PHARMACOTHERAPY

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BRIEF REPORT

Kratom Use and Toxicities in the United States

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Background Kratom is an herbal supplement containing alkaloids with opioid properties. This review was conducted to determine toxicities associated with kratom use in the United States in order to provide insight into its safety as a dietary supplement.

Methods We conducted a retrospective review of kratom exposures reported to the National Poison Data System to determine the toxicities associated with kratom use. We also reviewed records from a county medical examiner's office in New York State to identify kratom-associated fatalities.

Results A total of 2312 kratom exposures were reported, with 935 cases involving kratom as the only substance. Kratom most commonly caused agitation (18.6%), tachycardia (16.9%), drowsiness (13.6%), vomiting (11.2%), and confusion (8.1%). Serious effects of seizure (6.1%), withdrawal (6.1%), hallucinations (4.8%), respiratory depression (2.8%), coma (2.3%), and cardiac or respiratory arrest (0.6%) were also reported. Kratom was listed as a cause or contributing factor in the death of four decedents identified by the county medical examiner's office.

Conclusions Kratom use is increasing and is associated with significant toxicities. Our findings suggest kratom is not reasonably expected to be safe and poses a public health threat due to its availability as an herbal supplement.

Key Words opioid use disorder, opioids, kratom.

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Kratom, available as an unregulated herbal supplement in the United States, is prepared from the leaves of the Southeast Asian plant *Mitragyna speciosa*. The plant has been used for centuries in Southeast Asia by manual laborers for its stimulatory and analgesic effects.[1] In the United States, kratom has been predominantly used for self-treating pain or mood disorders.[2] Recently, kratom has gained acceptance among patients with opioid use disorder (OUD) as a practical alternative to evidence-based medication-assisted treatment, such as buprenorphine or methadone.[3,4] Anecdotal reports have posited that kratom is a safe treatment alternative to relieve opioid withdrawal, but clinical evidence to support this claim is lacking. Although a clear dose-response relationship has not been established, preliminary data suggest that lower doses of kratom produce stimulant-like effects and higher doses produce sedative effects.[5]

Mitragynine, the active component of kratom, has agonist activity at mu opioid receptors, and itself may lead to dependence and addiction.[6] Hydroxymitragynine, a minor component of kratom, also has opioid activity and is thought to be more potent than morphine. The addition of synthetic 7-hydroxymitragynine to kratom as an adulterant is thought to produce a product with more profound opioid effects.[7] A myriad of

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other alkaloids, with activity at adrenergic, serotonergic, and adenosine receptors, may produce other clinical effects, but their potency and activity are poorly understood.[5] We conducted a retrospective review of kratom exposures and associated clinical effects reported to the United States National Poison Data System (NPDS), along with a retrospective review of kratom-associated fatalities identified by a county medical examiner's office in New York State.

A kratom case was defined as any call to the NPDS reporting a human kratom exposure between January 1, 2011, and July 31, 2018. Exposures that included substances in addition to kratom in the substance list (multiple substance exposures) were excluded and the remaining exposures (single substance exposures) were reviewed for demographics and associated clinical effects. All case data, including the substance list, clinical effects, and demographics, were extracted based on NPDS case coding. A kratom death was defined as any decedent identified by the county medical examiner's office during the same time period, with kratom listed as a cause or contributory factor to the death. Postmortem toxicology results were reviewed for all decedents. Both reviews were determined to be exempt from review by our Institutional Review Board.

A total of 2312 kratom exposures were reported to the NPDS during the time frame reviewed, with an increase from 18 exposures in 2011 to 357 exposures in the first 7 months of 2018 (Figure 1). After excluding cases involving multiple substances, 935 single substance exposures to kratom were identified for review. A majority of exposures (56.5%) reported kratom being used as a tablet, capsule, or powder and nearly all exposures identified oral ingestion as the route of exposure (86.2%). Most cases reported the reason for the exposure as intentional abuse or misuse (61.6%). The most commonly reported adverse effects were agitation (18.6%), tachycardia (16.9%), drowsiness (13.6%), vomiting (11.2%), and confusion (8.1%). Severe adverse effects included seizure (6.1%), withdrawal (6.1%), hallucinations (4.8%), respiratory depression (2.8%), coma (2.3%), and cardiac or respiratory arrest (0.6%). Four cases of neonatal abstinence syndrome and two deaths were reported to the NPDS during this time frame.

A total of four decedents with kratom listed as a cause or contributing factor to the death were identified by the county medical examiner's office during the time frame evaluated. Kratom alone was identified as the cause of death in two decedents, a combination of kratom and ethanol was identified as the cause of death in one decedent, and mixed drug toxicity with kratom, clonazepam, and cocaine was identified as the cause of death in the fourth decedent. Postmortem blood mitragynine concentrations of 260 and 1400 ng/ml were reported in the two decedents where kratom was the only substance identified. These concentrations are higher than those reported in Thai individuals consuming traditional kratom tea without adverse effects.[1]

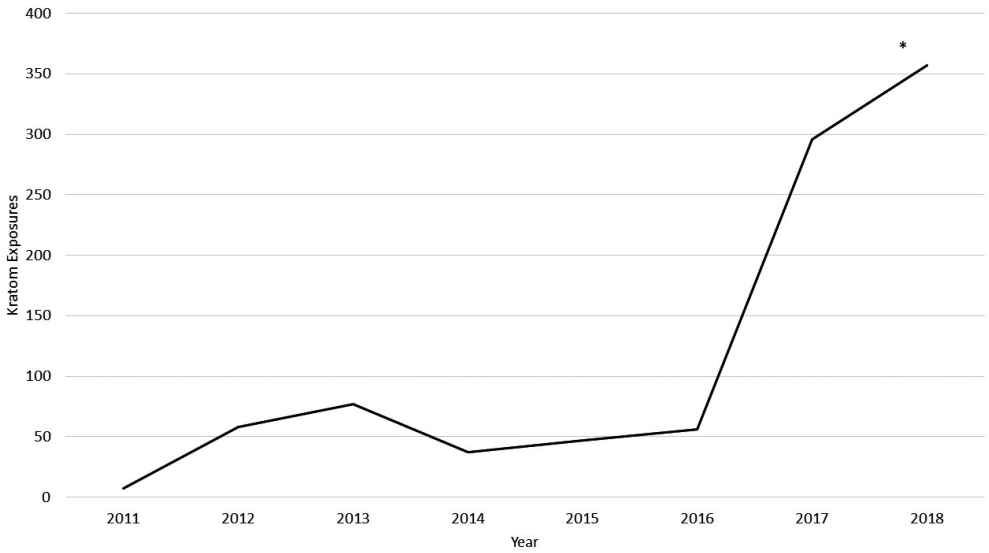

Figure 1. Kratom exposures reported to the National Poison Data System from January 1, 2011, to July 31, 2018. *Data for 2018 is partial and includes exposures from January 1, 2018, to July 31, 2018.

However, there are insufficient pharmacokinetic and postmortem data in patients using kratom for OUD to draw definitive conclusions. In the decedent with kratom and ethanol identified on postmortem analysis, a blood mitragynine concentration of 200 ng/ml and a blood ethanol concentration of 181 mg/dl were reported. In the decedent with mixed drug toxicity, a postmortem blood mitragynine concentration of 540 ng/ml was reported along with qualitative positives for blood cocaine and clonazepam.

Despite kratom's growing popularity as a safe and natural self-treatment option for patients with OUD, our findings suggest there are concerns for significant toxicity. Reports of kratom exposures to the NPDS are rising and have already been associated with serious opioid toxicities, including seizures, agitation, and death. Our county medical examiner's office has also identified four cases where kratom use appeared to contribute to the cause of death. Additionally, reports of withdrawal and neonatal abstinence syndrome suggest that kratom, similar to other opioids, can produce dependence. According to the United States Dietary Supplement Health and Education Act of 1994, herbal and dietary supplements must contain ingredients that are reasonably expected to be safe.[8] Our findings repudiate the idea that kratom meets this criterion. Kratom's opioid effects put patients at risk for withdrawal, respiratory depression, and death.

We concede that further research is needed to determine what role, if any, kratom may have in the treatment of OUD or chronic pain, and to identify the extent of kratom abuse in the United States. Of note, these data were derived from voluntarily reported exposures collected by the NPDS and a single medical examiner's office. We were not able to determine the incidence or prevalence of kratom use from this data set, and due to the voluntary nature of the reporting system, the data likely underrepresent the total number of exposures, toxicities, and deaths associated with kratom use. Data from NPDS are obtained from Poison Center coding and do not provide sufficient details to determine the circumstances surrounding the patient's reason for using kratom. Last, although examining only single substance exposures provides insight into kratom's clinical effects, it limits information on kratom's potential synergistic toxicity when taken with other substances. However, given these serious patient safety concerns and the 44 kratom-related deaths in the United States reported by the Food and Drug Administration, we agree with the United States Department of Health and Human Services that kratom's availability as an herbal supplement should be reconsidered.[9] Furthermore, kratom's rapid rise in popularity in the United States highlights the urgent need to expand access to evidence-based medication-assisted treatment for patients with OUD and to address the complex symptoms of chronic pain.

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