5-2019

When Street Drugs Stop at Hospital Doors: A Closer Look at Kratom and Phenibut Withdrawal

Monique Mun
Henry Ford Health System

Vanessa Patel
Henry Ford Health System

Catherine Frank
Henry Ford Health System

When street drugs stop at hospital doors: a closer look at Kratom and Phenibut withdrawal

Monique Mun, MD, Vanessa Patel, MD, Cathrine Frank, MD, Department of Psychiatry, Detroit, Michigan

Introduction

- The use of synthetic psychotropics is rapidly increasing across the globe – sometimes used recreationally and sometimes as prescribed medicine.
- Medical literature systematically discusses Kratom, a synthetic opioid used for opioid dependence, withdrawal and mood enhancement.
- Research gap remains wide about the toxicity, withdrawal, and management of withdrawal of those using Phenibut, a GABA derivative used for its anxiolytic effect.
- Additionally, there is a scarcity in literature regarding the combined use of Kratom with Phenibut.

Case Presentation

Case: 37-year-old Caucasian female with history of opioid and alcohol use disorder was admitted to a psychiatric hospital for worsening depression and suicidal ideation with a plan to slit her wrists. Previously, she was prescribed buprenorphine (Subutex) for opioid dependence, though discontinued it due to cost. Consequently, she was self-treating her opioid dependence with kratom for one year prior to presentation. As a result of the anxiety provoking and stimulating effects of kratom during the day, patient started to use phenibut as an anxiolytic and for sleep at night. Patient was using up to 50 grams of kratom per day, and 500 mg of phenibut twice daily. Last use of these substances was one day prior to admission.

Exam: On the day of admission, patient endorsed depressive symptoms and debilitating anxiety. She was noted to be tachycardic (HR 112) and hypertensive (BP 151/102). Labs were unremarkable. Urine drug screen was positive for benzodiazepine. On day two of admission, patient complained of nausea, rhinorrhea, diarrhea, worsened anxiety and heart palpitations.

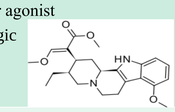
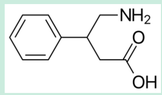
Management: Patient was placed on CIWA protocol with vitals-triggered lorazepam 2mg every 6 hours, vitals measured every shift, and lorazepam taper over three days. Comfort medications including anti-emetics, anti-spasmodics, and analgesics were also ordered as needed.

Figure 1

Figure 2

Figure 1: Kratom is sold as a powder in variety of strains – each strain is marketed as to produce a slightly different effect.
Figure 2: Phenibut is also available to purchase through online retail.

Pharmacology and Effects

	Kratom	Phenibut
Origin	• From a tropic tree (Mitragyna speciosa) native to Southeast Asia • Its leaves contain indole alkaloids: mitragynine (9-methoxy-corynantheidine) and 7-hydroxymitragynine.	• β-phenyl-γ-aminobutyric acid • Introduced and used in clinical practice in Russia in the 1960's.
Legal Status	• In most states: uncontrolled substance. Legal to possess. • Only controlled substance in Wisconsin, Arkansas, Tennessee, Indiana and Vermont. • Not approved for clinical use. • Available and sold as a supplement through online retail.	• Uncontrolled substance in the United States. Legal to possess. • Not approved for clinical use. • Available and sold as a supplement through online retail.
Mechanism of action	• 7-hydroxymitragynine is a highly selective μ and κ opioid receptor agonist • Mitragynine acts on the 5-HT2A serotonergic and alpha 2-adrenergic receptors • Metabolized by the liver. Half-life is approximately 24 hours. 	• GABA-B receptor agonist • Stimulates dopamine receptors • Antagonizes β-phenethylamine (endogenous anxiogenic) • Metabolized by the liver. Half-life is 5.3 hours. 
Effects and Use	• At lower doses: stimulating effects such as increased motivation, sociability, talkativeness, and increased energy. • At higher doses: decreased sensitivity to physical and emotional pain, and maintenance of opioid withdrawal.	• Anxiolytic, muscle relaxant, sleep aid; has been used for pre- and post-operative medication, and cognitive enhancement. • In Russia, has been prescribed to treat depression, PTSD, stuttering, and vestibular disorders.
Dosing	• 4 – 10 g/day. Maximum 50 g/day. • Ingested as capsule, powder, or liquid extract. 	• 250 – 500 mg/day. Maximum 1500 mg/day. • Ingested as capsule or powder.
Toxicity	• Associated with seizures, agitation, psychosis, hallucination, paranoia, arrhythmias, hypothyroidism, intrahepatic cholestasis, nephrotoxicity, coma, and death. ▪ In case series from Virginia Poison Center, seizures most frequently reported. ▪ Poison control center in the United States: most common effects were agitation/irritability (22.9%) and tachycardia (21.4%). • At least 44 cases of death linked to kratom use; however, usually other substances were involved. • Animal model studies showed mixed results regarding safety at high doses: ▪ Study in 2013 reported a dose of 200 mg had lethal effect in rats. ▪ Study by Macko et al. found no evidence of toxicity, measured as tremors or convulsions, at doses as high as 920 mg/kg in dogs.	• Associated with altered mental status, hypertension, tachycardia, dystonia, pupillary dilation, agitation, delirium, and respiratory depression. ▪ 3 reports of phenibut-induced agitation requiring IV sedation and intubation ▪ Tonic-clonic seizures have been reported by poison control centers • Intoxication resolves within 24 hours • No deaths have yet been reported with phenibut intoxication. 

Withdrawal and Management

	Kratom	Phenibut
Symptoms of withdrawal	• Not known to be life-threatening. • Symptoms of withdrawal include nausea, vomiting, abdominal cramping, muscle and bone pain, weakness, insomnia, hostility and aggression, emotional lability and psychosis. • Mild anxiety and depression have been reported after cessation of kratom.	• Can be severe; unknown if life-threatening. • Symptoms of withdrawal include heart palpitations, anxiety, insomnia, tremors, agitation, mood lability, hallucinations, disorganization and delusions. • Hardman et. al described a patient with withdrawal symptoms resembling serotonin or neuroleptic malignant syndrome: fever, tachycardia, rigidity, and inducible clonus.
Monitoring	• Severity of withdrawal can be measured using the Clinical Opiate Withdrawal Scale (COWS).	• In the case report by Ahuja et. al, patient endorsed minimal symptoms on Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA). • Currently no validated scale that captures withdrawal symptoms.
Medical management	• Can be managed similarly to opioid withdrawal with supportive treatment: anti-emetics, analgesics, and anti-spasmodic agents. • Galbis-Reig et al. described the use of symptom-triggered clonidine 0.1 mg – 0.2 mg every 2 hours based on COWS score, in addition to scheduled hydroxyzine 50 mg every 6 hours. ▪ Naltrexone therapy on discharge to prevent further withdrawal symptoms • Dihydrocodeine (opioid agonist) and lofexidine (a-adrenergic antagonist) have been reported to successfully manage kratom withdrawal.	• At least two case reports have described the use of baclofen taper due to its similarity in molecular structure and mechanism of action. ▪ 10 mg of baclofen for every 1 g of phenibut used • Brunner et. al demonstrated the use of phenobarbital for treatment of withdrawal symptoms. • May consider use of benzodiazepine, gabapentin and pregabalin.

Discussion

- Synthetic psychotropics are marketed as supplements and are an attractive alternative for patients to self-treat their substance use and psychiatric disorders.
- Providers should be aware when patients may be using multiple synthetic psychotropics.
- Combined use of kratom and phenibut is becoming increasingly popular, especially among patients with co-occurring opioid and alcohol use disorders, as seen in our patient in this case presentation.
- Research remains underdeveloped in regards to management of patients who are using multiple synthetic psychotropics . Thus, acute withdrawal from both kratom and phenibut was managed based on limited research.
- Future research should aid in establishing evidence-based guidelines for monitoring and managing kratom and phenibut withdrawal, in addition to better understanding of potential drug-drug interaction with other medications.

References

1. Ahuja, T., Mgbako, O., Katzman, C., & Grossman, A. (2018). Phenibut (β-Phenyl-γ-aminobutyric Acid) Dependence and Management of Withdrawal: Emerging Nootropics of Abuse.*Case Reports in Psychiatry*,*2018*, 1-3. doi:10.1155/2018/9864285
2. Brunner, E., & Levy, R. (2017). Case Report of Physiologic Phenibut Dependence Treated With a Phenobarbital Taper in a Patient Being Treated With Buprenorphine. *Journal of Addiction Medicine*, *11*(3), 239-240. doi:10.1097/adm.0000000000000303
3. Edward A. Jouney, "Phenibut (β-Phenyl-γ-Aminobutyric Acid): an Easily Obtainable "Dietary Supplement" With Propensities for Physical Dependence and Addiction," Current Psychiatry Reports, vol. 21, no. 4, 2019.
4. Eldridge, W. B., Foster, C., & Wyble, L. (2018). Neonatal Abstinence Syndrome Due to Maternal Kratom Use. *Pediatrics*, *142*(6). doi:10.1542/peds.2018-1839
5. Fluyau, D., & Revadigar, N. (2017). Biochemical Benefits, Diagnosis, and Clinical Risks Evaluation of Kratom. *Frontiers in Psychiatry*, *8*. doi:10.3389/fpsyt.2017.00062
6. Hardman, M. I., Sprung, J., & Weingarten, T. N. (2018). Acute phenibut withdrawal: A comprehensive literature review and illustrative case report. *Bosnian Journal of Basic Medical Sciences*. doi:10.17305/bjbms.2018.4008
7. Joshi, Y. B., Friend, S. F., Jimenez, B., & Steiger, L. R. (2017). Dissociative Intoxication and Prolonged Withdrawal Associated With Phenibut. *Journal of Clinical Psychopharmacology*, *37*(4), 478-480. doi:10.1097/jcp.0000000000000731
8. Khazaeli, A., Jerry, J. M., & Vazirian, M. (2018). Treatment of Kratom Withdrawal and Addiction With Buprenorphine. *Journal of Addiction Medicine*, *12*(6), 493-495. doi:10.1097/adm.0000000000000435
9. Lapin, I. (2006). Phenibut (β-Phenyl-GABA): A Tranquilizer and Nootropic Drug. *CNS Drug Reviews*, *7*(4), 471-481. doi:10.1111/j.1527-3458.2001.tb00211.x
10. Li, C., & Sundararajan, K. (2015). An Uncommon Case of Phenibut Toxicity in an Intensive Care Unit. *International Journal of Medical and Pharmaceutical Case Reports*, *5*(5), 1-6. doi:10.9734/ijmpcr/2015/21689
11. Overbeek, D., Abraham, J., & Munzer, B. (2019). Kratom (Mitragynine) Ingestion Requiring Naloxone Reversal. *Clinical Practice and Cases in Emergency Medicine*, *3*(1), 24-26. doi:10.5811/cpcem.2018.11.40588
12. Post, S., Spiller, H. A., Chounthirath, T., & Smith, G. A. (2019). Kratom exposures reported to United States poison control centers: 2011–2017. *Clinical Toxicology*, 1-8. doi:10.1080/15563650.2019.1569236
13. Wanankul, W., Trakulsrichai, S., Sathirakul, K., Auparakkitanon, S., Krongvorakul, J., Sueajai, J., . . . Sukasem, C. (2015). Pharmacokinetics of mitragynine in man. *Drug Design, Development and Therapy*, 2421. doi:10.2147/dddt.s79658
14. Wellington, G., Hussain, J., Brooks, J., Brooks, J., Haya, Kratom Crazy, & Redstorm Scientific. (n.d.). Learn Everything You Need To Know About Psychoactive Kratom. Retrieved March 12, 2019, from https://thethirdwave.co/psychedelics/kratom/#pharmacology
15. Zyabitseva, E. A., & Pavlova, I. V. (2008). Effects of the GABA receptor agonist phenibut on behavior and respiration in rabbits in emotionally negative situations. *Neuroscience and Behavioral Physiology*, *38*(6), 555-562. doi:10.1007/s11055-008-9025-2