

Zolpidem dependence in an adult with bipolar affective disorder and epilepsy: A case report

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ABSTRACT

Zolpidem is a short-acting non-benzodiazepine hypnotic agent, commonly recommended for short-term treatment of insomnia. Zolpidem has less dependence potential than benzodiazepines. Patients with mental illnesses often have disturbed sleep, for which zolpidem is often prescribed. Long-term use and self-medication (in more than recommended doses) are more likely to cause dependence. We report here a case of bipolar affective disorder with epilepsy, who developed dependence to zolpidem and had severe withdrawal symptoms. The management issues are also discussed with review of the literature.

INTRODUCTION

Zolpidem is a short-acting, non-benzodiazepine hypnotic agent.¹ Zolpidem is often prescribed for short-term treatment of insomnia. It helps in the induction of sleep. It is available in immediate-release and sustained (extended)-release formulations.² The elimination half-life of zolpidem is less than 3 hours.³ Hence, the withdrawal symptoms are expected to appear after several hours, though the risk of withdrawal is less with usage of zolpidem in therapeutic dosages (up to 10 mg/day for approximately a 1-month period).³ Rebound insomnia, next-day hangover, cognitive impairment (disturbance of memory and co-ordination) and psychomotor disturbances are seen with use of zolpidem.⁴ In the elderly population, the half-life of zolpidem is prolonged, so the withdrawal symptoms are expected to appear late. The sedative effect becomes greater when co-administered with medications with central nervous system depressant properties.⁵ We report here the case of a patient with bipolar affective disorder with epilepsy, who developed zolpidem dependence.

CASE HISTORY

A 56-year-old man was hospitalised for odd behaviour, irrelevant talk, increased

physical activity and aggressive behaviour, which were episodic in nature. These episodes often lasted for several minutes (15 to 30 min) and subsided after taking 10 mg of zolpidem. He also had decreased sleep and a burning sensation in the scalp for the past 20 days. The patient was a known case of bipolar affective disorder. At the age of 18 years, he had his first episode of mania. He had multiple mood episodes until he was 38 years of age. Most of the mood episodes were manic episodes (characterised by increased talkativeness, elevated affect, increased physical activity and grandiose thoughts) and one episode clearly indicative of depression (characterised by sadness of mood, withdrawn behaviour, decreased psychomotor activity and disturbed sleep). Past treatment details of bipolar disorder were not available. For the last 15 years (approximately), he was not taking any medications for his psychiatric illness.

He was also diagnosed with epilepsy 4 years ago and received various antiepileptic medications (levetiracetam 1500 mg/day followed by switching to valproate 1000 mg/day). On reviewing history, family members reported that the patient was taking 7 to 10 tablets of zolpidem of 10 mg strength per day (10 mg of zolpidem every 2 to 3 hours, resulting in 70 to 100 mg/day) for the past 2 months, which was abruptly reduced by the patient's family members for the past 20 days (to a dose of 20 mg/day). The patient was prescribed zolpidem by a general physician for sleep disturbances. The patient had delay in onset of sleep (sleep latency ranging from 1 to 2 hours) as well as decreased duration of sleep. No precipitating factor could be identified for his sleep disturbances. He had no history of similar sleep disturbance in the past, except for the disturbances of sleep during the mood episodes. The patient used to have 2 to 3 hours of sound sleep after taking zolpidem. To have longer



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duration of sleep, the patient had started self-medicating by increasing the number of tablets. Increased consumption of tablets of zolpidem was objectionable by family members, so they tried to limit the use of zolpidem. Family members reported that whenever he was not given a tablet of zolpidem or it was delayed by an hour or so, he used to become aggressive, restless and complain of a burning sensation in the scalp, which would subside within 15 to 30 min of intake of zolpidem. After taking zolpidem during the day time, the patient would remain calm and quiet, but would not sleep. During a 20-day period, the patient also had multiple episodes of seizure. The patient was evaluated for seizure. Neuroimaging findings revealed diffuse cerebral atrophy but the video electroencephalogram finding was within normal limits. His blood investigations revealed hyponatremia (serum sodium 127.3 mEq/lit). Possibilities of seizure due to hyponatremia or due to zolpidem withdrawal were considered. He was given a relatively higher dose of zolpidem (sustained-release preparations of zolpidem up to 50 mg/day). Hyponatremia was corrected, but his seizure persisted, so opinion was taken from neurology. As the patient had hyponatremia, he was given eslicarbazapine. At the dose of valproate 1000 mg/day and eslicarbazapine 600 mg/day, his seizure was well controlled. During this process, it was observed that on increasing the dose of zolpidem, his odd behaviour, irrelevant talk and increased physical activity have improved significantly. His burning sensation in the scalp had also improved. The patient's family history was insignificant. There was a history of occasional alcohol and tobacco use in the patient.

During assessment, the patient was found to be conscious and oriented but giving irrelevant answers at times with increased gesturing of hands. There was no obvious evidence of cognitive deficits. On mental status examination, his affect was perplexed in the initial few days. Subsequent interviews revealed euthymic affect. No delusions or hallucinations were elicited. Quetiapine (up to 100 mg/day) was given to control his agitation and insomnia. The patient was shifted from an immediate-release preparation to a sustained-release preparation of zolpidem with gradual dose reduction. Over a period of 6 weeks, zolpidem was stopped. He was discharged and followed regularly, with monitoring of serum electrolytes. At 6 months' follow-up, the patient was maintained well on the antiepileptic medications and quetiapine.

DISCUSSION

There are certain unique features in our patient. The patient had developed dependence to zolpidem in a short period of time (2 months). Maximum daily consumption of zolpidem was 100 mg/day. Certain unique withdrawal features (oddities of behaviour, increased psychomotor activity, irrelevant talk and burning sensation in the scalp) were elicited on reducing the dose of

zolpidem, which subsided after increasing its dose. Most of these symptoms were episodic in nature. As zolpidem is a short-acting hypnotic agent, withdrawal symptoms are expected to reappear in frequent intervals (within hours of stoppage). In our case, the patient was having withdrawal symptoms after 2 to 3 hours of last dose of zolpidem. Evidence supports the dependence potential of zolpidem. Patients withdrawing from zolpidem often develop insomnia, anxiety and autonomic overactivity.⁶ Some patients may report delirium, seizure and even psychotic features as withdrawal symptoms.^{7,8} Our patient had also developed multiple episodes of seizure after reduction of the dose of zolpidem. Hyponatremia was also present during that period. Initially, the seizures were attributed to hyponatremia. However, the seizures persisted even after correction of hyponatremia, so it is quite possible that zolpidem withdrawal might have resulted in a precipitation of seizure episodes. Patient's age, pre-existing seizure disorder, sleep deprivation and underlying hyponatremia are all potential risk factors that were attributed to current seizure episodes despite compliance to antiepileptic medications in adequate doses. Though the patient is a known case of bipolar affective disorder and epilepsy, the symptoms during the current consultation seem to be better explained by zolpidem withdrawal as they were episodically present when the patient was not taking zolpidem and improved immediately after taking zolpidem.

Shifting patients with zolpidem dependence from immediate-release preparations to sustained-release preparations and gradual dose tapering may be useful in such patients. Clinicians need to be cautious in prescribing zolpidem to elderly people, particularly those with seizure disorder or severe mental disorder. The recommendation should be for the short term and may be in the 'as and when required' basis than regular daily use.

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