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Circadian Dysregulation, Zolpidem Dependence, and Withdrawal Seizure in a Resident Physician Performing Shift Work

Alex S. Keuroghlian, MD, MSc¹, Alan S. Barry, MD^{1,2}, and Roger D. Weiss, MD^{1,2}

¹Department of Psychiatry, Harvard Medical School, Boston, Massachusetts

²Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, Massachusetts

The abrupt and frequent changes in a rotating work-shift schedule can lead to dysregulation of the circadian sleep/wake cycle.^{1,2} Many shift workers use hypnotic medications to achieve longer-lasting and higher-quality sleep, as well as acceptable work performance.³ The non-benzodiazepine hypnotic, zolpidem, is the most widely-prescribed sleep medication in the United States.⁴

Zolpidem has frequently been described as a safer, less addictive alternative to benzodiazepines for short-term treatment of insomnia.⁵ A study comparing zolpidem and triazolam, however, showed that the two drugs have comparable abuse potential.⁶ Reports have documented zolpidem dependence and withdrawal,^{5,7} as well as delirium,⁷ hallucinations,⁸ and seizure⁹ upon discontinuation of zolpidem.

Zolpidem is nevertheless increasingly being adopted by shift workers to treat dysregulated sleep, for example among United States Air Force crew members and American resident physicians.^{10–12} The case presented here is the first documented report of zolpidem dependence and withdrawal seizure in the setting of circadian rhythm disturbance from shift work, specifically in a resident physician on a rotating overnight call schedule.

CASE DESCRIPTION

The patient was a 34-year-old male resident physician with a history of bipolar disorder, alcohol abuse, and prescription opioid abuse. Four years ago he started self-prescribing oxycodone regularly for one year, until the medical licensing board learned of this behavior and placed him on probation. His license was suspended for 1.5 years, during which he was not working and stayed sober while participating in Alcoholics Anonymous and Narcotics Anonymous.

Upon returning to work, the patient resumed hospital duties with rotating overnight call, and circadian dysregulation soon ensued. He had previously experienced sleep cycle disturbances before taking his leave of absence from clinical work. He was diagnosed with bipolar disorder after a manic episode 9 months ago, and began lithium 900 mg daily; his mood remained euthymic thereafter, but circadian rhythm disruption persisted with the demands of rotating overnight call.

Address correspondence to Dr. Keuroghlian, McLean Hospital, 115 Mill St., Belmont, MA 02478. akeuroghlian@partners.org.

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The authors alone are responsible for the content and writing of this paper.

In the setting of irregular shift work and refractory circadian dysregulation, the patient started ordering zolpidem from online pharmacies and drinking heavily. He started taking 100–150 mg of immediate-release zolpidem daily after returning to residency 2.5 years ago, escalating to 200mg daily during the two months before admission. His last zolpidem use was three days prior to presentation. For several months prior to admission, he drank two bottles of wine approximately three times per week, with his last drink four days before admission. He had alcohol-related blackouts in the past, but no seizures. Notably, one parent was abusing zolpidem and another parent had alcohol dependence.

The patient had just completed a 30-hour hospital shift when he experienced a grand mal seizure. He was taken to an emergency room. His urine toxicology screen was negative, and his blood alcohol level was zero; a CT scan of his head was normal. He knew that zolpidem is not detected in most toxicology screens and did not inform the emergency room staff of his zolpidem use. His serum lithium level was 0.43. The staff concluded that his seizure was likely related to sleep deprivation and discharged him home. He contacted his psychiatrist, to whom he described his zolpidem and alcohol use. The psychiatrist recommended that he admit himself for inpatient treatment.

At admission, he reported an inability to cut back on zolpidem and alcohol use. He described a history of chronic sleep cycle disturbance and stated that he had been unable to fall asleep for the past two days. He had no manic symptoms. He reported blurred vision, headache, anxiety, and “jitters.” He met all seven DSM-IV criteria for zolpidem dependence. He denied psychotic symptoms, self-injurious behavior, or suicidal ideation.

Over the next three days, he was treated with a chlordiazepoxide taper, and a zolpidem taper of 30mg on day 1, 20mg on day 2, 10mg on day 3, then discontinuation. After hospital discharge, he entered a treatment program for physicians. Eight months later, he remained substance-free, while engaging in individual and group psychotherapy, active Alcoholics Anonymous, and pharmacotherapy for his bipolar disorder.

CONCLUSIONS

This report is the first documented case of zolpidem dependence due to shift work. We presume that his seizure was primarily caused by zolpidem withdrawal: he was using large doses of zolpidem daily until three days preceding the seizure. Zolpidem-related withdrawal seizures have recently been reported to occur as long as seven days after discontinuation of 200 to 400mg of daily zolpidem use.¹³ The seizure was less likely due to alcohol withdrawal, as he was drinking only three times per week, with his last drink four days prior to the seizure. Lithium toxicity is even more improbable as the cause of his seizure, since his serum lithium level was subtherapeutic.

As zolpidem use becomes increasingly prevalent among shift workers seeking to minimize the detrimental effects of disrupted sleep cycles, those with a history of substance use disorders, or who are otherwise predisposed to them, may be at increased risk of developing dependence upon zolpidem. Employers and workers in settings in which staff members experience abrupt work-sleep schedule changes should be aware of zolpidem’s potential for abuse, dependence, and potentially serious withdrawal.

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References

1. Crowley SJ, Lee C, Tseng CY, Fogg LF, Eastman CI. Complete or partial circadian re-entrainment improves performance, alertness, and mood during night-shift work. *Sleep*. 2004; 27:1077–1087. [PubMed: 15532201]
2. Eastman CI, Martin SK. How to use light and dark to produce circadian adaptation to night shift work. *Ann Med*. 1999; 31:87–98. [PubMed: 10344580]
3. Niedhammer I, Lert F, Marne MJ. Psychotropic drug use and shift work among French nurses (1980–1990). *Psychol Med*. 1995; 25:329–338. [PubMed: 7675921]
4. Barthelow, M. [Accessed August 7, 2012.] Top 200 Drugs of 2010. *Pharmacy Times*. 2011. <http://www.pharmacytimes.com/publications/issue/2011/May2011/Top-200-Drugs-of-2010>
5. Hajak G, Muller 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; 98:1371–1378. [PubMed: 14519173]
6. Rush CR, Baker RW, Wright K. Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans. *Psychopharmacology*. 1999; 144:220–233. [PubMed: 10435388]
7. Kao CL, Huang SC, Yang YJ, Tsai SJ. A case of parenteral zolpidem dependence with opioid-like withdrawal symptoms. *J Clin Psychiatry*. 2004; 65:1287. [PubMed: 15367062]
8. Manfredi G, Kotzalidis GD, Lazanio S, et al. Command hallucinations with self-stabbing associated with zolpidem overdose. *J Clin Psychiatry*. 2010; 71:92–93. [PubMed: 20129012]
9. Aragona M. Abuse, dependence, and epileptic seizures after zolpidem withdrawal: review and case report. *Clin Neuropharmacol*. 2000; 23:281–283. [PubMed: 11154097]
10. Caldwell JA, Caldwell JL. Fatigue in military aviation: an overview of US military-approved pharmacological countermeasures. *Aviat Space Environ Med*. 2005; 76:C39–51. [PubMed: 16018329]
11. Van Camp RO. Zolpidem in fatigue management for surge operations of remotely piloted aircraft. *Aviat Space Environ Med*. 2009; 80:553–555. [PubMed: 19522366]
12. Mcbeth BD, Mcnamara RM, Ankel FK, et al. Modafinil and zolpidem use by emergency medicine residents. *Acad Emerg Med*. 2009; 16:1311–1317. [PubMed: 20053252]
13. Wang LJ, Ree SC, Chu CL, Juang YY. Zolpidem Dependence and Withdrawal Seizure – Report of two cases. *Psychiatr Danub*. 2011; 23:76–78. [PubMed: 21448102]