

A case of a mixed overdose involving kratom (*Mitragyna speciosa*) leading to serotonin syndrome

Hannah Reid Zweifel¹, Jonathan Browne¹, Jeffrey M Levine^{1,2,*}

¹ Oregon Health and Sciences University, Portland, OR, USA

² University of California Riverside School of Medicine, Riverside, CA, USA

* Corresponding Author: Jeffrey M Levine E-mail: levineje@ohsu.edu

ABSTRACT

Objective: Drug overdose deaths have risen precipitously over the past two years in the United States. Polysubstance overdose with opiates and amphetamines have been of particular concern. Kratom (*Mitragyna speciosa*) is an unregulated widely available herb with both stimulant and opiate μ -receptor activity. Studies suggest that its use is quickly increasing.

Case: We describe a patient who presented to a psychiatric hospital with a mixed toxic syndrome due to chronic kratom and prescribed SSRI use compounded by acute intake of methamphetamine. The patient displayed psychosis, tremulousness, myoclonus, and extreme anxiety. Her clinical picture was consistent with both serotonin syndrome and opiate withdrawal.

Conclusion: We call attention to this case because polysubstance overdoses are common, and kratom is widely available. Complex toxic presentations that involve kratom are likely to be increasingly encountered.

Key words: Kratom, *Mitragyna*, Toxicity, Drug Abuse, Serotonin Syndrome

INTRODUCTION

Deaths from drug overdose are rising precipitously in the US driven particularly by synthetic opioids such as fentanyl (1). At the same time methamphetamine abuse is also on the rise, along with deaths from mixed overdoses involving both methamphetamine and opiates (2). Kratom is an unregulated herbal supplement with opiate μ -agonist characteristics that is widely available and whose use is also increasing (3). We report here a case of a serious but non-fatal mixed overdose that involved kratom, methamphetamine, and chronic SSRI prescription use. Since the prevalence of current antidepressant use in the U.S. approaches 14% of the population, we believe that this case illustrates a serious toxidrome that may be encountered by clinicians more frequently.

Kratom is derived from the leaf of the tree *Mitragyna speciosa* found in Southeast Asia. Traditionally kratom was brewed into a tea and used by day laborers to increase productivity. In low dosages, it appears to act as a stimulant (1-5 g per day); in higher concentrations, it has opioid and sedative effects (5-15 g) (3, 4, 5). Thus, depending on dosing, kratom can act as a stimulant, anxiolytic, analgesic, or antidepressant. Survey data in the US report that kratom is used for self-management of chronic pain, opioid withdrawal, and mood enhancement (6).

The major alkaloid of kratom is mitragynine, which is an agonist at the opiate μ -receptor. This action has been linked to kratom's analgesic effect but also to its potential to produce physical dependence. An active metabolite of mitragynine, 7-hydroxymitragynine (7-OH), is also responsible for kratom's dose-dependent antinociceptive properties (5, 7). In the native leaf and varying capsule products, 7-OH is found in lesser concentrations ranging from 0.01-0.04%, as compared to 4.7-8.7% mitragynine (8). However, relative amounts in some commercially available preparations appear to vary wildly, as one study found 7-OH in concentrations 109-520% greater than would occur naturally (9). This increased concentration is important because this metabolite has been shown to antagonize the μ -receptor with a potency surpassing that of morphine (10). Kratom also interacts with norepinephrine and serotonin receptors, perhaps adding to its perceived positive effects on mood (3).

Case Report Article

Received 08-11-2021

Accepted 26-11-2021

Available Online: 01-12-2021

Published 30-12-2021

Distributed under
Creative Commons CC-BY-NC 4.0

OPEN ACCESS



This increased concentration is important because this metabolite has been shown to antagonize the μ -receptor with a potency surpassing that of morphine (10). Kratom also interacts with norepinephrine and serotonin receptors, perhaps adding to its perceived positive effects on mood (3)

Kratom has been considered by some to be a relatively safe alternative to opioids, as it appears less likely to cause respiratory depression. One preclinical study demonstrated that knock-out mice missing the beta-arrestin G protein-coupled receptor regulatory protein showed resistance to the effects of morphine on respiratory depression and constipation, but enhanced and prolonged analgesic responses (11). In vitro studies have demonstrated that kratom is a μ -agonist that does not activate the β -arrestin-2 proteins, potentially explaining its reported lower side effect profile compared to opiate compounds (12). In addition, rodent studies have suggested that mitragynine increases levels of monoamine neurotransmitters including serotonin via hypothalamic-pituitary-adrenal axis interactions and induces Fos expression in the major serotonergic projection center of the brain, the dorsal raphe nucleus (13, 14). Therefore, while kratom is most commonly used as a replacement for opioids, its use as a substitute for antidepressants has also been of interest (5, 15).

Kratom does carry significant risks: One hundred fifty-two overdose deaths in which Kratom was involved were reported over 18 months 2016-2017. In seven cases, it was the only drug found in the blood of the deceased individual (16). In addition, kratom is a strong inhibitor of P450 3A4 and 2D6 and therefore has high potential for drug interactions with opioids, antidepressants, and benzodiazepines (17).

Case Presentation

The patient was a 48-year-old woman with a history significant for PTSD and kratom dependence who was admitted to an inner-city inpatient psychiatry unit for new-onset psychosis following an isolated episode of intranasal methamphetamine use. Notable comorbid conditions included hypertension, COPD, and chronic back pain. She had initiated kratom use four years prior to presentation as a substitute for prescription opiates for back pain. She reported daily use of 50-80 capsules containing 500 milligrams of kratom, an average of 20-40 grams of kratom per day. The patient had an extensive substance use history throughout her lifetime, but several multi-year periods of abstinence from all substances. At the time of presentation, the patient reported using only marijuana and kratom for the previous four years apart from two recent episodes of methamphetamine relapse, one month prior and again six days prior to presentation. Additionally, throughout this time, the patient was prescribed paroxetine 40 mg daily, along with gabapentin, varenicline, and as needed cyclobenzaprine. During the entire 4-year use of kratom and paroxetine prior to relapse on methamphetamine, she had experienced no psychotic symptoms.

Following her use of an unspecified amount of methamphetamine nasally, the patient began to experience psychomotor and psychotic symptoms. She presented to the emergency department voluntarily for complaints of auditory hallucinations and restlessness. Upon admission, approximately 48 hours after last methamphetamine or kratom use, exam was significant for hypertension, sinus

tachycardia without fever, auditory and visual hallucinations, ideas of reference, gross disorganization, delusional thoughts, and prominent mood lability. Neurologic exam was significant for diffuse hyperreflexia, shuffling gait, tremulousness and intermittent myoclonus. Urine toxicology was positive for tricyclic compounds (most likely due to cyclobenzaprine) and cannabis. Thyroid function testing was normal; HIV, hepatitis C, and RPR serologies were negative. Routine chemistries were normal. CBC was notable for MCV of 103.7 initially, later measured at 109.7 with normal B12 and folate levels. The patient denied chronic alcohol use.

The patient was administered olanzapine, divalproex, clonidine, and lorazepam. Paroxetine was decreased to 30 mg because of concern about her symptomatology suggesting serotonin syndrome but was not stopped entirely due to concerns about abrupt discontinuation, which can be associated prominent withdrawal agitation. Clonidine was added to address opioid withdrawal, but buprenorphine was withheld due to concern about the degree of the patient's confusion.

Over the next week, the patient's psychotic symptoms gradually resolved; vital signs and neurological examination returned to normal, with resolution of hyperreflexia and myoclonus.

DISCUSSION

To the best of our knowledge, this is the first case study to present a patient with likely serotonin syndrome involving heavy kratom use. We believe that this patient's chronic use of kratom, along with paroxetine, primed the patient for a disorder of serotonin excess. She fulfilled Hunter criteria for serotonin syndrome (18). Preclinical studies have suggested that methamphetamine acts as a serotonin 5-HT_{2A} agonist (19). It is probable that the patient's isolated methamphetamine ingestion acted as the inciting event in the context of kratom and a serotonin reuptake inhibitor.

Interestingly, during the admission the patient was noted to have a significant macrocytosis of unknown origin. As noted above, all standard laboratory investigations related to macrocytosis were normal. One cross-sectional study examining the haematological and clinical-chemistry changes associated with kratom use found no statistically significant change in any hematologic parameter of chronic kratom users; however, the effects of kratom on haematopoiesis remain unexplored (20). Although we cannot be certain that the patient's use of alcohol was not greater than she reported, the possibility that high dose kratom may affect haematopoiesis is open for further investigation. Kratom has been reported to be associated with hypothyroidism, but TSH was normal in this patient (21).

This case may be among the highest doses of daily kratom use reported, although we believe similar presentations are likely to emerge as recognition of kratom use and withdrawal increases. Kratom is regularly advertised and sold as a harmless supplement online, as well as in convenience stores and gas stations. In the case of this patient, she did not report her use of kratom until the second day of admission due to her belief that it was irrelevant to her current symptoms. Kratom cannot be detected by a standard urine drug screen, requiring instead methods such as gas chromatography-mass

spectrometry not in general clinical use (22). Awareness of the dangers of kratom has not kept pace with its increased use. While kratom has potential for future research and clinical application in pain management and in treatment of opioid use disorder, it is more likely to be encountered clinically at this time due to intoxication, abuse, and withdrawal (23). As this case indicates, these presentations can be manifold and can include serotonin syndrome and psychosis when mixed with other common drugs or medications.

Author Contributions: HRZ, JB, JML: Research of the literature, Patient examinations, JML: Manuscript preparation and revisions.

Financial & competing interest's disclosure: The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

- Ahmad FB, Rosson LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2021.
- O'Donnell J, Gladden RM, Mattson CL, Hunter CT, Davis NL. Vital signs: Characteristics of drug overdose deaths involving opioids and stimulants—24 states and the District of Columbia, January–June 2019. *Morbidity and Mortality Weekly Report*. 2020 Sep 4;69(35):1189.
- Veltri C, Grundmann O. Current perspectives on the impact of Kratom use. *Substance abuse and rehabilitation*. 2019;10:23.
- Sanderson M, Rowe A. Kratom. *CMAJ*. 2019 Oct 7;191(40):E1105-.
- Ellis CR, Racz R, Kruhlak NL, Kim MT, Zakharov AV, Southall N, Hawkins EG, Burkhart K, Strauss DG, Stavitskaya L. Evaluating kratom alkaloids using PHASE. *PLoS one*. 2020 Mar 3;15(3):e0229646.
- Grundmann O. Patterns of kratom use and health impact in the US—results from an online survey. *Drug and alcohol dependence*. 2017 Jul 1;176:63-70.
- Fluyau D, Revadigar N. Biochemical benefits, diagnosis, and clinical risks evaluation of kratom. *Frontiers in psychiatry*. 2017 Apr 24;8:62.
- Sharma A, Kamble SH, León F, Chear NJ, King TI, Berthold EC, Ramanathan S, McCurdy CR, Avery BA. Simultaneous quantification of ten key Kratom alkaloids in *Mitragyna speciosa* leaf extracts and commercial products by ultra-performance liquid chromatography–tandem mass spectrometry. *Drug testing and analysis*. 2019 Aug;11(8):1162-71.
- Lydecker AG, Sharma A, McCurdy CR, Avery BA, Babu KM, Boyer EW. Suspected adulteration of commercial kratom products with 7-hydroxymitragynine. *Journal of Medical Toxicology*. 2016 Dec;12(4):341-9.
- Matsumoto K, Horie S, Ishikawa H, Takayama H, Aimi N, Ponglux D, Watanabe K. (2004). Antinociceptive effect of 7-hydroxymitragynine in mice: Discovery of an orally active opioid analgesic from the Thai medicinal herb *Mitragyna speciosa*. *Life Sciences* 2004; 74:2143-2155.
- Raehal KM, Walker JK, Bohn LM. Morphine side effects in β -arrestin 2 knockout mice. *Journal of Pharmacology and Experimental Therapeutics*. 2005 Sep 1;314(3):1195-201.
- Kruegel AC, Grundmann O. The medicinal chemistry and neuropharmacology of kratom: a preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. *Neuropharmacology*. 2018 May 15;134:108-20.
- Suhaimi FW, Yusoff NH, Hassan R, Mansor SM, Navaratnam V, Müller CP, Hassan Z. Neurobiology of Kratom and its main alkaloid mitragynine. *Brain research bulletin*. 2016 Sep 1;126:29-40.
- Kumarnsit E, Vongvatcharanon U, Keawpradub N, Intasaro P. Fos-like immunoreactivity in rat dorsal raphe nuclei induced by alkaloid extract of *Mitragyna speciosa*. *Neuroscience letters*. 2007 Apr 12;416(2):128-32.
- Swogger MT, Hart E, Erowid F, Erowid E, Trabold N, Yee K, Parkhurst KA, Priddy BM, Walsh Z. Experiences of kratom users: a qualitative analysis. *Journal of psychoactive Drugs*. 2015 Oct 20;47(5):360-7.
- Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N. Notes from the field: unintentional drug overdose deaths with kratom detected—27 states, July 2016–December 2017. *Morbidity and Mortality Weekly Report*. 2019 Apr 12;68(14):326.
- Hassan Z, Muzaimi M, Navaratnam V, Yusoff NH, Suhaimi FW, Vadivelu R, Vicknasingam BK, Amato D, von Hörsten S, Ismail NI, Jayabalan N. From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. *Neuroscience & Biobehavioral Reviews*. 2013 Feb 1;37(2):138-51.
- Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *Qjm*. 2003 Sep 1;96(9):635-42.
- Madden JT, Reyna NC, Pentkowski NS. Antagonizing serotonin 2A (5-HT_{2A}) receptors attenuates methamphetamine-induced reward and blocks methamphetamine-induced anxiety-like behaviors in adult male rats. *Drug and Alcohol Dependence*. 2020 Oct 1;215:108178.
- Singh D, Müller CP, Murugaiyah V, Hamid SB, Vicknasingam BK, Avery B, Chear NJ, Mansor SM. Evaluating the hematological and clinical-chemistry parameters of kratom (*Mitragyna speciosa*) users in Malaysia. *Journal of ethnopharmacology*. 2018 Mar 25;214:197-206.
- Sheleg SV, Collins GB. A coincidence of addiction to “Kratom” and severe primary hypothyroidism. *Journal of addiction medicine*. 2011 Dec 1;5(4):300-1.
- Philipp AA, Meyer MR, Wissenbach DK, Weber AA, Zoentlein SW, Zweipfenning PG, Maurer HH. Monitoring of kratom or Krypton intake in urine using GC-MS in clinical and forensic toxicology. *Analytical and bioanalytical chemistry*. 2011 Apr;400(1):127-35.
- Stanciu CN, Gnanasegaram SA, Ahmed S, Penders T. Kratom withdrawal: a systematic review with case series. *Journal of psychoactive drugs*. 2019 Jan 1;51(1):12-8.