

Case in Point

Kratom: A New Product in an Expanding Substance Abuse Market

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Kratom, a drug that produces similar adverse effects like those produced by opioids in patients who have overdosed or are going through withdrawal, has grown in popularity and availability.

According to the United Nations Office on Drugs and Crime, the last decade saw an alarming rise in the use of recreational substances.¹ There was an escalation not only in the use of the more well-known street drugs (cannabis, stimulants, opiates, and hallucinogens), but also an exponential increase in the abuse of novel psychoactive substances. Although most health care providers (HCPs) are at least relatively familiar with some of these designer drugs—often synthesized analogues of common street drugs—region-specific herbal products with psychoactive properties are now entering the market worldwide. Certainly, the cause of this increased use is multifactorial: Ease of access to these drugs and ambiguous legality are believed to

be among the largest contributors. Infrastructure established through globalization promotes easy drug transportation and distribution across borders, and widespread Internet use makes knowledge of and accessibility to such substances exceedingly simple.^{2,3}

In particular, widespread online access has permanently altered the acquisition of knowledge in all realms—including drug use. Although Erowid Center remains one of the oldest and best-known of the “dark Internet” websites and bills itself as providing “harm reduction,” others have cropped up online and disseminate information about many forms of potentially psychoactive substances. Despite these websites’ purported *raison d’être*, recent studies have demonstrated these sites’ efficacy in promoting drug use under the guise of safety, particularly among adolescents and young adults. Among these is a qualitative study by Boyer and colleagues of 12 drug users admitted to a pediatric psychiatry unit. Through extensive questioning about the patient’s digital habits, the researchers demonstrated that the majority of subjects used these web-

sites and as a result either increased their drug use or learned about (and tried) new substances!⁴

One drug that has benefited from globalization and the Internet is kratom (*Mitragyna speciosa korth*). This formerly regionally confined herbal psychoactive substance is native to Southeast Asia, where it has been used (and abused) for centuries as a mild stimulant, to prevent opiate withdrawal, and for recreational purposes. In recent years, kratom has been marketed as a psychotropic drug and is increasingly popular in the U.S. and in the United Kingdom.^{2,5,6} In the U.S., this poses a problem for HCPs who often are unaware of this plant’s existence, much less its abuse potential or health effects.² Also known as ketum, kakuam, thang, thom, or biak, kratom is marketed in stores and online as a cheap, safe alternative to opioids.

Although considered a “substance of concern” without any approved medical use by the U.S. Drug Enforcement Agency (DEA), kratom is not a regulated or controlled substance in the U.S.³ In the past few months, out of concern for public safety, the DEA placed a temporary ban on kratom. The agency’s move

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was followed by a substantial negative reaction from kratom supporters and was quickly rescinded. As of September 2016, the DEA does not have a timetable for banning or scheduling the drug.

To that end, users consider kratom a legal high, and it is easily purchased online. A 2010 study in the United Kingdom examined websites where kratom and many other quasilegal substances (including *Salvia divinorum* and legal precursors to LSD) could be purchased for an average of £10 (about U.S. \$13).⁵ This study's authors also noted a significant lack of product information on these marketplaces. As these products are not overseen by any regulatory body, the risk of overdose or adulteration is extremely high.^{2,3,6-8} In fact, Krypton, a product sold online, was found to be adulterated with O-desmethyl-tramadol—the active metabolite of the synthetic opiate tramadol—and implicated in at least 9 deaths.⁷

This article presents a case of kratom abuse and will outline a brief history, the pharmacologic characteristics, clinical presentation of kratom abuse, and conclude with an overview of the treatment of kratom-related illness and evaluation of potential toxic sequelae. In light of the rapid proliferation of kratom in the U.S., a basic working knowledge of the drug is quickly becoming a must for federal HCPs.

CASE PRESENTATION

At his employer's request, a 33-year-old married man presented to his family physician for a worsening of his uncontrolled back pain from a herniated lumbar disc resulting from a motor vehicle collision 3 months before. At his physician's office he stated, "I don't care if I live or die, I'm tired of the pain," and "I'm going

to go off on somebody if I can't get this pain under control." He also endorsed having auditory hallucinations for several years and a history of violence and homicide. The problem arose precipitously after he thought that he was abusing his opiate medication, and it was discontinued. The patient was transferred to the local hospital and admitted to the psychiatric service for his suicidal ideations and risk of harming self and others.

On admission to the psychiatric service, the patient complained of body aches, chills, rhinorrhea, and significantly worsened irritability from his baseline. Initial point-of-care admission drug testing had been negative as had expanded urine tests looking for synthetic opioids, cannabinoids, and cathinones. The patient reported no opioid use but was unable to explain his current symptom patterns, which were worsening his chronic pain and hampering any attempt to build rapport. On hospital day 3, the patient's additional sequelae had passed, and psychiatric treatment was able to progress fully. On hospital day 4, the inpatient treatment team received a message from the patient's primary care manager stating that a friend of the patient had found a bottle of herbal pills in the patient's car. This was later revealed to be a kratom formulation that he had purchased online.

BACKGROUND

Kratom is the colloquial name of a tree that is native to Thailand, Malaysia, and other countries in Southeast Asia. These trees, which can grow to 50 feet high and 15 feet wide, have long been the source of herbal remedies in Southeast Asia (eFigure, available at www.fedprac.com).^{2,3} The leaves contain psychoactive substances that have a va-

riety of effects when consumed. At low doses, kratom causes a stimulant effect (akin to the leaves of the coca plant in South America); laborers and farmers often use it to help boost their energy. At higher doses, kratom causes an opioid-like effect, which at mega doses produces an intense euphoric state and has led to a steady growth in abuse worldwide. Although the government of Thailand banned the planting of *Mitragyna speciosa* as early as 1943, its continued proliferation in Southeast Asia and throughout the world has not ceased.^{2,3,6}

In the United Kingdom, kratom is currently the second most common drug that is considered a legal high, only behind salvia (*Salvia divinorum*), a hallucinogenic herb that is better known as a result of its use by young celebrities over the past decade.^{5,8} Presently, kratom's legal status in the U.S. continues to be nebulous: It has not been officially scheduled by the DEA, and it is easily obtained.

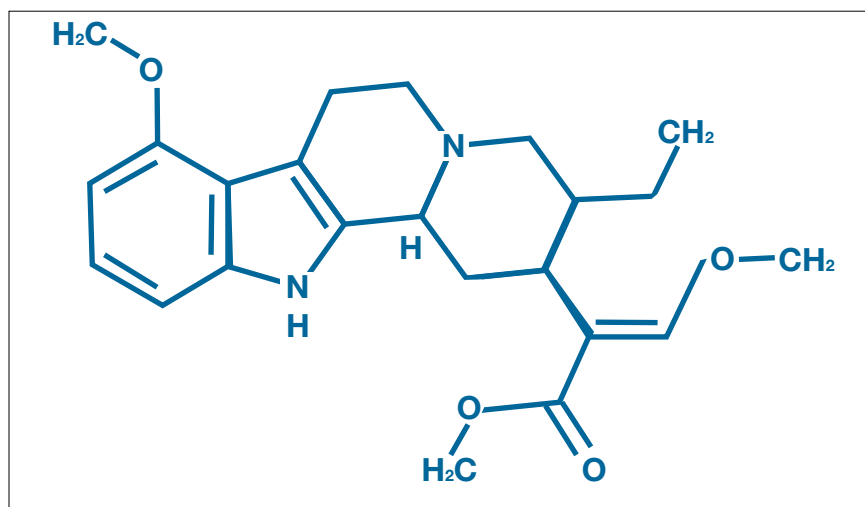
Kratom can be taken in a variety of ways: Crushed leaves often are placed in gel caps and swallowed; it can be drunk as a tea, juice, or boiled syrup; and it can be smoked or insufflated.^{2,3,5,6}

PHARMACOLOGY AND CLINICAL PRESENTATION

More than 20 psychoactive compounds have been isolated from kratom. Although a discussion of all these compounds is beyond the scope of this review, the 2 major compounds are mitragynine and 7-hydroxymitragynine.

Mitragynine

Mitragynine, the most abundant psychoactive compound found in kratom, is an indole alkaloid (Figure 1). Extraction and analysis of this compound has demonstrated

Figure 1. Mitragynine Chemical Structure

numerous effects on multiple receptors, including μ , δ , and κ opioid receptors, leading to its opioid-like effects, including analgesia and euphoria. Also similar to common opioids, withdrawal symptomatology can present after only 5 days of daily use. There is limited evidence that mitragynine can activate postsynaptic α -2 adrenergic receptors, which may act synergistically with the μ agonist with regard to its analgesic effect.^{2,5}

7-Hydroxymitragynine

7-hydroxymitragynine, despite being far less concentrated in kratom preparations, is about 13 times more potent than morphine and 46 times more potent than mitragynine. It is thought that its hydroxyl side chain added to C7 (Figure 2) adds to its lipophilicity and ability to cross the blood-brain barrier at a far more rapid rate than that of mitragynine.²

Mitragynine and 7-hydroxymitragynine remain the best-studied psychoactive components of kratom at this time. Other compounds that have been isolated, such as

speciociliatine, paynantheine, and speciogynine, may play a role in kratom's analgesic and psychoactive effects. Animal studies have demonstrated antimuscarinic properties in these compounds, but the properties do not seem to have any demonstrable effect at the opioid receptors.²

Intoxication and Withdrawal

Due to its increasing worldwide popularity, it is now imperative for HCPs to be aware of the clinical presentation of kratom abuse as well as the management of withdrawal in light of its dependence potential. However, large-scale studies have not been performed, and much of the evidence comes not from the medical literature but from prodrug websites like Erowid or SageWisdom.^{2,5-9} To that end, such information will be discussed along with the limited research and expert consensus available in peer-reviewed medical literature.

Kratom seems to have dose-dependent effects. At low doses (1 g-5 g of raw crushed leaves), kratom abusers often report a mild

energizing effect, thought to be secondary to the stimulant properties of kratom's multiple alkaloids. Users have reported mild euphoria and highs similar to those of the abuse of methylphenidate or modafinil.^{2,9,10} Also similar to abuse of those substances, users have reported anxiety, irritability, and aggressiveness as a result of the stimulant-like effects.

At moderate-to-high doses (5 g-15 g of raw crushed leaves), it is believed that the μ opiate receptor agonism overtakes the stimulant effects, leading to the euphoria, relaxation, and analgesia seen with conventional opioid use and abuse.^{2,10} In light of the drug's substantial binding and agonism of all opioid receptors, constipation and itching also are seen.² As such, if an individual is intoxicated, he or she should be managed symptomatically with judicious use of benzodiazepines and continuous monitoring of heart rate, blood pressure, respiratory rate, and oxygen saturation.^{2,10} Kratom intoxication can precipitate psychotic episodes similar to those caused by opiate intoxication, so monitoring for agitation or psychotic behaviors is also indicated.^{9,10}

The medical management of an acute kratom overdose (typically requiring ingestion of > 15 g of crushed leaves) begins with addressing airway blockage, breathing, and circulation along with continuous vital sign monitoring and laboratory testing, including point-of-care glucose, complete blood count, electrolytes, lactate, venous blood gas, and measurable drug levels (ethanol, acetaminophen, tricyclic antidepressants, etc).¹¹ If it is determined that kratom was the intoxicant, the greatest concern of death is similar to

that of opioid overdose: respiratory depression. Although there are no large-scale human studies demonstrating efficacy, multiple authors suggest the use of naloxone in kratom-related hypoventilation.^{9,10}

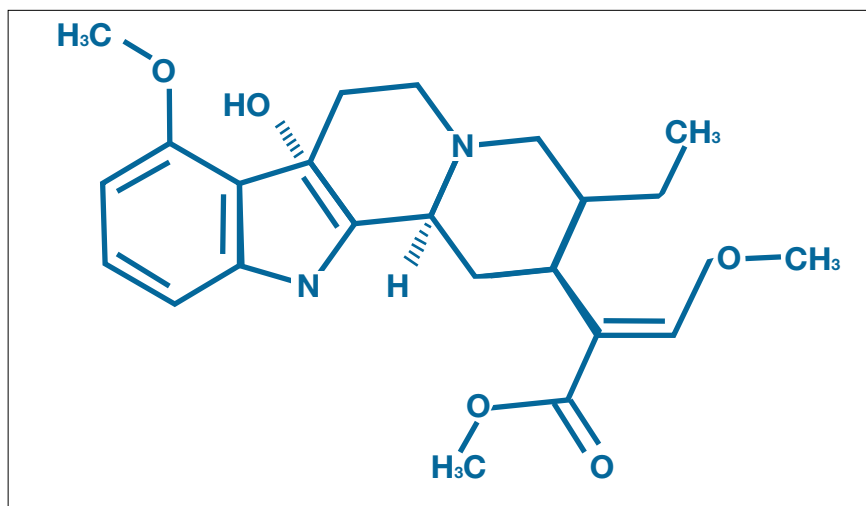
The development of dependence on kratom and its subsequent withdrawal phenomena are thought to be similar to that of opioids, in light of its strong μ agonism.^{2,5,9,10} Indeed, kratom has a long history of being used by opioid-dependent patients as an attempt to quit drug abuse or stave off debilitating withdrawal symptoms when they are unable to acquire their substance of choice.^{2,5-10} As such, withdrawal and the treatment thereof will also mimic that of opioid detoxification.

The kratom-dependent individual will often present with rhinorrhea, lacrimation, dry mouth, hostility, aggression, and emotional lability similar to the case study described earlier.^{2,9,10} Kratom withdrawal, much like intoxication, also may precipitate or worsen psychotic symptoms, and monitoring is necessary throughout the detoxification process.^{2,5,10} Withdrawal management should proceed along ambulatory clinic or hospital opioid withdrawal protocols that include step-down administration of opioids or with nonopioid medications for symptomatic relief, including muscle relaxants, α -2 agonists, and anti-diarrheal agents.^{5,9,10}

Kratom Toxicity

A review of the available medical literature has demonstrated a number of toxic effects with kratom abuse, either as the sole agent or in concert with prescribed medications, recreational coingestants, or as a result of manufacturer's adulteration with other chemicals or drugs. Of particular interest to

Figure 2. 7-Hydroxymitragynine Chemical Structure



HCPs are manic or psychotic episode precipitation, seizure, hypothyroidism, intrahepatic cholestatic injury, and even sudden cardiac death.^{2,3,5-10} In addition to the basic history, physical, and laboratory examination, the workup of patients identified as kratom users should include the following:

- Fastidious medication reconciliation with drug-interaction check;
- Exhaustive substance abuse history;
- Identification of the brand name and source of kratom purchased, to determine whether there are advertised coingestants or reports of adulteration;
- Electrocardiogram;
- Thyroid function testing;
- Hepatic function testing; and
- Comprehensive neurologic and mental status exams.

In chronic users of kratom, a number of effects have been seen whose etiologies have not yet been determined. These effects include depression, anxiety, tremulous-

ness, weight loss, and permanent psychosis.³⁻⁷ Additionally, a 2008 study by Kittirattanapaiboon and colleagues correlated drug use by those with concurrent mental health disorders (in particular, kratom, which was used in 59% of the $\geq 14,000$ individuals included in the study sample) with statistically significant higher suicide risk.¹²

DETECTION

Because kratom is a relatively new compound in the U.S., medical and forensic laboratories are only now implementing kratom detection protocols. Many laboratories now use high-performance liquid chromatography to analyze for mitragynine, 7-hydroxymitragynine, and 2 metabolites of mitragynine in urine.⁷ Le and colleagues were able to detect mitragynine in the urine in levels as low as 1 ng/mL, which is clinically useful as mitragynine has a half-life determined in animal studies to be 3.85 hours.¹³ Similar detection limits for mitragynine and 7-hydroxymitragynine are used only at Naval Medical Center Portsmouth in Virginia;

however, kratom was not detected in the study patient's urine because a urine test was not done until hospital day 5.

CONCLUSION

When gently confronted about the kratom found in his car, the case study patient admitted that he had purchased kratom online after he was "cut off" from prescription opioids for his pain. He admitted that although it was beneficial for his pain, he did notice worsening in his aggression toward his spouse and co-workers. This progressed to an exacerbation of his psychotic symptoms of hallucinations and persecutory delusions. These symptoms remained well hidden in this highly intelligent individual—but were present for years prior to his presentation at the hospital. The patient was discharged from the inpatient psychiatric unit on hospital day 16 with a diagnosis of schizoaffective disorder, depressive type in addition to opioid use disorder. The patient agreed to seek a pain management specialist and discontinue kratom use.

Kratom is an emerging drug of abuse in the Western World. Although significant research is being conducted on its possible medical uses, little is known about kratom

beyond the "trip reports" of kratom users posted online. Because of its technically legal status in the U.S. and multiple other Western countries, kratom is easily accessible and is difficult to detect. Health care providers need to be aware of kratom, and during their evaluations, question patients about kratom and other legal highs. ●

Author disclosures

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