Health Effects Associated With Kratom (*Mitragyna speciosa*) and Polysubstance Use: A Narrative Review

Substance Abuse: Research and Treatment
Volume 16: 1–7

DOI: 10.1177/11782218221095873
SAGE

Catherine W Striley[1], Carolin C Hoeflich[1], Andrew T Viegas[1,2], Lindsey A Berkowitz[1,3], Emily G Matthews[1], Leyla P Akin[1,4], Chidinma Iheanyi-Okeahialam[1], Urmeen Mansoor[1,5] and Christopher R McCurdy[6]

[1]Department of Epidemiology, College of Public Health & Health Professions and College of Medicine, University of Florida, Gainesville, FL, USA. [2]College of Pharmacy, University of Florida, Gainesville, FL, USA. [3]Department of Occupational Therapy, College of Public Health & Health Professions, University of Florida, Gainesville, FL, USA. [4]Department of Anthropology, London School of Economics and Political Science, London, England, UK. [5]College of Journalism and Communications, University of Florida, Gainesville, FL, USA. [6]Department of Medicinal Chemistry, College of Pharmacy, University of Florida, Gainesville, FL, USA.

ABSTRACT

BACKGROUND: Kratom (*Mitragyna speciosa*) consumption and associated health effects have raised debates in the United States. Although most people using this herb do not experience adverse health effects associated with kratom use, medical providers should be knowledgeable of emerging substances and concurrent, sequential, or simultaneous use of other drugs which may impact healthcare recommendations and prescribing practices.

METHODS: The objective of this narrative review was to elucidate selected health effects associated with using kratom—either alone or with other substances. Since scientifically controlled human subjects research on kratom use is still limited, relevant case reports were also described.

RESULTS: Cardiovascular, gastrointestinal, neurological, and psychiatric effects associated with kratom use were especially notable, and in-utero exposure accompanied concern regarding a neonate's risk for developing neonatal abstinence syndrome. Our ability to identify and understand the role of this herb in kratom-associated fatalities is complicated since kratom is not routinely screened for in standard forensic toxicology. If a screening is performed, it is usually for the major alkaloid, mitragynine, as a surrogate for kratom use. In addition to lacking a standard practice of screening decedents for kratom alkaloids, the association between mortality and kratom use may be confounded by polysubstance use, adulteration of kratom products, and drug-herb interactions.

CONCLUSIONS: Increasing medical awareness of this herb is vital to ensuring prompt administration of best-practice medical advice or treatment for people seeking information related to kratom use or for patients experiencing an adverse health effect that may be associated with using or withdrawing from kratom. Knowledge gained from continued surveillance and study of kratom and its associated health effects may assist in guiding clinical decision-making and preventing development of adverse health effects among people using kratom.

KEYWORDS: *Mitragyna*, herb-drug interactions, neonatal abstinence syndrome, mortality, mental health

RECEIVED: December 8, 2021. **ACCEPTED:** April 1, 2022.

TYPE: Concise Review

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Catherine W Striley was supported by an internal University of Florida—Pilot Project Award from the Center for Research at the Intersection of Substance Use and Pain (CRISP). Carolin C Hoeflich is supported by the UF Substance Abuse Training Center in Public Health from the National Institute on Drug Abuse (NIDA) of the National Institutes of Health under award number T32DA035167. Christopher R McCurdy is supported by grants from NIDA under awards UH3DA048353 and R01DA047855. The content is solely the responsibility of the author(s) and does not necessarily represent the official views of the National Institutes of Health.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Catherine W Striley, Department of Epidemiology, University of Florida, 2004 Mowry Road, Campus Box 100231, Gainesville, FL 32610, USA. Email: cstriley@ufl.edu

Introduction

Kratom (*Mitragyna speciosa*), a native plant in Southeast Asia,[1] has received public, scientific, and political attention in recent years.[2-4] In 2021, the World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) decided against recommending a critical review of kratom, electing instead to continue surveillance of this herb.[5] Although the United States (U.S.) Food and Drug Administration (FDA) does not report any FDA-approved uses for kratom,[6] the National Institute on Drug Abuse (NIDA) is funding numerous projects related to kratom and its alkaloids.[7] These research initiatives are particularly timely given popularity of kratom in the U.S.[8-10] and recent findings regarding the polypharmacological profile of this herb.[11]

In the U.S., kratom and kratom-based products can be purchased at head- or smoke-shops, online vendors, and selected chain stores.[12] Among a U.S. sample of more than 8000 adults endorsing current kratom use, nearly half (48.6%) endorsed typically consuming this herb as a powder with a beverage; use of powdered kratom in a pure or pill form as well as consumption of a self-prepared tea with kratom were also commonly reported kratom preparations.[13] Reported estimated prevalence of

past-year kratom use in the U.S. ranges from 0.7% to 4.1%.[10,14-16] People using this herb tend to be males,[13,15,17-19] middle-aged,[13,15,17,19] employed,[13,17-19] have an household income of $35 000 or more,[13,17,19] and possess at least some college education.[17] Prior research has revealed geographic variations in kratom exposure rates reported to U.S. poison control centers and in kratom use patterns.[8,19] Adverse effects associated with using kratom were reported by a fifth (19.3%) of the 2798 respondent adults endorsing past-year kratom use; less than 1% of all respondents who used kratom in the prior year sought treatment related to adverse health effects.[20] Approximately 2.4% of sampled adults disclosing past-year kratom use met criteria for a moderate or severe kratom-related use disorder in the prior year.[20] Given that the amount of kratom exposures reported to poison control centers in the U.S. is rapidly escalating,[8,9,21] it is essential that substance use researchers and medical community are aware of kratom, possible risks and benefits of kratom use, and potential drug-herb interactions when kratom is used with prescribed or non-prescribed substances.

Motives for kratom use include, but are not limited to, treating or managing pain, alleviating symptoms of psychiatric disorders such as depression or anxiety, or reducing, substituting, or quitting problematic use of other substances, such as opioids.[13,17,20] From 2867 U.S. adults who endorsed currently using kratom, an online survey revealed that nearly half (48.4%) disclosed that their primary reason for kratom use was to relieve pain; 9 out of 10 (90.7%) of these individuals found that kratom was "very" helpful in providing pain relief.[17] Among a sample of 26 Malay men with a past 12-month history of consuming kratom on a daily basis, a double-blind, laboratory-based study revealed a significant increase in pain tolerance, determined via Cold Pressor Task, an hour post-consumption of a kratom-based drink.[22] While this study is suggestive, further work is necessary to test the efficacy of kratom as a pain reliever, as well as to establish a side-effect profile.

Although two-thirds (67.9%) of adults—mostly located in the U.S.—who used kratom in the prior year did not experience any adverse effects associated with their use,[20] identifying and treating the etiology of kratom-associated adverse health outcomes is complicated by relatively high rates of polysubstance use or substance use disorders among populations using kratom.[10,15,23,24] When compared to U.S. respondents who never used kratom, surveyed adults who used kratom were significantly more likely to disclose monthly use of substances, such as cannabis, cocaine, ecstasy, heroin, methamphetamine, or nicotine.[15] Further, data from the 2019 National Survey on Drug Use and Health (NSDUH) revealed that among U.S. individuals who endorsed lifetime kratom use, 31.0% disclosed one or more past-year substance use disorders[23] (not due to kratom). The weighted prevalence of a past-year alcohol use disorder was 17.8% among U.S. individuals who used kratom in their lifetime, compared to 5.1% of those who never used kratom.[23] A past-year marijuana use disorder was also more prevalent among U.S. individuals who ever used kratom.[23] Thus, it is necessary for medical providers to not only be knowledgeable of kratom-associated health effects when kratom is used alone, but also be able to recognize potentially compounding adverse clinical effects associated with concurrent use of kratom and other substances.

Since generalists are often patients' first point-of-contact to receive medical guidance or healthcare services, awareness of kratom and health effects associated with kratom use, dependency, withdrawal, or polysubstance use is urgently needed in the medical community. Uncertainty regarding the clinical effects of this herb—especially at understudied doses or when kratom is used with other substances or FDA-approved medications—limits healthcare providers' capacity to deliver evidence-based and best-practice care for patients using kratom. Thus, this narrative review aimed to provide a broad overview of clinical reports and human subject research conducted related to physiological and psychiatric health effects associated with the use or withdrawal of kratom alone or concurrently with other substances. In particular, this review focused on some cardiovascular, gastrointestinal, neurological, and psychiatric considerations. Kratom-associated fatalities and neonatal abstinence syndrome were also discussed. Further, clinically relevant gaps in existing literature were identified.

Review

Cardiovascular

Clinical reports detailed patients who presented with kratom-associated, adverse cardiovascular effects, such as cardiac arrest, cardiac palpitations, elevated blood pressure, prolonged QT interval, or tachycardia.[25-35] Abdullah et al[25] described a patient who experienced cardiac arrest and had a history of ingesting kratom tea several times per day to self-treat opioid dependency. Further, Nacca et al[28] presented a case of intracerebral hemorrhage when a kratom-based product was adulterated with phenylethylamine. Prior work examined electrocardiogram (ECG) abnormalities among adults in Malaysia[36]; this cross-sectional study found no significant differences for any abnormalities in the ECG, sinus bradycardia, nor prolonged QTc interval in the resting ECG between individuals using kratom, compared to controls who did not use kratom.[36] Among this sample, adults who used kratom consumed an estimated mean of approximately 434 mg of mitragynine daily.[36] The odds of having sinus tachycardia were approximately 8.6 times greater among individuals using kratom, compared to controls.[36] U.S. poison control center data revealed that tachycardia was reported by approximately a fifth (22.5%) of adults (20 + years of age) exposed to kratom alone.[8] National Poison Data System data from 2014 to 2019 revealed that cardiovascular effects were reported by 36.8% of adults 60 to 69 years of age and by 51.9% of adults 70+ years old among cases in which kratom alone was used and one or more clinical effects was

stated.[37] These findings may be particularly relevant for health providers treating patients at a higher risk for developing adverse, cardiovascular health outcomes.

Gastrointestinal

Nearly 4 out of 5 (78.1%) surveyed individuals who disclosed current kratom use and one or more negative reactions associated with using kratom reported that they ever experienced kratom-associated stomach problems.[17] Constipation associated with kratom use was reported by 134 out of 2867 surveyed U.S. adults who endorsed current use of this herb.[17] Additionally, kratom-associated diarrhea has been endorsed by some individuals using kratom.[13] Among health effects associated with using kratom alone which were reported to U.S. poison control centers between 2011 and 2017, nearly a sixth (14.7%) adults 20 + years of age reported nausea, and 12.9% endorsed vomiting.[8] Nausea and vomiting associated with using kratom were also mentioned in some subreddit posts, published from June 2019 to July 2020.[38] Nausea, diarrhea, and vomiting were disclosed by some males in Malaysia who were withdrawing from kratom.[39] Vomiting and/or nausea associated with kratom use or withdrawal were also documented in clinical reports.[26,27,30,31,33,40-42] Some patients with a history of kratom use were observed to have symptoms of liver[31,34,42-48] or kidney[47,49] injury.

Neurological

Neurological health effects were reported among some individuals with a history of using kratom alone or with other substances. In a case reported by Castillo et al,[50] the patient, who experienced symptoms associated with posterior reversible encephalopathy syndrome, reported prior use of at least kratom and dextroamphetamine. A patient who consumed an unknown dose of a kratom-based product with phenylethylamine experienced an intracerebral hemorrhage; on hospital day three, the serum concentration of mitragynine was 340 ng/mL.[28] Case reports also described patients with other kratom-associated, neurological symptoms, such as seizure,[51-53] aphasia,[50] coma,[53] disorientation,[50] or headaches.[28,50] Indeed, headaches were disclosed by a fifth (19.4%) of 361 surveyed U.S. adults who currently use kratom and had one or more negative reactions associated with their use.[17]

Psychiatric

Psychiatric-related benefits and harms associated with kratom use have been detailed. Individuals reported using this herb for psychiatric/mental health concerns, such as anxiety, depression, post-traumatic stress disorder, or bipolar mood.[13,17,20] Among a sample of 280 posts published between June 2019 and July 2020 on kratom-based subreddits, beneficial effects associated with using kratom, such as anxiolytic properties, enhanced mood, feelings of euphoria, and increased energy, were mentioned in some posts.[38] Negative effects associated with use or cessation of kratom have also been observed. Kratom-associated irritation/agitation/irritability has been reported.[8,17] Irritability, increases in apathy, and reductions in motivation associated with using this herb were noted in some subreddit posts.[38] Some individuals who used kratom or a kratom-based product experienced cravings.[39,40] Symptoms associated with tolerance to or withdrawal from kratom have been reported.[20,38] Among a sample of males, mostly of Malay ethnicity, who used kratom for 6 or more months, examples of reported withdrawal symptoms included anger, nervousness, and feelings of restlessness.[39] Sablaban and Gautam[54] described a patient who experienced obsessive thoughts of a violent nature, homicidal ideation, and increased anxiety less than a day after attempting to wean off kratom. Visual and auditory hallucinations were reported in a postoperative patient.[27] Further, altered mental states, such as depressed mood, were reported among some individuals who experienced withdrawal from kratom.[39]

Fatalities

Mortalities associated with kratom use commonly report suspected polysubstance use close to the time of decedents' death.[55-63] Consequently, the risk of death due to using kratom alone is challenging to determine. Gershman et al[59] revealed that polysubstance use was involved in at least 14 of 15 deaths associated with kratom use in Colorado. A review of death certificates in Nevada suggested that mitragynine concentrations in decedents' blood samples did not significantly differ between cases in which mitragynine was documented as contributing to or causing death, and those in which mitragynine was identified, but not documented as a contributory factor nor cause of death.[63] Among autopsied cases from a hospital in Thailand, substances, such as antihistamine, benzodiazepines, ethanol, and methamphetamine, were noted in some blood samples from decedents with a positive mitragynine screening.[64] Thus, the relatively frequent presence of polysubstance use in kratom-associated fatalities raises questions regarding the mechanisms in which these substances interact and whether kratom itself could result in mortality. Kratom-associated fatalities may also be underreported, because, as noted, forensic toxicology guidelines currently do not include standard screenings for kratom alkaloids in decedents.

Neonatal abstinence syndrome

An increase in neonatal abstinence syndrome incidence has been observed in at least 25 U.S. states from 1999 to 2013.[65] This accompanies concern regarding prenatal use of understudied substances on the potential for adverse health effects for the infant, especially when used with pharmaceutical drugs or other substances. Clinical reports have detailed development of neonatal abstinence syndrome among children born to

mothers who used kratom—among other substances—during pregnancy.[66-72] For instance, Nellhaus et al[69] reported on a neonate with elevated Finnegan scores whose mother consumed kratom capsules—in addition to other substances and medications, such as cigarettes, caffeine, zolpidem—prenatally. This infant experienced symptoms commonly reported in cases of neonatal abstinence syndrome, such as undisturbed tremors, increased muscle tone, and a high-pitched cry.[69] Among cases reported to U.S. poison control centers, 7 neonates exposed to kratom were reported between 2016 and 2017[8]; 4 out of the 5 neonates who experienced signs of withdrawal were exposed to kratom only.[8] Thus, there is an urgent need to investigate if neonatal abstinence syndrome associated with in-utero kratom exposure is due to opioid or adrenergic withdrawal. Further, medical providers to be able to recognize adverse neonatal effects associated with in-utero exposure to kratom and other substances, if applicable.

Gaps in literature

These findings, predominantly from case studies, indicate that some people who use kratom are experiencing adverse events. Yet standards of care to address kratom-associated adverse health effects are lacking, and reported treatment has widely varied. Among 1174 individuals exposed to kratom alone, National Poison Data System data from 2011 to 2017 revealed that approximately half (52.0%) were given intravenous fluids, and nearly a third (31.3%) received benzodiazepines.[8] Some examples of other therapies provided to this sample, included naloxone, oxygen, and intubation.[8] Among reviewed clinical reports, treatment protocols varied on the perceived etiology and type of medical event(s) presented in each case. Cessation of kratom use, administration of buprenorphine-naloxone, and/or supportive care were commonly documented, although no controlled clinical studies have been reported to examine the appropriateness of these interventions.

A lack of a standard protocol to address kratom-associated health effects was also reflected in the treatment of neonatal abstinence syndrome or symptoms of dependence or withdrawal associated with in-utero exposure to kratom. For instance, palliative care and clonidine were successfully incorporated into the treatment of kratom-associated withdrawal symptoms in the neonate, described by Nellhaus et al.[69] Other cases utilized morphine to treat kratom-associated withdrawal symptoms.[66-68,70,72] Davidson et al[66] successfully managed one neonate's symptoms through oral morphine until the weaning process began 3 days after initiating morphine. Morphine therapy was also used to treat the case of neonatal abstinence syndrome, discussed by Smid et al.[68] However, Eldridge et al[67] reported that sinus bradycardia developed when morphine and clonidine were used individually in a neonate with neonatal abstinence syndrome. Although treatment protocols may vary due to the presence or absence of other substances used by a patient, best-practice guidelines to address adverse health effects associated with prenatal kratom use should be identified, pending further kratom-related research.

Uncertainty regarding best-practice patient care for kratom-associated medical events may be due to a scarcity of clinical and community-based research regarding use of kratom—both alone and when kratom is used with other substances or medications. Despite the utility of clinical case studies, case reports only provide limited information, depicting presentations of individual patients in unique contexts. For instance, several of the reviewed case reports did not describe kratom dosage. This is problematic since use of this herb may produce varying effects, depending on the dosage and method of ingestion.[13] Indeed, case reports and data from non-community samples are limited in their generalizability and representativeness of persons who use kratom. Further, it would be remiss not to emphasize that causal mechanisms are not able to be identified using clinical reports. Thus, cross-sectional and longitudinal surveillance in addition to clinical trials studies on kratom use and associated health effects are necessary before establishing best-practice medical support and guidelines for treatment-seeking patients using this herb.

Treatment planning for a patient who only uses kratom and reports a kratom-associated adverse health outcome may also have additional difficulty due to a paucity of regulations of and research on kratom-based products in North America. There is a possibility that some kratom-based products may be adulterated, potentially resulting in unintended exposure to chemical compounds such as phenylethylamine,[28] contaminants,[12] or concentrations of a kratom alkaloid.[73] Indeed, health effects associated with using kratom and other substances—either intentionally or unintentionally—may also differ depending on if the substance(s) were used concurrently, simultaneously, or sequentially with kratom. Further, a lack of widespread industry standards regarding the quality of kratom and kratom-based products also presents a problem for patients seeking medical advice on the harms and benefits of differing doses and routes of kratom administration. This is especially concerning in North America where many of the more severe, kratom-associated adverse health effects were reported.

There is a dearth of literature discussing how to modify frequency, amount, or route of kratom administration to reduce adverse health outcomes associated with kratom use. Since beneficial effects have been reported by individuals using this herb[13,17,20,38] and emerging research is examining whether kratom extracts could be used to safely decrease use of substances such as alcohol,[74] some patients may not want to abstain from using kratom. Further research on kratom dosage and use patterns among community-based samples is needed to develop the evidence base for the non-problematic use of kratom. This information may help clinicians advise patients on their use. Additional studies on populations at high risk for adverse and severe adverse events are also warranted.

Table 1. Primary findings detailed in this review.

KEY POINTS
• Medical providers, addiction specialists, and substance use researchers should be aware of kratom as well as potential benefits and risks associated with using kratom—without co-use of other substances or when kratom is used concurrently, sequentially, or simultaneously with other substances.
• Case reports and human subject research have documented beneficial and adverse health effects associated with using this herb.
• Given currently published scientific literature and clinical reports, it is difficult to determine the role of kratom in more severe, adverse health effects associated with kratom use due to relatively high rates of polysubstance use.
• Polysubstance use is commonly reported in kratom-associated fatalities, and kratom alkaloids are not included in standard toxicological screenings for decedents, potentially resulting in underreporting of kratom-associated deaths.
• Kratom-related research for U.S. populations is still in its infancy; additional research, including cross-sectional and longitudinal surveillance as well as clinical studies, is needed to better identify health effects associated with using kratom alone and to create evidence-based treatment recommendations for people experiencing adverse, kratom-associated health effects.

Conclusions

Given the relatively understudied, but rapidly expanding,[8,9,21] use of kratom in the United States, physicians and addictions specialists need to be aware of patients' use of this herb, especially when used in conjunction with medications, substances, herbs, or dietary supplements. To build the medical community's competency in assessing potential beneficial effects and identifying adverse health outcomes associated with kratom use, the present narrative review provided a broad overview of clinical reports and human subjects literature from the English-language publications describing health effects associated with exposure to kratom alone or with other substances (Table 1). Although this narrative review focused on neonatal abstinence syndrome as well as some cardiovascular, gastrointestinal, neurological, and psychiatric health considerations when treating patients who use kratom alone or concurrently, sequentially, or simultaneously with other substances, this is by no means an exhaustive list of kratom-associated health effects. Clinicians should be mindful of emerging literature detailing beneficial and harmful health effects, such as dizziness or respiratory depression, associated with kratom use, dependency, overdose, or polysubstance use.[13,25-27,29-31,33,35,40-43,49,50,54,75-84] Relatively high rates of polysubstance use and/or co-occurring substance use disorders[10,15,23,55] may also contribute to difficulties in establishing evidence-based treatment guidelines for patients experiencing an adverse health effect associated with using kratom individually or for people interested in receiving best-practice medical guidelines for kratom reduction, cessation, or responsible use.

This narrative review highlighted the pressing need for continued research regarding kratom use patterns in the U.S., the medicinal potential of this herb, and treatment considerations—when kratom is used individually or concurrently with other substances. Clinically, it is vital that medical providers and addiction specialists obtain comprehensive medical histories, including use of herbs, dietary supplements, and other legal substances, to be informed on a patient's use of kratom and concurrent use of other substances, if applicable. This is particularly imperative in the provision of competent care for patients who may have a greater risk for a kratom-associated, adverse health effect. Medical professionals should also consider including kratom alkaloids in standard toxicology screenings for fatalities given the rising popularity of this herb and the need for improved surveillance of kratom-associated deaths. Further, since comparatively few people using kratom report a moderate or severe kratom-related adverse event,[20] health providers should take into account the patient's individual experiences with this herb—and concurrent substances, if applicable—when developing treatment recommendations to enhance patient care outcomes for patients using kratom.

Research will also need to inform federal, specifically NIDA, policy-making and strategic planning. While the NIDA Director has been called on to testify before congress on this topic, kratom is not reflected in the current agency strategic planning document[85] but, as noted, NIDA has funded numerous research projects related to kratom's pharmacology, including to one of the co-authors of this document. Kratom use is part of the "real world landscape of drug use" (NIDA proposed strategic plan Goal 1, Action 1.2) and this review shows the importance of screening, prevention, and treatment (Goals 2 & 3) to meet the needs of some users.

Author Contributions

CWS conceptualized this review, acquired the funding, supervised the development of the manuscript, identified and reviewed the literature, as well as wrote, reviewed, and edited the manuscript. CCH identified and reviewed the literature, wrote the original draft, and reviewed and edited the manuscript. ATV, LAB, EGM, LPA, CI, and UM identified and reviewed the case reports and reviewed and edited the manuscript. CRM reviewed and edited the manuscript.

ORCID iDs

Catherine W Striley https://orcid.org/0000-0003-2973-7842

Carolin C Hoeflich https://orcid.org/0000-0002-1741-9671

REFERENCES

1. Cinosi E, Martinotti G, Simonato P, et al. Following "the Roots" of kratom (*Mitragyna speciosa*): the evolution of an enhancer from a traditional use to increase work and productivity in Southeast Asia to a recreational psychoactive drug in Western countries. *Biomed Res Int*. 2015;2015:968786.
2. Prozialeck WC, Lamar PC, Krupp M 2nd, Moon M, Phelps LE, Grundmann O. Kratom use within the context of the evolving opioid crisis and the COVID-19 pandemic in the United States. *Front Pharmacol*. 2021;12:729220.
3. Prozialeck WC, Avery BA, Boyer EW, et al. Kratom policy: the challenge of balancing therapeutic potential with public safety. *Int J Drug Policy*. 2019;70: 70-77.
4. Henningfield JE, Fant RV, Wang DW. The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. *Psychopharmacology*. 2018;235:573-589.
5. United Nations Office on Drugs and Crime Laboratory and Scientific Service Portals. December 2021 – WHO: World Health Organization recommends 3 NPS for scheduling. 2022. Accessed January 25, 2022. https://www.unodc.org/LSS/Announcement/Details/9570c3b9-128d-46f2-808a-7bf8ec20527d
6. U.S. Food & Drug Administration. FDA and Kratom. FDA. Published September 11, 2019. Accessed January 25, 2022. https://www.fda.gov/news-events/public-health-focus/fda-and-kratom
7. NIH. RePORT ⟩ RePORTER. Accessed January 24, 2022. https://reporter.nih.gov/search/VVcqfbDTDUObPjktZ9wbMQ/projects?projects=Active
8. Post S, Spiller HA, Chounthirath T, Smith GA. Kratom exposures reported to United States poison control centers: 2011-2017. *Clin Toxicol*. 2019;57:847-854.
9. O'Neill-Dee C, Spiller HA, Casavant MJ, Kistamgari S, Chounthirath T, Smith GA. Natural psychoactive substance-related exposures reported to United States poison control centers, 2000-2017. *Clin Toxicol*. 2020;58:813-820.
10. Schimmel J, Amioka E, Rockhill K, et al. Prevalence and description of kratom (*Mitragyna speciosa*) use in the United States: a cross-sectional study. *Addiction*. 2021;116:176-181.
11. Obeng S, Kamble SH, Reeves ME, et al. Investigation of the adrenergic and opioid binding affinities, metabolic stability, plasma protein binding properties, and functional effects of selected indole-based kratom alkaloids. *J Med Chem*. 2020;63:433-439.
12. Prozialeck WC, Edwards JR, Lamar PC, et al. Evaluation of the mitragynine content, levels of toxic metals and the presence of microbes in kratom products purchased in the western suburbs of Chicago. *Int J Environ Res Public Health*. 2020;17:5512.
13. Grundmann O. Patterns of kratom use and health impact in the US – results from an online survey. *Drug Alcohol Depend*. 2017;176:63-70.
14. Palamar JJ. Past-year kratom use in the U.S.: estimates from a nationally representative sample. *Am J Prev Med*. 2021;61:240-245.
15. Covvey JR, Vogel SM, Peckham AM, Evoy KE. Prevalence and characteristics of self-reported kratom use in a representative US general population sample. *J Addict Dis*. 2020;38:506-513.
16. Henningfield JE, Grundmann O, Garcia-Romeu A, Swogger MT. We need better estimates of kratom use prevalence. *Am J Prev Med*. 2022;62:132-133.
17. Coe MA, Pillitteri JL, Sembower MA, Gerlach KK, Henningfield JE. Kratom as a substitute for opioids: results from an online survey. *Drug Alcohol Depend*. 2019;202:24-32.
18. Rogers JM, Smith KE, Strickland JC, Epstein DH. Kratom use in the US: both a regional phenomenon and a white middle-class phenomenon? Evidence from NSDUH 2019 and an online convenience sample. *Front Pharmacol*. 2021;12: 789075.
19. Nicewonder JA, Buros AF, Veltri CA, Grundmann O. Distinct kratom user populations across the United States: a regional analysis based on an online survey. *Hum Psychopharmacol*. 2019;34:e2709.
20. Garcia-Romeu A, Cox DJ, Smith KE, Dunn KE, Griffiths RR. Kratom (*Mitragyna speciosa*): user demographics, use patterns, and implications for the opioid epidemic. *Drug Alcohol Depend*. 2020;208:107849.
21. Anwar M, Law R, Schier J. Notes from the field: kratom (*Mitragyna speciosa*) exposures reported to poison centers - United States, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65:748-749.
22. Vicknasingam B, Chooi WT, Rahim AA, et al. Kratom and pain tolerance: A randomized, placebo-controlled, double-blind study. *Yale J Biol Med*. 2020;93:229-238.
23. Xu KY, Mintz CM, Borodovsky JT, Glaser PEA, Bierut LJ, Grucza RA. Prevalence of kratom use and co-occurring substance use disorders in the United States. *Prim Care Companion CNS Disord*. 2021;23:21br02930.
24. Likhitsathian S, Jiraporncharoen W, Aramrattana A, et al. Polydrug use among kratom users: findings from the 2011 Thailand National Household Survey. *J Subst Use*. 2018;23:384-389.
25. Abdullah HMA, Haq I, Lamfers R. Cardiac arrest in a young healthy male patient secondary to kratom ingestion: is this "legal high" substance more dangerous than initially thought ? *BMJ Case Rep*. 2019;12:e229778.
26. Khazaeli A, Jerry JM, Vazirian M. Treatment of kratom withdrawal and addiction with buprenorphine. *J Addict Med*. 2018;12:493-495.
27. Kucharik M, Gupta A, Averkiou P, Luck GR, Ross AS. Complicated postoperative course secondary to kratom withdrawal: a case report. *J Surg Case Rep*. 2019;2019:rjz309.
28. Nacca N, Schult RF, Li L, et al. Kratom adulterated with phenylethylamine and associated intracerebral hemorrhage: linking toxicologists and public health officials to identify dangerous adulterants. *J Med Toxicol*. 2020;16:71-74.
29. Palasamudram Shekar S, Rojas EE, D'Angelo CC, Gillenwater SR, Martinez Galvis NP. Legally lethal kratom: a herbal supplement with overdose potential. *J Psychoactive Drugs*. 2019;51:28-30.
30. Singh V, Mulla N, Wilson JL, et al. Intractable nausea and vomiting in naïve ingestion of kratom for analgesia. *Int J Emerg Med*. 2020;13:42.
31. Tayabali K, Bolzon C, Foster P, Patel J, Kalim MO. Kratom: a dangerous player in the opioid crisis. *J Community Hosp Intern Med Perspect*. 2018;8:107-110.
32. Sheikh M, Ahmed N, Gandhi H, Chen O. Report of ventricular fibrillation in a 44-year-old man using kratom. *BMJ Case Rep*. 2021;14:e237837.
33. Wong A, Mun M. A case of kratom overdose in a pediatric patient. *Case Rep Psychiatry*. 2020;2020:8818095.
34. Watson CJ, Whitledge JD, Barbuto AF, Boyle KL, Ganetsky M. Toxicity of agents used for opioid withdrawal: a case-based approach. *Int Anesthesiol Clin*. 2020;58:19-27.
35. Diep J, Chin DT, Gupta S, Syed F, Xiong M, Cheng J. Kratom, an emerging drug of abuse: a case report of overdose and management of withdrawal. *A&A Practice*. 2018;10:192-194.
36. Leong Abdullah MFI, Tan KL, Narayanan S, et al. Is kratom (*Mitragyna speciosa* Korth.) use associated with ECG abnormalities? Electrocardiogram comparisons between regular kratom users and controls. *Clin Toxicol*. 2021;59:400-408.
37. Graves JM, Dilley JA, Terpak L, et al. Kratom exposures among older adults reported to U.S. poison centers, 2014-2019. *J Am Geriatr Soc*. 2021;69: 2176-2184.
38. Smith KE, Rogers JM, Schriefer D, Grundmann O. Therapeutic benefit with caveats?: analyzing social media data to understand the complexities of kratom use. *Drug Alcohol Depend*. 2021;226:108879.
39. Singh D, Müller CP, Vicknasingam BK. Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms and craving in regular users. *Drug Alcohol Depend*. 2014;139:132-137.
40. Galbis-Reig D. A case report of kratom addiction and withdrawal. *WMJ*. 2016;115:49-52; quiz 53.
41. Griffiths CL, Gandhi N, Olin JL. Possible kratom-induced hepatomegaly: a case report. *J Am Pharm Assoc*. 2018;58:561-563.
42. Osborne CS, Overstreet AN, Rockey DC, Schreiner AD. Drug-induced liver injury caused by kratom use as an alternative pain treatment amid an ongoing opioid epidemic. *J Investig Med High Impact Case Rep*. 2019;7:2324709619826167.
43. Riverso M, Chang M, Soldevila-Pico C, Lai J, Liu X. Histologic characterization of kratom use-associated liver injury. *Gastroenterol Res*. 2018;11:79-82.
44. Ahmad J, Odin JA, Hayashi PH, et al. Liver injury associated with kratom, a popular opioid-like product: experience from the U.S. drug induced liver injury network and a review of the literature. *Drug Alcohol Depend*. 2021;218:108426.
45. Fernandes CT, Iqbal U, Tighe SP, Ahmed A. Kratom-induced cholestatic liver injury and its conservative management. *J Investig Med High Impact Case Rep*. 2019;7:2324709619836138.
46. Aldyab M, Ells PF, Bui R, Chapman TD, Lee H. Kratom-induced cholestatic liver injury mimicking anti-mitochondrial antibody-negative primary biliary cholangitis: a case report and review of literature. *Gastroenterol Res*. 2019;12: 211-215.
47. Antony A, Lee TP. Herb-induced liver injury with cholestasis and renal injury secondary to short-term use of kratom (*Mitragyna speciosa*). *Am J Ther*. 2019;26: e546-e547.
48. Dorman C, Wong M, Khan A. Cholestatic hepatitis from prolonged kratom use: a case report. *Hepatology*. 2015;61:1086-1087.
49. Sangani V, Sunnoqrot N, Gargis K, Ranabhotu A, Mubasher A, Pokal M. Unusual presentation of kratom overdose with rhabdomyolysis, transient hearing loss, and heart failure. *J Investig Med High Impact Case Rep*. 2021;9 :23247096211005069.
50. Castillo A, Payne JD, Nugent K. Posterior reversible leukoencephalopathy syndrome after kratom ingestion. *Proc*. 2017;30:355-357.
51. Afzal H, Esang M, Rahman S. A case of kratom-induced seizures. *Cureus*. 2020;12:e6588.
52. Tatum WO, Hasan TF, Coonan EE, Smelick CP. Recurrent seizures from chronic kratom use, an atypical herbal opioid. *Epilepsy Behav Case Rep*. 2018;10:18-20.
53. Nelsen JL, Lapoint J, Hodgman MJ, Aldous KM. Seizure and coma following kratom (*Mitragynina speciosa* Korth) exposure. *J Med Toxicol*. 2010;6:424-426.
54. Sablaban IM, Gautam M. The diagnosis of severe obsessions in the setting of kratom withdrawal and treatment with lorazepam: case report. *J Addict Dis*. 2020;39:138-139.

55. Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N. Notes from the field: unintentional drug overdose deaths with kratom detected - 27 states, July 2016-December 2017. *MMWR Morb Mortal Wkly Rep*. 2019;68:326-327.
56. Holler JM, Vorce SP, McDonough-Bender PC, Magluilo J Jr, Solomon CJ, Levine B. A drug toxicity death involving propylhexedrine and mitragynine. *J Anal Toxicol*. 2011;35:54-59.
57. Kronstrand R, Roman M, Thelander G, Eriksson A. Unintentional fatal intoxications with mitragynine and O-desmethyltramadol from the herbal blend krypton. *J Anal Toxicol*. 2011;35:242-247.
58. McIntyre IM, Trochta A, Stolberg S, Campman SC. Mitragynine 'kratom' related fatality: a case report with postmortem concentrations. *J Anal Toxicol*. 2015;39:152-155.
59. Gershman K, Timm K, Frank M, et al. Deaths in Colorado attributed to kratom. *N Engl J Med*. 2019;380:97-98.
60. Corkery JM, Streete P, Claridge H, et al. Characteristics of deaths associated with kratom use. *J Psychopharmacol*. 2019;33:1102-1123.
61. Hughes RL. Fatal combination of mitragynine and quetiapine - a case report with discussion of a potential herb-drug interaction. *Forensic Sci Med Pathol*. 2019;15:110-113.
62. Matson M, Schenk N. Fatality of 33-year-old man involving kratom toxicity. *J Forensic Sci*. 2019;64:1933-1935.
63. Schmitt J, Bingham K, Knight LD. Kratom-associated fatalities in northern Nevada-what mitragynine level is fatal? *Am J Forensic Med Pathol*. 2021;42:341-349.
64. Jittasopa W, Srisont S. The causes of death and pathological findings of kratom users: a 5-year retrospective analysis. *Am J Forensic Med Pathol*. 2021;42:335-340.
65. Ko JY, Patrick SW, Tong VT, Patel R, Lind JN, Barfield WD. Incidence of neonatal abstinence syndrome - 28 states, 1999-2013. *MMWR Morb Mortal Wkly Rep*. 2016;65:799-802.
66. Davidson L, Rawat M, Stojanovski S, Chandrasekharan P. Natural drugs, not so natural effects: neonatal abstinence syndrome secondary to 'kratom'. *J Neonatal Perinat Med*. 2019;12:109-112.
67. Eldridge WB, Foster C, Wyble L. Neonatal abstinence syndrome due to maternal kratom use. *Pediatrics*. 2018;142:e20181839.
68. Smid MC, Charles JE, Gordon AJ, Wright TE. Use of Kratom, an opioid-like traditional herb, in pregnancy. *Obstet Gynecol*. 2018;132:926-928.
69. Nellhaus E, Andrews L, Haas J, et al. Neonatal withdrawal following in utero exposure to kratom. *Int J Clin Pediatr*. 2018;7:55-58.
70. Murthy P, Clark D. An unusual cause for neonatal abstinence syndrome. *Paediatr Child Health*. 2019;24:12-14.
71. Pizarro-Osilla C. Introducing. . . Kratom. *J Emerg Nurs*. 2017;43:373-374.
72. Mackay L, Abrahams R. Novel case of maternal and neonatal kratom dependence and withdrawal. *Can Fam Physician*. 2018;64:121-122.
73. Lydecker AG, Sharma A, McCurdy CR, Avery BA, Babu KM, Boyer EW. Suspected adulteration of commercial kratom products with 7-hydroxymitragynine. *J Med Toxicol*. 2016;12:341-349.
74. Gutridge AM, Robins MT, Cassell RJ, et al. G protein-biased kratom-alkaloids and synthetic carfentanil-amide opioids as potential treatments for alcohol use disorder. *Br J Pharmacol*. 2020;177:1497-1513.
75. Bowe A, Kerr PL. A complex case of kratom dependence, depression, and chronic pain in opioid use disorder: effects of buprenorphine in clinical management. *J Psychoactive Drugs*. 2020;52:447-452.
76. Buresh M. Treatment of kratom dependence with buprenorphine-naloxone maintenance. *J Addict Med*. 2018;12:481-483.
77. LaBryer L, Sharma R, Chaudhari KS, Talsania M, Scofield RH. Kratom, an emerging drug of abuse, raises prolactin and causes secondary hypogonadism: case report. *J Investig Med High Impact Case Rep*. 2018;6:2324709618765022.
78. Lydecker AG, Zuckerman MD, Hack JB, et al. Intravenous kratom use in a patient with opioid dependence. *J Toxic Pharm*. 2017;1:3.
79. Overbeek DL, Abraham J, Munzer BW. Kratom (mitragynine) ingestion requiring naloxone reversal. *Clin Pract Cases Emerg Med*. 2019;3:24-26.
80. Schmuhl KK, Gardner SM, Cottrill CB, Bonny AE. Home induction and outpatient treatment of kratom use disorder with buprenorphine-naloxone: A case report in a young adult. *Subst Abuse*. 2020;41:311-314.
81. Stanciu CN, Gnanasegaram SA, Ahmed S, Penders T. Kratom withdrawal: A systematic review with case series. *J Psychoactive Drugs*. 2019;51:12-18.
82. Tavakoli HR, Buchholz AC, Kabir IK, Deb A, Gayk JN. Kratom: a new product in an expanding substance abuse market. *Fed Pract*. 2016;33:32-36.
83. Vermaire DJ, Skaer D, Tippets W. Kratom and general anesthesia: a case report and review of the literature. *AA Pract*. 2019;12:103-105.
84. Tobarran N, Wolf C, Cumpston KL, Wills BK. Pressure necrosis requiring fasciotomy after kratom overdose. *J Addict Med*. 2022;16:252-253.
85. National Institute on Drug Abuse (NIDA). NOT-DA-20-059: Request for Information (RFI): Inviting Input on NIDAs Strategic Plan for 2021-2025. 2020. Accessed February 25, 2022. https://grants.nih.gov/grants/guide/notice-files/NOT-DA-20-059.html