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Treatment of concurrent etizolam and tianeptine withdrawal following accidental overdose

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Abstract

Background: The availability of nonapproved psychoactive substances with addiction potential from internet sources poses a significant threat to public health. Polysubstance abuse or inadvertent contamination of preparations may result in clinically challenging intoxication and withdrawal syndromes.

Case Report: We report a case of a 32-year-old male with an approximate 2-year history of taking internet-obtained etizolam and tianeptine who presented to the hospital following an overdose. He experienced subsequent withdrawal symptoms consistent with benzodiazepine and opioid withdrawal. Initial attempts at managing symptoms with chlordiazepoxide 25 mg every 6 hours did not relieve his symptoms. On day 3 of admission, addiction medicine was consulted and his regimen was changed to diazepam 80 mg daily with additional as-needed diazepam based on etizolam equivalence. He also received a 5-day methadone taper with plans to transition to buprenorphine in the outpatient setting. Upon discharge he was referred to an addiction medicine specialist who was willing to continue a slow diazepam taper and initiate medications for opioid use disorder to manage both substance use disorders.

Discussion: This case report demonstrates the effectiveness of diazepam in managing benzodiazepine withdrawal from etizolam while concurrently using methadone to manage opioid withdrawal symptoms from tianeptine in a hospitalized patient following overdose. We highlight the importance of a warm handoff in considering the outpatient discharge plan.

Keywords: benzodiazepine, diazepam, etizolam, tianeptine, withdrawal

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Background

Etizolam is a thienodiazepine benzodiazepine with anxiolytic and sedative properties. Etizolam is approved for medicinal use for anxiety disorders in Japan, Italy, and India but is widely available for purchase as a *research chemical* on the internet.[1,2] Etizolam-associated adverse effects include drowsiness, sedation, and slurred speech.[3] Toxicities observed have included CNS depression, ataxia, dysarthria, and respiratory depression.[4] Withdrawal symptoms include palpitations, poor sleep, agitation, and tremors.[2] Etizolam is most commonly ingested as an oral tablet, although powder, sublingual, liquid, blotting paper, and insufflated formulations have been reported.[5] Therapeutic doses range from 0.25 to 2 mg daily with a maximum of 3 mg daily.[2,3] Etizolam is approximately 6 to 10 times more potent than diazepam for most pharmacologic effects. Clinical studies[1,2,6] suggest that etizolam is about 10 times more potent

TABLE 1: Approximate equivalent benzodiazepine doses[6,11,17]

Benzodiazepine	Approximate Equivalent Oral Dosage, mg
Alprazolam	0.5
Chlordiazepoxide	10
Clonazepam	0.25
Diazepam	5
Etizolam	1-1.5[a]
Lorazepam	1
Oxazepam	15

[a]Note: Equivalency between etizolam and diazepam varies based on reference.

than diazepam for hypnotic effects. Table 1 describes equivalent benzodiazepine doses.

Tianeptine is an atypical tricyclic antidepressant approved for therapeutic use in several European countries. Although not approved in the United States, tianeptine is available for internet purchase in bulk powders, counterfeit pills mimicking hydrocodone and oxycodone, and stamp bags.[7] Tianeptine increases serotonin reuptake, has strong agonist activity at mu-opioid receptors, and may increase extracellular dopamine concentrations, resulting in abuse potential.[8] Usual therapeutic dosing is 25 to 50 mg daily. A recent review of tianeptine dependence and abuse found that the average daily dose of tianeptine in this population was over 1900 mg.[9] Acute intoxication results in alterations in neurologic status (drowsiness, agitation, confusion), tachycardia, hypertension, and gastrointestinal distress.[8] Withdrawal symptoms include agitation, anxiety, nausea, vomiting, diarrhea, myalgias, tachycardia, hypertension, tremor, and diaphoresis.[7,8]

This case describes a patient in the United States who experienced concurrent benzodiazepine and opioid withdrawal symptoms following an accidental overdose of internet-obtained etizolam and tianeptine.

Case Report

A 32-year-old male with a history of insomnia and benzodiazepine use disorder presented to the emergency department after being found at home unconscious with gurgling noises and cyanotic lips. He received naloxone 8 mg and a sternal rub, resulting in return of consciousness. In the emergency department the patient was tremulous and diaphoretic. His mental status was intact although he appeared sedated. Vital signs and pertinent laboratory values are described in Table 2. He received IV diazepam 5 mg and 4 L of lactated ringers resulting in quick normalization of the lactic acid and temperature. He was admitted to a medical-surgical unit.

TABLE 2: Vital signs and pertinent laboratory values upon initial presentation to the emergency department

Parameter/Laboratory Test	Value
Blood pressure, mm Hg	82/53
Pulse, beats/min	129
Temperature, °F	100.7
Lactate, mmol/L	7.0
Urine drug screen	Positive for benzodiazepines,[a] barbiturates

[a]Note: The patient received IV diazepam in the emergency department prior to the urine drug screen.

Patient interview and collateral obtained from family revealed that he had been ingesting several substances he procured from the internet including etizolam and tianeptine. He reported taking liquid etizolam daily for the past 1.5 years. The concentration of the etizolam bottle was labeled as 10 mg/mL. On the day of the overdose he ingested 1.5 mL (15 mg etizolam), noting that usually he takes 2 to 3 mL (20-30 mg) daily. He also reported taking "low doses" (unknown dosage) of tianeptine daily for the past 2 years, but at times takes "megadoses" (50 mg) to achieve opioid effects. On the day of the overdose, he took 50 mg, but stated that it was his first time using a new bag which was marketed to be more potent. He also endorsed occasional social use of phenibut, a glutamic acid derivative with anxiolytic and addictive properties which is not approved for use in the United States but is easily obtainable online.[10] He reportedly did not ingest phenibut on the day of overdose. The patient indicated that the overdose was unintentional although he had felt increasing depression in the weeks leading up to the incident. He was unaware of the addictive potential of these substances despite a history of prior withdrawal symptoms, and he had never experienced a seizure. He treated his symptoms in the past with diazepam and buprenorphine and requested treatment for his substance use disorders on this admission.

During the hospital admission, poison control services were contacted and they recommended IV fluid hydration and serial electrocardiograms for 24 hours to monitor the QTc interval. The patient maintained normal sinus rhythm throughout the hospital stay with no QTc prolongation noted. The day after admission, he began experiencing withdrawal signs and symptoms including dilated pupils, shivering, insomnia, diarrhea, myalgia, anxiety, and irritability. He additionally described tingling and numbness of bilateral lower extremities and auditory and visual hallucinations. These hallucinations included commands to hurt loved ones and seeing "demonic figures" and "weird

shapes" in the dark. The internal medicine service initiated oral methadone 5 mg twice daily to treat opioid withdrawal and chlordiazepoxide 25 mg every 6 hours to treat his benzodiazepine withdrawal, the latter of which the patient stated was being tapered too aggressively.

Addiction medicine was consulted. Using a conservative dose equivalence of 1 mg etizolam to 5 mg diazepam as described by Altamura et al,[11] we estimated that 20 to 30 mg of etizolam is equivalent to 100 to 150 mg of diazepam daily. We recommended oral diazepam 20 mg 4 times daily with additional diazepam 20 mg every 6 hours as needed for breakthrough symptoms. Gabapentin 300 mg 3 times daily was initiated. Recommended supportive medications included trazodone, clonidine, ibuprofen, loperamide, and ondansetron. Since the patient had already received methadone prior to the addiction medicine consult, we recommended a methadone taper followed by referral to outpatient services to initiate buprenorphine maintenance treatment so as not to complicate the hospital course with possible precipitated withdrawal. He received methadone 5 mg twice daily for 3 days, followed by 5 mg daily for 2 days.

The patient was discharged from the hospital on day 6 on a simplified regimen of diazepam 40 mg twice daily and gabapentin 300 mg 3 times daily. Outpatient follow-up was arranged with an addiction medicine specialist with a warm handoff plan to provide treatment for the benzodiazepine use disorder using a prolonged diazepam taper while concurrently treating the patient's tianeptine use using a medication for opioid use disorder (likely buprenorphine based on patient preference). Information regarding the patient's long-term disposition is limited as he was referred outside of our hospital network. At last known contact, the patient had successfully established care with the outpatient addiction medicine specialist to whom he had been referred.

Discussion

At therapeutic doses, etizolam may have a reduced potential to induce tolerance and dependence compared with other benzodiazepines.[2] However, the increasing prevalence of nonmedical *designer benzodiazepine* use in several countries over the past decade has resulted in increasing documented instances of etizolam dependence and abuse. In an evaluation of calls about designer benzodiazepines to the US National Poison Data System between 2014 and 2017, etizolam was the most common single agent exposure identified (162 out of 234 exposures, 69.2%). This study also identified an overall increase in exposure to designer benzodiazepines over the 4-year period, increasing from 26 exposures in 2014 to 112 in 2017.[12]

Furthermore, illicitly manufactured preparations may contain varying and unknown content, often leading to unpredictable consequences.[6] Garland and colleagues[13] examined the presence of designer benzodiazepines in over 38 000 healthcare urine samples, where 40 of these specimens contained a designer benzodiazepine, of which 34 were etizolam. Over 82% of samples were copositive with an opioid, and 47.5% with a prescription benzodiazepine. Numerous deaths involving etizolam have been described, often in the setting of mixed ingestions.[4] In 2019, the World Health Organization[2] declared etizolam a public health and social problem. Similarly, the opioid epidemic has been fueled by the availability of nonprescription opioid agonists such as tianeptine. A report[14] of tianeptine exposures in the United States between 2000 to 2017 revealed an increase in use between 2014 to 2017, suggesting that tianeptine also represents an emerging public health risk. Out of 218 calls related to tianeptine exposure, 83 involved coexposures to substances such as phenibut, alcohol, benzodiazepines and opioids.[14]

Polysubstance overdoses and withdrawal syndromes involving nonprescription substances present a challenging clinical scenario. In our patient, it is likely that the overdose was because of the tianeptine given the recent initiation of a more potent formulation. However it is impossible to know if use of additional substances or contaminants in the preparations might have contributed, as evidenced by presence of barbiturates in the urine. We aimed to treat both withdrawal syndromes concurrently, taking into account patient preference for treatment options. Our initial concern in approaching disposition for this patient was that it might be challenging to find an outpatient provider willing to prescribe benzodiazepines to a patient for whom there was no documented record of benzodiazepine use on the prescription drug monitoring record. Ultimately, proactive discussion with an outpatient addiction medicine specialist allowed for a smooth transition and a plan to treat both substance use disorders, highlighting the importance of a warm handoff in managing substance use disorders.

Conclusion

Clinicians often work with limited information when handling cases involving toxicity and withdrawal from nonprescription substances and may have to rely on case reports to guide their approach. To our knowledge, this is the first case detailing management of concurrent withdrawal from etizolam and tianeptine. Although prior case reports[15,16] have discussed the use of buprenorphine in managing tianeptine withdrawal symptoms, this is the first reported use of methadone to manage such symptoms.

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References

1. Drug Enforcement Administration [Internet]. Drug and chemical evaluation section: etizolam [updated 2020 Mar; cited 2022 Sep 1]. Springfield (VA): US Department of Justice. Available from: https://www.deadiversion.usdoj.gov/drug_chem_info/etizolam.pdf
2. WHO Expert Committee on Drug Dependence [Internet]. Critical review report: etizolam [updated 2019 Oct 21-25; cited 2021 Sep 22]. Geneva: World Health Organization; c2019. Available from: https://www.who.int/medicines/access/controlled-substances/Final_Etizolam.pdf
3. Tamburin S, Mantovani E, Bertoldi A, Federico A, Casari R, Lugoboni F. High-dose dependence and cognitive side effects to medical prescription of etizolam. Front Psychiatry. 2020;11:601827. DOI: 10.3389/fpsyt.2020.601827. PubMed PMID: 33329156; PubMed Central PMCID: PMC7671959.
4. Levine M, Lovecchio F. New designer drugs. Emerg Med Clin North Am. 2021;39(3):677-87. DOI: 10.1016/j.emc.2021.04.013. PubMed PMID: 34215409.
5. El Balkhi S, Monchaud C, Herault F, Géniaux H, Saint-Marcoux F. Designer benzodiazepines' pharmacological effects and potencies: how to find the information. J Psychopharmacol. 2020;34(9):1021-9. DOI: 10.1177/0269881119901096. PubMed PMID: 31971477.
6. Nielsen S, McAuley A. Etizolam: a rapid review on pharmacology, non-medical use and harms. Drug Alcohol Rev. 2020;39(4):330-6. DOI: 10.1111/dar.13052. PubMed PMID: 32243020.
7. Drug Enforcement Administration [Internet]. Drug and chemical evaluation section: tianeptine [updated 2019 May; cited 2022 Sep 1]. Springfield (VA): US Department of Justice. Available from: https://www.deadiversion.usdoj.gov/drug_chem_info/tianeptine.pdf
8. Rushton W, Whitworth B, Brown J, Kurz M, Rivera J. Characteristics of tianeptine effects reported to a poison control center: a growing threat to public health. Clin Toxicol. 2021;59(2):152-7. DOI: 10.1080/15563650.2020.1781151. PubMed PMID: 32552075.
9. Lauhan R, Hsu A, Alam A, Beizai K. Tianeptine abuse and dependence: case report and literature review. Psychosomatics. 2018;59(6):547-53. DOI: 10.1016/j.psym.2018.07.006. PubMed PMID: 30149933.
10. Hardman MI, Sprung J, Weingarten TN. Acute phenibut withdrawal: a comprehensive literature review and illustrative case report. Bosn J Basic Med Sci. 2019;19(2):125-9. DOI: 10.17305/bjbms.2018.4008. PubMed PMID: 30501608; PubMed Central PMCID: PMC6535394.
11. Altamura AC, Moliterno D, Paletta S, Maffini M, Mauri MC, Bareggi S. Understanding the pharmacokinetics of anxiolytic drugs. Expert Opin Drug Metab Toxicol. 2013;9(4):423-40. DOI: 10.1517/17425255.2013.759209. PubMed PMID: 23330992.
12. Carpenter JE, Murray BP, Dunkley C, Kazzi ZN, Gittinger MH. Designer benzodiazepines: a report of exposures recorded in the National Poison Data System, 2014–2017. Clin Toxicol. 2019;57(4):282-6. DOI: 10.1080/15563650.2018.1510502. PubMed PMID: 30430874.
13. Garland JM, Hull JD, Bender CL, Marshall L, Holt AC. Evidence of designer benzodiazepine use in routine healthcare urine drug specimens. J Addict Med. 2022;16(3):354-6. DOI: 10.1097/ADM.0000000000000884. PubMed PMID: 34172626.
14. El Zahran T, Schier J, Glidden E, Kieszak S, Law R, Bottei E, et al. Characteristics of tianeptine exposures reported to the National Poison Data System — United States, 2000–2017. MMWR Morb Mortal Wkly Rep. 2018;67(30):815-8. DOI: 10.15585/mmwr.mm6730a2. PubMed PMID: 30070980; PubMed Central PMCID: PMC6072055.
15. Trowbridge P, Walley AY. Use of buprenorphine-naloxone in the treatment of tianeptine use disorder. J Addict Med. 2019;13(4):331-3. DOI: 10.1097/ADM.0000000000000490. PubMed PMID: 30550394.
16. Szczesniak L, Sullivan R. Microdose induction of buprenorphine in a patient using tianeptine. J Addict Med. 2022;16(6):736-8. DOI: 10.1097/ADM.0000000000001003. PubMed PMID: 35709488.
17. Inada T, Inagaki A. Psychotropic dose equivalence in Japan. Psychiatry Clin Neurosci. 2015;69(8):440-7. DOI: 10.1111/pcn.12275. PubMed PMID: 25601291.