Kratom (*Mitragyna speciosa*): Friend or Foe?

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ABSTRACT

Increased use of the opioid-related plant kratom as an alternative treatment for opioid withdrawal symptoms has raised concerns regarding its potential for abuse and severe adverse effects. A review of the literature was performed to characterize kratom's pharmacology, clinical efficacy, and adverse effects to increase understanding and evaluate potential use as an alternative treatment for opioid dependence. Kratom use initiated as self-medication for an opioid use disorder or pain syndrome in the absence of effective alternatives is associated with a risk of kratom dependence, withdrawal, and life-threatening toxicity. The potential for a serious adverse reaction should discourage unregulated use of kratom products.

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Kratom is a psychoactive substance derived from the *Mitragyna speciosa* plant species native to Thailand and Southeast Asia,[1] with stimulant-like effects at lower doses and opioid-like effects at higher doses.[2–4] It has gained popularity in the United States as an inexpensive alternative for self-withdrawal treatment from opiates. Kratom is sold as capsules, tablets, loose raw leaves, gum, and powder through online vendors and at local smoke shops, bars, and gas stations. It is sold as kratom, mitragyna, and other street names such as ketum, thom, biak, and thang.[2,3,5–7] Kratom is also available as green powder sold with the label "Not for human consumption."[7] Kratom has been used with *O*-desmethyltramadol, which is marketed as krypton,[3,8] and may be added to synthetic cannabinoids such as K2 and spice.[3,9] Kratom does not appear in regular urine drug screens and may be undetected during routine screening of acute drug intoxication, overdose, or withdrawal, as careful history is required for identification.[2,3] There has been little scientific investigation to characterize kratom's pharmacology, mechanism of action, side effects, or risk of use. Kratom has been designated as illegal in several countries. It remains unrestricted in the United States but is listed as a "drug of concern" by the US Drug Enforcement Administration. This narrative review provides a survey of literature related to kratom's clinical profile based on available empirical evidence and case reports.

METHODS

A literature search was performed using 4 databases (MEDLINE, PubMed, CINAHL, and Google Scholar) to identify English-language articles published from January 2000 to March 2019. Search terms were *kratom*, *opioid withdrawal*, *opioid use disorder*, *opioid dependence*, and *mitragyna*. Studies were selected on the basis of novel information related to kratom's pharmacology, mechanism of action, clinical presentation, and adverse effects. Surveys and case reports were included given that kratom is not used clinically and the majority of kratom use is for recreational purposes. Commentaries were excluded. A total of 45 articles[1–45] were included in the final review.

RESULTS

Kratom Pharmacology

The psychoactive properties of kratom are mainly attributed to mitragynine and 7-hydroxymitragynine (7-OHMG).[10–12] Both compounds act through g-protein–coupled signaling with partial agonist effects on μ-opioid receptors and antagonist effects on the κ- and δ-opioid receptors.[10–12] The partial agonist activity at the μ-opioid receptor is believed to mitigate risks for respiratory

Clinical Points

- Kratom has gained popularity as an inexpensive and accessible alternative to manage symptoms of opioid use disorder and pain.
- Kratom use can lead to physical dependence and precipitate withdrawal symptoms with abstinence.
- Even short-term kratom use has been associated with serious medical comorbidities including hepatitis, seizures, and death.

depression in the event of overdose.[12] According to the literature,[2,3,13–16] kratom can prevent withdrawal symptoms from opioids but also has the capacity to induce its own withdrawal symptoms. Kratom has anti-inflammatory properties and has demonstrated parasympathetic-blocking effects.[3] These effects were reversible by use of naloxone, suggesting that they are mediated by opioid agonist actions.[3,17]

Mitragynine stimulates α_2-adrenergic receptors proposed to accentuate its sedative, hypnotic, and analgesic effects without increasing respiratory depression. Although this synergistic effect may be considered beneficial for opioid withdrawal therapy, the profile yields a potent central nervous system depressant effect that could be dangerous when combined with other sedative and hypnotic agents, such as opioids, alcohol, benzodiazepines, muscle relaxants, and anticonvulsants.[2,3,12,18,19] Mitragynine has additional effects on adenosine 2, dopamine, and 5-HT_7 receptors that are not fully characterized.[12,18]

Adverse Effects of Kratom

The Centers for Disease Control and Prevention reported 660 calls to US poison control centers related to kratom use from 2010 to 2015.[20] The number of calls increased from 26 in 2010 to 263 in 2015, with 496 calls received from health care providers seeking guidance. Isolated kratom use was noted in 428 of these cases.[20] Kratom use is reported in combination with other substances most commonly cited as benzodiazepines, narcotics, and acetaminophen.[20,21]

There are several published case reports[18,26–31,41–45] about the side effects and withdrawal symptoms associated with cessation of kratom use and how to successfully treat those withdrawal symptoms (Table 1). These case reports are of interest, as they can be helpful in clinical scenarios for which there is no guidance on how to treat kratom overdose and withdrawal. The most commonly reported adverse effects include nausea, vomiting, tremor, diaphoresis, tachycardia, hypertension, and elevated creatinine phosphokinase concentrations[3,16,22–25] (Table 2). Treatment for adverse effects includes use of intravenous fluids, sedatives, benzodiazepines, antiemetics, and, in rare cases, antihypertensives and oxygen.[3] A total of 36 deaths have been reported with illicit use of kratom-containing products. Nine deaths have been linked to krypton use (kratom and *O*-desmethyltramadol) and 1 death to kratom combined with propylhexedrine.[3]

Several reports[26–30] have identified severe liver injury and intrahepatic cholestasis with kratom. The first reported case[26] of kratom-induced hepatoxicity was in 2011 describing a 25-year-old man who developed abdominal pain and jaundice 10 days after use of kratom. His symptoms resolved after cessation of kratom intake.[26] Swogger et al[22] reported 2 separate cases: a female who developed acute jaundice following consumption of kratom and a male who presented with acute hepatitis after 2 weeks of kratom use. Other examples include a 58-year-old chronic kratom user who developed jaundice and hepatotoxicity,[27] a 21-year-old man with 1-month history of kratom use who presented with hepatosplenomegaly,[28] a 32-year-old man with cholestatic hepatitis after 2 weeks of kratom use,[29] and a 38-year-old man with an acute onset of kratom-induced hepatitis.[30] There are also case reports[31,32] that document seizures as an adverse effect of kratom use.

Kratom Withdrawal Symptoms After Cessation of Use

Prolonged use of kratom is associated with physiologic dependence capable of precipitating withdrawal symptoms with decreased use or abstinence. The literature suggests that withdrawal symptoms from cessation of kratom use are similar to opioid-like withdrawal symptoms (Table 3).[14,33–37] These opioid-like withdrawal symptoms were mitigated with naloxone,[3] clonidine,[33,34] and buprenorphine.[35,36]

Several case reports document withdrawal symptoms after kratom cessation such as severe muscle spasms, myalgia, chronic pain, sleeping difficulty, and intense cravings (Table 4). Many individuals reported that these symptoms and the intense craving made them unable to discontinue use of kratom.[13,15] Some case reports[3,33–36] describe successful treatment with different medications. Buresh[36] presented a case series featuring successful treatment of kratom dependence in 2 patients with the initiation of buprenorphine treatment. Khazaeli et al[35] reported another case of a patient with opioid use disorder who self-medicated with kratom and became addicted. Her kratom withdrawal symptoms were successfully treated with buprenorphine. The authors[35] recommend divided dosing of buprenorphine to maximize analgesia for patients who have used kratom to manage pain. Diep et al[37] reported successful treatment of kratom withdrawal with associated seizures using buprenorphine. Mackay and Abrahams[14] illustrated the case of a mother and neonate whose kratom withdrawal symptoms were successfully treated with morphine. Galbis-Reig[34] described successful treatment of kratom withdrawal symptoms in a female patient with clonidine and hydroxyzine. Stanciu et al[33] presented a case series of 2 patients successfully treated for kratom withdrawal with clonidine treatment.

Ecologic Factors Influencing Kratom Use

Most human studies[15,16,18,22,23,25] on kratom utilize observational survey designs and originate in Malaysia and Thailand, with very few surveys from the United States (Table 5). Vicknasingam et al[15] conducted an anonymous survey to assess patterns of ketum (kratom) use in Malaysia and effects

Table 1. Summary of Case Reports of Kratom Adverse Events

Case Report	Analysis Methods and Tests	Kratom Use Pattern	Treatment
Boyer et al, 2008[18] Male, age 43 y, admitted for evaluation of generalized tonic-clonic seizure	Urine toxicology screening, CT, and MRI	Kratom tea 4 times a day for 3.5 y	Buprenorphine/naloxone 16 mg/d
Kapp et al, 2011[26] Male, age 25 y, intrahepatic cholestasis	AST: 66 U/L, ALT: 94 U/L, ALP: 173 U/L, total bilirubin: 30.9 µmol/L, urine mitragynine detected by GC-MS	Intake dose: 4.6–7 g/d to 8.6–14 g/d 2 weeks before symptom onset	Self-resolution of symptoms
Dorman et al, 2015[27] Male, age 58 y, cholestatic hepatitis	AST: 49 U/L, ALT: 106 U/L, ALP: 790 U/L, total bilirubin: 25.6 µmol/L, direct bilirubin: 17.1 µmol/L	Ingestion of 1 tablespoon of powder daily for 3 months	Conservative management
Griffiths et al, 2018[28] Male, age 21 y, hepatomegaly	AST: 294 U/L, ALT: 319 U/L, ALP: 193 U/L, total bilirubin: 2.86 µmol/L; urine drug screen positive for cannabis; abdominal ultrasound and MRI: hepatosplenomegaly	12 kratom capsules daily (6 g) for 2 wk	Conservative management
Tayabali et al, 2018[29] Male, age 32 y, hepatitis	ALT: 365 U/L, AST: 222 U/L, ALP: 391 U/L, total bilirubin: 6.3 µmol/L; serum mitragynine and 7-OHMG	60 tablets over 1 wk	NAC 150 mg/kg/h; patient developed anaphylaxis and treatment was stopped
Riverso et al, 2018[30] Male, age 38 y, intrahepatic cholestasis	AST: 220 U/L, ALT: 389 U/L, ALP: 304 U/L, total bilirubin: 5.1 µmol/L; liver biopsy: intrahepatic liver injury	Unspecified pattern	Intravenous fluids and kratom cessation
Nelsen et al, 2010[31] Male, age 64 y, seizure	Urine drug testing, mitragynine urine concentration: 167 ng/mL; CT and MRI	Unspecified dose	Lorazepam 2 mg and phenytoin 1 gm
Neerman et al, 2013[41] Male, age 17 y, found deceased	Urine mitragynine level:167 ng/mL, LC-MS, autopsy	Empty bottle of kratom found on scene	Cause of death "accidental," lack of confirmed kratom use
Fernandes et al, 2019[42] Male, age 52 y, intrahepatic cholestasis	AST: 48 U/L, ALT: 62 U/L, ALP: 259 U/L, total bilirubin: 22.8 µmol/L	1 teaspoon of crushed leaves (–1.5 g/d)	Conservative treatment with ursodeoxycholic acid and kratom abstinence
Mousa et al, 2018[43] Male, age 31 y, acute hepatitis	AST: 191 U/L, ALT: 578 U/L, ALP: 191 U/L, total bilirubin: 2.2 µmol/L	Kratom tea for 2 wk	NAC
Osborne et al, 2019[44] Male, age 47 y, hepatitis	AST: 114 U/L, ALT: 324 U/L, ALP: 148 U/L, total bilirubin: 6.1 µmol/L, direct bilirubin: 5.1 µmol/L, creatinine: 17.1 µmol/L; urine protein and urobilinogen	Kratom capsule for 3 wk	Conservative management
Palasamudram Shekar et al, 2019[45] Male, age 36 y, intrahepatic cholestasis	AST: 1,347 U/L, ALT: 3,717 U/L, hyperkalemia, acute kidney injury, urine sample tested positive for 500 ng/mL of 7-hydroxymitragynine	Unspecified pattern	Conservative management

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography, GC-MS=gas chromatography-mass spectrometry, LC-MS=liquid chromatography-mass spectrometry, MRI=magnetic resonance imaging, NAC=*N*-acetylcysteine.

Table 2. Summary of Adverse Effects of Kratom Ingestion

General	Nausea,[3,16,22–24] vomiting,[3,22–24] constipation,[23–25] anorexia,[24] weight loss,[24] small black feces,[24] fatigue,[25] sweating[22]
Endocrine	Hypothyroidism
Gastrointestinal	Dry mouth,[24] nausea,[3,16,22–24] vomiting,[3,22–24] constipation,[23–25] small black feces,[24] diarrhea[16]
Hepatic	Jaundice, itching,[22] intrahepatic cholestasis[24,26]
Neurologic	Dizziness,[16,22,23,25] irritability,[23,25] poor concentration,[25] impaired memory,[25] decreased sexual drive,[25] tremors,[25] headaches,[16,25] seizure-like activity,[16,18,24,31,32,39] coma,[24,31] numbness[22]
Psychiatric	Visual alterations,[22] social withdrawal,[25] psychosis
Cardiac and pulmonary	Hypertension,[16,23] heart palpitations,[16,23] shortness of breath[23]
Altered consciousness[43]	…
Death[3,39,40]	…

reported by current users. A total of 136 respondents with a mean age of 38 years were stratified into short-term (53%) and long-term (47%) kratom users. Both groups reported using kratom to reduce addiction to other drugs and use of more expensive opioids (90.4%) and to treat symptoms of opioid withdrawal (83.8%). They reported benefits including increased propensity for hard work, heightened sexual desire, increased appetite, and reduced heroin withdrawal symptoms. Side effects from kratom included weight loss, dehydration, constipation, tiredness, and hyperpigmentation of cheeks. Seventy-eight percent of respondents reported symptoms of fatigue, lacrimation, rhinorrhea, insomnia, diaphoresis, and nerve pain when they stopped taking kratom.[15] This finding contrasts that of a prior study[25] in Thailand of an adult (mean age = 45 years) population with no evidence of previous drug use that identified increased physical endurance as a key motivational influence for use. A second survey[13] in Malaysia evaluated the frequency of dependence, cravings, and withdrawal symptoms in males taking kratom for longer than 6 months. Of the 293 respondents, clinically meaningful dependence was identified in 100% of respondents, with 55% reporting severe and 45% reporting moderate dependence. Sixty-five percent of respondents experienced mild withdrawal symptoms, while 35% reported moderate-to-severe symptoms. Further, significant cravings for kratom were reported in 77% of kratom users, while 23% had only mild cravings.[13] The consensus findings identified high rates of dependence associated with kratom use but limited impact on social functioning in this setting.[13]

Table 3. Summary of Case Reports of Kratom Withdrawal

Case Report	Analysis and Withdrawal Symptoms	Treatment of Withdrawal Symptoms	Success/Failure
Mackay and Abrahams, 2018[14] Female, age 29 y, and infant treated for withdrawal	• Diaphoresis, rhinorrhea, piloerection, anxiety, nausea • Postpartum symptoms of irritability, jitteriness, feeding intolerance • Infant neonatal abstinence syndrome	Mother: oral morphine 10 mg 3 times/d Infant: morphine in neonatal intensive care unit	Positive response with resolution of withdrawal symptoms
Stanciu et al, 2019[33] Patient 1: female, age 26 y, 1.5-y history of kratom abuse Patient 2: male, age 27 y, 2-y history kratom use	• Urine toxicology • Metabolic panel and ECG • Patient 1: presented to ED with restlessness, generalized body aches, anxiety, suicidal thoughts, tachycardia, fever • Patient 2: presented to ED with suicidal thoughts, hopelessness and helplessness, auditory hallucinations	Patient 1: clonidine 0.1 mg every 2 h and gabapentin 300 mg 3 times/d Patient 2: clonidine 0.1 mg 3 times/d	Positive response to clonidine initially
Galbis-Reig, 2016[34] Female, age 37 y, 2-y history of kratom use, withdrawal after 6 mo of use	• Urine toxicology by immunoassay • LC-MS • Myalgia, bone pain, blurred vision to pupillary dilatation	Symptom-triggered clonidine therapy 0.1–0.2 mg every 2 h and hydroxyzine 50 mg every 6 h for 3 d; discharged home with naltrexone 50 mg/d oral	Positive response to clonidine
Khazaeli et al, 2018[35] Female, age 52 y, 9-y history of opiate use disorder, kratom use for 9 mo	• Urine drug screen for mitragynine 48 d after last use of kratom	Buprenorphine initiated with resolution of opioid withdrawal and cravings	Positive response to buprenorphine
Buresh, 2018[36] Patient 1: female, age 60 y, with chronic pain Patient 2: male, age 57 y, 1-y history of kratom use	• Urine toxicology screen • Patient 1: irritability, rhinorrhea • Patient 2: anxiety, edginess, leg shaking, diazepam self-medication	Patient 1: treated with buprenorphine-naloxone (4-1 mg) with resolution of pain and no relapse Patient 2: home initiation of buprenorphine-naloxone (8-2 mg); later started on buprenorphine 24 mg	Positive response to buprenorphine with resolution of pain symptoms
Diep et al, 2018[37] Male, age 24 y, history of opiate use disorder, kratom 600 mg/d, kratom seizure, hypothermia	• Urine drug screen for mitragynine • Arterial blood gas acute respiratory acidosis • ECG QT interval prolongation, sinus bradycardia • White blood cell count elevated • Creatinine kinase elevated (rhabdomyolysis)	Started on lorazepam for seizures Day 13: buprenorphine 2 mg/d and hydroxyzine 50 mg/d followed by long-term maintenance	Positive response to buprenorphine

Abbreviations: ECG = electrocardiogram, ED = emergency department, LC-MS = liquid chromatography-mass spectrometry.

Table 4. Summary of Reported Withdrawal Symptoms Resulting From Extended Use of Kratom

Withdrawal Symptoms	Available Treatment Options
Anxiety and agitation[2,3,13,14,16]	Benzodiazepines, buprenorphine
Nausea,[3,13,16] vomiting,[3,13] diarrhea,[3,13,16] abdominal cramps[3,13]	Nonopioid antidiarrheal
Muscle, body, and joint pain,[3,13,16] nerve pain[29]	Nonsteroidal pain relievers
Insomnia,[13,15,16] sedation,[3] fatigue[15,16]	Buprenorphine and clonidine
Sweating, rhinorrhea, watery eyes[13,15]	Buprenorphine and clonidine
Tremors,[13,16] ataxia,[16] dystonia[16]	Buprenorphine and clonidine
Psychological restlessness,[13] anger,[13] depressed mood,[13] nervousness,[13] increased craving[15]	Buprenorphine and clonidine

A qualitative analysis by Swogger et al[22] described 161 individuals who submitted their own experience with kratom on the website Erowid.org. Erowid is a nonprofit organization that provides online informational resources about psychoactive substances.[22] Positive experiences reported by kratom users included relaxation, euphoria, state of well-being, pain relief, and enhanced empathy. Seventeen individuals reported successful use of kratom as replacement for unwanted substance use, especially opioids. Common reported adverse effects were nausea (16%) and withdrawal symptoms (10%), though the symptoms were milder compared to opiates. Although uncommon, visual alterations and sedation were noted, but many individuals reported benefits from milder withdrawal symptoms and stimulant effects, which appeared to drive the motivational attributes associated with use. Swogger and colleagues[22] concluded that kratom could potentially be used as adjunctive therapy for pain relief with less cognitive impairment and less sedation, but further research on safety and administration guidelines is needed.

A large cross-sectional online survey[23] (N = 8,049 respondents) of members of the American Kratom Association found kratom use was primarily associated with the self-treatment of acute and chronic pain and symptoms of opioid withdrawal. More than 80% of respondents reported decreased pain, increased energy, and less depressive mood with kratom. Furthermore, 49% of users stopped or reduced their use of opiates. The adverse effects most commonly reported with kratom use were nausea (13%), constipation

Table 5. Summary of Observational Studies of Kratom

Study	Type of Subjects	Positive Aspects of Using Kratom	Negative Aspects of Using Kratom
Vicknasingam et al, 2010[15] Cross-sectional survey of Malaysians	136 respondents aged 38 y 104 previous drug users; 62 were urine positive for other drugs	Reduce symptoms of opioid withdrawal, improved appetite, low cost	Withdrawal symptoms (craving, fatigue, lacrimation, rhinorrhea, sweating, insomnia, pain, discomfort in kidney area)
Trakulsrichai et al, 2013[16] Retrospective chart review (clinical data)	Rathimbodi toxic surveillance system 2005–2009 78 kratom exposure cases Mean age of 31 y	Not available	Withdrawal symptoms (nausea, diarrhea, loss of appetite, tremors, myalgias, fatigue, ataxia, dystonia, hypotension, palpitation, diaphoresis)
Boyer et al, 2008[18] Dataset construction of kratom mentions from drugbuyers.com posts	113,000 members aged 38 y 170 topic threads on kratom 2004–2005	Opioid replacement, inexpensive alternative to opioid analgesics and buprenorphine	None mentioned as this was an internet survey that focused on use
Swogger et al, 2015[22] Qualitative analysis (conventional content analysis)	161 individuals submitted reports on Erowid.org between 2001 and 2012	Euphoria, relaxation, enhanced empathy, sensory enhancement	Nausea, vomiting, chills, sweating, dizziness, itching, numbness
Grundmann, 2017[23] Cross-sectional online survey of the American Kratom Association	Facebook page, website forums, and membership e-mails 8,049 of 10,000 respondents (80%) completed the survey	Decreased pain, increased energy, treatment of depressed mood	Side effects (nausea/vomiting: 13%, constipation: 9%, and drowsiness: 5%) Withdrawal symptoms (anxiety)
Assanangkornchai et al, 2007[25] Cross-sectional survey of rural Thailand villagers	Men: n = 350, women: n = 83 149 long-term regular users 168 occasional users 116 nonusers	Feeling happy, euphoria, mood elevation, sleep regulation	Constipation, tremors, headaches, decreased sexual drive, dizziness, irritability

(9%), and dizziness or drowsiness (5%). The study[23] also identified a dose-dependent relationship with both beneficial and adverse effects of kratom.

Other reports[3,38] have documented therapeutic use of kratom to prevent opioid withdrawal. One report[38] presented the case of a 53-year-old man with a history of opioid use disorder recently tapered off methadone after 6 years of maintenance therapy who started using kratom to control his withdrawal symptoms and prevent a relapse. Another published report[3] described use of kratom to treat 2 individuals with a long history of heroin use. One patient did not have access to methadone and the other patient had persistent withdrawal symptoms despite methadone treatment. Both patients reported improvement of their symptoms after they started using kratom.[3]

CONCLUSION

The increasing popularity of kratom has been accompanied by dependence, adverse effects, and withdrawal symptoms following cessation of use. Use may be partly attributed to increasing costs of opioids, the era of the current opioid epidemic and reduction in prescriptions of opiates, online availability, and insufficient public awareness of potential side effects and propensity to experience withdrawal symptoms on cessation. One weakness of our analysis is the inclusion of anecdotal reports of kratom obtained through survey and analysis of online forums, which put the findings at risk for potential bias and other confounding factors.

Kratom's unique dual property as an opioid with stimulant properties makes it a potential alternative in the management of opioid withdrawal symptoms. Review of the literature suggests a high potential for abuse and dependence with kratom that may outweigh the potential benefits. The risk of increased central nervous system depression with concomitant sedative hypnotics and alcohol makes it a drug of concern. Also, reports[26–30,42,43] have shown an association between liver injury and kratom ingestion, supporting the need for controlled trials to further evaluate the safety and efficacy of kratom.

Because of the rise in kratom use in Western countries, medical providers should be aware of the effects of kratom. Physicians should also be aware of the withdrawal symptoms and need for treatment. Although data on kratom are of low quality, the findings from this study may provide a better understanding of the effects of kratom consumption in humans. More susceptible populations including those with compromised liver function or history of prior addiction as well as young adults and adolescents should be cautious when using this unregulated substance.

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