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# A comparison of complex sleep behaviors with two short-acting Z-hypnosedative drugs in nonpsychotic patients

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**Objective:** Complex sleep behaviors (CSBs) are classified as “parasomnias” in the *International Classification of Sleep Disorders, Second Edition* (ICSD-2). To realize the potential danger after taking two short-acting Z-hypnosedative drugs, we estimated the incidence of CSBs in nonpsychotic patients in Taiwan.

**Methods:** Subjects (N = 1,220) using zolpidem or zopiclone were enrolled from the psychiatric outpatient clinics of a medical center in Taiwan over a 16-month period in 2006–2007. Subjects with zolpidem (N = 1,132) and subjects with zopiclone (N = 88) were analyzed. All subjects completed a questionnaire that included demographic data and complex sleep behaviors after taking hypnotics.

**Results:** Among zolpidem and zopiclone users, 3.28% of patients reported incidents of somnambulism or amnesic sleep-related behavior problems. The incidence of CSBs with zolpidem and zopiclone were 3.27%, and 3.41%, respectively, which was significantly lower than other studies in Taiwan.

**Conclusion:** These results serve as a reminder for clinicians to make inquiries regarding any unusual performance of parasomnic activities when prescribing zolpidem or zopiclone.

**Keywords:** parasomnia, somnambulism, amnesic sleep-related behavior, sleepwalking, zolpidem, zopiclone

## Introduction

Complex sleep behaviors (CSBs) are complex activities, normally associated with wakefulness, that occur when the subject is in a sleep-like state after taking a hypnosedative drug; when the subject awakens the next morning, the subject has little or no memory of the activity. CSBs include sleepwalking with object manipulation,<sup>1,2</sup> sleep-related eating disorders,<sup>3,4</sup> and sexual assault.<sup>5</sup> These behaviors may not occur frequently, but clinical awareness of the potential for associated danger and harm is necessary. 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.<sup>6</sup>

Zolpidem, a nonbenzodiazepine receptor agonist, is a highly effective hypnotic with a short half-life, minimal daytime residual side effects at the recommended dose, a low risk for tolerance, dependence, or abuse,<sup>7,8</sup> a low rate (1.1%) of adverse events, and no life-threatening events.<sup>9</sup> Zolpidem does cause decreased rapid eye movement sleep while increasing total sleep time. Incidents of zolpidem-associated nocturnal wandering and abnormal sleep behavior have previously been reported as rare side effects.<sup>10</sup>

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Zopiclone, also a nonbenzodiazepine hypnotic with even greater addictive potential than benzodiazepines, has been described as a “benzodiazepine in disguise”.<sup>11–13</sup> It is thought to act on the GABA<sub>A</sub> receptor complex at a site distinct from the benzodiazepine binding site.<sup>14</sup> Tolerance to the effects of zopiclone can develop after a few weeks’ use and abrupt withdrawal, particularly with prolonged and high doses. Zopiclone can also cause seizures and delirium.<sup>15,16</sup> It is the first cyclopyrrolone possessing a pharmacological profile of high efficacy and low toxicity similar to that of benzodiazepines.<sup>17</sup> Its elimination half-life is 5–6 hours, it does not accumulate upon repeated administration, and its pharmacokinetic profile is not substantially modified in the elderly and renal failure patients.<sup>18</sup> In clinical trials, zopiclone (usually 7.5 mg) improved sleep in chronic insomniacs similarly to nitrazepam 5 mg, flurazepam 15–30 mg, triazolam 0.5 mg, and temazepam 20 mg, but in a single study was slightly less effective than flunitrazepam 2 mg in some evaluation criteria.<sup>17</sup> The drug is generally well tolerated by patients of all ages and the most frequently reported adverse effects are bitter taste and dry mouth.<sup>14</sup> Treatment for withdrawal due to adverse effects is seldom required and reports of rebound insomnia after zopiclone withdrawal are rare.<sup>14</sup> Minimal impairment of psychomotor skills and mental acuity may occur in the morning after a bedtime dose of zopiclone.<sup>17</sup>

## Methods

In this study, we employed a case-control design to address the issue of CSBs in nonbenzodiazepine users. Specifically, we were most interested in testing whether medication, sex, and age would be risk predictors for CSBs.

Data were collected through extensive chart reviews of nonpsychotic outpatients treated with zolpidem or zopiclone for insomnia at psychiatric services of Tri-Service General Hospital (Taipei City, Taiwan) over a 16-month period in 2006–2007. Those who developed adverse side effects were included for further interviews. The inclusion criteria were: (1) 18–86 years of age; (2) prescribed zolpidem or zopiclone; (3) diagnosed with affective disorders, anxiety disorders, or simple sleep disturbance; and (4) cohabited with others, such as a family member or partner. Exclusion criteria were living alone, also taking benzodiazepines at night, or history of eating disorders, mental retardation, dementia, attention-deficit/hyperactivity disorders, substance abuse, and/or seizure disorders.

A total of 1,220 patients were eligible for the study (486 males, 734 females). All of the patients were taking

hypnotic medications after evaluation and diagnosis by a psychiatrist on the basis of *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* criteria. The patients were then given a structured interview by a trained assistant with a special focus on the quality of sleep and associated complaints after zolpidem or zopiclone use. Data on the patients’ demographic and personal history, including age, sex, drug category, and diagnosis, were recorded.

## Statistical analysis

Descriptive results of continuous variables were expressed as mean (standard deviation) and categorical variables were expressed as frequency (%). All statistical analyses were performed with Student’s *t*-test, chi-square tests, and/or Fisher’s exact test using the Statistical Package for Social Sciences version 20.0 (SPSS, Inc, Chicago, IL, USA). A *P* < 0.05 was considered statistically significant.

## Results

Among 1,220 zolpidem or zopiclone users, 40 (3.28%) patients reported incidents of somnambulism or amnesic sleep-related behavior problems. Seventeen subjects were male and 23 were female. The average age was 39.16 years, and the average dosage of zolpidem/zopiclone was 10.0 mg per day. The five most common diagnoses were: major depressive disorder, recurrent; dysthymic disorder; major depressive disorder, single episode; insomnia; and bipolar disorder. The behavioral problems included 20 patients who could not remember what happened after taking zolpidem/zopiclone. Among them, eleven ate food, four walked in their houses, two talked with others, and three had other symptoms such as dizziness (Table 1). There was no significant association with older age (>65 years), sex, side effects, or drug category, although those who had side effects were younger than those without side effects (34.20 years versus 39.33 years, *P* = 0.033) (Table 2).

## Discussion

CSBs are categorized as “parasomnias” in the *International Classification of Sleep Disorders* (ICSD-2), which defines parasomnia as a sleep disturbance characterized primarily by undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep.<sup>19</sup> The incidence, mechanisms, and management of CSBs have been reported,<sup>20</sup> especially for zolpidem-induced amnesia and somnambulism.<sup>21</sup> The only unique risk predictor of zolpidem-related CSBs was a high dosage of zolpidem

**Table 1** Demographic data and complex sleep behaviors

Variables	Number	Percentage
<b>Age</b>		
Mean $\pm$ SD (range)	39.16 $\pm$ 14.98	18–86
<b>Sex</b>		
Male	486	39.84
Female	734	60.16
<b>Category</b>		
Zopiclone	88	7.21
Zolpidem	1132	92.79
<b>Side effects</b>		
Without side effects	1180	96.72
Total with side effects	40	3.28
Eating during the night	11	0.90
Excitement/talkativeness	2	0.16
Somnambulism	4	0.33
Antegrade amnesia	20	1.64
Others, such as dizziness	3	0.25

**Abbreviation:** SD, standard deviation.

(>10 mg/day).<sup>22</sup> However, comparisons of short-acting hypnotics are limited in Taiwan. We performed a chart review study for zolpidem and zopiclone in order to determine the incidence and risk factors for Z-drug-related CSBs.

A possible mechanism for hypnotic CSBs and amnesia is enhanced GABA activity at GABA<sub>A</sub> receptors, especially the  $\alpha 1$ -GABA<sub>A</sub> receptors. The amnesia that accompanies CSBs is possibly due to inhibition of the consolidation of short- to long-term memory, suggesting that the risk may extend to nonGABAergic effects as well. While amnesia and GABA-related receptor actions are the most frequently discussed mechanisms for CSBs in the literature, they do not fully explain such behaviors. This suggests that other mechanisms and factors play a role.

In comparison with the data of Hwang et al<sup>22</sup> and Tsai et al,<sup>21</sup> our investigation focused on adverse reactions to zolpidem and zopiclone in nonpsychotic Taiwanese patients. For zolpidem, our study included 1,132 patients, which was 4.4–9.1 times larger than samples in the previous two articles. For zopiclone, our study included 88 patients; the previous two articles did not study zopiclone. The incidence of CSBs

with these two short-acting Z-drugs was 3.28%, which was lower than the 5.1% reported by Tsai et al or the 15.2% reported by Hwang et al.<sup>21,22</sup> We suggest that the main causes for the difference is our study's larger patient sample size, removal of psychotic patients, and collecting data from outpatients treated by different attending physicians.

## Conclusion

Although mean age of those with CSBs was younger than those without CSBs in our study, clinicians should still be cautious when prescribing “Z-drugs” in the treatment of elderly patients with sleep problems. Despite the lower incidence of CSBs shown in our study compared to previous studies, careful attention when prescribing these short-acting Z-drugs is still advised. Much more severe adverse effects have been reported for zolpidem or other nonbenzodiazepine hypnotics, such as falls in hospitalized patients<sup>23</sup> or even hip fracture in nursing home residents.<sup>24</sup> The relationship between zolpidem- or zopiclone-related CSBs and falls and hip fracture remains unclear, but is important to clarify in future studies.

## Disclosure

The authors report no conflicts of interest in this work.

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**Table 2** Differential analysis by age, sex, drug category, and side effects of patients

Group	Sample size (n)	Mean (age)	Standard deviation	P-value
Male	486	36.54	15.47	<0.001
Female	734	40.90	14.40	
Zopiclone	88	38.58	14.62	0.704
Zolpidem	1132	39.21	15.01	
Without side effects	1180	39.33	14.99	0.033
With side effects	40	34.20	13.86	

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