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Review Article

A Narrative Review of Kratom in the Emergency Department: Presentation, Diagnosis, and Treatment

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Abstract

Background: Kratom (Mitragyna speciosa), a psychoactive plant with both opioid and stimulant properties, has gained popularity in the U.S. for self-treatment of a wide range of conditions, including pain, opioid dependency, withdrawal, and mood disorders. Despite its increasing use, kratom toxicity remains poorly understood by many healthcare providers, complicating emergency care. While evidence does exist supporting the benefits of kratom for conditions such as pain and withdrawal, it remains an under-studied substance with a potential for abuse.

Objective: This review aims to summarize the current literature on kratom's pharmacology, clinical presentation, diagnostic considerations, and management in the ED.

Methods: A systematic review of case reports, observational studies, and toxicology literature will be conducted using PubMed, Embase, and Google Scholar. Relevant studies on kratom-related ED visits, adverse effects, withdrawal syndromes, and treatment strategies will be analyzed.

Discussion: Kratom toxicity presents variably, ranging from mild symptoms (tachycardia, hypertension, agitation) to severe effects (seizures, respiratory depression, hepatotoxicity). Diagnostic challenges arise due to the absence of standardized testing. Management is primarily supportive, but opioid withdrawal treatment and benzodiazepines for agitation or seizures may be necessary. The potential for drug interactions and adulterants further complicates care.

Conclusion: Kratom use poses an emerging challenge in emergency medicine, necessitating greater awareness and standardized treatment protocols. This review aims to provide ED providers with an evidence-based understanding of kratom use, its clinical effects, diagnostic challenges, and best practices for management in acute care settings.

Key words: opioid and stimulant properties; opioid dependency; mood disorders; kratom's pharmacology; tachycardia; hypertension; agitation

Introduction

Mitragyna speciosa, known colloquially as kratom, is a species of evergreen tree native to Southeast Asia. It has been used in traditional herbal medicine for hundreds of years, valued for its analgesic and stimulant properties. The leaves can be chewed fresh, dried into powders or teas, or processed into a tar-like extract. [1] At low doses, kratom has a stimulatory effect, activating dopaminergic, serotonergic and adrenergic receptors, causing users to feel increased energy and alertness. At higher doses, it acts on the opioid receptor, causing sedation, analgesia, and euphoria. [1] In the past decade, kratom has gained increasing popularity in the United States, with consumers viewing it as a "natural" alternative for common stimulant and opioid medications. It has been studied in the treatment of pain, fatigue, opioid withdrawal, diarrhea and stomach pain but has emerging popularity as a recreational substance. [2] Despite these benefits, kratom remains poorly regulated, and has been implicated in many instances of toxicity, overdose, and even withdrawal. [2] It is estimated that every year, around 2 million Americans use kratom.3 In 2023, kratom metabolites were detected in drug overdose deaths of over 1150 people. [3]

As of 2017, the Drug Enforcement Administration (DEA) has listed kratom as a drug of concern, and the Food and Drug Administration (FDA) has issued warnings regarding its potential for addiction and adverse effects. [4] Kratom is currently federally legal, but has been banned in select states such as Alabama, Arkansas, Indiana, Rhode Island, Vermont and Wisconsin. [1] Additionally, it has been banned for human consumption in a few major cities such as San Diego and Denver, while remaining legal in the rest of the respective state. In other states, it is protected by age restrictions. [1] It can be obtained at specialty shops and online, and this poor regulation and

complicated legal status contributes to variability in product purity and the potential for contamination with other substances.

Pharmacology

There are over 40 alkaloids that have been isolated from kratom, however the primary active compound found in kratom is mitragynine (MG) (66% crude mass), and the primary metabolite 7-hydroxymitragynine (7-MP) [1][5]. 7-MP has exhibited 5x higher affinity for the u-opioid receptor compared to MG, and was demonstrated to be 10x as potent in antinociception compared to morphine. [6] Speciociliatine is another commonly implicated alkaloid that is present in smaller concentrations, but appears to play a significant role in the pharmacologic effects of kratom, and has a 3-fold higher binding affinity versus MP. These alkaloids act as partial agonists at the μ-opioid receptor, and competitive antagonists at the κ- and δ opioid receptors. [7] They have also been shown to exhibit activity at adrenergic, serotonergic and dopaminergic receptors. In addition to their complex variety of central nervous system effects, kratom alkaloids have demonstrated dose dependent effects. [7] At low doses of around 1-3 g, kratom has a stimulatory effect, causing users to feel increased energy and alertness. At higher doses of 5 g and up, it exhibits opioid-like effects, causing sedation, analgesia, and euphoria. [1,7] Unlike traditional opioids, it does not initiate the β-arrestin-2 pathway that results in the respiratory depression seen with full μ-opioid agonists such as fentanyl or morphine. [7]

Kratom is hepatically metabolized and reaches peak serum concentrations in 50 minutes. It has a half-life of 2-3 hours, and is eliminated in the urine via zero-order kinetics, making the duration and severity of symptoms highly dose-dependent. The phase 1 metabolism of mitragynine to 7-MP is mediated by CYP34A, causing inhibitory effects on the P450 pathway. [7] No LD50 or TD50 for kratom in humans exists at this time, though various sources estimate that between 10 - 30 grams would be considered a high enough dose to induce adverse effects. [8]

Presentation in the Emergency Department

While proponents tout its benefits for pain relief, opioid dependence and withdrawal, and mood disorders, the increased use of kratom has led to growing concerns over toxicity, dependence, and adverse events, many of which present in the emergency department. Among single substance exposures, kratom was associated with a 34% hospitalization rate and a 57.6% rate of having a serious medical outcome. One third of exposures were for treatment of opioid withdrawal, and users are far more likely to be male (68%). [3]

Patients presenting to the emergency department (ED) with kratom overdose or toxicity often exhibit a mix of stimulant and opioid-like effects, depending on the dose consumed. At lower doses (1-5 grams), they may report anxiety, agitation, tachycardia, and hypertension, while higher doses (5+ grams) more commonly lead to sedation, confusion, nausea, and vomiting. Some patients may experience seizures, hallucinations, or altered mental status, particularly if kratom is combined with other substances such as opioids, benzodiazepines, or alcohol. In severe cases, serotonin syndrome or hepatotoxicity have been reported, though rare.

Kratom dependence has been documented, and over half of patients with 6+ months of heavy use (3-4 times a week) have shown symptoms similar to opioid withdrawal. [9] Neonatal abstinence syndrome has also been reported with prolonged kratom use during pregnancy. [10,11]

Like in any toxicity, attempting to quantify dosing and patterns of use is an important step of history taking and may help inform clinical decision making.

Laboratory Testing

Mitragynine and its metabolites cannot be detected using a standard hospital urine drug screen. However, assays can be obtained for confirmatory or forensic purposes, and may help contribute to existing literature surrounding kratom use and toxicity. Kratom alkaloids can be detected in body fluids 1-9 days after ingestion, depending on the route, volume and frequency of administration. Additionally, kratom metabolites have been successfully detected in hair samples of chronic users. [12] While hair analysis is not utilized in the ED, this remains a viable consideration from a forensic perspective.

Preferred analytical testing methods have not been well established, but typically include GS-MS or HPLC-MS using blood or urine samples. [6] These methods are highly sensitive and specific and provide the ability to separate out individual alkaloids. Despite the drawback of slower turnaround times, these methods are currently the gold standard for confirmatory testing. In some studies, ELISA testing has also shown good sensitivity and specificity for detecting kratom alkaloids. While much quicker and more inexpensive than HPLC-MS, the ELISA method is less commonly used due to poor quantification and the increased risk of error. [12,13]

While standard UDS (urine drug screens) are unable to detect kratom metabolites, they are also still indicated in instances of suspected kratom toxicity, considering the majority of toxicities involving kratom occurred in the setting of polysubstance abuse. [14] Commonly implicated substances included opioids such as fentanyl and heroin, benzodiazepines, and alcohol, and opioids are detected in an estimated 80% of kratom associated fatalities. [15] It is also important to note that kratom metabolites may trigger a false positive for the methadone metabolite EDDP on UDS. [16]

Complications

Concerning sequelae of kratom toxicity as a sole agent is not well documented, but trends have emerged over the years. Case study review shows that complications such as rhabdomyolysis, AKI, cholangitis, liver failure, and respiratory depression can occur. [5,6] Many of the fatalities in which kratom was implicated included co-ingestion of substances such as benzodiazepines, opioids, THC, and antipsychotics. [14] The phase 1 metabolism of mitragynine to 7-MP is mediated by CYP34A, inhibiting P450. [7] This is highly suggestive that kratom can exacerbate toxicities of other medications when taken in combination.

Withdrawal

Kratom is often used by patients to help manage symptoms of opioid withdrawal. However, chronic or heavy use can result in dependence and ultimately in withdrawal. Symptoms have been documented to begin within 12-24 hours of cessation, and similar to opioid withdrawal. [9] Anxiety, irritability, tremors, rhinorrhea, and myalgias are the most commonly reported symptoms. [17] Neonatal abstinence syndrome has also been reported with prolonged kratom use during pregnancy. [10,17]

Fatalities

As of 2021, kratom has been associated with a total of 152 known deaths. [18] In 65% of these deaths, fentanyl was listed as a co-ingestion, and was listed as the cause of death. The exact mechanism for which it may cause death is unknown, but it is postulated to be related to respiratory depression or seizures. More research is needed to further understand the role of kratom in fatal toxicities and polypharmacy.

Management [20]

Due to the current lack of rapid detection capabilities, confirmatory testing of kratom in acute settings is not possible, and diagnosis is clinical. Luckily, treatment for kratom toxicity is primarily supportive, and may depend on presenting symptoms. Treatment of kratom withdrawal would be similar to the treatment of opioid withdrawal.

Stabilization first. As with any acute patient, primary management should consist of stabilizing the airway, breathing, and circulation. In any patient with concerning symptoms such as respiratory depression, sedation, seizures, or hemodynamic instability, peripheral IV access and continuous cardiac monitoring should be obtained. Oxygen should be administered as indicated.

Decontamination is not indicated. Use of GI decontamination with activated charcoal is not currently recommended, since mitragynine is rapidly absorbed, and charcoal use has not been shown to have any benefits.

Respiratory Depression should be addressed quickly. Naloxone (0.8 - 2 mg IV) is recommended for use in any patient with sedation or respiratory depression, particularly considering the high rates of opioid coingestion in kratom users. Intubation should be considered for any patients with intractable respiratory depression.

Flumazenil is not indicated due to no expected benefit, and increased risk of seizures with unknown benzodiazepine coingestion.

Agitation can be managed per standard protocols. Benzodiazepines (lorazepam 2-4 mg IV/IM) can be used as needed for patients requiring pharmacological sedation. Careful monitoring of respiratory parameters is required in these scenarios due to the increased risk of respiratory depression.

Nausea and Vomiting should be managed with antiemetics such as ondansetron. IV fluids can be given to improve fluid status.

Seizures can be managed with standard treatments such as midazolam (0.2 mg/kg IM) or lorazepam (2-4 mg IV). For refractory seizures, agents such as phenobarbital or propofol can be considered. These agents are considered to have increased efficacy for toxin induced seizures.

Hepatotoxicity typically resolves after cessation of use.

Disposition

Patients that are cardiovascularly stable, alert and oriented, and without concerning signs and symptoms, may be observed for 4-6 hours and discharged following an ambulation trial. [20]

Patients with respiratory or hemodynamic instability, or with toxic co-ingestions, should be monitored in a critical care setting. Any patient who has suffered a seizure related to kratom use should be monitored for a minimum of 24 hours prior to discharge. [20]

Kratom use disorder, including management of withdrawal symptoms, can be managed with buprenorphine. Limited evidence exists to date for dosing in the setting of kratom withdrawal, however maintenance doses of 4-8 mg have shown efficacy. [19] In patients who decline buprenorphine, clonidine can be used to mediate withdrawal symptoms. [19]

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Case Studies:

Case Citation	Patient demographics	Co-Ingestion	Signs and Symptoms	Outcome
Tobarran N, Wolf C, Cumpston KL, Wills BK. Pressure Necrosis Requiring Fasciotomy After Kratom Overdose. *J Addict Med*. 2022;16(2):252-253. doi:10.1097/ADM.0000000000000873	31 YOM	None	Sedation, loss of consciousness, compartment syndrome	Treatment for rhabdomyolysis, AKI, acute hepatic injury, discharge after 18 days.
Sangani V, Sunnoqrot N, Gargis K, Ranabhotu A, Mubasher A, Pokal M. Unusual Presentation of Kratom Overdose with Rhabdomyolysis, Transient Hearing Loss, and Heart Failure. *J Investig Med High Impact Case Rep*. 2021; 9:23247096211005069. doi:10.1177/23247096211005069	45 YOF	None	Lethargy, confusion, transient hearing loss, right LE swelling and pain.	Treatment for rhabdomyolysis, compartment syndrome, AKI, liver dysfunction, cardiomyopathy.
Shi T, Shea JL. A case of fatal overdose involving both hydromorphone and kratom. J Forensic Sci. 2024;69(1):355-358. doi:10.1111/1556-4029.15394	44 YOM	Hydromorphone, olanzapine	Found deceased with abdominal ascites > 4L	Tox screen showing 79 ng/mL of hydromorphone, 560 ng/mL of mitragynine, and 240 ng/mL of olanzapine
Hughes RL. Fatal combination of mitragynine and quetiapine - a case report with discussion of a potential herb-drug interaction. *Forensic Sci Med Pathol*. 2019;15(1):110-113. doi:10.1007/s12024-018-0049-9	27 YOM	Quetapine	Found deceased with autopsy evidence of hyperthermia and seizure activity	Tox screen with fatal levels of quetiapine in the presence of mitragynine suspected secondary to altered pharmacokinetics.
Matson M, Schenk N. Fatality of 33-Year-Old Man Involving Kratom Toxicity. *J Forensic Sci*. 2019;64(6):1933-1935. doi:10.1111/1556-4029.14082	33 YOM	Caffeine, cotinine, naloxone, THC	Found unresponsive, unable to resuscitate.	Tox screen with 1.9 mg/L mitragynine suspected toxicity
Kapp FG, Maurer HH, Auwärter V, Winkelmann M, Hermanns-Clausen M. Intrahepatic cholestasis following abuse of powdered kratom (Mitragyna speciosa). *J Med Toxicol*. 2011;7(3):227-231. doi:10.1007/s13181-011-0155-5	25 YOM	None	Presented 10 days after stopping 2 weeks of kratom ingestion with subjective fever, chills, abdominal pain, jaundice, pruritis. *14-21 g /day	Patient treated for intrahepatic cholestasis with full recovery
Allison DR, Mubarak M, Sharma N, Rao DS. Kratom (*Mitragyna speciosa*)-Induced Hepatitis. *ACG Case Rep J*. 2022;9(4): e00715. Published 2022 Apr 7. doi:10.14309/crj.0000000000000715	23 YOM	THC	Jaundice, pruritis, pale stool, dark urine, diffuse abdomnal discomfort, fatigue and bruising.	Hepatitis (DILI) with resolution after 3 months.

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