Risk Predictors for Hypnosedative-Related Complex Sleep Behaviors: A Retrospective, Cross-Sectional Pilot Study

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Objective: To explore the risk predictors for complex sleep-related behaviors (CSBs) in subjects with a *DSM-IV*–diagnosed depressive disorder, anxiety disorder, adjustment disorder, somatoform disorder, or sleep disorder taking hypnosedative drugs.

Method: One hundred twenty-five subjects using hypnosedatives were enrolled from the psychiatric outpatient clinics of a medical center in Taiwan from May 2006 to July 2006. All subjects completed a questionnaire that included demographic data, current and childhood sleep habits, and CSBs after taking hypnosedatives. Complex sleep-related behaviors were defined as somnambulism with object manipulation, sleep-related eating, and other amnestic sleep-related behaviors. Demographic and clinical variables were compared in those with CSBs and those without. Then multiple logistic regression analyses were performed in order to identify significant risk predictors for CSBs.

Results: Of the 125 subjects, 19 (15.2%) reported CSBs, all of whom took zolpidem. Among a total of 67 subjects taking zolpidem, those with CSBs were significantly more likely to be younger ($P = .023$), to be female ($P = .011$), to take a higher dose of zolpidem (> 10 mg/d; $P < .001$), and to not go to sleep immediately after taking zolpidem ($P = .047$). Multiple logistic regression analyses showed that a higher dose of zolpidem (> 10 mg/d) was the only significant predictor of CSBs (OR = 13.1; 95% CI, 2.6–65.9; $P = .002$).

Conclusions: This pilot study suggests that a higher dosage of zolpidem (> 10 mg/d) is the key risk predictor for CSBs.

J Clin Psychiatry 2010;71(10):1331–1335

Submitted: *January 27, 2009; accepted May 26, 2009.*
Online ahead of print: *April 20, 2010 (doi:10.4088/JCP.09m05083bro).*
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In recent years, complex sleep-related behaviors (CSBs) induced by hypnosedatives have been the focus of much attention, especially after the US Food and Drug Administration requested in March 2007 that manufacturers of 13 kinds of hypnosedative drugs modify their product labeling to include new safety warnings about these potentially dangerous behaviors. Complex sleep-related behaviors are officially categorized as "parasomnias" in *The International Classification of Sleep Disorders: Diagnostic and Coding Manual, 2nd Edition* (*ICSD-2*),[1] which defines parasomnias as undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep. Complex sleep-related behaviors are complex activities (normally associated with wakefulness) that occurred when the subject was in a sleep-like state after taking a hypnosedative drug and that the subject has little or no memory of upon awakening the next morning. Complex sleep-related behaviors include sleepwalking with object manipulation, sleep-related eating disorder (SRED), sleepdriving, sleep conversation, sleepsex, etc. These behaviors may not occur frequently, but clinical awareness of the potential associated danger and harm is necessary. Although benzodiazepines have been used for more than 40 years, only a few published reports have identified them as being involved in CSBs.[2–4]

Zolpidem, a nonbenzodiazepine receptor agonist (NBRA), is a highly effective hypnotic with a short half-life and minimal daytime residual side effects under recommended doses.[5] Compared with benzodiazepines, zolpidem induces a pattern of sleep more similar to natural sleep. In clinical experience, the highly hypnotic effect of zolpidem has been shown to have a low risk of tolerance, dependence, or abuse[5,6]; in addition, a large postmarketing study found a low rate (1.1%) of adverse events when taking zolpidem, and no life-threatening effects were mentioned.[7] In that study, nausea, dizziness, malaise, nightmares, agitation, and headache were found to be the most common adverse events. In another review, central nervous system–related adverse effects of zolpidem were reported to include light-headedness or dizziness, somnolence, headache, fatigue, memory deficits, nightmares, confusion, and depression.[8]

However, some recent studies have reported a relationship between zolpidem and CSBs, including sleepwalking with object manipulation,[9,10] SRED,[11,12] sleep shopping,[13] sleepsex,[14] etc. Although these problems have been the focus of more and more attention in clinical practice, the mechanism underlying the association between zolpidem and CSBs remains unclear. Several possible risk factors have been speculated, including zolpidem dosage,[15,16] sex,[16] drug-drug interaction with selective serotonin reuptake inhibitors,[17] protein-binding competition,[16] body weight,[18] and a combination of the following events: a past history of sleepwalking, medication increasing delta sleep, and a precipitating stimulus.[19] However, these speculations are based on case reports or case-series studies only.

As far as we know, no empirical study has systemically investigated the risk predictors for CSBs in hypnosedative users. In this study, we employed a case-control design to address this issue in benzodiazepine and NBRA users. Specifically, we were most interested in testing whether

medication, dosage, sex, and sleep habits would be risk predictors for CSBs.

METHOD

Subjects

We enrolled subjects from 5 outpatient clinics of the Department of Psychiatry of National Taiwan University Hospital from May 2006 to July 2006, one of which was a specialist clinic for patients with sleep disorders. The inclusion criteria were (1) 20–80 years of age; (2) having been exposed to hypnotics (including benzodiazepines and NBRAs) for more than 3 months within 2 years; (3) diagnosis of a depressive disorder, anxiety disorder, adjustment disorder, somatoform disorder, or sleep disorder; and (4) a cohabitant, such as a family member or partner. The exclusion criteria covered those with a diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, bipolar affective disorder, eating disorder, dementia, delirium, significant cognitive disorder, seizure disorder, substance use disorder, or severe unstable medical disease. A total of 194 subjects were invited to take part in our study. Of them, 68 were excluded due to the following reasons: 31 had an unqualified diagnosis, 9 had unavailable detailed information, 25 were not contactable, and 3 had a misunderstanding of questions from the questionnaire. The remaining 126 subjects fulfilling the inclusion but not the exclusion criteria were enrolled. To avoid confusion, 1 subject with pure visual hallucinations and no CSBs was also excluded from analysis.

Procedures

With the help of a trained research assistant, each subject completed a sleep questionnaire, which consisted of 4 parts: (1) demographic data, body height, body weight, and medical history (including electroconvulsive therapy); (2) usual sleep habits, including sleep schedule and bedtime routine (such as going to sleep immediately or not after taking hypnotics, concomitant alcohol use, etc); (3) childhood sleep habits and behaviors; and (4) sleep-related behaviors, including CSBs after taking hypnotics. Complex sleep-related behaviors included somnambulism with object manipulation, SRED, and other less frequent amnestic complex behavior (such as sleep conversations, sleepdriving, sleepsex, sleep shopping, etc). The definitions of sleepwalking and SRED are based on the *ICSD-2*.[1] Sleep conversation must involve a conversation with another person; therefore, it is not only simple sleeptalking. The occurrence of sleep-related perception disturbance (such as visual hallucination or sensory distortion) was also queried and recorded, but if it occurred alone without concurrent amnestic complex behaviors, it was not classified as a CSB.

Because CSBs are associated with amnesia, 2 psychiatrists (H.C.N., Y.T.L.) contacted each subject's cohabitant by telephone for further clarification of the information given and confirmation of true CSBs. Subjects' charts were also reviewed by the same psychiatrists for the collection of relevant clinical information, including (1) psychiatric diagnosis and medications at the time of occurrence of CSBs and (2) concurrent medical conditions rated using the modified Cumulative Illness Rating Scale (CIRS) with 13 body systems (excluding the psychiatric system).[20] Psychiatric diagnosis was defined according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria based on clinical assessment of the primary attending psychiatrist and the information collected from a chart review by a reviewer. If there was any doubt about or inconsistency between the diagnoses made by the primary psychiatrist and reviewer, they would discuss the case in order to reach a final diagnosis.

All participants provided written informed consent, and the Ethics Committee of National Taiwan University Hospital approved the study.

Statistical Analysis

Subjects with CSBs were compared with subjects without CSBs across variables of different domains using Fisher exact test (2-tailed) for categorical variables and the *t* test or Mann-Whitney test (2-tailed) for continuous variables in the whole sample. We grouped individual *DSM-IV* depressive disorders (such as major depressive disorder and dysthymic disorder) together as "depressive disorder" and individual anxiety disorders (such as generalized anxiety disorder and panic disorder) as "anxiety disorder," for the reason that almost all subjects were in a clinically stable or a remission state, and by doing so, multiple comparisons could be avoided. Because in the initial analysis it was found that virtually all subjects with CSBs were taking zolpidem, the same procedure was followed in the subsample of zolpidem users, but in more detail: for example, antidepressants were further categorized according to protein-binding affinity (ie, ≥ 80% vs < 80%) and cytochrome P450 (CYP) 3A4 inhibition, as these 2 factors have been reported to be associated with zolpidem-related CSBs. Those factors that were significant in univariate analysis were then entered into multiple logistic regression analysis to identify significant risk predictors for CSBs. Analysis was performed using the SPSS version 13.0 (SPSS Inc, Chicago, Illinois). A P value of $< .05$ was considered significant.

RESULTS

The demographic and clinical features of the 125 eligible subjects are listed in Table 1. Among them, 19 (15.2%) had a history of CSBs after taking hypnotics; the distribution of CSBs was as follows: 6 had somnambulance (including 3 also with sleep conversation), 7 had SRED (including 1 also with sleepdriving), and 6 had SRED with hallucinations. In comparison with those without CSBs, subjects with CSBs were significantly more likely to use zolpidem, to be female and younger, and to be less likely to go to sleep immediately after taking hypnotics (Table 1). In fact, 100% of those with CSBs were taking zolpidem, and the difference was most significant. There was no significant difference regarding age, body mass index, psychiatric diagnosis, CIRS score, other

Table 1. Demographic Data and Clinical Characteristics of All Subjects With and Without CSBs

	Total (n = 125)		With CSBs (n = 19)		Without CSBs (n = 106)		Statistics With CSBs vs Without CSBs	
Variable	n	%	n	%	n	%	*P* (Fisher exact)	
Female	69	55.2	17	89.5	52	49.1	.001	
Going to bed immediately	54	43.2	3	15.8	51	48.1	.011	
Medication								
Any antidepressant	92	73.6	14	73.7	78	73.6	> .99	
Any benzodiazepine	103	82.4	14	73.7	89	84.0	.326	
Zolpidem	67	53.6	19	100.0	48	45.3	< .001	
Zopiclone	11	8.8	1	5.3	10	9.4	> .99	
Diagnosis								
Depressive disorder	60	48.0	12	63.2	48	45.3	.213	
Anxiety disorder	37	29.6	2	10.5	35	33.0	.057	
Sleep disorder	19	15.2	4	21.1	15	14.2	.488	
Other[a]	14	11.2	2	10.5	12	11.3	> .99	
	Mean	SD	Mean	SD	Mean	SD	*t*	*P*
Age, y	51.6	13.6	45.1	11.7	52.8	13.7	2.307	.023
Body mass index, kg/m^2	22.8	3.4	23.0	4.7	22.8	3.2	−0.220	.826
CIRS score	1.4	2.0	1.5	1.8	1.4	2.0	−0.196	.845
No. of psychotropic drugs	2.6	1.0	2.9	1.1	2.5	0.9	−1.633	.105

[a]Other diagnoses include adjustment disorder and somatoform disorder.
Abbreviations: CIRS = Cumulative Illness Rating Scale, CSBs = complex sleep-related behaviors.

Table 2. Demographic Data and Clinical Characteristics of Subjects Taking Zolpidem With and Without CSBs

	Total (n = 67)		With CSBs (n = 19)		Without CSBs (n = 48)		Statistics With CSBs vs Without CSBs	
Variable	n	%	n	%	n	%	*P* (Fisher Exact)	
Female	44	65.7	17	89.5	27	56.3	.011	
Going to bed immediately	24	35.8	3	15.8	21	43.8	.047	
Medication								
Any antidepressant	51	76.1	14	73.7	37	77.1	.760	
Antidepressant with high protein-binding[a]	29	43.3	7	36.8	22	45.8	.590	
Antidepressant with high CYP 3A4 inhibition[b]	5	7.5	1	5.3	4	8.3	> .99	
Any benzodiazepine	54	80.6	14	73.7	40	83.3	.494	
Zolpidem > 10 mg/d	15	22.4	11	57.9	4	8.3	< .001	
Concomitant alcohol use	2	3.0	1	5.3	1	2.1	.490	
Diagnosis								
Depressive disorder	38	56.7	12	63.2	26	54.2	.590	
Anxiety disorder	15	22.4	2	10.5	13	27.1	.200	
Sleep disorder	11	16.4	4	21.1	7	14.6	.492	
Childhood sleepwalking	2	3.0	1	5.3	2	4.2	> .99	
Past history of ECT	0	0	0	0	0	0		
	Mean	SD	Mean	SD	Mean	SD	*t*	*P*
Age, y	50.8	13.1	45.1	11.7	53.1	13.0	2.334	.023
Body mass index, kg/m^2	22.8	3.5	23.0	4.7	22.7	2.9	−0.225	.824
CIRS score	1.0	1.7	1.5	1.8	0.9	1.7	−1.272	.208
No. of psychotropic drugs	2.9	0.9	2.9	1.1	2.9	0.8	0.139	.884

[a]Including bupropion, imipramine, desipramine, citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, trazodone, and mirtazapine.
[b]Including fluvoxamine, fluoxetine, and nefazodone.
Abbreviations: CIRS = Cumulative Illness Rating Scale, CSBs = complex sleep-related behaviors, CYP = cytochrome P450, ECT = electroconvulsive therapy.

medications (including any antidepressant, any benzodiazepine, or zopiclone), or total number of psychotropic drugs. Only 20 subjects (16%) received monotherapy (including 5 receiving zolpidem monotherapy). Among them, 3 subjects receiving zolpidem monotherapy had CSBs. Nine kinds of benzodiazepines were used in this sample, including alprazolam, clonazepam, diazepam, lorazepam, oxazepam, estazolam, flunitrazepam, brotizolam, and bromazepam. Because there may be individual differences in the actions of the benzodiazepines, we also compared the prevalence of each benzodiazepine (ranging from 2.4% to 30.4%) between the 2 groups, and the results indicated no significant difference.

As 100% of the subjects with CSBs were taking zolpidem, we examined the relevant risk factors in detail in the 67 subjects taking zolpidem. Among these 67 subjects, 19 (28.4%) suffered from CSBs (Table 2). When those with CSBs were compared with those without CSBs, 4 factors were found to be significantly associated with occurrence of CSBs: taking a higher dosage of zolpidem (> 10 mg/d), being female, having the habit of not going to sleep immediately after taking the hypnotic, and being of a younger age (Table 2). The mean (SD) zolpidem dose of the subjects with CSBs was significantly higher than that of the subjects without CSBs (15.3 mg [5.1] vs 9.4 mg [3.7], Mann-Whitney $U = 177.0$, $Z = 4.361$, $P < .001$). In fact, none of the 19 subjects with CSBs took a dose less than 10 mg/d. There were no differences in the other clinical correlates between the 2 groups, those correlates including body mass index, diagnosis, CIRS score, concomitant alcohol use, childhood history of somnambulance, past history of electroconvulsive therapy, total number of psychotropic drugs, exposure to any antidepressant or benzodiazepine, exposure to an individual benzodiazepine, and exposure to antidepressants with a high protein-binding affinity or high CYP 3A4 inhibition. When the factors that were significant in univariate analysis were entered into multiple logistic regression analysis, a higher dose of zolpidem (> 10 mg/d) was the only significant predictor versus the usual dose (≤ 10 mg/d; OR = 13.1; 95% CI, 2.6–65.9; $P = .002$).

Among the 19 subjects with CSBs, 5 had past history of rare CSBs (1 had somnambulance, another 4 had SRED), but none had history of sleepdriving, sleep conversation, or other CSBs. For the 5 with past history of rare occurrence of CSBs, the frequency and severity increased significantly after taking zolpidem. Regarding the onset of CSBs related to zolpidem intake, 1 out of the 19 subjects had onset of CSBs immediately after first intake, but the others usually had onset after several weeks or months from the beginning of intake of zolpidem. Most of the CSBs were recurrent and always disappeared after discontinuation of zolpidem. Regarding the habit of administration of hypnotics, none of the 19 subjects had the habit of middle-of-the-night administration of hypnotics.

DISCUSSION

This cross-sectional pilot study was conducted in order to explore risk predictors for CSBs in users of hypnosedatives, including benzodiazepines and NBRAs. The results showed that exposure to zolpidem was the most significant risk predictor for CSBs in all subjects using hypnosedatives. Among those exposed to zolpidem, a higher dosage of zolpidem (> 10 mg/d) was the only independent significant risk predictor for zolpidem-related CSBs.

Among the subjects taking hypnotics, those suffering from CSBs all took zolpidem. Although the occurrence of zolpidem-related CSBs has been infrequently reported in the literature, their prevalence seems to be not all that low in Chinese societies. Up to 5% of Chinese psychiatric outpatients taking zolpidem had experienced CSBs.[21,22] Similar to our results, Lam et al[22] found zolpidem was associated with a high risk (OR = 6.8–22.1) for somnambulance and SRED. Though benzodiazepines have been occasionally reported to induce CSBs, the actual incidence is unknown. Among benzodiazepines, triazolam has most often been reported as being associated with CSBs[3,4,23]; however, no subjects in our sample were taking triazolam, which may partly account for our findings. Interestingly, some benzodiazepines, in particular clonazepam, may have a therapeutic effect on spontaneous CSBs,[24–26] but, in our study, no individual benzodiazepine exhibited a significant protective effect. A higher binding affinity for γ-aminobutyric acid$_A$ ($GABA_A$) receptors, especially α_1GABA_A, is linked to a greater degree of amnesia in benzodiazepines,[27,28] of which triazolam is one example.[29] Zolpidem also has a higher affinity for α_1GABA_A receptors and greater in vitro intrinsic activity as compared with other NBRAs (such as zopiclone and zaleplon).[30–32] This finding may explain why exposure to zolpidem rather than zopiclone is a significant risk predictor for amnestic CSBs. Of course, the low prevalence of exposure to zopiclone (11/125; 8.8%) in our sample may also contribute to the lower risk of CSBs. Because only 5 subjects received zolpidem monotherapy in this study, our findings suggest that zolpidem in combination with other medications may induce CSBs. An antidepressant and/or benzodiazepine medication is often necessary, but not sufficient, for inducing a CSB, and only the addition of zolpidem resulted in CSB emergence. Apparently, our study did not address the issue of zolpidem monotherapy and CSBs. Further studies are warranted in this regard.

Our analysis showed that a higher dose of zolpidem (> 10 mg/d) was a significant risk factor for CSBs, with an odds ratio of 13.1 versus the usual recommended dose (≤ 10 mg/d). None of the 19 subjects having CSBs took a dose under 10 mg/d. Several studies and case reports supported dose-dependent adverse reactions of zolpidem, including CSBs,[12] amnesia,[33] psychosis,[15,34] and delirium.[16] More apparent residual cognitive and psychomotor impairment has been shown to be associated with a middle-of-the-night administration of a higher dose of zolpidem (20 mg) rather than a usual dose (10 mg).[35] But no subjects with CSBs had the habit of middle-of-the-night administration in our study. Whether middle-of-the-night administration has any impact on the development of CSBs remains to be elucidated.

Being of the female sex was found to be significantly associated with zolpidem-related CSBs in the univariate analysis and of borderline significance in multivariate analysis. Epidemiologic studies have reported comparable prevalence rates of sleepwalking in men and women,[36,37] but a higher prevalence of women in SRED.[1] For example, Schenck et al[38] reported that 16 of 19 patients (84.2%) with zolpidem-induced SRED were female. In our study, 89.5% of the patients with zolpidem-related CSBs were female. This finding could be related to the fact that two-thirds of our subjects with CSBs were having SRED. Another factor is pharmacokinetic differences, as young women have higher zolpidem plasma concentrations as compared with young men when taking the same dose.[39]

A population-based twin study showed that 84.5%–88.9% of adult sleepwalkers had a positive history of childhood sleepwalking,[37] but only 5.3% of subjects with CSBs reported a childhood history of sleepwalking in our study. This finding supports the hypothesis that CSBs are induced by nongenetic factors such as medications. Some reports have mentioned that protein binding may be an important issue in zolpidem-related CSBs. As zolpidem has a high protein-binding affinity, the amount of free zolpidem may be increased when combined with an antidepressant with a high protein-binding property, which can displace zolpidem from the carrier protein.[16] Other studies have reported that CSBs may occur after drug-drug interaction via CYP 3A4 isoenzyme inhibition when taking zolpidem and a selective serotonin reuptake inhibitor (such as fluvoxamine or fluoxetine) simultaneously.[16,40] We also examined these possibilities in our study, as 76% of the zolpidem users also took antidepressants; however, our results do not support the protein-binding or drug-drug interaction hypothesis. Future studies with larger sample sizes are therefore needed before definite conclusions can be reached.

There were several limitations to our study. First, the sample size of patients with CSBs was not large enough to draw definite conclusions. Larger-scale studies are necessary to replicate the results. Second, this was a retrospective study based on patients' self-reported information and chart reviews, so recall bias must be taken into account. However, we attempted to minimize bias by checking important information with subjects' cohabitants. Third, since the National Taiwan University Hospital is a medical center, the participants in our study may differ from the general population, so the results may not be generalizable. However, our study has strengths in its relatively "clean" sample (free from significant cognitive disorders) and systemic investigation of medication-related issues.

In summary, this study suggests that a higher dose of zolpidem (> 10 mg/d) is the most significant risk factor for CSBs. Clinicians should be cautious in prescribing higher than recommended doses of zolpidem in the treatment of patients with sleep problems.

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Drug names: alprazolam (Xanax, Niravam, and others), bupropion (Aplenzin, Wellbutrin, and others), citalopram (Celexa and others), clonazepam (Klonopin and others), desipramine (Norpramin and others), diazepam (Diastat, Valium, and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), triazolam (Halcion and others), zaleplon (Sonata and others), zolpidem (Zolpimist, Ambien, and others), zopiclone (Lunesta).

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Author contributions: Tzung-Jeng Hwang and Hsing-Chang Ni contributed equally to this work.

Potential conflicts of interest: **Dr Hwang** has received a research grant from AstraZeneca. **Drs Ni, Chen, Lin,** and **Liao** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: The study was supported by grants from Mr Ter-Fung Tsao's Foundation, Taipei, Taiwan, and Mr Ya-Ren Cheng's Foundation, Taipei, Taiwan.

Previous presentation: Parts of the data were presented at the 45th Annual Meeting of the Taiwanese Society of Psychiatry, November 4–5, 2006, at the Taichung Veteran General Hospital, Taichung, Taiwan.

Acknowledgment: This article is dedicated to the memory of Dr Yu-Joe Lee, MD, from the Department of Psychiatry, National Taiwan University Hospital, Taipei, for his kind mentorship. We thank Dr Shur-Fen Gau, MD, PhD, from the Department of Psychiatry, National Taiwan University Hospital, Taipei, and Dr Chun-Houh Chen, PhD, from the Institute of Statistical Science, *Academia Sinica*, Taipei, Taiwan, for their comments on this article. All the acknowledged persons have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

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