Chronic Phenibut Use: Symptoms, Severe Withdrawal, and Recovery

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ABSTRACT

Introduction: Phenibut is a psychoactive drug with GABA B agonism. It remains unregulated and easily attainable in the United States, where it has become a novel drug of abuse.

Case Presentation: We present the case of a 34-year-old man who used phenibut consistently for 3 years. After 6 months of use, he developed signs of dependence and failed outpatient detoxification. While taking high doses, he experienced parasomnia-like symptoms and periods of dysexecutive function. After abrupt cessation, he developed severe withdrawal symptoms, was hospitalized, and required intubation. His condition improved after 1 week of treatment. After recovery and discharge, he remains stable utilizing an extended taper of acamprosate and baclofen.

Discussion: Phenibut is not detected on urine drug screen and withdrawal symptoms are nonspecific. Optimal treatment of withdrawal remains unknown. Baclofen and phenobarbital have been successful for treatment of dependence.

Conclusion: Clinicians should be aware of phenibut abuse and the potential for dependence and withdrawal.

INTRODUCTION

Phenibut (β-phenyl–γ-aminobutyric acid) is a manufactured psychoactive drug with primary agonist activity at the GABA B receptor.[1] Producing anxiolytic effects in humans, it has been medically prescribed in Eastern Europe since its first synthesis in 1960s Russia.[1] In the United States, phenibut is easily attainable online, where it is marketed as a nootropic (cognitive enhancement) sold under brand names Anvifen, Fenibut, and Noofen. Phenibut is unregulated by the US Food and Drug Administration (FDA) and legal to possess. Australia, Hungary, and Lithuania have banned phenibut and have designated it a controlled substance. As a central nervous system depressant, phenibut misuse can result in intoxication, dependence, and withdrawal symptoms.[2] Phenibut is not detected on routine urine drug screens, and recent FDA queries of poison control databanks indicate a growing recreational use.[3] Despite this, published treatment recommendations for phenibut complications are limited to a small number of case reports. The following case represents, to our knowledge, the longest duration of phenibut use prior to treatment of withdrawal that exists in the medical literature. It chronicles a multiyear, high-volume use of phenibut, failed outpatient detoxification, severe withdrawal symptoms, successful treatment, and recovery.

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CASE PRESENTATION

A 34-year-old man with past medical history significant for opioid use disorder began purchasing a powdered form of phenibut via online retailers. His initial usage was 1 g per day mixed with water (recommended daily amount on packaging). While initially taking phenibut, he experienced improvements in anxiety, social confidence, and sleep. Over the following 2 months, he noted a decrease in effect and gradually increased his use to 4 to 5 g per day. Approximately 6 months after initial use and now using 8 to 12 g per day, he began to experience symptoms of insomnia, shakiness, numbness in his arms, and a sense of panic. These symptoms occurred in the morning and resolved after taking phenibut.

After onset of these symptoms, the patient presented to primary care and disclosed phenibut use and a fear of dependence. He was prescribed baclofen 5 mg 3 times a day and gabapentin 100 mg twice a day for withdrawal symptoms with instructions to taper phenibut 25% every 2 weeks.

At 1-month follow-up, the patient reported an inability to discontinue phenibut while utilizing baclofen and gabapentin. During this visit, he requested a stimulant prescription to address poor concentration but was denied because of continued phenibut use. Three weeks later, he reported successful discontinuation of phenibut and was prescribed a stimulant. Despite reporting a cessation of use, he continued to take phenibut and gradually increased his consumption over the following 2 years to approximately 28.5 g per day. It was in this context that he was referred to psychiatry for ongoing anxiety and attention deficit hyperactivity disorder symptoms.

At psychiatric intake, the patient had complaints of difficulty concentrating, poor sleep, and altered states that occurred after waking from sleep. He described these "altered states" as auditory hallucinations experienced immediately after waking, often accompanied by transient periods of confusion, difficulty speaking, and an inability to perform tasks such as opening doors or driving his car. These states did not improve after taking phenibut and could persist for up to 24 hours. They resulted in 2 motor vehicle accidents. The patient was referred to the neurology department to rule out organic disease prior to initiation of psychiatric medication. Initial workup included an electroencephalogram (EEG) that showed mild to moderate bilateral frontal slowing, brain magnetic resonance imaging (unremarkable), and overnight pulse oximeter (unremarkable). Risperidone 0.25 mg twice a day was trialed. During his neurology follow-up 3 weeks later, the patient described no improvement in symptoms. A sleep study was ordered, and risperidone was increased to 1 mg twice a day. When originally treated by primary care approximately 2 years prior, the patient's use of phenibut was documented in the history of present illness, but not in a location that would carry forward for viewing by subsequent clinicians, such as the social history in the electronic medical record. None of his current treating clinicians were aware of his ongoing use, which the patient did not disclose.

Five days later, the patient presented to the emergency department (ED) with symptoms of agitation, sweating, hallucinations, and confusion. He was unable to answer questions and history was provided by his girlfriend. She disclosed an approximate 3-year history of consistent phenibut use. Twenty-four hours prior to presentation, the patient had exhausted his supply. On assessment, he was disorientated and tachycardic with otherwise normal vital signs. He was given a single dose of 10 mg of baclofen and 2 doses of lorazepam 1 mg. Metabolic studies were unremarkable and head CT (without contrast) showed no acute pathology. Urine drug screen was performed in the ED and was positive for amphetamines, benzodiazepines, and methamphetamines. Notably, this screen was collected after lorazepam administration and home prescriptions included Vyvanse and Wellbutrin. He was admitted to hospital service—hospital day (HD) 0—for presumed phenibut withdrawal.

The patient was placed on Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) protocol and given olanzapine and haloperidol for symptom control. On HD 1, he was restless, continued to hallucinate, and demonstrated impulsive behavior that necessitated continuous care by multiple staff. Hematological labs showed mild leukocytosis (10.1x10^9/L), hypokalemia (3.4 mmol/L), and an elevated creatine kinase of 807 U/L. As a result of increasing medical needs and agitation, he was transferred to the critical care unit 18 hours after admission and had received 17 mg of lorazepam as directed by CIWA-Ar.

Upon presentation to the critical care unit, the patient was described as encephalopathic and psychotic appearing with dilated pupils and normal vital signs, except for mild hypertension. He exhibited twitching in all extremities, was unable to follow commands, and was experiencing visual hallucinations. His CIWA-Ar score ranged from 39 to 41. Diazepam 2.5 mg every 4 hours was added for agitation, and haloperidol was discontinued. With minimal change in withdrawal symptomatology, he was intubated for airway protection on HD 1. Lorazepam, olanzapine, midazolam, dexmedetomidine, and propofol were utilized for sedation, and CIWA-Ar scores improved to 4. Creatine kinase peaked at 1,114 U/L on HD 1 without signs of renal impairment (creatinine levels ranged 1.08-1.12 mg/dL). On HD 2 a phenobarbital taper was started: 270 mg on HD 2 and 3, 180 mg on HD 4 and 5, 90 mg on HD 6 through 8, and then discontinued. Baclofen 10 mg 3 times a day was started on HD 4. The patient was extubated on HD 5 following successful breathing trial and demonstrated ongoing hallucinations and impulsivity, despite maximum dosage of dexmedetomidine, diazepam 10 mg every 2 hours, and lorazepam 2 mg as needed. These symptoms continued until improvement on HD 7, wherein the encephalopathy improved and he began asking appropriate questions. Dexmedetomidine was subsequently discontinued and diazepam was decreased to 5 mg every 2 hours.

The patient was transferred onto the medical floor on HD 8 and showed a resolution in impulsivity and hallucinations. Diazepam was discontinued on HD 9 and baclofen was increased to 20 mg 3 times a day for compensation. He continued to show improvement and was discharged to home on HD 11. Discharge prescriptions included acamprosate 666 mg 3 times a day and baclofen 20 mg 3 times a day for prevention of cravings and withdrawal symptoms.

Two days after discharge, the patient was seen in outpatient psychiatry, where he denied symptoms of withdrawal. His mental status examination appeared to approximate baseline with minor evidence of cognitive delay. At 1-month follow-up, he denied

cravings, withdrawal symptoms, or relapses to phenibut. Baclofen was reduced to 15 mg 3 times a day and acamprosate to 333 mg 3 times a day. At 4-month follow-up, he continued to do well, and baclofen and acamprosate were further reduced to 10 mg 3 times a day and 333 mg 2 times a day, respectively.

DISCUSSION

Outpatient Treatment

Reports of successful treatment of phenibut dependence in outpatient and residential treatment settings often utilize pharmacological replacements, such as phenobarbital or baclofen, coupled with close monitoring to ensure adequate control of cravings.[4,5] This monitoring—daily or weekly—is likely necessitated by demonstrated ranges in the purities of phenibut products, 39.7% and 99%, purchased online.[6,7] This variation in purity complicates a clinician's ability to dose pharmacological replacements to corresponding levels of phenibut use. In our case, the patient's initial outpatient treatment would have benefited from higher surveillance to ensure efficacy of baclofen and gabapentin, which were chosen for their similar activity to phenibut at $GABA_B$ and $\alpha 2\delta$ subunit of voltage-dependent calcium channels, respectively.[1,8] Similarly, phenobarbital previously has been used as a phenibut replacement for its central GABA agonist properties.[5] Clinicians should be aware of this inherent difficulty if attempting outpatient treatment of phenibut dependence.

Unique Symptoms

The transient dysarthria and dyspraxia experienced immediately after waking by our patient are symptoms of phenibut use that are not currently described in the literature. His usage during these symptoms was approximately 28.5 g per day, many times higher than the recommended dosage of 0.25-2 g per day.[9] During this level of use, an EEG showed "focal bifrontal slowing," representing a potential association with his dysexecutive symptoms. Animal studies previously have demonstrated a reversible subcortical slowing on EEG following phenibut administration.[1] Although we lack a pre/post phenibut EEG to show a change and/or resolution, this represents a potential neuropsychiatric implication of phenibut use and an area for further investigation.

Hallucinations are a known symptom of phenibut withdrawal and intoxication.[2,9,10] However, the close temporal relationship between waking and auditory hallucinations experienced by our patient was not described in the existing literature. This waking/hallucination, parasomnia-like phenomena is referenced in large online forums of phenibut users, indicating a feature of use that is likely not unique to our patient.[11] Future directions in utilizing these internet communities could elucidate further novel symptoms or the true prevalence of those experienced by our patient.

Management of Withdrawal

The symptoms of phenibut withdrawal are believed to stem from a sensitization of dopaminergic and noradrenergic receptors following prolonged $GABA_B$ stimulation.[12] Discontinuation of phenibut would then stimulate these receptors, prompting the autonomic symptoms demonstrated by our patient while hospitalized: tachycardia, hallucinations, tremulousness, and hypertension. Other presentations outlined within the literature and not present in our case are mimics of serotonin and neuroleptic malignant syndrome.[2] Although the patient's home medications of risperidone and Wellbutrin could cause these syndromes, he was afebrile and lacked muscular rigidity on presentation. The absence of these characteristic findings and his recent cessation of phenibut made withdrawal syndrome a more likely diagnosis. While phenibut withdrawal symptoms are nonspecific, its diagnosis is further complicated by an inability to be detected on urine drug screen. This case illustrates the importance of screening for and documenting phenibut use in the electronic medical record. Reviews indicate many patients treated for phenibut dependence and intoxication have a history of substance use disorder, providing a focused population for screening.[9]

The positive urine drug screen results during hospitalization are partially explained by lorazepam administration (benzodiazepines) and active prescription for Vyvanse (amphetamines). Our patient denied methamphetamine use, and this positive could be explained by his prescription of Wellbutrin, which has demonstrated false positives for methamphetamine on urine drug screen.[13] A confirmatory screen of metabolites was not performed.

The optimal approach for phenibut withdrawal remains unclear. Our patient's treatment was largely directed towards symptom control utilizing sedative medications. Baclofen interacts with the $GABA_B$ receptor with an affinity 30 times greater than phenibut and represents a treatment often utilized for tapering when treating its dependence.[9,14] Despite the single dose of baclofen our patient received in the ED, his initial treatment approach utilized primarily benzodiazepines. He did not experience an improvement in symptomatology until multiple days of phenobarbital and baclofen therapy, making it difficult to discern between an association and causation of his recovery. Further research is needed to establish an optimal treatment of phenibut withdrawal.

During hospitalization, our patient was started on acamprosate in the belief that its modulation of central glutamate may decrease withdrawal symptoms and reduce future cravings, similar to its utility during alcohol withdrawal. This was well tolerated by the patient. Although we are unsure if it is beneficial in managing phenibut withdrawal, it was continued after discharge. To our knowledge, acamprosate has not previously been used for this purpose.

CONCLUSION

This case contributes to a small but growing number of reports of phenibut abuse, highlighting the difficulty in recognizing not only the signs of dependence, but also the most appropri-

ate approach to treatment of withdrawal. Clinicians should be encouraged to screen for use among patients and document findings in the electronic medical record. Close monitoring should be encouraged when attempting outpatient treatment of phenibut dependence. The most appropriate treatment of phenibut withdrawal remains unknown. Similarly, long-term management following withdrawal remains unclear. Currently, our patient is doing well and has no cravings or usage with an extended taper of baclofen and acamprosate.

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REFERENCES

1. Lapin I. Phenibut (beta-phenyl-GABA): a tranquilizer and nootropic drug. *CNS Drug Rev*. 2001;7(4):471-481. doi:10.1111/j.1527-3458.2001.tb00211.x

2. 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):125-129. doi:10.17305/bjbms.2018.4008

3. Graves JM, Dilley J, Kubsad S, Liebelt E. Notes from the field: phenibut exposures reported to poison centers - United States, 2009-2019. *MMWR Morb Mortal Wkly Rep.* 2020;69(35):1227-1228. doi:10.15585/mmwr.mm6935a5

4. Samokhvalov AV, Paton-Gay CL, Balchand K, Rehm J. Phenibut dependence. *BMJ Case Rep*. 2013;2013:bcr2012008381. doi:10.1136/bcr-2012-008381

5. Brunner E, Levy R. Case report of physiologic phenibut dependence treated with a phenobarbital taper in a patient being treated with buprenorphine. *J Addict Med.* 2017;11(3):239-240. doi:10.1097/ADM.0000000000000303

6. Downes MA, Berling IL, Mostafa A, Grice J, Roberts MS, Isbister GK. Acute behavioural disturbance associated with phenibut purchased via an internet supplier. *Clin Toxicol (Phila)*. 2015;53(7):636-638. doi:10.3109/15563650.2015.1059945

7. Wong A, Little M, Caldicott D, Easton C, Andres D, Greene SL. Analytically confirmed recreational use of phenibut (β-phenyl-γ-aminobutyric acid) bought over the internet. *Clin Toxicol (Phila)*. 2015;53(7):783-784. doi:10.3109/15563650.2015.1059944

8. Zvejniece L, Vavers E, Svalbe B, et al. R-phenibut binds to the α2-δ subunit of voltage-dependent calcium channels and exerts gabapentin-like anti-nociceptive effects. *Pharmacol Biochem Behav*. 2015;137:23-29. doi:10.1016/j.pbb.2015.07.014

9. Kupats E, Vrublevska J, Zvejniece B, et al. Safety and tolerability of the anxiolytic and nootropic drug phenibut: a systematic review of clinical trials and case reports. *Pharmacopsychiatry*. 2020;53(5):201-208. doi:10.1055/a-1151-5017

10. McCabe DJ, Bangh SA, Arens AM, Cole JB. Phenibut exposures and clinical effects reported to a regional poison center. Am J Emerg Med. 2019;37(11):2066-2071. doi:10.1016/j.ajem.2019.02.044

11. JustSayKnow. 2019 Updated phenibut guide. r/phenibut subreddit. January 11, 2019. Accessed November 28, 2020. https://www.reddit.com/r/phenibut/comments/aez8za/2019_updated_phenibut_guide/

12. Keegan DL, Richardson JS, Kirby AR. A possible neurochemical basis for the neuropsychiatric aspects of baclofen therapy. *Int J Neurosci*. 1983;20(3-4):249-254. doi:10.3109/00207458308986578

13. Brahm NC, Yeager LL, Fox MD, Farmer KC, Palmer TA. Commonly prescribed medications and potential false-positive urine drug screens. *Am J Health Syst Pharm.* 2010;67(16):1344-1350. doi:10.2146/ajhp090477

14. Dambrova M, Zvejniece L, Liepinsh E, et al. Comparative pharmacological activity of optical isomers of phenibut. *Eur J Pharmacol*. 2008;583(1):128-134. doi:10.1016/j.ejphar.2008.01.015

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