Two cases of seizures on sudden withdrawal of supratherapeutic doses of zolpidem (selective omega I benzodiazepine receptor agonist)

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ABSTRACT

Introduction: Zolpidem, a non-benzodiazepine hypnotic, reportedly with little abuse potential, is widely prescribed in clinical practice for the treatment of insomnia. Zolpidem abuse has begun to be reported in the literature, but serious withdrawal symptoms such as seizures rarely so. We present two cases of zolpidemwithdrawal seizures. Case Series: Two young patients started consuming zolpidem for insomnia secondary to psychiatric illness. They escalated the dose of zolpidem in order to maintain relaxation and pleasurable effect of the drug and eventually presented to casualty with withdrawal seizures. Conclusion: Rate of onset of drug effects and short half-life are thought to be critical determinants of reinforcing effects of a drug. Based on the pharmacokinetic data of the studies comparing zolpidem with alprazolam or diazepam, the reinforcing effect and dependence potential of the former was not expected to differ significantly from those of other benzodiazepines. Thus abuse potential of zolpidem was initially underestimated. Our two cases add to the growing evidence that zolpidem has significant risk of dependence especially for patients with comorbid psychiatric illness. Therefore, primary care physicians should prescribe zolpidem judiciously with the same caution as exercised for all benzodiazepine hypnotics.

Keywords: Dependence, Withdrawal seizure, Zolpidem, Benzodiazepine

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INTRODUCTION

The 1980s introduced new non-benzodiazepine hypnotics called the “Z-drugs”, into clinical practice. These drugs have rapid onset and short duration of action [1], which made them highly attractive alternatives for the short-term treatment of insomnia. Of these non-benzodiazepine hypnotics, zolpidem, an imidazopyridine is probably the most frequently prescribed non-benzodiazepine hypnotic in the United States [2]. As per the statistics provided by Mackay, total prescription sales for insomnia drugs across the world stood at $4.3 billion in 2009. Accounting for 48 percent of global sales, the US represents the most dominant region followed by France, Germany, Italy, Spain, UK, Brazil, Russia, India and China (MIDAS sales data, IMS Health, March 2010) [3].
Zolpidem binds selectively to the α1 benzodiazepine-binding site on the α1 subunit of the γ-aminobutyric acid type A (GABA-A) receptor distinguishing it from the nonselective affinity of benzodiazepines for GABA-A receptors containing the α1, α2, α3 and α5 subunits [4].

Clinically, zolpidem demonstrated hypnotic efficacy comparable to benzodiazepines, in people with sleep disturbances. In contrast to other benzodiazepines, zolpidem preserves stage 3 and 4 sleep (non–rapid eye movement [NREM] sleep) and increases slow-wave sleep duration [5, 6].

Concerns about zolpidem dependence following long-term treatment are becoming more marked while the popularity of the newer benzodiazepine-type hypnotics continues to rise. Relatively rapid onset and short-acting features raise the possibility of severe withdrawal after chronic use [7]. Although cases of zolpidem abuse and dependence have been reported since 1993 [8], serious symptoms such as withdrawal seizures are very rarely reported [9]. Here, we present two cases of zolpidem dependence complicated with withdrawal seizures.

**CASE SERIES**

**Case 1:** A 32-year-old married female, owing a chemist shop, was brought to the emergency room with history of sudden fall in her shop following loss of consciousness. On detailed evaluation she reported no prior history of epilepsy and denied any seizure-provoking factors such as sleep deprivation, excess caffeine intake, fever, infections, illicit drug use or headache. She reported consulting a psychiatrist a few times one year ago. The psychiatrist had diagnosed her as case of somatoform disorder and prescribed duloxetine and levosulpiride along with zolpidem (10 mg/day, hs) for complaints of occasional insomnia. She improved significantly and discontinued follow up and treatment after six months, but continued with zolpidem.

Contrary to the psychiatrist’s advice for occasional use of zolpidem (10 mg/day), she not only started regular use of the pill but also escalated the dose up to 200 mg/day in order to experience relaxation and pleasure.

About one year later, unavailability of zolpidem forced the patient to discontinue it all of a sudden. Zolpidem is a controlled drug in India, not available without prescription. Patient needed large numbers of pills that too off the record. When the management changed and her ‘liaison’ was no longer present, she could not procure the drug. After 20 hours of unavailability, she fell in her shop due to unconsciousness caused by tonic-clonic seizures. She experienced two generalized tonic-clonic seizures lasting for 5–7 minutes each. Both seizures were followed by postictal confusion for 30–40 minutes. Other notable withdrawal symptoms were insomnia, anxiety, dysphoric mood, hand tremors, restlessness and heaviness of head.

The patient was thoroughly investigated to rule out any other organic cause of seizures. Brain magnetic resonance imaging (MRI) showed no structural abnormality. Electroencephalography (EEG) revealed three-second epileptiform discharges of sharp waves. Urine tests for opioids and amphetamine components were all negative. Test for benzodiazepine levels in blood and urine were negative but level for zolpidem was not done as it was not available. She was hospitalized with a diagnosis of zolpidem dependence syndrome with withdrawal seizure.

Diazepam 30 mg/day in divided doses, orally and parentally was prescribed for detoxification with gradual tapering-off within a week as the withdrawal symptoms subsided. No more seizure attacks were noted throughout detoxification. She was discharged on ramelteon 8 mg hs for the insomnia. The patient continued the drug for next 10 days and revisited the psychiatric clinic with complaints of insomnia. She insisted for zolpidem to be prescribed again. The clinical psychologist conducted a psychoeducation session and enhanced her motivation to continue abstinence. This time, she was prescribed ramelteon 8 mg hs and trazodone 100 mg hs. The patient discontinued follow up but again presented to the emergency room a second time, in confusional state, about two months later. Relatives reported that she restarted the zolpidem as she was not satisfied with pleasurable effect of ramelteon and trazodone. She could not obtain zolpidem for last 24 hours and experienced two generalized tonic-clonic seizures. The detoxification process was re-started as before. At the time of case reporting, patient was admitted for detoxification and is doing well with mirtazapine.

**Case 2:** A 36-year-old male, married, teacher by profession, without any prior history of seizure disorder, began to visit our outpatient Psychiatry clinic with one year history of major depression. He was offered escitalopram 10 mg and zolpidem 10 mg. His depressive symptoms were completely relieved with escitalopram 20 mg/day in next four months but he developed zolpidem tolerance. Over the next six months, he increased the dose without the knowledge of the treating psychiatrist, using up to 240 mg/day in for its pleasurable effects. He believed it would increase his energy level.

One day while away from home, he forgot to carry zolpidem which forced its discontinuation for 24 hours. He experienced craving and withdrawal in the form of apprehension, restlessness, diaphoresis, irritability, tremors and insomnia. These events began at home. Eventually, he found himself in the emergency ward with a diagnosis of zolpidem dependence with withdrawal seizure. His relatives, who had observed two consecutive episodes of generalized tonic-clonic seizures, brought him there. The patient was investigated as per the seizure protocol for any other possible cause. Seizure protocol consisted of high resolution MRI (3 tesla), EEG, serum electrolytes and kidney function tests. All test reports were in normal range. Test for benzodiazepine levels on blood and urine
were negative but level for zolpidem was not done as it was not available. He was then detoxified with clonazepam 8 mg/day with gradual tapering-off within next 10 days.

On interview, his depressive symptoms had relapsed. We prescribed mirtazapine and amitriptyline successively in adequate doses and encouraged regular follow up to prevent relapse. At 6-month follow-up, the patient had fair compliance to this alternative treatment and had successfully abstained from zolpidem.

DISCUSSION

Zolpidem, a short-acting, non-benzodiazepine hypnotic with an elimination half-life of 1.5 to 3.2 hours [6], produces a selective hypnotic effect rather than anxiolytic, sedative, anticonvulsant and muscle-relaxant effects due to its peculiar neuropharmacological activity i.e. selectivity for omega 1-Benzodiazepine receptors [4, 10, 11].

A few publications have highlighted the abuse potential of zolpidem, which was initially underestimated. Zolpidem causes mild withdrawal effects on recommended daily dosage of 10mg. Patients who used higher doses for longer time, tend to escalate the dose as physical craving develops a few hours after ingestion, because of the short half-life.

Pharmacokinetic factors such as rate of onset of drug effect and short half-life are thought to be critical determinants of a drug’s reinforcing effects and abuse potential [12]. Few studies have compared zolpidem with alprazolam, triazolam or diazepam because their peak plasma concentrations appears rapidly. Based on pharmacokinetic data in these studies the reinforcing effects and abuse potential of zolpidem would not be expected to differ significantly from those of other benzodiazepines [13].

A hypothesis for zolpidem withdrawal suggests that long-term use of supra-therapeutic dosage of zolpidem saturates omega 1-benzodiazepine receptors and also binds to omega-2 sites on GABA-A receptors with lower affinity [13]. Abrupt cessation could lead to the development of withdrawal symptoms and potential seizure attacks similar to regular benzodiazepine withdrawal states [9, 14]. If the hypothesis that the zolpidem withdrawal mechanism is similar to benzodiazepine withdrawal is correct, the predictors of zolpidem withdrawal seizures should be similar to those that affect benzodiazepine withdrawal syndrome such as: 1) period of use, 2) dosage, 3) tapering rate, and 4) the half-life of the drug [15, 16].

Our cases above are consistent with suggested predictors of serious withdrawal symptoms as seizures occurred exclusively in patients who consumed supra-therapeutic doses of zolpidem for long and then abruptly discontinued it [15, 16].

Both of our patients used high-doses of zolpidem for about one year and were diagnosed as zolpidem dependence with complicated withdrawal as per ICD-10 diagnostic criterion. Both patients experienced seizures within 24 hours of discontinuation of zolpidem along with milder withdrawal symptom such as insomnia, apprehension, dysphoric mood, hand tremors, restlessness and heaviness of head, all very similar to those of short-acting benzodiazepines.

Both our patients had psychiatric comorbidity. The first case was diagnosed with somatoform disorder and second suffered from Major depression which initiated psychiatric consultation. Both patients developed zolpidem dependence (prescribed for secondary insomnia) and were eventually brought to emergency after withdrawal seizures. Both patients had different outcomes after detoxification. The first case resumed the drug after a very short period of abstinence and re-experienced withdrawal seizures. In spite of this, she was not motivated to quit zolpidem. In contrast, the second patient gave up zolpidem very comfortably and is maintaining abstinence since last six months.

Previous case reports of zolpidem dependence and withdrawal seizures rarely discussed its prognosis. Few reports argued that psychiatric comorbidity is a poor prognostic factor for zolpidem dependence [17] and common associated psychiatric comorbidities are mood disorders (frequently depression) and alcohol or substance abuse, which easily recur and are refractory to treatment [18–21]. In our case, one patient relapsed while the other did not. Further controlled and prospective association studies with larger sample size, are needed to determine prognostic factors. Zolpidem is a popular hypnotic and physicians need to be aware of its dependence potential.

CONCLUSION

The number of reported cases of zolpidem abuse or dependence is small compared to the widespread use of the drug. This low incidence might be due to a continued unawareness of clinicians and patients of the potential for abuse, acceptance of a certain level of overdosing by medical professionals and probably practitioners’ failure to report the cases as often they should.

Our two cases add to the growing evidence that zolpidem presents a potential for abuse especially to patients with comorbid psychiatric illness. Therefore, clinicians should prescribe zolpidem at the lowest effective dose for shortest possible duration with the same caution as exercised for all benzodiazepine hypnotics.

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Author Contributions
Shri Niwash Jangir – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article and approval of the version to be published
Rajeshwari Suthar – Acquisition of data, Analysis and interpretation of data, Critical revision of the article and approval of the version to be published
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