Phenibut: A Novel Nootropic With Abuse Potential

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There has been an increasingly popular trend to use drugs and supplements accessible from internet resources to enhance mood and cognitive functioning, often without medical consultation[1]; estimated sales approach 1 billion US dollars annually.[2] Some of these nootropics and supplements are medications that are prescribed in other countries but that have not received US Food and Drug Administration (FDA) approval. We describe a patient whose use of phenibut (4-amino-3-phenyl-butyric acid), a resurrected anxiolytic medication developed in the early 1960s, led to hospital presentation with agitated delirium and unintended life-threatening consequences.

Case Report

Mr A, a 27-year old white man, presented to the hospital after being found unresponsive at home. Physical examination initially revealed a hypertensive, obtunded male who was minimally responsive to pain. His vital signs were blood pressure, 182/90 mm Hg; heart rate, 92 beats/min; and respiratory rate, 22 breaths/min. Laboratory study results were notable for an elevated aspartate aminotransferase level of 80 IU/L and alanine aminotransferase level of 206 IU/L. Other laboratory tests and urine toxicology screen were not informative.

Within 2 hours, Mr A developed psychomotor restlessness, disorientation, and an inability to attend to staff redirection. Multiple doses of lorazepam, ketamine, olanzapine, and midazolam were ineffective in calming him, and restraints were required to prevent inadvertent harm to himself or others. He subsequently required intubation due to vomiting and aspiration concerns.

On psychiatric evaluation post-extubation, he was alert, without fluctuation of consciousness or psychomotor agitation. His speech was coherent. However, his thought process was illogical and tangential, without delusions or perceptual disturbances. He did not have a psychiatric history, which was corroborated by collateral informants.

Mr A disclosed having discovered phenibut from internet blogs, which he acquired inexpensively online. Subjectively, it induced a sense of well-being, contentment, and a "dreamy state," allowing him to be more social and reducing sexual inhibitions. The effects of phenibut were reportedly short-lived, necessitating repeated dosing to achieve sustained effects. He used doses as high as 5 g multiple times daily. Abrupt discontinuation precipitated withdrawal symptoms: hot and cold flashes, insomnia, intense restlessness, and extreme irritability. He was previously prescribed gabapentin for nonspecific pain and serendipitously discovered that gabapentin (up to 2,400 mg on an occasion) would mitigate symptoms. During his hospital stay, he was provided a benzodiazepine taper to manage withdrawal.

Discussion

This case illustrates the misuse and abuse potential of phenibut, an anxiolytic marketed for use in Russia and Ukraine that is structurally similar to baclofen and γ-hydroxybutyrate.[3] It predominantly acts as a $GABA_B$ receptor agonist and, to a lesser extent, a $GABA_A$ agonist. Phenibut has become increasingly popular in the United States, United Kingdom, and Australia due, in part, to its availability online. Because it is an analog of GABA, phenibut is often marketed as an amino acid, or nutritional supplement, by online vendors. Having been thus marketed, it has escaped FDA regulatory scrutiny.[4] Nonetheless, the FDA issued a warning and banned its retail sale in April 2019; phenibut is, however, still accessible through online vendors in capsule or powder form. Because of safety concerns related to abuse and toxicity, phenibut has been classified as a controlled substance in some countries, including Australia.

Users derive euphoria and a reduction of social anxiety with phenibut; some report that it enhances social engagement as well as enjoyment of music or sexual arousal.[5] Others use phenibut to self-medicate for benzodiazepine and alcohol withdrawal.[6]

Phenibut produces a toxidrome comparable to those of benzodiazepines, including reduced consciousness, delirium, and, in some cases, agitation.[7] The literature has suggested that there is an abuse potential associated with phenibut.[4,5] Additionally, several internet blogs discuss the recreational use of phenibut, and ingestion of amounts exceeding the recommended daily dose, 0.5–1.5 g, has been advocated to achieve enhanced calming and euphoric effects. However, tolerance can develop quickly.[3,5] Continued dose escalation can precipitate

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mydriasis, nausea, vomiting, and transaminitis,[8] as well as diminished responsiveness as was observed in our patient. Abrupt discontinuation after repeated use can precipitate withdrawal.[4,9] Although we found no reports of the use of gabapentin in the clinical management of withdrawal, our patient found that it mitigated phenibut withdrawal symptoms. $\alpha_2\delta$ Subunit antagonism of voltage-dependent calcium channels, a mechanism of action shared by both phenibut and gabapentin, might explain this effect.[9–11] Previous reports suggest that patients withdrawing from phenibut can be safely detoxified in clinical settings with baclofen, phenobarbital, or benzodiazepines.[6,9,10,12,13]

Although clinicians rely on standard immunoassay drug screens to determine which agent(s) underlie a patient's presentation, phenibut is not detected on such assessments. Liquid chromatography–mass spectrometry is required to determine its presence in plasma.[14]

Recreational phenibut use is potentially associated with severe health risks. Clinicians should be alert to the possibility of phenibut abuse and withdrawal, which can mimic benzodiazepine toxidrome and withdrawal.

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