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Dissociative intoxication and prolonged withdrawal associated with phenibut: a case report

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To the editors

Nootropic agents, or psychoactive substances intended to augment or enhance cognitive functioning, are becoming increasingly available through the internet. Phenibut (4-amino-3-phenyl-butyric acid), an analogue of gamma-aminobutyric acid (GABA), is licensed in Russia for a variety of indications including alcohol withdrawal, insomnia, and anxiety, though it is not approved for clinical use in the US, European Union, or Australia (1). Nevertheless, phenibut is widely available as a supplement through online vendors, and it is used as a nootropic to augment cognition, as an anxiolytic, and also for its reported euphoric effect. However, use of phenibut at doses above recommended ranges has resulted in intoxication and withdrawal syndromes seen in sedative/hypnotic abuse. Herein, we describe a case of phenibut intoxication and prolonged withdrawal presenting with agitated delirium.

Case Report

A 32-year-old adopted Caucasian male was brought to the emergency department (ED) by police after being found by his roommate inside a running car with a hose connecting the exhaust pipe to the inside cabin. The patient appeared to be in a dissociative state, endorsing a dream-like state with an “out-of-body” sensation, which compelled him to commit suicide. The patient reported not sleeping for the past four days, as well as taking phenibut 8–10 g/day, with increased intake to ~16 g/day in the week prior to admission. Additionally he was completing a stacking cycle of anabolic steroids (testosterone and nandrolone), for non-medical, aesthetic purposes, with last intramuscular (IM) self-injection occurring approximately 6 weeks prior to admission.

On initial intake in ED, vital signs were notable for tachycardia (140 s), but otherwise within normal limits, with electrocardiogram revealing sinus tachycardia. Exam at that time was notable for dilated pupils and flushed skin. Laboratory studies in the ED showed unremarkable complete metabolic panel and thyroid stimulating hormone, and a mildly

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Conflicts of Interest

Dr. Joshi, Dr. Friend, Dr. Steiger, and Ms. Jimenez report no actual or potential conflicts of interests, financial or otherwise, to declare.

elevated leukocytosis and mild transaminitis that was thought to be reactive and likely unrelated to phenibut or exhaust exposure. Lactate, acetaminophen, blood alcohol, urinalysis and urine drug toxicology screen either within normal limits or negative. The patient was given fluid resuscitation, one dose of oral chlordiazepoxide 50 mg, one dose of oral diazepam 5 mg, and one dose of intravenous lorazepam 2 mg with resolution of vital signs and physical exam abnormalities. On initial psychiatric consultation in ED, his thought process was notably illogical and tangential, but he was fully oriented, without any delusions or abnormal perceptions.

When the patient was admitted to the inpatient psychiatric unit, he had a normal physical exam, but was mildly distractible and anxious. Admission labs did not reveal any abnormalities. The patient did have slightly elevated total blood testosterone of 9.6 ng/ml (ref: 2.8–8.0 ng/ml), but free testosterone of 201, within normal limit for patient's age and gender.

Over the first day of psychiatric hospitalization (HD 1), the patient received 2 mg of oral lorazepam total for insomnia without any vital sign abnormalities. He was linear, able to sleep for 7.5 hours, and able to describe his recently increasing phenibut dependence. On the evening of HD 2, the patient became agitated requiring emergent IM injections of antipsychotics for his safety. He began suffering from insomnia, with increasing disorganization and difficulty recalling reason for hospitalization. The patient's mental status deteriorated with worsening orientation, clear delusions, and agitation with aggression. He attempted to climb unit walls, requiring further IM medications for safety. He was placed on scheduled olanzapine 5 mg twice a day for agitation, and was initiated on oral diazepam 10 mg every 4 hours as needed for signs of sedative/hypnotic withdrawal. On HD 3, after first administration of diazepam 10 mg, the patient paradoxically worsened in mental status, as he was noted to be tremulous, with visual hallucinations and continued disorientation. Diazepam was discontinued and baclofen was initiated at 10 mg TID, and titrated to 30 mg TID over the course of 2 days, during which time patient continued to experience intermittent agitated delirium. Ramelteon 8 mg was also started targeting sleep-wake cycle disruption. By HD 6, the patient began sleeping more than 3 hours a night. His disorganization improved by HD 7, and by HD 9, the patient was linear and fully oriented and no longer endorsed hallucinations. He was maintained on his regimen of baclofen 30 mg TID with goal to taper off by 10 mg total baclofen load per week, given previous reports describing slow medication tapers for withdrawal (2).

Discussion

Phenibut is chemically similar to gabapentin, as well as baclofen (which is a *p*-Cl-derivative of phenibut). It is thought to act primarily on metabotropic GABA_B receptors and to a lesser extent GABA_A, with some experimental reports suggesting action at dopamine and other receptors (1). Commercially available phenibut typically includes racemic mixtures of both *R*- and *S*- isomers, with preclinical data indicating that the majority of pharmacological activity relies on the *R*- enantiomer (1, 3, 4). While the vast majority of pharmacological activity of phenibut appears to be very similar to baclofen, at least one

preclinical report in mice reveals *R*-phenibut binding to the $\alpha 2$ - δ subunit of voltage-dependent calcium channels, exerting gabapentin-like effects (5).

Acute phenibut intoxications have varying presentations, ranging from sedation and lethargy at “normal doses,” typically under 2 g over a period of days to 1.5 months, to agitation and delirium, with acute ingestions of 25–75 g (6–8). Minimally responsive states have been reported with doses as low as 3 g daily for 4 days (8). Rare tonic-clonic seizures have also been reported by poison control centers in acute intoxications (6, 9). Treatment of acute phenibut intoxications can be supportive, requiring no medications or brief benzodiazepine treatment, with return to pre-intoxication baseline in hours without any lasting effect (6, 8). However, in one case presenting with agitated delirium, droperidol and ketamine were not sufficient for sedation and intubation was required for safety of the patient (6).

Physiologic phenibut dependence can occur within several days, and withdrawal has been characterized by mood lability, hostility/irritation, psychomotor agitation, insomnia, and palpitations (2, 7, 9, 10). Psychosis, hallucinations, insomnia have been reported in cases of withdrawal days after discontinuing doses at below 2 g/day (9–12). In outpatient settings, one case describes a patient self-reducing 1 gram daily dose by 50% over the course of 2 weeks without withdrawal symptoms, but another case of a patient taking 8 g/day required baclofen taper over the course of 20 weeks to mitigate withdrawal (2, 10).

The case described above is notable because the phenibut intoxication declared itself primarily with dissociative symptoms, including detachment from reality, as well as delusions that remitted briefly at time of intake, and then rapidly devolved into florid delirious agitation lasting one week. Our treatment approach in the inpatient setting of using baclofen to curb withdrawal described by Samokhvalov and colleagues, ~10 mg of baclofen to 1 g phenibut used daily, appears to have been useful in our case (2). However it must be emphasized that that commercially available phenibut has a wide range of purity, from ~40% reported by Downes et al., 2015 to 98%, reported by Wong et al., 2015, both by mass spectroscopy (6,7). While we were not able to verify phenibut purity in our case, and we had no blood or urine studies to confirm the amount of phenibut use, it stands to reason that baclofen ought to be initiated early in cases of suspected phenibut withdrawal.

Parenthetically, this patient’s manifestation of phenibut withdrawal could have been influenced by regular anabolic steroid use, either in affecting the severity of symptoms experienced, or conferring a unique vulnerability. However, this patient had used anabolic steroids without any psychiatric adverse effects in the past, and previous reports indicate that anabolic-steroid use is more associated with mania rather than delirium (13). Our case adds to the growing, but very limited, medical literature available in English of phenibut withdrawal. Psychiatrists, emergency room clinicians, and other health professionals should be alert to these presentations of phenibut use. More broadly, cases such as these demonstrate the imperative to better regulate not only phenibut availability, but also other nootropic agents for public safety.

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