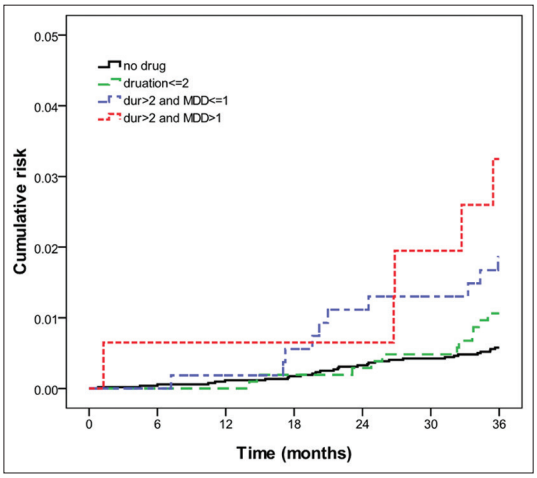

Figure 3: Combined effect of zolpidem dose and duration on cancer risk

newer nonbenzodiazepine, has been shown to be safe and effective in patients with insomnia,[14] its chronic usage should be carefully restricted and monitored.

Our results suggest that zolpidem usage for more than 2 months increases cancer risk significantly in patients with sleep disorder. Comparing with previous studies, this series further provided a critical period (>2 months) and mean daily dose (>1 DDD) for elevated risk of incident cancer for clinical physicians and the general population.

Table 3: Adjusted hazard ratios for zolpidem in patients with sleep disturbance

Variables	Hazard ratio	95% CI	*P* value
Univariate model			
MDD*	2.26	1.52-3.37	<0.001
Length of duration, month	1.05	1.02-1.08	0.001
Gender	0.81	0.46-1.43	0.463
Age, year	1.06	1.05-1.08	<0.001
Charlson comorbidity index score	2.55	1.20-5.39	0.015
Socioeconomic status			
Low	1		
Moderate	0.52	0.25-1.10	0.089
High	0.20	0.05-0.83	0.027
Antihypertensive drug	2.18	1.23-3.85	0.007
Antiglycemic drug	-	-	-
Psychotropic drug	1.57	0.83-2.97	0.166
Multivariable model			
Zolpidem usage			
No use	1		
Duration ≤2 months	1.40	0.69-2.81	0.350
MDD ≤1 DDD# with duration >2 months	1.81	0.87-3.80	0.114
MDD >1 DDD with duration >2 months	3.74	1.42-9.83	0.008
Gender	0.77	0.43-1.37	0.372
Age, year	1.06	1.04-1.08	<0.001
Charlson comorbidity index score	1.33	1.01-1.75	0.04
Socioeconomic status			
Low	1		
Moderate	1.07	0.48-2.38	0.871
High	0.43	0.10-1.84	0.255
Antihypertensive drug	0.95	0.51-1.77	0.867
Antiglycemic drug	-	-	-
Psychotropic drug	0.95	0.48-1.87	0.885

*MDD = Mean daily dose; #DDD = Defined daily use. - = HR can't be estimated (There was no data association between antiglycemic drug and outcomes)

Due to its short half-life and selective Type I $GABA_A$ receptor agonist, zolpidem is a widely used, standard treatment for patients with sleep disorder or insomnia.[3,15] Of the 8607 patients who reported side effects with zolpidem use on the eHealthMe website, which continuously monitors drug adverse effects, 71 (i.e., 0.82%) reported an incident cancer.[6] In our study, 1.5% persons with zolpidem usage developed incident cancer within 3 years. Zolpidem use was associated

with a 1.8-times higher risk of cancer events after adjusting for other medications and confounding factors. Our findings are consistent with Iqbal *et al*. that zolpidem usage was associated with a 1.13-times higher risk of cancer (95% CI, 1.09–1.17).[16] Higher doses and longer use were positively associated with cancer risk. This series revealed that a mean daily dose >1 DDD and drug usage >2 months was associated with 3.7 times risk (95% CI, 1.4–10) of incident cancer events in patients with sleep disorder.

The exact relationship between zolpidem and infection events remains unknown although several mechanisms are plausible. Benzodiazepines have been found to affect polymorphonuclear cell chemotaxis and phagocytosis.[17] Benzodiazepines in general suppress the immune response through peripheral and central benzodiazepine receptors.[18] The impairment of macrophage spreading could be attributed to the anti-inflammatory effect of the peripheral benzodiazepine receptor on blood cells through inhibition of the release of pro-inflammatory cytokines such as interleukin-6 and interleukin-13.[19] An uncontrolled small case series described carcinogenicity following the prescription of zopiclone or eszopiclone to HIV Type 1 infected individuals.[20] Eszopiclone and zolpidem use have been reported associated with increased risk of infection, raising the speculation that hypnotics impair immune surveillance.[21] A suppression of immune function may partly explain the increased risk of incident cancers. Sparse data on the new hypnotics (eszopiclone, zaleplon, zolpidem, and ramelteon) suggest an increased risk of cancer, which is supported by studies demonstrating a carcinogenic effect in rodents.[22]

Furthermore, hypnotics such as zolpidem can increase the incidence of sleep apnea and may suppress the respiratory drive. Zolpidem increased the apnea index and provoked greater oxygen desaturation than flurazepam and placebo in a controlled, double–blind, cross-over study. Such that 20 mg zolpidem failed to overcome the existing contraindications to administration of hypnotic drugs in patients with heavy snoring and obstructive sleep apnea syndrome.[23] Sleep apnea induced by medication may in turn induce early apoptosis of large granular lymphocytes which further compromises immunity and reduces immune surveillance.[24]

A greater incidence of depression with zolpidem use has been reported.[25] A decrease in the number of natural killer T-cells has also been reported in patients with major depressive disorder.[26] Depressed immunity to varicella zoster in older adults with major depressive disorder has been observed.[27] Compromised immunity may contribute to tumor formation.

Benzodiazepines can decrease lower esophageal sphincter tone, independently of the awareness or drowsiness of patients.[28] Zolpidem reduced the arousal response to nocturnal acid exposure and increased the duration of each esophageal acid reflux event.[29] Gastroesophageal reflux can lead to chronic sinusitis, recurrent croup, and laryngitis.[30] A recent meta-analysis reported an increased risk of infection with zolpidem use.[21] Infection may result from increased gastroesophageal regurgitation or from zolpidem usage and subsequent increased cancer development.[31] However, the exact relationship between zolpidem and cancer event remains unknown, and further research is needed to explore the possible mechanism.

This study has several limitations. First, the diagnosis of sleep disorder, incident cancer, and any other comorbid conditions are completely dependent on accurate recording of ICD-9-CM codes. However, the cancer events were further verified by their appearance in the registry for cancer and catastrophic illness patient database. Furthermore, the National Health Insurance Bureau of Taiwan randomly reviews charts and interviews patients to verify diagnosis accuracy. Hospitals with outlier charges or practice may undergo an audit, with subsequent heavy penalties for malpractice or discrepancies. Second, the database did not include detailed information on body mass index, smoking, or alcohol drinking. Further studies linking administrative data and primary surveys of health behaviors are warranted. Third, we did not control for depression, anxiety, and other emotional factors, which may have influenced these results. Fourth, the number of cases was small, warranting caution in interpreting the data. Finally, associations derived from epidemiological studies do not prove causality. It is hard to discern the correlation between the zolpidem usage and the sleep disorder in time sequence. We cannot exclude the possibility that zolpidem usage is a marker for other risk factors or cancer-related illness and acts a confounder in its association with cancer.

In summary, this study found that zolpidem use was associated with increased risk of cancer events in sleep disorder patients. For patients with sleep disorder who chronically use zolpidem, the likelihood of developing cancer events within 3 years is 1.7 times that of those who do not use zolpidem. Risks and benefits of chronic zolpidem usage should be explained to sleep disorder patients. Cognitive-behavioral therapy for patients with chronic insomnia may be more beneficial than use of hypnotics.[32]

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Conflicts of interest

There are no conflicts of interest.

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