OPEN

A Case of Kratom Use: Implications for Managing Addiction and Addressing Comorbidity in Overdose Survivors, and for the Education of Clinicians Who Are Not Addiction Specialists

Joseph H. Donroe, MD, MPH and David A. Fiellin, MD

As overdose mortality rises, overdose morbidity – complications seen as a result of overdose events – is rising too. Although comorbidity is often thought of as psychiatric or psychological, a case report of compartment syndrome, rhabdomyolysis, and acute renal insufficiency in a patient with loss of consciousness for 6 hours after smoking Kratom highlights medical comorbidity. The case is a reminder that a broad range of medical comorbidities can occur in patients with overdose and with unhealthy substance use. Patients with these comorbidities will often be cared for by clinicians who are not addiction specialists, who will need to have sufficient training to recognize and address them.

Key Words: comorbidity, drug overdose, Mitragyna

(*J Addict Med* 2022;16: 138–140)

Kratom use appears to be growing in the United States (US), though the true prevalence is largely unknown. One recent study estimated the prevalence of past year Kratom use in the US to be 0.8% and the American Kratom Association reports that nearly 5 million individuals have used Kratom.[1,2] People who use Kratom report a range of indications, including to relieve opioid withdrawal, to help decrease or taper off prescribed or illicit opioids, to treat pain and mental health symptoms such as anxiety, and for recreational use.[3] Kratom is marketed as an herbal drug derived from the *Mitragyna speciosa* tree and imported to the US from Southeast Asia. The primary psychoactive elements are the alkaloids mitragynine and 7-hydroxymitragynine which behave as partial agonists at the *mu* opioid receptor and as competitive antagonists of the *delta* and *kappa* opioid receptors. At low doses, Kratom has a stimulatory effect while at higher doses it has a sedative and analgesic effect.

Not unexpectedly, with rising use in the US, there has been an increasing number of reported cases of Kratom toxicity. From 2010 to 2015, there was a 10 fold rise in calls to poison centers related to Kratom exposure.[4] About 35% of these cases involved Kratom and other psychoactive substances such as alcohol, botanicals, benzodiazepines, ''narcotics,'' and acetaminophen.[4] From July 2016 to December 2017, the Centers for Disease Control and Prevention identified 152 overdose deaths in the US in which Kratom was detected on postmortem analysis; in the overwhelming majority, a coingested substance was also identified.[5] The frequent coingestion of Kratom with other substances, and adulterated supplies, makes it difficult to determine the extent to which there may be a causal relationship between Kratom use and fatal and other adverse outcomes. A case report in this issue of the *Journal* by Tobarron et al describes a severe case of rhabdomyolysis resulting from pressure necrosis following prolonged loss of consciousness after smoking Kratom.[6] The report includes minimal coingestions (venlafaxine and caffeine) that could not result in enough sedation to cause rhabdomyolysis. In all such cases, the possibility of undetected substances such as rare fentanyl analogs should be considered. The case, however, appears to add to a growing list of reports of severe toxicity associated with Kratom use. These include overdose, hepatotoxicity, bacterial infection from product contamination, psychosis, neonatal abstinence syndrome, hypothyroidism, acute respiratory distress syndrome, and seizures.[7,8] Given the potential for adverse effects from Kratom and potential for physiologic dependence, the US Drug Enforcement Administration (DEA), Department of Health and Human Services (DHHS), and Food and Drug Administration (FDA) have raised concerns.

From the Department of Internal Medicine, Yale School of Medicine, New Haven, CT (JHD, DAF); Program in Addiction Medicine, Yale School of Medicine, New Haven, CT (JHD, DAF); Department of Emergency Medicine, Yale School of Medicine, New Haven, CT (DAF); Health Policy and Management, Yale School of Public Health, New Haven, CT (DAF).

Received for publication February 7, 2021; accepted February 11, 2021.

The authors report no conflicts of interest.

Send correspondence to Joseph H. Donroe, MD, MPH, Yale University School of Medicine, 1450 Chapel Street, Office MOB 211, New Haven, CT 06511. E-mail: joseph.donroe@yale.edu.

ISSN: 1932-0620/21/1602-0138

DOI: 10.1097/ADM.0000000000000872

In 2016, the US DEA attempted to reclassify mitragynine and 7-hydroxymitragynine as schedule 1 drugs due to concerns about public safety. The DEA cited the potential for tolerance, withdrawal, and addiction, unpredictable effects due to the variability of the psychoactive alkaloid content, adulteration of Kratom with other psychoactive drugs, and the rising number of deaths and calls to poison centers related to Kratom intoxication.[9] The attempt to classify Kratom as a schedule 1 drug, however, was quickly withdrawn in response to public backlash over the decision.[10] In 2017, The US DHHS also made the recommendation that mitragynine and 7-hydroxymitragynine be classified as schedule 1 drugs and the FDA issued a public health advisory related to growing concerns for the risks associated with Kratom use.[11] However, at this time there is no federal regulation on Kratom use, though it is illegal to buy, use, or sell in several states and is a controlled substance in 16 other countries.[11] A group primarily responsible for organizing resistance to attempts to regulate Kratom is the American Kratom Association. Their expressed mission is to protect the use Kratom for the purposes of improved health and well-being. Advocates of Kratom use point to the low addiction potential compared to other opioids, the need for alternatives to opioid analgesics, the role for Kratom in managing opioid withdrawal, and the utility of Kratom in cutting down on prescribed and illicit opioid use, particularly in light of the current opioid crisis in North America.[3] This perspective highlights the potential benefits of Kratom but needs to be considered in light of concerns regarding purity, standardized dosing, and lack of high-quality empiric evidence for specific indications. It also ignores the potential for deliberate adulteration of Kratom through unregulated production and distribution, the harm from coingestion of Kratom with other sedatives, the effect that lack of regulation has on safety and the perception of safety, and the potential for interaction between Kratom and medications.[12,13]

The debate over regulating Kratom use and its potential role as a treatment for pain and opioid use disorder is ongoing and, like other active compounds, should ultimately be guided by science and rigorous study. What is not debatable, and what the growing popularity of Kratom informs us of, is that physicians and other clinicians should know when to suspect Kratom use and ask directly about it, in a nonjudgmental and patient-centered way. The reasons for Kratom use should be explored, the potential risks and perceived benefits discussed, and FDA-approved treatments for opioid use disorder or other conditions should be offered when indicated. It is known that providing treatment for addiction in hospitalized patients is effective though underutilized.[14] This is particularly relevant for Kratom, where knowledge of use may only become apparent after toxicity leads to hospitalization and use may reflect a pre-existing desire to treat an underlying opioid addiction. Additionally, there is accumulating data suggesting that Kratom withdrawal and addiction can be managed in a similar manner as opioid use disorder.[15]

The term ''comorbidity'' when used for patients with addiction, often centers around mental health and psychiatric disorders. The reported case of Kratom use and compartment syndrome, however, is an example of the myriad medical complications that can be associated with unhealthy substance use. Specifically, this patient manifests kidney, liver, cardiac, and musculoskeletal pathology that required the expertise of emergency medicine, nephrology, internal medicine, surgery, laboratory medicine, and toxicology. Although there is wide acceptance of the association between injection drug use and infectious complications, there is less discussion of the medical complications seen among those who survive an overdose. This case highlights the severe tissue and organ-related medical complications that can be seen in overdose survivors. In our practice, we also see neurologic complications in overdose survivors that can result in prolonged deficits. The wide array of clinical expertise that is brought to bear in this case demonstrates the value of broad clinician education across medical specialties for comorbid conditions and the need for vigilance regarding substance use and potential complications in those with substance use disorders. The case also highlights the potential and perhaps underrecognized long-term medical sequelae (eg, renal) that can be seen among overdose survivors that also need attention. The growing prevalence of overdose morbidity has implications for clinical education and the structure of health care systems that have largely been overlooked. These medical ''comorbid'' conditions in our patients require attention too.

REFERENCES

1. Schimmel J, Amioka E, Rockhill K, et al. Prevalence and description of Kratom (*Mitragyna speciosa*) use in the United States: A cross-sectional study. *Addiction*. 2021;116(1):176–181.
2. American Kratom Association. Kratom Fact Sheet. Available from: https://www.americankratom.org/images/file/Myths_Facts-on-Kratom-Legislative-Day-Handout-Final-2.pdf. Accessed February 1, 2021.
3. Coe MA, Pillitteri JL, Sembower MA, et al. Kratom as a substitute for opioids: Results from an online survey. *Drug Alcohol Depend*. 2019; 202:24–32.
4. Anwar M, Law R, Schier J. Notes from the field: Kratom (*Mitragyna speciosa*) exposures reported to poison centers - United States, 2010–2015. *MMWR - Morb Mortal Wkly Rep*. 2016;65(29):748–749.
5. Olsen EO, O'Donnell J, Mattson CL, et al. Notes from the field: Unintentional drug overdose deaths with Kratom detected - 27 states, July 2016-December 2017. *MMWR - Morb Mortal Wkly Rep*. 2019;68(14): 326–327.
6. Tobarran N, Wolf C, Cumpston KL, et al. Pressure necrosis requiring fasciotomy after Kratom overdose. *J Addict Med*. 2022;16:252–253.
7. Dixon RB, Waggoner D, Davis M, et al. Contamination of some Kratom products with salmonella. *Ann Clin Lab Sci*. 2019;49(5):675–677.
8. Alsarraf E, Myers J, Culbreth S, et al. Kratom from head to toe—Case reviews of adverse events and toxicities. *Curr Emerg Hosp Med Rep*. 2019;7(4):141–168.
9. Drug Enforcement Administration. Schedules of controlled substances: Temporary placement of mitragynine and 7-hydroxymitragynine into Schedule I. *Fed Regist*. 2016;81(169).
10. Drug Enforcement Administration. Withdrawal of notice of intent to temporarily place mitragynine and 7-hydroxymitragynine into Schedule I. *Fed Regist*. 2016;81(198).

11. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA advisory about deadly risks associated with Kratom. 2017. Available at: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fda-advisory-about-deadly-risks-associated-kratom. Accessed February 1, 2021.
12. Kamble SH, Sharma A, King TI, et al. Exploration of cytochrome P450 inhibition mediated drug-drug interaction potential of Kratom alkaloids. *Toxicol Lett*. 2019;319:148–154.
13. Lydecker AG, Sharma A, McCurdy CR, et al. Suspected adulteration of commercial Kratom products with 7-hydroxymitragynine. *J Med Toxicol*. 2016;12(4):341–349.
14. Weimer M, Morford K, Donroe J. Treatment of opioid use disorder in the acute hospital setting: A critical review of the literature (2014–2019). *Curr Addict Rep*. 2019;6(4):339–354.
15. Weiss ST, Douglas HE. Treatment of Kratom withdrawal and dependence with buprenorphine/naloxone: A case series and systematic literature review. *J Addict Med*. 2020;26:167–172.

