DAVE MURPHY

State Representative • 56th Assembly District

ASSEMBLY BILL 393

TESTIMONY OF STATE REPRESENTATIVE DAVE MURPHY

Chairperson Swearingen and members of the Assembly Committee on State Affairs, thank you for the opportunity to testify on Assembly Bill 393 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 in the battle against opioid dependency.

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attempts to federally schedule the chemical compounds of kratom, and as of 2018 the Federal Drug Administration has rescinded their recommendation to schedule kratom stating, "This decision is based on many factors, in part on new data, and in part on the relative lack of evidence,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."

Our bill proposes Wisconsin de-schedule mitragynine and 7-hydroxymitragynine and replace this prohibition with the provisions of Assembly Bill 393. Instead of making kratom unavailable to those that benefit from it, AB 393 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. It would also prohibit the sale of the kratom products to anyone under 21 years of age.

Thank you for your time and consideration.

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Wisconsin Medical Society

Wisconsin Society of Addiction Medicine
A Chapter of American Society of Addiction Medicine

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

FROM: Ritu Bhatnagar, MD, MPH, FASAM, DFAPA
President, Wisconsin Society of Addiction Medicine

DATE: September 13, 2023

RE: **Opposition** to 2023 Assembly Bill 393

Good day, Mr. Chairman and members of the Committee on State Affairs. My name is Dr. Ritu Bhatnagar. I am speaking from the perspective of a physician deeply involved in the treatment of addiction. I am a licensed psychiatrist who specializes in addiction psychiatry. I have worked for a decade in a specialty addiction treatment setting, and additionally, I am president of the Wisconsin Society of Addiction Medicine (WISAM), the medical specialty society representing physicians and other clinicians in Wisconsin who specialize in the prevention and treatment of addiction. I am here today on behalf of the Wisconsin Society of Addiction Medicine and the Wisconsin Medical Society to testify **in opposition** to Assembly Bill 393 relating to removing substances contained in kratom from the state's Controlled Substances Act.

I am glad that the legislature is looking carefully at kratom policy. We seek to encourage a forthright debate of the benefits and risks of legislating the use of kratom with an evidence-based approach. This bill does not do that.

Kratom is an intoxicating herbal extract derived from the leaves of evergreen trees (Mitragyna speciosa) in Southeast Asia.[1] Based upon current research, kratom is believed to act on opioid receptors.[2] At low doses, kratom functions as a stimulant, prompting users to feel more energetic. At higher doses, it reduces pain and may bring on euphoria. At very high doses, it acts as a sedative and can be deadly.[3]

According to figures from the Centers for Disease Control and Prevention (CDC), during an 18-month period in the U.S. from July 2016 to December 2017, kratom contributed to 91 fatal overdoses and was identified in the bloodstream of individuals in 152 other fatal overdose cases.[4] Until about 2016, deaths due to kratom were under-reported, perhaps due to limited toxicology. The fact is, most drug screens are not testing for mitragynine.
One of our members, Dr. David Galbis-Reig, a Wisconsin expert, testified in a situation where the person had overdosed: "At the time of his death, the young man's toxicology results showed no other opioids,

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[1] Department of Justice/Drug Enforcement Administration. (2020). Drug Fact Sheet: Kratom. dea.gov. https://www.dea.gov/sites/default/files/2020-06/Kratom-2020_0.pdf
[2] National Institute on Drug Abuse. (2019). Kratom. National Institutes of Health. https://nida.nih.gov/research-topics/kratom#why-use-kratom
[3] Stenson, J. (2019). What is kratom? The popular herbal supplement has caught flak from the FDA. NBCNews.com. https://www.nbcnews.com/health/health-news/what-kratom-popular-herbal-supplement-has-caught-flak-fda-n1066526
[4] Olsen, E. O. M., O'Donnell, J., Mattson, C. L., Schier, J. G., &; Wilson, N. (2019). Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected — 27 States, July 2016–December 2017. MMWR. Morbidity and Mortality Weekly Report, 68(14), 326–327. https://doi.org/10.15585/mmwr.mm6814a2

benzodiazepines, or controlled substances in his system – only mitragynine and his prescribed medications (none of which was a controlled substance)."

Literature reviews and records from poison control centers since its introduction to this country have shown the following risks: nausea, itching, sweating, dry mouth, constipation, increased urination, loss of appetite, hallucinations, psychosis and seizures.

There is a real risk of physiological dependence to kratom. 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 (Suboxone).

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, largely thought to be due to respiratory suppressive effects, just like with other opioids.

We have seen an increasing number of deaths associated with kratom the longer that it has been available in the U.S. market. Because the chemicals in kratom have a wildly disparate impact, it is hard to predict how any one person may experience the drug. So the risk of overdose can vary depending on the person and the other substances they are using.

We do know that naloxone (Narcan) can reverse a kratom overdose, just like it can reverse heroin or fentanyl overdose.

Phone calls about kratom to poison control centers nationwide skyrocketed by more than 50-fold from 13 in 2011 to 682 in 2017, as reported by the *Milwaukee Journal Sentinel* in February 2019.[5]

Despite its potential harm, kratom use is increasing and its marketing is becoming more aggressive. Kratom advocates assert that kratom is an effective treatment for wide-ranging conditions such as muscle pain, panic attacks, and extreme diarrhea. However, current research supporting kratom's medical benefits is insufficient to justify its substantial risk to consumers.[6] Further, due to the unregulated nature of the expanding kratom industry, retailers are not required to disclose health risks to consumers, jeopardizing product transparency and threatening public health.

There is NO evidence that Kratom (or its alkaloids) is an appropriate treatment for opioid use disorder or any other condition. The FDA does not permit labeling of Kratom as a treatment for any condition including opioid use disorder. **We have effective treatment options for opioid use disorder already and the state's resources are better spent increasing access to these medications.**

As of July 2023, 22 states and the District of Columbia regulate kratom or its components in some manner. In six states (Alabama, Arkansas, Indiana, Rhode Island, Vermont, and Wisconsin) kratom's psychoactive components are controlled substances.[7,8]

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[5] Garrison, J (2019). Poison reports related to herbal drug kratom soar, new study says. https://www.jsonline.com/story/news/nation/2019/02/23/kratom-poisonings-herbal-drug-used-opioid-withdrawal-soar/2949239002/

[6] Veltri, C., &; Grundmann, O. (2019). Current Perspectives on the Impact of Kratom Use. Substance Abuse and Rehabilitation, 10, 23–31. https://doi.org/10.2147/sar.s164261

[7] Gianutsos, G. (2017). The DEA Changes Its Mind on Kratom. U.S. Pharmacist. https://www.uspharmacist.com/article/the-dea-changes-its-mind-on-kratom

[8] Legislative Analysis and Public Policy Association (August 2023). Kratom: Summary of State Laws. https://legislativeanalysis.org/wp-content/uploads/2023/08/Kratom-Summary-of-State-Laws.pdf

What should drive our adoption of any public policy should be the evidence and the science, not what any other state is doing. It is actually helpful that we have other states to look at to see the effects. For example, in California, there are now facilities that specialize in treating kratom addiction.

Despite kratom being a controlled substance here in Wisconsin, my colleagues and I are evaluating people with kratom addiction. We use the same medications to treat kratom addiction as we do for opioid use disorder. Legalizing/regulating kratom will simply exacerbate the problems addiction medicine physician specialists are witnessing in our practices and increase the risk of harm to the community.

Having it remain a Schedule 1 controlled substance here is an opportunity for us to evaluate the science and consider the health implications on Wisconsin society. We would need to provide unbiased education to people about the real risks of kratom use before allowing it to be de-scheduled.

Current scientific evidence simply does not suggest that kratom offers enough medical benefits to justify its risks. Clearly, more research is necessary to accurately evaluate kratom's properties and we support conducting this research. There is an obvious conflict of interest in the legislation, with respect to regulation of kratom products by the very industry supporting its sale and expansion. Retailers and advocates have a clear financial incentive to continue downplaying its significant risk to consumers. There are even websites devoted to marketing strategies for kratom dealers: https://cbdmarketingsolutions.com/kratom-marketing/ which downplay the harms and misrepresent the benefits, even stating that it is a non-opioid. This site describes that as of 2016, "the assessed annual revenue from Kratom trades was slightly over **$1 billion**, with about 10,000 Kratom dealers serving the masses."

We may hear from the advocates for kratom that regulation will allow for there to be less likelihood of adulteration, bacterial contamination, or other quality concerns. However, of particular concern is the language in this bill (page 4, lines 17-20) that "A processor does not violate par. (a) if the processor shows by a preponderance of the evidence that the processor relied in good faith on the representation of a manufacturer, a packer, a distributor, or another processor relating to a product represented to be a kratom product," thereby allowing the processors to have no liability but retain the full potential for profit, all at our community's expense. They are socializing the risk and capitalizing on the reward.

Let's make sure we have a situation where manufacturers are held accountable for real and identifiable risks before more lives are lost.

We, as physicians, remain more interested in advocating for the health of our communities, and having seen the challenges in literature and in our practices, oppose the plan to remove kratom from the current schedule and legalized for manufacture, processing and sale without this review and education.

The Wisconsin Society of Addiction Medicine and the Wisconsin Medical Society strongly urge you and your colleagues, as lawmakers, to operate with extreme caution when considering legislation to expand the accessibility of kratom. The dangers of this opioid drug of abuse are clear.

Thank you for the opportunity to present on this emerging and important policy issue.

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

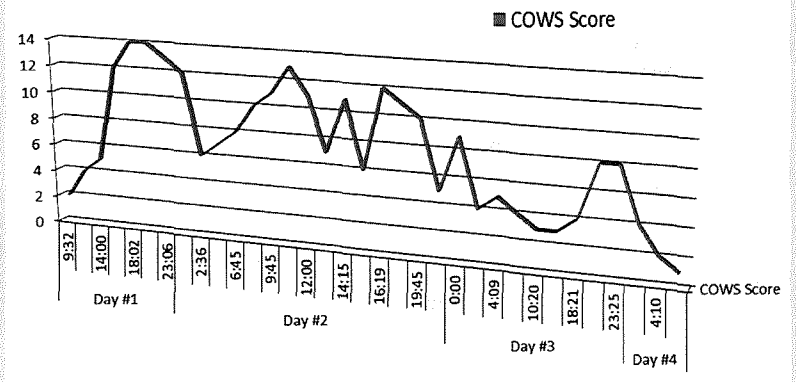
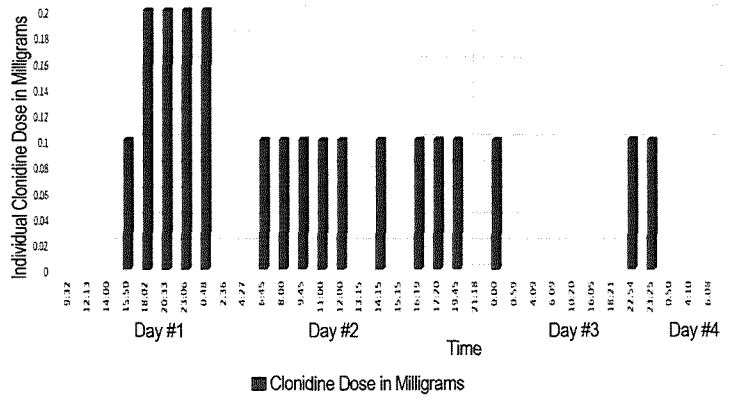


Figure 2. Kratom Withdrawal Clonidine Dose Requirements



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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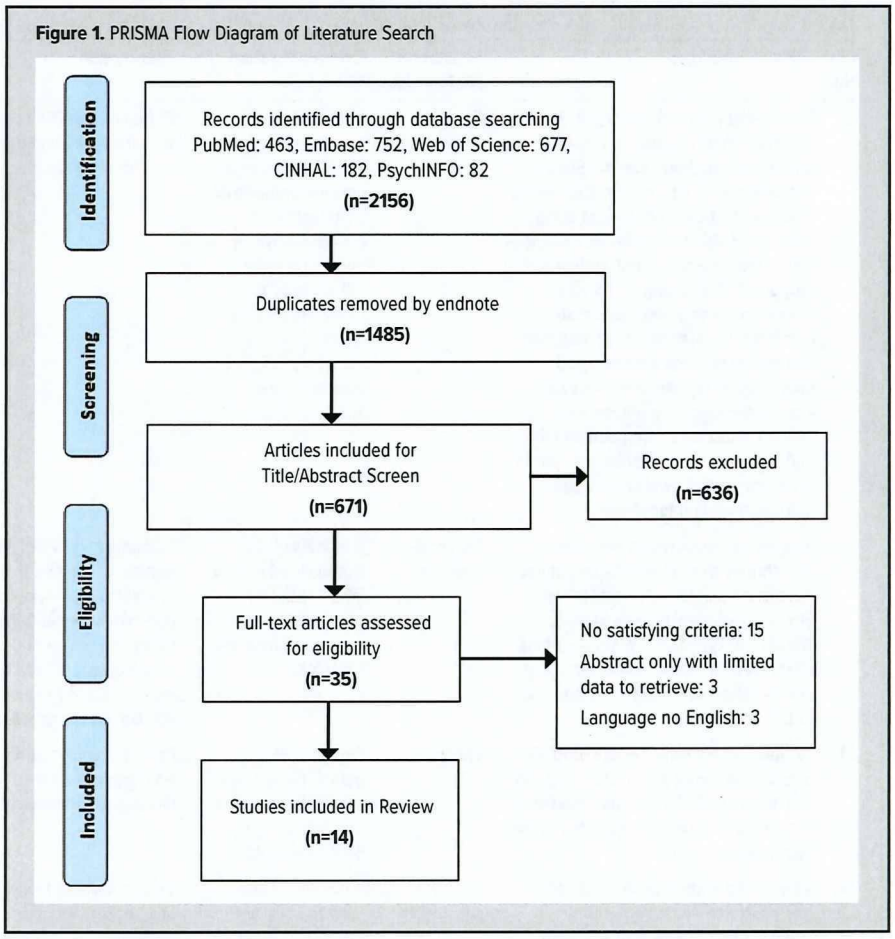
INTRODUCTION

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.

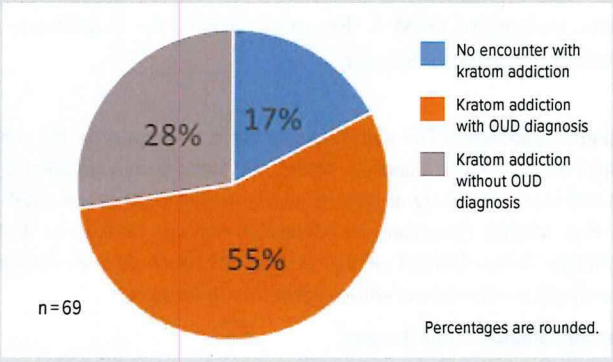
There is a clear need to establish a consensus on how to manage KUD independent of an OUD. As demonstrated in this review, there has been success with treating KUD using the same pharmacological agents as those approved for OUD. In the cases included here that did not involve a comorbid OUD diagnosis,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

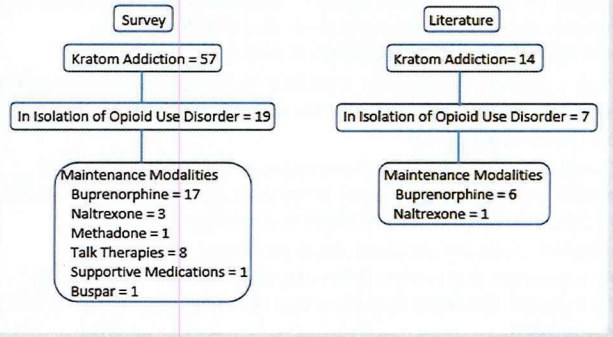
The cases resulting from the literature search and included in the analysis/comparison have a significant amount of heterogeneity in the descriptions, information provided (ie, kratom dose, route, etc), toxicology screens used for abstinence monitoring, reporting of maintenance follow-up duration, etc.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

Final Report from PHAR 537 – Medicinal Natural Products

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Abstract. As a semester-long course project, the third-year pharmacy students of PHAR 537 (Medicinal Natural Products) completed an "eight-factor analysis" of *Mitragyna speciosa* ("kratom"). The eight factors are considered as part of a process by which legislatures determine whether a product should be regulated as a controlled substance. We evaluated the literature concerning the pharmacokinetic and pharmacodynamic (PK/PD) properties of *M. speciosa*, and its impact on public health to the United States at large and Wisconsin specifically. Based on our review of the available literature, we conclude that regulation of *M. speciosa* in Wisconsin as a schedule-I substance is not justified at this time. We base this conclusion, in part, on the scientific evidence demonstrating that *M. speciosa* and its chemical constituents have lower potential for overdose and abuse relative to other agents that are not scheduled in this way. We believe that controlling *M. speciosa* and its chemical constituents under schedule-I harms public health and stifles much-needed research into its therapeutic and toxic properties.

I. Introduction

Per Wisconsin statute 961 (Uniform Controlled Substances Act), the state legislature has the authority to regulate the "manufacture, distribution, delivery, possession, and use of controlled substances for other than legitimate purposes" [1]. The authority to determine whether a substance shall be scheduled is given to the Controlled Substances Board (CSB) [2], and the CSB shall consider the following factors, generally known as the "eight factors" [3]:

(a) The actual or relative potential for abuse;
(b) The scientific evidence of its pharmacological effect, if known;
(c) The state of current scientific knowledge regarding the substance;
(d) The history and current pattern of abuse;
(e) The scope, duration and significance of abuse;
(f) The risk to the public health;
(g) The potential of the substance to produce psychological or physical dependence liability; and
(h) Whether the substance is an immediate precursor of a substance already controlled under this chapter.

Further, the CSB "shall add a substance to schedule I upon finding that the substance:

(a) Has high potential for abuse;
(b) Has no currently accepted medical use in treatment in the United States;
(c) Lacks the accepted safety for use in treatment under medical supervision." [4]

Alternately, the CSB could schedule a substance to schedule I if it is controlled in this way under 21 USC 812 (c) [5].

Controlling a substance under schedule I has broad consequences. First, there are legal consequences to individuals who are caught with a compound that is controlled under schedule-I, as the penalties for possessing schedule-I compounds are generally harsher than those for compounds that are regulated under higher schedules [6]. Patients that experience legitimate therapeutic value from products that are regulated under schedule-I would also be harmed, as scheduling substances in this way effectively prevents them from accessing the therapeutic agent. The process of controlling substances also has consequences for research and innovation. In terms of research, schedule-I substances are subject to stricter control and regulation, which adversely impacts the ability of faculty at smaller schools to engage in scholarship related to these substances [7]. Such scheduling also adversely impacts innovation: businesses seeking to develop

medicinal products would be disincentivized from working with partners in states that label products as schedule-I substances [7].

Recognizing the significance that scheduling a substance has on patient health and beyond, our class took on the challenge of conducting an "eight-factor analysis" of *Mitragyna speciosa*, also known as "kratom." Two constituents of *M. speciosa*, termed mitragynine (MG) and 7-hydroxy-mitragynine (7-OH-MG), are explicitly listed under schedule-I in the state of Wisconsin [8]. This project was conducted as a part of a 3rd year elective course for Pharm.D. graduate students at Concordia University Wisconsin called Medicinal Natural Products (PHAR 537). What follows is the result of our independent review of the available literature surrounding this medicinal plant. In the next section, we will summarize our findings in the context of the "eight factors" outlined above. Of note, none of the students of PHAR 537, nor the instructional faculty, have conducted research using *M. speciosa*, its constituents, or their derivatives, nor do any of the co-authors of this document have plans to do so in the immediate future. This project is an exercise in state and federal pharmacy law, and we intend for this analysis to be potentially of value to the Wisconsin CSB as they consider whether schedule-I is the appropriate place for the constituents of kratom.

II. Results and Discussion

Aiding our research were two recent reviews that were written by experts in the field of substance use disorders [9][10]. These two articles provided helpful content and context as we conducted this analysis. Since the second article was written in 2021, we also sought to find newer articles that were published in 2022 that could further aid the discussion. Our analysis can be considered complementary to these articles previously published; we agree with their assessment that kratom should not be considered a controlled substance at this time.

a. **Factor 1: The actual or relative potential for abuse.** For this factor, we considered behavioral tests in animals performed using kratom or its purified constituents (MG, 7-OH-MG).

The first test we considered under this factor was the intracranial self-stimulation (ICSS) test. In this test, an animal is placed in a chamber and will receive electrical stimulation when it presses a lever. The first ICSS test we reviewed was conducted in 2020 by Behnood-Rod, et al [11]. In this procedure, a dose of drug is considered rewarding if it decreases brain reward threshold and is considered aversive if it increases the brain reward threshold. At low doses, MG slightly lowered the reward threshold and at high doses, MG slightly increased reward threshold, indicating that there is a mild dose-dependent rewarding effect. 7-OH-MG slightly lowered reward threshold at lower doses, but significantly increased the reward threshold at higher doses, indicating that there is a strong aversive effect of 7-OH-MG at high doses. When compared to morphine, the effects of MG and 7-OH-MG are less rewarding.

The drug self-administration (SA) test determines whether an animal will work to receive a dose of drug. Under this paradigm, a drug that has high potential for abuse will be readily self-administered by an animal, and a drug that has low abuse liability will not. The first SA test we reviewed was conducted by Hemby, et al., in 2018 [12]. This test was set up to first train rats to self-administer morphine, then determine whether those rats would instead self-administer MG or 7-OH-MG. In this test, only 7-OH-MG substituted for morphine. After the rats were substituted to MG or 7-OH-MG, the rats that substituted with MG showed a significant decrease in morphine self-administration and those that received 7-OH-MG showed a significant increase in morphine self-administration. Major conclusions from this study were: 1) that MG does not show abuse liability; 2) that because MG significantly decreased morphine self-administration, MG is potentially therapeutically valuable as a treatment for opioid abuse; and 3) that 7-OH-MG has abuse liability. A second SA test that was published by Yue, et al. [13], also showed that MG has low abuse liability and decreases self-administration of heroin.

The conditioned place preference (CPP) test determines whether an animal spends more time in a drug-paired chamber (rewarding behavior) or less time in the drug-paired chamber (aversive behavior). Yussof, et al. [14] showed that MG produced CPP at doses of 10 and 30 mg/kg following injection, which was similar to morphine. Unlike morphine,

however, MG produced anxiolytic effects at low and high doses. A similar U-shaped dose-response curve was observed for locomotor behavior, with MG stimulating locomotion at low and high doses. The authors concluded that MG has abuse liability and can produce effects that are similar to those of psychostimulant and opiate drugs. Similar conclusions were drawn by Iman, et al. [15] and Japarin, et al. [16], though it should be noted that the rewarding effects of MG were observed when MG was administered at higher doses (10-30 mg/kg, *ip*).

In 2019, Meepon and Sooksawate [17] reported that MG at doses from 30-90 mg/kg (*ip*) induced preference for the drug-paired chamber in rats; however, at doses from 10-30 mg/kg, MG significantly blocked morphine CPP, suggesting that the rewarding effects of morphine could be attenuated by MG. MG at doses between 10-30 mg/kg (*ip*) also blocked naloxone-precipitated withdrawal from chronic morphine, again suggesting that MG holds promise as a potential treatment option for patients experiencing opioid withdrawal.

b. **Factor 2: The scientific evidence of its pharmacological effect.** For this factor, we reviewed additional behavioral tests that demonstrate that *M. speciosa* alkaloids have pharmacologic activity *in vivo*. The *in vivo* tests described above would also be considered evidence that MG and 7-OH-MG produce a pharmacologic effect in subjects.

The first test we considered was the drug discrimination (DD) test. In this test, an animal is trained to respond to the stimulus effects of a training drug and then compare whether the animal responds in a similar way to a test drug, in this case MG or 7-OH-MG. The DD test can be useful for determining whether a test drug works through a similar mechanism of action as a training drug.

The first DD test we reviewed was published in 2015 [18]. In this study, a two-lever DD test was used to see if male rats could discriminate MG from vehicle and whether MG would substitute for morphine in rats trained to discriminate morphine. The ability of rats to discriminate morphine from vehicle was also used as a comparator. This study found that MG discrimination in one group of rats was similar to morphine discrimination in a second group. Administration of MG resulted in full substitution for morphine. The authors concluded that the pharmacologic effects of morphine and MG are similar, and that MG appears to be responsible for the potential for kratom to be abused.

A second DD test [19] was published in 2019 and used male and female rats. In this study, the authors tested the ability of morphine and MG to disrupt operant responding for food and increase antinocicetption response to a thermal stimulus in the hot plate test. To determine whether the pharmacologic effects of MG were mediated by opioid receptors, the study included co-administration tests for MG with 1) the mu opioid receptor antagonist, naloxone, and 2) morphine. The results found that both MG and morphine decreased schedule-controlled responding and increased thermal antinociception, though MG was less potent than morphine. Naloxone did not block the effects of MG, suggesting a non-opioid mechanism of action for MG. The results of this study support that MG is effective in reducing pain stimuli, though the mechanism of action differs substantially from that of morphine.

c. **Factor 3: The state of current scientific knowledge regarding the substance.** For this factor, we considered *in vitro* receptor binding and efficacy studies. We also reviewed experiments that included human volunteers.

To determine the receptor binding profile of MG and 7-OH-MG, we first consulted the Ki Database provided by the Psychoactive Drug Screening Program (PDSP), which is housed at the University of North Carolina in Chapel Hill and supported as a free service by the National Institute of Mental Health (NIMH) [20]. The available binding data for MG is included in an accompanying spreadsheet. Among the opioid receptors, MG has highest affinity for mu (average MOR Ki 624.2 nM), then kappa (average KOR Ki 823.25 nM), then delta (DOR Ki 2637 nM). MG also has weak (micromolar) affinity for certain serotonin receptors (5-HT1A, 5-HT1D, 5-HT2B, 5-HT7), adrenergic receptors (alpha2A, alpha2B, alpha2C), and dopamine receptors (D2). For comparison, morphine has nM affinity for opioid receptors (MOR ~ KOR > DOR) and negligible affinity for other monoamine receptors.

Two papers described opioid receptor binding and efficacy of MG and 7-OH-MG in detailed functional assays [21][22]. In these experiments, researchers determined the functional selectivity (aka signaling bias) of kratom alkaloids

for activating G protein pathways or beta-arrestin pathways. Both studies found that MG and 7-OH-MG were G protein-biased partial agonists of MOR, KOR, and DOR, and neither recruited arrestins. In contrast, morphine is a non-biased MOR agonist; this distinction in PD profile is important, as beta-arrestin2 is associated with respiratory depression and constipation, two key adverse effects of MOR agonists [23].

A 2022 study published by Henningfield, et al., compared the respiratory depressant effects of oral MG (20-400 mg/kg, *po*) to oral oxycodone (6.75-150 mg/kg, *po*) in rats [24]. Whereas oxycodone produced significant, dose-dependent sedative and respiratory depressant effects, MG produced mild sedative effects at the highest doses and no respiratory depressant effects at any doses, demonstrating the significant different in observed pharmacologic profiles between canonical MOR agonists and kratom alkaloids.

Structurally, MG and 7-OH-MG are unrelated to other natural and synthetic MOR agonists (**Figure 1**). MG and 7-OH-MG are considered indole alkaloids, whereas morphine (a natural MOR agonist) is considered a phenanthrene derivative and fentanyl (synthetic MOR agonist) is a 4-anilidopiperidine. All of these MOR agonists share in common a basic amine group, thus they are all alkaloids. There are over 40 indole alkaloids present in the plant that have been reported to date. 7-OH-MG is present in the leaves of *M. speciosa*, though in quantities that are unlikely to contribute to its pharmacologic effect when taken orally; however, MG is metabolized into 7-OH-MG *in vivo*, and could indeed be considered an active metabolite of oral MG. More research is needed to determine this.

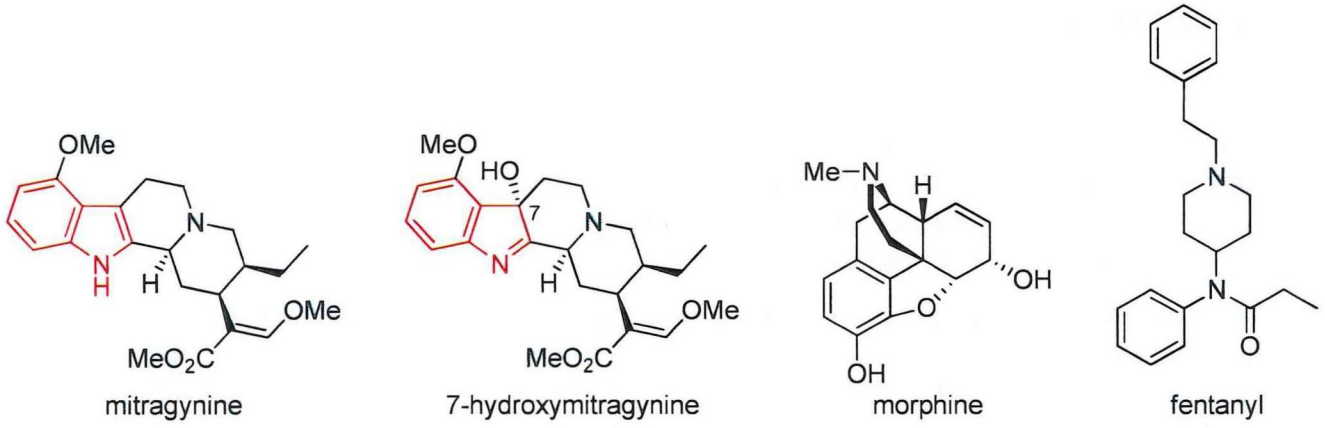

Figure 1. Structures of mitragynine (MG), 7-hydroxymitragynine (7-OH-MG), morphine (a naturally occurring MOR agonist), and fentanyl (a synthetic MOR agonist). The indole group of MG and 7-OH-MG is shown in red.

The PK profile of MG was determined in healthy male volunteers who were regular users of kratom [25]. When administered orally as a tea, the terminal half-life ($t_{1/2}$) was 23.24 ± 16.07 h, the time to Tmax was 0.83 ± 0.35 h, volume of distribution (Vd/F) was 38.04 ± 24.32 L/kg, and the clearance (CL/F) was 98.1 ± 51.34 L/h kg. In 2022, Tanna, et al., published the results of a clinical PK study using a single low (2g) dose of kratom orally to six healthy volunteers [26]. This study found the following parameters using a two-compartment model: $t_{1/2,\alpha}$ 1.76 ± 0.0163 h, Tmax 1.13 ± 0.111 h, V1/F 1170 ± 105 L, CL/F 227 ± 8.11 L/h. In contrast to the earlier study, this study used standardized kratom material that had thoroughly characterized alkaloid content.

According to Smith, et al., the median typical dose of kratom by frequent users was reported to be 4.57 ± 3.61 g, and the median number of doses per day was 2.68 ± 1.73 [27]. The median age of kratom use initiation (29.9 ± 8.8 y) was higher than for initiation of alcohol (15 ± 3.3 y), nicotine (15.9 ± 4.5 y), and cannabis (16.8 ± 5.4 y). Ya, et al., reported that the median oral bioavailability of MG is approximately 21% [28].

d. **Factor 4: The history and current pattern of abuse.** Kratom has been used traditionally in Southeast Asia, the Philippines, and New Guinea. Traditionally, the leaves (dried or fresh) are chewed or brewed into a tea. Kratom leaves are

used in this way to battle physical fatigue, improve mood, relieve pain, and help treat opiate addiction [29][30]. Use of kratom is restricted or banned in most of Europe, Indonesia, Argentina, Israel, New Zealand, and Australia [31]. In the United States, kratom is illegal to buy, sell, possess and use in 6 states: Alabama, Arkansas, Indiana, Rhode Island, Vermont, and Wisconsin [32]. Though the US Drug Enforcement Agency (DEA) initially proposed to control the use of kratom under its emergency scheduling authority in August 2016, this was withdrawn months later in October 2016 [33]. It is difficult to find reputable data regarding the current pattern of abuse of kratom in Wisconsin.

e. **Factors 5 and 6: The scope, duration, and history of abuse, and the risk to public health.** 0.8% of people over the age of 12 in the United States (2.1 million people) used kratom in 2020 [34]. For comparison, 17.9% (49.6 million) used cannabis in the past year, and 3.4% (9.5 million) misused opioids in the same period. Kratom use was lowest among younger people (adolescents age 12-17, 0.2%). According to the 2020 Annual Report of the American Association of Poison Control Centers [35], there were 1262 calls to poison control centers regarding kratom. For context, there were 10,636 calls regarding the FDA-approved cardiovascular drug clonidine, and 17,051 concerning the OTC antihistamine cetirizine (generic for Zyrtec®). **Table 1** compares poison center calls for kratom compared to heroin, prescription fentanyl products, and methadone, which is an FDA-approved treatment for opioid use disorder (OUD). When compared to these products, there were fewer calls made regarding kratom, and the incidence of major outcomes or death were also reduced. Notably, these data for kratom are an improvement over methadone. A 2022 report using data from the British Columbia Drug and Poison Information Centre in Canada found that there were 32 calls regarding kratom between 2012-2019, at increasing frequency near the end of the study period; there were no deaths and the authors attributed the increase potentially to more patients with opioid use disorder (OUD) using kratom to manage their disease [36].

Table 1. Calls to US poison centers regarding single substance pharmaceutical exposures to kratom, heroin, prescription fentanyl, and methadone, and selected outcomes. Data from ref [35].

	Number of calls	Outcome: Major (%)	Outcome: Death (%)
Kratom	1,262	66 (5.2%)	5 (0.4%)
Heroin	8,007	2,210 (27.6%)	124 (1.5%)
Fentanyl (prescription)	2,976	558 (18.8%)	31 (1.0%)
Methadone	2,345	193 (8.2%)	16 (0.6%)

There were 152 unintentional overdose deaths between July 2016 and December 2017 that tested positive for kratom [37]. Of those, in only 7 (4.6%) did the deceased test positively for kratom only. In this period, there were 27,338 drug overdose deaths, meaning kratom was detected in 0.56% of them. Of the polydrug deaths involving kratom, 65% of postmortem samples tested positively for fentanyl, 33% tested positively for heroin (as metabolites), and nearly 20% tested positively for prescription opioids. At doses over 25 g, patients are at risk of hospitalization due to respiratory depression, hallucinations, seizures, and psychosis [38].

A 2022 study investigated the impact of the covid-19 pandemic on kratom use in comparison to use of other drugs of abuse [39]. This study found that there 33% reported an increase in kratom use compared to the period before the pandemic and 24% reported a decrease in use. Alcohol, tobacco, and prescription opioid use were all more likely to have gotten worse during the pandemic. A 2022 study found that reasons for using kratom are diversifying, with users indicating that they are using the product as, among other things, a treatment substitute for opioids, alcohol, and stimulants [40].

Adverse effects of kratom include: loss of muscle coordination; constipation; dizziness; hypotension; increased alertness; and tachycardia. These adverse effects can vary in severity based on the amount and strain of product consumed. In one case report, a 15 year old Caucasian female presented to the emergency department after consuming 45 capsules of kratom 500 mg (22.5 g) in a suicide attempt [41]. Notably, the patient did not show signs of respiratory depression or loss of consciousness, which are hallmarks of the opioid toxidrome and could be life-threatening. Another

case report concerned a 37 year old Caucasian male who presented to the emergency department unresponsive, with minimal response to naloxone [42]. The patient's family reported that he consumed 500 g of kratom the previous day.

f. **Factor 7: The potential of the substance to produce psychological or physical dependence liability.** An individual is considered physically dependent on a substance if they experience withdrawal symptoms when drug use is abruptly ceased. In addition to the studies discussed above, we also reviewed investigations into kratom withdrawal and how kratom impacts withdrawal from other drugs of abuse.

Wilson, et al. [43] determined physical dependence using an induced hyperalgesia model in mice. Products tested include a kratom alkaloid extract (KAE) and MG, both administered orally. Induction of hyperalgesia was used as a marker for drug dependence. Additionally, the team investigated naloxone-precipitated withdrawal following chronic opioid treatment. Like morphine, KAE and MG produced hyperalgesia after 5 days. Following naloxone administration, the somatic signs of withdrawal were strongest with morphine and attenuated in mice dependent on KAE and MG. Furthermore, mice administered KAE or MG demonstrated fewer withdrawal signs than mice who continued to receive morphine. These results suggest 1) that KAE or MG has lower dependence liability than morphine, and 2) that KAE or MG could be useful as treatments for opioid withdrawal. A cross-sectional study conducted in Thailand found that users were likely to experience signs of physical dependence that were directly related to duration, frequency, and amount of kratom consumed [44]. As mentioned above, Gutridge, et al. [21] showed that kratom alkaloids were effective in reducing ethanol intake in mice, suggesting that kratom may have therapeutic potential in patients with alcohol use disorder (AUD).

g. **Factor 8: Whether the substance is an immediate precursor of a substance already controlled under this chapter.** As mentioned in section II.c and shown in **Figure 1**, MG and 7-OH-MG are structurally unrelated to other opioids and to other agents under strict control in Wisconsin.

III. Conclusions

Kratom is a plant-based product that has a long history of traditional use in Southeast Asia and recently has gained attention in the United States as both a recreational substance and an herbal treatment for drug and alcohol use disorders. Though the subjective and pharmacologic effects are similar to MOR agonists like morphine and fentanyl, the indole alkaloids present in *M. speciosa* are structurally and pharmacodynamically distinct.

Several points must be addressed when considering the translation of animal studies to the human condition. First, animal studies using purified MG and/or 7-OH-MG will not necessarily tell an accurate story of the pharmacologic profile of the *M. speciosa* plant material because other constituents of the plant – e.g., other minor indole alkaloids, terpenes, flavonoids, etc. – could influence MG or 7-OH-MG PK. This is commonly observed with natural products-based pharmacologic research. Second, many *in vivo* studies using purified alkaloids administer those compounds via injection (e.g., *ip*), which is not the way kratom is typically consumed [26].

It is important to consider polydrug abuse when reading drug overdose statistics. For example, Olsen, et al. [37] reported that nearly 2/3 of all drug overdose deaths in 2016-2017 involving kratom also tested positively for fentanyl, a high-potency/high-efficacy MOR agonist that, depending on dose, can have minimal response to naloxone [45]. A 2022 report [46] described kratom products that were adulterated with other high-potency MOR agonists, highlighting the need for detailed analysis of kratom products when asking the question, "what is to blame for this overdose?"

The limited number of case reports and national overdose deaths suggests that the risks of kratom are low. Nonetheless, the few case reports that are available require critical examination. For example, in ref [41], the patient consumed a quantity that is over 5x the typical psychoactive dose in a suicide attempt. An even higher dose was observed in ref [42]. Other issues associated with the interpretation of case reports were recently raised by Smith, et al. [47]. It has been understood since Paracelsus that "the dose makes the remedy or the poison," and so labeling a substance as "toxic" based on a small number of case reports where the dose is high seems excessive.

As a final consideration, an early eight-factor analysis of kratom [9] reported that "abrupt discontinuation [of kratom use] may be accompanied by withdrawal symptoms that are qualitatively similar but generally weaker than those observed following discontinuation of opioids." This was updated in 2021: "Some user reports suggest that regular kratom consumption carries risks of dependency and addiction, though with generally self-manageable withdrawal" [48]. The key phrase "self-manageable withdrawal" distinguishes kratom from other opioid agonists that have a severe withdrawal profile.

In conclusion, kratom is a plant product that produces subjective effects distinct from those of other opioids that have high abuse liability. The risk of life-threatening respiratory depressant effects appears to be very low, again different from MOR agonists with high risk of overdose like heroin and fentanyl. Though calls to poison centers in the United States and Canada appear to be increasing, the number of calls is low compared to other, high-risk drugs and may be due to self-medication as part of the ongoing opioid public health crisis. Preclinical assessment of kratom and its constituents suggest that the risk of dependence and withdrawal is minor compared to other drugs that are considered controlled substances, and that kratom and its alkaloid constituents may be therapeutically useful as treatments for substance use disorders when used under the supervision of a clinician. Finally, the US DEA and legislatures of 44 of 49 other US states do not believe that kratom or its constituents meet the requirements to be a schedule-I controlled substance. We agree.

IV. References

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[5] WI 961.13(2m). https://docs.legis.wisconsin.gov/statutes/statutes/961. Accessed 26 October, 2022.

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September 13, 2023

Wisconsin Assembly Committee on State Affairs

RE: Testimony in FAVOR of Kratom bill AB393

Good Afternoon Representative Swearingen and Members of the Committee,

As you are aware, I am Ila Webster and I live in Grafton, Wisconsin. I am here in support of the Kratom Bill AB 393.

It is a pleasure to have the opportunity to speak to you about my experience with kratom.

I have been living with pain for many of my 90 years. I have bilateral lipedema in my lower body which developed in high school and is very painful. I am prone to epicondylitis in both elbows and bursitis in my shoulders. I have a stress fracture at C5 in my spine and a bulging disc at L5. I have a Baker cyst behind my left knee, I am prone to costochondritis. And I have been diagnosed with severe diverticulosis, which periodically has led to diverticulitis. It doubles you up with pain. I cannot take anti-inflammatories due to GI bleeding from Motrin years back, so I am limited to Tylenol or Kratom.

I hope you will not dismiss this "as well, she's 90, so what do you expect?" I am the youngest of 10 children. My older siblings lived well into their 80s, 90s and 100s. My only living sister is now 93. So, genetics predict that I could live to be 100 and I am doing everything I can to make that happen.

When I am in Illinois and I can take kratom I function like a person 20 years younger and walk my 5000 steps throughout the day and do my exercise program with no problem. When it's back to Wisconsin I still do 5000 steps but it takes me longer and with a great deal of pain in my legs. I have been taking Kratom in Illinois for a few years with absolutely no side effects. My blood work is perfect as well as my heart.

As the saying goes; God helps those who help themselves, but sometimes He might want a little help from some friends. So, I am asking you to be a friend and pass AB 393. Thank you.

Respectfully,

Ila Webster
2321 Ridgewood Rd
Grafton, WI 53024

September 13, 2023

Wisconsin State Assembly Committee on State Affairs

Good Afternoon Chairman Swearingen and Members of the Committee,

My name is Heidi Sykora, My residence is in Grafton Wisconsin. I am a retired Nurse Practitioner. Thank you for allowing me to share my testimony in support of the Kratom Bill AB393.

I am here again after another year of schlepping myself and my mother back and forth from Wisconsin to Illinois. In the past year, kratom helped me improve my strength and endurance. It helped me recover to the point that I only needed it occasionally- until last Tuesday when I had an acute exacerbation leading to inflammation of my entire rib cage. If you've ever had broken ribs you understand the kind of pain I'm having.

Thank God for the natural perfect kratom plant. Thank God it happened in Illinois where I could get Kratom. Kratom didn't take all the pain away, but it was the most effective in reducing my pain level to at least allow me to get out of bed.

I didn't plan on an extended stay in Illinois and neither did my mother but If I went back to Wisconsin the only pain relief option would be an Opioid. At that level of pain Tylenol and ibuprofen aren't enough to reduce the pain enough to make it out of bed or to the bathroom independently.

Anyone who is opposed to passing this kratom legislation is telling me that you think a better option is for me to take Opioids. Why? Because the medical society says so? Or because a drug manufacturer has more influence than the best interests of the people of Wisconsin? These are the ones who brought us the Opioid crisis leading to thousands of deaths. You're telling me that you think Opioids are a safer option than the natural kratom plant? There is absolutely no evidence to support that. Kratom is a better, safer option and I challenge anyone to prove otherwise.
Please pass bill AB393 to prevent more opioid deaths and give Wisconsinites a safer natural alternative for pain relief.
Thank you for your time and consideration.

Respectfully,

Heidi Sykora DNP, GNP-BC-retired
2321 Ridgewood Rd.
Grafton, WI 53024
262-573-7848

To: Members, Assembly Committee on State Affairs
From: Badger State Sheriffs' Association (BSSA)
Wisconsin Sheriffs and Deputy Sheriffs Association (WS&DSA)
Date: September 13, 2023
RE: Wisconsin Sheriffs Oppose Assembly Bill 393 on Kratom Legalization

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Chairman Swearingen and Members of the Committee:

I am Dodge County Sheriff Dale Schmidt. I am the President of the Badger State Sheriffs' Association, and I am joined by representatives of the Wisconsin Sheriffs and Deputy Sheriffs Association. Together, our organizations represent Wisconsin's 72 elected County Sheriffs and more than 1,000 Sheriff's Deputies and County Jail Officers. Through our joint legislative committee, we work closely on public safety issues of concern to our members.

Our organizations are asking legislators to oppose Assembly Bill 393, which would legalize the manufacture, distribution, delivery, and possession of kratom in Wisconsin. We oppose AB 393 due to the lack of research and medical consensus on the impairment impacts of kratom.

Kratom is a controversial substance in America as it is not currently regulated on the federal level. The Drug Enforcement Agency (DEA) has listed kratom on its list of drugs of concern.[1] Meanwhile, the U.S. Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA) have both concluded that kratom should be listed under Schedule I of the Controlled Substances Act (CSA).[2] In August 2016, the DEA announced its intent to place the active compounds in kratom, mitragynine and 7-hydroxymitragynine, on Schedule I. Despite publicly stated and documented regulatory agency concerns, kratom remains unregulated federally. It has never been approved for any medical, therapeutic, or supplemental use.

Kratom use has been linked to psychotic episodes, overdose and intoxicated driving 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, [and] appears to have properties that expose users to the risks of addiction, abuse, and dependence."[4]

Wisconsin is one of six states that in 2013 took the proactive step to classify kratom as a Schedule I controlled substance.[5] Since there is no federal regulation, there are 44 states where

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[1] "Drugs of Abuse, A DEA Resource Guide: 2022 Edition," https://www.dea.gov/sites/default/files/2022-12/2022_DOA_eBook_File_Final.pdf.
[2] R. W. Patterson, Department of Human Health Services: 18. (2017).
[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."
[5] 2013 Wisconsin Act 351

kratom is available. Each of those states have taken different approaches to regulating the substance, and it remains uncontrolled in 28 states.[6] Across the country in states where kratom is available, dozens of wrongful death lawsuits are pending against kratom producers and retailers. A $2.5 million judgement for wrongful death due to kratom was awarded in the state of Washington in July of this year, the first such jury verdict in the country.[7]

Wisconsin's own medical, public health, and addiction experts have recommended against legalizing kratom in our state. At the request of legislators, the Wisconsin Controlled Substances Board (CSB) investigated kratom and took the rare step of approving a motion, by a vote of 8-1, declaring that "the Board's investigation raised significant concerns" and "does not recommend any action to de-schedule kratom" in Wisconsin.[8] The CSB includes several doctors, a nurse, a pharmacologist, and a psychiatrist specializing in addiction treatment. The Wisconsin Medical Society and Wisconsin Society of Addiction Medicine, representing medical practitioners across the state, have repeatedly warned about the dangers of this substance.

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 medical or FDA-approved uses? Legalizing Kratom would be detrimental to the public health of Wisconsin, not to mention the rippling effects through intoxicated driving, psychotic episodes, and other areas. **Because of the health and safety risks to our communities, we urge you to oppose efforts to legalize kratom in Wisconsin.**

[6] Legislative Analysis and Public Policy Association, "Kratom: Summary of State Laws," August 2023, https://legislativeanalysis.org/wp-content/uploads/2023/08/Kratom-Summary-of-State-Laws.pdf.
[7] National Public Radio, "Herbal supplement kratom targeted by lawsuits after a string of deaths," July 24, 2023, https://www.npr.org/2023/07/08/1186514144/kratom-herbal-supplement-lawsuits-deaths-fda.
[8] Wisconsin Medical Society, "State Controlled Substances Board tells Legislature: don't de-schedule kratom," March 16, 2023, https://www.wismed.org/wisconsin/wismed/News/Medigram/2023/march-16-2023/wismed/News/medigram/2023-medigram/march-16-2023.aspx.

RACHAEL A. CABRAL-GUEVARA

STATE SENATOR • 19TH SENATE DISTRICT

Testimony before the Assembly Committee on State Affairs

Senator Rachael Cabral-Guevara

September 13, 2023

Hello, Chairman Swearingen and members of the committee. Thank you for allowing me to provide testimony on Assembly Bill 393, an important bill regarding the regulation of kratom products in Wisconsin.

I know many folks will wonder: what is kratom in the first place? Kratom is a substance derived from a natural plant that can relive pain, make someone more alert, and is readily available.

Wisconsin is isolated with its scheduling of kratom products. Currently, it is legal in Iowa, Illinois, Michigan, and Minnesota. It is also legal federally.

This proposal would begin the process of regulating the manufacture, distribution, and consumption of kratom in Wisconsin. Currently, there is no law on the books to keep consumers safe while ingesting this product. As a health care provider, I can tell you that there is a danger in having unregulated products be consumed by patients. This bill would create the regulatory apparatus needed to keep folks safe.

This proposal would also ban the sale of kratom to those under 21. The abuse and addiction to any product typically starts at a young age. That is why it is important to have a strong enforcement mechanism against those who would otherwise sell these products to our kids.

I am hopeful you will be able to support this first step in regulating the production and consumption of kratom products.

P.O. Box 7882 • Madison, WI 53707-7882 • (608) 266-0718

Sen.Cabral-Guevara@legis.wisconsin.gov

TO: Assembly Committee on State Affairs
FROM: Steven Schmitz, Wisconsin Resident
RE: Assembly Bill 393
1225 W Winnebago St
Appleton, WI 54914

Thank you, literally from the bottom of my heart, for your work on a Kratom bill and the KCPA in our state.

I suffer from severe diabetic neuropathy, and at the end of my rope of having been prescribed awful medications such as Gabapentin and SNRIs, none of which helped my problem. Opioids can be effective, however, they can come with their own set of concerns, and the medical system has gone much too far, in their tightening of them.

Finding Kratom was a result of research I had to personally do. It has given me my life back. It has no opioid like effects, but *somehow* relieves my intense and unbearable neuropathy pain. Finding it in Michigan has literally been a godsend for me, allowing me to keep working as opposed to being on some disability situation, and allowing me to enjoy time spent with family, and all the other things that make life worth living.

I am in my late 50s, and am not ready to pack it in due to disability.

Law enforcement is wrong about it, and the medical establishment has tunnel vision. They look at propaganda, not any science. If they looked at the science, they would have a different take on it. We need the help of lawmakers like yourself to make the Kratom situation right.