Psychiatria Danubina, 2026 Vol. 38, No. 2, pp 217-220 https://doi.org/10.24869/psyd.2026.217 *Case Report*
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Zolpidem use disorder and withdrawal-related generalized seizures: A case report

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received: 1 January 2026; revised: 1 May 2026; accepted: 13 May 2026

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INTRODUCTION

Zolpidem is widely prescribed for the short-term management of insomnia and acts as a non-benzodiazepine hypnotic with selective affinity for the α1 subunit of the gamma-aminobutyric acid type A (GABA-A) receptor complex (Edinoff et al., 2021; Yüksel, 2003). This receptor selectivity underlies its sedative properties, while prolonged exposure may lead to receptor-level adaptations that contribute to tolerance and dependence (Ballenger, 2000; Yüksel, 2003). Although therapeutic doses of 5–20 mg/night are generally considered safe for short-term use, accumulating reports indicate that chronic or high-dose zolpidem can lead to dependence and withdrawal syndromes, including generalized tonic–clonic seizures. Recent case reports describe withdrawal seizures after abrupt discontinuation of daily doses typically ranging from about 100 to 300 mg, with some patients escalating to extreme doses over many years (Ballenger, 2000; Barbosa Eyler, 2023; Chishti, 2025; Mao, 2022; Mashiana, 2021; Sasaki, 2024; Tripodianakis et al., 2003; Yüksel, 2003).

Multiple international guidelines—49 including the European Sleep Research Society (ESRS), the American Academy of Sleep Medicine (AASM), and the American College of Physicians (ACP)—recommend cognitive behavioral therapy for insomnia (CBT-I) as the first-line treatment for chronic insomnia, while hypnotics should be limited to the lowest effective dose and shortest duration (Edinger et al., 2021; Qaseem et al., 2016; Riemann et al., 2017). These guidelines further emphasize ongoing evaluation of risk–benefit balance and comorbidities during hypnotic use and withdrawal (Edinger et al., 2021; Qaseem et al., 2016; Riemann et al., 2017). Despite these recommendations, inappropriate long-term use and illicit access continue to contribute to severe zolpidem dependence. Within this emerging body of literature, most withdrawal-related seizures have been reported at higher daily doses than typical prescribing ranges; we present a case in which recurrent generalized seizures occurred during long-term use of 80–100 mg/day, accompanied by EEG-documented epileptiform activity, thereby extending current evidence toward more moderate suprathera-peutic doses.

CASE PRESENTATION

A 34-year-old woman presented to an addiction clinic with long-standing zolpidem use disorder. The patient is not working and states that, apart from a few close friends, she has no emotional or social support. According to the patient, she had been experiencing problems with her husband for a long time, and they had been going through a divorce for the past five years in particular. She had taken 80–100 mg/day for seven years, progressively increasing the dose after inadequate responses to multiple antidepressants and hypnotics prescribed for postpartum-onset insomnia. Zolpidem was initially supplied informally by an acquaintance. As zolpidem is a controlled substance in Türkiye and not available over the counter, she later obtained it through unregulated sources. She reported dose escalations of approximately 10 mg every 2–3 months until reaching 100 mg/day. She had no history of alcohol or illicit substance use. There was no significant medical history. During the sixth year of use, she experienced six generalized tonic–clonic seizures, each occurring after dose reduction or abrupt cessation attempts. Lamotrigine 100 mg/day was initiated after the second seizure and later increased to 200 mg/day. Neurological evaluation revealed suspected generalized frontal epileptiform activity; cranial magnetic resonance imaging (MRI) was normal. Additionally, she was receiving fluoxetine 20 mg/day for depressive symptoms.

Upon admission, she reported ingesting four 10-mg tablets (40 mg) of zolpidem earlier that day. Within the first 24 hours, she developed autonomic and affective withdrawal symptoms, scoring 24 on the Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-AR). Diazepam 40 mg/day was initiated alongside lamotrigine and fluoxetine. Nineteen hours later, she developed a generalized tonic–clonic seizure requiring diazepam and intravenous valproate. EEG revealed generalized epileptiform activity, and valproate 500 mg/day was added. No further seizures were observed during follow-up, and a sleep EEG performed on the fourth day was normal.

Neurology consultation concluded that the seizures were attributable to zolpidem withdrawal. Diazepam was gradually tapered, and she was discharged on fluoxetine 20 mg/day, trazodone 50 mg/day, lamotrigine 200 mg/day, and valproate 500 mg/day.

DISCUSSION

Across earlier and more recent reports, zolpidem withdrawal seizures have typically been described in the context of chronic use at supratherapeutic doses: from around 100–150 mg/day in some cases up to 300 mg/day and beyond, with extreme patterns of long-term abuse reaching 600–2,000 mg/day or more (Ballenger, 2000; Barbosa Eyler, 2023; Chishti, 2025; Mao, 2022; Mashiana, 2021; Sasaki, 2024; Tripodianakis et al., 2003; Yüksel, 2003). Our patient developed recurrent generalized tonic–clonic seizures at a maximum of 100 mg/day, a dose above usual prescribing ranges but lower than that reported in most recent withdrawal seizure cases, suggesting that clinically significant neurophysiological instability may arise even at more moderate levels of dose escalation. In addition, a report of two cases described long-term high-dose zolpidem dependence in which abrupt discontinuation was followed by seizures, with EEG abnormalities documented during evaluation (Wang et al., 2011) Zolpidem's short elimination half-life contributes to dose-chasing behavior, reinforcing dependence and precipitating withdrawal symptoms when doses are delayed (Cavallaro et al., 1993; Edinoff et al., 2021). Electroencephalographic data in zolpidem withdrawal remain scarce. In our case, generalized epileptiform activity was documented during withdrawal and normalized on follow-up sleep EEG after stabilization, consistent with a transient, reversible disturbance of GABAergic inhibition. A recent case study similarly demonstrated dynamic EEG changes over time in a patient with zolpidem withdrawal seizures, reinforcing the notion that abrupt cessation can induce short-lived but marked alterations in cortical excitability. Moreover, experimental EEG work and case-based reviews suggest that chronic exposure to zolpidem may modify GABA-A receptor function and network activity, which could lower the seizure threshold during withdrawal (Mao, 2022; Sasaki, 2024).

Recent reports also underscore the heterogeneity of zolpidem withdrawal presentations. A 2025 case described a woman presenting with focal neurological deficits and subsequent generalized seizures that mimicked acute ischemic stroke, ultimately attributed to abrupt discontinuation of 50–200 mg/day zolpidem. Another report highlighted acute delirium following cessation of chronic high-dose use in a young adult, whereas a separate series documented severe withdrawal manifestations after over 10 years of escalating zolpidem misuse. Together with earlier seizure-focused case reports, these observations indicate that withdrawal syndromes can manifest along a spectrum from anxiety and delirium to generalized seizures and stroke-like presentations (Barbosa Eyler, 2023; Chishti, 2025; Mao, 2022; Mashiana, 2021; Sasaki, 2024).

Previous recommendations highlight supervised tapering with long-acting benzodiazepines and, when seizure risk is elevated, adjunctive antiepileptic therapy (Aragona, 2000; Cavallaro et al., 1993; Leal et al., 2024). Moreover, epidemiological data indicate rising misuse of Z-drugs (non-benzodiazepine hypnotics such as zolpidem, zopiclone, and zaleplon) and reinforce the importance of prioritizing CBT-I and behavioral interventions over long-term hypnotic therapy (Schifano et al., 2019). Consistent with these recommendations, an eight-week cognitive behavioural therapy program (two 45-minute sessions per week) has been associated with improved sleep in a patient with clinically significant insomnia (Venkataraman et al., 2025). While CBT-I is the best-established psychological treatment for chronic insomnia, other evidence-based approaches such as acceptance and commitment therapy for insomnia and mindfulness-based interventions have also shown efficacy, particularly in patients with marked hyperarousal, anxiety, or comorbid psychiatric conditions (Rush, 2022; Salari, 2020).

This report has several strengths, including detailed longitudinal documentation of dose escalation, multiple withdrawal-related seizures, and EEG-confirmed epileptiform activity that normalized after stabilization, which together provide support for a withdrawal-induced mechanism at relatively moderate supratherapeutic doses. At the same time, the findings must be interpreted in light of certain limitations: this is a single-case observation without serum zolpidem levels or continuous EEG monitoring,

and concomitant treatments (including lamotrigine, valproate, and antidepressants) may have influenced seizure threshold and withdrawal dynamics. Future prospective and multicenter studies are needed to better define risk factors, optimal tapering strategies, and the role of EEG monitoring in patients with suspected zolpidem withdrawal–related seizures.

CONCLUSION

Even moderate supratherapeutic zolpidem doses may precipitate significant withdrawal complications, including generalized seizures. EEG-confirmed epileptiform activity in this case supports the presence of withdrawal-induced neurophysiological instability. Clinicians should limit zolpidem prescriptions to short term use, monitor for misuse, and ensure supervised tapering—preferably with long acting benzodiazepines—when dependence develops. Behavioral insomnia treatments should be prioritized to prevent illicit access and dose escalation.

Ethical Considerations: Does this study include human subjects? YES
Authors confirmed the compliance with all relevant ethical regulations.

Conflict of interest: No conflict of interes

Funding sources: The authors received no funding from an external source

Author's contributions: Cemre Naz Coşkun: case management, conceptualization, writing – original draft, writing – review and editing. Enver Denizhan Ramakan: conceptualization, supervision, writing – review and editing, project administration.

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