Etizolam Use Disorder and Withdrawal in a Patient in Sustained Remission From Opioid, Cocaine, and Methamphetamine Use Disorders

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While the diagnostic criteria for substance use disorders are clearly defined, their clinical presentations can be quite varied. We present the case of a 29-year-old man in sustained remission from cocaine, methamphetamine, and opioid use disorders who developed a novel addiction to the benzodiazepine analog etizolam after obtaining it online.

Case Report

The patient was a 29-year-old man with a past psychiatric history of bipolar I disorder, unspecified anxiety and insomnia disorders, and cocaine, methamphetamine, and opioid use disorders all in sustained remission. The patient was followed regularly in the outpatient addiction psychiatry clinic and was prescribed quetiapine 400 mg at bedtime, suvarexant 20 mg at bedtime, hydroxyzine 50 mg/d, clonidine 0.1 mg/d, and clonazepam 2 mg twice/d. He was also prescribed buprenorphine-naloxone 8–2 mg twice/d for opioid use disorder maintenance treatment, on which he had been stable with no dosing changes for nearly 6 months.

The patient self-presented to the emergency department for medically supervised withdrawal from sedative-hypnotics. At presentation, the patient reported that over the preceding 8 months he had been taking etizolam, a benzodiazepine analog he had been ordering from the internet, initially to supplement his clonazepam prescription for better management of his anxiety. The patient reported having increased his dosage of etizolam over that period to roughly 40 mg/d and that it had "gotten out of control" and had impaired his functioning and relationships. The patient had not disclosed using this medication to his outpatient addiction psychiatry provider, and etizolam was not tested for on the urine drug screen (UDS) available at his outpatient clinic.

The patient was admitted to the medical floor and evaluated using the Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA),[1] owing to etizolam's similar mechanism of action to benzodiazepines and alcohol. The patient received oral lorazepam based on CIWA scoring for the duration of his admission. The patient's course of withdrawal was uncomplicated, and he was discharged on hospital day 5. He had a follow-up appointment scheduled with his outpatient addiction psychiatry provider for 1 week after discharge.

At the patient's outpatient follow-up visit, several changes to his psychotropic regimen were made and subsequently titrated to target his self-reported symptoms of anxiety. Because the patient had been safely withdrawn from his prescribed benzodiazepine and he had developed a sedative-hypnotic use disorder to the nonprescribed benzodiazepine analog etizolam, the decision was made to not resume clonazepam and instead to adjust his other medications for improved management of anxiety.

Starting at his 1-week follow-up and over the course of the coming month, the following changes were made: clonidine was increased from 0.1 mg to 0.2 mg/d, which was further titrated to 0.2 mg twice/d several weeks later. Hydroxyzine was increased from 50 mg/d to 50 mg twice/d plus 100 mg/d as needed for anxiety attacks. Additionally, propranolol 20 mg/d was initiated and subsequently titrated to 40 mg twice/d to further address anxiety symptoms. The patient also began attending individual psychotherapy every other week. The patient continued to report inadequately managed anxiety symptoms despite these changes, which was attributed to rebound anxiety from having misused sedative-hypnotics in the preceding months.

Discussion

As a sedative-hypnotic, etizolam is a thienotriazolodiazepine that is structurally similar to benzodiazepines, with a thiophene ring substituted for the benzene ring.[2] It is a full γ-aminobutyric acid-A receptor agonist with pharmacologic properties similar to diazepam but with 5–10 times higher potency than diazepam.[2] Etizolam exhibits metabolism by

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both cytochrome (CYP) 3A4 and CYP2C19 with linear elimination. There is variability in the literature about etizolam's half-life, with early studies showing a single-dose half-life of 3.4 hours and later reports citing a half-life between 12 and 14 hours.[3–5] Similar to benzodiazepines, its primary therapeutic effect is anxiolysis, and etizolam is approved for use in Japan, Italy, and India for generalized anxiety with depressive symptoms.[2] Etizolam is not approved for medical use in the United States.

Etizolam has previously been described as having misuse potential in Japan and India and more recently in Europe and America.[6–9] The use and misuse of etizolam in the United States is growing, as evidenced by an increase in poison control inquiries and law enforcement interaction with etizolam.[10,11] This increase may be in part due to its availability from internet retailers offering multiple layers of anonymity.[9,12]

This case describes a patient in sustained remission from cocaine, methamphetamine, and opioid use disorders who subsequently developed a new addiction to a novel psychoactive substance without relapsing on any of his previously used substances. This case is of particular interest because the development of the novel addiction was not precipitated by relapse on another substance, nor did it cause the patient to relapse on them. The patient also did not further supplement the use of etizolam with other novel psychoactive substances.

Conclusion

The clinical significance of this case is that an individual in sustained remission from one or several substance use disorders may develop a solitary addiction to a novel substance undetectable on standard urine drug screening but requiring medically supervised withdrawal. As such, monitoring patients solely based on their previously misused substances and routine UDS has the potential to provide an incomplete picture of their current condition. As misuse of etizolam and other novel psychoactive substances continues to rise in the United States and elsewhere, it is increasingly important to continually monitor patients with substance use disorders for the development of novel addictions as well as to provide safe and effective withdrawal management options.

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