

# PAROXYSMAL TONIC SPASM IN A PATIENT WITH THE SUDDEN ZOLPIDEM WITHDRAWAL: A CASE REPORT

Masoud Keighobadi, Narges Karimi

## Abstract

Zolpidem is an imidazopyridine derivative and a non-benzodiazepine hypnotic drug. There are several case reports of zolpidem abuse or dependence and zolpidem withdrawal. This study reports a case of paroxysmal tonic spasm (PTS) after abrupt withdrawal of high dose zolpidem. The case was a 21-year-old male patient with complaints of acute involuntary and painful spasms of all extremities after the sudden withdrawal of taking supratherapeutic zolpidem. In his medical records, He had the history of insomnia and psychiatric disorder. The patient's symptoms improved with intravenous injection of 10 mg diazepam slowly and zolpidem was tapered gradually. This case report indicates that zolpidem has a dependency and abuse properties. To the best of our knowledge, this is the first report of zolpidem withdrawal with PTS.

**Key words:** zolpidem, withdrawal, paroxysmal painful spasm, dependency, case report

Masoud Keighobadi<sup>1</sup>, Narges Karimi<sup>2</sup>

<sup>1</sup>Toxoplasmosis Research Center, Communicable Diseases Research Institutes, Mazandaran University of Medical Sciences, Sari, Iran

<sup>2</sup>School of Medicine, Immunogenetics Research Center, Clinical Research Development Unit of Bou Ali Sina Hospital, Mazandaran University of Medical Sciences, Sari, Iran

OPEN ACCESS

**Citation:** Keighobadi, M., Karimi, N. (2020). Paroxysmal tonic spasm in a patient with the sudden zolpidem withdrawal: A case report. *Clinical Neuropsychiatry*, 17(5), 314-316.

doi.org/10.36131/cnforitieditore20200507

© 2020 Giovanni Fioriti Editore s.r.l.

This is an open access article. Distribution and reproduction are permitted in any medium, provided the original author(s) and source are credited.

**Funding:** None.

**Competing interests:** None.

## Corresponding author

Narges Karimi, Associate professor of Neurology, M.D.  
Bou Ali Sina Hospital, Pasdaran Boulevard, Sari city, Mazandaran province, Iran. Postal code: 4815838477  
Email: Drkarimi\_236@yahoo.com  
Tel: +981133343018, Fax: +981133344506  
Mobile: +989122029074

## Introduction

Paroxysmal tonic spasms (PTS) has been described as abrupt onset of attacks in the form of tonic status, either unilateral or bilateral. It usually lasts seconds or minutes and is associated with extreme pain of the limbs. This disorder may be stimulated by intentional activities, sensory stimulation, hyperventilation or occur spontaneously (Abaroa et al., 2013). The patients are alert at the time of attacks and most patients have normal conditions between the attacks (Abaroa et al., 2013). This disorder is usually observed in association with structural lesions of central nervous system (CNS), such as the demyelination lesion and lacunar infarcts of pons and basal ganglia or metabolic abnormalities such as hyperglycemia, hypo- or hypercalcemia (Kellett, Young, & Fletcher, 1997; Marsilia, Gallerina, Bartaluccia, Marottia, & Marconia, 2018). The exact pathophysiology of tonic spasm has not been determined yet. Zolpidem is an imidazopyridine derivative and a non-benzodiazepine hypnotic drug with a high affinity to  $\alpha 1$  subunit of gamma amino butyric acid-A (GABA<sub>A</sub>) receptor which is prescribed in short-term treatment of insomnia. Zolpidem also has mild anxiolytic, myorelaxant and anticonvulsant effects (Chen, Chen, Liao, Tseng, & Lee, 2012; Monti, Spence, Buttoo, & Pandi-Perumal, 2017). There are several case reports of zolpidem abuse or dependency and zolpidem

withdrawal. Zolpidem withdrawal symptoms include insomnia, anxiety, tremor, palpitations, and convulsions (Pourshams, & Malakouti, 2014; Wang, Ree, Chu, & Juang, 2011). One study reported the onset of status dystonicus following zolpidem withdrawal (Kojovi & Gregori Kramberger, 2015). However, to the best of our knowledge, this is the first time to investigate a case of PTS associated with zolpidem withdrawal.

## Case presentation

A 21-year-old male patient with history of psychiatric disorder and insomnia from 3 years. was referred to our university hospital (Bou-Ali Sina), Sari city, Mazandaran province, Iran with acute onset of involuntary and painful movements of all extremities and neck. This symptom had been initiated one day before the admission. The sudden muscle spasms were precipitated spontaneously. The attack lasted less than two minute and repeated 10 to 15 times a day. Consciousness and awareness was always preserved during the attacks. The patient presented the abnormal movements that were in dystonic form with neck and head turned to the right, shoulder adduction and internal rotation, extension and stretching of upper and lower limbs along with sparing of face and trunk. The involvement of the limbs was bilateral

and simultaneous. The patient was able to speak at the time of the attacks but was unable to move until the attack had completely stopped. There was a rapid improvement in muscle contraction and no subsequent confusion. The patient had tachycardia, increased respiration, and diaphoresis during the attacks, though he was normal between attacks. The patient's symptoms were present on awakening and did not change during the physical examination and observation. He had no family history and past medical history of neurological disorders and he was not taking any medication other than zolpidem. In terms of psychiatric disorder, the patient had behavioral disorder approximately 3 years ago. He complained from anxiety, aggressive attacks and insomnia. He started taking zolpidem with dosage of 10 mg daily one year ago. After taking zolpidem, the patient's anxiety and restlessness decreased. After two months, he gradually increased his daily zolpidem consumption to 70–80 mg daily. After 6 months, he abruptly stopped taking zolpidem as a result of dizziness and nightmares. Approximately 24 hours after discontinuation of the drug, he showed the signs of abnormal movements.

At the admission time, the patient was agitated and had increased psychomotor activity. The vital signs of patient were temperature (T)=36.8°C axillary, pulse rate (PR)=90, respiratory rate (RR)=20, O<sub>2</sub> Sat=98%, and Blood Pressure (BP) 130/70. The neurological examination was normal. To rule out differential diagnosis, several lab tests and imaging were performed. The lab tests such as complete blood count, blood sugar, electrolytes, urea, calcium, phosphor, magnesium, erythrocyte sedimentation rate, thyroid and liver function tests were normal. Brain and cervical magnetic resonance imaging (MRI) with T1- and T2 weighted, FLAIR, post gadolinium-enhanced T1-weighted sequences, and a DWI sequence was normal. An awake 16-channel electroencephalogram (EEG) with the standard “10–20 system” was performed. It was normal in between attacks. The symptoms of patient improved with intravenously injection of 10 mg diazepam slowly and zolpidem was tapered gradually over one week. Therefore, he was discharged on zolpidem 5 mg bid and followed up for 8 months. After 4 weeks, zolpidem was stopped. After 8 months' follow-up, the patient remained asymptomatic and had no tonic attacks.

## Discussion

In this report, we described a male patient developing paroxysmal painful tonic spasms after abrupt discontinuing of high-dose zolpidem. The best of our knowledge, this is the first case of association of PTS with zolpidem withdrawal in the literatures. This patient was consuming zolpidem in the supratherapeutic doses consistently for a long time and therefore he became dependent on it. He had withdrawal symptoms with PTS after 24 hours of its discontinuation. He had no past history of neurological disorders and he was not taking any medicine other than zolpidem. Brain and cervical MRIs and also interictal EEG were normal. Zolpidem is a short-effect hypnotic drug that augments GABAergic neurotransmission through the benzodiazepine binding site on specific GABA-A receptors ( $\alpha 1$  subunit) but is not deliberated a typical benzodiazepine because of lack of diazepam cycle in chemical structure (Chen, Chen, Liao, Tseng, & Lee, 2012). Zolpidem was approved for the short-term treatment of insomnia almost twenty years ago (Monti, Spence, Buttoo, & Pandi-Perumal,

2017; Chen, Chen, Liao, Tseng, & Lee, 2012). Several reports described abuse and dependency and also withdrawal symptoms with zolpidem (Chen, Chen, Liao, Tseng, & Lee, 2012; Pourshams, & Malakouti, 2014; Wang, Ree, Chu, & Juang, 2011). The withdrawal symptoms of taking high-dose zolpidem are similar to the symptoms of benzodiazepines withdrawal, including tremor, insomnia, anxiety, autonomic nervous system dysfunction, and generalized tonic-clonic seizures (Chen, Chen, Liao, Tseng, & Lee, 2012).

Recently, Rossi et al reported a case with focal bilateral movement seizure due to abrupt stopping of chronic lormetazepam abuse (Rossi, Di Stefano, Lizzos, & Deiana, 2020). Some studies described rare symptoms of zolpidem withdrawal including status dystonicus and catatonia (Kojovi & Gregori Kramberger, 2015; Hsieh, Chen, Chiu, & Chang, 2011). Status dystonicus is life threatening complication of generalized dystonia associated with respiratory and metabolic complications (Kojovi & Gregori Kramberger, 2015). One of the differential diagnoses of paroxysmal movement disorder is functional (psychogenic) movement disorders (FMDs) that the clinical characteristics of this disorder such as variability, instability, suggestibility, distractibility, and suppressibility during physical examination helps to identify it (Thenganatt & Jankovic, 2019). In this case report, we described zolpidem-related withdrawal PTS. The pathophysiology of PTS is unclear. Although spreading activation of damage axons has been described, it is still a controversial issue (Abaroa et al., 2013). However, the exact mechanism of developing PTS following zolpidem-withdrawal is still unclear. Some studies have shown that GABA-A receptors may be present in different parts of the CNS and may be connected to other sites of GABA receptors. Hence, the sudden discontinuation of the drug probably caused a prompt reduction in GABA-A transmission in the CNS (Aragona, 2000). It is hypothesized that GABAergic depletion may play a role in causing PTS. Since the results of imaging, EEG, and lab tests were normal, it was postulated that the cause of tonic spasms in this patient was probably non-epileptic spasm due to abrupt discontinuation of zolpidem. A paroxysmal PTS is usually painful and does not have a clonic phase, whereas an epileptic spasm is usually painless and its duration is shorter than PTS. Accordingly, an ictal EEG and video-EEG are helpful in differentiating these two conditions. The symptoms of this patient improved with the injection of diazepam intravenously similar to the study carried out by Chen (Chen, Chen, Liao, Tseng, & Lee, 2012).

## Conclusion

This case report indicated that zolpidem is a drug that has a dependency and abuse properties. To the best of our knowledge, this is the first case study to report a possible association between PTS and withdrawal of zolpidem. Although the awareness of patient was preserved during the attacks and interictal EEG, and imaging were normal, but epileptic spasm cannot be completely ruled out. In this study, we could not perform video-EEG monitoring and ictal EEG due to some limitations.

## Acknowledgments

We thank the patient for her consent to publish this case report.

## References

- Abaroa, L., Rodríguez-Quiroga, S.A., Melamud, L., Arakaki, T., Garretto, N.S., & Villa, A.M. (2013). Tonic spasms are a common clinical manifestation in patients with neuromyelitis optica. *Arq Neuropsiquiatr.*, 71(5), 280-3. doi: 10.1590/0004-282X20130021
- Aragona, M. (2000). Abuse, dependence, and epileptic seizures after zolpidem withdrawal: review and case report. *Clin. Neuropharmacol.*, 23, 281-283. doi: 10.1097/00002826-200009000-00008.
- Chen, S.C., Chen, H.C., Liao, S.C., Tseng, M.C., & Lee, M.B. (2012). Detoxification of high-dose zolpidem using cross-titration with an adequate equivalent dose of diazepam. *Gen. Hosp. Psychiatry.*, 34(2), 210. doi: 10.1016/j.genhosppsych.2011.09.012.
- Hsieh, M.H., Chen, T.C., Chiu, N.Y., & Chang, C.C. (2011). Zolpidem-Related Withdrawal Catatonia: A Case Report. *Psychosomatics.*, 52, 475-477. doi: 10.1016/j.psych.2011.01.024.
- Kellett, M.W., Young, G.R., & Fletcher, N.A. (1997). Painful tonic spasms and pure motor hemiparesis due to lacunar pontine infarct. *Mov. Disord.*, 12, 1094-1096. <https://doi.org/10.1002/mds.870120646>.
- Kojovi, M., & Gregori Kramberger, M. (2015). Zolpidem withdrawal status dystonicus in the patient with advanced Parkinson's disease. *Parkinsonism and Related Disorders.*, 21, 661-662. doi: 10.1016/j.parkreldis.2015.03.015.
- Marsilia, L., Gallerina, S., Bartaluccia, M., Marottia, C., & Marconia, R. (2018). Paroxysmal painful spasms associated with central pontine myelinolysis in the context of nonketotic hyperglycemia. *Journal of the Neurological Sciences.*, 388, 37-39. doi: 10.1016/j.jns.2018.03.005.
- Monti, J.M. Spence, D.W., Buttoo K., & Pandi-Perumal, S.R. (2017). Zolpidem's use for insomnia. *Asian Journal of Psychiatry.*, 25, 79-90. doi: 10.1016/j.ajp.2016.10.006.
- Pourshams, M., & Malakouti, S.K. (2014). Zolpidem abuse and dependency in an elderly patient with major depressive disorder: a case report. *Daru.*, 22, 54. doi: 10.1186/2008-2231-22-54.
- Rossi, R., Di Stefano, F., Lizzos, S., & Deiana, G. (2020). Focal bilateral motor seizures precipitated by abrupt cessation of chronic Lormetazepam abuse. *Epilepsy & Behavior Reports.* (in press). <https://doi.org/10.1016/j.ebr.2020.100385>.
- Thenganatt, M.A., & Jankovic, J. (2019). Psychogenic (Functional) Movement Disorders. *Continuum (Minneapolis)*, 25, 1121-1140.
- Wang, L.J, Ree, S.C, Chu C.L, & Juang, Y.Y. (2011). Zolpidem dependence and withdrawal seizure--report of two cases. *Psychiatr Danub.*, 23(1), 76-8.