DAVE MURPHY

State Representative • 56th Assembly District

Assembly Committee on State Affairs

Public Hearing, December 8, 2021

Assembly Bill 599

Testimony of State Representative Dave Murphy

Mr. Chair and members of the committee, thank you for hearing Assembly Bill 599 today.

Kratom is a plant and member of the coffee family native to Southeast Asia. As an herbal supplement it has been cultivated and used in that part of world for centuries for pain relief, alertness, and general well-being. Studies have shown kratom to be an effective natural alternative to opioids, providing Americans with a safer way to address unmanageable pain and alleviate opioid dependency.

The ability for individuals to legally utilize kratom to alleviate their opioid dependency is a critical next step for the Wisconsin HOPE agenda.

In 2013, Wisconsin enacted SB 325, a model bill intended to address the national synthetic drug problem by identifying and scheduling hundreds of specific chemical compounds. Included on the list of state scheduled compounds was mitragynine and 7-hydroxymitragynine, both found naturally in the kratom leaf, effectively making natural kratom illegal to possess. Model legislation with this unintended consequence was adopted in only Wisconsin and five other states. Since that time, no other states have banned the sale or use of kratom. Initial concerns raised regarding the danger of these chemical compounds have since been attributed to another chemical compound not found naturally in kratom.

The U.S. Drug Enforcement Agency has rejected multiple attempts to federally schedule the chemical compounds of kratom and as of 2018 the Federal Drug Administration has rescinded their recommendation to schedule kratom stating, "This decision is based on

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many factors, in part on new data, and in part on the relative lack of evidence, combined with an unknown and potentially substantial risk to public health if these chemicals were scheduled at this time."

Just this October, the World Health Organization Executive Committee on Drug Dependency issued a report stating, "The Committee concluded that there is insufficient evidence to recommend a critical review of kratom."

Our bill proposes Wisconsin de-schedule mitragynine and 7-hydroxymitragynine and replace this prohibition with the Kratom Consumer Protection Act (KCPA). Instead of making kratom unavailable to those that benefit from it, the KCPA would regulate kratom products to ensure that kratom processors are registered with DATCP, products are pure kratom and not adulterated with a controlled substance or any ingredient that may cause injury, and prohibit the sale of the kratom products to anyone under 21 years of age.

MARK POCAN
2ND DISTRICT, WISCONSIN

COMMITTEE ON APPROPRIATIONS
COMMITTEE ON EDUCATION & LABOR
JOINT ECONOMIC COMMITTEE
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December 6, 2021

The Hon. Rob Swearingen
Chair
Assembly Committee on State Affairs
Wisconsin State Legislature

Dear Chair Swearingen:

I write in support of Assembly Bill 599 (AB 599), a bill to legalize the manufacture, distribution, delivery, and possession of kratom, being considered during Wednesday's public hearing in the Committee on State Affairs.

As a Member of Congress, I have worked with federal representatives in both parties to continue the research and legal use of kratom due to its promising help in a number of health conditions as well as its ability to help many people overcome addiction. I've been moved by the many, many personal stories of the benefits of kratom from people across the nation.

According to the Wisconsin Legislative Reference Bureau: "Under current law, kratom is classified as a Schedule I controlled substance and if a person manufactures, distributes, or delivers kratom, [they are] guilty of a misdemeanor. [AB 599] removes kratom from the schedule of controlled substances and legalizes the manufacture, distribution, delivery, and possession of kratom, subject to certain limitations."[1] This legislative outcome is consistent with the emerging view in Washington, D.C. where kratom is now supported on a bipartisan basis, it will be receiving millions of dollars in new research funding, and its benefits have been recognized by the Director of the National Institute on Drug Abuse (NIDA) within the National Institutes of Health (NIH).

In a recent letter addressed to both the U.S. Ambassador to the United Nations and the Secretary of the U.S. Department of Health and Human Services[2], Senator Mike Lee – a Republican from Utah – and I wrote "to ask that the United States oppose any effort to add kratom and its alkaloids to the 1971 U.N. Convention on psychotropic substances as a banned substance." Additionally, we noted that "In 2016, 145,906 Americans including consumers, scientists, and state and federal lawmakers raised their voices in opposition to the Department of Health and Human Services' (HHS) proposal to schedule kratom as a controlled substance."

Similar to this strong support for kratom from Members of the U.S. House of Representatives and the U.S. Senate – across party lines – the Fiscal Year 2022 Labor, Health and Human Services,

[1] https://docs.legis.wisconsin.gov/2021/related/proposals/ab599
[2] https://www.americankratom.org/mediak/news/bi-partisan-letter.html

Education, and Related Agencies Subcommittee appropriation legislation in the House of Representatives contains the following[3]:

> "Kratom.—The [Appropriations] Committee recognizes that NIDA-funded research has contributed to the continued understanding of the health impacts of kratom, including its constituent compounds, mitragynine and 7-hydroxymitragynine. The Committee is aware of the potential promising results of kratom for acute and chronic pain patients who seek safer alternatives to sometimes dangerously addictive and potentially deadly prescription opioids and of research investigating the use of kratom's constituent compounds for opioid use disorder. The Committee directs NIDA to continue to invest in this important research, especially considering the increase in overdose deaths during the COVID–19 pandemic." (p. 135)

> "Kratom.—The [Appropriations] Committee directs the Secretary to maintain current Agency policy to not recommend that the substances mitragynine and 7-hydroxymitragynine, known as kratom, be permanently controlled in Schedule I of the Controlled Substances Act, either temporarily or permanently [...] The Committee encourages AHRQ to continue to fund research on natural products that are used by many to treat pain in place of opioids, including kratom [...] The Committee recommends an additional $3,000,000 for this research and directs AHRQ to make center-based grants to address research which will lead to clinical trials in geographic regions which are among the hardest hit by the opioid crisis." (p.189)

And, finally, while testifying before the Appropriations Committee in the U.S. House of Representatives on May 25th of this year, Dr. Nora Volkow, the Director of NIDA, stated: "Kratom, most notably mitragynine, has many interesting properties that could be of value potentially as a medication for pain. Also, interestingly, they could hold value as treatment for addiction [...] it is so important to actually do research on this substance."[4]

Clearly, Wisconsin is out of sync with the nation when it comes to kratom, however this legislation would rectify that and put us with the other 44 states that do not restrict kratom in the way our state currently does. I commend the authors of this bill for their work, and this Committee for including AB 599 as part of Wednesday's public hearing. I hope you will look at this bill favorably.

Sincerely,

Mark Pocan
Member of Congress

[3] https://www.congress.gov/117/crpt/hrpt96/CRPT-117hrpt96.pdf
[4] https://appropriations.house.gov/events/hearings/fy-2022-budget-request-for-the-national-institutes-of-health

To:	Members, Assembly Committee on State Affairs
From:	Badger State Sheriffs' Association (BSSA) Wisconsin Sheriffs and Deputy Sheriffs Association (WS&DSA)
Date:	December 9, 2021
RE:	**Testimony in Opposition to Assembly Bill 599: Kratom Legalization**

Good afternoon, Chairmen Swearingen, and committee members. My name is Dale Schmidt, and I am the Dodge County Sheriff as well as the 1st Vice President and Legislative Chair for the Badger State Sheriffs. Together with the Wisconsin Sheriffs and Deputy Sheriffs Association, our organizations represent all of Wisconsin's 72 Sheriffs and over 1,000 deputies and jail officers.

Our organizations oppose AB 599, which would legalize the manufacture, distribution, delivery, and possession of kratom in Wisconsin. As law enforcement officers representing small and larger Wisconsin communities, we are concerned about efforts to legalize a substance that the Drug Enforcement Administration has identified as a "drug of concern:" *Kratom is a tropical tree native to Southeast Asia. Consumption of its leaves produces both stimulant effects (in low doses) and sedative effects (in high doses), and can lead to psychotic symptoms, and psychological and physiological dependence. The psychoactive ingredient is found in the leaves from the kratom tree. These leaves are subsequently crushed and then smoked, brewed with tea, or placed into gel capsules.*[1]

Currently, there are no recognized medical uses for kratom; indeed, the Food and Drug Administration (FDA) has warned consumers not to use any product containing kratom or the psychoactive compounds derived from the plant. At the FDA's direction, U.S. Marshals have seized large shipments of raw and processed kratom across the country, including a 2016 shipment of kratom dietary supplements worth more than $400,000 in South Beloit, Illinois, just over the border from our state.[2]

Kratom use has been linked to psychotic episodes, overdose deaths, and the abuse of other drugs. According to the Centers for Disease Control and Prevention, many victims of kratom-involved and kratom-positive overdose deaths also tested positive for fentanyl, heroin, or prescription opioids.[3] The FDA has noted that kratom "affects the same opioid brain receptors as morphine, appears to have properties that expose users to the risks of addiction, abuse, and dependence."[4]

At a time when so many Wisconsin communities are dealing with the devastating effects of opioid abuse, why would we legalize a dangerous substance, with links to opioid addiction and death, that lacks any FDA-approved uses? Legalizing Kratom would be detrimental to the public health of Wisconsin, not to mention the rippling effects through OWI and other areas. **Because of the health and safety risks to our communities, we urge you to oppose efforts to legalize kratom in Wisconsin.**

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[1] U.S. Drug Enforcement Administration, "Drugs of Abuse: A DEA Resource Guide," 2017 Edition, https://www.dea.gov/sites/default/files/2018-06/drug_of_abuse.pdf.
[2] U.S. Food and Drug Administration, "FDA and Kratom," 11 September 2019, https://www.fda.gov/news-events/public-health-focus/fda-and-kratom.
[3] Centers for Disease Control and Prevention, "Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected," April 12, 2019, https://www.cdc.gov/mmwr/volumes/68/wr/mm6814a2.htm?s_cid=mm6814a2_w.
[4] U.S. Food and Drug Administration, "FDA and Kratom."

Written Comment by Professor Dr. Dr. (h.c.) Marilyn A. Huestis

Thomas Jefferson University, and President, Huestis & Smith Toxicology, LLC

To The
Wisconsin Committee on State Affairs Hearing on AB 599
8 December 2021

I am a forensic toxicologist and former Chief of Chemistry and Drug Metabolism, National Institute on Drug Abuse (NIDA), NIH for more than 23 years. Since my recent retirement, I remain highly active in the field as a collaborator with many other researchers, as a Professor, Thomas Jefferson University, Honorary Professor, Queen Mary University of London, England, President of Huestis & Smith Toxicology, LLC, on the World Antidoping Agency's Prohibited Drug List Committee and consultant to diagnostic and pharmaceutical companies, and state and federal governments. As a Senior Science and Policy Advisor with Pinney Associates, I worked with the American Kratom Association and its research supporting affiliate, the Center for Plant Science and Health. I am the author of 535 manuscripts and book chapters and Past President of The International Association of Forensic Toxicologists, the Society of Forensic Toxicologists and Past Chair of the Toxicology Section of the American Academy of Forensic Sciences.

I am writing about designating kratom's primary active constituent mitragynine as cause of death in postmortem investigations. Currently, there is no consensus on a lethal mitragynine concentration. There is a substantial overlap between non-toxic, therapeutic, and lethal mitragynine blood concentrations. The possibility that kratom exposure alone is the primary contributor to death in some cases cannot be ruled out but most investigations of kratom-associated deaths describe the presence of other potentially lethal drug concentrations, deaths due to trauma, and/or limited toxicology testing. The National Institute on Drug Abuse stated, "There have been multiple reports of deaths in people who had ingested kratom, but most have involved other substances." The FDA website description of "Mentions of Kratom in Overdose Deaths in the US" https://www.drugpolicyfacts.org/node/3978) was not updated with information from more recent and thorough investigations that clearly documented all three of these factors in the presented death cases. As the CDC stressed in its report (Olsen et. al., 2019), in the few cases where only mitragynine was identified, toxicology testing was limited and did not include screening for many other potentially lethal drugs. Also, the FDA described one kratom-associated death of "particular concern" because the Agency had not found evidence of other drug use; however, the US DHHS later determined that the death was due to trauma in a motor vehicle crash.

The US Assistant Secretary of Health rescinded the FDA's recommendation for scheduling kratom in 2018 stating there is "still debate among reputable scientists over whether kratom by itself is associated with fatal overdoses." In almost all cases, other potent drugs were also identified, making it difficult to define the contribution of mitragynine. I personally reviewed all the published kratom reported deaths world-wide and reached the same conclusion as the CDC that lack of comprehensive toxicological testing precludes assigning causation to mitragynine. Mitragynine concentrations ranged from 3.5 to 3500 ng/mL and in most of these, the authors state that there was limited toxicological testing to rule out the presence of other

drugs. Mitragynine alone was reported in only seven cases; however, in four cases there was sufficient blood for expanded toxicology testing. Other drugs that could have contributed to the death were identified in all four cases.

Novel synthetic opioids, a NPS subclass, are agonists at opioid receptors producing analgesia, sedation, and respiratory depression, contributing greatly to the North American opioid epidemic. In my review of published kratom-associated deaths, frequently fentanyl, NPS fentanyl analogs, heroin and other NPS opioids were identified. NPS are not routinely included in toxicological testing and may be taken unknowingly as adulterants in the unregulated drug supply, especially in drugs purchased online. In addition, researchers found multiple packaged commercial kratom products with artificially elevated concentrations of 7-hydroxy-mitragynine, presumably due to intentional adulteration to make the product more potent (Lydecker et. al., 2016). We agree with other kratom experts (e.g., Prozialeck et. al., 2019) that marketed kratom products should be regulated to prevent boosting 7-hydroxy-mitragynine concentrations or per serving content above those naturally present, due to the greater safety risks of 7-hydroxy-mitragynine at supranatural concentrations. Dr. Abhisheak Sharma and his University of Florida colleagues, analyzed thousands of fresh kratom samples and always found less than 0.01% 7-hydroxy-mitragynine, the limit of quantification of the method. However, controlling 7-hydroxy-mitragynine concentrations by scheduling effectively bans naturally occurring kratom products for consumer use. Scheduling kratom, mitragynine or 7-hydroxy-mitragynine would lead to an unregulated illicit kratom market and could exacerbate the concern of fortifying kratom or mitragynine products with 7-hydroxy-mitragynine.

Another example included in the FDA report of mitragynine-associated deaths was a case report of nine Swedish deaths (Kronstrand et. al., 2011). The authors concluded that the kratom powdered leaf product purchased online was laced with a toxic dose of O-desmethyltramadol and the nine cases should not have been characterized as kratom caused deaths. The complexities of making conclusions on a cause of death associated with mitragynine concentrations are also highlighted in Papsun et. al., 2019 that concluded "Quantitative reports of mitragynine in biological specimens from forensic investigations in the literature are sparse and may be influenced by poor analyte stability and inadequate resolution of mitragynine from its diastereomers, which could lead to falsely elevated concentrations and subsequently render those reported concentrations inappropriate for comparison to a reference range."

In the latest peer reviewed report of 35 mitragynine-associated deaths (Schmitt et. al., 2021), there was no statistically significant difference in blood concentrations between cases where mitragynine was not listed as a cause of death (mean, 315 ± 297 ng/mL) and cases in which mitragynine was listed as a contributor to death (mean, 269 ± 382 ng/mL; $P < 0.201$). In the only case where mitragynine was considered to be the only drug contributing to death, aripiprazole, an atypical antipsychotic was present at 310 ng/mL but phenibut, a central nervous system depressant prescribed in Russia to treat anxiety, was found at the scene but was not included in toxicological testing.

In addition, as described on NIDA's Kratom Facts web page, the stimulant effects of mitragynine and 7-hydroxy-mitragynine are due to its binding to adrenergic receptors and their

sedating and analgesic effects due to binding to the G-protein coupled opioid receptors. However, the opioid G-protein receptor binding is biased and does not include recruitment of beta-arrestin, resulting in less respiratory depression. https://www.drugabuse.gov/publications/drugfacts/kratom).

Dr. Jack Henningfield and I recently completed a controlled high dose mitragynine vs 60 and 150 mg/kg oxycodone administration study in rats according to an FDA-recommended protocol to evaluate respiratory depression. While significant respiratory depression and some deaths were observed in oxycodone-treated animals, no significant respiratory depression and no deaths were reported in mitragynine-treated animals. We are preparing the data for publication but FDA and NIDA were briefed on outcomes, and we are happy to brief the State of Wisconsin legislative committee. I am advising on a human controlled dosing study of pure mitragynine and other kratom-derived products that is currently being conducted with approval by Health Canada. Full safety evaluation and pharmacokinetics of mitragynine and 7-hydroxy-mitragynine are included. To date, there are no serious adverse events and doses were well tolerated.

I conclude that there is a lack of sufficient scientifically sound evidence that kratom or its alkaloids pose an imminent public health threat that warrants scheduling. Regulations are needed as already established in five US states and Canada to ensure that kratom products are not adulterated or artificially elevated in alkaloid content. In addition, more comprehensive toxicological analysis must be performed prior to designating mitragynine as cause of death.

Thank you for your efforts and the opportunity to comment.

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Wisconsin Medical Society

TO: Assembly Committee on State Affairs
Representative Rob Swearingen, Chair

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

DATE: December 8, 2021

RE: **Opposition** to 2021 Assembly Bill 599

On behalf of nearly 10,000 physician members statewide, thank you for this opportunity to share our opposition to 2021 Assembly Bill 599, which would remove elements found in kratom from our state's Controlled Substances Act. The Society and the Wisconsin Society of Addiction Medicine (WISAM) oppose the legalization of kratom in Wisconsin and urge you to protect Wisconsin citizens from a legalization/regulatory scheme that would increase access to a drug the U.S. Food and Drug Administration has warned "appears to have properties that expose users to the risks of addiction, abuse and dependence."[1]

FDA Warnings are Clear: "Regulation" of Kratom Does Not Protect Consumers
The FDA's posted warning about kratom is clear and should be heeded:

> 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 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.

Assembly Bill 599's sections 3 and 4 would remove the substances cited in the FDA's warning, mitragynine and 7-hydroxymitragynine, from the state's Controlled Substances Act. The Wisconsin Medical Society and WISAM believe this would be harmful to Wisconsin's citizens.

The kratom industry and other supporters of AB 599 allege that "[k]eeping kratom illegal isn't solving any problems."[2] To the contrary, the previously cited FDA warning included a number of actions the agency has taken across the country, including a 2016 action in South Beloit, IL, where U.S. Marshals seized 90,000 bottles labeled as "dietary supplements" containing kratom. The FDA's press release[3] about the action makes it clear that such actions are taken for public safety reasons when kratom suppliers attempt to skirt FDA requirements about adulterated dietary supplements:

> "We have identified kratom as a botanical substance that could pose a risk to public health and have the potential for abuse," said Melinda Plaisier, the FDA's associate

[1] "FDA and Kratom", Sept. 11, 2019: https://www.fda.gov/news-events/public-health-focus/fda-and-kratom
[2] Memo to Legislature, American Kratom Association, July 15, 2021
[3] https://www.fda.gov/news-events/press-announcements/us-marshals-seize-dietary-supplements-containing-kratom

> commissioner for regulatory affairs. "The FDA will continue to exercise our full authority under law to take action on these new dietary ingredients, especially if they ignore the notification requirements, as part of our commitment to protecting the health of the American people."

Leading health care systems also warn their patients about kratom – including using kratom as a way to, as the cosponsor memo for AB 599 put it, "alleviate their opioid dependency." The Mayo Clinic has a web page[4] to help answer the question: "Kratom for opioid withdrawal: Does it Work?" From that resource:

> ## Natural, but not safe
>
> Because kratom may ease withdrawal symptoms, researchers have studied it as a potential treatment. The evidence suggests that rather than treating addiction and withdrawal, the use of kratom may lead to them.
>
> In one study, people who took kratom for more than six months experienced withdrawal symptoms similar to those that occur after opioid use. Over time, people who use kratom may develop cravings for it and need the same medications that are used to treat opioid addiction, such as buprenorphine (Buprenex) and naloxone (Narcan, Evzio). When kratom is used during pregnancy, the infant may experience symptoms of withdrawal after birth.
>
> As with pain medications and recreational drugs, it is possible to overdose on kratom. The treatment for kratom overdose is similar to that for opioid overdose, and people experience many of the same treatment problems. Kratom has caused at least 36 deaths. Although people may enjoy the good feelings that kratom can produce, kratom has not proved to be an effective treatment for opioid withdrawal.

Continuing Research into Kratom Use Shows Troubling Effects

Legalizing/regulating kratom will simply exacerbate the problems addiction medicine physician specialists are witnessing in their practices. The active components of kratom, mytraginine and 7-hydroxy-mitragynine, act like opioids in the body, and addiction to kratom requires treatment just like that of an opioid use disorder. The *Wisconsin Medical Journal* in April 2021 published a literature review[5] of how best to treat what the paper terms "Kratom Use Disorder (KUD)." In their introduction, the paper's authors highlight the concerning trend about kratom's effects (citations omitted):

> 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. Aside from the Food and Drug Administration (FDA) reports of concern and adverse effects exhibited through increased calls to poison control centers and overdose deaths, the notion of addiction is rapidly emerging.

For more Wisconsin physician-conduced research into kratom and its harmful effects, please review the materials accompanying this memo. Thank you again for this opportunity to provide the Society's and WISAM's opposition to AB 599. Please feel free to contact the Society with any questions on this or other health care issues.

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[4] https://www.mayoclinic.org/diseases-conditions/prescription-drug-abuse/in-depth/kratom-opioid-withdrawal/art-20402170

[5] https://wmjonline.org/wp-content/uploads/2021/120/1/54.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.

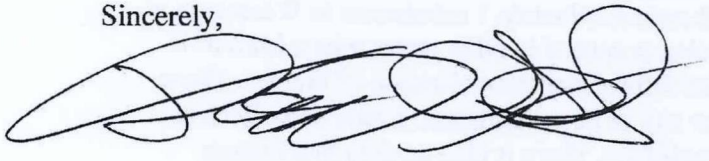
Finally, any attempt to introduce this bill as part of the HOPE legislation under the guise of treatment for OUD is anti-scientific and harmful. The FDA has issued warning letters to

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

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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.

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CME available. See page 53 for more information.

Figure 1. *Clinical Opioid Withdrawal Scale Scores Over Time*

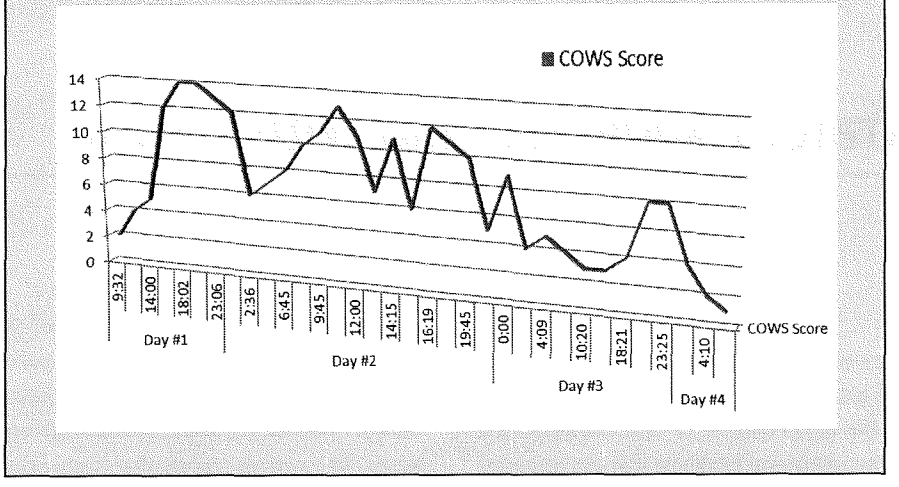
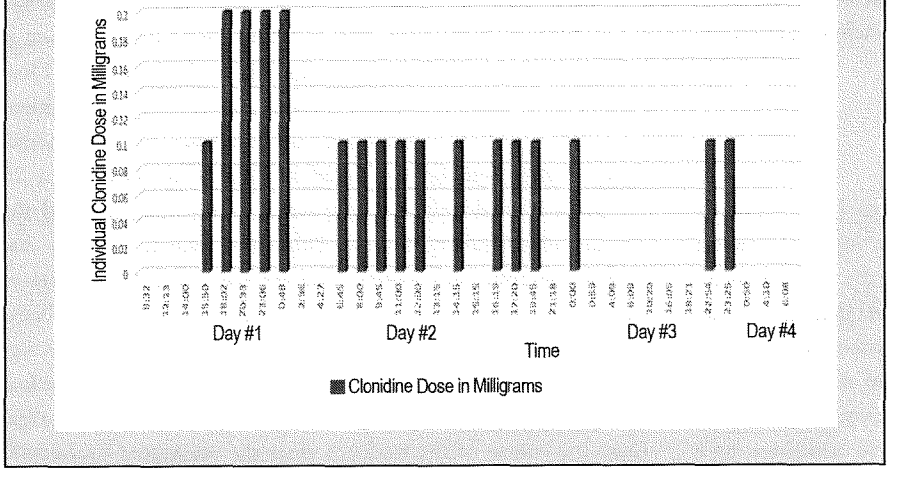


Figure 2. Kratom Withdrawal Clonidine Dose Requirements



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.

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

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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.

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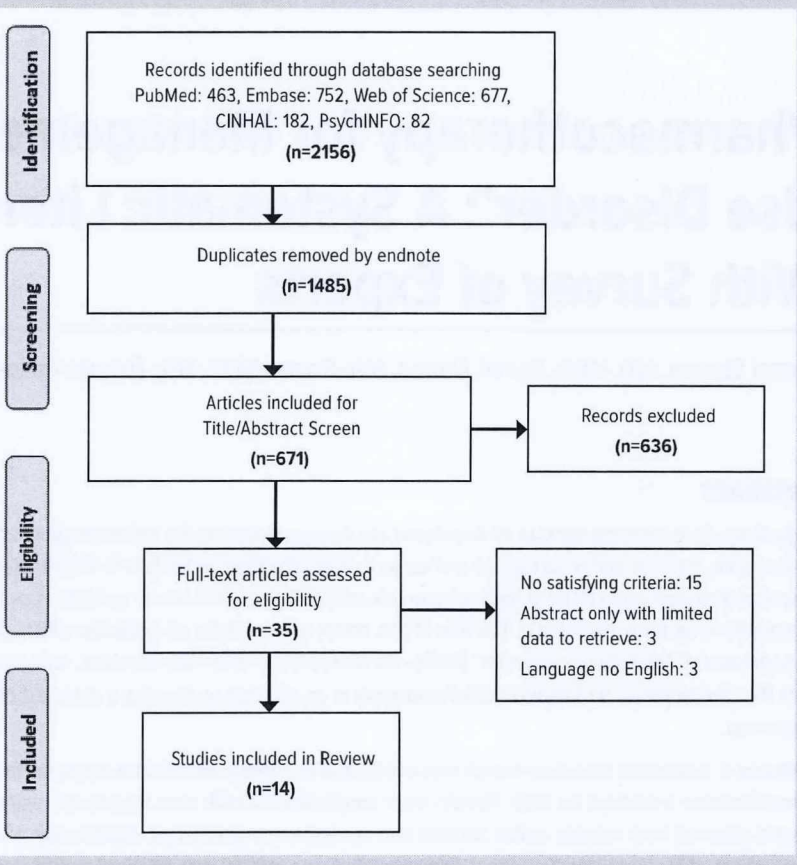
INTRODUCTION

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.

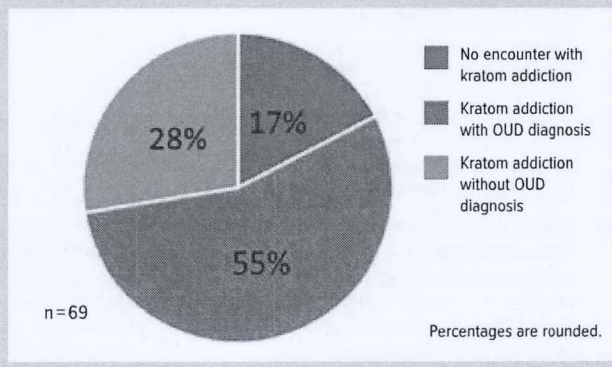
There is a clear need to establish a consensus on how to manage KUD independent of an OUD. As demonstrated in this review, there has been success with treating KUD using the same pharmacological agents as those approved for OUD. In the cases included here that did not involve a comorbid OUD diagnosis, 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

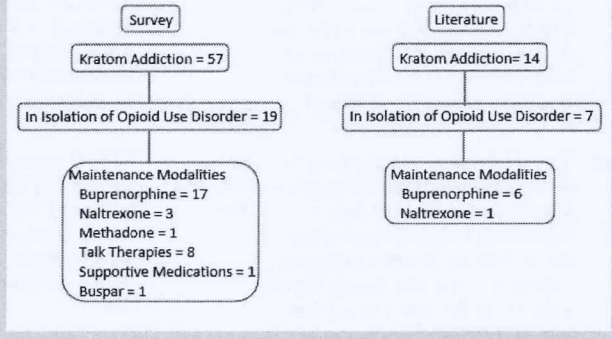
The cases resulting from the literature search and included in the analysis/comparison have a significant amount of heterogeneity in the descriptions, information provided (ie, kratom dose, route, etc), toxicology screens used for abstinence monitoring, reporting of maintenance follow-up duration, etc. 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.

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I am a Healthcare Executive and Nurse Practitioner who retired early due to disability. Despite struggling through many health issues during my life, I pushed through work and school earning my doctorate in nursing in 2011. Unfortunately, by 2015 my health issues led to an inability to stand longer than a few minutes, severe pain, fatigue, frequent choking, and gait instability. Finally, after extensive research and multiple specialist visits, I was diagnosed with several rare congenital disorders including:

1. Chiari malformation-the cerebellum in my brain was below my skull and placing pressure on my spinal cord and flattened my brain stem.
2. Tethered Spinal Cord- caused severe nerve pain to my trunk and legs.
3. Ehlers-Danlos hypermobility- a connective tissue disorder that leads to instability of joints and severe chronic pain.

Unfortunately, I was never able to find a low-risk tolerable way to control my pain and fatigue. Even after major surgery removing a portion of my skull and sewing a patch to my brain, I was only able to tolerate the prescribed Oxycodone for a week due to dizziness, confusion, and fatigue. I am so drug sensitive even acetaminophen (Tylenol) makes me so sleepy that I can only take it at bedtime. I did take Naproxen (Aleve) daily for 3 months which was minimally helpful but had to discontinue it due to the side effects.

Luckily, my son introduced me to Kratom. I like to say that I gave him his life, but he gave me mine back! Although I am still limited in my activity, my comfort level and fatigue have improved significantly with the use of Kratom without the side effects that I experience with other medications.

The fact that it is illegal to take Kratom in Wisconsin has been an extreme hardship and has affected my family's life significantly. I spend half of my time in Illinois away from my husband where I can take Kratom and have a healthy level of activity.

Please pass this legislation so I don't have to move to Illinois!

Sincerely,

Heidi Sykora RN, DNP

8 December 2021

Written Comment by Jack E. Henningfield, PhD

Vice President, Research, Health Policy and Abuse Liability, PinneyAssociates,

Bethesda, Maryland

To The

Wisconsin Committee on State Affairs Hearing on AB 599

I am Jack Henningfield, Vice President, Research Health Policy, and Abuse Liability at PinneyAssociates where I consult on the abuse/dependence potential of new medicines, tobacco products, cannabinoids, and natural products including kratom. I am also Professor, Adjunct, Behavioral Biology at Johns Hopkins University. Formerly, I was Chief of the Clinical Pharmacology Branch, and the Biology of Dependence and Abuse Potential Assessment Section of the National Institute on Drug Abuse, or NIDA. Through PinneyAssociates, I advise the American Kratom Association (AKA) on kratom science.

I recently completed an update of the abuse potential of kratom which includes over 100 new studies in the past three years. This updated 8-Factor Analysis, that was supported by the AKA, but which had no input or oversight by AKA, is available on the AKA website. A more recent peer-reviewed assessment of kratom abuse potential and safety includes addition studies and should be online in a special issue of Frontiers in Pharmacology addressing kratom science. It has been accepted for publication following peer-review and should be available online within a few weeks.

As a scientist, throughout my career I have worked closely with health policy staff at the Food and Drug Administration FDA), the Department of Health and Human Services (HHS), the National Institutes of Health (NIH), and the Drug Enforcement Administration (DEA) to protect the public by evaluating emerging substances, any safety threat they pose, and their associated addiction liability. All of us shared the common goal of protecting the public, and I continue to have enormous respect for my colleagues even where we occasionally disagree.

Kratom is an area where a substantial disagreement currently exists between the policy staff at the FDA and the scientists at NIH, NIDA, HHS, and DEA. It was not always the case. When the reports of 9 deaths in 2009 in a 12-month period from a powdered kratom product sold on the Internet known as Krypton, that legitimately raised the safety signal on kratom with public health officials around the world.

Over the next several years, the FDA widely disseminated their concerns about kratom that convinced six states, including Wisconsin, to ban kratom based largely on those 9 deaths in Sweden. The FDA also confidently assured the states that the DEA would classify two of kratom's alkaloids as Schedule 1 substances.

But the seven years since Wisconsin's policy makers were assured the DEA would be scheduling kratom, it has not happened. The reason is found in the 8-Factor Analysis where the science clearly

demonstrates that the FDA's assumptions about the safety profile and the addiction liability of kratom were plainly wrong. In fact, in the most recent assessment of the FDA's claims about kratom in a letter on August 16, 2018, by the HHS Assistant Secretary of Health Dr. Brett Giroir that withdrew the scheduling recommendation, it was determined that the FDA failed to provide the evidence and data required to ban kratom, and that "new data" disputed the FDA's claims about kratom. Dr. Giroir called it "disappointingly poor evidence and data" and cited the "significant risk of immediate public health consequences for potentially millions of users if kratom or its components are included in Schedule I."

In 2014, the FDA laid out a case based largely on assumptions to convince states to ban kratom, but the emerging science dramatically contradicts those now outdated assumptions. Today, the threat appears to be part of a common problem where unscrupulous bad actors are spiking otherwise safe substances with dangerous adulterants. With kratom, it is fentanyl, heroin, morphine – all of which are deadly when unsuspecting consumers think they are buying pure kratom.

Extensive new research, much of it supported by the U.S. National Institute on Drug Abuse, supports the following conclusions:

(1) The pharmacology of kratom reveals the profile of a relatively low abuse potential and low risk substance compared to most scheduled substances, and use is overwhelmingly by the oral route and does not escalate to injection, smoked, or nasal routes as is common with opioids and stimulants.

(2) Despite use by an estimated 10-16 million adults in the US, none of the major national surveys used to identify substance use public health threats indicate an imminent threat; the Drug Enforcement Administration or DEA, has never listed kratom in its annual drug threat reports, and in 2018 the Assistant Secretary of Health, Dr. Giroir, rescinded the 2017 FDA scheduling recommendation.

(3) National surveys in the US and Canada and studies in SEA region indicate that most consumption is to enhance health and well-being, and contributes to improved social and occupational performance, which is in contrast to prototypic controlled substances.

(4) There is evidence that removal of kratom would pose an individual and public health risk in countries (e.g., the US and Canada), and regions, (e.g., SEA) where kratom is widely used by people to abstain from opioids (also see Assistant Secretary Giroir's letter)

(5) New research confirms that kratom is rich in alkaloids with potential medicinal value. NIDA is funding extensive research that may lead to safer new medicines modeled or derived from kratom, but this is likely a decade or more away and scheduling would severely impede such research.

(6) Nature got it right: The most abundant alkaloid, mitragynine, common to most marketed products, primarily accounts for kratom's effects, is of relatively low risk and abuse potential, whereas other alkaloids, including the mitragynine metabolite, 7-hydroxymitragynine, is present at such low levels as to not substantially contribute to abuse potential or risks, or are of low pharmacological activity.

(7) I encourage regulatory frameworks such as were adopted by 5 states in the US to ensure that marketed products are pure and not adulterated or artificially elevated in alkaloid content, and with other risk-reducing provisions. Canada also has a potential model regulatory approach.

(9) Drs. Marilyn Huestis and Joseph Rodricks and I recently completed a study of the respiratory effects of oral mitragynine compared to oxycodone in a rat model published by FDA. Oxycodone produced dose related reductions in blood gas measures of respiratory depression and deaths. Over a wide range of doses, mitragynine did not produce dose-related respiratory depressant effects.

Thank you for your efforts and the opportunity to comment. I will be pleased to provide PDFs of research addressing any of my comments.