Zolpidem-induced Psychiatric Symptoms

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Objective: Zolpidem is considered a safe and effective hypnotic agent for the short-term treatment of insomnia. Sporadic cases of zolpidem-induced psychiatric symptoms, however, such as somnambulism, delirium or psychotic symptoms have been reported. We report 10 additional cases with zolpidem-induced psychiatric symptoms in patients from a single psychiatric clinic. These cases illustrate the need for clinicians to carefully monitor patients for adverse events associated with zolpidem. Case reports: We identified 10 patients with zolpidem-induced psychiatric symptoms from a review of medical records between June 2002 and February 2003. Among these patients, three had amnesia, three had somnambulism, three had symptoms of delirium and one had psychotic symptoms. Two of these patients had exhibited dangerous behaviors towards their family members. All of these patients denied any history of above psychiatric problems before the use of zolpidem as well as any recurrence after discontinuation. Conclusion: Zolpidem may induce amnesia, somnambulism, delirium or psychotic symptoms in a small percentage of patients. Careful monitoring of these potential adverse events and alerting of patients to their possible occurrence is warranted.

Key words: zolpidem, somnambulism, delirium, psychotic symptoms
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Introduction

The physiology of sleep, memory, awareness and arousal can be influenced by different drugs [1]. Zolpidem is a benzodiazepine (BZD) agonist, which is a non-BZD hypnotic of the imidazopyridine group with a rapid onset and short duration of action. Its side effect profile is milder than those of benzodiazepines and barbiturates used for treating insomnia [2]. However, zolpidem was also reported to be associated with many psychiatric symptoms, such as somnambulism [3,4], delirium [5] and psychotic symptoms [6] in sporadic cases. These psychiatric side effects could be dangerous due to the possibility of accidental injuries including falling down and hurting others.

Case Report

We identified 10 patients with zolpidem-induced psychiatric symptoms, such as amnesia, somnambulism, delirium or psychotic symptoms from a review of medical records between June 2002 and February 2003. The clinical data of these patients are summarized in the table.
All of these patients denied any history of amnesia, somnambulism, delirium or psychotic state before using zolpidem, and all of them denied recurrence after discontinuation of zolpidem, or shifting to estazolam or clonazepam. The dosage of zolpidem in all cases was 10 mg before sleep.

As shown in the table, the age of these patients ranged from 21 to 71 years. Main diagnostic categories were defined according to the Diagnostic and Statistical Manual, 4th edition [7] and included adjustment disorder with anxious mood (5 patients), dysthymic disorder (3 patients), major depressive disorder (1 patient), and bipolar I disorder, in the depressed phase (1 patient). The duration from the starting zolpidem to reporting CNS side effects ranged from 3 to 150 days. The most common drugs used in combination treatment were antidepressants (citalopram, sertraline, paroxetine, fluvoxamine) and valproic acid. After discontinuing zolpidem and shifting to the other hypnotics (estazolam or clonazepam) and continuing all other concomitantly used medications, above psychiatric symptoms disappeared completely in all patients.

Three patients (case 4, 5, 9) had amnesia about nocturnal binge eating or phone calling. Three patients (case 3, 7, 8) had delirium with confusion, disorientation, irrelevant speech and disorganized behaviors, and these psychotic symptoms were recognized by their family members. One patient (case 1) had psychotic symptoms with auditory and visual hallucinations. He described that he saw himself walking out from his wedding picture and talking to him vividly. The following morning, this patient had only a vague memory of the incident.

Three patients (case 2, 6, 10) had clinical features of somnambulism. The most serious behavioral manifestation involved placing a baby in a hot water bath (case 2). This young mother was under the pressure of having to take a license examination for operating a vehicle and had symptoms of anxiety and insomnia for which she had taken the medication. After taking zolpidem as a hypnotic, she awoke during sleep without full consciousness and gave the baby a bath in hot water. After hearing the baby screaming, her husband found the terrible scene and sent the baby to the hospital immediately. The baby had first to the third degree burns injury over 50% skin of the body surface area. The patient regained consciousness with amnesia about this event and expressed her horror and regret about what she had done to her baby. Another patient behaved violently towards his wife (case 10) after taking zolpidem, but awoke with amnesia about the incident. Another unusual behavior manifestation occurred in a patient (case 6) who slept alone and discovered that she had eaten raw meat beside the bed during the night, and suffered from nausea and a disgusted feeling on observing the scene on awakening in the morning.

These three cases had their episodes of somnambulism which occurred during the first third of their normal sleep period, as reported by their family members. During these episodes, they could be awakened only with difficulty and responded poorly to others’ attempts at communication. None of these patients had any memory about these activities. These clinical features fulfilled the criteria of somnambulism (sleepwalking disorder). However, none of the patients was examined by night sleep electroencephalography (EEG).

Discussion

Somnambulism, or sleepwalking, generally occurs during stages 3 and 4 of slow-wave sleep.
During an episode of somnambulism, the normal arousal mechanism is altered, and the patients have partial arousal without full consciousness. Electroencephalographic changes associated with the use of zolpidem include suppression of REM sleep [9]. Some drugs produce a physiological state during slow-wave sleep that can present clinically as somnambulism [8]. It is difficult to distinguish somnambulism from other parasomnias that may have similar presentations, such as disoriented arousal, night terrors, hypnagogic hallucinations and sleep paralysis, nocturnal seizures, REM behavior disorder [7]. A definitive diagnosis of somnambulism usually requires all-night sleep recordings [8], which were not performed on our patients.

A post-marketing surveillance report of 16,944 cases treated with zolpidem [10] found the frequencies of zolpidem-induced psychiatric symptoms were rare: agitation 0.1% (19), hallucination 0.03% (5), amnesia 0.02% (3). But the report did not describe any case of somnambulism or delirium. Our literature review found a few case reports of zolpidem-related somnambulism and one case report of zolpidem-related delirium. This series of zolpidem-induced psychiatric symptoms includes three cases of somnambulism and three cases of delirium associated with zolpidem treatment only in a single outpatient clinic. The relatively high number of cases of zolpidem-induced psychiatric symptoms identified in this study suggests the condition is not as rare as is suggested by previous reports.

Toner et al [2] postulated that there are four major variables associated with susceptibility to developing hallucinations or delirium during zolpidem use. These are gender, zolpidem dose, protein binding affinity and the degree of cytochrome P450 3A4 isoenzyme inhibition by concomitantly used antidepressants. Gender plays an important role since 82.4% of the previous cases of zolpidem induced hallucinations were in female patients. All zolpidem induced hallucinations occurred with doses greater than 5 mg per day. There were no reports of hallucinations when patients took doses of 5 mg or less. The concomitant use of an antidepressant (fluoxetine, fluvoxamine, paroxetine, sertraline, trazodone) which is highly protein bound may displace zolpidem from the carrier protein and increase the amount of free zolpidem. The antidepressants that are most likely to exert inhibition of cytochrome P450 3A4 isoenzyme are nefazodone, fluvoxamine, and norfluoxetine [11]. In this series, there was no gender predominance and the dosage of zolpidem in all cases was 10 mg before sleep. Zolpidem treatment was combined with citalopram, fluvoxamine, sertraline or trazodone in six cases.

In this series, three patients had activities of nocturnal eating and phone calling, but had amnesia for the event on the next day. Three patients had typical symptoms of delirium with confusion, disorientation, irrelevant speech, disorganized behaviors and one patient had typical psychotic symptoms of auditory and visual hallucinations after taking zolpidem. Two patients had somnambulism with decreased ability of judgment which resulted in harming a baby by putting it in hot water, and nocturnal eating of uncooked meat. Another patient had a somnambulistic episode involving violence to his wife. Although clinical features of these three cases fulfilled the criteria of somnambulism, all night sleep EEG data was not obtained to confirm the diagnosis.

The main DSM-IV diagnoses in these patients were adjustment disorder with anxious mood, dysthymic disorder and major depressive disorder, but these categories were not associated with the severity of behavioral symptoms and the psychiatric symptoms which occurred during zolpidem
treatment. The duration of zolpidem treatment prior to onset of these psychiatric symptoms varied from 3 to 150 days, and was related to the observation and reporting of related symptoms by the patient, family members or doctors who prescribed zolpidem. We also found, however, that some patients or family members told their doctors about these symptoms of somnambulism, delirium or psychotic symptoms, but their doctors did not consider these symptoms to be related with the zolpidem use. Therefore, patient suffering from zolpidem-induced side effects was prolonged due to lack of recognition by their doctors.

Trazodone 50 mg was used to augment the hypnotic effect of zolpidem for two patients (case 3 and 10). However, trazodone is not therapeutic for depressive or anxiety disorders if the daily dosage is less than 300 mg. A recent review article concluded that it is uncertain whether trazodone's risk/benefit ratio warrants its use in nondepressed patients with insomnia [12].

Although the safety and effectiveness of zolpidem as a short-acting hypnotic agent has been established, the current series as well as our findings from literature review illustrate the importance of awareness of that sporadic psychiatric symptoms may occur including zolpidem-induced amnesia, somnambulism, delirium, psychotic symptoms, and dangerous behaviors towards family members. We suggest that all patients taking zolpidem as hypnotic agent should be warned about these possible psychiatric side effects prior to prescription. Use of zolpidem as a hypnotic agent should be reconsidered because of these psychiatric side effects and its high cost as compared to regular benzodiazepines.

References

Table 1. Demographic and clinical data of 10 patients with zolpidem-induced psychiatric symptoms

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>DSM-IV</th>
<th>Days</th>
<th>Combined drugs of treatment</th>
<th>Replaced with other hypnotics</th>
<th>Main psychiatric symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>M</td>
<td>300.4</td>
<td>3</td>
<td>citalopram (20 mg)</td>
<td>estazolam</td>
<td>auditory and visual hallucination, partial amnesia</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>F</td>
<td>309.24</td>
<td>10</td>
<td>nil</td>
<td>clonazepam</td>
<td>hurt the baby with hot water, somnambulism</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>M</td>
<td>309.24</td>
<td>4</td>
<td>trazodone (50 mg)</td>
<td>estazolam</td>
<td>confusion, disorientation, disorganized behaviors, irrelevant speech (delirium)</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>F</td>
<td>300.4</td>
<td>7</td>
<td>fluvoxamine (100 mg)</td>
<td>estazolam</td>
<td>binge eating and phone calling, amnesia</td>
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<tr>
<td>5</td>
<td>21</td>
<td>M</td>
<td>296.5</td>
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<td>estazolam</td>
<td>binge eating and phone calling, amnesia</td>
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<td>diazepam (10 mg)</td>
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<td>62</td>
<td>F</td>
<td>300.4</td>
<td>7</td>
<td>fluvoxamine (50 mg)</td>
<td>estazolam</td>
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<td>7</td>
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<td>150</td>
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<td>estazolam</td>
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<td>estazolam</td>
<td>confusion, disorientation, clonazepam disorganized behaviors, irrelevant speech (delirium)</td>
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<tr>
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<tr>
<td>10</td>
<td>60</td>
<td>M</td>
<td>309.24</td>
<td>19</td>
<td>trazodone (50 mg)</td>
<td>estazolam</td>
<td>violence towards his wife, somnambulism</td>
</tr>
</tbody>
</table>

*DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition

*The duration from starting zolpidem to reporting the occurrence of somnambulism
目的：Zolpidem 被認為是安全且有效的安眠藥，但有些個案報告指出 zolpidem 會造成夢遊症、譫妄或精神病性症狀。本文報告 10 位個案出現 zolpidem 引起之精神症狀副作用，並回顧相關文獻及建議小心監測服用 zolpidem 可能造成的危險副作用。病例報告：我們發現 10 位個案使用 zolpidem 之後，出現精神症狀副作用，其中 3 位出現失憶、3 位出現夢遊、3 位出現譫妄、1 位出現精神病性症狀。而且有 2 位病患在夢遊時對家人造成身體傷害。所有個案在使用 zolpidem 之前，並無失憶、夢遊、譫妄或精神病性症狀病史，停止使用之後，全都不再復發。結論：Zolpidem 可能造成失憶、夢遊、譫妄及精神病性症狀。因此，臨床使用 zolpidem 過程，必須對所有個案監測是否出現這些潛在的副作用。

關鍵詞：zolpidem，夢遊症，譫妄，精神病性症狀

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