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Adverse Reactions to Zolpidem: Case Reports and a Review of the Literature

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Abstract

Objective:

Zolpidem, a nonbenzodiazepine hypnotic, is very effective and widely prescribed in clinical practice for the treatment of insomnia and is thought to have few adverse effects. However, zolpidem-induced adverse effects have begun to be reported in the literature, but few systemic descriptions of the adverse effects (especially for psychotic reactions) of zolpidem have been undertaken. In light of the accumulating reports of adverse reactions to zolpidem, we present 2 case reports of zolpidem-induced adverse effects and review the literature on this subject.

Data Sources:

Articles were selected by the authors on the basis of our experience and by a PubMed search using the terms *zolpidem* or *side effects* or *adverse effects* or *adverse reactions*.

Study Selection and Data Extraction:

Publications relevant to the objective of this article were obtained (1992–2010), and some adverse neuropsychiatric reactions were summarized.

Data Synthesis:

Zolpidem has been associated with the development of adverse neuropsychiatric reactions, such as hallucinations/sensory distortion, amnesia, sleepwalking/somnambulism, and nocturnal eating. The

following 4 variables should be considered when prescribing zolpidem: (1) gender: women have been found to have a significantly higher serum zolpidem concentration than men; (2) zolpidem dose: the adverse reactions that develop are dose dependent; (3) protein binding affinity: a high proportion of zolpidem is protein bound; therefore, low serum albumin results in a higher level of free zolpidem leading to adverse psychiatric reactions; and (4) cytochrome P450 (CYP) isoenzyme inhibition: concomitant administration of zolpidem and other drugs may cause interactions that lead to increased concentrations of zolpidem.

Conclusions:

Zolpidem is clinically very effective in treating insomnia. However, while rare, zolpidem-induced unusual complex behavior may develop. Primary care physicians should be alert to the possible unusual complex adverse effects of zolpidem.

Zolpidem is a novel, rapid-onset, short-acting, imidazopyridine hypnotic drug. Chemically unrelated to benzodiazepines, zolpidem is thought to have fewer adverse effects, especially with respect to residual sedation, amnesia, and the potential for rebound insomnia and dependence. It is a strong sedative with only minor anxiolytic, myorelaxant, and anticonvulsant properties and has been shown to be effective for the induction and maintenance of sleep in adults. Zolpidem, in contrast to the benzodiazepines, has been found to preserve stage 3 and 4 sleep (non-rapid eye movement [NREM] sleep), and zolpidem and zopiclone produce similar increases in slow-wave sleep.^{1,2} Zolpidem also does not induce consistent objective rebound insomnia. The use of zolpidem has therefore become increasingly accepted as very safe, and the number of patients prescribed this medication has increased.

On the other hand, while rare, the number of reported adverse reactions has begun to increase. There have been several reports describing neuropsychiatric reactions such as visual hallucinations/sensory distortion, delirium, amnesia, sleepwalking/somnambulism, and nocturnal eating associated with zolpidem use. In light of the accumulating reports of adverse psychiatric reactions to zolpidem, we review the literature pertaining to this subject and present 2 case reports from our own clinical practice.

METHOD

We reviewed publications relevant to zolpidem-induced adverse neuropsychiatric reactions selected on the basis of our experience and by a PubMed search (1992–2010) using the terms *zolpidem* or *side effects* or *adverse effects* or *adverse reactions*. Some adverse neuropsychiatric reactions are summarized. In [Table 1](#), reported cases of zolpidem-induced adverse reactions are presented.

Clinical Points

- ♦ Primary care physicians and psychiatrists should be alert to the possible unusual complex adverse reactions of zolpidem.
- ♦ While rare, patients taking zolpidem may develop adverse neuropsychiatric reactions, such as hallucinations/sensory distortion, amnesia, sleepwalking/somnambulism, and nocturnal eating.

LITERATURE REVIEW AND CASE REPORTS

Pharmacokinetics/Pharmacodynamics

A dose of zolpidem 10 mg in the nonelderly and a reduced dose of 5 mg in elderly individuals are clinically effective. Unlike benzodiazepines, the pharmacologic activity of zolpidem results from selective binding to central benzodiazepine receptors of the $\omega 1$ subtype,³ but zolpidem possesses low affinities for

the ω_2 and ω_3 receptor subtypes.⁴ Zolpidem interacts with the distinct binding sites of the γ -aminobutyric acid (GABA) receptor complex in a fashion similar to the benzodiazepines. Zolpidem appears to potentiate GABA-ergic transmission, thus resulting in the inhibition of neural excitation. Zolpidem shows greater selectivity for α -containing receptors compared to zopiclone, triazolam, or midazolam.⁵

More than 90% of zolpidem exists in its protein-bound form, and it is rapidly absorbed with a bioavailability of approximately 70%.¹ After a single 20-mg oral dose, typical values of the pharmacokinetic variables of zolpidem in humans are a peak plasma concentration occurring 0.75 to 2.6 hours postdose and a terminal elimination half-life of 1.5 to 3.2 hours. Compared with the majority of benzodiazepines, zolpidem is relatively short acting, with an ultrashort half-life,² and increases sleep stability by significantly improving the sleep depth and sleep quality.⁶ Zolpidem is therefore useful for the rapid induction of sleep, is almost devoid of residual effects even at high doses, and offers a good margin of safety for daytime activities.^{1,3}

Zolpidem undergoes extensive hepatic metabolism by a variety of cytochrome (CYP) isoenzymes. The major routes of its metabolism are oxidation and hydroxylation. None of the metabolites of zolpidem have any degree of pharmacodynamic activity. Most (48%–67%) of the products of its metabolism are excreted in the urine, with the rest being excreted into the bile.¹

There is an increase in peak plasma concentration and area under the plasma concentration–time curve in the elderly.¹ Elderly patients have lower clearance and volumes of distribution. The available evidence suggests that zolpidem produces no rebound or withdrawal effects and that patients experience good daytime alertness.^{1,3}

The evidence is concordant in showing that a 10-mg dose in the nonelderly is associated with a clinically appropriate degree of efficacy together with a low incidence of adverse effects.² There is an abundance of information regarding the safety of zolpidem in the treatment of insomnia. In a large postmarketing surveillance database study involving 16,944 patients,⁷ only 182 patients (1.1%) reported an adverse effect. The most common adverse events were headache, somnolence, and dizziness.² The risk of abuse and tolerance with zolpidem also is low when used as directed.²

Hallucinations/Sensory Distortion

In 1992, Ansseau et al⁸ reported the cases of 2 patients who developed visual hallucinations and amnesia shortly after the intake of zolpidem. Iruela et al⁹ reported a case of a patient presenting with macropsia without amnesia. Since then, the number of reports of neuropsychiatric reactions (hallucinations and sensory distortions) associated with zolpidem use has increased, indicating that zolpidem should not be considered risk free, even at therapeutic doses, and might produce transient cognitive and behavioral impairments similar to those caused by benzodiazepines.^{8–21} These reports suggested some common clinical characteristics: the patients were almost all female, they experienced adverse reactions at doses greater than 10 mg, the reactions began 20–30 minutes after ingestion, the reactions spontaneously cleared without treatment after several hours or discontinuation of zolpidem use, and almost all patients experienced amnesia, with some of them suggesting delirium.^{10,21}

In a postmarketing study of zolpidem,⁴ delirium or confusion was seen in less than 1% of patients. Hallucinations or illusions were seen in 0.3% of patients. A great majority of these cases (82.4%) involved female patients. The various publications describing visual hallucinations showed that these adverse events occurred in subjects who differed with regard to concomitant medication, age, and sex.⁴ However, de Haas et al¹⁸ reported the case of a patient who developed visual hallucinations after zolpidem intake and whose plasma levels were in the midrange of those of subjects without hallucinations and were comparable to the levels measured in other clinical studies. The authors speculated that the hallucinations caused by zolpidem were related to individual variations in pharmacodynamic sensitivity or neuroanatomical differences.¹⁸

Toner et al⁴ postulated that the following 4 variables should be considered when prescribing zolpidem:

(1) Gender: women have been found to have a significantly higher serum zolpidem concentration (40%) than men.

(2) Zolpidem dose: zolpidem-induced hallucinations occurred with doses greater than 5 mg/d and were dose dependent.

(3) Protein-binding affinity: a high proportion of zolpidem is protein bound. In cases of patients with low levels of albumin, such as those suffering from malnutrition, a low serum albumin level would result in a higher level of free albumin. Other antidepressants that are highly protein bound may also displace zolpidem from its carrier protein and increase the amount of free zolpidem.

(4) CYP3A4 isoenzyme inhibition: zolpidem is metabolized via the CYP3A4 isoenzyme. Medication could decrease zolpidem metabolism, leading to toxicity, especially by concomitant use with antidepressants.

We experienced a case involving visual hallucinations and sensory distortion after the intake of zolpidem, and it is reported as follows.

Case 1

Ms A, a 16-year-old high school female outpatient with social phobia (*DSM-IV* criteria), took 5 mg of zolpidem at bedtime for insomnia for the first time. She had no history of visual problems or alcohol or other substance abuse. Thirty minutes after taking zolpidem, Ms A began to experience a variety of unusual visual experiences. She saw the room's light moving down onto her face and “many eyes” watching her from inside the walls. The patient was frightened by these visual experiences. One hour later, Ms A's visual distortion and hallucinations spontaneously cleared without treatment. Ms A subsequently fell asleep. She had full recollection of these experiences in the morning.

Interactions with concurrent use of antidepressants.

Various reports have described adverse reactions in patients receiving concomitant selective serotonin reuptake inhibitors (SSRIs). The majority of the patients experiencing hallucinations (58.8%) were taking antidepressants concomitantly.⁴ Zolpidem is mainly metabolized via the CYP3A4 isoenzyme and is partially metabolized by CYP2C9 and CYP1A2.²² The serum zolpidem concentration is increased by concomitant use of SSRIs or other drugs that possess a degree of CYP3A4 inhibition.¹⁷

Katz¹⁰ reported a case of an adolescent who experienced hallucinations and delirium that might have been induced by a paroxetine-zolpidem interaction. Inami et al²⁰ reported the case of a 31-year-old Japanese woman who developed episodes of visual hallucinations and sensory distortion after taking paroxetine and zolpidem. She had a history of mild depression and insomnia for 3–4 months and was referred for treatment. At 11:30 PM, she took 10 mg of zolpidem for the first time and 10 mg of paroxetine. The patient reported visual hallucinations that started 10–15 minutes after drug intake.²⁰ She saw a person pulling her hair, her hands having 20 fingers, and a child with a black face. Her husband noticed that she was slightly incoherent and talkative. The next morning, she could not remember anything of the previous night. The hallucinations lasted 6 days and disappeared after discontinuation of zolpidem. The authors postulated that a zolpidem-paroxetine interaction induced her visual hallucinations and amnesia and that these psychotic symptoms resulted from acute intoxication.²⁰

Paroxetine strongly inhibits CYP2D6 but does not inhibit CYP3A4. Therefore, previous studies suggested that both zolpidem and paroxetine were highly protein bound and that both interact via competitive binding, leading to increased concentrations of zolpidem, which might have resulted in the adverse reaction.^{10,12} In addition, Coleman et al²³ reported a case of a 54-year-old man who presented with

hallucinations during treatment with zolpidem and fluoxetine. Fluoxetine is also a potent inhibitor of CYP2D6 and a moderate inhibitor of CYP2C9.

On the other hand, in a case of concomitant use of zolpidem and fluvoxamine, Kito and Koga¹⁷ reported a case of an elderly patient with visual hallucinations and amnesia that might have been related to a possible fluvoxamine-zolpidem interaction. Fluvoxamine potently inhibits CYP1A2 and CYP2C19 and has mild to moderate inhibitory effects on CYP2C9, CYP2D6, and CYP3A4.²⁴ Therefore, concomitant use of zolpidem and fluvoxamine would result in an increased fluvoxamine concentration and the occurrence of visual hallucinations and amnesia.

Concomitant administration of zolpidem and SSRIs is relatively safe according to previous findings, but physicians should consider possible zolpidem-SSRI interactions as a cause of adverse psychiatric reactions. Several case reports also suggest that interactions between zolpidem and SSRIs may lead to prolonged zolpidem-associated hallucinations.¹⁵

Amnesia.

Canada¹⁴ reported 2 cases involving amnesia possibly associated with zolpidem administration. Two patients experienced amnesia after taking zolpidem (5 mg and 10 mg). Neither patient could recall telephone conversations within an hour of taking zolpidem. Neither patient experienced psychotic symptoms such as hallucinations.¹⁴

As for amnesia, some 15% of patients experienced anterograde amnesia after zolpidem administration, and, in approximately 50% of those patients, it occurred within 30 minutes.²⁵ A 10-mg zolpidem dose produced a 16% frequency and a 20-mg dose produced a 21% frequency of amnesia postoperatively.²⁶ The amnesia was characterized as anterograde, dose related, occurring shortly after zolpidem intake, and without obvious abnormal behavior.^{27,28} Zolpidem seems to have no effect on retrograde memory, but some effects are seen on anterograde memory.

Sleepwalking/somnambulism.

We found several case reports regarding the unusual side effects of zolpidem, including multiple case reports of sleepwalking/somnambulism. Sleepwalking is relatively common in childhood but is rather infrequent in adulthood. Although its cause is uncertain, it is believed that stress, medication (lithium, neuroleptics, benzodiazepines, and other sedatives), substance abuse, and brain injury play a large role.²⁹

Mendelson³⁰ first reported a case of sleepwalking after the intake of zolpidem. The patient got up and began walking around on top of the bed during stage 4 sleep on polysomnography. He had received a routine polysomnography. The patient reported that he thought he had been asleep and was dreaming about standing on a step stool and needing to get higher. He had no memory of actually walking about. Since then, there have been several reported cases of somnambulism occurring after the intake of zolpidem for insomnia.^{29,31-35} Those with a history of sleepwalking in childhood may be more susceptible to sleepwalking after taking zolpidem.³⁰

The mechanism of the induction of somnambulism/amnesic sleep-related behaviors remains unclear. Sleepwalking, or somnambulism, is a series of complex behaviors that are initiated during slow-wave sleep (stage 3 or 4 NREM sleep) and result in purposeless movements or walking during sleep. Sleepwalking represents a disorder of arousal. Even though it minimally affects sleep architecture, zolpidem may increase stage 3 and 4 sleep. Sharma and Dewan³⁴ reported a case of zolpidem-induced somnambulism and described that, during an episode of somnambulism, the normal arousal mechanism was altered, which resulted in partial arousal without full consciousness. They suggested that zolpidem produced a physiologic state during slow-wave sleep that presented clinically as somnambulism and

electroencephalographic changes associated with the use of zolpidem including suppression of REM sleep.³⁴

Recently, Tsai et al²⁸ reported somnambulism or amnesic sleep-related behavioral problems in 13 (5.1%) patients out of a total of 255 zolpidem users and found that anterograde amnesia appears to be a zolpidem dose-dependent phenomenon that is reported to occur more frequently at doses higher than 15 mg/night. Ganzoni et al³⁶ observed anterograde amnesia/somnambulism in 1.1% of 1,972 insomnia patients taking zolpidem.

We experienced a case involving sleepwalking after the concomitant use of zolpidem and fluvoxamine, and it is reported here as follows.

Case 2

Ms A, a 15-year-old high school female outpatient with a 2-month history of depression and insomnia, had been treated with 5 mg of zolpidem as needed for insomnia at bedtime. She had no history of psychosis, substance abuse, or sleep disturbance. We prescribed 25 mg/d of fluvoxamine for her depressive symptoms. After 2 weeks on this concomitant medication, the patient took zolpidem at 9:00 PM. At 12:30 AM, Ms A woke up and walked out of her house without changing her clothes and visited her friend's house 1½ miles away. She spoke to her friend with incoherent speech. After 30 minutes, the friend's mother brought Ms A home. She subsequently fell asleep. The patient had no memory of this event in the morning. Zolpidem treatment was stopped, and, since then, no complaints of sleepwalking have developed. This sleepwalking episode was attributed to the interaction between zolpidem and fluvoxamine.

The mechanisms of various neuropsychiatric reactions (hallucinations, amnesia, sleepwalking) are not known. We speculate that these reactions may be related to the rapid increase of serum concentration of zolpidem and may lead to a possible toxic effect on the central nervous system.

Nocturnal Eating

Nocturnal eating syndrome is a recent addition to the *International Classification of Sleep Disorders: Diagnostic and Coding Manual*, 2nd edition.³⁷ In the manual, the condition is described as a problem not only of children, but also of adults. Recently, increasing attention has been paid to patients who experience nocturnal eating after taking zolpidem. Harazin and Berigan³¹ reported a case of nocturnal eating with somnambulism after the intake of zolpidem. On the fourth night of taking 10 mg of zolpidem, a 46-year-old man prepared a meal and consumed it and returned to bed at midnight. He also developed somnambulism with amnesia. Once the medication was discontinued, the unusual behavior stopped.³¹

Morgenthaler and Silber³² reported 5 cases involving the onset or worsening of amnesic nocturnal eating behavior after initiation of zolpidem therapy. These patients' problems were subsequently resolved by discontinuation of zolpidem and treatment of the underlying intrinsic sleep disorder.³² Tsai et al²⁷ described 3 female patients who, while taking zolpidem, experienced anterograde amnesia and compulsive activities, which were reported as cleaning, shopping, and eating. One of the patients experienced uncontrolled eating as a compulsive act. Hoque and Chesson³⁸ reported a case of a 51-year-old woman who developed sleepwalking, sleep-related eating disorder, and sleep-induced driving.

Najjar³⁹ described 3 types of nocturnal eating. First group: patients experience nocturnal eating as a symptom of a diurnal eating disorder. Second group: patients demonstrate nocturnal eating as a result of an eating disorder that presents predominantly during sleep. These patients generally complain of insomnia and are fully awake during their nocturnal eating episode.³⁹ Third group: patients frequently are amnesic completely or partially to the eating episode, which occurs during NREM sleep. Najjar³⁹ reported

the case of a 46-year female patient who developed a sleep-related eating disorder and experienced amnesia when she was treated with zolpidem.

In some series of sleep-related eating disorders, the majority of patients are found to have concurrent conditions such as restless legs syndrome, periodic limb movement disorder, or obstructive sleep apnea.^{32,39,40} Vetrugno et al⁴¹ recently reported a series of patients with sleep-related eating disorders and emphasized the frequent occurrence of restless legs syndrome and periodic limb movement disorder during sleep and the efficacy of dopamine agonists in treating this disorder. They therefore suggested that nocturnal eating may be due to a dopaminergic dysfunction in the central nervous system. Yun and Ji⁴⁰ identified a common occurrence of restless legs syndrome in zolpidem-induced sleep-related eating disorders. They suggested that the possibility of sleep-related eating disorders should be considered when physicians prescribe hypnotics for treatment of restless legs syndrome.

In addition, Tsuji et al⁴² reported 3 cases of female patients with sleep-related nocturnal eating disorders induced by zolpidem. These patients suffered from some kind of psychosocial stress related to eating. Interestingly, one of them was diagnosed with borderline personality disorder.⁴² Further studies are warranted to investigate the relationship between nocturnal eating and personality disorders.

Dependence/abuse/withdrawal.

Zolpidem is clinically effective, safe, and well tolerated and also has a favorable pharmacokinetic profile for use as a hypnotic. It is thought that tolerance does not develop during zolpidem administration, and, so, rebound insomnia and other withdrawal effects do not develop after abrupt discontinuation of zolpidem, and the risk of abuse or dependence is minimal.

However, over the past decade, several case reports of zolpidem dependence have been published. These patients presented with chronic dependence, tolerance, misuse, and withdrawal symptoms. Hajak et al⁴³ suggested that transient rebound insomnia was observed following discontinuation of treatment with zolpidem, but not gaboxadol, in a randomized, double-blind, placebo-controlled study. It seems that the behavioral effects of zolpidem are generally similar to those of benzodiazepines.⁴⁴⁻⁴⁶ Furthermore, some patients developed hallucinations related to the rapid withdrawal of zolpidem.⁴⁷

Patients with a history of abuse or dependence and those with psychiatric diseases are at risk of abusing or becoming dependent on zolpidem. Therefore, clinicians should prescribe zolpidem with the same caution as exercised for benzodiazepine hypnotics and pay attention to these effects in order to prevent drug abuse and dependence.⁴³

CONCLUSION

We reviewed the literature that described the neuropsychiatric reactions in association with zolpidem. Zolpidem is clinically effective and useful in treating insomnia. While rare, zolpidem-induced unusual complex behavior may develop. Zolpidem should be used at the lowest effective dose for as short a duration as possible. Female patients and/or older patients may require smaller doses than males and/or younger patients. Primary care physicians should be alert to the possible unusual complex adverse effects of zolpidem.

Drug names: alprazolam (Xanax, Niravam, and others), bupropion (Aplenzin, Wellbutrin, and others), citalopram (Celexa, Lexapro, and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), lorazepam (Ativan and others), olanzapine (Zyprexa), omeprazole (Prilosec and others), paroxetine (Paxil, Paxeva, and others), pramipexole (Mirapex and others), sertraline (Zoloft and others), trazodone (Oleptro and others), triazolam (Halcion and others), venlafaxine (Effexor and others), zolpidem (Ambien, Zolpimist, and others).

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