The ToxIC NOSE (Novel Opioid and Stimulant Exposure)

Report #12 from ToxIC's Rapid Response Program for Emerging Drugs

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Kratom: A Dangerous Opioid Alternative

Introduction

Kratom is derived from the *Mitragyna speciosa* tree that is native to Southeast Asia. As a member of the coffee family, it has been utilized for centuries for its stimulatory and analgesic effects. Its use as a remedy for opioid withdrawal is historically rooted in Thailand around the 1940s after opium costs suddenly increased causing people to seek alternative substances.[1]

Classic opioids like fentanyl act through the mu-opioid receptor to cause euphoria, but have minor effects on serotonin release which is associated with improved mood.[2] Kratom has activity at the mu-opioid receptor, in addition to effects on serotonin, dopamine, and alpha-adrenergic receptors.[1,3,4] This wide variety of pharmacologic actions may account for some of the variability in

The ToxIC Novel Opioid and Stimulant Exposure (NOSE) Reports

Through the ongoing support of the Opioid Response Network (ORN) since 2020, the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC) has implemented an enhanced sentinel detector field within the ToxIC Core Registry to identify novel and emerging opioid and stimulant exposures. Once an emerging trend or risk is identified, ToxIC releases a quarterly report.

The goal of this project is to disseminate this novel information to the medical toxicology community as well as the ORN as part of a Rapid Response program.

For more information on the ToxIC Core Registry and data collection, please visit: www.toxicregistry.org

its clinical effects—at low doses, it seems to have more stimulatory effects while at higher doses, central nervous system (CNS) and opioid-like effects predominate.[3]

Kratom has increased in popularity within the United States since the early 2000s, coinciding with the beginning of prescription opioid regulations.[4,5] It is promoted as a "legal high," available widely, from gas stations to health food stores.[1] Claims of its benefits include energy, relaxation, euphoria, and pain control.[1] Kratom has also been marketed as a "safer alternative" to illicit opioids, and as an aid to treat alcohol or opioid use disorder.[3] However there are no randomized controlled trials that demonstrate these assertions.[1] Concerning effects associated with kratom use include high potential for dependence, opioid withdrawal syndrome, seizures, liver injury, and respiratory depression.[3,6]

This report summarizes the features of kratom exposures reported to the ToxIC Core Registry and contrasts them with classic opioid toxidromes. A specific case of kratom withdrawal is also presented to highlight the dangers of this unregulated substance.

ToxIC Data Review

Between January 2013 and April 2023, 79 cases of kratom exposures were reported to the ToxIC Core Registry (see Figure 1). All of these cases presented to a hospital and were seen by a medical toxicology physician. The median age was 33 years; there were 8 pediatric (< 18 years old) cases including 2 children under 1 years old of age. The majority of cases were in males (79.7%).

The reason for kratom exposure in over half of the cases (59.5%) was intentional. The most common sub-reason for this intentional exposure was misuse in 57.4% of cases (e.g. to elicit a pleasurable sensation/euphoria or to avoid withdrawal), followed by therapeutic intent in 23.4% of cases. Opioid withdrawal (10.1%) was another primary reason for presentation to the hospital, 87.5% of which reported no opioids as co-exposures. Almost half of patients (49.4%) had a substance in addition to kratom listed as one of their exposures as shown in Table 1.

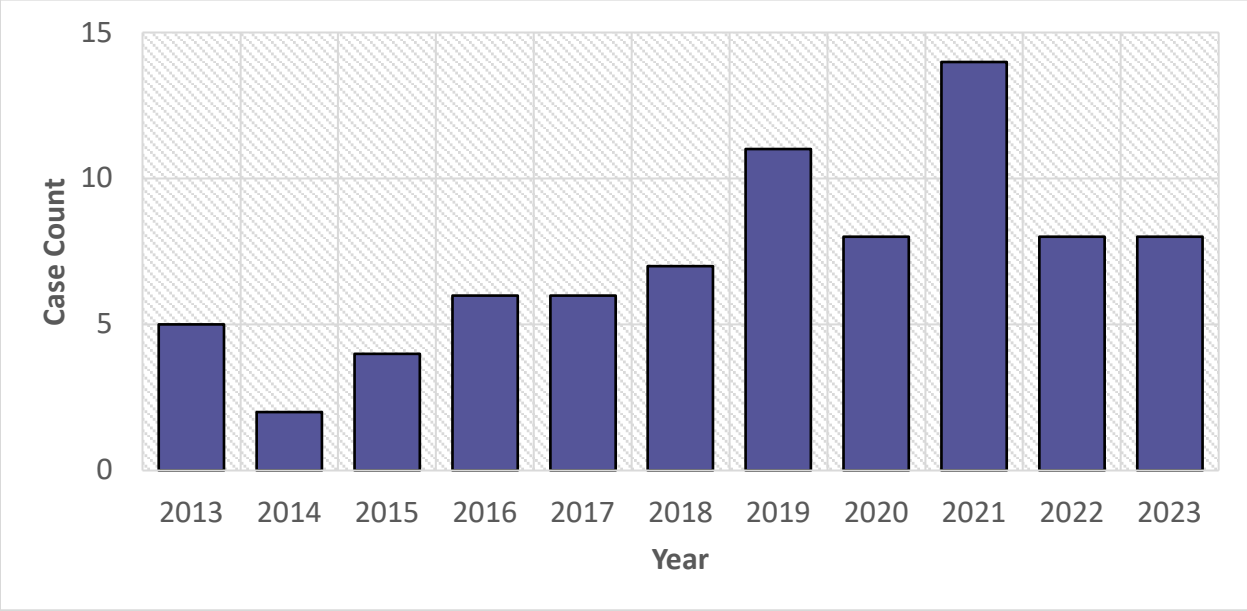
Central nervous system (CNS) effects varied widely, with 30.4% (24/79) of patients exhibiting agitation, 27.8% (22/79) exhibiting CNS depression/sedation, and 8.8% (7/79) exhibiting seizure activity. The clinical presentation of respiratory depression was reported in 15.2% (12/79) of patients. Naloxone was given to 12.7% (10/79) of the patients overall.

Several patients had case narratives in a separate description field that provided interesting insights into the clinical presentation not captured in the standard response categories. Three patients were using kratom to self-medicate their pain, one patient was using kratom to self-medicate alcohol use disorder, and one patient was described as using kratom to self-medicate their opioid use disorder. The treating medical toxicology physician specifically attributed a withdrawal syndrome to kratom discontinuation in two patients. Other adverse effects that were specifically described included two cases of kratom-related respiratory depression and another case of kratom-related cholestatic liver injury.

Table 1. Frequency of specific drug co-ingestions reported with kratom in the ToxIC Core Registry from 2013-2023

Substances reported	**Number (% total) of cases [N=79]**
Kratom + any co-ingestion	39 (49.4%)
Kratom + another opioid	12 (15.2%)
Kratom + marijuana	7 (8.9%)
Kratom + benzodiazepine	5 (6.3%)
Kratom + amphetamine or methamphetamine	5 (6.3%)
Kratom + ketamine	3 (3.8%)
Kratom + cocaine	2 (2.5%)

Figure 1. Kratom cases reported to the ToxIC Core Registry by year between 2013-2022



Case Presentation

A male infant was born at 36 weeks and 6 days to a 41-year-old female with a remote history of alcohol use disorder. Though the infant's mother was abstinent from alcohol use, she heard about a natural supplement from friends in the recovery community that would help with energy and anxiety. The supplement came as a liquid and contained a combination of natural substances that included kratom. She was drinking this product multiple times per day and was unaware of any risk of adverse effects on her pregnancy or risk of dependence. Her obstetric and gynecology (Ob/Gyn) physician became concerned with her use of kratom in pregnancy and attempted to wean her off of kratom with buprenorphine, but the mother continued to use kratom throughout her pregnancy. The mother was unable to tolerate more than a very low dose (1 mg) of buprenorphine per day due to excessive sleepiness.

On the infant's first day of life, the baby was noted to have elevated scores on the neonatal abstinence syndrome (NAS) scale for increased muscle tone, frequent crying, and poor feeding. He was started on morphine and clonidine for neonatal opioid withdrawal syndrome that was attributed to the mother's chronic kratom use and the very low dose of buprenorphine that she had been taking daily towards the end of pregnancy. When the baby was 2 days old, he developed a whole-body rash that was attributed to kava, a plant based non-opioid sedative ingredient in the supplement the mother had been taking daily. The infant's stay in the neonatal intensive care unit (NICU) was complicated by high sodium levels, seizures, and a bloodstream infection—however, he eventually made a full recovery. He was discharged from the NICU and continued to taper the morphine dose slowly as an outpatient.

Discussion

The active compounds in kratom are mitragynine and 7-hydroxymitragynine (7-HMG).[1] Both have been shown to activate the mu-opioid receptor—the same receptor responsible for the analgesic and respiratory depression effects seen with morphine, fentanyl, heroin, and other opioids.[1,3] Of these two active compounds, 7-HMG has been shown to have much higher potency at the mu-opioid receptor than mitragynine.[6] Interestingly, a chemical analysis of the powdered leaf form of kratom that is most commonly sold in the United States showed a three- to four-fold higher 7-HMG content than is found in natural leaves—a finding that suggests that some companies are artificially increasing the 7-HMG content in their formulation to create a more potent, and potentially more dangerous product.[7] This increased potency may account

for reported cases of kratom toxicity and profound withdrawal which present identically to classic opioid overdose or withdrawal syndromes.

The case above highlights a mother who did not previously have an opioid use disorder history, but tried kratom because she thought it was a natural substance that would help with her energy level and anxiety. There have been several similar case reports published of maternal kratom use causing neonatal opioid withdrawal syndrome, even in the absence of other substances known to have opioid activity.[8,9] As was described in the case presented here, many of these other cases also involved mothers who were unaware that kratom could pose a risk to the fetus. Newer techniques involving umbilical cord blood analysis for kratom may help clarify infants' exposure histories in cases where no clear-cut history of maternal drug use is forthcoming[10]—a situation that might arise due to the aggressive marketing of these products as "natural" and safe dietary supplements as opposed to psychoactive drugs with the potential to cause an opioid overdose and/or physical dependence.

Conclusion

Although benefits are reported by those who use kratom, toxicity and withdrawal syndromes have been reported to the ToxIC Core Registry in both kratom users and in infants born to mothers who used kratom regularly during pregnancy. This NOSE report highlights the importance of increased public awareness of the potential risks of kratom use.

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About the *Opioid Response Network (ORN)*:

ORN provides free, localized training and education for states, communities, organizations and individuals in the prevention, treatment and recovery of opioid use disorders and stimulant use. Learn more and submit a request at http://www.opioidresponsenetwork.org/.

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