Clinical Correlates of Zolpidem-Associated Complex Sleep-Related Behaviors: Age Effect

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ABSTRACT

Objective: Complex sleep-related behaviors (CSBs) are often associated with hypnotic use, especially zolpidem. The age effect on the occurrence of CSBs has not been adequately investigated. This study aimed to investigate and compare the clinical correlates of CSBs between adult and elderly subjects who were taking zolpidem.

Method: A total of 253 adults (aged 20–55 years) and 64 elderly subjects (aged ≥ 65 years) who were administered zolpidem for at least 3 months were enrolled from psychiatric outpatient clinics from June 2011 to May 2012. The sociodemographic characteristics of the participants, the dose of zolpidem, and the occurrence of CSBs were collected. Logistic regression analysis was used to examine the clinical correlates of CSBs.

Results: In total, there were 62 members of the adult group (24.5%) and 11 elderly subjects (17.2%) with CSBs; however, the difference did not reach statistical significance. Logistic regression analysis showed that there was a main effect of zolpidem dose (≥ 10 mg; OR = 2.82, *P* = .038) and alcohol use (OR = 2.05, *P* = .026), but not sex or age group. There were interactive effects between age group and zolpidem dose (*P* = .043), indicating that a higher dose of zolpidem was associated with CSBs only in the adult group and not in the elderly group. Adults with CSBs used a higher dose of zolpidem than adults without (mean ± SD: 15.4 ± 6.8 mg vs 11.3 ± 5.7 mg), whereas elderly patients with CSBs did not use a higher dose of zolpidem than those without (12.2 ± 5.4 mg vs 11.9 ± 7.0 mg).

Conclusions: A higher dose of zolpidem was correlated with CSBs only in the adult group and not in the elderly group. Future studies investigating the factors, other than dose, related to CSBs in the elderly will be performed.

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Most of the available hypnotics are well tolerated and safe for many people. However, after collecting antecedent case reports and reviewing the available postmarketing adverse event information, the US Food and Drug Administration launched a warning regarding several complex sleep-related behaviors (CSBs) as potential adverse effects of sedative-hypnotic drugs in 2007.[1] CSBs are complex activities, such as sleep driving, making phone calls, preparing and eating food, and having sex, that may occur after ingestion of a sedative hypnotic. A person experiencing a CSB is not fully awake and has little or no memory of the event.[2] The occurrence of CSBs is not uncommon. Among outpatients, a rate of CSBs of up to 15.2% for all types of hypnotic-sedative drugs has been reported, and the rate increases to 28.4% for those using zolpidem.[3] CSBs also possibly cause legal problems and serious harm, including suicide and homicide.[4–6] There has been growing clinical awareness of CSBs recently.

The exact mechanisms responsible for CSBs are unknown. Activation of γ-aminobutyric acid (GABA) activity via α_1-$GABA_A$ receptors is a possible mechanism causing CSBs. Agents with higher binding affinity at α_1-$GABA_A$ receptors may increase the risk of CSBs.[2] Among all sedative-hypnotic drugs, zolpidem, a nonbenzodiazepine hypnotic, is the one most frequently reported to be associated with CSBs.[7,8] It has been suggested that zolpidem enhances GABA activity at α_1-$GABA_A$ receptors and causes amnesia and CSBs.[2] Zolpidem has been recognized as a hypnotic that results in lesser dependence and better reconstruction of sleep architecture for patients with insomnia.[9–11] However, a later study[12] found that, in fact, the propensity toward addiction may be somewhat higher for zolpidem than for other benzodiazepines. Besides case reports or case-series studies, few empirical studies have investigated the correlates of zolpidem-associated CSBs. A recent clinical study[3] reported that a higher dosage of zolpidem is the main clinical correlate of CSBs.

Early studies supported the superiority of zolpidem, reporting it to be better than other hypnotic-sedative medicines for the elderly in terms of residual cognitive or psychomotor impairment and sleep structure.[13–15] However, a recent risk-benefit analysis of the treatment of the elderly with insomnia did not support this strength.[16] CSB occurrence in the elderly is an important issue; however, there have been few case reports of CSBs in those aged over 65 years. Elderly subjects with CSBs associated with zolpidem presented sleep eating and sleepwalking along with object manipulation at zolpidem doses ranging from 5–20 mg per night.[17,18] However, thus far, no empirical study of CSBs in the elderly has been conducted.

The features of CSBs in the elderly possibly differ from those in adult counterparts. The elderly are generally more susceptible to adverse side effects of medications. Side effects of zolpidem, such as cognitive impairment, dizziness, and residual daytime sleepiness, have been reported to be more common in the elderly than in younger adults.[16,19] Moreover, the inevitable age-associated pharmacokinetic changes and high frequency of comorbidity with general medical conditions may lead to differences in the rates of side effects in the elderly, with a tendency toward higher rates. However, a

Clinical Points

- Zolpidem-associated complex sleep-related behaviors (CSBs) are common in both adult and elderly groups.
- Concomitant use of alcohol is clinically correlated with zolpidem-associated CSBs.
- A higher dose of zolpidem was correlated with CSBs in the adult group only, not in the elderly group.

Taiwanese study including participants of a wide age range (20–80 years) suggested that aging seemed to be a protective factor against CSBs in an uncontrolled analysis, although the tendency disappeared in a controlled analysis.[3] Whether the rate of CSBs is higher or lower in the elderly than in the adult population is still unclear. Therefore, an empirical study to investigate the clinical differences in CSBs between elderly and younger adult subjects would be worthwhile.

In this study, we compared an elderly group to an adult group in terms of rates, clinical pictures, and clinical correlates of CSBs. We hypothesized that (1) as with other side effects of zolpidem, CSBs would be more frequent in the elderly group and (2) a higher dose of zolpidem would be correlated with CSBs among both age groups.

METHOD

Participants and Diagnosis

Study participants were recruited from 8 psychiatric outpatient clinics during a 1-year study period (from June 2011 to May 2012) in order to compare the age differences in terms of clinical correlates. Two age groups were selected: an adult group aged 20 to 55 years and an elderly group 65 years or older. The inclusion criterion was use of zolpidem for at least 3 months. The exclusion criteria were (1) comorbid major systemic or neurologic illness (eg, stroke, Parkinson's disease, epilepsy, traumatic head injury) and (2) being too frail to complete all of the assessments. The protocol was approved by the Institutional Review Board of Kaohsiung Medical University. All patients provided written informed consent.

Sociodemographic variables, including age, sex, educational level, and marital status, were collected. The dose and total duration of zolpidem usage were also collected. The primary *ICD-10* psychiatric diagnosis and physical diseases were derived from the psychiatric chart record, and we also checked whether participants had used alcohol in the previous month. The Complex Sleep-Related Behavior Questionnaire (CSRBQ)[3] was used to evaluate CSBs. The CSRBQ comprises 4 questions related to previous experience with sleepwalking, sleep-related eating disorder, sleep conversation, and sleep object manipulation. All CSBs must have met 2 criteria: they occurred while the person was asleep, and the person was unaware of the behavior upon awakening. Sleep conversation had to involve a conversation with another person. A research assistant interviewed each of the study participants using the CSRBQ when they came to the clinic. Recurrence of any CSB was coded as a "yes" response.

Procedure and Statistical Analysis

Data analysis was performed using SPSS 15.0 statistical software (SPSS Inc). Independent *t* tests and χ^2 tests were used to analyze the differences in sociodemographic characteristics of the participants, differences in the doses of zolpidem used by the 2 groups, and differences between those with CSBs and those without. Associations between 2 continuous variables were assessed using Pearson *r* correlations. Logistic regression analysis was used to examine the main and interactive effects of clinical correlates on CSBs. A *P* value of .05 was used to indicate significance for all statistical tests.

RESULTS

During the study period, 253 adults and 64 elderly participants completed the whole assessment. Table 1 shows the demographic and clinical characteristics of the study participants. No statistically significant differences were noted in the demographic data between the 2 groups, with the exceptions of age and educational level. The mean age of the adult group was 43.1 years (SD = 8.7 years), and that of the elderly group was 73.4 years (SD = 6.3 years). The educational level of the adult group was 12.5 years (SD = 4.0 years), and that of the elderly group was 6.7 years (SD = 5.0 years). The distributions of psychiatric diagnoses differed between the 2 groups. The elderly had more physical diseases (53.1% vs 26.5%, $P < .001$) and less alcohol use (6.3% vs 23.7%, $P = .001$). The dose of zolpidem did not differ between the 2 groups (12.3 ± 6.2 mg for the adults vs 12.0 ± 6.8 mg for the elderly; $P = .70$), while the duration of zolpidem use was longer for the elderly (92.7 ± 93.5 months vs 62.1 ± 55.2 months, $P = .015$).

In total, 62 subjects (24.5%) in the adult group and 11 (17.2%) in the elderly group had CSBs; however, the difference did not reach statistical significance ($\chi^2 = 1.54$; $P = .247$). Among those with CSBs, 40 (64.5%) had sleepwalking, 37 (59.7%) had sleep-related eating behavior, and 31 (50%) had sleep conversation in the adult group, while 4 (36.4%) had sleepwalking, 5 (45.5%) had sleep-related eating behavior, and 2 (18.2%) had sleep conversation in the elderly group.

CSBs were not associated with sex ($\chi^2 = 0.25$; $P = .62$), physical illness ($\chi^2 = 0.13$; $P = .72$), psychiatric diagnosis ($\chi^2 = 4.40$; $P = .36$), concurrent antidepressant use ($\chi^2 = 0.64$; $P = .43$), antipsychotic use ($\chi^2 = 0.42$; $P = .52$), benzodiazepine use ($\chi^2 = 1.2$; $P = .27$), or use of other psychotropics ($\chi^2 = 2.65$; $P = .11$), but were related to alcohol use ($\chi^2 = 4.33$; $P = .04$). Patients with CSBs took a higher dose of zolpidem than those without (mean ± SD: 14.9 ± 6.7 mg vs 11.4 ± 6.0 mg; $t = 4.2$, $P < .001$), but there was no statistical difference in duration of zolpidem use (mean ± SD: 70.6 ± 63.2 months vs 67.4 ± 66.5 months; $P = .72$).

To control for the potential confounding effects of psychiatric diagnosis, physical disease, duration of zolpidem, alcohol use, and age and to examine the modifier role of gender, separate logistic regression analyses were conducted to examine the main effects of zolpidem dose and age group and their interactive effects. In model 1, logistic regression

Table 1. Sociodemographic and Clinical Data of Subjects Taking Zolpidem[a]

	Adult Group (n = 253)	Elderly Group (n = 64)	*P*
Age, mean (SD), y	43.11 (8.69)	73.40 (6.25)	
Gender, female	160 (63.2)	45 (70.3)	.310
Educational level, mean (SD), y	12.51 (3.97)	6.73 (4.96)	< .001
Marital status, married	117 (46.2)	34 (53.1)	.33
Psychiatric diagnosis			
Mood disorder	138 (54.5)	37 (57.8)	.639
Psychotic disorder	57 (22.5)	6 (9.4)	.018
Anxiety disorder	40 (15.8)	8 (12.5)	.509
Primary insomnia	13 (5.1)	6 (9.4)	.202
Others	5 (2.0)	7 (10.9)	.001
Psychotropic medication[b]	171 (96.1)	55 (90.2)	
Antidepressant	100 (56.2)	41 (67.2)	.131
Antipsychotic	79 (44.4)	8 (13.1)	< .001
Benzodiazepine	129 (72.5)	44 (72.1)	.96
Others	33 (18.5)	16 (26.2)	.20
Physical disease	67 (26.5)	34 (53.1)	< .001
Alcohol use in past month	60 (23.7)	4 (6.3)	.001
Duration of zolpidem use, mean (SD), mo	62.05 (55.19)	92.70 (93.49)	.015
Dose of zolpidem, mean (SD), mg	12.30 (6.23)	11.95 (6.75)	.696
Any complex sleep-related behaviors	62 (24.5)	11 (17.2)	.247

[a]Data expressed as n (%) unless otherwise noted.
[b]Data from subsample of 239 subjects (178 adults and 61 elderly subjects); data were unavailable for some subjects.

Table 2. Clinical Correlates of Complex Sleep-Related Behaviors Using Logistic Regression Analysis

	B (SE)	*P*	OR (95% CI)
Model 1			
Constant	−1.72 (0.23)	< .001	0.18
Sex	−0.23 (0.29)	.44	0.80 (0.45–1.14)
Age group	0.12 (0.51)	.82	1.12 (0.42–3.02)
Total dose (< 10 mg or ≥ 10 mg)	1.04 (0.50)	.038	2.82 (1.06–7.49)
Age group by total dose	−1.50 (0.74)	.043	0.22 (0.05–1.00)
Model 2 (model 1 + psychiatric diagnosis)			
Mood disorder	−0.79 (0.68)	.249	0.46 (0.12–1.73)
Psychotic disorder	−1.46 (0.76)	.055	0.23 (0.05–1.03)
Anxiety disorder	−0.96 (0.76)	.206	0.38 (0.09–1.70)
Primary insomnia	−0.65 (0.84)	.441	0.52 (0.10–2.73)
Model 3 (model 2 + alcohol use in past month)			
Alcohol use in past month	0.72 (0.32)	.026	2.05 (1.09–3.87)

analysis showed that there was a main effect of zolpidem dose (≥ 10 mg; OR = 2.8, *P* = .038), but not with sex. In addition, there were interactive effects of age and zolpidem dose (*P* = .043). Model 2 put the variable of psychiatric diagnosis into model 1 and showed no psychiatric diagnosis was related to CSBs. When we further examined the variable of alcohol use, model 3 presented a main effect of alcohol use with OR = 2.05 (*P* = .026), in addition to zolpidem dose, and interactive effects of age and zolpidem dose (Table 2). The potential modifier effect of gender on zolpidem dose was also examined, but no interactive effect on CSBs was found (*P* = .49).

The dose difference between subjects with and without CSBs by age group was reexamined. Adults with CSBs used a higher dose of zolpidem than adults without (mean ± SD: 15.4 ± 6.8 mg vs 11.3 ± 5.7 mg), but elderly subjects with CSBs did not use a higher dose of zolpidem than those without (12.2 ± 5.4 mg vs 11.9 ± 7.0 mg). The results indicated that a higher dose of zolpidem was associated with CSBs only in the adult group and not in the elderly group. We then conducted a second analysis to investigate the clinical correlates, other than dose of zolpidem, that may explain the differences between the study participants with and without CSBs by age group. However, the distributions of gender, psychiatric diagnoses, physical illness, duration of zolpidem use, and alcohol use did not differ between the 2 groups in either of the age groups (Table 3).

DISCUSSION

The results of this study revealed that the rate of CSBs was not higher in the elderly group than in the adult group. The absolute rate of occurrence was lower in the elderly group; however, the difference did not reach statistical significance. A higher dose of zolpidem was associated with a higher occurrence of CSBs in the adult group, but not in the elderly group. Alcohol use was also a correlate of CSBs.

The frequencies of CSBs were 24.5% in the adult group and 17.2% in the elderly group. The rates were a little lower than that reported in a previous study, which indicated that CSBs occurred in 28.4% of those using zolpidem.[3] Furthermore, in contrast to our hypothesis, the frequency of CSBs was not greater among the elderly, and the absolute value was in fact lower in the elderly group. The findings suggested that CSBs are not similar to other adverse effects more often seen in the elderly. It should be considered that CSBs may be less frequent in the elderly, although our findings did not show a significant statistical difference to support this notion. A similar feature was seen in a previous study, which showed that younger age was a risk factor for CSBs in an uncontrolled analysis. A type II error, failure to reject a false null hypothesis due to limited sample size, should be taken into account when considering this result. Concomitant use of alcohol increased the risk of CSBs among patients taking zolpidem. Alcohol may have a pharmacokinetic and pharmacodynamic drug-drug interaction with zolpidem. Since cytochrome P450 (CYP) 3A4, the major isoform responsible for zolpidem metabolism,[20] is also involved in alcohol metabolism,[21] the pharmacokinetic interaction may lead to level changes in zolpidem used concurrently with alcohol. Alcohol may also have a pharmacodynamic interaction with hypnosedatives that arises from its effects at $GABA_A$ receptors[22]; hence, concomitant use of GABAergic zolpidem and alcohol may increase the risk of CSBs.[23]

The dose of zolpidem has been repeatedly reported to be associated with CSBs. However, we did not find that the elderly were at higher risk of developing CSBs. One possible explanation for this is that the required dose of zolpidem was lower in the elderly. However, the dose issue seems not to be the explanation for our results, as the mean dose of zolpidem between the 2 groups was very similar. An intriguing finding from our study was that in the elderly group there was no mean dose difference between subjects with CSBs and those without. The findings indicated that there are factors other

Table 3. Clinical Correlates of Complex Sleep-Related Behaviors (CSBs) by Age Group[a]

	Adult Group			Elderly Group		
	With CSBs (n = 62)	Without CSBs (n = 191)	*P*	With CSBs (n = 11)	Without CSBs (n = 53)	*P*
Gender, female	40 (64.5)	120 (62.8)	.811	9 (81.8)	36 (67.9)	.359
Psychiatric diagnosis						
Mood disorder	40 (64.5)	98 (51.3)	.070	5 (45.5)	32 (60.4)	.362
Psychotic disorder	9 (14.5)	48 (25.1)	.082	0 (0)	6 (11.3)	.241
Anxiety disorder	8 (12.9)	32 (16.8)	.470	2 (18.2)	6 (11.3)	.531
Primary insomnia	4 (6.5)	9 (4.7)	.590	1 (9.1)	5 (9.4)	.972
Others	1 (1.6)	4 (2.1)	.813	3 (27.3)	4 (7.5)	.056
Psychotropic medication[b]						
Antidepressant	27 (60.0)	73 (54.9)	.55	8 (80.0)	33 (64.7)	.346
Antipsychotic	17 (37.8)	62 (46.6)	.302	1 (10.0)	7 (13.7)	.75
Benzodiazepine	36 (80.0)	93 (69.9)	.191	7 (70.0)	37 (72.5)	.869
Others	4 (8.9)	29 (21.8)	.054	3 (30.0)	13 (25.5)	.767
Physical disease	17 (27.4)	50 (26.2)	.869	5 (45.5)	29 (54.7)	.742
Alcohol use in past month	20 (32.3)	40 (20.9)	.085	1 (9.1)	3 (5.7)	.539
Duration of zolpidem use, mean (SD), mo	64.98 (51.70)	61.09 (56.38)	.631	105.40 (108.58)	90.30 (91.34)	.643

[a]Data expressed as n (%) unless otherwise noted.
[b]Data from subsample of 239 subjects (178 adults and 61 elderly subjects); data were unavailable for some subjects.

than the dose of zolpidem that explain the occurrence of CSBs in the elderly.

We attempted to investigate whether other demographic or clinical correlates were associated with CSBs in the elderly. However, the risks of measured comorbidity with psychiatric or medical illness and the duration of zolpidem use could not explain the CSBs in the elderly. Elderly patients are usually administered more types of medication. This raises the possibility of drug-drug interaction between other medications and zolpidem, leading to CSBs. Previous studies have demonstrated that specific combinations of psychotropics were risk factors for other particular parasomnias; for example, the combination of antidepressants and nonbenzodiazapine hypnotics is related to sleepwalking and sleep-related eating disorder.[24] It can be speculated that the elderly participants with CSBs took zolpidem in combination with an antidepressant, even though they did not have a higher dose of zolpidem. However, our results did not reveal an association with mood or anxiety disorder diagnoses in elderly subjects with CSBs. As the patients were administered various antidepressants, it is difficult to exclude an association between zolpidem, a concurrently used antidepressant, and CSBs. Another speculation is that comorbidity with physical illness was a risk factor for CSBs among the elderly taking a zolpidem dose equal to that of subjects without CSBs. Most importantly, zolpidem has drug interactions with medications for physical illnesses, especially those primarily metabolized via the CYP3A4 isoenzyme.[25,26] However, with its limited sample size, our study could not address this speculation. A future study with a large sample size and specialized analysis of concurrent medications may be warranted.

Some caveats regarding the methods of this study need to be mentioned. First, the small sample size, especially of the elderly group, hindered the possibility of multivariate testing to control for potential confounding effects. Second, the cross-sectional design also limited the ability to make causal inferences. In addition, in this study, we skipped an age group, that is, people between 56 and 64 years, in order to make a clear comparison between the adult group and the elderly group. The results, therefore, cannot be generalized to the omitted age group. Third, the recruitment of study participants took place in psychiatric outpatient clinics only, not in primary care or other specialized clinics. Recruitment from such settings would have provided a larger sample of study participants that might include, for instance, elderly subjects with a comorbid medical condition, who are hypothesized to be at risk for CSBs. Further study with enrollment from different settings may overcome this limitation. Finally, a more sophisticated polysomnographic measure, in addition to an interview, may be a better method of defining CSBs in future studies.

In conclusion, this study suggests a high frequency of CSBs among patients using zolpidem, both adults and the elderly. The findings indicated that a higher dose of zolpidem was associated with CSBs in adults, but not in the elderly. The clinical correlates of CSBs in the elderly merit further investigation.

Drug names: zolpidem (Ambien, Edluar, and others).

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