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Zolpidem Dependence, Withdrawal Seizure and Comorbidity Following Different Outcomes: Two case Reports and a Review of the Literature

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Some patients who have secondary insomnia due to psychiatric disorder or physical illnesses tend to develop zolpidem dependence and even rare and severe complications such as withdrawal seizures. Psychiatric comorbidity seems to increase abuse and dependence tendency more than comorbidity of medical illnesses does. Herein, we present two cases of zolpidem dependence complicated with withdrawal seizures; the patients completed zolpidem detoxification and had different outcomes after discharge. Psychiatric comorbidity is probably a poor prognostic factor for abstinence from zolpidem.

Key words: abuse, dependence, outcome, withdrawal seizure, zolpidem

INTRODUCTION

The imidazopyridine zolpidem is a short-acting nonbenzodiazepine hypnotic that binds selectively to the $\omega 1$ benzodiazepine-binding site on the $\alpha 1$ subunit of the γ-aminobutyric acid type A (GABA-A) receptor. This is in contrast with the nonselective affinity of benzodiazepines (including diazepam and chlordiazepoxide) for GABA-A receptors containing the $\alpha 1$, $\alpha 2$, $\alpha 3$, or $\alpha 5$ subunits[1]. Zolpidem is assumed to have a lower potential to develop tolerance and dependence than benzodiazepines. It was introduced into clinical practice in the 1980s for the short-term treatment of insomnia with a recommended dosage of 10 mg daily at bedtime[1-4]. However, cases of zolpidem abuse and dependence have been reported since 1993[5]. Seizure is a rare and serious withdrawal symptom of zolpidem; it was first reported in 1996 and seemed to develop exclusively in those who had taken supratherapeutic doses for a long time but discontinued it abruptly[6-15]. The character of patients who tend to develop zolpidem dependence and even withdrawal seizures is an intriguing issue because zolpidem has recently become a popular hypnotic. Here, we present two cases of zolpidem dependence complicated with withdrawal seizures. They have different outcomes after detoxification.

CASE REPORTS

Case 1

Mr. A is a 30-year-old single, unemployed man with a three-year history of major depression. He had no prior epilepsy history and denied any seizure-provoking factors such as sleep deprivation, excess caffeine intake, fever, infections, illicit drug use, or headaches. He began to visit our psychiatric clinic in 2004. Zolpidem tolerance and withdrawal symptoms such as rebound insomnia, anxiety, restlessness, diaphoresis, agitation, and tremors were found in 2005. He escalated his zolpidem dose to 100 mg per day from day to night for two years, and found relaxation, pleasure, and intermittent anterograde amnesia after taking a high dose of zolpidem. He took zolpidem selectively and was not adherent to other medications. He was brought to our emergency room because of sudden unconsciousness and generalized tonic — clonic seizure for five minutes within 24 hours of discontinuing zolpidem. Another episode of the generalized tonic — clonic seizure developed again for 10 minutes, followed by 50 minutes of postictal confusion in the emergency room. Brain computed tomography showed no remarkable abnormality and electroencephalography (EEG) revealed three-second epileptiform discharges of sharp waves. Urine tests for opioids, amphetamine, and benzodiazepine components were all negative. Therefore, he was hospitalized under the diagnosis of zolpidem withdrawal seizure. Chlordiazepoxide 15 mg per day was prescribed for detoxification with gradual tapering-off within four days as the withdrawal symptoms subsided. No more seizure attacks were noted throughout

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detoxification, but he relapsed to zolpidem dependence soon after discharge. We prescribed antidepressants such as mirtazapine and trazodone successively, but the patient did not receive the alternative medications. He had no motivation to abstain from zolpidem and continued to ask for zolpidem to satisfy his physical and psychological craving. Eventually, his follow-up was lost because of attention by his health insurance institution regarding his overcollection of zolpidem through hospital shopping.

Case 2

Mrs. B is a 37-year-old married woman without any history of epilepsy or psychiatric disorder. She had neuralgia over her right radial nerve about four years ago and started to take zolpidem 10 mg/day for secondary insomnia in 2003. Her neuralgia was relieved half a year later, but she developed zolpidem tolerance for three years and took zolpidem at a daily maximal dose of 600-700 mg. Withdrawal symptoms including insomnia, anxiety, dysphoria, hand tremors, restlessness, headache, and neck stiffness were noted. Her relatives had observed three episodes of generalized tonic—clonic seizures within 24-48 hours of withdrawal when she tried abstaining from zolpidem. The patient made repeated efforts to abstain but failed. She visited our psychiatrist and zolpidem dependence with withdrawal seizure history was diagnosed. Therefore, she was hospitalized and treated with anticonvulsant valproate 1000 mg/day and diazepam 20 mg/day. Diazepam was tapered slowly within one week as withdrawal symptoms subsided. No seizure attack developed during abstinence and her EEG showed normal awake waves. She was discharged one week later with valproate 1000 mg/day and diazepam 8 mg/day. The valproate and diazepam were tapered off gradually in the outpatient department; meanwhile trazodone 150 mg/day and zopiclone 15 mg/day were added for her insomnia. At 10-months' follow-up, the patient had fair compliance to alternative hypnotics and had successfully abstained from zolpidem.

DISCUSSION

Zolpidem is a short-acting hypnotic with an elimination half-life of about 1.5-2.5 hours; its specific-binding character produces a selective hypnotic effect rather than anxiolytic, sedative, anticonvulsive, and muscle-relaxant effects[1-4]. It also results in limited withdrawal effects under its recommended daily dosage of 10 mg. Because of the short half-life of zolpidem, patients who have used a high dose of zolpidem for a period tend to escalate the dose when physical craving develops hours later. We have reviewed the literature regarding zolpidem abuse, dependence, and zolpidem withdrawal seizure (ZWS); our case findings are consistent with the serious withdrawal symptoms that develop exclusively in those persons who have taken supratherapeutic doses of zolpidem for a long time and then abruptly discontinued it.

Both of our patients who had used high-dosage zolpidem for 2-3 years were diagnosed as zolpidem dependence, based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[16]. They showed zolpidem withdrawal symptoms such as anxiety, nervousness, diaphoresis, restlessness, irritability, fatigue, light-headedness, tremor, insomnia, weakness, and withdrawal seizure within 24-48 hours. These withdrawal symptoms are similar to those of short-acting benzodiazepines (BZDs). A hypothesis for zolpidem withdrawal has been proposed that suggests long-term use of a supratherapeutic dosage of zolpidem would saturate the $\omega 1$ sites and also bind to lower affinity $\omega 2$ sites on GABA-A receptors[18]. Abrupt cessation could lead to the development of withdrawal symptoms and potential seizure attacks like those found in BZD withdrawal[7,8,15]. If the hypothesis that the zolpidem withdrawal mechanism is similar to BZD withdrawal is correct, the predictors of ZWS should be similar to those that affect BZD withdrawal syndrome such as: (1) period of use, (2) dosage; (3) tapering rate; and (4) the half-life of the BZD[19,20].

In contrast to previously reported cases of ZWS (shown in Table 1)[6-15], our two patients had taken daily doses ranging from 100 mg to 700 mg. They thus fit the first two predictors; they continued using zolpidem at high doses for years. Patient 1 had only taken zolpidem with a highest daily dose of 100 mg for 2 years and experienced generalized tonic — clonic seizures twice within 24 hours after sudden withdrawal. To the best of our knowledge, this is a relatively low dosage to be complicated with withdrawal seizures in zolpidem dependence compared with prior associated reports. Hence, a temporal factor is probably more important than a dosage factor in the development of zolpidem dependence and ZWS[21]. That epileptic seizures occurred after abrupt discontinuation of zolpidem fits the third predictor—tapering rate; they often developed within 4 hours to 4 days after withdrawal[6-15]. Generalized tonic—clonic seizure is a common type of seizure in ZWS, as well as in our two patients[7,8,11,12,14,15]. However, there was a patient with history of zolpidem abuse 600 mg daily for several months that demonstrated tonic seizure and unconsciousness after cessation of zolpidem[10]. So far, reported cases of ZWS are distributed among young to middle-aged adults ranging from 29 to 50 years[6-10,12-15].

Table 1 Summary of clinical features of zolpidem withdrawal seizures

Author	Year	Gender	Age	Zolpidem dosage (mg/day)	Period	Diagnoses	Seizure type	Onset after discontinuation
Yeh et al. (current study)	2008	M	30	100	2 years	Major depression, zolpidem dependence	GTC	24hr
	2008	F	37	600-700	3 years	Radial neuropathy with neuralgia, zolpidem dependence	GTC	24-48hr
Huang et al.	2007	F	34	1000-2000	<2 years	Dysthymic disorder, zolpidem dependence	GTC	?
Cubala et al.	2007	F	29	160	2 years	Organic dissociative disorder, zolpidem dependence	GTC	12hr
Sethi et al.	2005	M	42	50-200	1.5 years	Panic attack, zolpidem dependence	+	48hr
Krueger, et al.	2005	F	39	600	2 years	Chronic facial pain, zolpidem dependence	GTC	24hr
Boulanger-Rostowsky et al.	2004	F	?	240	?	Borderline personality disorder	+	?
Tripodianakis et al.	2003	F	43	600	< 6 months	Depression with insomnia, zolpidem abuse	Tonic	Few hours
Barrero-Hernandez et al.	2002	F	50	450	?	Chronic insomnia and anxiety	GTC	12hr
Aragona	2000	F	43	450-600	2 months	Chronic insomnia	GTC	4hr
Gilbert et al.	1997	M	37	130	2 months	Chronic pudendal neuralgia	GTC	24hr
Sanchez et al.	1996	M	33	300-400	<2 months	Depression, Alcohol abuse	+	96hr

M: male, F: female, GTC: generalized tonic-clonic seizure
+ Withdrawal seizure without mention its type
? No mention in the article

We noticed that the majority of ZWS cases are women[10,22]. Markowitz and Brewerton[23] have reported that young women achieve around a 50% higher plasma zolpidem level than men do under the same administrated dose. Cubala[22] introduced the concept that sex hormones would influence cytochrome P450 enzyme (CYP 450) activity, increasing the biotransformation of zolpidem to its active metabolite. Oral contraceptives taken by young women also affect zolpidem pharmacokinetics and result in high serum levels of zolpidem[22]. In addition, the higher prevalence of insomnia in women than in men may be a factor for women having a higher zolpidem use rate and becoming predominant in ZWS.All of the conditions described above may produce a high probability of gender difference. Further studies are needed to investigate whether female sex is an independent factor for ZWS.

Both of our patients had different outcomes after detoxification. Patient 1 had psychiatric comorbidity with major depression. It was the core symptoms that initiated the zolpidem use and exacerbated the psychological and physical craving. He showed no motivation to abstain, even though the serious complications such as withdrawal seizure occurred. Poor outcome in the maintenance of zolpidem abstinence was notable in this patient and is a psychiatric disorder. In contrast, patient 2 had neuralgia and was treated with zolpidem because of pain-related insomnia. Although her pain resolved half a year later, zolpidem dependence developed and she could not abstain from it unaided. Throughout psychiatric intervention, she was hospitalized for pharmacotherapy. To date, she has successfully abstained from zolpidem without any seizure attack and has maintained this condition for 10 months.

Previous case reports regarding ZWS were rarely discussed with its prognosis of zolpidem abuse or dependence. In contrast to patient 1 who soon relapsed, patient 2 has successfully abstained from zolpidem. It is interesting that different outcomes seem to depend on their comorbidity. Most of the comorbidities in ZWS are psychiatric disorders[6,9,10,12,13,15,17], such as mood disorders (frequently depression), alcohol or substance abuse, which easily recurred and were refractory to treatment. Patients with psychiatric comorbidity often produced symptoms of insomnia and had high potential to misuse substances including alcohol, drugs, and hypnotics[17], as their coping strategy or self-medication behavior. It is impossible to treat their insomnia by only incrementing zolpidem, and patients will self-medicate by increasing their zolpidem dose to satisfy their psychological craving. Thus a vicious cycle of zolpidem abuse or dependence and psychiatric comorbidity exists. Likewise, patients with general medical conditions such as pain-related illness were also reported to develop zolpidem abuse or dependence with ZWS as in our patient 2[7,12]. Secondary insomnia due to physical illness could be treated more simply, if the primary illness was resolved. Psychiatric comorbidity may be a poor prognostic factor for abstinence from zolpidem.

We reviewed the pharmacotherapy for ZWS in the literature and found that rapid-onset and long-acting BZDs such as diazepam and chlordiazepoxide are effective in ameliorating zolpidem withdrawal symptoms and in preventing withdrawal seizures. Patient 1 used chlordiazepoxide 15 mg/day for detoxification. Patient 2 was treated by concomitant use of valproate 1000 mg/day and diazepam 20 mg/day for detoxification. No seizure attack developed during the detoxification process using BZDs with or without concurrent use of anticonvulsants. The utility of concomitant use of anticonvulsants and BZDs in zolpidem withdrawal is inconclusive. Some studies showed that concomitant use of anticonvulsants and BZDs in BZD detoxification permitted more rapid and better tolerated withdrawal symptoms than did detoxification using BZDs alone[20]. In our experience, the combined use of anticonvulsants and BZDs is most effective in zolpidem withdrawal.

Zolpidem abuse or dependence always accompanied long-term use, especially in patients who had psychiatric comorbidity and other physical illnesses. Psychiatric comorbidity is probably a poor prognostic factor in zolpidem dependence. Successful abstinence is independent of severity of craving, but dependent on the period of use, dosage, and presence of psychiatric comorbidity. It is important to prescribe zolpidem at its recommended dose 10 mg/day only for a short time, and to give advice to the patient about its potential risk for abuse or dependence after long-term use. Clinicians should be alert to the possibility of zolpidem abuse or dependence, especially if patients exhaust zolpidem earlier than anticipated and ask for more. Once the presence of ZWS occurs, it suggests the possibility of zolpidem abuse or dependence[9]. Shifting to other hypnotics and treating the patient's underlying psychiatric or general medical condition that is affecting sleep quality are important. As for treatment of BZD withdrawal, in our experience diazepam and chlordiazepoxide are suggested for the treatment of zolpidem withdrawal symptoms and to prevent seizure attacks. Anticonvulsants may be useful for abstinence of zolpidem in long-term follow-up. Knowledge regarding treatment of ZWS is needed, and while physicians prescribe zolpidem as a useful hypnotic, cases of abuse or dependence increase sequentially. Because there are few long-term studies regarding the adverse effects of zolpidem, future long-term, controlled, and prospective studies regarding zolpidem dependence and ZWS are desirable.

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