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Think Kratom Is a Safe Opioid Substitute? Think Again!

History, Evidence, and Possible Future for Mitragyna speciosa

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I work in a busy rural freestanding ED. The prescription opioid crisis has had significant impact on our community. Several times last month, I had patients who reported using kratom. It seems easy to obtain, and patients report kratom is as effective as morphine and safe to use. What do we know about this substance? Will this herb become a substitute for opioids? Is kratom safe?

Whether for pain relief or as part of religious rituals, use and abuse of plant-based chemicals are woven throughout human history.¹ Emerging in the shadows of the current prescription opioid crisis is kratom; well known in Asia and finding a foothold in Western Europe and the United States. Those who treat patients for pain and opioid addiction need to become familiar with this unregulated opioid receptor agonist with significant abuse potential and risk.²

Kratom is an unscheduled opioid receptor agonist often marketed as a dietary supplement. Active alkaloids isolated from kratom such as mitragynine and 7-hydroxymitragynine act on μ - and δ -opioid receptors, as well as α -2 adrenergic and 5-HT_{2A} receptors. Although the US Food and Drug Administration (FDA) has banned its use as a dietary supplement, kratom continues to be widely available and much less expensive than buprenorphine. At this time, there is no evidence to support kratom as a safe alternative for opioid addiction.^{1,2}

The United Nations Office on Drugs and Crime has issued warnings regarding the emerging threat of new

psychoactive substances (NPSs) derived or modified from natural elements. Although most NPSs are composed of synthetic chemicals and identified as “bath salts” or “designer drugs” and even “legal highs,” a currently common NPS derived from natural elements is kratom.¹ Kratom (*Mitragyna speciosa* Korth belonging to the Rubiaceae coffee family) is a tropical tree native to Southeast Asia, the Philippines, and New Guinea. Considered by some as an opioid substitute, leaves contain numerous phytochemicals including flavonoids, polyphenols, and various glycosides. Mitragynine is the major component, and amount varies with the location and season for growth; mitragynine is approximately 13 times more powerful than morphine. Kratom grown in Southeast Asia has a higher mitragynine content.¹

First reports of kratom use for the treatment of opium addiction date back to 1836. Reported benefits include analgesic, anti-inflammatory, and antipyretic effects. Recreational use of kratom has now spread widely across Europe and in the United States because of easy access via the Internet and because kratom's main alkaloid component mitragynine is not yet a controlled drug, unlike its derivative 7-hydroxymitragynine, which is a controlled substance in several countries outside the United States.³

Kratom has a long history of being sold as a dietary supplement, an opium substitute, and for the relief of fatigue for many years in Southeast Asia. Despite the FDA ban on the importing of kratom, use in the United States has increased as evidenced by increasing numbers of calls to poison control centers from 2010 to 2015 and reported use of kratom in combination with benzodiazepines, narcotics, and other substances.⁴ Even though possession of kratom leaves has been illegal in Thailand since the 1943 and banned in Malaysia, illicit use is also increasing.⁵

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Kratom leaves are usually ingested by chewing 10 to 30 fresh leaves a day or consuming dry powdered leaves directly or brewed as a tea. Kratom is rarely smoked.¹ Effects in humans are dose dependent. Small doses produce stimulatory effects like cocaine or amphetamines, whereas large doses are associated with sedative-narcotic effects similar to opioids. Pharmacology is complex with actions on dopaminergic, serotonergic, GABAergic, and adrenergic sites. Mitragynine acts on μ -, κ -, and δ -opioid receptors with high protein binding and hepatic metabolism. Half-life is variable depending on purity of the extract and individual factors.^{2,5} Low doses (approximately 1-5 g of fresh leaves) combat fatigue and improve working endurance. Approximately 5 to 15 g of fresh leaves acts as an opium substitute for opium addiction used for self-treatment of withdrawal symptoms. If taken at very high doses (>15 g), persons report an onset of sedation with hypnotic effects and stupor experiences, such as those associated with by opioid consumption.³ Hypertension, renal toxicity, impaired cognitive function and behavior, and liver injury are associated with repeated use of kratom. Withdrawal symptoms include tremor, anorexia, weight loss, decreased libido, insomnia, muscle spasms and pain, fever, diarrhea, and psychosis.^{1,5}

UNEXPECTED ASSOCIATED RISKS

Kratom products are marketed as leaves, pills, capsules, powder, and tea. Names for kratom identified by the US Drug Enforcement Administration (DEA) include *Mitragyna speciosa*, *mitragynine extract*, *biak-biak*, *cratom*, *gratom*, *itbang*, *kakuam*, *katawn*, *kedemba*, *ketum*, *krathom*, *krton*, *mambog*, *madat*, *Maeng da leaf*, *nauclea*, *Nauclea speciosa*, or *thang*, and kratom may be added to other products without identification in the labeling.⁶

The Centers for Disease Control and Prevention and FDA with state and local health officials continue to evaluate a dangerous multistate outbreak of salmonellosis from multiple serotypes of *Salmonella*.^{4,6} Findings indicate that kratom and products containing kratom were the likely sources for the outbreak. Thirty-eight persons aged 1 to 73 years were hospitalized with no deaths reported. Fifty-seven of 78 persons reported consuming kratom before becoming ill; most using Maeng da red vein kratom. As of April 5, 2018, 132 people in 38 states have been infected.⁶

As a result, the FDA issued mandatory recall orders for products containing powdered kratom concomitant with voluntary recalls by multiple companies across the United States. The high frequency of multiple *Salmonella* serotypes discovered with the recall is a serious health concern. As of April 19, 2018, of 66 samples analyzed from distributors and retail locations of interest, 33 were found positive for 1 or more strains of *Salmonella*. Consumers need to know the difficulties in tracking kratom

entry into the United States and the lack of industry standards for kratom purity and manufacturing. Considering the high rate of *Salmonella*-positive cases found in recent product testing, the FDA cannot provide any assurance that available kratom products are not contaminated with *Salmonella*.⁶

LOTS OF SELF-REPORTS AND NO HARD EVIDENCE

An anonymous online survey was conducted in October 2016 of 10 000 current kratom users through available social media and from the American Kratom Association (<https://speciosa.org/home/>); 8049 respondents completed the survey. Investigators found that kratom was primarily used by a middle-aged (31-50 years) males (56.91%) with income \$35 000 or higher with private insurance (61.31%). Kratom was used to self-treat pain (68%) and emotional or mental conditions (66%) and for withdrawal symptoms associated with prescription opioid use. Subjects (40.05%) reported discussing kratom use with their physician, nurse, or pharmacist. Subjects reported dose-dependent nausea and constipation with high doses (5g) and with and frequent dosing (≥ 22 doses/wk).⁷

Persons consuming kratom for prescription drug dependency withdrawal were 21 years or older, having Medicaid or no insurance, and earning \$35 000 to \$49 999 a year. Persons 41 years or older, self-employed, or a student, or having a bachelor's or graduate degree and earning 75 000 or more were associated with significantly lower probability for kratom use. Self-reported beneficial effects included decreased pain (85.1%), increased energy (83.75%), and less depressed mood (80.00%).⁷

Subjects reported withdrawal symptoms within 12 to 48 hours of kratom discontinuation. Toxicity symptoms with use were reported by 42.55% of the sample, rated as 2 (40.40%) or 3 (36.13%) on a 5-point Likert scale, with 1 being very severe and 5 being not severe at all.⁷

In another review of studies related to kratom use and mental health published between January 1960 and July 2017, limited evidence suggested kratom as a potential harm reduction tool, particularly as an opioid substitute for persons with addiction. Reports by users that kratom reduces pain, enhances mood, and relieves anxiety suggest a deeper pharmacological evaluation is needed. Weak evidence suggests that withdrawal symptoms may be mild relative to those of opioids. However, users describe withdrawal from kratom is very uncomfortable, and maintaining abstinence is difficult.⁸

POLICY, RULES, PROTEST

In August 2016, the DEA issued a notice of intent to temporarily classify the 2 psychoactive chemicals contained in kratom (mitragynine and 7-hydroxymitragynine) as Schedule I drugs.¹¹ Schedule I designated drugs are defined as having high potential for abuse and potential to

create severe psychological and/or physical dependence.^{4,9,10} This announcement sparked protest from patients and advocacy groups including the American Kratom Association and Botanical Educational Alliance, who claimed kratom was safer for opiate withdrawal and chronic pain than prescription agents with lower numbers of deaths.¹⁰ On September 13, 2016, a demonstration took place at the White House in Washington, DC, and a petition with more than 130 000 signatures was sent to President Barack Obama. Advocates including congressional representatives and senators provided petition letters to the DEA to reconsider the kratom classification scheduled to begin September 30, 2016. In response to these public challenges, on October 12, 2016, the DEA withdrew the intent, placing the intent on hold, citing the need for a scientific evaluation by the FDA.^{9,10,12}

On November 14, 2017, the FDA issued a public health advisory related to mounting concerns regarding the risk associated with kratom and reported deaths with use. While the FDA continues to evaluate evidence, consumers are warned not to use any products labeled as containing the botanical substance kratom or its psychoactive compounds, mitragynine and 7-hydroxymitragynine.⁴ At this time, the FDA has not approved kratom for any medical use, and the DEA lists kratom as a drug and chemical of concern.¹³

WHAT NOW?

Kratom is an emerging public health threat.¹⁴ Patients need to understand that “legal” and “available” are not the same as “safe.” Although it is possible that kratom metabolites could be developed into new agents in the future, serious adverse events need to be avoided now.⁵ Evidence suggests that kratom is widely used in the United States. Danger lies in the lack of regulatory controls, production standardization, and sale of adulterated kratom products contaminated with potentially toxic and infectious substances.⁹ Claims for a less expensive nonprescription alternative opioid coupled with easy Internet access are placing patients and prescribers at serious risk. Prescribing pain or opioid substitution therapy to a regular kratom user can have deadly consequences related to lethal mixes of metabolites. Preclinical findings, case reports, and online anecdotal reports suggest kratom is not safe and is associated with drug dependence, withdrawal, and serious adverse events with multidrug or alcohol use.¹⁴

Given the widespread use of kratom and social media attention, it is important for clinicians to be knowledgeable and add to clinical evidence.⁹ While the FDA evaluates safety information regarding the effects of kratom, healthcare professionals and consumers are encouraged to report any adverse reactions to the FDA MedWatch program at www.fda.gov/medwatch/report.htm.

At this time, methadone and buprenorphine are prescribed substitutes for oxycodone and heroin. Will kratom or its constituents be an additional future option to reduce harms associated with prescription opioid abuse as well as opioid addiction?⁸ Limited reports suggest that kratom dependence may be less severe than opioid dependence.⁸ Going forward, experts suggest that healthcare must address first the current management of opioid addiction. What is the goal—abstinence or harm reduction? With clearer treatment goals and clinical trials, perhaps kratom constituents will be identified as a safe and effective alternative to opioids or a gateway to opioid addiction.⁹

Kratom can prevent persons from seeking safe and effective treatment for addiction. Claims that kratom is a natural substitute for opium, with morphine-like effects, are unproven and dangerous, given the scientific evidence supporting kratom’s potential for abuse, addiction, and serious health consequences, including death. At this time, buprenorphine, methadone, and naltrexone are approved by the FDA for the treatment of opioid addiction, and the FDA is committed to promoting innovation and access to these treatments to help those suffering from an opioid use disorder transition to lives of sobriety.^{15,16} Kratom remains on the DEA list for Drugs of Concern list or substances not currently regulated by Controlled Substances Act but pose risk for persons who abuse them.¹⁴

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