Wisconsin Medical Society

TO: Wisconsin Controlled Substances Board
Doug Englebert, Chair

FROM: Mark Grapentine, JD – Chief Policy and Advocacy Officer

DATE: March 10, 2023

RE: Potential CSB action on the illegal substances in kratom

On behalf of nearly 10,000 physician members across the state, thank you for this opportunity to request that the Controlled Substances Board (CSB) take action ensuring that the harmful substances in kratom are not made more widely available in Wisconsin. Federal agencies have warned the public about the dangers associated with kratom, medical experts have identified kratom as unsafe, addictive, and ineffective, and the Wisconsin State Legislature has spoken by proactively placing substances found in kratom in Wisconsin's Uniform Controlled Substances Act.

Wisconsin's citizens are best served by keeping kratom illegal in our state.

The CSB Should Consider Federal Agency Warnings per State Statute Allowance
Wisconsin Statutes § 961.11(1r) specifically allows the CSB to consider findings from the U.S. Food and Drug Administration (FDA) or the U.S Drug Enforcement Administration (DEA) as "prima facie evidence" that relate to the much-discussed advisory factors in § 961.11 (1m). Contrary to the kratom industry's assertion that federal agency warnings are historic relics, both agencies continue to warn the public about kratom's potential to cause addiction, abuse, and severe harm.

The FDA continues to host a webpage specific to kratom, updated less than one year ago. The FDA's language gets right to the point[1]:

> **The U.S. Food and Drug Administration is warning consumers not to use *Mitragyna speciosa*, commonly known as kratom, a plant which grows naturally in Thailand, Malaysia, Indonesia, and Papua New Guinea. FDA is concerned that kratom, which affects the same opioid brain receptors as morphine, appears to have properties that expose users to the risks of addiction, abuse, and dependence.**
>
> **There are no FDA-approved uses for kratom, and the agency has received concerning reports about the safety of kratom. FDA is actively evaluating all available scientific information on this issue and continues to warn consumers not to use any products labeled as containing the botanical substance kratom or its**

[1] https://www.fda.gov/news-events/public-health-focus/fda-and-kratom

psychoactive compounds, mitragynine and 7-hydroxymitragynine. FDA encourages more research to better understand kratom's safety profile, including the use of kratom combined with other drugs.

The FDA, in concert with the Federal Trade Commission, continues to sanction business touting their kratom products as effective therapies for conditions such as opioid addiction and withdrawal symptoms. As a recent (June 30, 2022) warning letter issued to the company "Kratom Exchange" stresses, false claims about a product's therapeutic efficacy is only one part of the harm foisted on a vulnerable public. "**Further, the unproven treatments could cause patients to forego or delay FDA-approved treatments for opioid addiction and withdrawal,**" the letter states. "**The marketing and sale of unapproved opioid addiction treatment products is potentially a significant threat to the public health**."[2]

The DEA also looks unfavorably on kratom. Its most recent Drug Fact Sheet (June 5, 2020) on the substance notes that "**the abuse of kratom has increased markedly in recent years.**" In describing the drug's effects, the fact sheet notes that "**Kratom consumption can lead to addiction. Several cases of psychosis resulting from the use of kratom have been reported, where individuals addicted to kratom exhibited psychotic symptoms, including hallucinations, delusion, and confusion.**"[3]

These various warnings from both the FDA and the DEA certainly speak to many of the factors in Wis Stats § 961.11 (1m), such as the actual/relative potential for abuse (1m)(a); history and current patterns of abuse (1m)(d); scope, duration and significance of abuse (1m)(e); and the potential of the substance to produce psychological or physical dependence liability (1m)(g).

Medical Experts Have Identified Kratom as Unsafe and Ineffective

The legal status of kratom in many states has led to abuse and addiction – so much so that leading health care systems feel compelled to warn the public that the substance has no medical use and can result in significant user harm.

The world-renowned Mayo Clinic last updated its webpage "Kratom: Unsafe and ineffective" in June 2022. It does an excellent job describing the many concerns surrounding this drug:[4]

Kratom: Unsafe and ineffective

Users swear by kratom for mood enhancement and fatigue reduction, but safety issues and questions about its effectiveness abound.

If you read health news or visit vitamin stores, you may have heard about kratom, a supplement that is sold as an energy booster, mood enhancer, pain reliever and antidote for opioid withdrawal. However, the truth about kratom is more complicated, and the safety problems related to its use are concerning.

Kratom is an herbal extract that comes from the leaves of an evergreen tree (Mitragyna speciosa) grown in Southeast Asia. Kratom leaves can be chewed, and dry kratom can be

[2] https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/kratom-exchange-633972-06302022

[3] https://www.dea.gov/sites/default/files/2020-06/Kratom-2020.pdf

[4] https://www.mayoclinic.org/healthy-lifestyle/consumer-health/in-depth/kratom/art-20402171

swallowed or brewed. Kratom extract can be used to make a liquid product. The liquid form is often marketed as a treatment for muscle pain, or to suppress appetite and stop cramps and diarrhea. Kratom is also sold as a treatment for panic attacks.

Kratom is believed to act on opioid receptors. At low doses, kratom acts as a stimulant, making users feel more energetic. At higher doses, it reduces pain and may bring on euphoria. At very high doses, it acts as a sedative, making users quiet and perhaps sleepy. Some people who practice Asian traditional medicine consider kratom to be a substitute for opium.

Some people take kratom to avoid the symptoms of opioid withdrawal and because kratom may be bought more easily than prescription drugs.

Kratom is also used at music festivals and in other recreational settings. People who use kratom for relaxation report that because it is plant-based, it is natural and safe. However, the amount of active ingredient in kratom plants can vary greatly, making it difficult to gauge the effect of a given dose. Depending on what is in the plant and the health of the user, taking kratom may be very dangerous. Claims about the benefits of kratom can't be rated because reliable evidence is lacking.

Although people who take kratom believe in its value, researchers who have studied kratom think its side effects and safety problems more than offset any potential benefits. Poison control centers in the United States received about 1,800 reports involving use of kratom from 2011 through 2017, including reports of death. About half of these exposures resulted in serious negative outcomes such as seizures and high blood pressure. Five of the seven infants who were reported to have been exposed to kratom went through withdrawal. Kratom has been classified as possibly unsafe when taken orally.

Kratom has a number of known side effects, including:

- Weight loss
- Dry mouth
- Chills, nausea and vomiting
- Changes in urine and constipation
- Liver damage
- Muscle pain

Kratom also affects the mind and nervous system:

- Dizziness
- Drowsiness
- Hallucinations and delusion
- Depression and delusion
- Breathing suppression
- Seizure, coma and death

Kratom takes effect after five to 10 minutes, and its effects last two to five hours. The effects of kratom become stronger as the quantity taken increases. In animals, kratom appears to be more potent than morphine. Exposure to kratom has been reported in an infant who was breastfed by a mother taking kratom.

Many of the problems that occur with pain medications happen when these drugs are used at high doses or over a long period of time. It's not known exactly what level of kratom is toxic in people, but as with pain medications and recreational drugs, it is possible to overdose on kratom.

At one time, some researchers believed that kratom might be a safe alternative to opioids and other prescription pain medications. However, studies on the effects of kratom have identified many safety concerns and no clear benefits.

Kratom has been reported to cause abnormal brain function when taken with prescription medicines. When this happens, you may experience a severe headache, lose your ability to communicate or become confused.

In a study testing kratom as a treatment for symptoms of opioid withdrawal, people who took kratom for more than six months reported withdrawal symptoms similar to those that occur after opioid use. Too, people who use kratom may begin craving it and require treatments given for opioid addiction, such as naloxone (Narcan) and buprenorphine (Buprenex).

Kratom also adversely affects infant development. When kratom is used during pregnancy, the baby may be born with symptoms of withdrawal that require treatment.

In addition, substances that are made from kratom may be contaminated with salmonella bacteria. As of April 2018, more than 130 people in 38 states became ill with Salmonella after taking kratom. Salmonella poisoning may be fatal, and the U.S. Food and Drug Administration has linked more than 35 deaths to Salmonella-tainted kratom. Salmonella contamination has no obvious signs, so the best way to avoid becoming ill is to avoid products that may contain it.

Kratom is not currently regulated in the United States, and federal agencies are taking action to combat false claims about kratom. In the meantime, your safest option is to work with your doctor to find other treatment options.

References

1. Chien GCC, et al. Is kratom the new "legal high" on the block?: The case of an emerging opioid receptor agonist with substance abuse potential. Pain Physician. 2017;20:E195.
2. Feng L, et al. New psychoactive substances of natural origin: A brief review. Journal of Food and Drug Analysis. 2017;25:461.
3. Griffin III OH, et al. Do you get what you paid for? An examination of products advertised as kratom. Journal of Psychoactive Drugs. 2016;48:330.
4. Drug Enforcement Administration. Kratom (Mitragyna speciosa korth). https://www.deadiversion.usdoj.gov/drug_chem_info/kratom.pdf. Accessed April 17, 2018.
5. Yusoff NHM, et al. Opioid receptors mediate the acquisition, but not the expression of mitragynine-induced conditioned place preference in rats. Behavioural Brain Research. 2017;332:1.
6. Diep J, et al. Kratom, an emerging drug of abuse: A case report of overdose and management of withdrawal. Anesthesia & Analgesia Case Reports. In press. Accessed May 2, 2018.
7. Swogger MT, et al. Experiences of kratom users: A qualitative analysis. Journal of Psychoactive Drugs. 2015;47:360.
8. Fox J, et al. Drugs of abuse and novel psychoactive substances at outdoor music festivals in Colorado. Substance Use & Misuse. In press. Accessed May 2, 2018.

9. Kowalczuk AP, et al. Comprehensive methodology for identification of kratom in police laboratories. Forensic Science International. 2013;233:238.
10. Fluyua D, et al. Biochemical benefits, diagnosis, and clinical risks of kratom. Frontiers in Psychiatry. 2017;8:62.
11. Castillo A, et al. Posterior reversible leukoencephalopathy syndrome after kratom ingestion. Baylor University Medical Center Proceedings. 2017;30:355.
12. Grundmann O. Patterns of kratom use and health impact in the US — Results from an online survey. Drug and Alcohol Dependence. 2017;176:63.
13. Drago JD, et al. The harm in kratom. The Oncologist. 2017;22:1010.
14. Pizarro-Osilla C. Introducing…kratom. In press. Accessed May 2, 2018.
15. Kruegel AC, et al. The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. Neuropharmacology. In press. Accessed May 2, 2018.
16. Ismail I, et al. Kratom and future treatment for the opioid addiction and chronic pain: Periculo beneficium? Current Drug Targets. In press. Accessed May 2, 2018.
17. Singh D, et al. Kratom (Mitragyna speciosa) dependence, withdrawal symptoms and cravings in regular users. Drug and Alcohol Dependence. 2014;139:132.
18. Swogger MT, et al. Kratom use and mental health: A systematic review. Drug and Alcohol Dependence. 2018;183:134.
19. Food and Drug Administration. FDA investigates multistate outbreak of salmonella infections linked to products reported to contain kratom. https://www.fda.gov/Food/RecallsOutbreaksEmergencies/Outbreaks/ucm597265.htm. Accessed April 17, 2018.
20. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA advisory about deadly risks associated with kratom. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584970.htm. Accessed April 17, 2018.
21. Voelker R. Crackdown on false claims to ease opioid withdrawal symptoms. JAMA. 2018;319:857.
22. Post S. Kratom exposures reported to United States poison control centers: 2011-2017. Clinical Toxicology. Published online February 20, 2019.
23. Drug Enforcement Administration. Kratom—drug fact sheet. https://www.dea.gov/sites/default/files/2020-06/Kratom-2020.pdf. Accessed January 26, 2022.
24. Therapeutic Research Center. Kratom. https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=1513. Accessed January 26, 2022.
25. Umbehr G, et al. Acute liver injury following short-term use of the herbal supplement kratom. JAAPA. 2022;35:39.

The nationally-recognized Cleveland Clinic has a similar webpage posting in Q&A form titled "What You Should Know About Kratom."[5] Similar to the FDA's tenor, the posting starts off with a strong warning: "**Kratom is one of those plants that you might assume is a safer, natural alternative to other drugs,**" the page says. "**But don't be fooled: There's a dark side to kratom-derived pills, powders and teas.**"

[5] https://health.clevelandclinic.org/what-is-kratom/

After describing the source of the drug, how it is used, why people choose to use it, and its known side-effects, the piece is bookended by another strong warning: "**Due to its dangerous health effects — plus the very real risk of getting your hands on low-quality and contaminated kratom products — you should not use kratom in any form.**"

Closer to home, Wisconsin addiction medicine experts have studied kratom's effects on patients and have published a literature review about "Kratom Use Disorder,"[6] and a case report on kratom addiction and withdrawal.[7] Those publications, as well as a letter from the literature review's author to the Wisconsin Medical Society, is attached to this memo.

These actions by leading health systems and research from Wisconsin's addiction medicine experts pertain to additional factors in Wis Stats § 961.11 (1m), such as the scientific evidence of the drug's pharmacological effect (1m)(b) the state of current scientific knowledge regarding kratom (1m)(c) and the risk to the public health (1m)(f).

The Wisconsin Legislature's Unanimous Action From the 2013-14 Session Should Be Respected
The Wisconsin State Legislature should be commended for its bold, bipartisan and proactive activities to fight the scourge of drug addiction and abuse. The legislature's Heroin, Opioid Prevention and Education (HOPE) Agenda was impressive not only for giving law enforcement and medical professionals additional tools to help combat ballooning addiction numbers, but perhaps more so for dramatically reducing the stigma that had long been associated with addiction to drugs like heroin. 2013 Act 351 – the legislation that placed the harmful substances from kratom in the state's Uniformed Controlled Substances Act – was one of the HOPE Agenda's first seven enacted bills. All passed unanimously by both the State Assembly and the State Senate.

Recent attempts to legalize kratom have failed due to lack of legislative support. Last session, 2021 Assembly Bill 599 was introduced at the behest of the American Kratom Association, which is a powerful lobbying entity operating nationwide. When the bill was introduced, it could have been sent to numerous health-related Assembly committees. The Committee on Health, the Committee on Substance Abuse and Prevention, or the Committee on Judiciary would all have been natural landing places for the bill; instead, it was curiously referred to the Committee on State Affairs, whose membership does not generally take up matters such as legalizing a drug.

The bill was placed on the Assembly calendar for a floor vote before the full body in February 2022. But when it came time to bring up and debate the bill, it was quietly skipped. It is rare to see such a thing happen like that in our State Assembly – it was certainly a signal that when more legislators became aware of what the bill was attempting to accomplish, an overall negative vote became obvious. A Senate companion bill, 2021 Senate Bill 958, was hastily introduced in early February 2022. That bill was referred to the Senate Committee on Judiciary and Public Safety. It did not receive even a public hearing.

A small number of state legislators wish to see kratom legalized. The majority of their peers want no such thing. The CSB should not step in to create a result where a majority of elected policymakers have chosen not to do so.

Thank you for your service on the Controlled Substances Board. Your work to help protect the public from dangerous substances is deeply appreciated by the state's physicians. If you have any questions, please feel free to contact me at any time.

[6] https://wmjonline.org/120no1/stanciu/
[7] https://wmjonline.org/wp-content/uploads/2016/115/1/49.pdf

WISAM WISCONSIN SOCIETY of ADDICTION MEDICINE

07/14/2021

Mark Grapentine, JD
Chief Policy and Advocacy Officer
Wisconsin Medical Society
Mark.grapentine@wismed.org

Dear Mr. Grapentine,

Thank you for bringing proposed legislation, LRB-3796/1, to the attention of the Wisconsin Society of Addiction Medicine (WISAM). WISAM strongly opposes LRB-3796/1, which would remove mitragynine and 7-hydroxy-mitragynine - both constituents of the plant kratom - from the schedule 1 controlled substances list in Wisconsin.

Mitragynine (a partial mu-opioid agonist) and 7-OH-Mitragynine (a full mu-opioid agonist, which is similar in action to other opioid analgesics and is likely the greatest contributor to overdose deaths associated with kratom) should remain schedule 1 substances in Wisconsin at this time. Legislation similar to LRB-3796/1 is being proposed in other states where kratom is illegal as part of a lobbying effort that could lead to further commercialization of kratom. There is currently no sound scientific data that kratom, or any of its constituents, is safe and effective for the management of acute or chronic painful conditions. There is also no data that kratom helps treat patients with opioid use disorder (OUD), while there are already FDA-approved treatment options in buprenorphine and methadone for OUD. Of note, I am an author on two, published papers (enclosed) illustrating that the active components of kratom act like opioids in the body and that addiction to kratom requires medical treatment. Thus, access to buprenorphine and methadone for OUD should be prioritized over the legalization of a substance with kratom's concerning record.

Further, as for overdose potential related to kratom, I have served as an expert witness for the plaintiff in a lawsuit in Montana against a distributor of kratom following an overdose death of a young man who incorrectly believed that kratom was safe. The young man believed that it was safe because of the information he had read from participants in the kratom industry, including unsubstantiated statements regarding the potential benefits of kratom for pain management and OUD. At the time of his death, the young man's toxicology results showed no other opioids, benzodiazepines, or controlled substances in his system - only mitragynine and his prescribed medications (none of which was a controlled substance). The case eventually settled after my extensive testimony on the literature regarding the dangers of kratom and that, in my expert opinion, it was the only possible explanation for this gentleman's overdose death.

Finally, any attempt to introduce this bill as part of the HOPE legislation under the guise of treatment for OUD is anti-scientific and harmful. The FDA has issued warning letters to

marketers and distributors of kratom that make false claims that kratom has been shown to treat opioid withdrawal symptoms or OUD.

For far too long, persons with OUD and their family members have been misled into believing that kratom is a safe and effective treatment for OUD. As noted above, there are indeed safe and effective FDA-approved treatments for OUD; kratom is neither safe nor effective for this condition. People struggling with OUD should not be misled into taking kratom for this condition, thereby not availing themselves of safe, effective, FDA-approved medications that are proven to help prevent dysfunction, disability, and death.

WISAM truly hopes that our state representatives will not introduce or pass legislation that would allow for a commercial model of legalization for an opioid-like substance like kratom. This would be a tragic mistake. Please do not hesitate to contact me with any questions or concerns or to provide further expert assistance.

Sincerely,

David Galbis-Reig, M.D., DFASAM
President, Wisconsin Society of Addiction Medicine

References

Galbis-Reig D. A case report of kratom addiction and withdrawal. WMJ. 2016;115(1): 49-52.

Stanciu C, Ahmed S, Hybki B, Penders T, Galbis-Reig D. Pharmacotherapy for management of 'kratom use diosrder': a systematic literature review with survey of experts. WMJ. 2021; 120(1): 54-61.

Pharmacotherapy for Management of 'Kratom Use Disorder': A Systematic Literature Review With Survey of Experts

Cornel Stanciu, MD, MRO; Saeed Ahmed, MD; Bryan Hybki, MD; Thomas Penders, MS, MD; David Galbis-Reig, MD

ABSTRACT

Objectives: An increasing number of Americans are turning to kratom for self-management of various pain, anxiety, and mood states and as an opioid substitute. Addiction to this unique botanical develops and carries a high relapse risk and, to date, there are no guidelines on how to maintain long-term abstinence. The aim of this article is to compile all available information on management of "kratom use disorder" (KUD)—as coined here—from the literature, with evidence from the clinical practice of expert addictionologists in an attempt to develop a standard of care consensus.

Methods: A systematic literature search was conducted to capture all relevant cases pertaining to maintenance treatment for KUD. Results were supplemented with case reports and scientific posters gleaned from reliable online sources and conference proceedings. Additionally, a survey of members of the American Society of Addiction Medicine (ASAM) was administered to assess the practice patterns of experts who treat patients with KUD in isolation of a comorbid opioid use disorder (OUD).

Results: Based on a literature review, 14 reports exist of long-term management of KUD, half of which do not involve a comorbid OUD. Pharmacological modalities utilized include mostly buprenorphine but also a few cases of naltrexone and methadone, all with favorable outcomes. This is supported by the results of the expert survey, which demonstrated that those who have managed KUD in isolation of a comorbid OUD reported having utilized buprenorphine (89.5%), as well as the other medications for opioid use disorder (MOUD).

Conclusions: This is the first comprehensive review to examine the existing literature referring to management of KUD in combination with a survey of current experts' clinical consensus regarding pharmacological management. Based on this information, it seems reasonable that the indication for MOUD should be extended to cases of moderate to severe KUD.

• • •

Author Affiliations: Dartmouth Geisel School of Medicine, Hanover, NH (Stanciu); New Hampshire Hospital, Concord, NH (Stanciu); Rutland Regional Medical Center, Rutland, VT (Ahmed); Dartmouth Hitchcock Medical Center, Lebanon, NH (Hybki); Brody School of Medicine, East Carolina University, Greenville, NC (Penders); Walter B Jones Drug and Alcohol Treatment Center, Greenville, NC (Penders); Ascension All Saints Hospital, Racine, Wis (Galbis-Reig).

Corresponding Author: David Galbis-Reig, MD, DFASAM, Medical Director of Addiction Services, Ascension Wisconsin Healthcare - All Saints, 1320 Wisconsin Ave, Racine, WI 53403; email dgalbisreig@aol.com; ORCID ID 0000-0003-2919-2854.

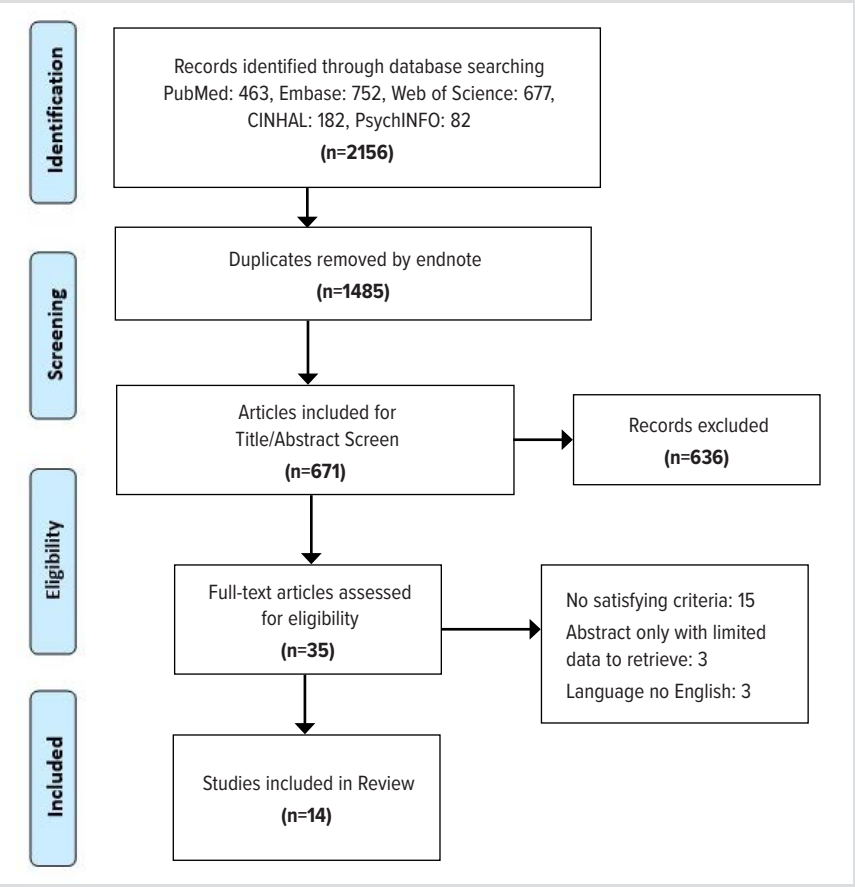
INTRODUCTION

The increasing consumption of kratom (*Mitragyna speciosa*) is emerging as a public health concern among Americans, and forecasting models indicate its use will continue to rise.[1] Aside from the Food and Drug Administration (FDA) reports of concern[2] and adverse effects exhibited through increased calls to poison control centers[3] and overdose deaths,[4] the notion of addiction is rapidly emerging. In Southeast Asia where this botanical is indigenous, 55% of regular users develop dependence and tolerance. Withdrawal and cravings also have been reported.[5-8] There is now substantial evidence showing it is possible for individual kratom users to meet all Diagnostic and Statistical Manual, Fifth Edition (DSM-5) criteria associated with a substance use disorder diagnosis.[9] A category for "kratom use disorder" (KUD)—as we coin in this paper—does not formally exist in the DSM-5, which was last revised in 2013. In the United States, a survey of 8,000 users conducted through American Kratom Association (AKA)[10] revealed that although some disclosed use with an underlying intent to self-manage opioid misuse including withdrawal, 68% reported using to self-manage chronic pain and 65% for anxiety or mood states, where opioids are not involved at all.

The effects of kratom to date are attributed primarily to the 2 active alkaloids—mitragynine (MG) and 7-hydroxymitragynine (7-HMG)—although more than 25 other alkaloids have been identified in the plant.[11] Both exert their primary action through agonism at the μ opiate receptor and weak antagonism at δ and κ receptors.[12,13] There is also evidence that MG is involved in sero-

tonergic (antagonist at serotonin 5-HT-2A receptors), dopaminergic (agonist at dopamine D1 receptors), and noradrenergic (agonist at postsynaptic alpha-2 receptors) pathways.[14-17] These translate to users experiencing stimulant-like and opioid-like intoxicating syndromes when either low or high doses are consumed. In traditional medicine, kratom leaves have been used for pain relief; to increase appetite, mood, energy, and sexual desires; to provide wound healing based on anti-inflammatory properties; as a local anesthetic; and to manage coughs, diarrhea, and intestinal infections, among other uses. It is apparent that MG, 7-HMG, and the rest of the plant's constituents are involved in a multitude of other pathways as well, which have yet to be determined. Although there have been efforts by the FDA to classify MG and 7-HMG as an opioid based on the Public Health Assessment via Structural Evaluation (PHASE) model,[18] this is a very complex botanical with much more unique pharmacodynamic and intracellular signaling actions, hence deserving its own category and classification.

Figure 1. PRISMA Flow Diagram of Literature Search



In a previous review of kratom withdrawal,[6] we outlined that symptoms respond akin to that of opioid withdrawal through symptomatic management of a hyperadrenergic state and/or use of opioid receptor agonists (methadone) or partial agonists (buprenorphine). We also alluded to the notion of cravings being present and that there is a high risk of relapse to use on cessation. To date, no guidelines exist regarding the long-term management of KUD. In medical terminology, the "standard of care" is established based on what the average physician in the appropriate specialty community would do when faced with a specific situation. When it comes to KUD management, there is a great need to establish such a standard of care. In this article we report on all the evidence currently available in the literature and combine it with survey information regarding pharmacological management by the addiction medicine specialty community. The aim here is to evaluate potentially beneficial pharmacotherapy only and not specifically any behavioral treatments.

METHODS

Literature Search

We searched PubMed/MEDLINE, PsycINFO, PsycARTICLES, CINAHL, EMBASE, Scopus, Cochrane, and Academic OneFile for English-language medical literature published between January 1, 1970, and January 1, 2020, using the search terms: "kratom," "mitragyna speciose," "mitragynine," and "7-hydroxymitragynine."

Regarding inclusion and exclusionary criteria, our interest revolved around clinical cases reporting the use of any pharmacotherapy in management of remission from kratom use in both humans and animals. Only English literature was considered.

The original search yielded a total of 2156 returns: PubMed (n = 463), Embase (n = 752), Web of Science (n = 677), CINHAL (n = 182), and PsychINFO (n = 82). After removing duplicates, 671 citations were left. Authors CS and BH examined each by title and abstract. After eliminating studies based on exclusionary criteria and applying the inclusion criteria, 14 papers met the original search criteria (Figure 1, Tables 1 and 2). Any disagreements would have been mediated for proper allocation by a third reviewer, but that was not required. Results were supplemented by references gleaned from recent reviews and citations of searched returns, as well as credible reports from academic conferences (Figure 1).

Survey

A survey was designed via Qualtrics (https://www.qualtrics.com) and distributed to the 40 state chapter presidents of the American Society of Addiction Medicine (ASAM), with a request to extend it to their specific membership group. At the time of the survey,

Table 1. Cases Reporting Maintenance Pharmacotherapy of Patients With Kratom Use Disorder and Opiod Use Disorders

Ref No.	Clinical Paradigm	Reason for Kratom Use	Extent of Kratom Used	Intervention	Maintenance Regimen	Outcome
16	43-year-old man with history of chronic pain from thoracic outlet syndrome treated with hydromorphone. Started subcutaneously injecting crushed 10 mg tablets of hydromorphone and using kratom to help ameliorate withdrawal when hydromorphone not available. Stopped hydromorphone 3.5 years before presenting and was strictly using kratom. Started taking modafinil 100 mg to help with alertness and presented to ED after experiencing a generalized tonic-clonic seizure. Following discharge, stopped kratom and reported a less intense but more protracted withdrawal compared to opioids persisting for 10 days.	Opioid substitution	Initially used unknown amount of kratom to manage episodic withdrawal from hydromorphone. Ultimately continued using unknown quantity of kratom as a tea 4 x/day; reported spending $15,000/year on kratom.	Started on BUP/NX following withdrawal from kratom to assist with cravings, 16-4 mg.	BUP/NX 16-4 mg/day	Ongoing abstinence confirmed by urine toxicology, maintained on BUP/NX 16-4 mg/day.
20	52-year-old woman with depression and chronic pain admitted to inpatient psychiatric unit for suicidal ideations. She was experiencing opioid-like withdrawal symptoms. Years prior had developed iatrogenic opioid addiction and switched to kratom 9 months prior to presentation.	Pain management	9 months of use. Gradually increased from 1 tbsp/day powdered plant matter to 1 tbsp 4-6 times/day.	As inpatient, BUP/NX induction occurred, requiring 16/4 mg on day 1 for withdrawal symptoms. Initial plan was for taper but, due to difficulty tapering, was discharged with 2-0.5 mg 4 times/day. BUP/NX increased to 8-2 mg 2x/day to manage cravings as outpatient.	BUP/NX 8-2mg 2x/day	Ongoing abstinence at 18 months, corroborated via negative urine toxicologies.
21	32-year-old man with history of PTSD, alcohol use disorder, and OUD in remission from heroin for 2 years. Presented to outpatient clinic for help with kratom dependence.	Energy	8 months of use. Started using 1 capsule kratom product/day; increased to 5-10 capsules/day.	As outpatient, started on BUP/NX 4-1 mg/day; increased to 16-4 mg/day due to withdrawal symptoms.	BUP/NX 16-4 mg/day	No cravings endorsed at follow-up visits; toxicology screens unremarkable.
22	28-year-old woman at 19 weeks of gestation with history of alcohol use disorder in remission, stimulant (methamphetamine) and OUD (heroin) complicated by a bipolar spectrum diagnosis; presented to ED for symptoms of withdrawal due to kratom use.	Opioid substitution	4 months of use prior to presentation via smoking; unknown amount, frequency.	Upon admission to inpatient unit, BUP/NX induction occurred. Discharged on 4-1 mg 4 times/day. At 36 weeks gestation, BUP/NX increased to 20-3 mg daily to address withdrawal symptoms.	BUP/NX 4-1 mg 4 x/day; increased to 20-3 mg/day at 36 weeks gestation	Upon induced delivery at 39 weeks, patient continued with BUP/NX 20-3 mg during hospitalization; discharged on it with ongoing abstinence at follow-up.
23	57-year-old man with chronic back pain, anxiety, depression; originally prescribed oxycodone but developed iatrogenic addiction. After oxycodone was discontinued, transitioned to using kratom 1 year prior to presenting. Noted withdrawal when without kratom and sought help.	Pain management	1 year of use; unknown dose, duration, frequency, route of administration. Purchased from online retailer; spent ~$2500/month.	Outpatient induction to BUP/NX was performed; patient transitioned to 24-6 mg/day for maintenance.	BUP/NX 24-6 mg daily	Abstinence maintained at 7-month follow-up; confirmed by urine toxicology.
24	54-year-old man with history of depression, anxiety, and 16-year history of iatrogenic opioid addiction. Used kratom to assist quitting opioids but experienced difficulty when trying to stop. Presented to outpatient addiction treatment clinic for help.	Opioid substitution	Unknown amount, formulation, duration.	Inducted on BUP/NX 8-2 mg on day 1; increased to 16-4 mg on day 2 to target withdrawal symptoms and cravings.	BUP/NX 8-2 mg 2x/day	Maintained abstinence at 2 months while on BUP/NX 8-2 mg 2x/day. Weeks 2-5 post induction, urine mitragynine levels were 52.7, 36.6, 1.2, and < 1 ng/mL (negative), respectively.
25	Report of 9 veterans using kratom in 2013 and 8 more between 2016 and 2017. Two-thirds used kratom daily. One used kratom solely for pain and had an alcohol use disorder. Remainder had history of severe OUD and other substance use disorders. Kratom listed as opioid of choice in 50%; 40% noted tolerance and withdrawal.	Opioid substitution, pain management	Two-thirds had reported daily use of kratom. Formulation included tea/drink, capsules, leaves added to food, or multiple means.		BUP/NX, methadone, naltrexone	All who were opioid dependent were treated with BUP/NX, referred to a methadone clinic, or treated with naltrexone.

Abbreviations: ED, emergency department; BUP/NX, buprenorphine/naloxone; tbsp, tablespoon; PTSD, posttraumatic stress disorder; OUD, opioid use disorder.

ASAM's membership was 6,365. By using formulas for the maximum error of the estimates, we determined that—for a 95% confidence interval and margin of error of 0.4—a sample size of 564 was required.[19] The survey was distributed initially on January 9, 2020 and was available for 10 days, with 1 brief communication reminder sent during this period to the ASAM chapter presidents. A total of 711 participation invites were sent. Participants were registered electronically through an individualized link, responses were anonymous, and no personal identifiers were collected.

The survey was intended to gauge whether specialists have encountered patients suffering from KUD and how they have managed abstinence in such cases. Our main interest was in pharmacological management of KUD in isolation of past or comorbid OUD histories. Specific questions and flow are detailed in Appendix A.

Eighty-two participants completed the survey, a response rate of 11.5%. Data generated were analyzed via Qualtrics. Some participants who had encountered KUD in isolation of OUD also entered comments regarding management and outcomes (see Appendix B).

RESULTS

Literature Search

The literature review yielded 14 reports involving patients for whom long-term maintenance of KUD was required, including 7 with concomitant OUD diagnoses. Of those 7 patients, all received buprenorphine for maintenance with doses of 16 mg daily; 1 patient required increase from 16 mg to 20 mg due to pregnancy, and another required 24 mg daily. All had switched to kratom use to replace their opioid addiction.

Of the 7 patients without concomitant OUD, 4 were using kratom for pain management, 1 for anxiety/insomnia, 1 for concentration and focus, and 1 patient's reason for use was unclear. For maintenance, 1 patient was started on naltrexone, and 5 were started on buprenorphine at the following doses: 8 mg eventually tapered to 2 mg prior to pregnancy, 16 mg, 6 mg (2 patients), and 4 mg daily. The other patient was on buprenorphine initially; however, due to chronic pain, he eventually was switched to methadone. See Tables 1 and 2 and Figure 1 for a summary.

Survey

Eighty-two ASAM members completed the survey, and 69 qualified for study inclusion based on their credentials (physicians only). A total of 57 (82.6%) endorsed having encountered patients with KUD, including 19 (27.5%) who had patients with KUD only—no past or comorbid OUD (Figure 2). In managing their abstinence, 17 used buprenorphine (17/19, 89.5%)—including 6 who combined it with talk therapy 1 used methadone, and 3 used naltrexone. Additionally, 1 respondent used buspirone in conjunction with therapy, and another used talk therapy only (Figure 3). (Some of the participant-reported outcomes are included in Appendix B.)

Statistical Analysis

A biostatistician analyzed 2 research questions: (1) Does the proportion of those with kratom addiction in isolation of comorbid OUD from the survey match that found through the literature review? and (2) Among those without comorbid OUD from the survey, does the profile of maintenance modalities match that from the literature review? To address these questions, the survey data was compared with the historical data via a 1-sample proportion test.

Out of the 69 qualifying participants who completed the survey, 57 encountered cases of KUD, including 19 (19/57, 33.3%) cases in isolation of comorbid OUD. This is contrasted to the 14 reports found in the literature, with 7 (7/14, 50%) in isolation of OUD comorbidity. In terms of the profile for maintenance modalities, 17 survey respondents (17/19, 89.5%) endorsed having used buprenorphine maintenance, compared to 6 (6/7, 85.7%) found in the literature. A 1-sample proportion test shows that the proportion in isolation of OUD from the survey is significantly different from the proportion of 0.50 found in the literature (95% CI, 0.22-0.47; $P = 0.02$). Given the small sample size of data and the fact that the upper limit of the confidence interval is close to 0.50, it is reasonable to believe that such a difference is not large. There is no significant difference between the profile of buprenorphine maintenance reported in the survey versus that found in the literatures (95% CI, 0.69-0.97; $P = 0.64$).

DISCUSSION

Kratom is a botanical with a known addiction liability and, in vulnerable individuals, dependence may develop rather quickly with tolerance noted at 3 months and 4- to 10-fold dose escalations required within the first few weeks.[31] Kratom addiction carries a relapse risk as high as 78% to 89% at 3 months post-cessation.[7,8,32] Although there are numerous pathways that kratom's constituents act upon, the opioid pathway has received the most interest with respect to mediation of withdrawal and addiction.[33,34] This is consistent with the notion that stimulant effects are noted at low doses—5 grams or less daily, while opioid effects at higher doses and the doses used by those addicted to it indeed seem to range from 14 grams to 42 grams daily.[31] Unfortunately, most of the cases included in our review do not reference doses. In the 3 that do (all without comorbid OUD), 1 describes an individual using 7 grams every 4 hours, and 2 involve doses of 30 grams daily. One of the experts surveyed also mentioned having managed patients with histories of 30 grams daily use.

There are 2 main pathways describing how individuals are introduced to kratom – opioid substitution by those with OUD[35,36] and self-management of various ailments (ie, anxiety and mood states, pain) by those without OUD. The cases included in this review corroborate this notion. For patients with OUD, relapse rates without MOUD are in the 90% range[37-39]–similar to relapse

Table 2. Cases Reporting Maintenance Pharmacotherapy of Patients With Kratom Use Disorder Without Co-occurring Opiod Use Disorder

Ref No.	Clinical Paradigm	Reason for Kratom Use	Extent of Kratom Used	Intervention	Maintenance Regimen	Outcome
22	32-year-old woman at 22 weeks gestation presented to specialty clinic for pregnant women with substance use disorders. Had previously undergone radiation for Hodgkin's lymphoma, resulting in chronic shoulder pain and anxiety. Managed on oxycodone until previous pregnancy, but had been self-managing with kratom for previous 7 months. Attempted to stop kratom at 16 weeks gestation but resumed due to withdrawal.	Pain management, anxiety	7 months of use; unknown dose, duration, frequency, and route of administration.	After kratom abstinence period, patient started on BUP as outpatient; reported good results with 8 mg/day. Given concern of neonatal abstinence syndrome, tapered off BUP over 2 weeks but experienced severe depression and was restarted and maintained on 2 mg for remainder of pregnancy.	BUP 2 mg during pregnancy	Upon planned C-section at 39 weeks gestation, patient maintained on BUP; abstinence maintained at follow-up visits.
23	60-year-old woman with chronic pain and history of alcohol dependence in sustained remission presented following unintentional overdose on illicit methadone. No history of OUD; endorsed kratom use and was on a long-term opioid regimen with tramadol and oxycodone with no evidence of misuse. Discharged following admission and stabilization, but presented several months later because of difficulty stopping kratom due to rebound pain and withdrawal symptoms.	Pain management	At time of evaluation, 0.25 ounces every 4 hours; purchased via online retailer.	Outpatient induction to BUP/NX performed; patient then transitioned to 4-1 mg 4 x/day maintenance.	BUP/NX 4-1 mg 4x/day	Abstinence maintained at 9-month follow-up; confirmed by urine toxicology.
26	37-year-old woman with history of postpartum depression and 2-year history of kratom use to self-manage pain stemming from fibromyalgia and after surgery for carpal tunnel syndrome. Experienced withdrawal symptoms when trying to cut back; attempted outpatient detox with low-dose clonidine without success. Contacted mental health and addiction service for inpatient kratom detox; ultimately admitted for inpatient detox.	Pain management	Started using unknown amount of kratom capsules; transitioned to using kratom extract purchased from online retailer over 2 years.	As inpatient, treated with symptom-triggered clonidine protocol and supportive medications for 3 days prior to discharge.	Naltrexone 50 mg/day	Patient discharged to partial hospitalization program and instructed to start oral naltrexone on day 7 post-discharge.
27	20-year-old man with history of ADHD (treated with stimulant) presented to office-based addiction treatment clinic for KUD management. Had used kratom past 2 years to manage anxiety and insomnia but developed tolerance. Cessation attempts led to opioid-like withdrawal.	Anxiety, insomnia	2 years of use; increased gradually to every 2 hours for 30 g total daily dose. Obtained from local gas station and mixed with water into tea.	Outpatient induction to BUP/NX performed, starting with 4-1 mg 12 hours after last kratom use and with moderate withdrawal. Attempt to taper to 2-0.5 mg over 4 days resulted in withdrawal symptoms and dose was brought back up.	BUP-NX 4-1 mg daily	Noted difficulty tapering off BUP/NX with supervision. After 3 months treatment, had 1 setback on kratom when out of BUP/NX. Has maintained sobriety after several months, working to taper off BUP/NX.
28	35-year-old male veteran presented to addiction treatment clinic reporting escalating kratom use over past 3 years. Started using kratom for concentration but use gradually increased and became singular focus over work, school, and personal activity. Was able to reduce from 30g daily to 5g/day following motivational interviewing, but experienced withdrawal.	Focus, concentration	Daily use increased from 10 g/day initially to 30 g/day. First obtained from gas station; consumed in smoothie or shake form.	Outpatient induction to BUP/NX performed, 4-1 mg 2x/day.	BUP/NX 8-2 mg/day for 16 months, then decreased to 6-1.5 mg/day	BUP/NX increased to 12-3 mg to target evening cravings; decreased back to 8-2 mg/day due to sedation. Maintained abstinence at 16 months, corroborated by urine toxicology screens for mitragynine. After 16 months, BUP/NX dose decreased to 6-1.5 mg/day, with goal of tapering off over 1 year.
29	24-year-old man with history of alcohol use disorder, Asperger's, and kratom use presented to ED after being found down, minimally responsive, hypothermic, and having a witnessed seizure by emergency medical personnel. Upon stabilization in ICU, was transferred to inpatient psychiatric unit.		Unclear duration, but was using 600 mg/day prior to presentation.	BUP 2 mg started on hospital day 13 on psychiatric ward to target kratom cravings. On day 25, BUP increased to 4 mg 2x/day due to persistent signs/symptoms of withdrawal. Discharged to a rehab center on day 28. BUP discontinued initially but restarted at 2-0.5 mg 3x/day due to withdrawal symptoms.	BUP/NX 2-0.5 mg 3x/day.	Tapered off BUP/NX after 45 days at rehab center and discharged home.

continued on next page

Table 2 continued. Cases Reporting Maintenance Pharmacotherapy of Patients With Kratom Use Disorder Without Co-occurring Opiod Use Disorder

Ref No.	Clinical Paradigm	Reason for Kratom Use	Extent of Kratom Used	Intervention	Maintenance Regimen	Outcome
30	44-year-old man with history of alcohol use disorder presented to detox unit for help stopping kratom. Began use after brief use of nonprescription oxycodone for chronic abdominal pain. Noted difficulty stopping after 1 year due to withdrawal.	Pain management	1 year of use. Initally used a "tincture" dosed by "dropper squeeze;" gradually increased to "6 dropper squeezes" every 4-6 hours.	Inpatient induction to BUP to help with withdrawal.		At 15 months post discharge revealed use of oral opiates, including methadone and oxycodone, for chronic pain syndrome.

Abbreviations: BUP/NX, buprenorphine/naloxone; OUD, opioid use disorder; detox, detoxification; ADHD, attention deficit hyperactivity disorder; ED, emergency department.

rates for KUD—versus less than 50% when MOUD are implemented.[7,8,32] Hence, for those with both OUD and KUD, it is logical to utilize MOUD. In all such cases reported above, buprenorphine was used with good results in terms of opioid and kratom abstinence.

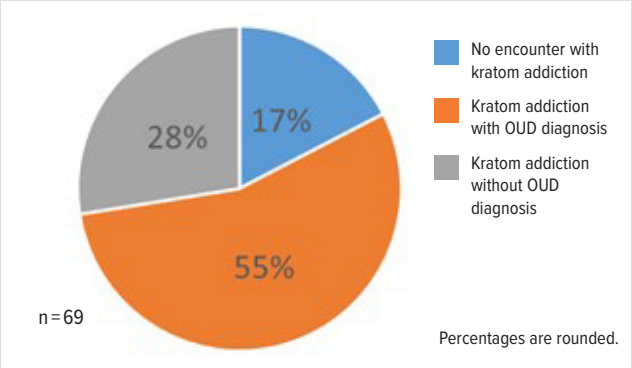
There is a clear need to establish a consensus on how to manage KUD independent of an OUD. As demonstrated in this review, there has been success with treating KUD using the same pharmacological agents as those approved for OUD. In the cases included here that did not involve a comorbid OUD diagnosis, clinicians have utilized naltrexone (n=1 case) and buprenorphine for maintenance. The use of MOUD to treat KUD has been hindered historically by the medicolegal aspects governing these agents, yet reports of treatment do exist and are corroborated by results of the survey conducted as part of this review.

There is pharmacodynamic evidence to suggest for those with OUD, ~70% mu receptor occupancy is required to achieve suppression of psychological aspects of opioid addiction.[40] Depending on the severity of one's OUD, for example high dose and intravenous use, upwards of 90% occupancy may be required.[41] Although the first may be achieved with 2-3 ng/mL plasma concentration of buprenorphine (corresponding with 8-16 mg oral dose), the latter would require 5-6 ng/mL (corresponding to 20-32 mg oral dose).[41] It is still uncertain what the opioid receptor dynamic with MG and 7-HMG is, however, it is believed that—at least for MG—it is very similar to buprenorphine.[12,13] From the cases included here, it appears that lower buprenorphine doses tend to be required for KUD in absence of OUD. Antagonist treatment has even been used in 1 case.

Limitations

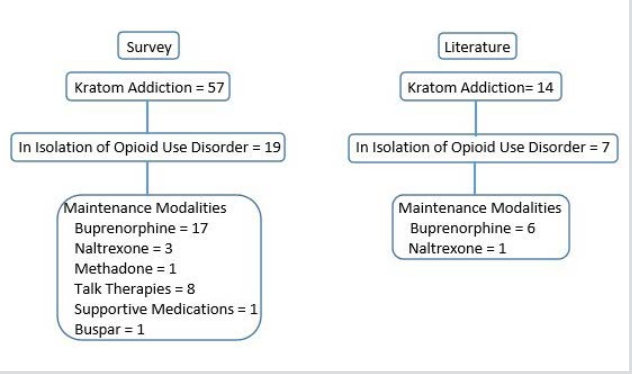
The cases resulting from the literature search and included in the analysis/comparison have a significant amount of heterogeneity in the descriptions, information provided (ie, kratom dose, route, etc), toxicology screens used for abstinence monitoring, reporting of maintenance follow-up duration, etc. Nonetheless, they all used buprenorphine or naltrexone for management of long-term abstinence as a general consensus.

Figure 2. Percentage of Survey Participants Who Have Encountered Any Kratom Addiction



Abbreviation: OUD, opioid use disorder

Figure 3. Pharmacological Modalities for Managing Kratom Use Disorder When Found in Isolation of Opioid Use Disorder



CONCLUSION

Through our survey, we assessed clinical practice patterns for management of KUD without the confounding OUD diagnosis, which would be a clear indication MOUD—the standard of care. A substantial number of respondents (82.6%) have encountered cases of KUD, of which the majority involved a comorbid OUD diagnosis. Those who endorsed treating cases of kratom addiction that did not involve a comorbid OUD reported having used primarily buprenorphine (89.5%) to manage abstinence, with the

rest using naltrexone and methadone. Based on some of the comments in Appendix B, the outcomes have been good and, like with OUD, counseling alone is not sufficient.

Together, the literature review and survey data suggest that a standard of care for maintenance of abstinence from kratom use in those with KUD hints towards the use of MOUD. This is especially true for individuals with histories of using in excess of 24 grams of kratom daily. The maintenance buprenorphine doses seem to be lower than those needed for OUD.

In light of the detrimental risks associated with growing reports of kratom use disorder and lack of any randomized controlled trials to explore treatment, this review provides sufficient evidence that the indication of MOUD should be extended to KUD as well. This is especially true if one's use of kratom involves high doses and meets DSM-5 diagnostic criteria for a moderate or severe substance use disorder.

Acknowledgements: The authors would like to acknowledge the contribution made by Karen Goodman, MSLIS, MA; Medical Librarian Dorothy M. Breene Memorial Library at New Hampshire Hospital, as well as Elizabeth Jenkins, MS(LIS), Education and Information Services Librarian at Boston University Alumni Medical Library for their assistance with the literature search and procurement of articles needed for this review.

Funding/Support: None declared.

Financial Disclosures: None declared.

Appendices: Available at www.wmjonline.org.

REFERENCES

1. Stogner JM. Predictions instead of panics: the framework and utility of systematic forecasting of novel psychoactive drug trends. *Am J Drug Alcohol Abuse*. 2015;41(6):519-526. doi:10.3109/00952990.2014.998367

2. Post S, Spiller HA, Chounthirath T, Smith GA. Kratom exposures reported to United States poison control centers: 2011-2017. *Clin Toxicol (Phila).* 2019;57(10):847-854. doi:10.1080/15563650.2019.1569236

3. 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(29):748-9. doi:10.15585/mmwr.mm6529a4

4. 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(14):326-327. doi:10.15585/mmwr.mm6814a2

5. Suwanlert S. A study of kratom eaters in Thailand. *Bull Narc.* 1975;27(3):21-27.

6. Stanciu CN, Gnanasegaram SA, Ahmed S, Penders T. Kratom withdrawal: a systematic review with case series. *J Psychoactive Drugs*. 2019;51(1):12-18. doi:10.1080/02791072.2018.1562133

7. Singh D, Müller CP, Vicknasingam BK. Kratom (Mitragyna speciosa) dependence, withdrawal symptoms and craving in regular users. *Drug Alcohol Depend.* 2014;139:132-137. doi:10.1016/j.drugalcdep.2014.03.017

8. Singh D, Müller CP, Vicknasingam BK, Mansor SM. Social functioning of kratom (Mitragyna speciosa) users in Malaysia. *J Psychoactive Drugs*. 2015;47(2):125-131. doi:10.1080/02791072.2015.1012610

9. Penders T, Stanciu C. Kratom, A Substance of Increasing Concern. Providers Clinical Support System. November 28, 2018. Accessed January 21, 2020. https://pcssnow.org/event/kratom-a-substance-of-increasing-concern/

10. Grundmann O. Patterns of kratom use and health impact in the US—results from an online survey. *Drug Alcohol Depend*. 2017;176:63-70. doi:10.1016/j.drugalcdep.2017.03.007

11. Hassan Z, Muzaimi M, Navaratnam V, et al. From kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. *Neurosci Biobehav Rev.* 2013;37(2):138-151. doi:10.1016/j.neubiorev.2012.11.012

12. Kruegel AC, Grundmann O. The medicinal chemistry and neuropharmacology of kratom: a preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. *Neuropharmacology*. 2018;134(Pt A):108-120. doi:10.1016/j.neuropharm.2017.08.026

13. Váradi A, Marrone GF, Palmer TC, et al. Mitragynine/corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit β-arrestin-2. *J Med Chem*. 2016;59(18):8381-8397. doi:10.1021/acs.jmedchem.6b00748

14. Apryani E, Hidayat MT, Moklas MA, Fakurazi S, Idayu NF. Effects of mitragynine from Mitragyna speciosa korth leaves on working memory. *J Ethnopharmacol.* 2010;129(3):357-360. doi:10.1016/j.jep.2010.03.036

15. Babu KM, McCurdy CR, Boyer EW. Opioid receptors and legal highs: Salvia divinorum and kratom. *Clin Toxicol (Phila)*. 2008;46(2):146-152. doi:10.1080/15563650701241795

16. Boyer EW, Babu KM, Adkins JE, McCurdy CR, Halpern JH. Self-treatment of opioid withdrawal using kratom (Mitragynia speciosa korth). *Addiction*. 2008;103(6):1048-1050. doi:10.1111/j.1360-0443.2008.02209.x

17. Boyer EW, Babu KM, Macalino GE. Self-treatment of opioid withdrawal with a dietary supplement, kratom. *Am J Addict*. 2007;16(5):352-356. doi:10.1080/10550490701525368

18. Statement from FDA Commissioner Scott Gottlieb, MD, on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse. FDA Statement. February 6, 2018. Accessed December 18, 2019. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-scientific-evidence-presence-opioid-compounds

19. Jones J. Statistics: lecture notes. Accessed December 18, 2019. https://people.richland.edu/james/lecture/

20. Khazaeli A, Jerry JM, Vazirian M. Treatment of kratom withdrawal and addiction with buprenorphine. *J Addict Med.* 2018;12(6):493-495. doi:10.1097/ADM.0000000000000435

21. Cheng J, Kmiec JA, Lin L, Glance JB. Treatment of kratom dependence: a case report. Poster presented at: The 50th American Society of Addiction Medicine Annual Conference; April 4-7, 2019; Orlando, FL. Accessed December 18, 2019. https://www.eventscribe.com/2019/posters/ASAM/SplitViewer.asp?PID=MzM0OTQ4NTYyNTY

22. Smid MC, Charles JE, Gordon AJ, Wright TE. Use of kratom, an opioid-like traditional herb, in pregnancy. *Obstet Gynecol.* 2018;132(4):926-928. doi:10.1097/AOG.0000000000002871

23. Buresh M. Treatment of kratom dependence with buprenorphine-naloxone maintenance. *J Addict Med*. 2018;12(6):481-483. doi:10.1097/ADM.0000000000000428

24. Bath M. Buprenorphine-naloxone treatment of kratom addiction: a unique case report and literature review. Poster presented at: American Academy of Addiction Psychiatry Annual Meeting and Scientific Symposium: December 6-9, 2018; Bonita Springs, FL.

25. Hartwell K, Maxwell A. Kratom (Mitragynine) use on the rise: a case series from a VA substance treatment and recovery program. *Am J Addict.* 2018;27:296. doi:10.1111/ajad.12753

26. Galbis-Reig D. A case report of kratom addiction and withdrawal. *WMJ*. 2016;115(1):49-52.

27. 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 Abus*. 2020;41(3):311-314. doi:10.1080/08897077.2019.1671945

28. Agapoff JR, Kilaru U. Outpatient buprenorphine induction and maintenance treatment for kratom dependence: a case study. *J Subst Use*. 2019;24(6):575-577. doi:10.1080/14659891.2019.1638459

29. 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 Pract.* 2018;10(8):192-194. doi:10.1213/XAA.0000000000000658

30. Sheleg SV, Collins GB. A coincidence of addiction to "kratom" and severe primary hypothyroidism. *J Addict Med.* 2011;5(4):300-301. doi:10.1097/ADM.0b013e318221fbfa

31. Alsarraf E, Myers J, Culbreth S, Fanikos J. Kratom from head to toe—case reviews of adverse events and toxicities. *Curr Emerg Hosp Med Rep.* 2019;7(4):141-168. doi:10.1007/s40138-019-00194-1

32. Vicknasingam B, Narayanan S, Beng GT, Mansor SM. The informal use of ketum (Mitragyna speciosa) for opioid withdrawal in the northern states of peninsular Malaysia and implications for drug substitution therapy. *Int J Drug Policy.* 2010;21(4):283-288. doi:10.1016/j.drugpo.2009.12.003

33. White CM. Pharmacologic and clinical assessment of kratom: an update. *Am J Health Syst Pharm.* 2019;76(23):1915-1925. doi:10.1093/ajhp/zxz221

34. White CM. Pharmacologic and clinical assessment of kratom. *Am J Health Syst Pharm*. 2018;75(5):261-267. doi:10.2146/ajhp161035

35. Smith KE, Bunting AM, Walker R, Hall MT, Grundmann O, Castillo O. Non-prescribed buprenorphine use mediates the relationship between heroin use and kratom use among a sample of polysubstance users. *J Psychoactive Drugs*. 2019;51(4):311-322. doi:10.1080/02791072.2019.1597224

36. 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(4):384-389. doi:10.1080/14659891.2018.1436599

37. Stein MD, Cioe P, Friedmann PD. Brief report: buprenorphine retention in primary care. *J Gen Intern Med*. 2005;20(11):1038-1041. doi:10.1111/j.1525-1497.2005.0228.x

38. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet*. 2003;361(9358):662-668. doi:10.1016/S0140-6736(03)12600-1

39. Ling W, Charuvastra C, Collins JF, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction*. 1998;93(4):475-486. doi:10.1046/j.1360-0443.1998.9344753.x

40. Nasser AF, Heidbreder C, Gomeni R, Fudala PJ, Zheng B, Greenwald MK. A population pharmacokinetic and pharmacodynamic modelling approach to support the clinical development of RBP-6000, a new, subcutaneously injectable, long-acting, sustained-release formulation of buprenorphine, for the treatment of opioid dependence. *Clin Pharmacokinet*. 2014;53(9):813-824. doi:10.1007/s40262-014-0155-0

41. Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. *Drug Alcohol Depend.* 2014;144:1-11. doi:10.1016/j.drugalcdep.2014.07.035

A Case Report of Kratom Addiction and Withdrawal

David Galbis-Reig, MD

ABSTRACT

Kratom, a relatively unknown herb among physicians in the western world, is advertised on the Internet as an alternative to opioid analgesics, as a potential treatment for opioid withdrawal and as a "legal high" with minimal addiction potential. This report describes a case of kratom addiction in a 37-year-old woman with a severe opioid-like withdrawal syndrome that was managed successfully with symptom-triggered clonidine therapy and scheduled hydroxyzine. A review of other case reports of kratom toxicity, the herb's addiction potential, and the kratom withdrawal syndrome is discussed. Physicians in the United States should be aware of the growing availability and abuse of kratom and the herb's potential adverse health effects, with particular attention to kratom's toxicity, addictive potential, and associated withdrawal syndrome.

CASE PRESENTATION

A 37-year-old white woman with no previous history of substance abuse treatment was admitted to the inpatient mental health and addiction service after contacting the unit for treatment of an "addiction to kratom." The patient denied any past medical history except for postpartum depression that was partially responsive to sertraline, which the patient discontinued on her own. The patient reported that she works as a teacher and was first introduced to kratom 2 years prior to admission by a fellow teacher who was using it to treat her fibromyalgia pain. Because the patient had been in pain from recent carpal tunnel surgery and was concerned about taking opioid analgesics due to their "addictive potential," her colleague convinced her that kratom, a "nonaddictive, natural option" to "pain killers," could be a good alternative to treat her pain. She gave the patient some capsules containing dried, crushed kratom leaves. The patient reports that it provided her pain relief and also gave her a "boost of energy." Given the expense, however, she decided to purchase the concentrated extract off the Internet on the assumption that it would last longer because it would require less of the substance. Over the course of the next 2 years, the patient continued to purchase kratom extract from a single Internet site based in Florida for $150 for a 20 ml bottle labeled only with the name of the company and the country of origin (in this case Bali). The patient reported that within 6 months she realized that she was using much more of the kratom than she intended. When she attempted to cut back, she discovered that she would experience cravings as well as significant withdrawal symptoms consisting of severe abdominal cramps, sweats, blurred vision, nausea, vomiting, and diarrhea. Over the course of the next 1.5 years she attempted to detoxify in the outpatient setting with medication support from 2 outpatient providers using low dose clonidine, without success. By this point, the patient had also lost a significant amount of weight, stating that the kratom curbed her appetite. Her husband later told the physician that she was hiding the fact that she had continued to use kratom, was hiding the bottles around the home, and had gone to significant lengths to ensure that he would not discover that she had continued to order kratom online by having the product shipped to local FedEx stores. The patient admitted she was worried that she would lose her family if she did not stop taking the kratom. Despite its effects on her health (weight loss, insomnia, cravings, and decreased overall energy level) and the conflict that her use had been creating in her marriage, she had continued to take the kratom extract. Both her husband and father gave her an ultimatum to stop using the kratom, which led to her contacting the inpatient mental health and addiction unit for assistance.

• • •

Author Affiliations: Wheaton Franciscan Healthcare–All Saints, Racine, Wis.

Corresponding Author: David Galbis-Reig, MD, Medical Director of Addiction Services, Wheaton Franciscan Healthcare–All Saints, 1320 Wisconsin Ave, Racine, WI 53403; phone 262.687.2365; fax 501.423.1588; e-mail dgalbisreig@aol.com.

CME available. See page 53 for more information.

Figure 1. Clinical Opioid Withdrawal Scale Scores Over Time

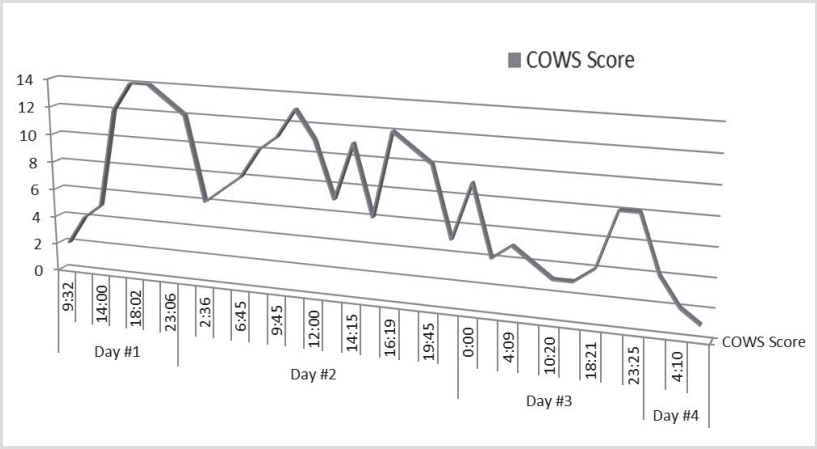
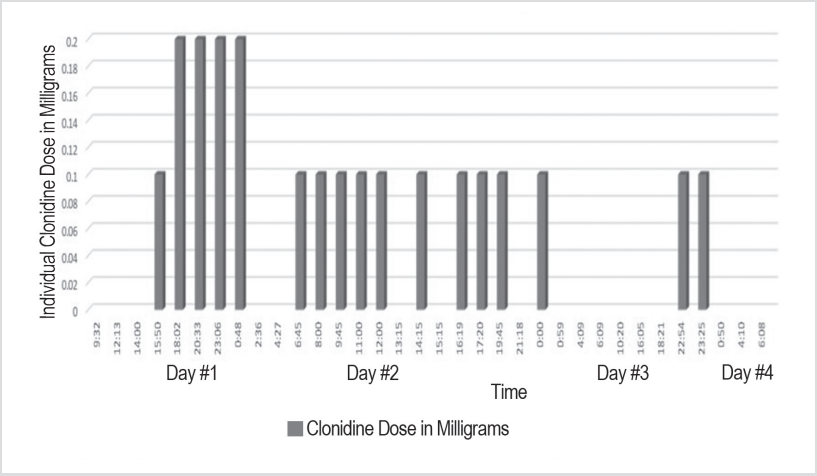


Figure 2. Kratom Withdrawal Clonidine Dose Requirements



On presentation, the patient's pupils measured approximately 2-3 mm in diameter and she complained only of mild diaphoresis. She admitted to taking her last dose of kratom at 5 AM on the day of admission. She brought her last vial of kratom, which contained approximately 2 ml of a clear fluid that she admitted was concentrated kratom extract diluted with water. Unfortunately, there was not enough of the diluted concentrate left in the bottle for laboratory analysis. The initial examination was unremarkable except for mild diaphoresis of the palms and back of the neck and significant cachexia. Electrolytes, renal function, hemogram, and liver studies were within normal limits. Urine toxicology by immunoassay was negative for all drugs of abuse including oxycodone, opioids, and methadone. A sample of urine was sent for liquid chromatography-mass spectrometry (LC-MS) to detect mitragynine (the active alkaloid in kratom), results of which came back positive at a cutoff value of 10 ng/ml. While an exact toxic concentration has not been clearly established for mitragynine, case reports suggest that side effects of mitragynine, including risk of torsade de pointes, appear to be dose dependent.[1,2] The patient was started on the opioid withdrawal protocol using symptom-triggered clonidine at a dose of 0.1-0.2 mg every 2 hours based on the Clinical Opioid Withdrawal Scale (COWS) Score, a validated scale that scores typical opioid withdrawal symptoms such as pupillary dilatation, diaphoresis, gastrointestinal distress, anxiety, fever, bone and joint pains, increased lacrimation or rhinorrhea, tremors, and yawning based on the severity of the symptoms. Scheduled hydroxyzine 50 mg by mouth every 6 hours also was started, along with a 0.1 mg per day clonidine patch to assist with withdrawal symptoms. By 1 PM on the day of admission, the patient's withdrawal symptoms started to increase rapidly as she developed myalgias, bone pain, abdominal cramping pain, nausea, and blurred vision due to rapid pupillary dilatation. The patient developed severe withdrawal symptoms by mid-afternoon, which progressed rapidly requiring up to 2 mg of oral clonidine over the next 36 hours as noted by the Clinical Opioid Withdrawal Scale (COWS) Scores (Figure 1) and frequency and dose of clonidine administered (Figure 2). Fortunately, the hyperautonomic symptoms improved rapidly over the course of 2 to 3 days. During previous attempts at detoxification, the patient described a prolonged period of severe depression and anxiety. Given the patient's previous history of postpartum depression only partially treated with sertraline, she also was started on extended release venlafaxine beginning at a dose of 37.5 mg and titrated daily up to 150 mg for her depression. In order to avoid benzodiazepines, the patient was started on pregabalin at a dose of 25 mg by mouth every 8 hours and titrated to 50 mg every 8 hours prior to discharge for her anxiety. The patient's condition stabilized over the course of 3 days in the hospital. After a family meeting with her husband and father, the patient was discharged to home with an appointment to begin participation in a dual partial hospital program. She was provided with a prescription to start naltrexone 50 mg by mouth daily for opioid antagonist therapy to begin no sooner than 7 days after discharge to avoid precipitating any additional withdrawal symptoms.

Table. Literature Review of Kratom Case Reports, Case Series, and Investigations

Authors	Number of Cases	Type of Article	Outcome	Comments
Nelson JL, et al[7]	1	Case report	Generalized tonic-clonic seizure; discharged to home	Kratom combined with Modafanil
Kronstrand R, et al[8]	9	Retrospective case series	Death	All 9 cases involved combined kratom and O-desmethyltramadol (Krypton).
Singh D, et al[9]	293	Cross-sectional survey of kratom user	Dose dependent effects of toxicity, addiction, and withdrawal	First study to measure kratom dependence, withdrawal symptoms, and drug craving.
Forrester MB[10]	14	Retrospective case series	All patients treated and recovered	Retrospective case series of kratom exposure reports to Texas Poison Centers.
Trakulsrichai S, et al[11]	52	Retrospective review series	Most cases with good prognostic outcome	Study describes toxicity and withdrawal reported to Ramathibodi Case Poison Center in Thailand.
McIntyre IM, et al[12]	1	Case report	Death	Kratom overdose; tissue samples also demonstrated mirtazapine, venlafaxine, and diphenhydramine.
Karinen R, et al[13]	1	Case report	Death	Kratom overdose; blood analysis also demonstrated citalopram, zopiclone, and lamotrigine.
Neerman MF, et al[14]	1	Case report	Death	Kratom overdose; toxicology also revealed therapeutic levels of over-the-counter cold medicine and benzodiazepine.

DISCUSSION

Kratom (*Mitragynia speciosa* Korth) is an herb indigenous to Thailand and other countries in Southeast Asia that has been used by people in that part of the world for hundreds of years to stave off fatigue and to manage pain, opioid withdrawal, and cough.[3] In the past decade, the herb has made its way around the world via Internet sales as an alternative to opioids for pain relief. Unfortunately, kratom is not well known by physicians in the United States. Kratom contains a number of active phytochemicals, but the chemical entity mitragynine (the plant's primary alkaloid) is widely regarded to produce the majority of the plant's psychoactive effects, with additional contributions from other phytochemicals, including 7-hydroxymitragynine (7-HMG) and mitraphylline.[4,5] When ingested orally, the bioavailability of mitragynine is estimated in the laboratory to be approximately 3.03% with an onset of action of approximately 5 to 10 minutes.[2] The half-life of mitragynine is not known with certainty, but its effects appear to last several hours consistent with the initiation of withdrawal symptoms within 12 to 24 hours (as occurred in the current case).[2] At low doses, mitragynine has stimulant effects, but at high doses, mitragynine behaves like an opioid and has been shown to have agonist activity at the Mu and Kappa-opioid receptors.[6] Kratom is not currently scheduled by the Drug Enforcement Agency (DEA) but is listed on its "Drugs and Chemicals of Concern" list and is sold on the Internet as a "nonaddictive" herbal alternative for pain control.[6,7] It also is used by many as a "legal high" and to assist with withdrawal from opioids. Despite its nonscheduled status with the DEA, in 2013 Wisconsin Act 351 classified kratom as a schedule 1 controlled dangerous substance, making it illegal to possess or use in Wisconsin.[8,9] Mitragynine, the primary active component of kratom, currently is being investigated as a potential analgesic with a diminished risk of respiratory depression in overdose compared to traditional opioid analgesics.[6] At the present time, however, the clinical properties of mitragynine and its potential for development as a therapeutic agent are only in the early stages of investigation.

The Internet is ripe with sites and articles that proclaim the analgesic and stimulant properties of kratom while downplaying its adverse side effects and addictive potential. Numerous case series and reports, however, have described the addictive potential of kratom, both in herbal form and as an extract. The oldest of these published articles dates back to 1975 with an early description of kratom addiction in the Thai population.[10] In a more recent study carried out to determine the risk of suicide among illicit drug users in Thailand, the investigators report that the primary drug of abuse in their study was kratom (illegal in Thailand since 1943), which was used by 59% of the 537 respondents who admitted to illicit drug use, followed by methamphetamine (24%).[11] This epidemiological study, however, did not distinguish between abuse and addiction.

More recently, a number of case series and reports of kratom toxicity have started to surface in the United States and Europe (Table). In one such report, a male patient abusing and addicted to hydromorphone attempted to use kratom to prevent withdrawal and was admitted to the hospital after he mixed the kratom with modafanil and suffered a generalized tonic-clonic seizure.[12] It is unclear if the seizure was a result of the kratom or the combination of the 2 drugs. In a separate case series from Sweden, investigators report on 9 cases of krypton intoxication and death.[13] Krypton is an herbal preparation of dried, crushed kratom leaves mixed with another mu-opioid receptor agonist, O-desmethyltramadol.[13] The abuse potential, toxicity, and withdrawal symptoms associated with kratom use have been described in at least 3 case series.[14-16] Three additional case reports also have demonstrated the potentially fatal effects of kratom without the addition of other mu-opioid agonists.[17-19]

The addictive potential of kratom (specifically mitragynine) has been well described in a discriminative stimulus rat model of addiction with properties similar to morphine and cocaine.[20] While the toxicity and addictive potential of kratom and its derivatives has not been well described in human populations, several case series and reports describe a clear addiction potential and a potentially severe, opioid-like withdrawal syndrome in humans.[14,16] Toxicity has included reports of palpitations, seizures, and coma.[12,16] The most extensive description of kratom withdrawal suggests symptoms of physical withdrawal that include myalgias, pupillary dilatation, insomnia, rhinorrhea, lacrimation, fever, hot flashes, anorexia, and diarrhea as well as psychological withdrawal symptoms that include agitation, anxiety, irritability, and depression.[14] Given the mu-opioid agonist effects of the alkaloids mitragynine and 7-hydroxymitragynine found in kratom, the symptom complex of kratom withdrawal is, not surprisingly, similar to the opioid withdrawal syndrome. The investigators of the aforementioned cross-sectional survey study declare that "kratom use is associated with drug dependence, drug withdrawal, and craving" consistent with drug addiction.[14]

Empirical evidence regarding how best to treat the kratom withdrawal syndrome and assist with long-term maintenance of sobriety from kratom is currently lacking, though the current case report suggests that a combination of high dose alpha-2 agonist therapy and hydroxyzine may provide relief from both the physical and mental symptoms of kratom withdrawal. Theoretically, buprenorphine and methadone agonist therapy also might be utilized for long-term maintenance of sobriety in kratom addiction, though kratom's current classification as a distinct chemical entity not related to the opioid class of chemicals creates some medico-legal and regulatory issues that require consideration with respect to opioid agonist therapy. As a result, and because there are no regulatory issues with antagonist therapy, the patient was prescribed oral naltrexone to assist with craving and maintenance of sobriety from kratom.

CONCLUSION

Kratom (*Mitragynia speciosa* Korth), an herb originating in Southeast Asia, which currently is not scheduled by the DEA, but is classified as a schedule 1 dangerous controlled substance in Wisconsin,[21] possesses psychoactive properties that include both stimulant and opioid-like effects. Kratom has grown, and continues to grow, in popularity in the United States and in Wisconsin. Withdrawal symptoms are mediated by the opioid properties of the plant's primary alkaloid compounds and can successfully be treated using an alpha-2 agonist and hydroxyzine as demonstrated by the current case report in which symptom-triggered clonidine therapy was utilized with COWS in conjunction with scheduled hydroxyzine. Physicians should be aware of the growing availability of kratom and its potential adverse health effects, especially its toxicity, addictive potential, and withdrawal syndrome.

Funding/Support: None declared.

Financial Disclosures: Dr Galbis-Reig reports ownership of stock in GW Pharmaceuticals and Cortex Pharmaceuticals, Pfizer Inc bonds, and spousal ownership of stock options in Abbvie, Abbott Pharma, and Hospira.

Planners/Reviewers: The planners and reviewers for this journal CME activity have no relevant financial relationships to disclose.

REFERENCES

1. Prozialeck W, Jivan J, Andurkar S. Pharmacology of kratom: an emergening botanical agent with stimulant, analgesic, and opioid-like effects. *Am Osteopath Assoc.* 2002;112(12):792-799.

2. Manda V, Avula B, Ali Z, Khan I, Walker L, Khan S. Evaluation of the in vitro absorption, distribution, metabolism, and excretion (ADME) properties of mitragynine, 7-hydroxymitragynine, and mitraphylline. *Planta Med.* 2014;80(7):568-576.

3. Le D, Goggin M, Janis G. Analysis of mitragynine and metabolites in human urine for detecting the use of the psychoactive plant kratom. *J Anal Toxicol.* 2012;36(9):616-625.

4. Suwanlert S. A study of kratom eaters in Thailand. *Bulletin Narcotics.* 1975;27(3):21-27.

5. Kittirattanapaiboon P, Suttajit S, Junsirimongkol B, Likhitsathian S, Srisurapanont M. Suicide risk among Thai illicit drug users with and without mental/alcohol use disorders. *Neuropsychiatr Dis Treat.* 2014;10:453-458.

6. Nelson J, Lapoint J, Hodgman M, Aldous K. Seizure and coma following kratom (*Mitragynina speciosa* Korth) exposure. *J Med Toxicol.* 2010;6:424-426.

7. 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.

8. Greenemeier L. Should kratom use be legal? *Scientific American.* September 30, 2013. http://www.scientificamerican.com/article/should-kratom-be-legal/. Accessed January 14, 2016.

9. Drug Enforcement Administration, Office of Diversion Control. January 1, 2013. http://www.deadiversion.usdoj.gov/drug_chem_info/kratom.pdf. Accessed January 14, 2016.

10. Singh D, Muller C, Vicknasingam B. Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms, and craving in regular users. *Drug Alcohol Depend.* 2014;139:132-137.

11. Forrester M. Kratom exposures reported to Texas poison centers. *J Addict Dis.* 2013;32(4):396-400.

12. McIntyre I, Trochta A, Stolberg S, Campman S. Mitragynine 'Kratom' related fatality: a case report with postmortem concentrations. *J Anal Toxicol.* 2015;39(2):152-155.

13. Karinen R, Fosen J, Rogde S, Vindenes V. An accidental poisoning with mitragynine. *Forensic Sci Int.* 2014;245c:e29-e32.

14. Trakulsrichai S, Tongpo A, Sriapha C, et al. Kratom abuse in Ramathibodi Poison Center, Thailand: a five-year experience. *J Psychoactive Drugs.* 2013;45(5):404-408.

15. Neerman M, Frost R, Deking J. A drug fatality involving kratom. *J Forensic Sci.* 2013;58(Suppl 1):S278-S279.

16. Harun N, Hassan Z, Navaratnam V, Mansor S, Shoaib M. Discriminative stimulus properties of mitragynine (kratom) in rats. *Psychopharmacology (Berl).* 2015;232(13): 2227-2238.

17. Lu J, Wei H, Wu J, et al. Evaluation of the cardiotoxicity of mitragynine and its analogues using human induced pluripotent stem cell-derived cardiomyocytes. *PLoS One.* 2014;9(12):1-18.

18. Ulbricht C, Costa D, Dao J, et al. An evidence-based systematic review of kratom (Mitragyna speciosa) by the Natural Standard Research Collaboration. *J Diet Suppl.* 2015;10(2):152-170.

19. Drug Enforcement Administration. Office of Diversion Control. KRATOM (*Mitragyna speciosa korth*). January 2013. http://www.deadiversion.usdoj.gov/drug_chem_info/kratom.pdf. Accessed January 14, 2016.

20. Synche Enterprises. Kratom Legal Status. February 9, 2015. http://www.synche.com/tag/kratom-legal-status/. Accessed January 14, 2016.

21. Wisconsin State Legislature. 2013 Wisconsin Act 351. April 24, 2014. https://docs.legis.wisconsin.gov/2013/related/acts/351. Accessed January 14, 2016.