

Kratom: What we know, what to tell your patients

Educate patients about the risks of this increasingly popular but unregulated substance

M*itragyna speciosa*, better known as kratom, is a tropical evergreen tree that is native to Southeast Asia. Botanically, it is a member of the Rubiaceae family, as is the coffee plant, and physical laborers among indigenous populations have historically chewed the leaves or brewed them as a tea to improve endurance and reduce fatigue.¹ Kratom is psychoactive; small amounts (up to 5 g of plant material) possess stimulant properties, while larger doses (>5 g) produce opioid-like, sedative, euphoric, and antinociceptive effects.²

In recent years, kratom has gained popularity in Western parts of the world due to its unique properties and perceived safety as a botanical product. Individuals may use kratom to boost their energy, relieve pain, or treat a wide range of physical or mood problems. Increasingly, kratom is being used by people who abuse opioids to self-manage opioid withdrawal, or for its euphoric effects. But kratom carries several important risks, including addiction, serious adverse effects, and possibly death. In this article, we review the epidemiology and pharmacology of kratom, and provide some guidance for educating patients about this substance.

Widely used but not FDA approved

Although kratom is not regulated or approved by the FDA, 3 to 5 million Americans use it regularly.³ According to an

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M. SOMCHAI/SHUTTERSTOCK

Cornel N. Stanciu, MD, MRO, FASAM, FAPA

Assistant Professor
Dartmouth's Geisel School of Medicine
Hanover, New Hampshire
Director of Addiction Services
New Hampshire Hospital
Concord, New Hampshire

Bryan G. Hybki, MD

PGY-4 Psychiatry Resident
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire

Thomas M. Penders, MS, MD

Affiliate Professor
East Carolina University Brody School of Medicine
Attending Psychiatrist
Walter B. Jones Alcohol and Drug Abuse Treatment Center
Greenville, North Carolina



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Chronic kratom use can result in weight loss, insomnia, constipation, dehydration, skin hyperpigmentation, and extreme fatigue



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Box

The legal status of kratom

The use and sale of kratom is illegal in several countries, including Australia, Poland, Denmark, Sweden, Malaysia, and Vietnam. In the United States, kratom was legal to grow and purchase in all 50 states until 2015, when the Drug Enforcement Administration (DEA) identified kratom as a “substance of concern.” In August 2016, the DEA submitted a notice of intent to place mitragynine and 7-hydroxymitragynine, 2 alkaloids of kratom that have opioid-like properties, into Schedule I of the Controlled Substance Act; however, due to significant public pressure, the DEA withdrew the request in October 2016.

As of February 2020, kratom was illegal to buy, sell, or use in Wisconsin, Rhode Island, Vermont, Indiana, Arkansas, Alabama, specific counties of some states, and the District of Columbia. Legislation was pending in New York, Missouri, and Louisiana.

Source: Reference 5

internet survey, kratom users are mostly college-educated, employed white men, age 31 to 50, who take the substance to manage pain or to treat general anxiety and mood disorders.⁴ Some individuals use kratom as an opioid substitute to reduce symptoms of opioid withdrawal.⁴

Kratom is available from a wide range of manufacturers in various formulations, including powders, tablets, liquids, and gum. It is sometimes sold in combination with other agents as a single product. Low-cost, over-the-counter kratom products are available as “dietary supplements” in retail stores or online. Although the product packaging sometimes recommends a specific dose, the amount of active ingredients (as well as other agents) is unknown. Kratom is illegal in several states (*Box*⁵).

The 2 alkaloids of interest

More than 40 alkaloids have been isolated from kratom leaves. The proportions of these alkaloids vary significantly depending on the environment in which the plant is grown, the breeding and harvesting techniques, and the age of the plant.⁶ Two

alkaloids of significant interest are mitragynine (*Figure 1, page 39*) and 7-hydroxymitragynine (*Figure 2, page 39*), both of which are unique to *M. speciosa* and have opioid-like properties. Administering these alkaloids to morphine-dependent rats resulted in cross-tolerance and precipitated withdrawal when the rats were given naloxone.⁷ The potency of kratom at the mu opioid receptor has been found to exceed that of morphine.

Competitive binding studies that examined the affinity of mitragynine and 7-hydroxymitragynine at the various opioid receptor subtypes found a preference for the kappa receptors (antagonism), followed by mu (partial agonism), and lastly delta. This profile of mitragynine is very similar to that of buprenorphine.⁸ The affinity of 7-hydroxymitragynine for the mu receptor (agonism) is significantly greater than that of mitragynine.⁹ Mitragynine also interacts with noradrenergic and serotonergic pathways by stimulating postsynaptic alpha-2 adrenergic receptors and inhibiting 5-HT_{2A} receptors.⁹ These properties are responsible for kratom’s ability to manage opioid withdrawal symptoms, which are generally attributed to a hyperactive noradrenergic system. There also is evidence that the hepatic metabolite 7-hydroxymitragynine is important in mediating the analgesic component of mitragynine.¹⁰

The initial effects of kratom typically begin within 10 to 20 minutes of consumption, and the full effects are experienced in 30 to 60 minutes.¹ The half-life of mitragynine in humans has not yet been determined, but is believed to be relatively short.¹¹ In rats, the half-life of mitragynine is 2 to 3 hours.¹² Individuals who use kratom to prevent opioid withdrawal have reported taking it as often as every 6 to 12 hours.¹³

Metabolism of mitragynine is predominantly carried out through cytochrome P450 (CYP) 3A4, with minor contributions by 2D6 and 2C9. A total of 13 metabolites are produced, including 7-hydroxymitragynine.¹⁴ Kratom’s constituents also interact with the CYP system, inhibiting 2C9, 2D6, and 3A4 isoenzymes, and to some extent, 1A2.

Figure 1

Chemical structure of mitragynine

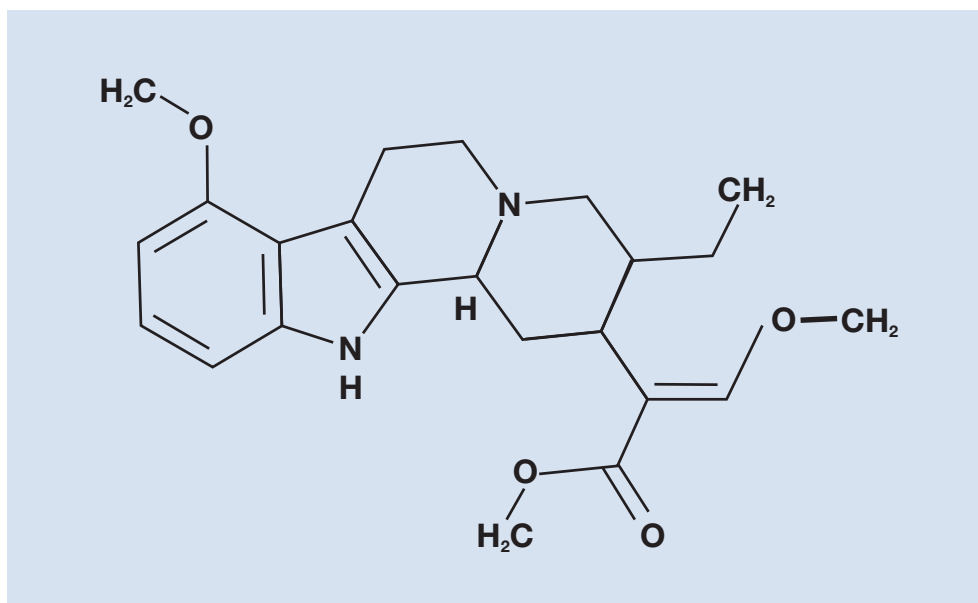
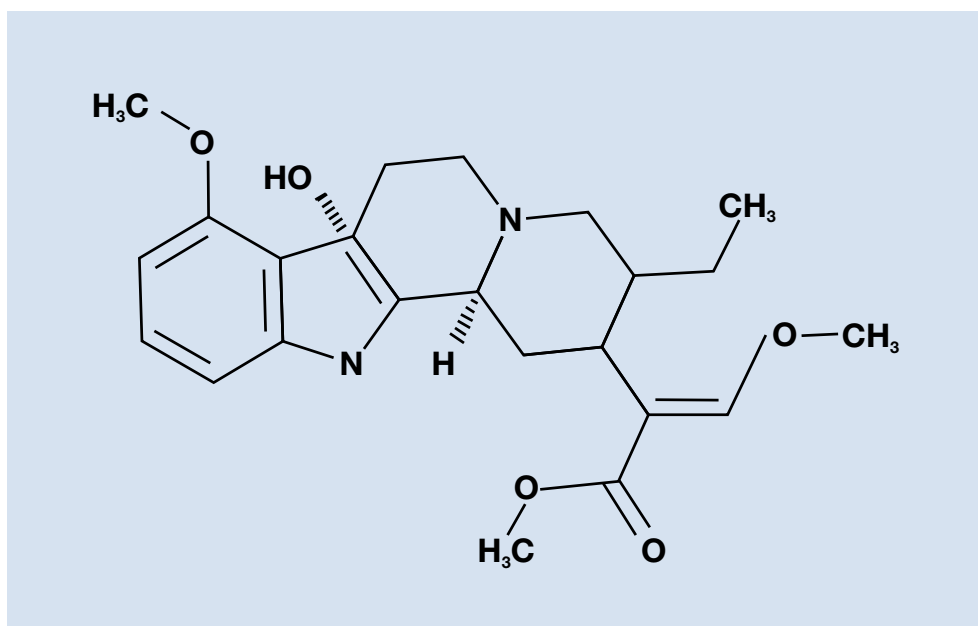


Figure 2

Chemical structure of 7-hydroxymitragynine



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As of February 2018, the FDA had received reports of 44 deaths associated with kratom

Adverse effects can be fatal

An animal study revealed that when administered intravenously, mitragynine and 7-hydroxymitragynine have a similar toxicity profile to heroin.¹⁵ When these alkaloids were administered in ascending doses, increases in blood pressure and elevations in liver function tests

and creatinine levels from baseline were observed.

Chronic kratom use can result in weight loss, insomnia, constipation, dehydration, skin hyperpigmentation, and extreme fatigue.¹⁶ There have also been reports of seizures, delusions, hallucinations, respiratory depression, hepatotoxicity, coma, and



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Abrupt discontinuation of high-dose, long-term kratom use can produce withdrawal symptoms

death.^{17,18} An emerging concern is the potential development of fatty liver infiltrates leading to cholestatic liver damage.¹⁹⁻²⁵ One case report described a young man who developed a serum aspartate aminotransferase level of 1,300 IU/L (reference range: 5 to 45 IU/L) and a serum alanine aminotransferase level of 3,700 IU/L (reference range: 5 to 60 IU/L) after he ingested a kratom product.²⁶ Histologically, the pattern of liver injury mimics primary biliary cholangitis.²⁷

In recent years, calls to poison control centers in the United States related to kratom exposure have risen. Between 2011 and 2017, the number of calls increased from 1 a month to 2 each day.²⁸ The US National Poison Data System has also noted an increase in the number of calls in reference to kratom. It received 2,312 calls from January 2011 through July 2018, with 18 calls occurring in 2011, and 357 within the first 7 months of 2018.²⁹

As of February 2018, the FDA had received reports of 44 deaths associated with kratom.³⁰ There have been reports of fatal overdoses involving kratom, particularly when kratom is co-ingested or used with adulterated and/or combination agents, including one case that involved quetiapine.³¹⁻³³ There have been reports of deaths believed to be attributed to the use of kratom alone; in one such case, a 35-year-old man experienced a fatal cardiac arrest due to kratom use with no other coingestants.³⁴ Among the reports of deaths in which kratom was the only substance consumed, the mitragynine blood levels of the deceased individuals were found to be higher than the levels associated with individuals who had consumed traditional kratom teas.²⁹

There is a lack of quality control of commercially available kratom preparations. The FDA has found kratom products that exceeded the level of safe exposure to nickel and lead.³⁵ There have also been reports of Salmonella outbreaks associated with kratom products.³⁶

Detecting kratom use

Mitragynine is a lipophilic alkaloid that is poorly soluble in water³⁷ and eliminated

primarily in urine.¹² Based on data from treatment center admissions, kratom can be detected in urine samples for 5 to 6 days after use.^{24,38,39} However, kratom is not detectable by a standard urine toxicology screen; therefore, a high degree of suspicion and special confirmatory testing are necessary. The breakdown products of mitragynine can be detected through gas chromatography coupled with mass spectrometry (GC/MS), liquid chromatography with linear ion trap mass spectrometry, or electrospray tandem mass spectrometry.⁴⁰⁻⁴²

A familiar withdrawal syndrome

Abrupt discontinuation of high-dose, long-term kratom use can produce withdrawal symptoms.¹³ Symptoms of kratom withdrawal resemble those of opioid withdrawal. These include physiological symptoms (mydriasis, nausea, sweating and chills, muscle and body aches, tremors and twitches, diarrhea, rhinorrhea, and lacrimation) and psychological symptoms (insomnia, restlessness, irritability/hostility, fatigue, anxiety, mood disturbances, and hallucinations).¹³ Symptoms are first noted starting 12 hours after the last use of kratom, and can last up to 7 days.⁴³ Withdrawal intensity has been positively correlated with the daily amount of kratom consumed, as well as the duration and frequency of use.^{13,16}

In 2 case reports, the newborns of women who used kratom during pregnancy experienced neonatal abstinence syndrome.^{44,45} In these 2 reports, symptoms such as jitteriness, irritability, feeding intolerance, and vomiting emerged on postpartum Day 2. The newborns were admitted to a neonatal ICU and started on a standard opioid protocol with IV morphine and subsequently tapered with an oral formulation over 5 days.^{44,45}

Helping patients who use kratom

The best approach to treating a patient who is experiencing kratom withdrawal is symptomatic management, as would be appropriate for a patient experiencing opioid withdrawal.¹³ However, the use of agents such as methadone or buprenorphine

for patients undergoing kratom withdrawal has not been thoroughly evaluated; very few reports have been published.^{46,47}

Similarly, while the standard of care for treating a patient with opioid use disorder is medication-assisted treatment in combination with counseling and behavioral therapies, there is little evidence on the efficacy of such treatments for patients who use kratom. There are no specific guidelines, and the risk of relapsing to kratom use is high.^{48,49} Nonetheless, some clinicians have used the same protocol for patients with opioid use disorder to treat patients using kratom, and several published case reports describe this approach.^{50,51} Because administering buprenorphine/naltrexone to a patient who is dependent on kratom can precipitate withdrawal, clinicians should follow a similar initiation protocol as for opioid dependence when starting a patient on these agents (ie, a washout period with a challenge test would be prudent prior to starting naltrexone).

In cases of kratom overdose, naloxone has been shown to reverse the analgesic effects of mitragynine in rats. However, in a case report of an individual who accidentally overdosed on a kratom product, naloxone had a modest effect.⁵²

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Related Resources

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Drug Brand Names

Buprenorphine • Subutex, Sublocade	Methadone • Methadose Naltrexone • Revia
Buprenorphine/naltrexone • Suboxone	Naloxone • Narcan Quetiapine • Seroquel

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continued

Clinical Point

Some clinicians have used the same protocol for patients with opioid use disorder to treat patients using kratom

Bottom Line

Kratom is a botanical substance that acts like a stimulant at low doses and an opioid at higher doses. Patients might use it to treat mood-related symptoms, relieve pain, or manage opioid withdrawal. Kratom use has been associated with the development of addiction as well as a multitude of serious adverse effects, including hepatotoxicity and overdose. Long-term management may be required for a patient who uses kratom.



Teaching patients about kratom

Clinical Point

In a case study, naloxone had a modest effect in reversing kratom overdose

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