

# Successful Treatment of Zolpidem Dependency with Replacement Benzodiazepine Therapy: A Case Study

Hamid Khosrojerdi<sup>1</sup>, Reza Afshari<sup>2</sup>, Kazem Ghaemi<sup>3</sup>, Esmail Farzaneh<sup>4</sup>, Omid Mehrpour<sup>5,6</sup>

<sup>1</sup>Addiction Research Center, Imam Reza Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, <sup>2</sup>BC Centre for Disease Control, Vancouver, Canada, <sup>3</sup>Department of Neurosurgery, Birjand University of Medical Sciences, Birjand, Iran, <sup>4</sup>Department of Forensic Medicine and Toxicology, Ardabil University of Medical Sciences, Ardabil, Iran, <sup>5</sup>Atherosclerosis and Coronary Artery Research Center, Birjand University of Medical Science, Birjand, Iran, <sup>6</sup>Medical Toxicology and Drug Abuse Research Center (MTDRC), Birjand University of Medical Sciences (BUMS), Moallem Avenue, Birjand 9713643138, Iran

## ABSTRACT

Zolpidem is a non-benzodiazepine hypnotic drug used in short-term insomnia management. It is considered to be a safer drug than benzodiazepines. Zolpidem was initially considered to have lower incidences of dependence and tolerance than benzodiazepines. However, studies, have shown that zolpidem can lead to dependency. Although various cases of zolpidem dependence have been reported till date, but there is few published reports regards the medication to be used in the detoxification .We present a 21-year-old woman with history of zolpidem dependency .She had previously been using zolpidem for 3 years. She admitted and treated with replacement therapy with benzodiazepine. The equivalent diazepam was calculated (100 mg) and the replacement therapy consisted of 70 mg diazepam divided in doses of 20 mg in the morning, 20 mg midday, and 30 mg at night. A psychiatrist and a psychologist visited her in the morning and evening, respectively. Diazepam was tapered by 5 mg per day after 48 h; she was discharged when the dose was tapered to 60 mg per day with subsequent daily outpatient visits for continued dose tapering. Dose tapering was more gradual in comparison to the inpatient setting, namely by 5 mg every 5 days; overall, final tapering to a 20 mg daily dose took 60 days. She stopped diazepam usage after 65 days. She was followed-up for a 6-month period and urinary immunoassays ruled out benzodiazepine usage; all urinary tests were negative. This case of zolpidem dependency successfully treated by substitution with an equipotent, longer half-life benzodiazepine followed by tapering of benzodiazepine to discontinuation; this method can help in the prevention of seizures. Furthermore, it is advisable to manage replacement therapy in an inpatient setting. This method can help in the prevention of seizures. Meanwhile, it is advisable to manage replacement therapy in an inpatient setting.

**Keywords:** Zolpidem, dependency, benzodiazepine

## INTRODUCTION

Zolpidem is a non-benzodiazepine hypnotic drug used in short-term insomnia management. This agent

binds to the gamma-aminobutyric acid-A (GABAA) receptor and selectively acts on benzodiazepine receptor subtypes<sup>1</sup>. It is considered to be a safer drug than benzodiazepines<sup>2</sup>. Furthermore, zolpidem was initially considered to have lower incidences of dependence and tolerance than benzodiazepines<sup>1, 2</sup>. However, experimental studies, reviews, and case reports have shown that zolpidem can lead to dependency<sup>3,4</sup>.

Systematic review studies on the safety of zolpidem showed that dose self-escalation can result in tolerance to its hypnotic and sedative effects<sup>5</sup>. Symptoms such as

---

### Corresponding author:

#### Omid Mehrpour

MD, Medical Toxicology and Drug Abuse Research Center (MTDRC), Birjand University of Medical Sciences (BUMS), Moallem Avenue, Birjand 9713643138, Iran, Tel and Fax: +98-563440488  
Email:Omid.mehrpour@yahoo.com.au

sweating, tachypnea, tachycardia, tremors, and extreme anxiety have been observed following zolpidem discontinuation<sup>5</sup>. In addition, discontinuation syndrome symptoms include fatigue, flushing, panic attacks, abdominal discomfort, uncontrolled crying, nausea, emesis, and delirium<sup>6</sup>. Withdrawal seizures may also happen after sudden discontinuation<sup>7</sup>. Although various cases of zolpidem dependence have been reported till date, but there is few published reports regards the medication to be used in the detoxification<sup>3</sup>.

We herein present a case of zolpidem dependency successfully treated by substitution with an equipotent, longer half-life benzodiazepine followed by tapering of benzodiazepine to discontinuation.

### CASE REPORT

We present a 21-year-old woman with history of zolpidem dependency. She had no current or past history of substance abuse and did not smoke or drink alcohol. Her medical history was unremarkable. The patient did not report history of confirmed neurologic or psychiatric disorders, although she mentioned some degree of anxiety but she was not visited by physician or psychiatrist. She had no personal or family history of chronic medical problems. She had previously been using zolpidem for 3 years. She had initiated its use based on some friends' recommendation to control her anxiety with the primary dose of 50 mg every 12 hours. She had gradually increased the total dose of the medication to 200 mg/day. Although she used the medication with such a high dose, her sleep duration was 5.5 hours in 24 hours, far less than the standard daily duration. The main cause of her sleep disturbance needed neurologic and psychiatric evaluations. She had diagnostic criteria for substance abuse and substance dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> Edition (DSM-IV). Behavioral studies have denoted the presence of tolerance (item 1) and withdrawal (item 2). Urinary tramadol, methadone, morphine, barbiturate, and marijuana were assessed by immunoassay urine tests to confirm only zolpidem usage. All biochemistry laboratory tests were normal.

She was initially managed in an inpatient setting to taper zolpidem dose. During the course of her treatment, she complained of insomnia and fatigue. Zolpidem tapering treatment commenced with 10 mg orally at morning time every 2 days and the bedtime

dose was continued on an as-needed basis for insomnia. The patient complained of insomnia and fatigue in the first week and experienced headaches and nightmares in the second week. The dose reached 140 mg zolpidem daily after 12 days, after which she suddenly decided on discharge due to personal problems. Within a few days of treatment initiation, the patient's family had complained about the prolonged period of hospitalization and requested her to be discharged and managed in an outpatient setting.

The patient was visited two months later and she had unfortunately returned to 200 mg zolpidem daily (same as the previous dose); she was re-admitted and treated with replacement therapy. The equivalent diazepam was calculated (100 mg) and the replacement therapy consisted of 70 mg diazepam divided in doses of 20 mg in the morning, 20 mg midday, and 30 mg at night<sup>8</sup>. A psychiatrist and a psychologist visited her in the morning and evening, respectively. Diazepam was tapered by 5 mg per day after 48 h; she was discharged when the dose was tapered to 60 mg per day with subsequent daily outpatient visits for continued dose tapering. Dose tapering was more gradual in comparison to the inpatient setting, namely by 5 mg every 5 days; overall, final tapering to a 20 mg daily dose took 60 days. She stopped diazepam usage after 65 days. She was followed-up for a 6-month period and urinary immunoassays ruled out benzodiazepine usage; all urinary tests were negative.

She experienced less rebound insomnia (significant worsening of sleep difficulties) and recurrence of insomnia following repeated administration of diazepam in comparison to tapering methods; recurrence of insomnia appears more slowly and progressively in comparison to tapering methods within 2–3 weeks. Replacement therapy helped in the reduction of inpatient time without the risk of convulsion.

### DISCUSSION

Dependence criteria are difficult to determine because various case reports use a different terminology for pharmacodependence, abuse, and addiction. The WHO pharmacodependence experts committee<sup>9</sup> played an important role in the elaboration of the terminology related to pharmacodependence. DSM-IV and its definition criteria are compatible with WHO definitions. Therefore, we considered DSM-IV criteria

for diagnosis.

Dependency must be managed by the clinician through different aspects of treatment from a physiological, psychological, psychiatric, and social perspective. Zolpidem detoxification by gradual dose reduction is a challenging treatment given that seizures can occur following rapid dose reduction<sup>7</sup>. The withdrawal symptoms of zolpidem reported in less than 1% of the users emerge within 48 hours of discontinuation<sup>10</sup>. There is very few published reports regards the medication to be used in the zolpidem detoxification<sup>3</sup>. Case reports showed that Quetiapine and Flumazenil can be used in an inpatient setting to mitigate the taper dose approach<sup>7,11</sup>. We think replacement therapy using the long-acting benzodiazepine (diazepam) instead of zolpidem is a more acceptable treatment; such treatments are used in opium and cigarette dependency.

It has been observed that zolpidem may bind less specifically to brain receptors at higher levels. If drug levels are high enough, then GABAA receptors containing  $\alpha 1$  subunits can be saturated and the drug can also bind to lower-affinity receptors that contain the  $\alpha 2$  and/or  $\alpha 3$  subunits<sup>12</sup>. In our case, these paradoxical effects did not occur. Some reports emphasize that zolpidem is used to achieve euphoria and stimulation and not for sedation<sup>13</sup>. However, our patient used it only for sedation.

Molecular biology, via possible mutations of GABAA receptors, may provide some answers as to why some patients increase the dose gradually seeking something other than the drug's hypnotic effect. Changes in the expression of genes encoding various  $\alpha$  or  $\gamma$  subunits of the GABAA receptor complex can affect receptor affinity to such a degree that the benzodiazepine site can lose its activity resulting in differences in sensitivity, as occurs in cases of extreme intoxication, where there seems to be no certain correlation between clinical symptoms and ingested dose<sup>13</sup>.

While the existence of previous dependence or psychiatric disease is often reported as a risk factor for substance abuse, our patient did not present evidence of abuse or psychiatric disorders. In many studies, a history of substance abuse is a risk factor for other dependencies<sup>15-18</sup>; however, in the present case the patient had no experience with opium, opioid, stimulants, or hallucinogenic agents.

Despite of the widespread use of zolpidem, the number of reported cases of zolpidem abuse or dependence is very small. This low incidence may be due to a continued unawareness of patients of the potential for abuse of zolpidem, even if it concerns only a small proportion of patients. Furthermore, practitioners do not report abuse or dependence as often as they should. In fact, the drug is routinely used as a long-term treatment; and a definitive level of overdosing is accepted by medical professionals, which explains the low rate of reports<sup>13,14</sup>.

## CONCLUSION

Our case of zolpidem dependency successfully treated by substitution with an equipotent, longer half-life benzodiazepine followed by tapering of benzodiazepine to discontinuation; this method can help in the prevention of seizures. Furthermore, it is advisable to manage replacement therapy in an inpatient setting.

**Conflict of Interest:** None

**Funding of Support:** None

**Ethical Clearance:** Informed consent was given by the patient for publication of the case study.

## REFERENCES

1. Lemmer B. The sleep-wake cycle and sleeping pills. *Physiol Behav.* 2007 Feb;90(2-3):285-93
2. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs.* 2000 Apr;59(4):865-89.
3. Fernandes WH, Pereira YD S, O' Tereza S. A case of Zolpidem dependence successfully detoxified with gabapentin. *Indian J Psychiatry.* 2013 Jul; 55(3):290-92. doi: 10.4103/0019-5545.117152.
4. Hajak G, Müller WE, Wittchen HU, Pittrow D, Kirch W. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addiction.* 2003 Oct;98(10): 1371-8.
5. Greenblatt DJ, Roth T. Zolpidem for insomnia. *Expert Opin Pharmacother.* 2012 Apr;13(6):879-93. doi: 10.1517/14656566.2012.667074. Epub 2012 Mar 19.

6. Aggarwal A, Sharma DD. Zolpidem withdrawal delirium: a case report. *J Neuropsychiatry Clin Neurosci.* 2010 Fall;22(4):451-o.e27-451.e28. doi: 10.1176/appi.neuropsych.22.4.451-o.e27.
7. Quaglio G, Lugoboni F, Fornasiero A, Lechi A, Gerra G, Mezzelani P. Dependence on zolpidem: two case reports of detoxification with flumazenil infusion. *Int Clin Psychopharmacol.* 2005 Sep; 20(5):285-7.
8. Chen SC, Chen HC, Liao SC, Tseng MC, Lee MB. Detoxification of high-dose zolpidem using cross-titration with an adequate equivalent dose of diazepam. *General hospital psychiatry.* 2012 Apr 30;34(2):210-e5.
9. WHO expert committee on drug dependence. Thirty-third report. Geneva: World Health Organization; 2003. Available from: [http://www.who.int/substance\\_abuse/right\\_committee/en/](http://www.who.int/substance_abuse/right_committee/en/)
10. Mattoo SK, Gaur N, Das PP. Zolpidem withdrawal delirium. *Indian J Pharmacol.* 2011 Nov;43(6): 729-30. doi: 10.4103/0253-7613.89838.
11. Mariani JJ, Levin FR. Quetiapine treatment of zolpidem dependence. *Am J Addict.* 2007 Sep-Oct;16(5):426
12. Geracitano R, Fischer D, Kasugai Y, Ferraguti F, Capogna M. Functional expression of the GABA(A) receptor  $\alpha 2$  and  $\alpha 3$  subunits at synapses between intercalated medial paracapsular neurons of mouse amygdala. *Front Neural Circuits.* 2012 May; 6:32. doi: 10.3389/fncir.2012.00032.
- eCollection 2012.
13. Victorri-Vigneau C, Dailly E, Veyrac G, Jolliet P. Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *Br J Clin Pharmacol.* 2007 Aug;64(2):198-209.
14. Farzaneh E, Mehrpour O, Alfred S, Moghaddam HH, Behnoush B, Seghatoleslam T. Self-poisoning suicide attempts among students in Tehran, Iran. *Psychiatr Danub.* 2010 Mar;22(1):34-8.
15. Karrari P, Mehrpour O, Afshari R, Keyler D. Pattern of illicit drug use in patients referred to addiction treatment centres in Birjand, Eastern Iran. *J Pak Med Assoc.* 2013 Jun;63(6):711-6.
16. Taghaddosinejad F, Mehrpour O, Afshari R, Seghatoleslami A, Abdollahi M, Dart RC. Factors related to seizure in tramadol poisoning and its blood concentration. *J Med Toxicol.* 2011 Sep;7(3):183-8. doi: 10.1007/s13181-011-0168-0.
17. Alinejad S, Kazemi T, Zamani N, Hoffman RS, Mehrpour O. A systematic review of the cardiotoxicity of methadone. *EXCLI J.* 2015; 14: 577-600.
18. Farzaneh E, Mostafazadeh B, Mehrpour O. Seizurogenic effects of low-dose naloxone in tramadol overdose. *Iranian Journal of Pharmacology & Therapeutics.* 2012; 11(1):6-9.