

Kratom use: Overview, risks and cautions

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Dear Editor,

Kratom refers to products sourced from the leaves of the *Mitragyna speciosa*, a tropical tree of the same name in Southeast Asia¹. The leaves are typically ingested by brewing them as a tea or pulverizing them into a powder to be taken in a capsule or mixed into food or drink², but it may be sold in a concentrated extract, as well^{1,3}.

This drug has been used for hundreds of years in Southeast Asia for multiple indications, including fatigue, anxiety, analgesia, diarrhea, cough, and depression. It is also used in some ceremonies and social gatherings¹. This plant is noted to have a mixture of both stimulant and opiate-like properties, that appears to be dose-dependent, with individuals reporting stimulant effects at low doses and opioid effects at higher doses⁴.

Pharmacology

Kratom contains more than 40 alkaloids within its leaves but the main chemical component that has been noted in this plant is mitragynine and its active metabolites, like 7-hydroxymitragynine (7-HMG)^{2,3}. These alkaloids are primary opioid agonists associated with mu, delta, and kappa opioid receptors. Mitragynine is metabolized in the liver to 7-HMG, which has 46 times more affinity for opioid receptors than mitragynine and 13 times more affinity than morphine. One important distinction between typical opioids and kratom is that the alkaloids in kratom do not initiate the beta-arrestin pathway. The beta-arrestin pathway is implicated in causing several adverse reactions from opioids, including respiratory depression, sedation, and constipation².

In addition to activity on opioid receptors, these constituents may also stimulate alpha-2 adrenergic receptors and antagonize 5-HT₂ receptors. Outside the central nervous system, these components may block hERG channels in the

heart, leading to cardiotoxicity³.

Kratom alkaloids are hepatically metabolized via CYP3A4, CYP2D6, and CYP2C9⁵, which increases the potential for significant drug interactions. The half-life of kratom is reported to be 3 hours^{2,5}.

Clinical manifestations

Symptomology associated with kratom has been shown to be dose-dependent. At lower doses, individuals often report stimulant effects like increased alertness, energy, and increased heart rate³. This may be accompanied by other feelings of anxiety and agitation³. As the dose increases, individuals tend to experience opioid-like effects, including pain relief and euphoria³. However, they may experience the side effects of constipation, nausea, and sedation. Chronic use of high-dose kratom has been associated with hyperpigmentation of the cheeks, anorexia, weight loss, tremor, and addiction⁴. Chronic use may also increase the risk of damage to the liver¹.

Toxicity and overdose may occur when patients consume more than 8 g of kratom². Symptoms associated may vary, however, when such large doses are taken, the patient may present with confusion, tremors, high blood pressure, decreased respiratory rate, nausea, and vomiting¹. Multiple organ systems may be affected when kratom is taken in toxic doses. Hepatotoxicity, cardiotoxicity, lung injury, kidney injury, seizure, and coma have all been reported.

Additionally, the additive effects on adolescent's concomitant use with tobacco, marijuana and other substances are unknown⁶.

Potential for addiction and withdrawal

Despite some public belief that kratom is not addictive, there are many reports of individuals becoming dependent

on this substance⁷. Physical dependence may occur to the point where individuals may develop tolerance to kratom and experience withdrawal symptoms when they are not able to utilize the substance⁷. The symptoms of withdrawal often present similarly to opioid withdrawal and may include agitation, irritability, nausea, decreased appetite, hypertension, sweating, hot flashes, severe body aches and muscle pains, diarrhea, and difficulty sleeping⁷. There have been reports of using dihydrocodeine (an opioid agonist) and lofexidine (an alpha-adrenergic antagonist) to manage withdrawal; however, no treatments have been thoroughly studied for the indication of managing kratom withdrawal⁴. Nevertheless, kratom withdrawal can be extremely uncomfortable for patients, and patients will often need medical care to manage symptoms and prevent relapse³.

Prevalence of use and legality

The Drug Enforcement Administration (DEA) does not classify kratom or its active ingredients as a controlled substance in the United States Controlled Substance Act at this time². While it is not classified as a controlled substance, the Food and Drug Administration (FDA) does warn against its use. To our knowledge, there are currently no drug products marketed that contain kratom or its active components in the United States and the FDA has concluded that kratom is not appropriate for use as a dietary supplement⁹. There is insufficient evidence to show its safety as a supplement and it has the potential to cause adverse effects⁸. It is not legally sold as a drug product, food additive, or supplement in the United States⁹. While some states in the United States have made kratom illegal (Alabama, Arkansas, Indiana, Tennessee, Vermont, and Wisconsin, as of 2024), kratom is widely available in most states via online purchase or in person in stores, including gas stations, dispensaries, tobacco retailers, and drug paraphernalia stores or 'head shops'⁹. Outside the United States, kratom use is on the rise in Europe⁵. The legal sale and use of kratom varies between the countries of Europe. Poland, Ireland, and Romania have laws prohibiting the sale and use of kratom; however, most countries in Europe do not regulate its use and it can be easily purchased⁵.

There has been a noted increase in the prevalence of kratom use in the United States. Between 2011 to 2017, there were over 1800 calls to the poison control centers regarding kratom use. In 2011, there were 13 calls regarding this substance, while in 2017 there were 682 calls¹⁰. This illustrates a dramatic increase in use. In 2021, 1.7 million people reported using kratom in the last year¹¹, which is likely an underestimation of actual use. These data suggest that many patients that healthcare providers interact with may have used this substance in the past or are currently utilizing it. Concerning is the increased prevalence of users in the adolescent population, reports include 68000 users in 2019⁶.

There are multiple reasons why people may be using

kratom. It is often used as a recreational drug and may create feelings of happiness or euphoria³. Individuals may view it as an alternative option to opioids. People may be using this drug to self-medicate for symptoms of pain³, anxiety, or depression¹, or as a treatment for opioid dependence and withdrawal^{1,2}.

Role of the healthcare provider

With the increased prevalence of kratom use in the United States, it is exceedingly important for healthcare providers to be knowledgeable on this subject. Providers play a major role in identifying kratom use in patients, referring them for further care, and educating both the public and other healthcare providers about this drug. When patients inquire about the safety of kratom use, providers should counsel them on the potentially harmful effects of this drug. Providers should dispel any public belief that kratom is a safe alternative to opioids, as the FDA reports it is unsafe to use as a dietary supplement or as a treatment modality at this time. Patients who have a current opioid addiction should be referred to a provider or treatment facility to receive FDA-approved treatment for addiction and withdrawal symptoms from opioids. They should be discouraged from self-treatment with kratom. Healthcare providers can identify signs and symptoms of kratom use and identify when patients may need medical care for toxicity, addiction, or withdrawal. School counselors and behavior health providers are in a unique position to monitor and educate students about kratom use and toxicity potentials.

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CONFLICTS OF INTEREST

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