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High-dose zolpidem withdrawal seizure in a patient with spinocerebellar ataxia

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1) The material in this paper has not been reported or published, nor has been submitted for publication elsewhere.
2) The requirement for authorship that is laid down by the editor board of JCP has been met, and the manuscript has been read and approved by all authors.
3) This study had no material or financial support.

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To the Editor:

Spinocerebellar ataxia (SCA) is an inherited disorder of brain function characterized by progressive incoordination of gait and often associated with poor coordination of hands, speech, and eye movements. It is a slowly progressive disease which gradually worsens over a period of years.

Zolpidem is a nonbenzodiazepine sedative in the imidazopiridine class and is chemically distinct from other sedatives. It is a short-acting hypnotic with a selective agonist effect for GABA type A receptors in the brain. It was considered originally by physicians as almost devoid of abuse and dependence potential. Intriguingly, aside from its hypnotic effect, zolpidem has been shown to improve catatonia[1], aphasia[2], Parkinson's disease[3], and ataxia[4]. However, reports of zolpidem abuse or dependence were increasing [5,6] and more attention should be paid in terms of zolpidem withdrawal. We report a SCA case who took zolpidem for movement difficulties initially, developed dependence on high-dose zolpidem and encountered serious withdrawal symptoms. We also reviewed literatures about the possible mechanism for zolpidem's effect on SCA.

Case report: A 40-year-old married woman was referred for psychiatric consultation due to high-dose zolpidem use. She was diagnosed with SCA type IV at age 35 with

initial symptoms of unsteady gait and mild slurred speech. Her father and brother were also afflicted with SCA. This time she was admitted via emergency room to our Neurology Department because of conscious loss. Generalized seizure lasted for 1 minute at home, initial management at ER with phenytoin intravenous drip terminated further progression. Toxicology test revealed plasma alcohol was undetected while BZD level was 64.80 ng/mL.

She claimed she had triazolam and alcohol abuse during early adulthood due to insomnia. Other illicit substance use was denied. She started using zolpidem 3 years ago for insomnia and paradoxically zolpidem relieved her ataxia and spasticity. She recalled she can move her arms and turn her trunk more easily although it only lasted around 1 hour. The dose of zolpidem was gradually escalated by the patient to reach optimal effect. The dose usually amounted to 1000 mg/day for the past 1 year. Nausea, palpitation, jitters, hand tremor and perspiration were noted if she didn't take enough drugs. She was bed-ridden due to SCA and was cared by her husband. Although she consumed high-dose of zolpidem, her husband tried to cater for all her needs out of sympathy. Zolpidem had been prescribed from different physicians. Withdrawal seizures were noted several times if she fell short of zolpidem supply.

Patient was detoxified by tapering zolpidem gradually over 2 weeks. We prescribed

trazodone 100mg before sleep and diazepam 20mg/day, propranol 30mg/day for anxiety. No seizure attack was noted during hospitalization. She was referred to psychiatric clinic for further management.

The imidazopyridine hypnotic zolpidem binds preferably to the alpha 1 subtype of the benzodiazepine (BZ) receptor, which is part of GABAa-receptor complex. This highly accounts for its sedative effect, whereas the anxiolytic action of BZ appears to be mediated by receptors that contain the $\alpha 2$ subunit[7]. Zolpidem at high doses might lose its selectivity on $\alpha 1$ subunits and bind to lower-affinity $\alpha 2$ units leading to anxiolytic effect. Thus high-dose zolpidem may have a paradoxical effect for alleviating anxiety and abrupt discontinuation would produce withdrawal symptoms such as palpitation, anxiety, tremor or seizure similar to benzodiazepine withdrawal.

There is no definite treatment that can prevent or slow the progression of SCA. Clauss et al.[4] reported transient improvement of SCA with zolpidem in four cases. SPECT demonstrated GABAergic function may be decreased in cerebral cortex, thalamus, striatum, and cerebellum in patients with SCA[8]. Zolpidem has been shown to mildly improve catatonia, aphasia, and Parkinson's disease[9]. Such motor improvement may be due to selective inhibition by zolpidem of GABAergic inhibitory neurons in the internal globus pallidus and substantia nigra pars reticulata, resulting in activation of the

thalamus and cerebral cortex[9]. PET imaging also showed normalized tracer uptake in the left thalamus and cerebellum after treatment with zolpidem[4]. Our case further corroborates that zolpidem has a mode of action apart from hypnotic properties. To our knowledge, this is the first case report concerning high-dose zolpidem withdrawal seizure in a SCA patient. We should be more cautious in prescribing zolpidem in patients with past drug abuse or dependence to prevent unwanted consequence. Further investigation of the pharmacological efficacy of zolpidem in SCA might be needed.

Acknowledgement

This study had no material or financial support.

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