Kratom from Head to Toe—Case Reviews of Adverse Events and Toxicities

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Abstract

Purpose of Review This review describes case reports for patients with kratom-associated adverse events in order to assist clinicians with patient management. A stepwise approach is proposed for assessing active kratom users as well as considerations for the management of toxicities or withdrawal.

Recent Findings Multiple in vitro and in vivo studies illustrate the pharmacologic and toxicologic effects of kratom extract. No randomized controlled trials in humans exist that assess the safety and efficacy of the substance. Cross-sectional surveys from active users and reports from poison control centers have shown acute and chronic physiological and psychological adverse events.

Summary Reports of adverse effects associated with kratom use have demonstrated hypothyroidism, hypogonadism, hepatitis, acute respiratory distress syndrome, posterior reversible encephalopathy syndrome, seizure, and coma. Overdose toxidrome leads to respiratory failure, cardiac arrest, and fatalities. Adult and neonatal withdrawal symptoms have also occurred. Clinicians should be aware of the risks and benefits of kratom use.

Keywords Kratom · *Mitragyna speciosa* · Adverse events · Toxicity

Introduction

We completed a review of *Mitragyna speciosa* (MS), which is a psychoactive plant that belongs to the Rubiaceae family, or coffee family (Fig. 1) [1, 2]. Human consumption of the plant leaves was first documented in the late nineteenth century when native's used it for ceremonial and medicinal purposes in the tropical and subtropical regions of southeast Asia and Africa [2, 3]. Traditionally, MS was used to control ailments such as fever, diarrhea, cough, fatigue, and decreased libido, in addition to treat conditions such as enteritis, parasitic and herpes zoster infections, diabetes, hypertension, and depression [2–8]. Natives consumed MS by various routes: chewed raw, boiled in water as a beverage, or inhaled as a vapor [6–8]. Today, MS

is known as kratom, first named by natives in Thailand [8]. Kratom use has surpassed its region of origin and reached consumers around the world, mainly for its proclaimed psychoactive properties [9]. In 2016, The American Kratom Association (AKA) estimated that there are 3–5 million active and regular kratom users in the United States (USA). [10] Despite longstanding and increasing kratom use, controlled trials evaluating efficacy and safety have not been performed [11•]. Surveys of active kratom users reported dual and dose-dependent stimulant-like properties and opioid-like euphoric effects: as decreased pain (85%), increased energy (84%), and less depressive mood (80%) [12•]. These effects are exploited medicinally for analgesia, withdrawal from illicit drug or prescription opioid medicine, or background mental/emotional disorder [13]. The positive experiences from kratom such as euphoria, relaxation, sociability, and productivity have been attractive for recreational use in substance use disorder and in cultural festivities [14, 15].

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Pharmacology and Preclinical Studies

Kratom contains about 25 pharmacologically active alkaloids, of which mitragynine (MG) and 7-hydroxymitragynine (7-

Fig. 1 *Mitragyna Speciosa* tree, leaf, and capsules. **a** Tree. **b** Leaf. **c** Capsules. Adopted from Drug Enforcement Agency (DEA) [1]

HMG) are the most prevalent [16]. MG and 7-HMG are dose-dependent agonists of the μ -, κ -, and δ -opioid receptors in the central nervous system (CNS) as well as non-opioid receptors [6, 7, 16, 17•, 18, 19]. Their non-selectivity likely results in the beneficial multimodal effects of kratom especially for analgesia and mood elevation [20]. In vitro studies have exhibited cytotoxic effects on human neuronal, hepatic, and cardiac myocyte cell lines and have shown neuromuscular blocking effects [21–24]. Kratom was also reported to inhibit CYP 450 hepatic enzyme, particularly CYP 3A4, 2D6, and 1A2 [29, 30]. In toxicological in vivo animal studies, test subjects exhibited adverse effects such as hepatitis, nephrotoxicity, reduced sperm production, addiction and tolerance, long-term cognitive deficits, generalized convulsions, and fatalities with high doses [18, 19, 25–28].

Emerging Use and Regulatory Concerns

Increasing kratom use has resulted in increased reports of adverse events. Attributing these reports solely to kratom is complicated by the absence of standardized product manufacturing and voluntary adverse event reporting. Between 2011 and 2017, calls to US Poison Control Centers (PCC) show that kratom poisoning and fatality cases have increased 58-fold in 6 years. One-third of these cases resulted in healthcare facility admission [31•]. Cross-sectional surveys highlighted opioid-like adverse events such as intoxication, addiction, and kratom-associated withdrawal symptoms [11•, 33–38]. Many western countries and a number of US states have banned kratom possession and/or sales. Despite these control efforts, availability online has eased the accessibility to kratom products. In the USA, many kratom products used are without good manufacturing practices outlined by the Food and Drug Administration (FDA) or subject to quality assessments. In February 2018, the FDA issued warnings regarding 44 fatalities associated with kratom [32]. In 2019, two warnings were issued regarding selected kratom product impurities; a warning in February for potential heavy metal poisoning following laboratory discovery of elevated lead and nickel levels and another warning in March for nationwide recall for potential *Salmonella*

contamination following a series of *Salmonella* infection outbreaks [39, 40]. A 2017 survey showed that about 40% of active kratom users consult their healthcare professionals (physician, nurse, or pharmacist) about use indicating that there is a public need for evaluating risks and benefits [11•]. This review is intended to help healthcare professionals assess the adverse events associated with kratom use. In addition, we propose a stepwise algorithm for assessing patients actively using kratom and discuss considerations for management of kratom-associated adverse events and toxicities.

Literature Case Review

We performed a systematic literature review using MEDLINE, Embase, and Google Scholar. Main search terms were “*Mitragyna speciosa*” and “kratom” combined with appropriate Boolean phrase. We included only case reports and case series written in English that were published from January 2008 to March 2019. Botanical, pharmacokinetic, analytical, or preclinical studies, and surveys were excluded. Overall, there were 41 cases on kratom-associated adverse events or toxicities (Table 1). Kratom-associated adverse events were as follows: kratom-associated withdrawal symptoms (KAWS) in adults [41–52], kratom-associated neonatal abstinence syndrome (KANAS) [48, 52–56], hypothyroidism [43], hypogonadism [57], kratom-induced hepatotoxicity (KIH) [58–65], CNS effects causing seizure and coma or posterior reversible encephalopathy syndrome (PRES) [39, 66, 67], acute respiratory distress syndrome (ARDS) [68, 69], overdose toxidrome [70, 71], and fatalities [72–80]. There were six case series of aggregated patient’s data [48, 49, 51, 73, 77, 80]. There were also mixed presentations: KAWS and seizure [41], hypothyroidism [43], or KANAS [48].

Kratom-Associated Withdrawal in Adults [41–52]

Tolerance generally occurred after 3 months [42], and a few patients described escalating their doses four to ten

Table 1 Summary of case reports on kratom-associated adverse events

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Cases of kratom-associated withdrawal syndrome (KAWS) in adults					
Boyer et al. [41] 2008 (USA)	A 43-year-old man admitted for evaluation of a generalized tonic-clonic seizure and coincided with signs of opioid withdrawal	ACTIVE <ul style="list-style-type: none"> Chronic pain HISTORY <ul style="list-style-type: none"> Substance abuse (hydromorphone) 	PURPOSE <ul style="list-style-type: none"> Chronic pain DOSE <ul style="list-style-type: none"> Opioid sparing FORM <ul style="list-style-type: none"> Four times daily Tea <ul style="list-style-type: none"> Four times daily DURATION <ul style="list-style-type: none"> 3.5 years 	SUBJECTIVE <ul style="list-style-type: none"> Time since last dose: NR KAWS: reported symptoms similar to opioid withdrawal Pattern of addiction: only as she tries to cut back on use, KAWS develop Experiences from kratom: substantial pain relief, improved alertness without drowsiness Described co-ingesting modafinil OBJECTIVE <ul style="list-style-type: none"> Physician observed features of KAWS such as rhinorrhea, insomnia, poor concentration, and myalgias persisting for 10 days from his last kratom dose Vitals: pulse 123 beats per minute, blood pressure 130/74 mm/Hg Confirmed identity of kratom via high-performance liquid chromatography protocols 	INTERVENTION <ul style="list-style-type: none"> Induction/maintenance Buprenorphine/naloxone, reaching a maintenance dose of 16 mg per day EFFECT <ul style="list-style-type: none"> Immediate effects Rhinorrhea and pain ceased on the day 1 Upon discharge, the patient ceased use of kratom abruptly Better pain control Long-term effects Follow-up urine screens (unknown interval) for drugs of abuse have remained negative
McWhirter & Morris [42] 2010 (UK)	A 44-year-old man was referred to the substance misuse service by a general psychiatrist for assistance with a kratom detoxification.	ACTIVE <ul style="list-style-type: none"> Anxiety and depression (mirtazapine) HISTORY <ul style="list-style-type: none"> Alcohol dependence and polysubstance misuse 	PURPOSE <ul style="list-style-type: none"> Well-being and anxiety DOSE <ul style="list-style-type: none"> 40 g in 4 doses daily FORM <ul style="list-style-type: none"> Oral liquid DURATION <ul style="list-style-type: none"> Three years 	SUBJECTIVE <ul style="list-style-type: none"> Time since last dose: 12 h KAWS: cravings, anxiety, restlessness, sweating and itch Pattern of addiction: Initially took single 4-g dose. Then, due to tolerance after 3 months, dose increased to 8 g; then 12.5 g twice daily, and finally 10 g every 6 h. Attempted to self-detoxify using diazepam. Experiences following kratom: initially, experienced 4 h of euphoria, increased productivity, industriousness and relaxation. Later, experienced withdrawal symptoms despite being on every 6 h dose Motive: Patient wished to detoxify because of cost and KAWS OBJECTIVE	INTERVENTION <ul style="list-style-type: none"> Detoxification (admitted at detoxification ward) Dihydrocodeine 60 mg 4 times daily plus lofexidine 0.2 mg twice daily, titrated against the severity of withdrawal symptoms Used opioid withdrawal symptoms chart: pulse, sweating, restlessness, pupil size, bone or joint aches, runny nose or tearing, gastrointestinal upset, tremor, yawning, anxiety or irritability, and gooseflesh skin EFFECT <ul style="list-style-type: none"> Immediate effects Day 1: Patient felt very anxious, cold, restless and nauseated but reduced by dihydrocodeine. Due to poor sleep, patient took his kratom as normal Day 2: Patient felt cravings, chills, nausea, aches, pains, irritable, and visibly tremulous which all improved following dose. Blood pressure and heart rate normalized. Day 3: symptoms were subjectively and objectively much improved. Dihydrocodeine was reduced to 30 mg twice daily and lofexidine was discontinued.

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Sheleg & Collins [43] 2011 (USA)	A 44-year-old man presented to specialty clinic for alcohol and drug recovery	ACTIVE • Chronic pain syndrome (methadone and oxycodone) HISTORY • Alcohol abuse	PURPOSE • Pain • Opioid spare DOSE • 6 drops 4–6 h FORM • Oral liquid DURATION • One year	SUBJECTIVE • Time since last dose: 12 h • KAWS: cramping abdominal pain, sweating, and diarrhea • Pattern of addiction: NR A laboratory analysis of the kratom was not performed.	<ul style="list-style-type: none"> • Day 4: patient reported feeling “back to normal” albeit and was discharged with no further dihydrocodeine or lofexidine • Long-term efficacy • Patient had remained abstinent from kratom when followed up in the outpatient clinic at 2 weeks after discharge • Detoxification from kratom was described as more difficult than alcohol. • Ongoing sleep disturbance and cravings for the substance reemerged and had started to meetings for aid in abstinence
Galbis-Reig [44] 2016 (USA)	A 37-year-old white woman admitted to the inpatient mental health and addiction service after contacting the unit for treatment of an “addiction to kratom”	ACTIVE • None HISTORY • Postpartum depression (sertraline)	PURPOSE • Pain from Capel tunnel surgery FORM • Oral capsule DURATION • Two years	<p>SUBJECTIVE</p> <ul style="list-style-type: none"> • Time since last dose 10 h • KAWS: cravings, severe abdominal cramps, sweats, blurred vision, nausea, vomiting, and diarrhea • Experiences from kratom: pain relief and “boost of energy” • Pattern of addiction: hiding the bottles, failed attempt to cut back without experiencing withdrawal symptoms. Increased the use over a period of 6 months <p>unintentionally (tolerance). Was trialed on clonidine without success</p> <p>OBJECTIVE</p>	<ul style="list-style-type: none"> • Symptom-triggered clonidine at a dose of 0.1–0.2 mg every 2 h based on the clinical opioid withdrawal scale (COWS) + scheduled hydroxyzine 50 mg every 6 h + 0.1 mg/day clonidine patch • COWS use the following to assess severity: pupillary dilatation, diaphoresis, gastrointestinal distress, anxiety, fever, bone and joint pains, increased lacrimation or rhinorrhea, tremors, and yawning <p>EFFECT</p> <ul style="list-style-type: none"> • Immediate effects • COWS score was high enough for patient requiring up to 2 mg of oral clonidine over the next 36 h. <p>Hyper-autonomic symptoms improved rapidly over the course of 2 to 3 days.</p>

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Tavakoli et al. [45] 2016 (USA)	A 33-year-old man presented to family physician for a worsening of uncontrolled back pain from motor accident 3 months ago	ACTIVE • Back pain HISTORY • Auditory hallucinations • Violence and homicide attempt	PURPOSE • Pain • Opioid spare FORM • Oral pills	<ul style="list-style-type: none"> Examination was unremarkable except for mild diaphoresis of the palms and back of the neck, dilated pupil (2–3 mm) and significant cachexia. Urine toxicology was negative for all drugs of abuse. Urine MG was positive (cutoff 10 mcg/L) using liquid chromatography–mass spectrometry method <p>SUBJECTIVE</p> <ul style="list-style-type: none"> KAWS: body aches, chills, rhinorrhea, and significantly worsened irritability from his baseline Experiences from kratom: exacerbation of patient's background psychotic symptoms of hallucinations and persecutory delusions. It was beneficial for pain, but he did notice worsening in his aggression toward his spouse and coworkers. <p>OBJECTIVE</p> <ul style="list-style-type: none"> Urine tests negative for synthetic opioids and cannabinoids 	<ul style="list-style-type: none"> Started venlafaxine for depression and pregabalin for anxiety since this occurred with previous attempts to detoxify from kratom Following 3 days of admission, the patient was discharged and provided with a prescription to start naltrexone 50 mg by mouth daily to begin no sooner than 7 days for any cravings Long-term effects NR <p>INTERVENTION</p> <ul style="list-style-type: none"> None, patient was admitted to psychiatric unit and diagnosed with schizoaffective disorder, depressive type in addition to opioid use disorder Proposed to discontinue kratom use Antipsychotic medications started and patient was discharged on day 16 <p>EFFECTS</p> <ul style="list-style-type: none"> Immediate effect and long-term effects NR
Jayadeva et al. [46] 2017 (USA)	A 34-year-old Caucasian man presented to hospital requesting detoxification under inpatient detoxification unit	HISTORY • Opioid use disorder • Posttraumatic stress disorder • Major depressive disorder	PURPOSE • Opioid use DOSE • 10 g twice daily FORM • Tea	<p>SUBJECTIVE</p> <ul style="list-style-type: none"> Time since last dose: NR, self-transitioned from kratom to buprenorphine/naloxone (4 mg/1 mg) prior presentation KAWS: restlessness, anxiety, sleep disturbance, sweats, and diarrhea Pattern of addiction: escalated his use of kratom to 10 g twice daily due to KAWS Experiences following kratom administration: no feelings of euphoria, instead experiences relief from the elimination of KAWS Motive: patient wished to detoxify under specialist supervision. <p>OBJECTIVE</p> <ul style="list-style-type: none"> Urine tests negative for synthetic opioids and cannabinoids 	<p>INTERVENTION</p> <ul style="list-style-type: none"> Detoxification Self-transitioned from kratom to buprenorphine/naloxone (4 mg/1 mg) at home Continued on buprenorphine/naloxone at the hospital <p>EFFECT</p> <ul style="list-style-type: none"> Immediate effects Completed a 3-day uncomplicated detoxification and discharged to residential addiction program after detoxification Long-term effects NR

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Lydecker et al. [47] 2017 (USA)	A 29-year-old man presented to the ED complaining of pain in arms	HISTORY • Substance use disorder	PURPOSE • Opioid spare DOSE • 1 ml 6 times daily FORM • Intravenous	<ul style="list-style-type: none"> Urine toxicology was positive for opioids. SUBJECTIVE <ul style="list-style-type: none"> Time since last dose: 6 h KAWS: runny nose, watery eyes, goose bumps, the pukes and the shakes, all are less intense than opioid Experiences from kratom: initially, stimulant effects then this effect weaned hence increased the use of the product Pattern of addiction: initially drinking kratom tea daily, then several times daily, until he found a way to inject it intravenously. Now injecting kratom extract in alcohol. Tried tramadol and diphenhydramine to help with KAWS OBJECTIVE <ul style="list-style-type: none"> Normal vitals: afebrile with a pulse of 95 beats per minute, blood pressure of 138/82 mmHg Cubital fossae notable for erythema, consistent with superficial thrombophlebitis Elevated white blood cell count of 12.1 cells/μl Urine positive for tramadol, meprobamate, diphenhydramine, and APAP, but negative for MG and 7-HMG 	INTERVENTION <ul style="list-style-type: none"> Planned to detoxify but lost on follow-up Provided 1 g of cefazolin for thrombophlebitis
Mackay & Abrahams [48] 2017 (Canada)	A 29-year-old woman admitted on postpartum day 2 from another hospital with the goal of tapering her daily kratom use while admitted to perinatal addictions unit	ACTIVE • Back pain HISTORY • Anxiety • three abortions • Substance abuse (Oxycodone)	PURPOSE • Pain DOSE • 18–20 g three times daily FORM • Powder DURATION • Two years	SUBJECTIVE <ul style="list-style-type: none"> Time since last dose: 4–6 h KAWS: diaphoresis, rhinorrhea, myalgia, anxiety, nausea, diarrhea, and piloerection Experiences from kratom: effectively treated her back pain and improved her mood and anxiety. Pattern of addiction: symptoms develop if dose was delayed by 4 to 6 h. Tolerance occurred but NR the interval. 	INTERVENTION <ul style="list-style-type: none"> Detoxification (aim to reduce kratom use) Morphine 10 mg orally 3 times daily, offered because of affordability EFFECTS <ul style="list-style-type: none"> Immediate effects Kratom dose was reduced to 10 g (instead of 20 g) Symptoms improved over few days of administration Patient was slowly weaned off kratom and morphine. Long-term effects Kratom was stopped in 4 weeks after starting detoxification which was the entire length of hospitalization.

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Buresh [49] 2018 (USA)	A 60-year-old woman who was referred from intensive care for unintentional opioid overdose and now presenting to buprenorphine practice clinic for maintenance course	ACTIVE <ul style="list-style-type: none"> Alcohol dependence (remission) Chronic pain (tramadol, duloxetine, pregabalin) Opioids misuse (methadone) 	PURPOSE <ul style="list-style-type: none"> Pain DOSE <ul style="list-style-type: none"> 0.25 oz four times daily 	OBJECTIVE <ul style="list-style-type: none"> Recently delivered mother SUBJECTIVE <ul style="list-style-type: none"> Time since last dose: Self-transitioned detox after 17 h of withdrawal symptom, now unknown when detox was taken prior to presentation. KAWS: rhinorrhea, irritability, and increased pain Pattern of addiction: unable to stop using kratom due to rebound pain and withdrawal symptoms when dose is decreased OBJECTIVE <ul style="list-style-type: none"> Urine toxicology was positive for tramadol and negative for opiates. SUBJECTIVE <ul style="list-style-type: none"> Time since last dose: Self-transitioned detox after 14 h of withdrawal symptom, now unknown when detox was taken prior to present. KAWS: anxiety, edginess, and leg shaking Pattern of addiction: After initiation, patient quickly developed a tolerance and escalated use (interval NR). Once stopped, patient reported KAWS. OBJECTIVE <ul style="list-style-type: none"> Urine toxicology was positive for codeine and morphine and negative for all other substances. SUBJECTIVE <ul style="list-style-type: none"> Time since last dose: 6–12 h KAWS: dysphoria, nausea, muscle aches, sweating, goose bumps, and insomnia, rhinorrhea, diarrhea, upset stomach, anxiety, restless legs, and increased pain Pattern of addiction: Powder was hidden from family. Dose escalated from a ¼ to 1 tsp. 4 to 6 times daily in an effort to achieve 	<ul style="list-style-type: none"> Though discussed, patient wanted to be off kratom and other substance, so maintenance was not provided. INTERVENTION <ul style="list-style-type: none"> Induction/maintenance (aim to be off opioids and kratom) Started one dose of buprenorphine/naloxone 4–1 mg at home and now increased to 4–1 mg 4 times daily at hospital. EFFECT <ul style="list-style-type: none"> Immediate effects Resolution of her pain symptoms Urine drug testing has been negative for full-agonist opioids and positive for buprenorphine/noribuprenorphine. Long-term effects Follow up in 9 months shows continued pain control and functional goal INTERVENTION <ul style="list-style-type: none"> Reduced pregabalin dose (from 300 mg to 200 mg BID) INTERVENTION <ul style="list-style-type: none"> Induction/maintenance (aim to control chronic pain and KAWS) Started one dose of buprenorphine/noribuprenorphine 8–2 mg at home EFFECT <ul style="list-style-type: none"> Immediate effects During 1-month use, dose increased to 24 mg daily (dosed 6 mg 4 times daily) based on pain intensity Long-term effects Seven months after start, urine toxicology was positive for buprenorphine/noribuprenorphine and negative for other opiates
Khazaeli et al. [50] 2018 (USA)	A 52-year-old woman admitted to an inpatient acute psychiatry unit with a chief complaint of increased depression, anxiety, and fleeting suicidal thoughts. She also reported symptoms consistent with opioid withdrawal.	ACTIVE <ul style="list-style-type: none"> Depression Opioid misuse Chronic pain Anxiety (trazadone, sertraline, gabapentin, clonazepam) 	PURPOSE <ul style="list-style-type: none"> Pain DOSE <ul style="list-style-type: none"> 1 tsp. every 4–6 h DURATION <ul style="list-style-type: none"> Nine months 	OBJECTIVE <ul style="list-style-type: none"> Urine toxicology was positive for codeine and morphine and negative for all other substances. SUBJECTIVE <ul style="list-style-type: none"> Time since last dose: 6–12 h KAWS: dysphoria, nausea, muscle aches, sweating, goose bumps, and insomnia, rhinorrhea, diarrhea, upset stomach, anxiety, restless legs, and increased pain Pattern of addiction: Powder was hidden from family. Dose escalated from a ¼ to 1 tsp. 4 to 6 times daily in an effort to achieve 	INTERVENTION <ul style="list-style-type: none"> Induction/maintenance Started buprenorphine/naloxone 4/1 mg given every 2 h with close monitoring for mental status and withdrawal symptoms EFFECT <ul style="list-style-type: none"> Immediate effects Day 1: total of four doses were given and patient reported improvement of KAWS Day 2: taper off, dose was decreased to 2/0.5 mg 4 times daily

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Stanciu et al. [51] 2018 (USA)	A 26-year-old Caucasian female presented to the ED very tearful, endorsing symptoms of restlessness, generalized body aches, overwhelming anxiety, and thoughts of suicide with no particular plan	ACTIVE • None	PURPOSE • Energy DURATION • Two years	<p>pain relief, gradually over 9 months.</p> <p>OBJECTIVE</p> <ul style="list-style-type: none"> • Urine toxicology screening was positive only for benzodiazepines. • Urine testing for kratom was not done. <p>SUBJECTIVE</p> <ul style="list-style-type: none"> • Time since last dose: not reported • KAWS: anxiety • Pattern of addiction: cannot go without them over 12 h • Experiences from kratom: initially began experimenting with kratom as a “natural” energy supplement giving her energy, stamina and “into the moon.” • No background mental disorder <p>OBJECTIVE</p> <ul style="list-style-type: none"> • Vitals: tachycardia of 102 beats per minute, hypertension of 158/100, and a body temperature of 107 °F with normal pulse • COWS score of 16 	<ul style="list-style-type: none"> • Day 3: kept on same dose as maintenance dose for the rest of admission • Day 6: patient was discharged home on buprenorphine/naloxone 2/0.5 mg 4 times • Patient’s vital signs were stable in admission. • Other medications at hospitalization: lorazepam for jerks and baclofen to help with clonazepam dose tapering. <p>Home medications were resumed</p> <ul style="list-style-type: none"> • Long-term effects • Dose was later increased to 8/2 mg twice • Self-reported sober with no symptoms of opioid withdrawal or craving • Self-reported compliance to maintenance treatment for 18 months (urine samples check) <p>INTERVENTION</p> <ul style="list-style-type: none"> • Detoxification • Started symptom-triggered clonidine 0.1 mg every 2 h as needed, and on scheduled gabapentin, 300 mg, three times daily • Other: lorazepam 0.5 mg PO on two occasions, 30 min apart, with little resolution of anxiety symptoms while waiting for evaluation <p>EFFECT</p> <ul style="list-style-type: none"> • Immediate effects • Day 1: four doses of clonidine. Gabapentin did control some of the restlessness, but she had a difficult time sleeping due to sweating • Day 2: COWS reduced to 8 and only required 1 dose of Clonidine. Irritability was challenging • Day 3: COWS reduced to 1 and no clonidine was not required, and gabapentin was discontinued • Day 5: discharged from hospital without any drug • Long-term effects • NR
	A 27-year-old unmarried male was referred to a psychiatric hospital following presentation to an ED at a general hospital with complaint of suicidal ideation and feelings of hopelessness and helplessness	ACTIVE • Bipolar • Schizophrenia • Substance abuse (Clonazepam) HISTORY • Opioid abuse (Methadone maintenance)	PURPOSE • Opioid spare DOSE • 5 g per day DURATION • Three years	<p>SUBJECTIVE</p> <ul style="list-style-type: none"> • Time since last dose: 24 h • KAWS: • Pattern of addiction: requested to continue to use them during his hospitalization • Experiences from kratom: decreased his craving for opioids <p>OBJECTIVE</p> <ul style="list-style-type: none"> • Vitals: tachycardia of 102 beats per minute, hypertension of 158/100, 	<p>INTERVENTION</p> <ul style="list-style-type: none"> • For mood improvement and hallucinations, quetiapine was started. • For benzodiazepine withdrawal, diazepam taper was given then gabapentin • For KAWS (based on daily COWS assessment), patient was offered clonidine 0.1 mg three times as needed <p>EFFECTS</p> <ul style="list-style-type: none"> • Immediate effects • No COWS score exceeded 8 and the patient received a total of six doses of clonidine.

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Smid et al. [52] 2018 (USA)	A 32-year-old pregnant white woman at 22 weeks (6 months) of gestation was referred to a specialty prenatal clinic for pregnant women with substance use disorders for kratom dependence.	ACTIVE <ul style="list-style-type: none"> • Substance use disorders • Pain (oxycodone) • Anxiety HISTORY <ul style="list-style-type: none"> • Hodgkin's lymphoma (treated with radiation) 	PURPOSE <ul style="list-style-type: none"> • Pain and anxiety FORM <ul style="list-style-type: none"> • Tea DURATION <ul style="list-style-type: none"> • Several months until week 16 of gestation (4 months), but could not stop it • Overlap with pregnancy: 6 months 	<p>and a body temperature of 107 °F with normal pulse</p> <ul style="list-style-type: none"> • COWS score of 16 SUBJECTIVE <ul style="list-style-type: none"> • Time since last dose: NR • KAWS: not reported, only as she tries to cut down on use • Pattern of addiction: only as she tries to cut back on use, KAWS develop OBJECTIVE <ul style="list-style-type: none"> • Urine toxicology was negative for opioids and positive for MG and 7-HMG (61 and 980 ng/dL, respectively) using gas chromatography and mass spectrometry. 	<ul style="list-style-type: none"> • At discharge, patient showed no depressive or psychotic symptoms, and no residual craving for opioids • Long-term effects • NR INTERVENTION <ul style="list-style-type: none"> • Induction/maintenance (aim to control KAWS, pain, and prevent KANAS) but initially, detoxification was intended • Buprenorphine 8 mg EFFECT <ul style="list-style-type: none"> • Immediate effects • Initiation and stabilization were achieved at 8 mg for KAWS and pain • Maintained on buprenorphine 2 mg during pregnancy • Long-term effects • Delivered a healthy baby with no NAS, and mother was kept on buprenorphine while at hospital • Mother and neonate continued to do well, without clinical or toxicologic evidence of maternal relapse or NAS
	A term female neonate was born from a detoxified mother, yet the neonate showed signs of NAS at day 4 of age.	MOTHER <ul style="list-style-type: none"> • Active bipolar disorder (escitalopram, lamotrigine, and quetiapine) • History of substance use disorders (IV heroin) • History of alcohol use disorder (remission) NEONATE <ul style="list-style-type: none"> • NR 	PURPOSE <ul style="list-style-type: none"> • Recreational FORM <ul style="list-style-type: none"> • Inhaled DURATION <ul style="list-style-type: none"> • Started 4 months before presentation (presented on week 19 of gestation) • Overlap with pregnancy: 4 months 	SUBJECTIVE <ul style="list-style-type: none"> • Pregnant mother was initiated on buprenorphine/naloxone on week 19 of gestation for prevention of neonatal KAWS and maintained at a dose of 20 mg buprenorphine daily until delivery on week 39 of gestation • Buprenorphine/naloxone overlap = last 20 weeks of pregnancy EFFECT <ul style="list-style-type: none"> • Healthy infant delivered but shown KANAS on day 4 of life after delivery. Morphine was started and patient was weaned and discharged on hospital day 12 	INTERVENTION <ul style="list-style-type: none"> • Pregnant mother was initiated on buprenorphine/naloxone on week 19 of gestation for prevention of neonatal KAWS and maintained at a dose of 20 mg buprenorphine and 3 mg naloxone daily until delivery on week 39 of gestation • Buprenorphine/naloxone overlap = last 20 weeks of pregnancy • Healthy infant delivered but shown KANAS on day 4 of life after delivery. Morphine was started and patient was weaned and discharged on hospital day 12
Cases of kratom-associated neonatal abstinence syndrome (KANAS)					
Pizarro-Osilla [53] 2017 (USA)	A 1-day-old, term infant presented to the ED with signs of opioid withdrawal	MOTHER <ul style="list-style-type: none"> • Anxiety NEONATE <ul style="list-style-type: none"> • Hypoglycemia 	PURPOSE <ul style="list-style-type: none"> • Relaxation DURATION <ul style="list-style-type: none"> • Overlap with pregnancy: 4 months 	OBJECTIVE <ul style="list-style-type: none"> • KANAS observed: breathing difficulties, irritability, jitteriness, muscle hypertonicity, and a high-pitched, inconsolable cry 	INTERVENTION <ul style="list-style-type: none"> • Methadone IV EFFECTS <ul style="list-style-type: none"> • NR
Mackay & Abrahams	An infant, 37 preterm, was transferred to a tertiary neonatal intensive care unit (NICU) to be	MOTHER <ul style="list-style-type: none"> • Back pain NEONATE	PURPOSE <ul style="list-style-type: none"> • Pain DOSE	OBJECTIVE	INTERVENTION <ul style="list-style-type: none"> • Morphine IV up to a maximum of 10 mcg/kg/h EFFECT

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
[48] 2017 (Canada)	treated for NAS, diagnosed at day 2 of birth.	• NR	<ul style="list-style-type: none"> • 18–20 g three times daily FORM • Powder DURATION • Two years • Overlap with pregnancy: entire pregnancy 	<ul style="list-style-type: none"> • KANAS observed: feeding intolerance, jitteriness, irritability, and emesis • Increasing neonatal abstinence (NAS) scores (score type was NR) 	<ul style="list-style-type: none"> • Stepped down to oral morphine once able to tolerate • Transferred to mother on day 7 of birth
Eldridge et al. [54] 2018 (USA)	A term male neonate was admitted following birth after exhibiting signs opioid withdrawal at 33-h of age.	MOTHER <ul style="list-style-type: none"> • History of substance abuse (oxycodone, last taken 2 years before pregnancy) 	PURPOSE <ul style="list-style-type: none"> • Sleep OPioid use FORM <ul style="list-style-type: none"> • Tea DURATION <ul style="list-style-type: none"> • Overlap with pregnancy: entire pregnancy 	SUBJECTIVE <ul style="list-style-type: none"> • Mother denies KAWS on herself. • Mother toxicological screen yielded negative for opioids OBJECTIVE <ul style="list-style-type: none"> • KANAS observed: sneezing, jitteriness, excessive suck, facial excoriations, resting tremors, irritability, high-pitched cry, and hypertonia • Urine drug screen yielded a negative result of MG and 7-HMG • Finnegan scores were elevated, ranging from 9 to 14 	INTERVENTION <ul style="list-style-type: none"> • 1st line trialed: morphine 30 mcg/kg/3 h titrated per Finnegan score • 2nd line trialed for this refractory case: clonidine 1 µg/kg every 3 h EFFECT <ul style="list-style-type: none"> • First day of life: Finnegan score dropped significantly to 2 to 3 • Excessive sedation and bradycardia occurred despite rapid weaning of morphine dose and frequency, but Finnegan scores also low • Third day of life: Morphine was discontinued, but patient developed rebound withdrawal and Finnegan scores were 11 to 13 • Clonidine (1 mcg/kg every 3 h) was trialed, Finnegan scores improved, but also patient was bradycardic • Fifth day of life: clonidine was discontinued • Spontaneous improvement while off detox • Eighth day of life: patient discharged
Smid et al. [52] 2018 (USA)	A term female neonate was born from a detoxified mother, yet the neonate showed signs of NAS at day 4 of age	MOTHER <ul style="list-style-type: none"> • Active bipolar disorder (escitalopram, lamotrigine, and quetiapine) • History of substance use disorders (IV heroin) • History of alcohol use disorder (remission) NEONATE <ul style="list-style-type: none"> • NR 	PURPOSE <ul style="list-style-type: none"> • Recreational FORM Inhaled DURATION <ul style="list-style-type: none"> • Started four months before presentation (presented on week 19 of gestation) • Overlap with pregnancy: 4 months 	SUBJECTIVE <ul style="list-style-type: none"> • Pregnant mother was initiated on buprenorphine/naloxone on week 19 of gestation for prevention of neonatal KAWS and maintained at a dose of 20 mg buprenorphine and 3 mg naloxone daily until delivery on week 39 of gestation. • Buprenorphine/naloxone overlap = last 20 weeks of pregnancy OBJECTIVE <ul style="list-style-type: none"> • Healthy infant delivered but shown KANAS on day 4 of life after delivery • KANAS: NR SUBJECTIVE <ul style="list-style-type: none"> • Mother denied KAWS on herself 	INTERVENTION <ul style="list-style-type: none"> • Morphine EFFECT <ul style="list-style-type: none"> • Patient was weaned and discharged on hospital day 12.
Davidson et al. [55]	A full-term female neonate was transferred to a	MOTHER <ul style="list-style-type: none"> • Pain 	DOSE <ul style="list-style-type: none"> • 5 g 1–3 times daily 	SUBJECTIVE <ul style="list-style-type: none"> • Mother denied KAWS on herself 	INTERVENTION

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
2018 (USA)	tertiary care center after 24 h of birth due to signs of withdrawal symptoms	<ul style="list-style-type: none"> • Smoking • Anxiety (pregabalin, clonazepam) NEONATE <ul style="list-style-type: none"> • NR 	FORM <ul style="list-style-type: none"> • Oral tablets 	OBJECTIVE <ul style="list-style-type: none"> • KANAS: reduced oral intake, jitteriness, hypertonia, sneezing, and excessive crying • Small of gestational age and attributed to mother smoking • CBC was within normal limits and the urine toxicology panel was negative. • Finnegan score was consistent with KANAS (severity was > 10). SUBJECTIVE <ul style="list-style-type: none"> • Mother did not report KAWS OBJECTIVE <ul style="list-style-type: none"> • KANAS observed: jittery and have increased tone with handling (6 to 8 h of birth), excessive sucking to irritability (12-h-of-life) • Finnegan scores were elevated, at 18 	<ul style="list-style-type: none"> • Morphine PO 0.1 mg/kg/day titrated under Finnegan score monitored every 3–4 h EFFECTS <ul style="list-style-type: none"> • Infant responded to therapy and weaning was initiated on day 3 of treatment. • Infant was observed for 48 h after discontinuing and discharged after 14 days of stay.
Murthy and Clark [56] 2019 (Canada)	A live female neonate born in excellent was admitted to neonatal intensive care unit for irritability, sleeplessness between feeds and excessive sucking at 22 h of age	MOTHER <ul style="list-style-type: none"> • Asthma • Restless leg syndrome • Anxiety • Urinary tract infection 	PURPOSE <ul style="list-style-type: none"> • Anxiety DOSE <ul style="list-style-type: none"> • 3–4 times daily FORM <ul style="list-style-type: none"> • Tea FORM <ul style="list-style-type: none"> • Oral tablets DURATION <ul style="list-style-type: none"> • A year prior pregnancy 	INTERVENTION <ul style="list-style-type: none"> • Morphine EFFECTS <ul style="list-style-type: none"> • Symptoms improved by reflection of low NAS score on two occasions, once 2 days after commencing treatment and the second attempt, a few days later • Discharged on day 12 with oral morphine • Continued to be on morphine due to residual KANAS • Time to star weaning took slightly more than 2 months • Mother was motivated to detoxify so underwent a psychiatry and the addiction program and got detoxified from kratom after 7 days 	
Case of hypogonadotropic hypogonadism and hyperprolactinemia					
LaBryer et al. [57] 2018 (USA)	A 42-year-old white man who presented to primary care physician with complaints of low energy and poor libido	<ul style="list-style-type: none"> • NR 	<ul style="list-style-type: none"> • NR 	SUBJECTIVE <ul style="list-style-type: none"> • Low energy and poor libido OBJECTIVE <ul style="list-style-type: none"> • Prolactin = 24 ng/mL (reference = 2.6–12 ng/mL) • Testosterone = 8.4 (reference 8.7–25.1 pg/mL) • Normal luteinizing hormone and follicle-stimulating hormone tests • Normal thyroid-stimulating hormone test • Free T4 was NR 	INTERVENTION <ul style="list-style-type: none"> • Cessation of kratom for 2 months EFFECT <ul style="list-style-type: none"> • Symptoms resolution and levels of prolactin and testosterone normalized after 2 months • Prolactin = 6 mg/mL (reference = 2.6–12 ng/mL) • Testosterone = 14.6 pg/mL (reference = 8.7–25.1 ng/mL)
Case of severe primary hypothyroidism					
Sheleg and Collins [43] 2011 (USA)	A 44-year-old man presented to specialty clinic for alcohol and drug recovery	ACTIVE <ul style="list-style-type: none"> • Chronic pain syndrome (methadone and oxycodone) HISTORY <ul style="list-style-type: none"> • Alcohol abuse 	PURPOSE <ul style="list-style-type: none"> • Pain <ul style="list-style-type: none"> • Opioid spare DOSE <ul style="list-style-type: none"> • 6 drops 4–6 h FORM	SUBJECTIVE <ul style="list-style-type: none"> • Hypothyroidism: gained 60 pounds, lethargy, and myxedematous face developing after 7 months of use OBJECTIVE	INTERVENTION <ul style="list-style-type: none"> • Levothyroxine 150 mcg PO daily for hypothyroidism • Fifteen months after discharge, oral levothyroxine dose was reduced from 150 µg to 50 µg daily indicating improvement of thyroid function

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Cases of kratom-induced hepatitis (KIH)					
Kapp et al. [58] 2011 (USA)	A 25-year-old man who was admitted to hospital for noticeable jaundice and pruritus following 3 weeks of last kratom dose	• NR	<p>• Oral liquid DURATION One year</p> <p>DOSE • 1–2 tsp. (2.3–3.5 g) twice daily increased to 4–6 tsp.</p> <p>FORM • Tea DURATION • Three weeks</p>	<p>• Thyroid panel showed severe primary hypothyroidism</p> <p>SUBJECTIVE • Experience: mildly relaxing, causing tiredness, and noticed a loss of appetite, without observing any stimulating effects. • Increased dose by 3- to 6-times starting dose over 2 weeks then stopped abruptly • Pertinent positive: fever and chills (day 2 after cessation), intense abdominal pain and concomitant brown discoloration of the urine (day 8 after cessation), and noticeable jaundice and pruritus (day 9 after cessation) Presented on day 10 after cessation</p> <p>OBJECTIVE • Vitals were unremarkable; jaundice was prominent. • Labs on admission: Bilirubin: 28.6 mg/dL (Ref. < 0.3 mg/dL), ALP 173 U/L (ref. 40–130 U/L), AST 66 U/L (Ref. < 50 U/L), ALT 94 U/L (Ref. < 50 U/L), INR 1.15 • Infection and drug screens were negative. • Abdomen scans showed signs of steatosis of the liver. Neither gallstones nor intra- or extrahepatic bile duct dilation was detected. • Liver biopsy identified a drug-induced cholestatic injury without hepatocellular damage (so-called pure cholestasis). • Day 12 and day 14 after cessation, serum MG was 20 mcg/L. • Urine MG was positive on day 14 and negative on day 47 using gas</p>	<p>INTERVENTION • No intervention</p> <p>EFFECT • Follow-up in clinic and showed slowly falling direct bilirubin levels on day 35 and 47 from kratom cessation</p>

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Dorman et al. [59] 2014 (Germany)	A 58-year-old Caucasian man was admitted to the hospital for jaundice and liver injury suspected to be from kratom use.	ACTIVE • Schizoaffective disorder (Quetiapine, sertraline) HISTORY • KIH (1 tsp. daily for 3 months)	PURPOSE • Relaxation DOSE • Daily FORM • Tea DURATION • Two to 4 weeks	chromatography–mass spectrometry SUBJECTIVE • Pertinent positive: jaundice, dark urine • Pertinent negative: fever, rash, or pruritus • He stopped taking kratom when he developed dark urine and then sought medical attention when he developed jaundice few days after cessation. Denied taking other herbals, dietary supplements, or drugs of abuse or drinking excessive alcohol OBJECTIVE • Vitals were normal. • Mild confusion, but no evidence of edema or ascites • Labs on admission: Bilirubin: 25.6 mg/dL (Ref. < 0.3 mg/dL), ALP 790 U/L (ref. 40–130 U/L), AST 49 U/L (Ref. < 50 U/L), ALT 106 U/L (Ref. < 50 U/L), INR 1.1 • Infection and drug screens were negative. • Abdominal scan showed irregular hepatic texture, but no biliary obstruction and a liver biopsy was not performed.	INTERVENTION • No intervention EFFECT • Patient appeared stable overall and discharged 2 days later at which time liver tests were improving (but not normalized) and psychotropic medications were resumed. • Labs at discharge: Bilirubin: 20.8 mg/dL (Ref. < 0.3 mg/dL), ALP: 730 U/L (ref. 40–130 U/L), ALT 93 U/L (Ref. < 50 U/L), INR 1.0
Riverso et al. [60] 2018 (USA)	A 38-year-old man presented to the ED complaining of dark-colored urine and light-colored stools.	• NR	PURPOSE • Fatigue	SUBJECTIVE • Co-ingested APAP, but not on other medication • Pertinent positive: dark-colored urine and light-colored stools. Dark-colored urine continued to worsen whereas fever and chills improved over 4 days. • Later at the ED presentation, patient also reported sternal pleuritic no radiating chest pain, mild shortness of breath, mild cough. OBJECTIVE • No scleral icterus or jaundice shown	INTERVENTION • Supportive care with intravenous fluid EFFECT • Appeared stable overall and was discharged 8 days after presentation at which liver function had improved • Labs on discharge: Bilirubin: 1.6 mg/dL (Ref. < 1 mg/dL), ALP: 266 U/L (ref. 40–130 U/L), AST 142 U/L (Ref. < 50 U/L), ALT 410 U/L (Ref. < 50 U/L)

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Mousa et al. [61] 2018 (USA)	A 31-year-old man reported to the ED with a 4-day history of tea-colored urine, malaise, fatigue, and fever.	• NR	PURPOSE <ul style="list-style-type: none"> • Fatigue • Opioid use DURATION <ul style="list-style-type: none"> • 2 weeks 	<p>• Labs on admission: Bilirubin: 5.1 mg/dL (Ref. < 1 mg/dL), ALP: 304 U/L (ref. 40–130 U/L), AST 220 U/L (Ref. < 50 U/L), ALT 389 U/L</p> <p>• Abdominal scan shown no biliary obstruction</p> <p>• Liver biopsy showed mild portal mixed inflammation and bile duct injury.</p> <p>SUBJECTIVE</p> <ul style="list-style-type: none"> • Pertinent positive: 4-day history of tea-colored urine, malaise, fatigue, and intermittent fever <p>OBJECTIVE</p> <ul style="list-style-type: none"> • No scleral icterus was present or jaundice • Medical history, review of systems, vitals, physical examination, basic laboratory tests, viral hepatitis panel, and abdominal imaging were otherwise negative except for abnormal liver function test. • Labs on admission: Bilirubin: 2.2 mg/dL (Ref. < 1 mg/dL), ALP 191 U/L (ref. 40–130 U/L), AST 191 U/L (Ref. < 50 U/L), ALT 578 U/L (Ref. < 50 U/L) 	<p>• Loading dose of <i>N</i>-acetylcysteine (NAC) 140 mg/kg followed by 70 mg/kg maintenance dose every 4 h for 17 doses (total 18 doses)</p> <p>INTERVENTION</p> <ul style="list-style-type: none"> • Symptoms resolved after NAC and discharged on day 4 of admission • Further outpatient follow-up showed resolution of the liver injury • Labs on discharge/last day of NAC: Bilirubin: 1.7 mg/dL (Ref. < 1 mg/dL), ALP: 208 U/L (ref. 40–130 U/L), AST 191 U/L (Ref. < 50 U/L), ALT 624 U/L (Ref. < 50 U/L) • Labs on 2 months post-discharge: Bilirubin: 0.4 mg/dL (Ref. < 1 mg/dL), ALP: 52 U/L (ref. 40–130 U/L), AST 16 U/L (Ref. < 50 U/L), ALT 34 U/L (Ref. < 50 U/L)
Griffiths et al. [62] 2018 (USA)	A 21-year-old man presented to a local urgent care provider with complaints of vomiting, fatigue, abdominal pain, and brown urine.	<ul style="list-style-type: none"> • Social substances (alcohol) • Illicit drugs use (Mushrooms) 	PURPOSE <ul style="list-style-type: none"> • Recreational DOSE <ul style="list-style-type: none"> • 12 capsules daily (10 g 2 days before admission) FORM <ul style="list-style-type: none"> • Oral capsules DURATION <ul style="list-style-type: none"> • One month 	<p>• Pertinent positive: vomiting, fatigue, abdominal pain, and brown urine</p> <p>• Not taking other medications or over-the-counter products</p> <p>OBJECTIVE</p> <ul style="list-style-type: none"> • No scleral icterus • A urine drug screening was positive for cannabis (> 50 ng/ml) • Ethanol, APAP, and salicylates were within normal limits or undetectable. • A viral hepatitis panel was negative • Labs on admission: Bilirubin: 2.8 mg/dL (Ref. < 1 mg/dL), ALP: 193 U/L (ref. 40–130 U/L), 	<p>• Supportive care with intravenous fluid 200-ml bolus then 150 ml/h infusion, 1 dose of 4 mg ondansetron intravenous for nausea, 20 mg famotidine by mouth twice daily, and 50 mg tramadol by mouth every 6 h as needed</p> <p>INTERVENTION</p> <ul style="list-style-type: none"> • Fluids were started in the ED and continued for 24 h • Received 3 doses of tramadol, each dose about 12 h apart • Discharged after 2 days without indication of liver function trends • Labs on discharge: Bilirubin: 2.3 mg/dL (Ref. < 1 mg/dL), ALP: 152 U/L (ref. 40–130 U/L), AST 166 U/L (Ref. < 50 U/L), 139 U/L (Ref. < 50 U/L), INR 1.09

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Antony & Lee [63] 2018 (USA)	A 70-year-old man presented with jaundice.	ACTIVE • Hypertension (amlodipine) • Osteoarthritis (oxycodone)	PURPOSE • Pain DOSE • Twice daily DURATION • Two-three weeks	<p>AST 294 U/L (Ref. < 50 U/L), ALT 139 U/L (Ref. < 50 U/L)</p> <ul style="list-style-type: none"> • Abdominal scan shown dilation of the bile duct • Abdominal imaging revealed hepatosplenomegaly with a small ascites • World Health Organization Uppsala Monitoring Centre classified KIH risk under possible.” <p>SUBJECTIVE</p> <ul style="list-style-type: none"> • Positive pertinent: yellow skin, nausea, fatigue, weakness, and 9 kg of weight loss in 3 weeks • Negative pertinent: fever, chills, vomiting, abdominal pain, diarrhea <p>OBJECTIVE</p> <ul style="list-style-type: none"> • Afebrile, stable, and no encephalopathy • Viral hepatitis, and jaundice work up was negative • Abdominal scans were unrevealing. • Labs on admission: Bilirubin: 33.7 mg/dL (Ref. < 1 mg/dL), ALP: 230 U/L (ref. 40–130 U/L), AST 53 U/L (Ref. < 50 U/L), ALT 59 U/L • Serum creatinine was 2.27 mg/dL indicating kidney injury • The extensive workup for acute viral hepatitis, various liver diseases, and jaundice was negative, and imaging of the abdomen was • Roussel Uclaf Causality Assessment Method (RUCAM) classified risk under “highly probable” <p>INTERVENTION</p> <ul style="list-style-type: none"> • Supportive care with intravenous fluid <p>EFFECT</p> <ul style="list-style-type: none"> • Initially, symptoms of cholestasis improved with supportive care which allowed the patient to be discharged. Patient was readmitted again for anemia 3 days after. • Bilirubin on readmission was 17.8 mg/dL and improved to 15.7 before discharge • Serum creatinine on readmission was 2.94 mg/dl and improved to 2.05 mg/dl after hydration • Creatinine improved but remained mildly elevated at 1.8 mg/dL after 3 months 	
Tayabali et al. [64] 2018 (USA)	A 32-year-old Caucasian man presented to the ED with yellow looking skin associated with nausea, fatigue, joint pains, and night sweats of 2 weeks duration.	ACTIVE • Hypertension • Anxiety • Back pain (APAP)	PURPOSE • Pain DOSE • 60 tablets per week FORM • Oral tablets	<p>SUBJECTIVE</p> <ul style="list-style-type: none"> • Positive pertinent: yellow skin, fatigue, joint pains, night sweats, pale stools and dark urine • Negative pertinent: pruritus, weight changes or appetite <p>INTERVENTION</p> <ul style="list-style-type: none"> • Received a loading dose of 150 mg/kg/h of NAC, but patient developed an anaphylactic reaction and doses were held <p>EFFECT</p>	

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Osborne et al. [65] 2019 (USA)	A 47-year-old man presented to internal medicine clinic with complaints of dark urine, pruritus, subjective fevers, and fatigue for several days' duration.	ACTIVE <ul style="list-style-type: none"> Hypertension Prediabetes Anxiety Depression (Valsartan, metoprolol, escitalopram, clonazepam) 	PURPOSE <ul style="list-style-type: none"> Pain DOSE <ul style="list-style-type: none"> Multiple times DURATION <ul style="list-style-type: none"> Around time of presentation 	<p>• No allergies, no smoking, no illicit drug use, no sick contacts, recent hospitalizations, or travel</p> <p>OBJECTIVE</p> <ul style="list-style-type: none"> Clinically stable with a slightly elevated blood pressure of 141/82 mmHg Jaundiced skin and icterus in the sclera and oral mucosa Infection and drug screens were negative. Labs on admission (day 1): Bilirubin: 6.3 mg/dL (Ref. < 1 mg/dL), ALP: 391 U/L (ref. 40–130 U/L), AST 222 U/L (Ref. < 50 U/L), ALT 365 U/L (Ref. < 50 U/L) Abdominal scan ruled out biliary tract disease International Organizations of Medical Sciences Scale classified KIH risk under “probable” Urine MG = 47.8 mg/L and urine 7-HMG (Qualitative) = Positive using liquid mass chromatography spectrometry test <p>SUBJECTIVE</p> <ul style="list-style-type: none"> Positive pertinent: fevers (ranging from 100 °F to 101 °F for 2 days), dysuria, urinary frequency, urinary urgency, and darkening of his urine despite large volumes of oral intake, generalized malaise, a reduction in appetite, and pruritus No recent travel, hospitalizations, new medications APAP for symptom control (not more than 3000 mg limit) Negative pertinent: rash or change in skin color <p>OBJECTIVE</p> <ul style="list-style-type: none"> Vitals are normal. Non-icteric sclera and sublingual jaundice Viral hepatitis workup was negative. 	<ul style="list-style-type: none"> Admitted for 2 days, liver enzymes started trending down, jaundice resolved, and the patient reported feeling better. Upon discharge, liver enzymes had not normalized, but considered stable and safe for discharge. Labs on discharge (day 3): Bilirubin: 2.8 mg/dL (Ref. < 1 mg/dL), ALP: 314 U/L (ref. 40–130 U/L), AST 136 U/L (Ref. < 50 U/L), ALT 299 U/L (Ref. < 50 U/L)

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Case of posterior reversible leukoencephalopathy syndrome (PRES)					
Castillo et al. [66] 2017 (USA)	A 22-year-old man presented with a severe headache (“absolute worse pounding”) that had started earlier that morning.	ACTIVE • Depression (fluoxetine) • Insomnia (quetiapine) • Substance misuse (dextroamphetamine and marijuana)	PURPOSE • Abuse	<p>SUBJECTIVE</p> <ul style="list-style-type: none"> Severe headache not unrelieved by APAP Co-ingested dextroamphetamine <p>OBJECTIVE</p> <ul style="list-style-type: none"> Disorientation and aphasia, Glasgow coma scale score 14 Blood pressure 180/105 mmHg, heart rate 54 beats per minute Head imaging consistent with PRES and a left occipitoparietal intraparenchymal bleed Drug screen was positive for amphetamine, benzodiazepine, cannabinoids, and opiates. <p>INTERVENTION</p> <ul style="list-style-type: none"> Supportive measure with nicardipine infusion Patient was hospitalized for 5 days during which his head imaging improved, and blood pressure was within normal limit 	<p>40–130 U/L, AST 34 U/L (Ref. < 50 U/L), ALT: 45 U/L (Ref. < 50 U/L)</p> <ul style="list-style-type: none"> Labs on admission: Bilirubin: 5.8 mg/dL (Ref. < 1 mg/dL), ALP: 170 U/L (ref. 40–130 U/L), AST 108 U/L (Ref. < 50 U/L), ALT 265 U/L (Ref. < 50 U/L) Ultrasound identified hepatic steatosis Abnormal labs: ferretin, CMV IgM RUCAM score was suggestive of a “probable” diagnosis.
Cases of seizure and coma					
Boyer et al. [41] 2008 (USA)	A 43-year-old man admitted for evaluation of a generalized tonic-clonic seizure and coincided with KAWS.	ACTIVE • Chronic pain HISTORY • Substance abuse (hydromorphone injection)	PURPOSE • Pain • Opioid spare FORM • Tea DURATION • 3.5 years	<p>SUBJECTIVE</p> <ul style="list-style-type: none"> Co-ingested with 100 mg of modafinil with kratom and developed tonic-clonic seizure lasting for 5 min Denied previous history of seizures or head trauma, alcohol, or recent illicit drug abuse <p>OBJECTIVE</p> <ul style="list-style-type: none"> Physical exam was normal except for meiosis. Laboratory studies were normal. Toxicology screening identified modafinil <p>SUBJECTIVE</p> <ul style="list-style-type: none"> Co-ingested with <i>Datura stramonium</i> teas <p>INTERVENTION</p> <ul style="list-style-type: none"> Nothing provided for seizure prophylaxis 	
Nelsen et al. [67] 2010 (USA)	A 64-year-old man was brought up to the ED by emergency services after found	ACTIVE • Recent colostomy	PURPOSE • Pain	<p>SUBJECTIVE</p> <ul style="list-style-type: none"> Co-ingested with <i>Datura stramonium</i> teas <p>INTERVENTION</p> <ul style="list-style-type: none"> Lorazepam 2 mg and a loading dose of 1 g of phenytoin 	EFFECT

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
	unconscious and seizing at home.	<ul style="list-style-type: none"> • Chronic pain (Oxycodone) • Depression (Amitriptyline) 		<ul style="list-style-type: none"> • 1st seizure: occurred 30 min after administering kratom at home and witnessed by wife. Once EMS arrived, the seizure has already terminated. • 2nd seizure: occurred after 1 h of arrival at ED <p>OBJECTIVE</p> <ul style="list-style-type: none"> • Glasgow coma score was 6, heart rate 110 bpm, blood pressure 143/70 mmHg • Lower extremity spasticity on manipulation • APAP, salicylate, and ethanol were negative, but urine screening was positive for oxycodone, cannabinoid, and antidepressants. • MG in the urine was 0.167 ± 0.015 mg/L using high-performance liquid chromatography coupled to an electrospray tandem mass spectrometry. • Head imaging without contrast was suspicious for a possible hypersensitivity in the right occipital lobe. 	<ul style="list-style-type: none"> • Patient was intubated and extubated after 30 h (fully awake)
Cases of acute respiratory distress syndrome (ARDS)					
Pathak et al. [68] 2014 (USA)	A 22-year-old Hispanic man who was brought to the ED after found down in the yard ingesting kratom capsules.	<ul style="list-style-type: none"> • NR 	<p>FORM</p> <ul style="list-style-type: none"> • Oral capsule 	<p>SUBJECTIVE</p> <ul style="list-style-type: none"> • Co-ingested alcohol <p>OBJECTIVE</p> <ul style="list-style-type: none"> • Hypoxic and chest radiograph showed bilateral opacity • Blood ethanol level was high, other toxicology screen was negative • Bronchoscopy did not show infection or alveolar hemorrhage • Echocardiogram was normal <p>SUBJECTIVE</p> <ul style="list-style-type: none"> • Worsening cough and dyspnea requiring readmission <p>OBJECTIVE</p> <ul style="list-style-type: none"> • Chest radiograph demonstrated bilateral patchy airspace disease 	<p>INTERVENTION</p> <ul style="list-style-type: none"> • Started on volume control ventilation but he continued to be hypoxic despite being on 100% FIO2 and PEEP of 15. He was switched to airway pressure release ventilation and was on FIO2 of 100% <p>EFFECT</p> <ul style="list-style-type: none"> • Also developed renal failure requiring dialysis • Improvement occurred, so patient was slowly weaned off the ventilator and was extubated after 2 weeks <p>INTERVENTION</p> <ul style="list-style-type: none"> • Started on broad-spectrum antibiotics • Developed severe hypoxemic respiratory failure requiring mechanical intubation <p>EFFECT</p> <ul style="list-style-type: none"> • Patient improved and was extubated 3 days diuresis and lung protective ventilation
Jaliawala et al. [69] 2018 (USA)	A 32-year-old woman presented with worsening cough and dyspnea requiring readmission from recent community-acquired pneumonia.	<ul style="list-style-type: none"> • Hypertension • Back pain (Opiates) • Recent hospitalization from community-acquired pneumonia 	<ul style="list-style-type: none"> • NR 		

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Cases of overdose					
Overbeek et al. [70] 2019 (USA)	A 38-year-old female presented to ED for altered mental status and decreased respiratory rate.	ACTIVE HISTORY <ul style="list-style-type: none"> • Depression • Prior hospitalization for altered mental status, likely due to polysubstance overdose 	• NR	<ul style="list-style-type: none"> • Infectious workup, including respiratory viral panel, bronchoalveolar lavage, and blood cultures was negative • Bronchoscopy did not show infection or alveolar hemorrhage • Echocardiogram of left ventricular ejection was normal 	<p>SUBJECTIVE</p> <ul style="list-style-type: none"> • Admitted using kratom upon discharge though she denied intentional overdose <p>OBJECTIVE</p> <ul style="list-style-type: none"> • Obtunded with minimal responsiveness to painful stimuli • Experiencing respiratory depression with bradypnea • Urine was positive for kratom only, when gas chromatography/mass spectrometry was used <p>INTERVENTION</p> <ul style="list-style-type: none"> • Received two doses of 0.4 mg of naloxone for concern of opioid toxidrome and respiratory depression <p>EFFECT</p> <ul style="list-style-type: none"> • Patient's depressed mental status resolved, and respiratory rate increased • Other: she was monitored in the ED, receiving supportive care and intravenous fluids, haloperidol for acute agitation (though that worsened her mental status for 12 h without affecting respiratory drive) • Patient improved with supportive care over the next 24 h
Palasamudram Shekar et al. [71] 2019 (USA)	A 36-year-old Caucasian male presented to ED intubated by EMS after found unresponsive at home by his family.		<p>PURPOSE</p> <ul style="list-style-type: none"> • Stamina <p>DOSE</p> <ul style="list-style-type: none"> • 60 tablets per week <p>FORM</p> <ul style="list-style-type: none"> • Oral tablets 	<p>SUBJECTIVE</p> <ul style="list-style-type: none"> • Kratom was brought to ED with family <p>OBJECTIVE</p> <ul style="list-style-type: none"> • Naloxone was administered by the EMS and further intubated • Glasgow coma scale (GCS) of 3; pinpoint pupil and not reactive to light and cool peripheries • Vitals: heart rate (HR) 130 bpm, blood pressure (BP) 80/40 mmHg, temperature 36.8 °C, partial pressure of oxygen (PaO₂) of 200 on mechanical ventilator support, with fraction of inspired oxygen 80% • Labs on admission: AST 1347 U/L, ALT 3717 U/L, hyperkalemia, acute kidney injury, increased serum anion gap of 18, lactic acid of 7.1 mmol/L, and creatinine kinase of 700 U/L • Urine and blood toxicology screens were negative, and only positive to 	<p>INTERVENTION</p> <ul style="list-style-type: none"> • Patient was hemodynamically stabilized with fluid resuscitation and intravenous norepinephrine <p>EFFECT</p> <ul style="list-style-type: none"> • Over the week, pupillary reflexes returned to normal, neurological examination, vital signs and the abnormal laboratory values also normalized. • Patient was extubated by the end of week two discharged to an acute rehabilitation institute for physical therapy

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Cases of fatalities					
Authors, year (country)	Presentation		Comorbidity	Time to autopsy	Mitragynine level detected
Holler et al. [72] 2011 (USA)	20-year-old man found dead at site		• NR	• NR	B: 0.39 mg/L U: 1.2 mg/L
Kronstrand et al. [73] 2011 (Sweden)	Case series of 9 fatalities aged 22 (least) to 35 (highest)	• NR (2 cases) • Substance abuse (7 cases)	• NR	• Pulmonary congestion and/or edema: (11 cases) • Liver steatosis (2 cases) • Brain edema (4 cases)	B: 0.07 mg/L (least) to 0.18 mg/L (highest) U: NR
Neeman et al. [74] 2013 (USA)	17-year-old man found dead at site		• Substance abuse • Back pain	• NR	B: 0.60 mg/L U: NR
McIntyre et al. [75] 2014 (USA)	24-year-old man pronounced dead after EMS arrival to site		• Alcohol abuse • Depression	• 29 h	B: 0.23 mg/L U: 0.37 mg/L
Karinen et al. [76] 2014 (Norway)	A man found dead at site		• Substance abuse	• 72 h	B: 1.06 mg/L U: 3.47 mg/L
Domingo et al. [77] 2017 (Germany)	Case series of 2 fatalities aged 20 and 22 males that were found dead at site		• 1st case: abuse and psychosis • 2nd case: autism	• Both in 48 h • 2nd case: NR	B: 0.79 mg/L and 0.01 mg/L U: NR and 1.2 mg/L
Aggarwal et al. [78] 2018 (UK)	26-year-old pronounced dead after arrival to ED		• NR	• NR	B: negative U: negative
Hughes [79] 2018 (USA)	A 27-year-old man was found deceased inside his secured residence.		• Asperger syndrome • Bipolar disorder	• NR	B: positive U: NR

Table 1 (continued)

Authors, year (country)	Patient	Comorbidity	Kratom use	Assessment	Intervention and progress
Gershman et al. [80] 2019 (USA)	Case series 15 fatalities median age of 28 years (range, 24 to 53) whom 13 were males and 2 were females of which 14 were found unresponsive at site and one patient developed apparent seizure and cardiac arrest		<ul style="list-style-type: none"> Substance abuse Varied 	<p>wet clothing adjacent to a bathtub full of water</p> <ul style="list-style-type: none"> Seizure/convulsions (evidenced by the intramuscular hemorrhage of the tongue) Deaths from MG only (4) Hepatomegaly or hepatic injury (2) Interstitial nephritis (1) Mechanical asphyxia (1) Seizure and cardiac arrest (1) 	<p>11 cases involved multidrug ingestion (two to six drugs)</p> <p>8 persons had positive test results for opioids</p> <p>B: 5 were positive and 10 had quantified levels between 16 mcg/L (least) to 4.8 mg/L (highest)</p> <p>U: NR</p>

APAP acetaminophen, *B* blood, *ED* emergency department, *EMS* emergency medical service, *MG* mitragynine, *NAC* N-acetylcysteine, *NR* not reported in case, *isp* teaspoonful, *U* urine

times their initial dose within as early as a few weeks [44, 50] to achieve the same effect. Perceived experiences may also change with the course of intake. Generally, initial experience is beneficial; some patients describe a sense of euphoria, productivity, relaxation, and pain control. Addiction has led to intravenous administration of kratom extract with reported occurrences of thrombophlebitis and infection requiring antibiotics [47]. Duration of kratom addiction ranges from 1 to 3 years, and the doses used by addicted patients ranged from 14 to 42 g per day. KAW was described in several adult populations: those with chronic pain, substance use disorder, pregnant women, and recently delivered mothers. Most patients presented to a healthcare professional with self-identified symptoms of withdrawal and expressed their desire to obtain a supervised kratom detoxification or induction/maintenance regimen because of a failed attempt to self-abstain. Many patients often encounter KAW following use as an opioid alternative for pain control or reduction of chronic opioid use. Patients have also described withdrawal after recreational intravenous use along with other illicit substances. Symptoms of KAW generally develop within 6–12 h after last reported use. Symptoms have included rhinorrhea, restlessness, anxiety, irritability, sleep disturbance, sweating, chills, craving, pain, pruritis, goose bumps, abdominal cramps, and diarrhea. Though similar to opioid withdrawal, KAW has been reported to be less severe. Change in patient's psychiatric functioning has not been reported except in patient with a diagnosed schizoaffective disorder [45, 51]. Substance-seeking behavior has been observed, and some patients may hide doses after claiming abstinence. Case reports have highlighted the benefits of using pharmacological interventions for the purpose of long-term abstinence from kratom use via maintenance therapies [41, 49, 50, 52] or acute control of KAW [42–44, 46, 48, 51] via detoxifying regimens.

For induction/maintenance, only partial μ -opioid receptor agonist regimens have been used, such as buprenorphine plus naloxone [41, 49, 50, 52], buprenorphine/norbuprenorphine [49], or buprenorphine [52]. These regimens showed benefits beyond control of KAW such as reducing dose requirements of pain medication [49], or prevention of KANAS [52]. Symptom-triggered dose-escalation was used for immediate effects, often escalating the buprenorphine dose by 2–4 mg as needed. To monitor adherence to therapy and abstinence from kratom, blood and urine testing for buprenorphine, MG, and 7-HMG was performed.

For detoxification regimens, shorter course therapies were used and their efficacy on kratom abstinence beyond the supervised course is not reported. Agents used included partial μ -opioid receptor agonists such as buprenorphine [43] or buprenorphine/naloxone [46], weak or full μ -opioid receptor

agonists such as dihydrocodeine [42], morphine [48], or alpha-2 agonists such as oral clonidine [44, 51]. Antihistamines or pregabalin were added in some instances for symptom management.

Kratom-Associated Neonatal Abstinence Syndrome [48, 52–56]

In Smid and colleagues' case, kratom use was stopped and kratom-associated neonatal abstinence syndrome (KANAS) was prevented when a buprenorphine regimen was started in week 22 of gestation. However, this same regimen failed to prevent KANAS in another pregnant woman when it was started at week 19 of gestation [52]. In one case report, kratom was used by the mother regularly for 2 years [48]. In all cases, kratom use overlapped with the entire course of pregnancy. KANAS occurred in 6–96 h after birth, with noted effects including reduced oral intake, excessive sucking, jitteriness, irritability, facial excoriations, hypertonia, sneezing, and excessive inconsolable high-pitched cry. The Finnegan score is a nursing assessment tool that grades the severity of the most common signs and symptoms of NAS, producing a final score with increasing severity.

It was used in three KANAS cases to grade the severity and guide therapy [54–56]. Their Finnegan score was calculated to be at the "Severe" category threshold (> 9 points) on presentation. Management of KANAS involved administration of full μ -opioid receptor agonists for detoxification. Almost all cases used morphine; only one case used intravenous methadone. Two cases reported using morphine as 10 mcg/kg/h either continuously or administered every 3 h [48, 54] and one case used 100 mcg/kg/day [55]. In all cases, the neonate responded to therapy on initiation. The Finnegan score was reported to drop by 7–9 points from baseline presentation indicating an improvement of KANAS. However, bradycardia and excessive sedation were associated with morphine use [54]. Weaning from morphine therapy was initiated by day 2 or 3. Oral morphine was used as a step-down approach once oral intake was tolerated. Though morphine has shown success in KANAS, Eldridge and colleagues' case report has indicated possible rebound of KANAS following morphine discontinuation [54]. The cause was thought to be premature discontinuation 2 days after the start of morphine therapy. In this circumstance, clonidine 1 mcg/kg every 3 h subsequently showed improvement in NAS scores. This therapy was used for 1 day and discontinued thereafter. Total days of stay for patients ranged from 8 to 14 days but weaning off morphine can take up to 2 months due to risk of rebound KANAS [56]. In Davidson and colleagues' case report, the neonate was monitored for 48 h after discontinuation of therapy [55].

Endocrine Effects: Hypothyroidism and Primary Hyperprolactinemia [43, 57]

There were two cases that reported effects on the endocrine system. In LaBryer and colleagues' case report, kratom administration was associated with elevated prolactin and reduced testosterone levels leading to hyperprolactinemia and hypogonadotropic hypogonadism without an alternative identifiable cause [57]. The clinical significance of this change was manifested by decreased energy and libido. Cessation of administration for 2 months lead to normalization of these hormones without a need for intervention. Notably, thyroid-stimulating hormone (TSH) levels were normal in this case. Sheleg and Collins presented a case with KAWS which included signs and symptoms of hypothyroidism confirmed by elevated TSH [43]. This developed after 7 months of consuming kratom tincture daily. The patient received an opioid detoxification regimen using buprenorphine for KAWS and levothyroxine for hypothyroidism. Fifteen months later, levothyroxine dose was reduced to 50 mcg per day after improvement in thyroid function. Conversely, a cross-sectional study of 19 long-term kratom consumers (76 to 94 mg of MG per day for more than 2 years) neither found the substance impairing to the levels of tetraiodothyronine, testosterone, or gonadotrophins nor did it show a dose-dependent effect of kratom on these hormones [81].

Kratom-Induced Hepatotoxicity [58–65]

Kratom-induced hepatotoxicity (KIH) has been reported after 2 to 4 weeks of use and rechallenge has led to recurrence [59, 65]. The reported dose resulting in KIH was 14 to 21 g per day. In one case report, there was rapid dose-escalation (3 to 6 times the starting dose in 2 weeks) [58]. In all cases, patients presented to the emergency department for symptoms associated with hepatotoxicity including at least one of the following symptoms: dark-colored urine, light-colored stools, profound weakness, weight loss, nausea, vomiting, fever, or night sweats. Dark-colored urine was the most commonly reported symptom. Yellow skin, scleral icterus, and pruritus were also reported. Most patients were hemodynamically stable on presentation; one case showed mildly elevated blood pressure at > 140/80 mmHg in a patient with chronic hypertension [64]. The diagnosis of KIH was made on the basis of exclusion of all other causes of hepatotoxicity. An extensive workup for acute viral hepatitis A, B, and C and assays of hepatotoxic substances such as salicylates, acetaminophen, and CNS medications were used to determine if the exhibited hepatotoxic effects were correlated. Four case reports studied the likelihood of KIH using association scales in which all found a 'probable' association [62–65]. Scales used included the Roussel Uclaf Causality Assessment Method, World Health

Organization Uppsala Monitoring Centre and the International Organizations of Medical Sciences Scale. Jaundice was reported in four cases where the total bilirubin was the highest of all KIH cases, ranging from 6.5 mg/dL to 33.7 mg/dL (reference < 1 mg/dL) [58, 59, 63, 64]. After kratom cessation, total bilirubin decreased within 2 days to 7 days [58–64]. The highest alkaline phosphatase recorded was 790 units/L (reference 35–129 units/L). Complete normalization of total bilirubin and alkaline phosphatase occurred approximately 2 months after cessation [61, 65]. Early reports of KIH confirmed intrahepatic cholestasis based on hepatic function tests, abdominal and hepatic imaging, and histological findings. More recently, two case reports highlighted the possibility of a hepatocellular injury [62, 65]. Both of these two cases had confounding causes for hepatocellular injury, including positive IgM for cytomegalovirus [65] and positive urine cannabinoid [62].

In two case reports, N-acetylcysteine (NAC) was offered as hepatoprotective agent. Mousa and colleagues case reported using intermittent bolus infusion regimen (140 mg/kg followed by 70 mg/kg for 18 doses) in which the patient received the full 18 doses over a 4-day course and authors reported resolution of symptoms and down-trending hepatic enzymes [61]. Tayabali and colleagues started NAC with a loading dose of 150 mg/kg but the patient developed an anaphylactoid reaction soon after the loading dose was administered resulting in a termination of infusion within an hour after initiation [64]. Although signs and symptoms were reported to be improved in 2 days, the role of NAC in KIH is not fully understood or established.

Central Nervous System Effects: Posterior Reversible Encephalopathy Syndrome and Seizure [51, 66, 67]

Posterior reversible encephalopathy syndrome and seizure (PRES) has been reported in patients that combined kratom use with marijuana, fluoxetine, and quetiapine [66]. In this patient, supportive care and lowering blood pressure with nicardipine infusion helped to improve the patient's condition. Two cases reported of seizure activity within 30 min of kratom ingestion in addition to animal studies previously mentioned [25], indicate that kratom may be a pro-convulsant [41, 67]. These cases also detected levels of other substances including modafinil and antidepressants which are known to lower seizure threshold. The dose and duration of kratom use in these cases was not reported. Standard medications for seizure control such as lorazepam and phenytoin were used successfully in reversing the onset of the seizure. In one case, the urine concentration of MG was measured at 0.167 mg/L. Interestingly, this level is half the MG urine concentration in reported fatalities (range from 0.37 to 3.47 mg/L) [72, 74, 76, 77].

Acute Respiratory Distress Syndrome [68, 69]

Two patient cases have reported respiratory compromise leading to acute respiratory distress syndrome (ARDS) and subsequent need for mechanical ventilation. In both cases, all other causes of respiratory failure from infectious or hemorrhagic causes were ruled out. In the case reported by Pathak and colleagues, the patient was witnessed to have ingested both kratom and alcohol [68]. The duration for mechanical ventilation was for 2 weeks in this patient. In the case reported by Jaliawala and colleagues, mechanical ventilation was needed for 3 days [69]. Both cases reported no attempt to reverse kratom with naloxone.

Toxidromes and Fatalities [70–80]

Kratom toxicity is presumed to resemble an opioid toxidrome: manifested by mydriasis, depressed respiratory function, altered mental status, hypotension, and hypothermia. Two recent case reports showed the role of naloxone reversal on the kratom toxidrome, although it was administered due to suspected co-intoxication with an opioid [70, 71]. In the case of Overbeek and colleagues, the patient received two prehospital doses of naloxone 0.4 mg which led to improvement in respiratory rate and mental status [70]. With supportive care and intravenous fluids, the patient continued to improve over a 24-h period and ultimately survived. Shekar and colleagues reported a case where additional measures were needed following the naloxone reversal dose [71]. The patient was discharged to a rehabilitation institute 2 weeks

after they were admitted to the inpatient facility. The patient's urine 7-HMG was greater than 500 mcg/L.

In the fatal case reported by Aggarwal and colleagues, the patient presented to the hospital with cardiac arrest [78]. Initially, return of spontaneous circulation (ROSC) was achieved within 1 h of hospital arrival with advanced cardiac life support (ACLS) including vasopressors, inotropes, and sodium bicarbonate. Naloxone was given as an opioid antagonist, but its effect was non-discernible. A standard lipid emulsion dose (1.5 mL/kg intravenous bolus) was also administered with an observed response for approximately 1 h, which resulted in a 16% improvement in alveolar-arterial oxygenation lasting for only a few minutes followed by a 30% reduction in epinephrine requirement lasting approximately 1 h. However, the patient's cardiorespiratory function subsequently deteriorated leading to death 12 h after ROSC. The author reported modest cardioprotective properties of intralipid on assumption of cardiotoxicity from kratom components. Neither qualitative nor quantitative serum assays for kratom were investigated, and the amount of the reported ingestion was unknown. The urine was negative for MG but positive for codeine, which the patient allegedly took only one standard dose.

Most fatalities were young males with a history of substance abuse or psychiatric disorder. All fatalities were pronounced dead at the scene, except two cases in which the patients were brought to an emergency department. Attempts with ACLS were unsuccessful [73, 78]. In both cases that presented to the emergency department, kratom was suspected to be ingested within 24 h prior to presentation [73, 78]. In the majority of fatal cases, the cause of death was attributed to pulmonary congestion and/or edema. Other causes of death were liver steatosis, brain edema,

Fig. 2 Assessment of kratom safety and management of kratom abstinence

Table 2 Management considerations for kratom-associated adverse events and toxicities

	Case report summaries	Management considerations in addition to standard care
Kratom-associated withdrawal symptoms (KAWS)	<ul style="list-style-type: none"> Onset occurred within 6–12 h after kratom cessation. Symptoms presented similar to opioid withdrawal; rhinorrhea, restlessness, anxiety, irritability, sleep disturbance, sweats, chills, craving, pain, itch, goose bumps, abdominal cramps, and diarrhea. Tolerance occurred weeks to months and patients started dose-escalation starting in weeks after first intake. Blood or urine samples could be tested for principal substances in kratom; mitragynine and 7-hydroxymitragynine. Occurred more often in patients with chronic pain or polysubstance abuse; especially opioids abuse disorder. 	<ul style="list-style-type: none"> Induction/maintenance therapies may be useful for prevention of kratom-associated neonatal abstinence syndrome in expecting mother, reducing pain medication dose, reducing pain intensity, or establishing kratom abstinence. Detoxification therapies may be used for acute KAWS. Opioid withdrawal scales used may be used for symptom-triggered strategy in dose-escalation. Potential agents: buprenorphine-alone, buprenorphine/naloxone, or replacement opioids when partials agonist are not available. Adjunctive therapy, such as clonidine, can be used for symptoms of acute withdrawal. Blood or urine samples of mitragynine and 7-hydroxymitragynine may be used to establish abstinence from kratom and buprenorphine levels used to establish adherence to maintenance therapy.
Kratom-associated neonatal abstinence syndrome (KANAS)	<ul style="list-style-type: none"> Onset has occurred in 8–96 h-of-life with increasing intensity. Symptoms may include reduced oral intake, excessive suck, jitteriness, irritability, facial excoriations, hypertonia, sneezing, and excessive inconsolable high-pitched cry. 	<ul style="list-style-type: none"> Maternal induction/maintenance therapies may be useful for prevention of kratom-associated neonatal abstinence syndrome. Neonatal detoxification therapies include methadone or morphine-based therapies. Clonidine has been used for patient intolerant to first-line therapy. Finnegan score can be used for dose-titrating and monitoring for efficacy. Caution with morphine side effects including bradycardia and sedation. Neonates should be monitored after discontinuation for rebound symptoms.
Hypothyroidism	<ul style="list-style-type: none"> Onset occurred in 7 months after kratom initiation Symptoms included weight gain, lethargy, and myxedematous face Thyroid function panel was consistent with hypothyroidism. 	<ul style="list-style-type: none"> Correct with levothyroxine and titrate according to thyroid function panel. Kratom discontinuation and appropriate detoxification schedule may be needed.
Hypogonadism	<ul style="list-style-type: none"> Symptoms included low energy and poor libido Prolactin level and testosterone level were consistent with primary hypogonadism. 	<ul style="list-style-type: none"> Symptom resolution and hormonal normalization may not occur for months after kratom discontinuation.
Kratom-induced hepatotoxicity (KIH)	<ul style="list-style-type: none"> Patients may present with jaundice and dark-colored urine, ascites and mild renal failure have also occurred. Onset has occurred in 2–4 weeks following ingestion or excessive dose-escalation. Cholestasis injury or hepatocellular injury may occur. 	<ul style="list-style-type: none"> Kratom discontinuation and appropriate detoxification schedule was needed. Supportive care with intravenous hydration was included. Longer hydration up to 24-h session was provided in acute kidney injury. N-acetylcysteine has been used for symptom improvement. In cases, bilirubin trended down in 2–7 days and resolution occurred in 2–3 months. Alkaline phosphatase (ALP) normalized in 60 days.
Posterior reversible encephalopathy syndrome (PRES)	<ul style="list-style-type: none"> Accompanied with severe headache, disorientation, and aphasia Vital signs and head imaging consistent with PRES including elevated blood pressure and Glasgow coma scale (GCS) CNS-modifying medications and illicit substances were co-ingested causing possible kratom-drug interaction or drug-drug interaction; namely fluoxetine, dextroamphetamine and quetiapine, amphetamines, and marijuana. 	<ul style="list-style-type: none"> Kratom discontinuation and appropriate detoxification schedule was needed. Supportive care with nicardipine infusion for control of blood pressure was included.
Seizure	<ul style="list-style-type: none"> Can occur immediately after kratom ingestion CNS-modifying medications or herbal products with pro-convulsant properties were co-ingested; namely modafinil or Datura stramonium extract tea 	<ul style="list-style-type: none"> Kratom discontinuation and appropriate detoxification schedule was needed. Standard anti-epileptic medications such as lorazepam with or without phenytoin load showed control.
Acute respiratory distress syndrome (ARDS)	<ul style="list-style-type: none"> Symptoms worsened; started with cough and dyspnea then progressed to hypoxia Occurred after a week from a recently treated community-acquired pneumonia 	<ul style="list-style-type: none"> Improvement and successful extubation has occurred within 3–14 days of ingestion.
Toxidrome	<ul style="list-style-type: none"> Ethanol ingestion complicated presentation Occurred within 24 of kratom administration Associated with altered mental status, pulmonary depression, cardiac arrest, seizure, or fatalities Occurred in young users with polysubstance misuse and psychiatric disorders 	<ul style="list-style-type: none"> Initiate basic life support (BLS) or advanced cardiac life support (ACLS) as indicated Naloxone rescue can be provided and repeated as necessary. Intralipid intravenous bolus 1.5 ml/kg may be used if all other supportive care measures are not successful.

seizure, hyperthermia, and mechanical asphyxia. All autopsy blood samples confirmed the presence of at least one other CNS depressant [78]. There is speculation that these fatalities may be caused by mixed drug ingestions leading to synergistic or additive effects, yet fatalities have also occurred from kratom alone. Significant variability in extraction methods and assays, as well as the timing of autopsies post mortem, makes it difficult to conclude a lethal blood concentration of MG. Blood concentrations in fatal cases have ranged from 10 to 4800 mcg/L. Of note, the report by Karinen and colleagues is the only case that tested for and reported positive blood concentrations of the other potent component in kratom, 7-HMG at 2200 mcg/L [76].

Assessing Kratom in Active Users and Managing Associated Complications

Case reports and series are reported voluntarily; therefore, there is inconsistency among reports for assessment and management. Based on available evidence from these reports, we propose a stepwise approach to assess kratom safety and efficacy in active users (Fig. 2) and a summary of kratom-associated adverse events (Table 2).

Conclusion

Kratom has been used both medicinally and recreationally and its use has continued to increase. Case reports and case series of kratom-associated adverse events, toxicities, and fatalities are alarming. Healthcare professionals' awareness of trends in use as well as associated risks is necessary to discuss risks and benefits of use with patients and provide prompt management of adverse events. Controlled studies are needed in the future to examine the impacts of kratom use and provide insight into optimal management and regulation.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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