ARTICLE

Kratom and Phenibut: A Concise Review for Psychiatric Trainees

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Nootropics are psychoactive substances that are widely accessible to purchase in the United States. Two such substances, kratom, a naturally derived nootropic, and phenibut, a gamma-aminobutyric acid (GABA) analogue, are psychoactive substances that have neuropsychiatric effects mimicking those of prescribed medications. They are marketed as supplements and perceived by some consumers as an attractive alternative to prescribed psychiatric medications. They are also used recreationally, which has raised concerns about them as emerging drugs of abuse. Psychiatric trainees should be aware of the potential of use by their patients, as well as the effects of toxicity and withdrawal. This article provides a concise review for psychiatric trainees of existing literature regarding kratom and phenibut.

According to the *World Drug Report 2019* from the United Nations Office on Drugs and Crime, there was a 30% increase in the use of recreational substances over the past decade, with an unprecedented rise in the rate of new psychoactive substances on the market (1). Nootropics, a subset of psychoactive substances that have chemical properties similar to those of prescribed medications, have been claimed to improve mood and enhance cognitive functioning. They are marketed as supplements and may be perceived as a safe and natural alternative to prescribed psychiatric medications. Yet they remain largely unregulated. They can be used recreationally, which has raised concerns about them as emerging drugs of abuse. In addition, the existing literature is limited about their safety and efficacy. Two nootropics that are on the market are kratom, a natural nootropic, and phenibut, a synthetic gamma-aminobutyric acid (GABA) analogue. This article presents a concise review for psychiatric trainees of existing literature regarding kratom and phenibut, focusing on toxicity and management of withdrawal.

KRATOM

Kratom is a naturally derived nootropic that is marketed to enhance mood and concentration and to manage symptoms of opioid withdrawal. Kratom originates from a tropical tree (*Mitragyna speciosa*) native to Southeast Asia (2). The active ingredients are derived from its leaves: mitragynine (9-methoxy-corynantheidine) and 7-hydroxymitragynine (2). There has been a dramatic increase in kratom exposure in the United States in the past decade. From 2011 through 2017, U.S. poison control centers reported 1,807 cases of kratom exposure, of which approximately two-thirds occurred from 2016 to 2017 (3).

Legal Status

As of 2020, kratom is listed as a schedule I controlled substance due to its stimulant and hallucinogenic properties and is banned in six states: Alabama, Arkansas, Indiana, Rhode Island, Vermont, and Wisconsin (4). Otherwise, it is legal to sell and possess. It is sold as a supplement and is available through online retail and supplement stores.

Mechanisms of Action and Uses

The active ingredients of kratom are 7-hydroxymitragynine (a highly selective μ and κ opioid receptor agonist) and mitragynine (which acts on various brain receptors, including 5-HT_{2A} serotonergic, alpha 2-adrenergic, and dopamine receptors). At low doses, it can produce the stimulating effects of increased motivation, sociability, talkativeness, and increased energy. At high doses, it is known to produce analgesic effects and is used as maintenance for opioid withdrawal (2).

Dosing and Metabolism

Online retailers recommend a dose of 4 to 10 grams per day, with a maximum dose of 50 grams per day. Kratom can be ingested as a powder, capsule, liquid extract, or tea. It has a half-life of approximately 24 hours and is metabolized by the liver (5). It does not show up on the standard urine drug screen, but mitragynine can be detected by gas chromatography–mass spectrometry and liquid chromatography–tandem mass spectrometry (LC-MS) (2).

Toxicity

Toxicity from kratom has been associated with seizures, agitation, psychosis, hallucinations, paranoia, arrhythmias, hypothyroidism, intrahepatic cholestasis, nephrotoxicity, and death (2). From 2011 to 2017, U.S. poison control centers reported that the most common side effects were agitation-irritability (22.9%) and tachycardia (21.4%) (3). The same study reported 11 deaths linked to kratom use, including two from kratom exposure alone (3). However, no causality of deaths has been established with kratom, because causes of deaths linked

to kratom are confounded by the use of other substances.

Withdrawal

Symptoms of withdrawal include nausea, sweating and chills, mydriasis, muscle and body aches, tremors, fatigue, diarrhea, rhinorrhea, and lacrimation (6). Neuropsychiatric symptoms of withdrawal include insomnia, restlessness, irritability and hostility, anxiety, mood disturbances, and hallucinations (6). There are no validated tools to monitor for symptoms of withdrawal. However, because of kratom's opioid-like properties, the Clinical Opiate Withdrawal Scale (COWS) has been used in case reports (6, 7). There have been only a few case reports describing supervised kratom detoxification. The recommended management for withdrawal is similar to that for opioid withdrawal, with supportive therapy in managing the hyperadrenergic state. Symptoms are typically managed with symptom-triggered clonidine based on the COWS score, in addition to a scheduled anxiolytic (hydroxyzine or gabapentin), prescribed over the course of 4 to 5 days (6, 7). Concurrent use of scheduled dihydrocodeine and lofexidine, with decreased doses over 4 days based on clinical improvement, has also been reported to successfully manage symptoms of withdrawal (8).

Maintenance Therapy

There is still a scarcity of literature regarding maintenance therapy for kratom dependence. There have been two case reports of successfully transitioning patients to buprenorphine-naloxone maintenance therapy (9). To date, there are no studies on the effectiveness of naltrexone for kratom dependence (6).

PHENIBUT

Phenibut (β-phenyl-γ-aminobutyric acid) is a synthetic nootropic that is a GABA analogue. It was initially introduced and used in clinical practice in Russia in the 1960s to treat depression, posttraumatic stress, stuttering, and vestibular disorders and as a pre- and postoperative medication (10). Over the past decade, there has been a 64% increase in total publications on PubMed associated with the search term "phenibut."

Legal Status

Phenibut is still an uncontrolled substance in the United States, and it is legal to sell and possess phenibut (11). It has not been approved for clinical use in the United States.

Mechanism of Action and Uses

Phenibut is used as an anxiolytic, muscle relaxant, and sleep aid and for cognitive enhancement. It acts mainly as a GABA-B receptor agonist, with some activity at the GABA-A receptor, in addition to stimulating dopamine receptors and antagonizing β-phenethylamine (endogenous anxiogenic) (11).

Dosing and Metabolism

Phenibut is available and sold in the United States as a supplement through online retail. It can be ingested as a capsule or in powder form. Phenibut has a half-life of 5.3 hours (12). It does not show up on the standard urine drug screen. Its plasma concentration can be determined from LC-MS (13). Online retailers suggest a daily dose of 250 mg to 500 mg, with a maximum daily dose of 1,500 mg.

Toxicity

Toxicity is associated with altered mental status, hypertension, tachycardia, dystonia, pupillary dilation, agitation, delirium, tonic-clonic seizures, and respiratory depression. At least three case reports of phenibut toxicity have described severe agitation requiring IV sedation and subsequent intubation and mechanical ventilation (14, 15). Rhabdomyolysis secondary to agitation has also been reported (14). To date, no deaths have been reported with phenibut toxicity.

Withdrawal

Symptoms of phenibut withdrawal include heart palpitations, anxiety, insomnia, tremors, agitation, mood lability, hallucinations, disorganization, and delusions. Symptoms of withdrawal can be heterogeneous. Hardman et al. (11) described a patient with withdrawal symptoms resembling serotonin syndrome or neuroleptic malignant syndrome (fever, tachycardia, rigidity, and inducible clonus), which did not respond to cyproheptadine. Currently, there are no validated scales to monitor symptoms of phenibut withdrawal. The Clinical Institute Withdrawal Assessment of Alcohol Scale–Revised has been used in some cases, with mixed utility (12, 16). Benzodiazepines (chlordiazepoxide, lorazepam, diazepam, valium, and nitrazepam) have been used as either a scheduled taper or as-needed medications based on the severity of withdrawal symptoms (12, 16–18). Antipsychotics (haloperidol and olanzapine) in conjunction with benzodiazepines have been used to manage agitation and aggression due to withdrawal (11). In one case report, withdrawal symptoms were successfully managed with phenobarbital taper, starting at an initial dose of 64.8 mg four times daily over the first 24 hours and then tapered down by 25%–50% every 2 to 3 days over 9 days (19). In addition, at least two case reports have described the use of scheduled baclofen tapers to successfully manage symptoms of withdrawal due to its similarity in molecular structure and mechanism of action to phenibut (12, 20). In a report by Ahuja et al. (12), baclofen taper was started at 5 mg three times daily for 2 days, followed by 5 mg twice daily on day 3 and then a dose deescalation by 2.5 mg daily until discontinuation of baclofen. Samokhvalov et al. (20) substituted baclofen for phenibut (1 gram of phenibut to 8–10 mg of baclofen) over 9 weeks, and then baclofen was tapered off over the following 12 weeks.

Maintenance Therapy

To the best of our knowledge, there are no studies about maintenance therapy for phenibut dependence.

CONCLUSIONS

Kratom and phenibut are emerging psychoactive substances with cognitive and mood-enhancing effects that have been increasing in popularity in the United States. With globalization and the ubiq-

KEY POINTS/CLINICAL PEARLS

- Kratom and phenibut are labeled nootropics because of their ability to enhance mental functioning, with chemical properties similar to those of prescribed medications.
- Kratom is a highly selective μ and κ opioid receptor agonist, with some activity at the 5-HT_{2A} serotonergic, alpha 2-adrenergic, and dopamine receptors, that produces effects of increased motivation and energy, sociability, talkativeness, and analgesia.
- Phenibut is a gamma-aminobutyric acid B receptor agonist that serves as an anxiolytic, muscle relaxant, and sleep aid and is also used for cognitive enhancement.

uity of the Internet, the market for psychoactive substances has grown as a result of dissemination of information and products from other countries. The concern lies in the fact that accessibility of these psychoactive substances has outpaced our current clinical knowledge about them. In addition, these substances may be used by patients to self-treat their psychiatric illnesses or substance use disorders, even though the safety and efficacy of the substances has not been established. Thus psychiatrists should be aware of "alternative" psychoactive substances that may not be reported when they elicit a standard history. Moreover, clinical presentation of toxicity and withdrawal from both these substances mimics common psychiatric disorders, and kratom or phenibut toxicity or withdrawal should be considered as a differential diagnosis for patients with an acute presentation and a negative urine drug screen. Although there is a growing body of literature about kratom and phenibut, a research gap remains in regard to the long-term neuropsychiatric effects of their use and to treatment for maintaining abstinence from these substances.

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