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Zolpidem Dependency and Withdrawal Seizure: A Case Report Study

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Introduction: *Zolpidem* is a short acting inducer of sleep and thought to lack benzodiazepine properties such as anxiolysis, anticonvulsion, muscle relaxation and side effects such as dependency. Recently, some cases of *Zolpidem* abuse and dependency have been reported. In review of literature, we found that the lowest reported dosage of *Zolpidem*, which caused dependency, was 160 mg daily.
Case Presentation: We reported a 30-year-old unmarried Iranian woman with dysthymic disorder and chronic insomnia treated with *Zolpidem* irregularly. She started to use *Zolpidem* with 5mg per day irregularly since a year ago but augmented its daily dosage gradually to 100 to 150 mg per day in divided doses. After a period of 16 hours without taking *Zolpidem* she developed a withdrawal syndrome, with generalized tonic-clonic seizures for two times. She was managed with supportive care and recovered completely.
Conclusions: *Zolpidem* dependency and withdrawal seizure can occur with a dosage under last reported doses. Therefore, possibility of mentioned problems cannot be excluded at any dosage and physicians should pay more attention to potential of *Zolpidem* to create these adverse effects.

Keywords:Zolpidem; Dependence; Benzodiazepine

1. Introduction

Zolpidem (an imidazopyridine derivative agent) is a non-benzodiazepine hypnotic drug with a high affinity to α1 subunit of gamma amino butyric acid-A (GABA-A) receptor and minor anxiolytic and anti-convulsant effects which is indicated for short-term management of insomnia (1). *Zolpidem* is thought to be a safer drug than benzodiazepines (BZD) because of no evidence of abuse or dependence potential and a less liability for abuse and dependence (2). Against so many studies indicating no evidence regarding abuse or dependence potential by *Zolpidem*, case reports of *Zolpidem* abuse or dependence (3-5) and epileptic-seizure related to *Zolpidem* withdrawal (6-8) are increasing. To our knowledge, most of these case reports have been reported from Western countries (9) and in the Asian population, one case of *Zolpidem* dependence (10) and one case of *Zolpidem* withdrawal seizure (6) were reported. Nonetheless, in Iranian people, we did not find any similar report. Moreover, withdrawal seizure in our case with 100 to 150 mg/day of *Zolpidem* is the minimum dosage reported up to now.

2. Case Presentation

On October 2013, a 30 year-old unmarried Iranian woman (known case of dysthymic disorder) was admitted to Emergency Department (ED) of 22-Bahman Psychiatric Hospital (Qazvin, Iran) with seizure without any history of head trauma. No medications were administered en route to the hospital. For about five minutes early after admission, she had seizure one time again, thus she suddenly had tonic-clonic seizure (full body "shaking" movements lasting approximately two minutes) with upward gaze and loss of consciousness. Then, postictal confusion with clouded consciousness, regressed attitude and behavior and psycho-motor retardation happened for about two hours. After postictal phase, she indicated to use *Zolpidem* for a year due to insomnia and not receiving any other medication. She started to use *Zolpidem* with 5 mg per day irregularly since a year ago but augmented its daily dosage gradually from three months before to 100-150 mg per day in divided doses. She used this dosage for about one month prior to her seizure. She had drug tolerance, abuse and dependence and if she had not used tablets, she would become irritable with decreased energy, feeling of weakness and tremor of hands and feet. In the day of admission, she had not used *Zolpidem* to maintain her alertness for an important ceremony and after a period of 16 hours without taking *Zolpidem*, she developed an abstinence syndrome, with generalized tonic clonic seizures. In her medical history, she did not have any systemic, organic, metabolic or endocrine problems unless a history of adenoidectomy 25 years ago and dysthymic disorder from one year ago. She had not experienced any seizure already. In her drug history, she just had used *Zolpidem* with the mentioned dosage. Some of patient's characteristics were summarized in Table 1.

Table 1. Some Laboratory and Clinical Results of Patient

	Results
Oral temperature, °C	36.8
Heart rate, beats/min	106
Respiratory rate, breaths/min	23
Systolic blood pressure, mmHg	128
Diastolic blood pressure, mmHg	78
Percutaneous O_2 saturation, %	99
Serum glucose, mg/dL	112

Her pupils were 4 mm and reactive bilaterally. The initial resting 12 lead electrocardiography (EKG) showed normal sinus rhythm without any abnormal changes. There was no localizing or lateralizing neurological signs. Full blood count, urea, electrolytes, calcium, magnesium, hematology studies, renal, thyroid and liver function tests had normal results. Substance-drug abuse tests had negative results. Due to the urgency of patient and availability of computed tomography (CT) scan, we first performed spiral brain CT scan without contrast, which had normal findings. The next day we requested brain magnetic resonance imaging (MRI) and electroencephalography (EEG), which had normal findings. After all evaluations, we did not find any other etiologies except *Zolpidem* withdrawal. Our patient was detoxified by tapering *Zolpidem* gradually over one week. We prescribed quetiapine 25 mg before sleep and clonazepam 1 mg per day. No other seizure attack was noted during hospitalization. Finally, after about 10 days hospitalization, she was discharged with a healthy condition with venlafaxine 75 mg thrice daily (t.i.d), clonazepam 1mg daily and quetiapine 25 mg daily at bed time (for her insomnia). In about 6 months follow-up after the first seizure, she had no further seizure attacks.

3. Discussion

During the last decade, *Zolpidem* (a non BZD hypnotic drug) was considered a new way for treatment of patients with insomnia as it was suggested that it has the efficacy of BZDs for insomnia but without many side effects. It was suggested that *Zolpidem* lacked muscle relaxant, anticonvulsant and anxiolytic properties and poor potential for abuse or dependence (11). GABA-A receptors include α_1, α_2, α_3, α_4, and α_5 subunits receptors. The α_1 subunit involves in sleeping mechanisms and α_2 subunit contributes to anxiolytic action. BZDs have nonselective affinity to GABA-A subunits (12). Despite the fact, *Zolpidem* has been suggested to have selective activity on α1 subunit, but low affinity for α_2, therefore it has minor anxiolytic action. Our patient reported anxiolysis after using *Zolpidem*. It might be due to effects of this drug in high doses (such as that used by our patient) not only on α_1 subunit, but also on other subunits of GABA-A receptors (leading to an anxiolytic effect). In some cases, *Zolpidem* has been used to achieve euphoria and stimulation and not for sedation (3, 13, 14). Since this effect lasted not more than one hour, they repeated the intake in the daytime. A hypothesis about *Zolpidem* withdrawal is long-term supratherapeutic doses saturation of the lower-affinity α_2, α_3 and α_5 subunits on GABA-A receptors along with α_1 subunits (15). Therefore, high-dose *Zolpidem* may have a paradoxical effect to decrease anxiety, and abrupt discontinuation of high doses would produce withdrawal symptoms such as anxiety, tremor, palpitation, or seizure (similar to BZDs withdrawal). Withdrawal symptoms of *Zolpidem* were reported in less than 1% of subjects appearing within 48 hours of discontinuation (16). One of the probable factors associated with adverse effects of *Zolpidem* is gender. Women have been found to have a significantly higher serum *Zolpidem* concentration than men at equivalent dosage (17). Some studies demonstrated that sudden discontinuation of *Zolpidem* by doses within the normal recommended range 2 to 4 weeks after treatment has not been associated with withdrawal symptoms (2, 18). *Zolpidem* dependence and withdrawal symptoms have been reported in patients with doses between 160 to 2000 mg per day (7, 10). Therefore, to our knowledge, withdrawal seizure in our case with the mentioned dosage of *Zolpidem* is the minimum dose reported up to now. According to other case reports and studies and our case, *Zolpidem*, soon after sudden discontinuation, causes withdrawal symptoms including insomnia, anxiety and epileptic attack, especially at high doses and long-term use. Concerns about *Zolpidem* abuse, dependence and withdrawal seizure are increasing in the recent years due to increased number of reported cases. Maybe, this event is due to unawareness of many physicians and patients about the potential of *Zolpidem* to create these problems. In addition, use of this drug out of its therapeutic goals and short half-life predisposes adverse events. Our case suggested that *Zolpidem* can potentially lead to dependence and withdrawal seizure in Iranian population, also can occur with a dosage under last reported doses. Besides, the possibility of mentioned problems cannot be excluded at any dosage. We suggest physicians to pay more attention to the potential of *Zolpidem* to create dependence and withdrawal seizure. Besides, they should always keep its effects in their mind and subtilize during prescription of *Zolpidem* for any patients and at any doses, especially for those with a previous history of drug or substance abuse and at high doses. This study presented a new dosage of *Zolpidem* that causes withdrawal seizure. However, this is a case study and it needs further studies to conclude about adverse effects of *Zolpidem*.

Authors' Contributions

Seyed Alireza Haji Seyed Javadi and Farid Hajiali were involved in acquisition of clinical data and reviewing the scientific literature. Farid Hajiali and Marjan Nassiri-Asl wrote the manuscript. All authors read and approved the final manuscript.

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